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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 July 2023 (13.07.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/130181 A1

(51) International Patent Classification:
C07C 323/36 (2006.01) *A61K 31/42* (2006.01)
A61K 31/36 (2006.01) *A61K 31/137* (2006.01)
A61K 31/40 (2006.01) *A61K 31/277* (2006.01)

(21) International Application Number:
PCT/CA2023/050003

(22) International Filing Date:
04 January 2023 (04.01.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/296,430 04 January 2022 (04.01.2022) US
63/422,730 04 November 2022 (04.11.2022) US

(71) Applicant: **BRIGHT MINDS BIOSCIENCES INC.** [CA/CA]; 1055 West Georgia Street, 1500 Royal Centre, P.O. Box 11117, Vancouver, British Columbia V6E 4N7 (CA).

(72) Inventors: **KOZIKOWSKI, Alan**; N3371 River Drive, Wallace, Michigan 49893 (US). **TUECKMANTEL, Werner**; 3620 Breckenridge Court, Apt. 3, Fitchburg, Wisconsin 53713 (US).

(74) Agent: **TSENG, Pablo**; c/o McMillan LLP, 1500-1055 West Georgia Street, P.O. Box 11117, Royal Centre, Vancouver, British Columbia V6E 4N7 (CA).

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

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

Published:
— *with international search report (Art. 21(3))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) Title: PHENETHLYAMINES AND METHODS OF PREPARATION THEREOF

(57) Abstract: The present disclosure relates to compounds of Formula I that exhibit 5-HT_{2A} receptor agonist activity and low $5HT_{2B}$ receptor agonist activity or deemed $5HT_{2B}$ receptor agonist inactivity. In at least some cases, such compounds show selectivity for the 5-HT_{2A} receptor over the 5-HT_{2C} receptor. As contemplated herein, phenethylamines may be used for the treatment of neuropsychiatric, neurodegenerative, neuroinflammatory and pain disorders including depression, drug (e.g. tobacco, opiate, and cocaine) addiction, alcoholism, post-traumatic stress disorder (PTSD), and neuropathic pain syndromes including cluster headaches and chemotherapy induced peripheral neuropathy.

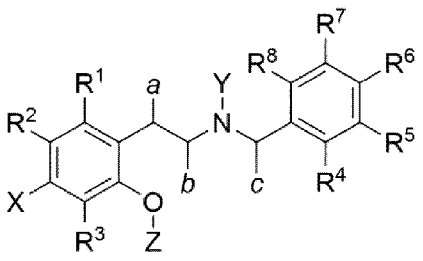


FIGURE 2

WO 2023/130181 A1

PHENETHYLAMINES AND METHODS OF PREPARATION THEREOF

TECHNICAL FIELD:

[0001] This present disclosure relates to phenethylamines and methods of preparing the same. The present disclosure also relates to uses of phenethylamines as selective agents at serotonin receptors.

BACKGROUND:

[0002] Psilocybin is a naturally occurring psychedelic compound produced by more than 200 species of mushrooms collectively known as "psilocybin mushrooms". As a prodrug, psilocybin is quickly metabolized by the body to generate the bioactive compound psilocin, which has mind-altering effects not unlike those produced by other psychedelics such as lysergic acid diethylamide (LSD), mescaline, and N,N-dimethyltryptamine (DMT). These effects include, *inter alia*, euphoria, visual and mental hallucinations, changes in perception, distortions in one's sense of time, and spiritual experiences; these effects can also include possible adverse reactions such as nausea and panic attacks. For reference, the chemical structure of psilocin is provided in Figure 1 herein.

[0003] As agonists of the 5-HT_{2A} and 5-HT_{2C} receptors, psilocybin and psilocin have been recognized for their therapeutic potential. Since 5-HT_{2A} receptor activation appears to increase locomotor activity whereas 5-HT_{2C} receptor activation appears to decrease locomotor activity, compounds possessing varying degrees of 5-HT_{2A} and 5-HT_{2C} activity will show varying levels of psychedelic activity (Halberstadt AL, van der Heijden I, Ruderman MA, Risbrough VB, Gingrich JA. Geyer MA, Powell SB, *Neuropsychopharmacology*, 2009, 34(8):1958-67). While psilocybin, along with other psychedelic drugs, were explored more than 60 years ago by Hofmann and his co-workers at the time (see for example, Hofmann, A., Troxler, F. US 3,075,992; US 3,078,214), clinical investigations into these drugs waned substantially by the early 1970s – particularly after these drugs were placed on Schedule 1 of the *Controlled Substance Act* in the United States of America. Notwithstanding their listing as controlled substances in certain jurisdictions however, research into psilocybin and other psychedelic drugs never fully stopped, and recent clinical investigations have led to a revived interest in the potential application of psychedelic drugs (including psilocybin) in evolving medical areas, such as the treatment of central nervous system (CNS) diseases. CNS diseases include both difficult-to-treat mental health disorders (Daniel J, Haberman M. Clinical potential of psilocybin as a treatment for mental health conditions. *Ment.*

Health Clin. **2017**, *7*(1), 24-8), such as treatment resistant depression or drug resistant depression, and neurological disorders such as cluster headaches.

[0004] While psilocybin has recognized therapeutic potential for treating certain CNS diseases and disorders, it is also recognized as a 5-HT_{2B} receptor agonist which means that psilocybin exhibits cardiotoxic activity. As such, there is an unmet need for safer drugs that at least lack cardiotoxic 5-HT_{2B} agonist activity. Furthermore, and at least in some instances, there is an unmet need for safer drugs that maintain 5-HT_{2A} receptor agonist activity but that lack cardiotoxic 5-HT_{2B} agonist activity.

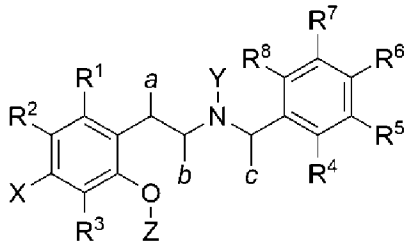
[0005] In recent years, a variety of N-substituted phenethylamines have been identified as 5-HT_{2A} selective. Notably, 25CN-NBOH and closely related analogs have been found to show selectivity for the 5-HT_{2A} receptor over the 5-HT_{2C} receptor and thus exhibit more robust psychedelic activity (see Synthesis and structure-activity relationships of N-benzyl phenethylamines as 5-$HT_{2A/2C}$ agonists. Hansen M, Phonekeo K, Paine JS, Leth-Petersen S, Begtrup M, Bräuner-Osborne H, Kristensen JL. ACS Chem Neurosci. 2014 Mar 19; 5(3): 243-9. doi: 10.1021/cn400216u). However, these compounds are not without their potential drawbacks. Firstly, certain members of this phenethylamine class of compounds may generate reactive benzoquinone metabolites, though it has been found that removal of one of the methoxy groups from such compounds can mitigate against the generation of such metabolites while retaining 5-HT_{2A} selectivity. Secondly, certain members of this phenethylamine class of compounds have been shown to be extremely toxic to humans, notably causing cardiac arrest (Zawilska JB, Kacela M, Adamowicz P, *Front. Neurosci.* 2020; 14: 78).

SUMMARY:

[0006] The present disclosure relates to compounds that belong to the phenethylamine class of molecules that exhibit 5-HT_{2A} receptor agonist activity while exhibiting low $5HT_{2B}$ receptor agonist activity or deemed $5HT_{2B}$ receptor agonist inactivity. In at least some cases, such compounds show selectivity for the 5-HT_{2A} receptor over the 5-HT_{2C} receptor. The compounds disclosed herein may be useful in the treatment of depression including major depressive disorder, drug resistant depression, and psychotic depression, addiction including alcoholism, tobacco addiction, cocaine addiction, and opioid addiction, pain indications including neuropathic pain, pain from chemotherapy associated neuropathy, phantom limb pain and fibromyalgia, inflammation (including chronic and acute), eating disorders including anorexia, autism, cluster headaches, migraines, dementia including Alzheimer's dementia, Parkinson's disease dementia and Lewy body dementia,

post-traumatic stress disorder, emotional distress associated with cancer, Fragile-X syndrome, autism spectrum disorder, bipolar disease, obsessive compulsive disease, Rett syndrome, and other CNS disorders.

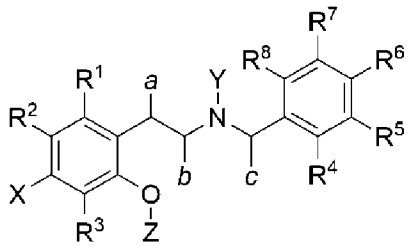
[0007] According to a part of the present disclosure, there are chemical entities of Formula I, or isotopologues or pharmaceutically acceptable salts thereof:



Formula I

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X, Y, Z, *a*, *b*, and *c* are defined herein.

[0008] According to another part of the present disclosure, there are chemical entities of Formula I, or isotopologues or pharmaceutically acceptable salts thereof:



Formula I

wherein: **(a)** R^1: (i) may be selected from the group consisting of H, C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, OH, C_1-C_4 alkoxy, substituted C_1-C_4 alkoxy, C_1-C_4 alkylthio, substituted C_1-C_4 alkylthio, and halogen, if each of R^2 and R^3 is independently selected from H, CH_3, or halogen; or (ii) together with R^2 form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety; or (iii) together with *b* form an alkanediyl, alkenediyl, or heteroalkanediyl moiety; **(b)** R^2: (i) may be selected from the group consisting of H, C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, OH, C_1-C_4 alkoxy, substituted C_1-C_4 alkoxy, C_1-C_4 alkylthio, substituted C_1-C_4 alkylthio,

and halogen, if each of R^1 and R^3 is independently selected from H, CH_3, or halogen; or (ii) together with R^1 form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety; and **(c)** R^3: (i) may be selected from the group consisting of H, C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, OH, C_1-C_4 alkoxy, substituted C_1-C_4 alkoxy, C_1-C_4 alkylthio, substituted C_1-C_4 alkylthio, and halogen, if each of R^1 and R^2 is independently selected from H, CH_3, or halogen; or (ii) together with Z form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety.

[0009] One of R^4, R^5, R^6, R^7, and R^8 may be selected from the group consisting of R^9, OR^9, SR^9, $S(O)R^9$, $S(O)_2R^9$, $N(R^9)C(O)R^9$, $N(R^9)C(O)OR^9$, $N(R^9)C(O)N(H)R^9$, $N(R^9)C(O)N(C_1$-C_6 alkyl$)R^9$, $N(R^9)S(O)_2R^9$, CH_2OR^9, CH_2SR^9, $CH_2S(O)R^9$, $CH_2S(O)_2R^9$, $CH_2N(R^9)C(O)R^9$, $CH_2N(R^9)C(O)OR^9$, $CH_2N(R^9)C(O)N(H)R^9$, $CH_2N(R^9)C(O)N(C_1$-C_6 alkyl$)R^9$, $CH_2N(R^9)S(O)_2R^9$, $CH{=}NOR^9$, $C(C_1$-C_6 alkyl$){=}NOR^9$, $C(O)OR^9$, $C(O)N(H)R^9$, $C(O)N(C_1$-C_6 alkyl$)R^9$, $CH_2C(O)OR^9$, $CH_2C(O)N(H)R^9$, $CH_2C(O)N(C_1$-C_6 alkyl$)R^9$, CN, and halogen, a second one of R^4, R^5, R^6, R^7 or R^8 may be selected from the group consisting of H, C_1-C_4 alkyl, CHF_2, CF_3, OH, OCH_3, OC_2H_5, $OCHF_2$, OCF_3, and halogen, and the remainder of R^4, R^5, R^6, R^7, and R^8 may be each independently H, CH_3, or halogen. If R^4 and R^5 together form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety, then each of R^6, R^7, and R^8 may be independently selected from the group consisting of H, CH_3, and halogen. If R^4 and *b* together form an alkanediyl, alkenediyl, or heteroalkanediyl moiety, then one of R^5, R^6, R^7, and R^8 may be selected from the group consisting of H, C_1-C_4 alkyl, CHF_2, CF_3, OH, OCH_3, OC_2H_5, $OCHF_2$, OCF_3, and halogen, and the remainder of R^5, R^6, R^7, and R^8 may each be independently selected from the group consisting of H, CH_3, and halogen. If R^4 and *c* together form an alkanediyl, alkenediyl, or heteroalkanediyl moiety, then one of R^5, R^6, R^7, and R^8 may be selected from the group consisting of H, C_1-C_4 alkyl, CHF_2, CF_3, OH, OCH_3, OC_2H_5, $OCHF_2$, OCF_3, CN, and halogen, and the remainder of R^5, R^6, R^7, and R^8 may each be independently selected from the group consisting of H, CH_3, and halogen.

[0010] X may be selected from the group consisting of CN, $C(O)NH_2$, $C(O)N(H)R^9$, $C(O)N(C_1$-C_6 alkyl$)R^9$, $C(O)(C_4$-C_6 heterocyclyl), CHF_2, CF_3, OH, $O(C_1$-C_6 alkyl), $OCHF_2$, OCF_3, $S(C_1$-C_6 alkyl), SCF_3, $SCHF_2$, F, Cl, aryl, and heteroaryl generally. Y may be selected from the group consisting of H, CH_3, $C(O)R^9$, $CH_2OC(O)R^9$, and $C(O)OR^9$. Z: (i) may be selected from the group consisting of H, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, C_2-C_{10} heteroalkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, (C_3-C_6 cycloalkyl)(C_1-C_8 alkyl), (C_3-C_6 cycloalkyl)(C_1-C_8 heteroalkyl), C_4-C_6 heterocyclyl, (C_4-C_6 heterocyclyl)(C_1-C_8 alkyl), (C_4-C_6 heterocyclyl)(C_1-C_8

heteroalkyl), aryl(C_1-C_8 alkyl), aryl(C_1-C_8 heteroalkyl), heteroaryl(C_1-C_8 alkyl), heteroaryl(C_1-C_8 heteroalkyl), $C(O)R^9$, $C(O)OR^9$, $CH_2OC(O)R^9$, $C(O)NH_2$, $C(O)N(H)R^9$, $C(O)N(C_1$-C_6 alkyl)R^9, and $C(O)(C_4$-C_6 heterocyclyl); or (ii) together with R^3 may form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety.

[0011] Two of *a*, *b*, and *c* may each be independently selected from the group consisting of H, CH_3, and C_2H_5, while the third of *a*, *b*, and *c* may be H, but if *c* and R^4 together form an alkanediyl, alkenediyl, or heteroalkanediyl moiety then *a* and *b* may each be independently selected from H or CH_3.

[0012] R^9 may, independently for each occurrence, be selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, substituted C_1-C_6 alkyl, substituted C_1-C_6 heteroalkyl, C_2-C_6 alkenyl, C_2-C_6 heteroalkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, (C_3-C_6 cycloalkyl)(C_1-C_6 alkyl), (C_3-C_6 cycloalkyl)(C_1-C_6 heteroalkyl), C_3-C_6 heterocyclyl, (C_3-C_6 heterocyclyl)(C_1-C_6 alkyl), (C_3-C_6 heterocyclyl)(C_1-C_6 heteroalkyl), aryl, aryl(C_1-C_6 alkyl), aryl(C_1-C_6 heteroalkyl), heteroaryl, heteroaryl(C_1-C_6 alkyl), and heteroaryl(C_1-C_6 heteroalkyl).

[0013] The chemical entities of Formula I disclosed herein are 5-HT_{2A} subtype selective receptor agonists. Chemical entities of Formula I, and isotopologues and pharmaceutically acceptable compositions thereof, are believed to be useful for treating a variety of diseases and disorders associated with 5-HT_{2A} receptor agonism. Such diseases and disorders include those described herein.

[0014] This summary does not necessarily describe the entire scope of all aspects of the disclosure. Other aspects, features and advantages will be apparent to those of ordinary skill in the art upon review of the following description of specific embodiments.

BRIEF DESCRIPTION OF DRAWINGS:

[0015] In the accompanying drawings, which illustrate one or more embodiments:

[0016] FIGURE 1 depicts the chemical structure of psilocin.

[0017] FIGURE 2 depicts the chemical structure of Formula I.

[0018] FIGURE 3 is a graph depicting an HTR versus dose for compound 109 (as described herein), as administered to mice.

[0019] FIGURE 4 is a graph depicting an HTR over time per dose (mg/kg) for compound 109 (as described herein), as administered to mice.

[0020] FIGURE 5 is a graph depicting the horizontal activity and vertical activity of rat subjects in locomotor activity tests, in response to a intraperitoneal dose of compound 109 (as described herein).

[0021] FIGURE 6 depicts a synthetic scheme for compounds having a chemical structure of Formula I.

[0022] FIGURE 7 depicts a synthetic scheme of a benzyl moiety in compounds having a chemical structure of Formula I.

[0023] FIGURE 8 depicts a synthetic scheme of a phenethyl moiety in compounds having a chemical structure of Formula I.

[0024] FIGURE 9a depicts a synthetic scheme of compound 12 (as described herein).

[0025] FIGURE 9b depicts another synthetic scheme of compound 12 (as described herein).

[0026] FIGURE 10 depicts a synthetic scheme of a phenethylamine building block for compound 32 (as described herein).

[0027] FIGURE 11 depicts a synthetic scheme for a benzylamine building block for compound 76 (as described herein).

[0028] FIGURE 12a depicts a moiety of a chemical structure of Formula I, wherein *a* is a methyl group.

[0029] FIGURE 12b depicts a moiety of a chemical structure of Formula I, wherein *b* is a methyl group.

[0030] FIGURE 12c depicts a moiety of a chemical structure of Formula I, wherein *c* is a methyl group.

[0031] FIGURE 13 depicts a scheme for the synthesis of one of four stereoisomers of compound 86 (as described herein), in which *b* and *c* are connected to form a ring.

DETAILED DESCRIPTION:

[0032] Directional terms such as “top,” “bottom,” “upwards,” “downwards,” “vertically,” and “laterally” are used in the following description for the purpose of providing relative reference only, and are not intended to suggest any limitations on how any article is to be positioned during use, or to be mounted in an assembly or relative to an environment. The use of the word “a” or “an” when used herein in conjunction with the term “comprising” may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one” and “one or more than one.” Any element expressed in the singular form also encompasses its plural form. Any element expressed in the plural form also encompasses its singular form. The term “plurality” as used herein means more than one, for example, two or more, three or more, four or more, and the like.

[0033] As used herein and unless otherwise specified, the term “about”, when used to describe a recited value, means within 10% of the recited value.

[0034] As used herein and unless otherwise specified, the term "alkanediyl", used alone or as part of a larger moiety, means a substituted or unsubstituted, linear, divalent hydrocarbon chain that can be attached by way of its terminal carbon atoms and that is completely saturated. Unless otherwise specified, an alkanediyl group contains 1 to 5 carbon atoms ("C_1-C_5 alkanediyl"). Non-limiting examples of alkanediyl groups include methylene, ethylene, trimethylene, tetramethylene, and pentamethylene. A substituted alkanediyl group is one having at least one but no more than five substituents, and no more substituents than the number of hydrogen atoms in the unsubstituted group. Non-limiting examples of substituted alkanediyl groups include difluoromethylene, hydroxyethylene, methoxyethylene, $CH_2CH_2C(O)$, $CH_2C(CH_3)_2CH_2$, $CH_2CH_2CH(CF_3)CH_2$, and the like.

[0035] As used herein and unless otherwise specified, the term "alkenediyl", used alone or as part of a larger moiety, means a substituted or unsubstituted, linear, divalent hydrocarbon chain having at least two carbon atoms and at least one carbon-carbon double bond, that can be attached by way of its terminal carbon atoms. Unless otherwise specified, an alkenediyl group contains 2 to 5 carbon atoms ("C_2-C_5 alkenediyl"). Non-limiting examples of alkenediyl groups include vinylene (CH=CH), propene-1,3-diyl (CH_2CH=CH), 1-butene-1,4-diyl (CH_2CH_2CH=CH), 2-butene-1,4-diyl (CH_2CH=$CHCH_2$), and 1,3-butadiene-1,4-diyl (CH=CHCH=CH). For illustration purposes, if a first end of a 1,3-butadiene-1,4-diyl group is attached to a first carbon atom of a carbon-carbon (CC) double bond or an aromatic ring, and a second end of the 1,3-butadiene-1,4-diyl group is attached

to a second carbon atom of the CC double bond or the aromatic ring, and the second carbon atom is adjacent to the first carbon atom, then said two adjacent carbon atoms and the 1,3-butadiene-1,4-diyl group together represent a benzene ring. For illustration purposes, if a first end of a vinylene group is attached to a first carbon atom of a CC double bond or an aromatic ring, and a second end of the vinylene group is attached to a heteroatom (selected from the group consisting of N, O, and S) that is adjacent to a second carbon atom of the CC double bond or the aromatic ring, and the second carbon atom is adjacent to the first carbon atom, then the vinylene group together with said two adjacent carbon atoms and said heteroatom attached to the second carbon atom represent a pyrrole, furan, or thiophene ring.

[0036] As used herein and unless otherwise specified, the term "alkenyl" refers to a substituted or unsubstituted, linear or branched, univalent hydrocarbon chain having at least two carbon atoms and at least one carbon-carbon double bond. Examples of alkenyl groups include allyl, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 1,3-butadien-2-yl, 2,4-pentadien-1-yl, 1,4-pentadien-3-yl, and the like.

[0037] As used herein and unless otherwise specified, the term "alkoxy", used alone or as part of a larger moiety, refers to the groups -O-alkyl and -O-cycloalkyl. As used herein and unless otherwise specified, the term "substituted alkoxy", used alone or as part of a larger moiety, refers to the groups -O-(substituted alkyl) and -O-(substituted cycloalkyl).

[0038] As used herein and unless otherwise specified, the term "alkyl", used alone or as part of a larger moiety, means a substituted or unsubstituted, linear or branched, univalent hydrocarbon chain that is completely saturated. Unless otherwise specified, an alkyl group contains 1 to 7 carbon atoms ("C_1-C_7 alkyl"). For example, in some embodiments, alkyl groups contain 1 to 6 carbon atoms ("C_1-C_6 alkyl"); in some embodiments, alkyl groups contain 1 to 5 carbon atoms ("C_1-C_5 alkyl"); in some embodiments, alkyl groups contain 1 to 4 carbon atoms ("C_1-C_4 alkyl", alternatively "lower alkyl"); and in some embodiments, alkyl groups contain 3 to 7 carbon atoms ("C_3-C_7 alkyl"). Non-limiting examples of saturated alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl, s-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. Examples of lower alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, i-butyl, and t-butyl. A substituted alkyl group is one having at least one but no more than five substituents, and no more substituents than the number of hydrogen atoms in the unsubstituted group. In some embodiments, the substituents are fluorine atoms. Non-limiting examples of substituted alkyl groups include 2-hydroxyethyl, 2-methoxyethyl, CHF_2, CF_3, CH_2CF_3, CF_2CF_3, 4-fluorobutyl, and the like.

[0039] As used herein and unless otherwise specified, the term "alkylthio", used alone or as part of a larger moiety, refers to the groups -S-alkyl and -S-cycloalkyl. "Substituted alkylthio", used alone or as part of a larger moiety, refers to the groups -S-(substituted alkyl) and -S-(substituted cycloalkyl).

[0040] As used herein and unless otherwise specified, the term "alkynyl" refers to a substituted or unsubstituted, linear or branched, univalent hydrocarbon chain having at least two carbon atoms and at least one carbon-carbon triple bond. Non-limiting examples of alkynyl groups include ethynyl, 1- and 3-propynyl, 3-butyn-1-yl, and the like.

[0041] As used herein and unless otherwise specified, the term “aryl”, used alone or as part of a larger moiety (for example, "(aryl)alkyl") refers to a univalent monocyclic or bicyclic carbocyclic aromatic ring system. Unless otherwise specified, aryl groups contain 6 or 10 ring members. Non-limiting examples of aryl include phenyl, naphthyl, and the like. The term “aryl” also refers to aryl groups that may be unsubstituted or substituted. For example, aryl groups can be unsubstituted or can be substituted with one, two, or three groups selected independently from the group consisting of halogen, OH, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_1-C_6 alkylthio, substituted C_1-C_6 alkylthio, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_3-C_6 cycloalkyl, substituted C_3-C_6 cycloalkyl, C(O)OH, C(O)(C_1-C_6 alkyl), C(N-OH)(C_1-C_6 alkyl), C(O)(C_1-C_6 alkoxy), $C(O)NH_2$, C(O)NH(C_1-C_6 alkyl), C(O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), C(O)-heterocyclyl, NHC(O)(C_1-C_6 alkyl), $N(CH_3)C(O)$(C_1-C_6 alkyl), and cyano.

[0042] As used herein and unless otherwise specified, the term "chemical entity" refers to a compound having the indicated structure, whether in its "free" form (e.g., "free compound" or "free base" or "free acid" form, as applicable), or in a salt form, particularly a pharmaceutically acceptable salt form, and furthermore whether in solid state form or otherwise. In some embodiments, a solid state form is an amorphous (i.e., non-crystalline) form; in some embodiments, a solid state form is a crystalline form (e.g., a polymorph, pseudohydrate, hydrate, or solvate). Similarly, the term encompasses the compound whether provided in solid form or otherwise. Unless otherwise specified, all statements made herein regarding "compounds" apply to the associated chemical entities, as defined.

[0043] As used herein and unless otherwise specified, the terms “comprising”, “having”, “including”, “containing”, and grammatical variations thereof, are inclusive or open-ended and do not exclude additional, un-recited elements and/or method steps. For example, "A includes 1, 2, and 3" means

that A includes but is not limited to 1, 2, and 3.

[0044] As used herein and unless otherwise specified, the term “consisting essentially of” when used herein in connection with a composition, use, or method, denotes that additional elements, method steps or both additional elements and method steps may be present, but that these additions do not materially affect the manner in which the recited composition, method, or use functions.

[0045] As used herein and unless otherwise specified, the term “consisting of” when used herein in connection with a composition, use, or method, excludes the presence of additional elements and/or method steps.

[0046] As used herein, the term “cpd” is an abbreviation for the word “compound”.

[0047] As used herein and unless otherwise specified, the term "cycloalkyl", used alone or as part of a larger moiety, for example "(cycloalkyl)alkyl", refers to: (i) a substituted or unsubstituted, univalent monocyclic hydrocarbon radical that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic; or (ii) bicyclo[m.n.o]alkyl wherein each of “m”, “n”, and “o” is independently an integer ranging from zero to 5, and the sum “m”+”n”+”o” ranges from 2 to 6. In some embodiments, cycloalkyl groups contain 3 to 8 ring carbon atoms ("C_3-C_8 cycloalkyl"). Non-limiting examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like, as well as bicyclo[2.2.1]heptyl (also called norbornyl) and bicyclo[1.1.1]pentyl. A substituted cycloalkyl group is one having at least one but no more than five substituents. In some embodiments, the substituents are fluorine atoms. Non-limiting examples of substituted cycloalkyl groups include 2-methylcyclopropyl, 4-hydroxycyclohexyl, 2-methoxycyclopentyl, 4,4-difluorocyclohexyl, and the like.

[0048] As used herein and unless otherwise specified, the term "halogen" or "halo", used alone or as part of a larger moiety, refers to fluoro, chloro, bromo, or iodo.

[0049] As used herein and unless otherwise specified, the term “hERG risk” refers to the risk of a compound potentially inhibiting the human ether-a-go-go-related gene (hERG) K^+ channel, thereby leading to QT prolongation.

[0050] As used herein and unless otherwise specified, the term “heteroalkanediyl” refers to a substituted or unsubstituted alkanediyl group, as defined herein, in which one or more of the

constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. Non-limiting examples for heteroalkanediyl groups include NH, O, S, CH_2NH, CH_2O, CH_2S, CH_2CH_2NH, CH_2CH_2O, CH_2CH_2S, CH_2NHCH_2, CH_2OCH_2, CH_2SCH_2, OCH_2O, OCH_2S, SCH_2S, $CH_2CH_2CH_2NH$, $CH_2CH_2NHCH_2$, $CH_2CH_2CH_2O$, $CH_2CH_2OCH_2$, $CH_2CH_2CH_2S$, and $CH_2CH_2SCH_2$. For illustration purposes, if the points of attachment of a heteroalkanediyl group are non-equivalent (e.g., $CH_2CH_2NHCH_2$), and the points are attached to non-equivalent positions of a chemical structure, then the attachment of the heteroalkanediyl group to the chemical structure can occur in either direction (e.g., $CH_2CH_2NHCH_2$ or $CH_2NHCH_2CH_2$).

[0051] As used herein and unless otherwise specified, the term "heteroalkenediyl" refers to a substituted or unsubstituted alkenediyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. Non-limiting examples for heteroalkenediyl groups include CH=N, CH=CHNH, CH=CHO, CH=CHS, $CH=NCH_2$, N=N, CH=NNH, CH=NO, CH=NS, NHCH=N, OCH=N, SCH=N, HNN=N, CH=CHCH=N, CH=CHN=CH, CH=CHN=N, CH=NCH=N, N=CHCH=N, CH=NN=CH, $CH=CHCH_2NH$, $CH=CHCH_2O$, and $CH=CHCH_2S$. For illustration purposes, if the points of attachment of a heteroalkenediyl group are non-equivalent (e.g., in CH=CHS), and the points are attached to non-equivalent positions of a chemical structure, then the attachment of the heteroalkenediyl group to the chemical structure can occur in either direction (e.g., CH=CHS or SCH=CH). For illustration purposes, if a first point of attachment of a heteroalkenediyl group is attached to a first carbon atom of a CC double bond or an aromatic ring, and a second point of attachment of the heteroalkenediyl group is attached to a second carbon atom of the CC double bond or the aromatic ring, and the first carbon atom and the second carbon atom are adjacent to each other, then said two adjacent carbon atoms and the heteroalkenediyl group together represent a heteroaromatic ring; particularly, (i) if the formed heteroaromatic ring is five-membered, then the single saturated atom of the heteroalkenediyl group is selected from the group consisting of N, O, and S, and (ii) if the formed heteroaromatic ring is a six-membered, then the heteroalkenediyl group comprises only C and N atoms as a part of its backbone and contains two conjugated double bonds. For illustration purposes, if a first point of attachment of a heteroalkenediyl group represented by the formula X=Y, wherein X and Y are independently selected from the group consisting of C and N, is attached to a first carbon atom of a CC double bond or an aromatic ring, and a second point of attachment of the heteroalkenediyl group is attached to a heteroatom (selected from the group consisting of N, O, and S) that in turn is attached to a second carbon atom of the CC double bond or the aromatic ring, and the second carbon atom is adjacent to the first carbon atom, then the moiety X=Y together with said two

adjacent carbon atoms and said heteroatom attached to one of them represent a five-membered heteroaromatic ring.

[0052] As used herein and unless otherwise specified, the term “heteroalkenyl” refers to a substituted or unsubstituted alkenyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur.

[0053] As used herein and unless otherwise specified, the term “heteroalkyl” refers to a substituted or unsubstituted alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur.

[0054] As used herein and unless otherwise specified, the term “heteroaryl”, used alone or as part of a larger moiety, e.g., "(heteroaryl)alkyl", refers to a univalent monocyclic or bicyclic group having 5 to 10 ring atoms, preferably 5, 6, 9, or 10 ring atoms, having 6 or 10 π electrons shared in a cyclic array, and having, in addition to ring carbon atoms, from one to four ring heteroatoms. Examples of heteroaryl groups include thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, indolizinyl, benzofuranyl, benzothiophenyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, quinolyl, isoquinolyl, purinyl, naphthyridinyl, pteridinyl, and the like. Heteroaryl groups may be unsubstituted or may be substituted with one, two, or three groups selected independently from halogen, OH, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_1-C_6 alkylthio, substituted C_1-C_6 alkylthio, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_3-C_6 cycloalkyl, substituted C_3-C_6 cycloalkyl, C(O)OH, C(O)(C_1-C_6 alkoxy), $C(O)NH_2$, C(O)NH(C_1-C_6 alkyl), C(O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), C(O)-heterocyclyl, NHC(O)(C_1-C_6 alkyl), $N(CH_3)C(O)$(C_1-C_6 alkyl), and cyano.

[0055] As used herein and unless otherwise specified, the term “heterocyclyl”, used alone or as part of a larger moiety (for example, "(heterocyclyl)alkyl") refers to a univalent stable 4- to 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and has, in addition to ring carbon atoms, one to four heteroatoms. Non-limiting examples of heterocyclyl groups include tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, morpholinyl, and the like. Heterocyclyl groups can be unsubstituted or can be substituted. For example, heterocyclyl groups can be unsubstituted or can be substituted with one, two, or three groups selected independently from the group consisting of halogen, OH, O(C_1-C_6 alkyl), O(substituted C_1-C_6 alkyl), C_1-C_6 alkyl, substituted C_1-C_6 alkyl, and C_3-C_6 cycloalkyl.

[0056] As used herein and unless otherwise specified, the term "HTR" refers to head-twitch response, which is a measurement of 5-HT_{2A} activation *in vivo*.

[0057] As used herein and unless otherwise specified, the term "inactive" (and all related terms thereto including "inactivity"), when used the context of "EC_{50} (nM)" and "Eff%" as such terms would be understood by a person skilled in the art or equivalent skilled person, and when used in reference to the activity at the 5-HT_{2B} receptor, means a concentration of greater than 10,000 nM (when used in the context of "EC_{50} (nM)") or an efficacy of 30% or lower (when used in the context of "Eff%").

[0058] As used herein and unless otherwise specified, the term "isotopologue" refers to a species that differs from a specific compound only in the isotopic composition thereof. For example, all hydrogen atoms in a compound are independently of natural isotopic composition or of any isotopic composition enriched or depleted in one or both of the heavy isotopes, ^{2}H (D, deuterium) and ^{3}H (T, tritium), ranging from a depletion to zero% to an enrichment to 100%.

[0059] As used herein and unless otherwise specified, the term "low 2B activity" refers to a situation where the 5-HT_{2A} agonist activity (or 5-HT_{2A} receptor sensitivity) of a compound, as measured in terms of "EC_{50} (nm)", is 500 times or more greater than the 5-HT_{2B} agonist activity (or 5-HT_{2B} receptor sensitivity) of said compound and the Eff% at each receptor is less than 90% at the measured EC_{50} for each receptor. For example, a compound is deemed to have "low 2B activity" if such compound possesses: (i) an EC_{50} and Eff% of 1.0 nm and 95% respectively at the 5-HT_{2A} receptor; and (ii) an EC_{50} and Eff% of 700 nm and 95% respectively at the 5-HT_{2B} receptor.

[0060] As used herein and unless otherwise specified, the term "mice" refers to male C57BL/6J mice (6-8 weeks old).

[0061] As used herein and unless otherwise specified, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts of the compounds provided in this disclosure include salts derived from suitable inorganic and organic acids and bases. Non-limiting examples of pharmaceutically acceptable salts include salts of compounds comprising an amino group that are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric

acid, citric acid, succinic acid, or malonic acid. Other non-limiting examples of pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydriodide, 2-hydroxyethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, pivalate, propionate, stearate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Other pharmaceutically acceptable salts include those that are derived from appropriate bases such as alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4}$ alkyl$)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further non-limiting examples of pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0062] As used herein and unless otherwise specified, the term “subject” includes a mammal (e.g., a human, and in some embodiments including prenatal human forms). In some embodiments, a subject suffers from a relevant disease, disorder, or condition. In some embodiments, a subject is susceptible to a disease, disorder, or condition. In some embodiments, a subject displays one or more symptoms or characteristics of a disease, disorder, or condition. In some embodiments, a subject does not display any symptom or characteristic of a disease, disorder, or condition. In some embodiments, a subject is a mammal with one or more features characteristic of susceptibility to or risk of a disease, disorder, or condition. In some embodiments, a subject is a patient. In some embodiments, a subject is an individual to whom diagnosis and/or therapy is and/or has been administered. In some embodiments, a subject is a fetus, an infant, a child, a teenager, an adult, or a senior citizen (i.e., the subject is of advanced age, such as older than 50). In some embodiments, a child refers to a human that is between two and 18 years of age. In some embodiments, an adult refers to a human that is eighteen years of age or older.

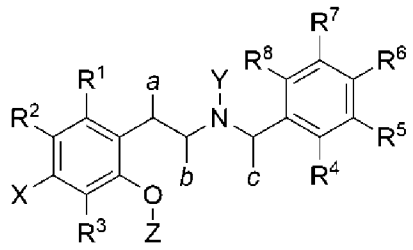
[0063] As used herein and unless otherwise specified, the phrase "such as" is intended to be open-ended. For example, the phrase "A can be a halogen, such as chlorine or bromine" means that “A” can be, but is not limited to, chlorine or bromine.

[0064] Reference to specific moieties, functional groups, or substituents contemplates (where applicable) tautomers thereof.

[0065] Unless otherwise stated, structures depicted herein include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure (e.g., the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers). Unless otherwise stated, the compounds disclosed, taught, or otherwise suggested in this disclosure contemplate all single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures thereof. Unless otherwise stated, the compounds disclosed, taught, or suggested in this disclosure contemplate all tautomeric forms thereof. Additionally, unless otherwise stated, structures depicted herein include compounds that differ only in the presence of one or more isotopically enriched atoms. Such compounds may be useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents. Additionally, incorporation of heavier isotopes such as deuterium (^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increase *in vivo* half-life, or reduced dosage requirements.

[0066] Chemical entities described herein are further illustrated by the classes, subclasses, and species disclosed herein. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987. In this disclosure, any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom.

[0067] Referring to Figure 2, and according to embodiments of the chemical entities disclosed herein (including isotopologues or pharmaceutically acceptable salts thereof), there are chemical entities of Formula I:



Formula I

wherein:

R^1: **(i)** can be selected from the group consisting of H, C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, OH, C_1-C_4 alkoxy, substituted C_1-C_4 alkoxy, C_1-C_4 alkylthio, substituted C_1-C_4 alkylthio, and halogen, if each of R^2 and R^3 is independently selected from H, CH_3, or halogen; or **(ii)** together with R^2 can form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety, which moiety can further be substituted with a first substituent selected from the group consisting of C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, CN, and halogen, and, if such moiety contains at least one additional H atom, a second substituent selected from the group consisting of C_1-C_4 alkyl, substituted C_1-C_4 alkyl, and halogen, if R^3 is H, CH_3, or halogen. For example, if R^3 is H, CH_3, or halogen, then R^1 and R^2 together can form CH_2CH_2, $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $(CH_2)_5$, CH=CHCH=CH, CH_2CH_2O, CH_2OCH_2, OCH_2CH_2, $CH_2CH_2CH_2O$, $CH_2CH_2OCH_2$, $CH_2OCH_2CH_2$, $OCH_2CH_2CH_2$, OCH=CH, CH=CHO, OCH_2O, OCH_2CH_2O, CH_2CH_2S, CH_2SCH_2, SCH_2CH_2, $CH_2CH_2CH_2S$, $CH_2CH_2SCH_2$, $CH_2SCH_2CH_2$, $SCH_2CH_2CH_2$, SCH=CH, CH=CHS, ON=CH, CH=NO, OCH=N, N=CHO, SN=CH, CH=NS, SCH=N, N=CHS, NHCH=CH, CH=CHNH, -NHN=CH, CH=NNH, NHCH=N, N=CHNH, CH=CHCH=N, CH=CHN=CH, CH=NCH=CH, or N=CHCH=CH; or **(iii)** together with *b* can form an alkanediyl, alkenediyl, or heteroalkanediyl moiety, which moiety can be substituted with a substituent selected from the group consisting of C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, CN, and halogen, and, if such moiety contains at least one additional H atom, a second substituent selected from the group consisting of C_1-C_4 alkyl, substituted C_1-C_4 alkyl, and halogen, if each of R^2 and R^3 is independently selected from H, CH_3, or halogen. For example, if R^2

and R^3 are each independently H, CH_3, or halogen, then R^1 and *b* can form any one of the following non-limiting linkages: CH_2, CH_2CH_2, $CH_2CH_2CH_2$, CH=CH, CH_2CH=CH, CH=$CHCH_2$, OCH_2, OCH_2CH_2, CH_2OCH_2, SCH_2, SCH_2CH_2, and CH_2SCH_2;

R^2: **(i)** is selected from the group consisting of H, C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, OH, C_1-C_4 alkoxy, substituted C_1-C_4 alkoxy, C_1-C_4 alkylthio, substituted C_1-C_4 alkylthio, and halogen, if each of R^1 and R^3 is independently selected from H, CH_3, or halogen; or (ii) together with R^1 can form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety, which moiety can be substituted with a first substituent selected from the group consisting of C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, CN, and halogen, and, if such moiety contains at least one additional H atom, a second substituent selected from the group consisting of C_1-C_4 alkyl, substituted C_1-C_4 alkyl, and halogen, if R^3 is H, CH_3, or halogen;

R^3: **(i)** is selected from the group consisting of H, C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, OH, C_1-C_4 alkoxy, substituted C_1-C_4 alkoxy, C_1-C_4 alkylthio, substituted C_1-C_4 alkylthio, and halogen, if each of R^1 and R^2 is independently selected from H, CH_3, or halogen; or **(ii)** together with *Z* can form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety, which moiety can be substituted with one selected from the group consisting of C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, OH, C_1-C_4 alkoxy, C_1-C_4 alkylthio, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, CN, and halogen, if each of R^1 and R^2 is independently selected from the group consisting of H, CH_3, and halogen;

wherein:

one of R^4, R^5, R^6, R^7, and R^8 is selected from the group consisting of R^9, OR^9, SR^9, $S(O)R^9$, $S(O)_2R^9$, $N(R^9)C(O)R^9$, $N(R^9)C(O)OR^9$, $N(R^9)C(O)N(H)R^9$, $N(R^9)C(O)N(C_1$-C_6 alkyl)R^9, $N(R^9)S(O)_2R^9$, CH_2OR^9, CH_2SR^9, $CH_2S(O)R^9$, $CH_2S(O)_2R^9$, $CH_2N(R^9)C(O)R^9$, $CH_2N(R^9)C(O)OR^9$, $CH_2N(R^9)C(O)N(H)R^9$, $CH_2N(R^9)C(O)N(C_1$-C_6 alkyl)R^9, $CH_2N(R^9)S(O)_2R^9$, CH=NOR^9, C(C_1-C_6 alkyl)=NOR^9, $C(O)OR^9$, $C(O)N(H)R^9$, $C(O)N(C_1$-C_6 alkyl)R^9, $CH_2C(O)OR^9$, $CH_2C(O)N(H)R^9$, $CH_2C(O)N(C_1$-C_6 alkyl)R^9, CN, and halogen, a second one of R^4, R^5, R^6, R^7 or R^8 is selected from the group consisting of H, C_1-C_4 alkyl, CHF_2, CF_3, OH, OCH_3, OC_2H_5, $OCHF_2$, OCF_3, and halogen, and the remainder of R^4, R^5,

R^6, R^7, and R^8 are each independently H, CH_3, or halogen;

or if R^4 and R^5 together form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety, which moiety can be substituted with a group selected from the group consisting of H, C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, C_1-C_4 alkoxy, OCF_3, C_1-C_4 alkylthio, CN, and halogen, then each of R^6, R^7, and R^8 is independently selected from the group consisting of H, CH_3, and halogen. Non-limiting examples of alkanediyl moieties include CH_2CH_2, $CH_2CH_2CH_2$, and $CH_2CH_2CH_2CH_2$. A non-limiting example of an alkenediyl moiety is CH=CHCH=CH. Non-limiting examples of heteroalkanediyl moieties include CH_2CH_2O, CH_2OCH_2, OCH_2CH_2, $CH_2CH_2CH_2O$, $CH_2CH_2OCH_2$, $CH_2OCH_2CH_2$, $OCH_2CH_2CH_2$, OCH_2O, OCH_2CH_2O, CH_2CH_2S, CH_2SCH_2, SCH_2CH_2, $CH_2CH_2CH_2S$, $CH_2CH_2SCH_2$, $CH_2SCH_2CH_2$, $SCH_2CH_2CH_2$, $NHCH_2CH_2$, and $NHCH_2NH$. Non-limiting examples of heteroalkenediyl moieties include OCH=CH, CH=CHO, SCH=CH, CH=CHS, ON=CH, CH=NO, OCH=N, N=CHO, SN=CH, CH=NS, SCH=N, N=CHS, NHCH=CH, CH=CHNH, NHN=CH, CH=NNH, NHCH=N, N=CHNH, CH=CHCH=N, CH=CHN=CH, CH=NCH=CH, and N=CHCH=CH;

or if R^4 and *b* together form an alkanediyl, alkenediyl, or heteroalkanediyl moiety, which moiety can be substituted with (a) a first group selected from the group consisting of C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, CN, and halogen, and (b) a second group selected from the group consisting of C_1-C_4 alkyl, substituted C_1-C_4 alkyl, and halogen, then one of R^5, R^6, R^7, and R^8 is selected from the group consisting of H, C_1-C_4 alkyl, CHF_2, CF_3, OH, OCH_3, OC_2H_5, $OCHF_2$, OCF_3, and halogen, and the remainder of R^5, R^6, R^7, and R^8 are each independently selected from the group consisting of H, CH_3, and halogen. Non-limiting examples of alkanediyl moieties include CH_2 and CH_2CH_2. A non-limiting example of an alkenediyl moiety is CH=CH. Non-limiting examples of heteroalkanediyl moieties include OCH_2 and SCH_2;

or if R^4 and *c* together form an alkanediyl, alkenediyl, or heteroalkanediyl moiety, then one of R^5, R^6, R^7, and R^8 is selected from the group consisting of H, C_1-C_4 alkyl, CHF_2, CF_3, OH, OCH_3, OC_2H_5, $OCHF_2$, OCF_3, CN, and halogen, and the remainder of R^5, R^6, R^7, and R^8 are each independently selected from the group consisting of H, CH_3, and halogen. Non-limiting examples of alkanediyl moieties include CH_2, CH_2CH_2, and $CH_2CH_2CH_2$. Non-limiting examples of alkenediyl moieties include CH=CH, CH_2CH=CH, and CH=$CHCH_2$. Non-

limiting examples of heteroalkanediyl moieties include CH_2OCH_2, OCH_2CH_2, CH_2SCH_2, and SCH_2CH_2;

wherein:

X is selected from the group consisting of CN, $C(O)NH_2$, $C(O)N(H)R^9$, $C(O)N(C_1\text{-}C_6$ alkyl$)R^9$, $C(O)(C_4\text{-}C_6$ heterocyclyl), CHF_2, CF_3, OH, $O(C_1\text{-}C_6$ alkyl), $OCHF_2$, OCF_3, $S(C_1\text{-}C_6$ alkyl), SCF_3, $SCHF_2$, F, Cl, aryl, and heteroaryl generally, but otherwise selected from the group consisting of CN, $C(O)NH_2$, $C(O)N(H)R^9$, $C(O)N(C_1\text{-}C_6$ alkyl$)R^9$, $C(O)(C_4\text{-}C_6$ heterocyclyl), CHF_2, CF_3, OH, $O(C_1\text{-}C_6$ alkyl), $OCHF_2$, OCF_3, $S(C_1\text{-}C_6$ alkyl), SCF_3, $SCHF_2$, aryl, and heteroaryl in other instances if Z is alkyl and R^4 is hydroxy;

Y is selected from the group consisting of H, CH_3, $C(O)R^9$, $CH_2OC(O)R^9$, and $C(O)OR^9$;

Z: **(i)** is selected from the group consisting of H, $C_1\text{-}C_{10}$ alkyl, substituted $C_1\text{-}C_{10}$ alkyl, $C_1\text{-}C_{10}$ heteroalkyl, $C_2\text{-}C_{10}$ alkenyl, $C_2\text{-}C_{10}$ heteroalkenyl, $C_2\text{-}C_{10}$ alkynyl, $C_3\text{-}C_6$ cycloalkyl, ($C_3\text{-}C_6$ cycloalkyl)($C_1\text{-}C_8$ alkyl), ($C_3\text{-}C_6$ cycloalkyl)($C_1\text{-}C_8$ heteroalkyl), $C_4\text{-}C_6$ heterocyclyl, ($C_4\text{-}C_6$ heterocyclyl)($C_1\text{-}C_8$ alkyl), ($C_4\text{-}C_6$ heterocyclyl)($C_1\text{-}C_8$ heteroalkyl), aryl($C_1\text{-}C_8$ alkyl), aryl($C_1\text{-}C_8$ heteroalkyl), heteroaryl($C_1\text{-}C_8$ alkyl), heteroaryl($C_1\text{-}C_8$ heteroalkyl), $C(O)R^9$, $C(O)OR^9$, $CH_2OC(O)R^9$, $C(O)NH_2$, $C(O)N(H)R^9$, $C(O)N(C_1\text{-}C_6$ alkyl$)R^9$, and $C(O)(C_4\text{-}C_6$ heterocyclyl); or **(ii)** together with R^3 form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety, which moiety can further be substituted with one group selected from the group consisting of $C_1\text{-}C_4$ alkyl, substituted $C_1\text{-}C_4$ alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, OH, $C_1\text{-}C_4$ alkoxy, $C_1\text{-}C_4$ alkylthio, OCF_3, CN, and halogen. Examples of alkanediyl moieties include CH_2CH_2 and $CH_2CH_2CH_2$; non-limiting examples of alkenediyl moieties include CH=CH; non-limiting examples of heteroalkanediyl moieties include CH_2O, CH_2CH_2O, CH_2S, and CH_2CH_2S; and non-limiting examples of heteroalkenediyl moieties include CH=N;

wherein:

with regard to *a*, *b*, and *c*: **(i)** two of *a*, *b*, and *c* are each independently selected from the group consisting of H, CH_3, and C_2H_5, while the third of *a*, *b*, and *c* is H; or **(ii)** *b* and *c* together are CH_2, CH_2CH_2, $CH_2CH_2CH_2$, or CH_2OCH_2, while *a* is H or CH_3; or **(iii)** if *b* and R^1 together form an alkanediyl, alkenediyl, or heteroalkanediyl moiety, which moiety can be substituted with a first substituent selected from the group consisting of $C_1\text{-}C_4$ alkyl,

substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, CN, and halogen, and, if the moiety contains at least one additional H atom, a second substituent selected from the group consisting of C_1-C_4 alkyl, substituted C_1-C_4 alkyl, and halogen, then one of *a* and *c* is H, CH_3, or C_2H_5, and the other of *a* and *c* is H. Non-limiting examples of alkanediyl moieties include CH_2, CH_2CH_2, and $CH_2CH_2CH_2$. Non-limiting examples of alkenediyl moieties include CH=CH, CH_2CH=CH, and CH=$CHCH_2$. Non-limiting examples of heteroalkanediyl moieties include CH_2O, CH_2CH_2O, CH_2OCH_2, CH_2S, CH_2CH_2S, and CH_2SCH_2; or **(iv)** if *b* and R^4 together form an alkanediyl, alkenediyl, or heteroalkanediyl moiety, which moiety can be substituted with a first substituent selected from the group consisting of H, C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, CN, and halogen, and, if the moiety contains at least one additional H atom, a second substituent selected from the group consisting of C_1-C_4 alkyl, substituted C_1-C_4 alkyl, and halogen, then one of *a* and *c* is H, CH_3, and C_2H_5, and the other of *a* and *c* is H. Non-limiting examples of alkanediyl moieties include CH_2 and CH_2CH_2. A non-limiting example of an alkenediyl moiety is CH=CH. Non-limiting examples of heteroalkanediyl moieties include CH_2O and CH_2S; or **(v)** if *c* and R^4 together form an alkanediyl, alkenediyl, or heteroalkanediyl moiety, then *a* and *b* are each independently selected from H or CH_3. Non-limiting examples of alkanediyl moieties include CH_2, CH_2CH_2, and $CH_2CH_2CH_2$. Non-limiting examples of alkenediyl moieties include CH=CH, and CH_2CH=CH. Non-limiting examples of heteroalkyl moieties include CH_2O, CH_2OCH_2, CH_2CH_2O, CH_2S, CH_2SCH_2, and CH_2CH_2S;

and wherein:

R^9 is, independently for each occurrence, selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, substituted C_1-C_6 alkyl, substituted C_1-C_6 heteroalkyl, C_2-C_6 alkenyl, C_2-C_6 heteroalkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, (C_3-C_6 cycloalkyl)(C_1-C_6 alkyl), (C_3-C_6 cycloalkyl)(C_1-C_6 heteroalkyl), C_3-C_6 heterocyclyl, (C_3-C_6 heterocyclyl)(C_1-C_6 alkyl), (C_3-C_6 heterocyclyl)(C_1-C_6 heteroalkyl), aryl, aryl(C_1-C_6 alkyl), aryl(C_1-C_6 heteroalkyl), heteroaryl, heteroaryl(C_1-C_6 alkyl), and heteroaryl(C_1-C_6 heteroalkyl).

EXAMPLES OF EMBODIMENTS OF CHEMICAL ENTITIES

[0068] Examples of chemical entities of Formula I are provided in Table 1 below.

Table 1. Examples of Compounds of Formula I *

#	X	Y	Z	R^3	R^2	R^1	*a*	*b*	*c*	R^4	R^5	R^6	R^7	R^8
1	CN	H	Me	H	H	H	H	H	H	H	H	H	H	H
2	CN	H	Me	H	H	F	H	H	H	H	H	H	H	H
3	CN	H	Me	H	F	H	H	H	H	H	H	H	H	H
4	CN	H	Me	H	F	H	H	H	H	OH	H	H	H	H
5	CN	H	Me	F	H	F	H	H	H	H	H	H	H	H
6	CN	H	Me	H	H	H	H	H	H	F	H	H	H	H
7	CN	H	Me	H	H	H	H	H	H	H	F	H	H	H
8	CN	H	Me	H	H	H	H	H	H	H	H	F	H	H
9	CN	H	Me	H	H	Cl	H	H	H	H	H	H	H	H
10	CN	H	Me	H	Cl	H	H	H	H	H	H	H	H	H
11	CN	H	Me	Cl	H	H	H	H	H	H	H	H	H	H
12	CN	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
13	CN	H	Me	H	H	H	H	H	H	H	Cl	H	H	H
14	CN	H	Me	H	H	H	H	H	H	H	H	Cl	H	H
15	CN	H	Me	H	H	Me	H	H	H	H	H	H	H	H
16	CN	H	Me	H	Me	H	H	H	H	H	H	H	H	H
17	CN	H	Me	Me	H	H	H	H	H	H	H	H	H	H
18	CN	H	Me	H	H	H	H	H	H	Me	H	H	H	H
19	CN	H	Me	H	H	H	H	H	H	H	Me	H	H	H
20	CN	H	Me	H	H	H	H	H	H	H	H	Me	H	H
21	CN	H	Me	H	H	CF_3	H	H	H	H	H	H	H	H
22	CN	H	Me	H	CF_3	H	H	H	H	H	H	H	H	H
23	CN	H	Me	CF_3	H	H	H	H	H	H	H	H	H	H
24	CN	H	Me	H	H	OMe	H	H	H	H	H	H	H	H

25	CN	H	Me	H	OMe	H	H	H	H	H	H	H	H	H
26	CN	H	Me	OMe	H	H	H	H	H	H	H	H	H	H
27	CN	H	Me	H	H	H	H	H	H	OMe	H	H	H	H
28	CN	H	Me	H	H	H	H	H	H	H	OMe	H	H	H
29	CN	H	Me	H	H	H	H	H	H	H	H	OMe	H	H
30	CN	H	Me	H	$(CH=CH)_2$		H	H	H	Cl	H	H	H	H
31	CN	H	Me	H	CH_2CH_2O		H	H	H	Cl	H	H	H	H
32	CN	H	Me	H	CH=CHO		H	H	H	Cl	H	H	H	H
33	CN	H	Me	H	OCH_2O		H	H	H	Cl	H	H	H	H
34	CN	H	Me	H	CH=CHNH		H	H	H	Cl	H	H	H	H
35	CN	H	Me	H	CH=NO		H	H	H	Cl	H	H	H	H
36	CN	H	Me	CHF_2	H	H	H	H	H	H	H	H	H	H
37	CN	H	H	H	H	H	H	H	H	Cl	H	H	H	H
38	CN	H	CHF_2	H	H	H	H	H	H	Cl	H	H	H	H
39	CN	H	CF_3	H	H	H	H	H	H	Cl	H	H	H	H
40	CN	H	Et	H	H	H	H	H	H	Cl	H	H	H	H
41	CN	H	Bu	H	H	H	H	H	H	Cl	H	H	H	H
42	CN	H	cpm	H	H	H	H	H	H	Cl	H	H	H	H
43	CN	H	CH_2CH_2		H	H	H	H	H	Cl	H	H	H	H
44	CN	H	CH=CH		H	H	H	H	H	Cl	H	H	H	H
45	CN	H	CH_2O		H	H	H	H	H	Cl	H	H	H	H
46	CN	H	CH_2CH_2O		H	H	H	H	H	Cl	H	H	H	H
47	CN	H	CH=N		H	H	H	H	H	Cl	H	H	H	H
48	CN	H	N=CH		H	H	H	H	H	Cl	H	H	H	H
49	CN	H	Me	H	H	H	H	H	CH_2		H	H	H	H
50	CN	H	Me	H	H	H	H	H	CH_2CH_2		H	H	H	H

51	CN	H	Me	H	H	H	H	H	$(CH_2)_3$		H	H	H	H
52	CN	H	Me	H	H	H	H	H	CH_2O		H	H	H	H
53	CN	H	Me	H	H	H	H	H	CH_2OCH_2		H	H	H	H
54	CN	H	Me	H	H	H	H	H	CH_2CH_2O		H	H	H	H
55	CN	H	Me	H	H	H	H	H	H	OH	H	H	H	H
56	CN	H	Me	H	H	H	H	H	H	H	OH	H	H	H
57	CN	H	Me	H	H	H	H	H	H	H	H	OH	H	H
58	CN	H	Me	H	H	H	H	H	H	Cl	H	H	H	Cl
59	CN	H	Me	H	H	H	H	H	H	F	H	F	H	H
60	CN	H	Me	H	H	H	H	H	H	Cl	H	H	H	Cl
61	CN	H	Me	H	H	H	H	H	H	*d*	H	H	H	H
62	CN	H	Me	H	H	H	H	H	H	*e*	H	H	H	H
63	CN	H	Me	H	H	H	H	H	H	CH_2CH_2O		H	H	H
64	CN	H	Me	H	H	H	H	H	H	CH=CHO		H	H	H
65	CN	H	Me	H	H	H	H	H	H	OCH_2O		H	H	H
66	CN	H	Me	H	H	H	H	H	H	CH=CHNH		H	H	H
67	CN	H	Me	H	H	H	H	H	H	CH=NO		H	H	H
68	CN	H	Me	H	H	H	H	H	H	OCH_2CH_2		H	H	H
69	CN	H	Me	H	H	H	H	H	H	OCH=CH		H	H	H
70	CN	H	H	H	H	H	H	H	H	SCH=CH		H	H	H
71	CN	H	H	H	H	H	H	H	H	NHCH=CH		H	H	H
72	CN	H	Me	H	H	H	H	H	H	NHC(F)=N		H	H	H
73	CN	H	Me	H	H	H	H	H	H	N(Me)CH=N		H	H	H
74	CN	H	Me	H	H	H	H	H	H	ON=CH		H	H	H
75	CN	H	Me	H	H	H	H	H	H	N=CH-CH=CH		H	H	H

76	CN	H	Me	H	H	H	H	H	H	N=CH-CH=CH		H	F	H
77	CN	H	Me	H	H	H	H	H	H	Cl	H	OH	H	H
78	CN	H	Me	H	H	H	H	H	H	CN	H	H	H	H
79	CN	H	Me	H	H	H	H	H	H	H	H	H	H	H
80	CN	H	Me	H	H	H	Me	H	H	Cl	H	H	H	H
81	CN	H	Me	H	H	H	H	Me	H	Cl	H	H	H	H
82	CN	H	Me	H	H	H	H	H	Me	Cl	H	H	H	H
83	CN	H	Me	H	H	H	H	CH_2		Cl	H	H	H	H
84	CN	H	Me	H	H	H	H	CH_2CH_2		Cl	H	H	H	H
85	CN	H	Me	H	H	H	H	CH_2CH_2		OH	H	H	H	H
86	CN	H	Me	H	H	H	H	$(CH_2)_3$		Cl	H	H	H	H
87	CN	H	Me	H	H	H	H	CH_2OCH_2		Cl	H	H	H	H
88	CN	Me	Me	H	H	H	H	H	H	Cl	H	H	H	H
89	CN	Ac	Me	H	H	H	H	H	H	Cl	H	H	H	H
90	CN	Bz	Me	H	H	H	H	H	H	Cl	H	H	H	H
91	CN	*f*	Me	H	H	H	H	H	H	Cl	H	H	H	H
92	*d*	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
93	CF_3	H	Me	H	H	H	H	H	H	OH	H	H	H	H
94	CHF_2	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
95	OH	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
96	OMe	H	Me	H	H	H	H	H	H	OH	H	H	H	H
97	$OCHF_2$	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
98	OCF_3	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
99	SCF_3	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
100	*g*	H	Me	H	H	H	H	H	H	Cl	H	H	H	H

101	4-isoxazolyl	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
102	2-oxazolyl	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
103	2-thiazolyl	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
104	2-pyrimidyl	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
105	5-pyrimidyl	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
106	3-pyridyl	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
107	4-pyridyl	H	Me	H	H	H	H	H	H	Cl	H	H	H	H
108	CN	H	Me	H	H	H	H	H	H	SMe	H	H	H	H
109	CN	H	H	H	H	H	H	H	H	SMe	H	H	H	H

#	X	Y	Z	R^3	R^2	R^1	*b*	*a*	*c*	R^4	R^5	R^6	R^7	R^8
110	CN	H	Me	H	H	CH_2		H	H	OH	H	H	H	H

#	X	Y	Z	R^3	R^2	R^1	*a*	*c*	*b*	R^4	R^5	R^6	R^7	R^8
111	CN	H	Me	H	H	H	H	H	CH_2O		H	H	H	H

#	X	Y	Z	R^3	R^2	R^1	*a*	*b*	*c*	R^4	R^5	R^6	R^7	R^8
112	OMe	H	Me	H	H	H	H	H	H	H	H	H	H	OH
113	CN	H	Me	H	H	H	H	H	H	H	H	H	H	OH
114	CN	H	H	H	H	H	H	H	H	H	H	H	H	OH
115	CN	H	CF_3	H	H	H	H	H	H	H	H	H	H	OH
116	CF_3	H	H	H	H	H	H	H	H	OH	H	H	H	H

117	CN	H	Me	H	F	H	H	H	H	H	H	H	H	OH
118	CN	Me	Me	H	H	H	H	H	H	H	H	H	H	Cl
119	OMe	H	H	H	H	H	H	H	H	H	H	H	H	SMe
120	OH	H	H	H	H	H	H	H	H	H	H	H	H	SMe
121	SMe	H	H	H	H	H	H	H	H	H	H	H	H	SMe
122	SMe	H	H	H	H	H	H	H	H	H	H	H	H	OH
123	CHF_2	H	H	H	H	H	H	H	H	H	H	H	H	SMe
124	CN	H	H	H	H	H	H	H	H	OCF_3	H	H	H	H
125	hexyl	H	Me	H	H	H	H	H	H	H	H	H	H	OH
126	Benzyl	H	Me	H	H	H	H	H	H	H	H	H	H	OH
127	O-Phenyl	H	Me	H	H	H	H	H	H	H	H	H	H	OH
128	CN	H	Me	H	F	H	H	H	H	H	H	H	H	SMe
129	CN	H	Me	H	F	H	H	H	H	H	H	H	H	OH
130	F	H	H	H	H	H	H	H	H	H	H	H	H	OMe
131	Cl	H	H	H	H	H	H	H	H	H	H	H	H	OH

#	X	Y	Z	R^3	R^2	R^1	*a*	*b*	*c*	R^4	R^5	R^6	R^7	R^8
132	H	H	H	H	F	H	H	H	H	OCH_2O		H	H	H

[0069] Abbreviations used in the table above have the following meanings: Ac = acetyl; Bz = benzoyl; Bu = butyl; cpm = cyclopropylmethyl; *d* = $C(O)N(CH_3)_2$; *e* = $S(O)_2NH_2$; Et = ethyl; *f* = C(O)OMe; *g* = $C(O)NHCH_3$; Me = methyl.

PHARMACOLOGY

Serotonin Receptor 5-HT$_2$ Functional Assays

[0070] Non-limiting examples of methods of measuring serotonin receptor functional activation are described as follows.

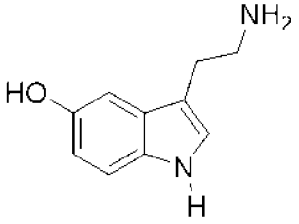
[0071] To measure serotonin receptor functional activation, either Gq dissociation by bioluminescence resonance energy transfer (BRET) or Gq-dependent calcium flux was performed for selected compounds. To measure 5-HT$_2$ receptor-mediated Gq activation via Gq/γ1 dissociation as measured by BRET (McCorvy JD, Wacker D, Wang S, Agegnehu B, Liu J, Lansu K, Tribo AR, Olsen RHJ, Che T, Jin J, Roth BL. Structural determinants of 5-HT$_{2B}$ receptor activation and biased agonism. *Nat Struct Mol Biol*. 2018; 25(9): 787-96), HEK293T cells were sub-cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% dialyzed fetal bovine serum (FBS) and were co-transfected in a 1:1:1:1 ratio with *R*Luc8-fused human Gαq (Gαq- *R*Luc8), a GFP^2-fused to the C-terminus of human Gγ1(Gγ1-GFP^2), human Gβ1, and 5-HT$_2$ receptor using TransiT-2020. After at least 18-24 hours, transfected cells were plated in poly-lysine coated 96-well white clear bottom cell culture plates in DMEM containing 1% dialyzed FBS at a density of 25,000-40,000 cells in 200 µL per well and incubated overnight. The following day, medium was decanted, and cells were washed with 60 µL of drug buffer (1× HBSS, 20 mM HEPES, pH 7.4), then 60 µL of drug buffer was added per well. Cells were pre-incubated at in a humidified atmosphere at 37°C before receiving drug stimulation. Drug stimulation utilized 30 µL addition of drug (3X) diluted in McCorvy buffer (1× HBSS, 20 mM HEPES, pH 7.4, supplemented with 0.3% BSA fatty acid free, 0.03% ascorbic acid) and plates were incubated at for 1 hour at 37°C. Substrate addition occurred 15 minutes before reading and utilized 10 µL of the *R*Luc substrate coelenterazine 400a for Gq dissociation BRET^2 (Prolume/Nanolight, 5 µM final concentration). Plates were read for luminescence at 400 nm and fluorescent GFP^2 emission at 510 nm at 1 second per well using a Mithras LB940 multimode microplate reader (*e.g.* one provided by Berthold). The BRET ratios of fluorescence/luminescence were calculated per well and were plotted as a function of drug concentration using Graphpad Prism 8 (Graphpad Software Inc., San Diego, CA). Data were normalized to % 5-HT stimulation and analyzed using nonlinear regression "log(agonist) vs. response" to yield E_{max} and EC_{50} parameter estimates.

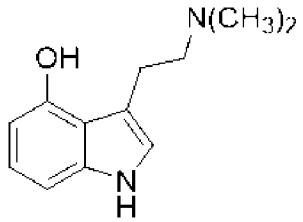
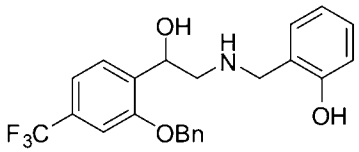
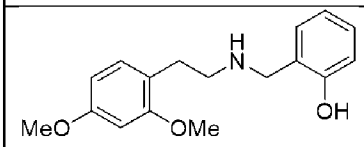
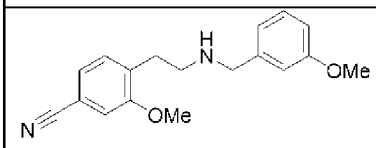
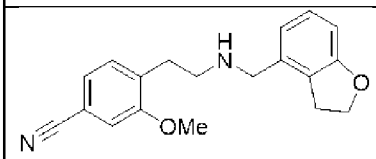
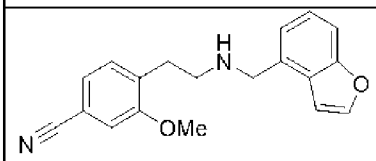
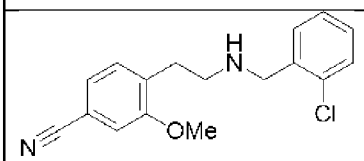
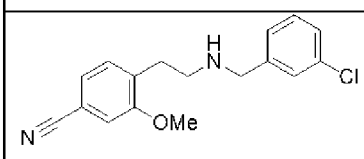
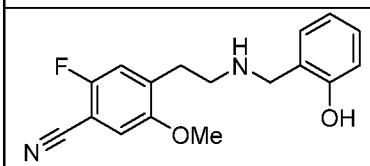
[0072] Calcium flux was measured using stable-expressing 5-HT$_2$ Flp-In 293 T-Rex Tetracycline inducible system by methods known in the art (*e.g.* Investigation of the Structure–Activity

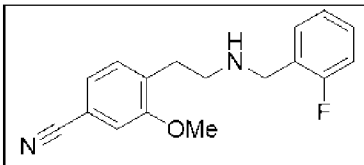
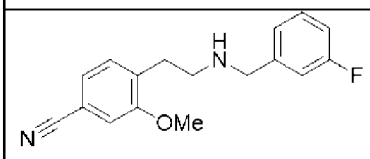
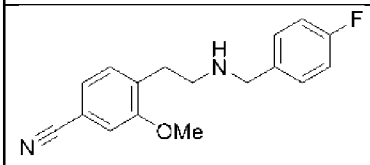
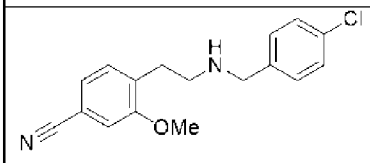
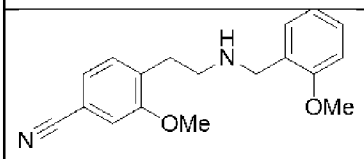
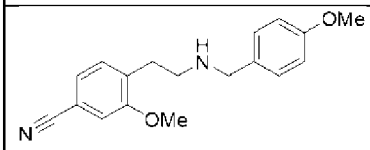
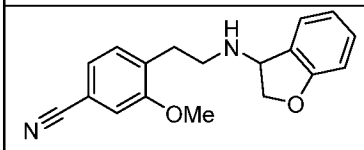
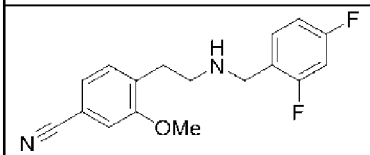
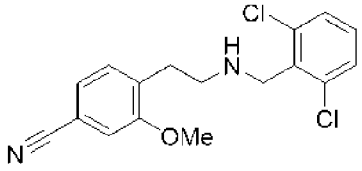
Relationships of Psilocybin Analogues, *ACS Pharmacol. Transl. Sci.* 2020, Publication Date: December 14, 2020, https://doi.org/10.1021/acsptsci.0c00176). Cell lines were maintained in DMEM containing 10% FBS, 10 µg/mL Blasticidin, and 100 µg/mL hygromycin B. At least 20-24 hours before the assay, receptor expression was induced with tetracycline (2 µg/mL), and cells were seeded into 384-well poly-L-lysine-coated black plates at a density of 7,500 cells/well in DMEM containing 1% dialyzed FBS. On the day of the assay, the cells were incubated for 1 hour at 37 °C with Fluo-4 Direct dye (Invitrogen, 20 µL/well) reconstituted in drug buffer (20 mM HEPES-buffered HBSS, pH 7.4) containing 2.5 mM probenecid. Drug dilutions were prepared at 5X final concentration in McCorvy buffer (20 mM HEPES-buffered HBSS, 0.1% BSA, 0.01% ascorbic acid, pH 7.4). After dye load, cells were allowed to equilibrate to room temperature for 15 minutes, and then placed in a FLIPR^{TETRA} fluorescence imaging plate reader (Molecular Devices). The FLIPR^{TETRA} was programmed to read baseline fluorescence for 10 s (1 read/s), and afterward 5 µL of drug per well was added, and fluorescence was read for a total of 5-10 min (1 read/s). Fluorescence in each well was normalized to the average of the first 10 reads for baseline fluorescence, and then either maximum-fold peak increase over baseline or area under the curve (AUC) was calculated. Either peak or AUC was plotted as a function of drug concentration, and data were normalized to percent 5-HT stimulation. Data were plotted, and non-linear regression was performed using "log(agonist) vs. response" in Graphpad Prism 8 to yield E_{max} and EC_{50} parameter estimates.

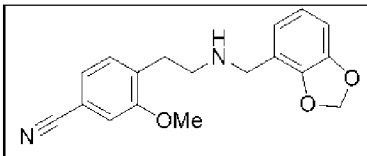
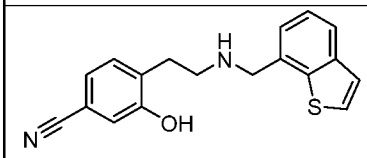
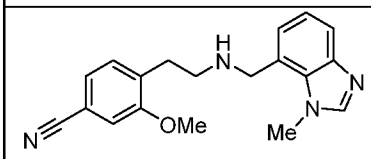
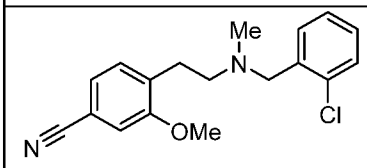
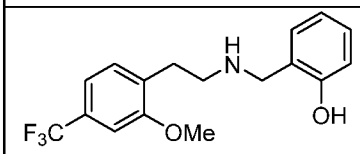
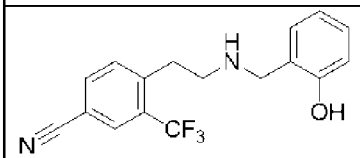
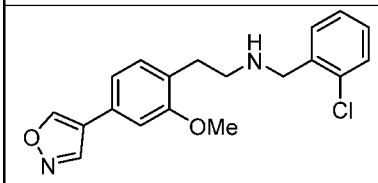
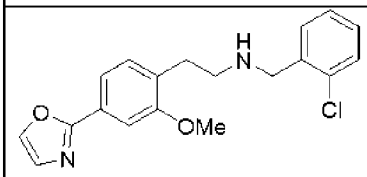
[0073] The functional activity of various compounds disclosed herein at each of the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors was measured against and relative to the functional activity of 4-hydroxytryptamine at those receptors. A comparison of the functional activities is provided in Table 2 as follows. At least three replicate trials were performed for each compound:

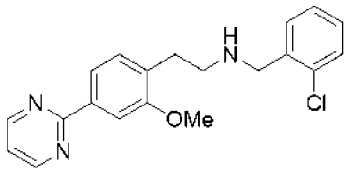
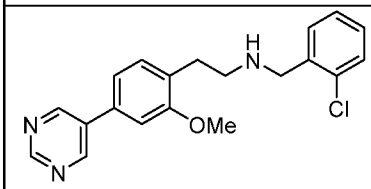
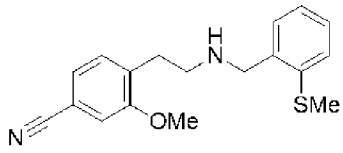
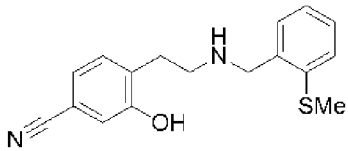
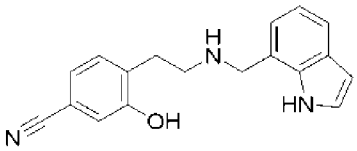
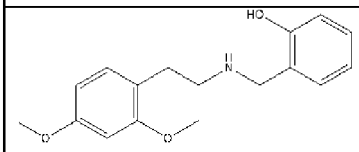
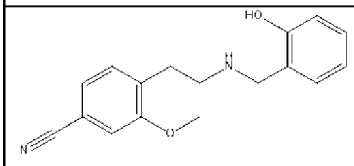
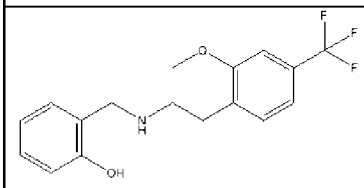
Table 2

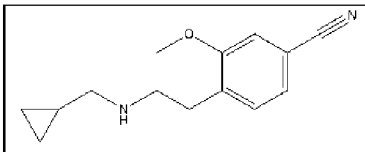
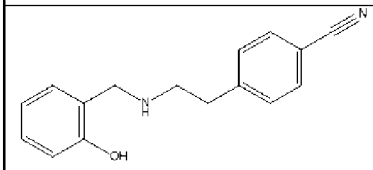
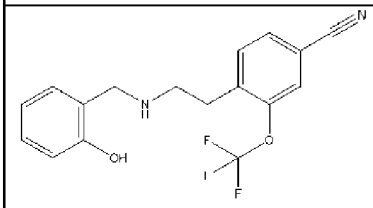
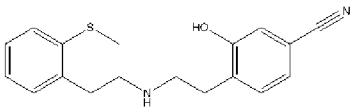
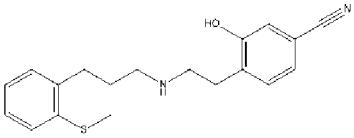
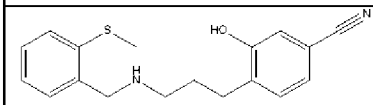
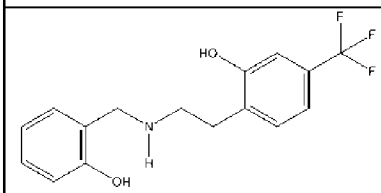
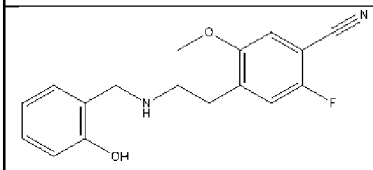
Compound	Identification	5-HT_{2A} BRET		5-HT_{2B} BRET		5-HT_{2C} BRET	
-	-	EC_{50} (nM)	Eff%	EC_{50} (nM)	Eff%	EC_{50} (nM)	Eff%
	5-hydroxytryptamine (serotonin) (reference compound)	2.9	100	0.8	100	0.35	99

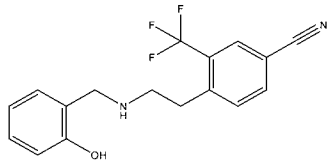
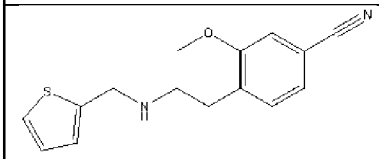
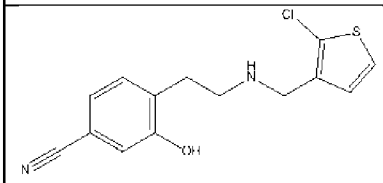
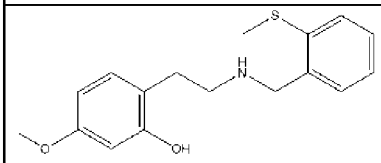
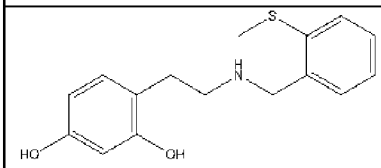
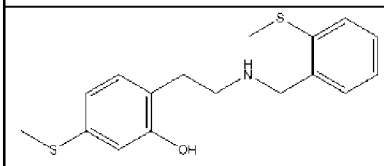
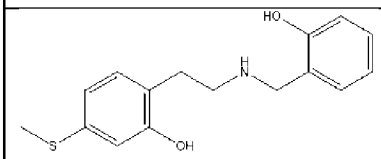
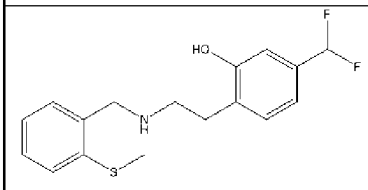
	psilocin (reference compound)	8.34	82	1.07	63	7.79	95
	Reference Compound 1a (reference compound)	451	91	342	56	326	105
	*Cpd #96* (reference compound)	2.3	95	Inactive		7.2	109
	*Cpd #28*	84	68	Inactive		873	91
	*Cpd #63*	135	62	Inactive		2090	78
	*Cpd #64*	29.8	82	8920	93	357	104
	*Cpd #12*	102	90	Inactive		1200	130
	*Cpd #13*	393	69	Inactive		1840	96
	*Cpd #4*	2.4	99	4090	73	37.5	115

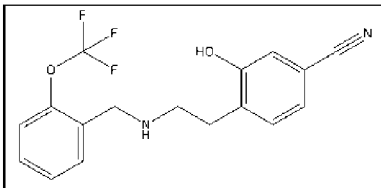
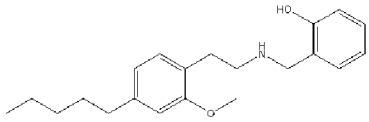
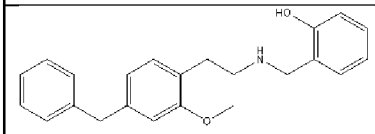
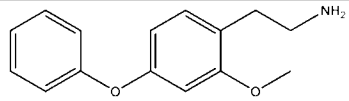
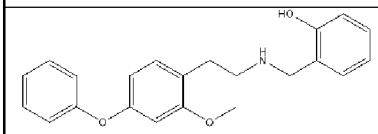
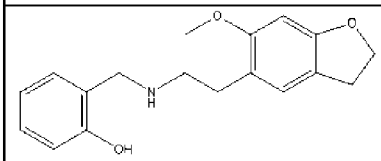
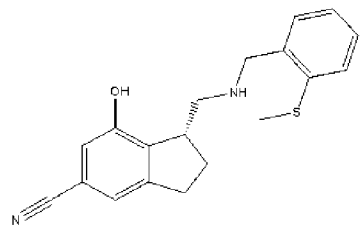
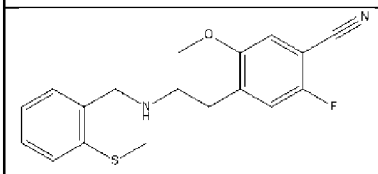
	*Cpd #6*	381	81	Inactive		2120	130
	*Cpd #7*	133	84	Inactive		800	126
	*Cpd #8*	13100	52	Inactive		8740	79
	*Cpd #14*	14300	40	Inactive		13300	74
	*Cpd #27*	4.2	96	423	66	15.9	109
	*Cpd #29*	3950	59	Inactive		924	75
	*Cpd #52*	1040	69	Inactive		12100	125
	*Cpd #59*	14100	58	Inactive		9930	94
	*Cpd #58*	496	79	Inactive		2170	85

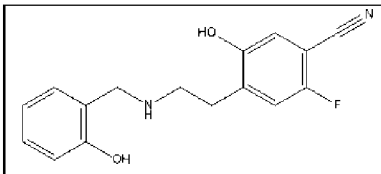
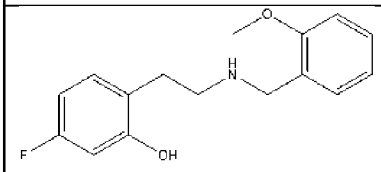
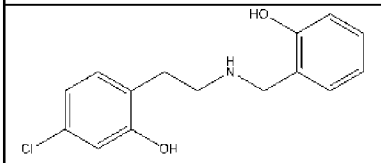
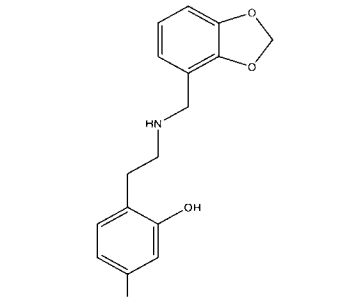
	*Cpd #65*	19.7	84	Inactive		496	97
	*Cpd #70*	0.3	11	Inactive		5400	160
	*Cpd #73*	73	4	Inactive		0.04	7
	*Cpd #88*	0.01	14	4980	20	310000	86
	*Cpd #93*	0.7	96	62.3	53	1.1	105
	*Cpd #112*	432	90	Inactive		2.6	83
	*Cpd #101*	270	65	Inactive		9520	116
	*Cpd #102*	2090	61	5370	143	1640	101

	*Cpd #104*	4890	71	Inactive		5690	106
	*Cpd #105*	1610	86	Inactive		1490	107
	*Cpd #108*	2.4	99	2380	128	16	103
	*Cpd #109*	5.1	102	3140	95	253	114
	*Cpd #71*	1140	59	Inactive		10700	92
	*Cpd #112*	2.3	95	Inactive		7.2	109
	*Cpd #113*	4.9	90	1286	34	30.3	102
	*Cpd #93*	1.17	91	96.2	52	1.3	103

	*Cpd #133*	10740	64	0.07	-6	34440	71
	*Cpd #114*	154	88	6490	11	322	92
	*Cpd #115*	211.9	94	Inactive		379.7	104
	*Cpd #134*	384	67	620	85	160	87
	*Cpd #135*	423	51	502	15	121	65
	*Cpd #136*	1382	55	7330	49	412	43
	*Cpd #116*	1	89	Inactive		1.7	100
	*Cpd #117*	3.8	97	4359	68	40.8	115

	*Cpd #137*	312	89	Inactive		56.5	83
	*Cpd #138*	187	75	0.03	-2	198	102
	*Cpd #139*	1260	80	Inactive		4670	91
	*Cpd #119*	4.6	100	2543	108	113.8	119
	*Cpd #120*	518	90	Inactive		Inactive	
	*Cpd #121*	3.6	94	175.2	89	44.1	110
	*Cpd #122*	1.6	92	inactive		3.6	108
	*Cpd #123*	3.2	96	6721	95	30	120

	*Cpd #124*	159	83	453.3	97	21.1	98
	*Cpd #125*	13.5	96	Inactive		55.8	105
	*Cpd #126*	1.2	99	0.02	-23	3.8	111
	*Cpd #140*	2887	87	Inactive		795.5	107
	*Cpd #127*	27.1	100	3.8	-20	148.2	104
	*Cpd #141*	2.3	96	78.5	59	1.6	107
	*Cpd #142*	1958	68	18.5	-20	17600	108
	*Cpd #128*	7.8	99	722.7	109	114.3	118

	*Cpd #129*	7.8	95	249.3	62	67	105
	*Cpd #130*	18	84	Inactive		8.7	101
	*Cpd #131*	2.4	93	Inactive		1.8	103
	*Cpd #132*	49	70	Inactive		770.1	84

[0074] Many of the compounds disclosed in this disclosure show activity in the range of up to 400 nM at the 5-HT_{2A} receptor, while showing "inactivity" at the 5-HT_{2B} receptor and possessing greater activity at the 5-HT_{2A} receptor than at the 5-HT_{2C} receptor. Many of the compounds disclosed in this disclosure selectively activate the 5-HT_{2A} receptor and show "inactivity" or limited activity at the 5-HT_{2B} receptor. For example, the compounds disclosed in this disclosure may show activity at the 5-HT_{2A} receptor in the range of less than about 1nM to about 400nM, about 1nM to about 300nM, about 1nM to about 200nM, about 1nM to about 100nM, about 1nM to about 90nM, about 1nM to about 80nM, about 1nM to about 70nM, about 1nM to about 60nM, about 1nM to about 50nM, about 5nM to about 95nM, about 5nM to about 80nM, about 5nM to about 65nM, about 5nM to about 50nM, about 10nM to about 90nM, about 10nM to about 80nM, about 10nM to about 70nM, or any specific percentage therebetween. For example, the compounds disclosed in this disclosure may show selectivity for the 5-HT_{2A} receptor over the 5-HT_{2C} receptor in the following ranges: about 1 to about 100 fold, about 10 to about 100 fold, about 10 to about 90 fold, about 10 to about 80 fold,

about 10 to about 70 fold, about 10 to about 60 fold, about 10 to about 50 fold, about 20 to about 100 fold, about 20 to about 80 fold, about 20 to about 60 fold, about 30 to about 90 fold, about 30 to about 60 fold, or any specific range therebetween. In an embodiment, the compound disclosed in this disclosure shows a selectivity for the 5-HT_{2A} receptor over the 5-HT_{2C} receptor of 10 to 100 fold.

[0075] Table 3 below summarizes the 5-HT receptor activity of psilocin, compound 109, and compound 93:

Table 3

	Psilocin		**Compound 109**		**Compound 93**	
	EC_{50}, nM	Eff, %	EC_{50}, nM	Eff, %	EC_{50}, nM	Eff, %
5-HT_{1A}	46.9	93	4269	3	Not active	
5-HT_{1B}	14.3	94	Not active		Not active	
5-HT_{1D}	2.2	102	378.7	6	Not active	
5-HT_{1E}	10.4	90	813.8	12	70060	211
5-HT_{1F}	9.3	93	582.0	12	8086	69
5-HT_{2A}	14.3	80	4.8	99	0.3	96
5-HT_{2B}	2.1	32	3094	84	64.2	50
5-HT_{2C}	16.7	86	225.4	110	1.5	99
5-HT_{4}	562.6	81	0.2	-3	Not active	
5-HT_{5A}	349	48	12330	-133	Not active	
5-HT_{6}	182.5	74	5394	18	0.6	-12
5-HT_{7}	524.5	86	Not active		0.5	-12

[0076] Phenethylamines of Formula 1 are generally known to potentially possess "hERG risk". As a result of, many compounds disclosed in Table 1 and Table 2 were screened for the potential of "hERG risk" using pharmacological assays (*e.g.* Eurofins™ hERG Qube APC Assay). Compounds that exhibited strong potency at the 5-HT_{2A} receptor were further assessed on "hERG risk" based on comparative exposure/IC_{50}. A hERG IC_{50} value that is 30-fold greater than therapeutic free plasma concentration is the threshold for deeming a compound to be of low "hERG risk".

[0077] An important factor for hERG risk evaluation at early drug discovery stage is the hERG IC_{50}/in vitro 5-HT_{2A} ratio; compounds exhibiting a ratio of over 200 will exhibit a ratio of hERG IC_{50} over estimated therapeutic plasma C_{max} of greater than 30 (which is generally indicative of low hERG risk potential at clinically relevant dose levels); compounds exhibiting a ratio between 150-200 are generally indicative of moderate hERG risk potential; compounds exhibiting a IC_{50} (hERG) / EC_{50} (5-HT_{2A}) ratio of less than or equal to 150 are generally indicative of high hERG risk potential. Table 4 summarizes the assessed "hERG risk" of various compounds in Tables 1 and 2.

Table 4

Compound #	IC_{50} , µM	EC_{50} $BRET_{2A}$	IC_{50} (hERG) / EC_{50} (5-HT_{2A}) ratio	hERG risk potential
109	2.9	4.8	604	Low
108	1.78	2.4	742	Low
27	2	4.2	476	Low
117	0.9	3.8	237	Low
93	0.62	1,2	517	Low
112	6	2.3	2609	Low
12	1.72	102	17	High
65	2	19.7	102	High
28	1.6	84	19	High
63	1.6	135	12	High
64	0.9	29.8	30	High
131	1.31	2.1	624	Low

122	0.79	1.4	564	Low
Ref Compound 1a	2.3	451	5	High

[0078] Various compounds disclosed herein were subjected to an *in vitro* SafetyScreen44™ panel for identifying off-target activity. Compounds of interest that are identified in the panel are then tested in follow up functional assays to identify if such compounds have a significant off-target risk. As summarized below in Table 5, compound 109 does not possess significant off-target activity. It is predicted that other compounds share similar characteristics with compound 109 and also lack of the off-target activity.

Table 5

Compound	**SafetyScreen44™ panel hits**	**Follow up studies**
109	α 1a α 2a Kappa (KOP) μ (MOP) 5-HT transporter (SERT)	No significant off-target activity

[0079] Additional experimentation was performed on compound 109. Table 6 summarizes, among other things, the anticipated hepatic clearance of compound 109 in various species, as specified in Table 6 and as determined by calculating the *in vitro* hepatocyte clearance over time and scaling such rate with such species' hepatocyte count and the anticipated liver blood flow rate in such species.

Table 6

Species	***In vitro* $T_{1/2}$ (min)**	***In vitro* Cl_{int} (μL/min/10^6 cells)**	**Scale-up Cl_{int} (mL/min/kg)**	**Hepatic Extraction Ratio (E)**	**Predicted hepatic CL (mL/min/kg)**

Human	2.28	608.72	1548.76	0.99	20.43
Monkey	2.78	499.05	1796.57	0.98	42.57
Dog	6.96	199.06	1369.52	0.98	30.22
Rat	5.93	233.71	1093.74	0.95	52.55
Mouse	<2.26	>614.02	>7253.14	>0.99	>88.90

[0080] Table 7a and Table 7b summarize, among other things, the observed plasma and Brain PK properties in animals, and the observed plasma and Brain PK properties predicted in humans, for compound 109 in Table 7a and compound 93 for Table 7b:

Table 7a

Species	**BW (kg)**	**Cl_{tot} [mL/h/Kg]**	**Vz [mL/Kg]**	**$T_{1/2}$ Vz (h)**	**IM f (%)**	**Brain Plasma AUC Ratio**
mice	0.029	17170.2	14040	0.6	144.5	8.39
rat	0.207	3204	9370	2.1	92.8	2.18
Dog	8.240	2382	4330	1.3	120.0	No Data Provided
Human (predicted)	70.0	971.1	2775.3	2.0	100.0	2.14

Table 7b

Species	**BW (kg)**	**Cl_{tot} [mL/h/Kg]**	**Vz [mL/Kg]**	**$T_{1/2}$ Vz(h)**	**Brain/plasma Ratio**
mice	0.0265	11795	15112	0.9	15.6
rat	0.232	7622	15192	1.38	19.6
Dog	9.22	3188	7703	1.66	No Data Provided

Human (predicted)	70	2271	6391.8	1.95	9.55

[0081] HTR was assessed using a head-mounted neodymium magnet and a magnetometer detection coil, as described in Halberstadt *et al.*, *Psychopharmacology (Berl.)*, 2013, 227(4): 727-739. Table 8 below summarizes the ED_{50} in head twitch in mice of various compounds disclosed herein as compared to psilocybin. Figure 3 illustrates the HTR relative to dose for compound 109:

Table 8

Cpd #	**ED_{50} in Head Twitch**
Psilocybin	0.38 mg/kg
112	0.73 mg/kg
109	2.69 mg/kg
108	7.23 mg/kg
93	0.28 mg/kg
27	3.00 mg/kg
117	2.09 mg/kg
131	1.24 mg/kg

[0082] The experimental data summarized in Tables 6-8 demonstrate that compound 109 exhibits high brain penetration, but less central hallucinogenic (or psychedelic) effects than traditional psychedelic compounds such as psilocybin.

[0083] Referring to Figure 4, the short-lasting (less than 30 minutes) psychedelic effect of compound 109 is further illustrated. Per Figure 4, HTR over time per different doses of compound 109 (as measured in mg/kg) is shown. Similar short lasting (less than 30 minutes) psychedelic effects (as suggested by HTR data) is observed in other compounds disclosed in this disclosure. Compound 109 and other like compounds also exhibit long lasting antidepressant effects (neuroplasticity modulation). In contrast, many psychedelic compounds known in the art, liked psilocybin, have long lasting (more than 30 minutes) psychedelic effects; such long lasting psychedelic effects are

undesirable from a medical treatment perspective.

[0084] Additional experimentation was also done on compound 109. Namely, an intraperitoneal dose of up to 30 mg/kg of compound 109 and various reference compounds were delivered into healthy rat subjects and surgery induced abnormal rat subjects (olfactory bulbectomized rats). With regard to compound 109, there is no suggestion that an intraperitoneal dose of up to 30 mg/kg of such compound affects the normal locomotor activity of healthy rat subjects. However, a single dose of such intraperitoneal dose showed significant and long lasting inhibition of abnormal behavioral activity in the surgery induced abnormal rat subjects, in contrast to its short plasma $t_{1/2}$ of less than an hour in healthy rat subjects. Without being bound by theory, it is believed that these observations are a result of long lasting neuroplasticity effects of compound 109 on surgery induced abnormal rat subjects. Figure 5 summarizes the results of this experiment. Using psilocybin as a comparative psychedelic, the results of this experiment support the notion that compound 109 provides sustainable acute antidepressant effects. Note that "VEH" refers to vehicle, and "PSIL" refers to psilocybin, in Figure 5.

[0085] Compound 93 also exhibited high clearance in *in vitro* tests. The results of this experiment are summarized in Table 9 below:

Table 9

Species	*In vitro* $T_{1/2}$ (min)	*In vitro* Cl_{int} (µL/min/10^6 cells)	Scale-up Cl_{int} (mL/min/kg)	Predicted hepatic CL (mL/min/kg)
Human	25.28	54.83	139.52	18.03
Monkey	2.97	466.96	1681.07	42.50
dog	4.11	337.46	2321.69	30.49
Rat	>2.26	<614.02	<2873.63	<54.16
Mouse	>2.26	<614.02	<7253.14	<88.90

METHODS OF CHEMICAL SYNTHESIS:

[0086] Non-limiting examples of procedures for preparing the compounds described herein are provided below.

[0087] *N*-Benzylphenethylamines can be prepared by N-benzylation of phenethylamines or N-phenethylation of benzylamines. These reactions may be carried out in a manner that leads directly to products in the oxidation state of amines using, for example, halides or sulfonates as alkylating agents. The amine nitrogen may be present in free form; or to avoid the common side-reactions of dialkylation and quaternization, the amine nitrogen may carry a protecting group that is removed at a later stage of the synthesis. The reactions may also be carried out using electrophiles at a higher oxidation state to obtain products such as imines or carboxamides that need to be reduced in situ or in a subsequent step to arrive at the desired amines. For example, a commonly employed protocol to effect the reductive alkylation of a primary amine consists of treating the amine with an aldehyde in the presence of a mild reducing agent, such as sodium borohydride, sodium cyanoborohydride, or sodium triacetoxyborohydride. Dialkylation and direct reduction of the aldehyde prior to imine formation represent frequently observed side reactions. Amines also readily react with acylating agents, such as acyl halides, carboxylic acid anhydrides, or free carboxylic acids in the presence of condensating agents, of which numerous representatives are known from research in the field of peptide synthesis, to form carboxamides. Unlike the often hydrolytically sensitive imines, carboxamides are stable compounds that are isolated and then reduced to amines in a subsequent step. This reduction process requires either strong reducing agents, such as lithium aluminum hydride, sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®), or borane, which are usually incompatible with the nitrile function that is present in many of the target compounds; or the carboxamide needs to be activated by formation of a mixed imidic acid anhydride upon treatment with a strong electrophile. Employing triflic anhydride in that role, carboxamides are reduced to amines without affecting nitriles and a variety of other reducible functional groups by sodium borohydride (Huang, P.-Q.; Geng, H. *Org. Chem. Front.* **2015**, *2*, 150) or by the mild hydride donor, Hantzsch ester (Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817). For *a* = *b* = *c* = H, the general synthetic scheme for the present target compounds of Formula I is shown in Figure 6.

[0088] The building blocks for the benzyl portion of phenethylamine can, among other possible approaches, be prepared by standard functional group transformations as shown (without details in the scheme) in Figure 7; in such Figure, Ar is a phenyl group bearing the substituents R^4, R^5, R^6, R^7, and R^8 as in Formula I.

[0089] The same and additional functional group transformations can be enlisted to obtain commercially unavailable patterns of the substituents R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8. Halogen

substituents, including F, can be accessed by halodecarboxylation of carboxylic acids (Varenikov, A.; Shapiro, E.; Gandelman, M. *Chem. Rev.* 2021, *121*, 412). Aromatic fluorides can also be obtained from numerous other aromatic starting materials (Campbell, M. G.; Ritter, T. *Chem. Rev.* **2015**, *115*, 612), for example from aromatic amines through the Balz-Schiemann reaction, or from other halides by halogen exchange. Transition-metal-mediated halogen exchange is applicable to a variety of combinations of the leaving and incoming halogen (Evano, G.; Nitelet, A.; Thilmany, P.; Dewez, D. F. *Front. Chem.* 2018, *6*, article No. 114). Aryl triflates, readily available derivatives of phenols, also participate in this type of reaction (Sather, A. C.; Lee, H. G.; De La Rosa, V. Y.; Yang, Y.; Müller, P.; Buchwald, S. L. *J. Am. Chem. Soc.* 2015, *137*, 13433). Trifluoromethylated aromatics can be synthesized, for example, from carboxylic acids with SF_4; from amines by Sandmeyer reaction with sodium trifluoromethanesulfonate (Hong, J.; Wang, G.; Huo, L.; Zheng, C. *Chin. J. Chem.* 2017, *35*, 761) or Togni's reagent II (1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one; Hong, J.; Huo, L.; Yang, Y.; Wang, G.; Zheng, C. *Chem. Select* 2017, *2*, 3716); or from aryl halides by transition-metal-catalyzed nucleophilic trifluoromethylation (Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V.-D.; Roy, S. *Tetrahedron* 2011, *67*, 2161). Difluoromethyl substituents are frequently generated from aldehydes by deoxofluorination. The group of reagents capable of performing this transformation has recently been enlarged by the combination of Selectfluor® and diphenyl sulfide (He, G.; Xiao, X.; Jin, H.-Z.; Lin, J.-H.; Zhong, T.; Zheng, X.; Xiao, J. C. *Tetrahedron* 2021, *83*, article No. 131963). (Trifluoromethoxy)arenes can be obtained from phenols by reaction of their derived xanthates with the commercial fluorinating agent, XtalFluor-E® (diethylaminodifluorosulfinium tetrafluoroborate (Yoritate, M.; Londregan, A. T.; Lian, Y.; Hartwig, J. F. *J. Org. Chem.* 2019, *84*, 15767). Aromatic amines are transformed to (trifluoromethoxy)arenes through action of $AgOCF_3$ on their derived diazonium salts (*Org. Lett.* 2019, *21*, 8003). The trifluoromethylthio group can be introduced into aromatics by displacement of other heteroatoms with the SCF_3 moiety, or by electrophilic substitution of hydrogen in electron-rich aromatics (Barata-Vallejo, S.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* 2016, *14*, 7150). (Trifluoromethylthio)arenes are also obtained from arylthiols by reaction with electrophilic or free-radical trifluoromethylating agents, such as *S*-(trifluoromethyl)sulfonium salts or CF_3 halides (review together with other methods: Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* 2015, *115*, 731). (Difluoromethoxy)- and (difluoromethylthio)arenes are obtained from phenols and arenethiols, respectively, and various sources of difluorocarbene, in a recent example, an *S*-(difluoromethyl)diarylsulfonium salt (Liu, G.-K.; Qin, W.-B.; Li, X.; Lin, L.-T.; Wong, H. N. C. *J. Org. Chem.* 2019, *84*, 15948).

[0090] Building blocks for the phenethyl portion can, among other possible approaches, be prepared by standard functional group transformations as generally shown in the scheme depicted in Figure 8, wherein Ar is a phenyl group bearing the substituents R^1, R^2, and R^3 as in Formula I.

[0091] As an example for the synthetic methods of the preceding paragraphs, two syntheses of the compound **12** are depicted in Figures 9a and 9b.

[0092] Various heterocycles annulated to either benzene ring are encountered in certain compounds of this disclosure, resulting from the presence of linkages between R^1 and R^2, R^3 and Z, and/or R^4 and R^5. As examples, syntheses of the phenethylamine building block for compound 32 (with a linkage between R^1 and R^2) and of the benzylamine building block for compound 76 (with a linkage between R^4 and R^5) are depicted in Figures 10 and 11 respectively.

[0093] Figures 12a, 12b, and 12c respectively depict the syntheses of building blocks in which *a*, *b*, or *c* is a methyl group.

[0094] Figure 13 shows a scheme for the synthesis of one of four stereoisomers of compound 86, in which *b* and *c* are connected to form a ring, having the absolute and relative stereochemistry shown.

[0095] Deuterium may be incorporated into the present compounds in various ways, using deuterated versions of reagents and building blocks under the same or similar conditions as those employed for their counterparts with natural hydrogen isotope composition. The reduction of carboxamides with commercially available $LiAlD_4$ or BD_3-THF complex results in amines deuterated on the methylene group that originates from the amides' carbonyl group. Similarly, reductive aminations/alkylations can be effected with $NaBD_4$ and $NaBD_3CN$. Aromatics and heteroaromatics can also be deuterated by reaction with an excess of D_2O in the presence of a heterogeneous transition metal catalyst (Sawama, Y.; Park, K.; Yamada, T.; Sajiki, H. *Chem. Pharm. Bull.* **2018**, *66*, 21-28). Deuteration of specific positions in aromatic or heteroaromatic rings is achievable by halogen-metal exchange reactions on compounds that bear a halogen atom (typically Br or I) at the position to be deuterated, followed by quenching of the (hetero-)arylmetal intermediate with a deuterating agent such as D_2O or CH_3OD; or by free-radical deuterodehalogenation of the same precursors with Bu_3SnD and a radical starter such as azobis(isobutyronitrile) or dibenzoyl peroxide; or by reaction of the same precursors with a deuteride source such as Bu_3SnD or formic acid-d_2 and a transition metal catalyst.

Methods of Use

[0096] Compounds described herein are believed to be useful in the treatment of depression (including major depressive disorder), drug resistant depression, psychotic depression, and PTSD, as well as to serve as stimulants, anorectics, decongestants, bronchodilators, and as psychedelics. In addition, the compounds disclosed herein are also believed to be useful in the treatment of addiction including alcoholism, tobacco addiction, cocaine addiction, and opioid addiction, pain indications including neuropathic pain, pain from chemotherapy associated neuropathy, phantom limb pain and fibromyalgia, inflammation (including chronic and acute), eating disorders including anorexia, autism, cluster headaches, migraines, dementia including Alzheimer's dementia, Parkinson's disease dementia, and Lewy body dementia, emotional distress associated with cancer, Fragile-X syndrome, autism spectrum disorder, bipolar disease, obsessive compulsive disease, Rett syndrome, and other CNS disorders.

[0097] Substituted phenethylamines make up a group of phenethylamine derivatives that contain phenethylamine as a "backbone"; in other words, this chemical class includes derivatives that are formed by replacing one or more of the hydrogen atoms in the phenethylamine scaffolding with other substituents. The class of substituted phenethylamines includes all substituted amphetamines, and substituted methylenedioxyphenethylamines (e.g., MDMA), and contains many drugs which act as empathogens, stimulants, psychedelics, anorectics, bronchodilators, decongestants, and/or antidepressants, inter alia.

[0098] Another potential use of these analogs is in the treatment of seizure disorders, including but not limited to infantile seizure disorders such as Dravet syndrome (Sourbon, J. *et al.* "Serotonergic Modulation as Effective Treatment for Dravet Syndrome in a Zebrafish Mutant Model", *ACS Chem. Neurosci.* 2016, 7, 588−598).

[0099] Another potential use of these analogs is in the treatment of compulsive disorders, anxiety disorders, fear disorders and aggressiveness in animals; non-limiting examples of animals include dogs, cats, pigs, mice and rats. Another potential use of these analogs is in inducing contraction of the ureter in animals; non-limiting examples of animals include dogs, cats, pigs, mice and rats.

[00100] The compounds described herein are believed to be safer than psilocybin, given that they lack at least some of the undesirable characteristics of 5-HT_{2B}-agonist related activities.

Methods for Administration

[00101] As contemplated herein, a therapeutically effective amount of a compound described herein is administered to a subject in need thereof. Whether such treatment is indicated depends on the subject case, and is further subject to medical assessment (diagnosis) that takes into consideration signs, symptoms, and/or malfunctions that are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

[00102] As contemplated herein, a compound described herein may be administered by any suitable route known in the art. Such routes include, but are not limited to, oral, buccal, inhalation, topical, sublingual, rectal, vaginal, intracisternal or intrathecal through lumbar puncture, transurethral, nasal, percutaneous, transdermal, and parenteral administration (including intravenous, intramuscular, subcutaneous, intracoronary, intradermal, intramammary, intraperitoneal, intraarticular, intrathecal, retrobulbar, intrapulmonary injection and/or surgical implantation at a particular site). Parenteral administration may be accomplished using a needle and syringe or using a high pressure technique.

[00103] Pharmaceutical compositions include those wherein a compound described herein is present in a sufficient amount to be administered in an effective amount to achieve its intended purpose. The exact formulation, route of administration, and dosage is determined by a qualified medical practitioner in view of the diagnosed condition or disease. Dosage amount and interval can be adjusted individually to provide levels of a compound described herein that is sufficient to maintain the desired therapeutic effects. It is possible that the compound described herein may only require infrequent administration (*e.g.* monthly, as opposed to daily) to achieve the desired therapeutic effect.

[00104] As contemplated herein, a therapeutically effective amount of a compound described herein adapted for use in therapy varies with the nature of the condition being treated, the length of time that activity is desired, and the age and the condition of the patient, and ultimately is determined by the attendant physician. Dosage amounts and intervals can be adjusted individually to provide plasma levels of the compound that are sufficient to maintain the desired therapeutic effects. The desired dose conveniently may be administered in a single dose, or as multiple doses administered at appropriate intervals, for example as one, two, three, four, or more subdoses per day. Multiple doses often may be desired or required.

[00105] As contemplated herein, the compounds described herein may be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration

and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the compounds described herein are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the compounds described herein.

[00106] Water is a preferred carrier when a compound described herein is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions may also be used as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical carriers also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[00107] These pharmaceutical compositions may be manufactured, for example, by conventional mixing, dissolving, granulating, dragee-making, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of a compound described herein is administered orally, the composition typically is in the form of a tablet, capsule, powder, solution, or elixir. When administered in tablet form, the composition additionally can contain a solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder contain about 0.01% to about 95%, and preferably from about 1% to about 50%, of a compound described herein. When administered in liquid form, a liquid carrier, such as water, petroleum, or oils of animal or plant origin, can be added. The liquid form of the composition can further contain physiological saline solution, dextrose or other saccharide solutions, or glycols. When administered in liquid form, the composition contains about 0.1% to about 90%, and preferably about 1% to about 50%, by weight, of a compound described herein.

[00108] When a therapeutically effective amount of a compound described herein described herein is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains an isotonic vehicle. A compound described herein can be infused with other fluids over a 10-30 minute span or over several hours.

[00109] The compounds described herein may be readily combined with pharmaceutically acceptable carriers well-known in the art. Such carriers enable the active agents to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

[00110] Pharmaceutical preparations for oral use can be obtained by adding a compound described herein to a solid excipient, with or without grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added.

[00111] A compound described herein may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampules or in multidose containers, with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

[00112] Pharmaceutical compositions for parenteral administration include aqueous solutions of the active agent in water-soluble form. Additionally, suspensions of a compounds described herein can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils or synthetic fatty acid esters. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension.

[00113] In some embodiments, the suspension also can contain suitable stabilizers or agents that increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. Alternatively, a present composition can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[00114] A compound described herein also may be formulated in rectal compositions, such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases. In addition to the formulations described previously, a compound described herein also can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, a

compound described herein may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins.

[00115] A compound described herein may be administered orally, buccally, or sublingually in the form of tablets containing excipients, such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents. The compounds described herein also may be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, the compounds described herein may be best used in the form of a sterile aqueous solution which can contain other substances, for example, salts or monosaccharides, such as mannitol or glucose, to make the solution isotonic with blood. At least in some embodiments, compounds described herein are psilocybin analogs.

GENERAL:

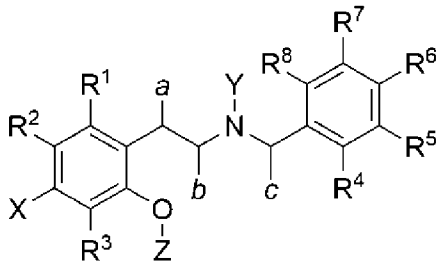
[00116] It is contemplated that any part of any aspect or embodiment discussed in this specification may be implemented or combined with any part of any other aspect or embodiment discussed in this specification. While particular embodiments have been described in the foregoing, it is to be understood that other embodiments are possible and are intended to be included herein. It will be clear to any person skilled in the art that modification of and adjustment to the foregoing embodiments, not shown, is possible.

[00117] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which the content of this disclosure belongs. In addition, any citation of references herein is not to be construed nor considered as an admission that such references are prior art that are relevant to the content of this disclosure.

[00118] The scope of the claims should not be limited by the example embodiments set forth herein, but should be given the broadest interpretation consistent with the description as a whole.

WHAT IS CLAIMED IS:

1. A chemical compound of Formula 1, or isotopologue or pharmaceutically acceptable salt thereof:



Formula I

wherein:

R^1: **(i)** is selected from the group consisting of H, C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, OH, C_1-C_4 alkoxy, substituted C_1-C_4 alkoxy, C_1-C_4 alkylthio, substituted C_1-C_4 alkylthio, and halogen, if each of R^2 and R^3 is independently selected from H, CH_3, or halogen; or **(ii)** together with R^2 form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety; or **(iii)** together with *b* form an alkanediyl, alkenediyl, or heteroalkanediyl moiety;

R^2: **(i)** is selected from the group consisting of H, C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, OH, C_1-C_4 alkoxy, substituted C_1-C_4 alkoxy, C_1-C_4 alkylthio, substituted C_1-C_4 alkylthio, and halogen, if each of R^1 and R^3 is independently selected from H, CH_3, or halogen; or **(ii)** together with R^1 form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety;

R^3: **(i)** is selected from the group consisting of H, C_1-C_4 alkyl, substituted C_1-C_4 alkyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, 2-oxetanyl, 3-oxetanyl, OH, C_1-C_4 alkoxy, substituted C_1-C_4 alkoxy, C_1-C_4 alkylthio, substituted C_1-C_4 alkylthio, and halogen, if each of R^1 and R^2 is independently selected from H, CH_3, or halogen; or **(ii)** together with Z form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety;

wherein:

one of R^4, R^5, R^6, R^7, and R^8 is selected from the group consisting of R^9, OR^9, SR^9, $S(O)R^9$, $S(O)_2R^9$, $N(R^9)C(O)R^9$, $N(R^9)C(O)OR^9$, $N(R^9)C(O)N(H)R^9$, $N(R^9)C(O)N(C_1\text{-}C_6$ alkyl)R^9, $N(R^9)S(O)_2R^9$, CH_2OR^9, CH_2SR^9, $CH_2S(O)R^9$, $CH_2S(O)_2R^9$, $CH_2N(R^9)C(O)R^9$, $CH_2N(R^9)C(O)OR^9$, $CH_2N(R^9)C(O)N(H)R^9$, $CH_2N(R^9)C(O)N(C_1\text{-}C_6$ alkyl)R^9, $CH_2N(R^9)S(O)_2R^9$, $CH{=}NOR^9$, $C(C_1\text{-}C_6$ alkyl)$=NOR^9$, $C(O)OR^9$, $C(O)N(H)R^9$, $C(O)N(C_1\text{-}C_6$ alkyl)R^9, $CH_2C(O)OR^9$, $CH_2C(O)N(H)R^9$, $CH_2C(O)N(C_1\text{-}C_6$ alkyl)R^9, CN, and halogen, a second one of R^4, R^5, R^6, R^7 or R^8 is selected from the group consisting of H, $C_1\text{-}C_4$ alkyl, CHF_2, CF_3, OH, OCH_3, OC_2H_5, $OCHF_2$, OCF_3, and halogen, and the remainder of R^4, R^5, R^6, R^7, and R^8 are each independently H, CH_3, or halogen;

or if R^4 and R^5 together form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety, then each of R^6, R^7, and R^8 is independently selected from the group consisting of H, CH_3, and halogen;

or if R^4 and *b* together form an alkanediyl, alkenediyl, or heteroalkanediyl moiety, then one of R^5, R^6, R^7, and R^8 is selected from the group consisting of H, $C_1\text{-}C_4$ alkyl, CHF_2, CF_3, OH, OCH_3, OC_2H_5, $OCHF_2$, OCF_3, and halogen, and the remainder of R^5, R^6, R^7, and R^8 are each independently selected from the group consisting of H, CH_3, and halogen;

or if R^4 and *c* together form an alkanediyl, alkenediyl, or heteroalkanediyl moiety, then one of R^5, R^6, R^7, and R^8 is selected from the group consisting of H, $C_1\text{-}C_4$ alkyl, CHF_2, CF_3, OH, OCH_3, OC_2H_5, $OCHF_2$, OCF_3, CN, and halogen, and the remainder of R^5, R^6, R^7, and R^8 are each independently selected from the group consisting of H, CH_3, and halogen;

wherein:

X is selected from the group consisting of CN, $C(O)NH_2$, $C(O)N(H)R^9$, $C(O)N(C_1\text{-}C_6$ alkyl)R^9, $C(O)(C_4\text{-}C_6$ heterocyclyl), CHF_2, CF_3, OH, $O(C_1\text{-}C_6$ alkyl), $OCHF_2$, OCF_3, $S(C_1\text{-}C_6$ alkyl), SCF_3, $SCHF_2$, F, Cl, aryl, and heteroaryl generally;

Y is selected from the group consisting of H, CH_3, $C(O)R^9$, $CH_2OC(O)R^9$, and $C(O)OR^9$;

Z: **(i)** is selected from the group consisting of H, $C_1\text{-}C_{10}$ alkyl, substituted $C_1\text{-}C_{10}$ alkyl, $C_1\text{-}C_{10}$ heteroalkyl, $C_2\text{-}C_{10}$ alkenyl, $C_2\text{-}C_{10}$ heteroalkenyl, $C_2\text{-}C_{10}$ alkynyl, $C_3\text{-}C_6$ cycloalkyl, ($C_3\text{-}C_6$ cycloalkyl)($C_1\text{-}C_8$ alkyl), ($C_3\text{-}C_6$ cycloalkyl)($C_1\text{-}C_8$ heteroalkyl), $C_4\text{-}C_6$ heterocyclyl, ($C_4\text{-}C_6$ heterocyclyl)($C_1\text{-}C_8$ alkyl), ($C_4\text{-}C_6$ heterocyclyl)($C_1\text{-}C_8$ heteroalkyl), aryl($C_1\text{-}C_8$ alkyl), aryl(C_1-

C_8 heteroalkyl), heteroaryl(C_1-C_8 alkyl), heteroaryl(C_1-C_8 heteroalkyl), $C(O)R^9$, $C(O)OR^9$, $CH_2OC(O)R^9$, $C(O)NH_2$, $C(O)N(H)R^9$, $C(O)N(C_1$-C_6 alkyl)R^9, and $C(O)(C_4$-C_6 heterocyclyl); or **(ii)** together with R^3 form an alkanediyl, alkenediyl, heteroalkanediyl, or heteroalkenediyl moiety;

wherein two of *a*, *b*, and *c* are each independently selected from the group consisting of H, CH_3, and C_2H_5, while the third of *a*, *b*, and *c* is H, but if *c* and R^4 together form an alkanediyl, alkenediyl, or heteroalkanediyl moiety then *a* and *b* are each independently selected from H or CH_3; and

wherein R^9 is, independently for each occurrence, selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, substituted C_1-C_6 alkyl, substituted C_1-C_6 heteroalkyl, C_2-C_6 alkenyl, C_2-C_6 heteroalkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, (C_3-C_6 cycloalkyl)(C_1-C_6 alkyl), (C_3-C_6 cycloalkyl)(C_1-C_6 heteroalkyl), C_3-C_6 heterocyclyl, (C_3-C_6 heterocyclyl)(C_1-C_6 alkyl), (C_3-C_6 heterocyclyl)(C_1-C_6 heteroalkyl), aryl, aryl(C_1-C_6 alkyl), aryl(C_1-C_6 heteroalkyl), heteroaryl, heteroaryl(C_1-C_6 alkyl), and heteroaryl(C_1-C_6 heteroalkyl).

2. The compound as claimed in claim 1, or isotopologue or pharmaceutically acceptable salt thereof, wherein: (i) X is selected from the group consisting of CN, OH, O(C_1-C_6 alkyl), $OCHF_2$, OCF_3, S(C_1-C_6 alkyl), SCF_3, $SCHF_2$, F, Cl, aryl, and heteroaryl; and (ii) Z is selected from the group consisting of H and C_1-C_{10} alkyl.

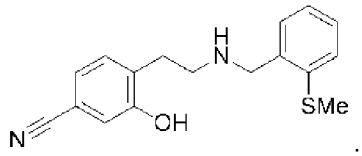
3. The compound as claimed in claim 2, or isotopologue or pharmaceutically acceptable salt thereof, wherein X is selected from the group consisting of CN, OH, OCH_3, F, Cl, CF_3, SCH_3, an oxazole, a pyrimidine, and an isoxazole.

4. The compound as claimed in claim 2 or 3, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^4 is selected from the group consisting of H, F, Cl, OH, OR^9, and SCH_3.

5. The compound as claimed in claim 4, or isotopologue or pharmaceutically acceptable salt thereof, wherein: (i) X is CN; (ii) Z is H or CH_3; and (iii) R^4 is SCH_3.

6. The compound as claimed in claim 5, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, a, b, y, c, R^5, R^6, R^7, and R^8 are H.

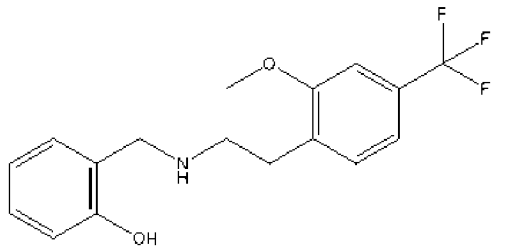
7. The compound as claimed in claim 5, or isotopologue or pharmaceutically acceptable salt thereof, wherein the compound has the following structure:



8. The compound as claimed in claim 4, or isotopologue or pharmaceutically acceptable salt thereof, wherein: (i) X is CF_3; (ii) Z is CH_3; and (iii) R^8 is OH.

9. The compound as claimed in claim 8, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, a, b, y, c, R^4, R^5, R^6, and R^7 are H.

10. The compound as claimed in claim 8, or isotopologue or pharmaceutically acceptable salt thereof, wherein the compound has the following structure:



11. The compound as claimed in claim 2 or 3, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^4 and *c* together form a heteroalkanediyl moiety.

12. The compound as claimed in claim 2 or 3, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^4 and R^5 together form a heteroalkanediyl moiety.

13. The compound as claimed in claim 12, or isotopologue or pharmaceutically acceptable salt thereof, wherein the heteroalkanediyl moiety is selected from the group consisting of $NHCH_2CH_2$, $NHCH_2NH$, and SCH_2CH_2.

14. The compound as claimed in claim 2 or 3, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^5 is selected from the group consisting of OR^9, and F, Cl.

15. The compound as claimed in claim 14, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^9 is a C_1-C_6 alkyl.

16. The compound as claimed in claim 2 or 3, or isotopologue or pharmaceutically acceptable

salt thereof, wherein R^5 and R^4 together form a heteroalkanediyl moiety.

17. The compound as claimed in claim 16, or isotopologue or pharmaceutically acceptable salt thereof, wherein the heteroalkanediyl moiety is OCH_2CH_2 or OCH_2O.

18. The compound as claimed in claim 2 or 3, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^6 is selected from the group consisting of H, F, Cl, and OR^9.

19. The compound as claimed in claim 2 or 3, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^8 is selected from the group consisting of H, F, Cl, OH, OR^9, and SCH_3.

20. The compound as claimed in claim 19, or isotopologue or pharmaceutically acceptable salt thereof, wherein: (i) X is CN; (ii) Z is H or CH_3; and (iii) R^8 is SCH_3.

21. The compound as claimed in claim 19, or isotopologue or pharmaceutically acceptable salt thereof, wherein: (i) X is CF_3; (ii) Z is CH_3; and (iii) R^4 is OH.

22. The compound as claimed in claim 2 or 3, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^8 and *c* together form a heteroalkanediyl moiety.

23. The compound as claimed in claim 2 or 3, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^8 and R^7 together form a heteroalkanediyl moiety.

24. The compound as claimed in claim 23, or isotopologue or pharmaceutically acceptable salt thereof, wherein the heteroalkanediyl moiety is selected from the group consisting of $NHCH_2CH_2$, $NHCH_2NH$, and SCH_2CH_2.

25. The compound as claimed in claim 2 or 3, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^7 is selected from the group consisting of OR^9, and F, Cl.

26. The compound as claimed in claim 25, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^9 is a C_1-C_6 alkyl.

27. The compound as claimed in claim 2 or 3, or isotopologue or pharmaceutically acceptable salt thereof, wherein R^7 and R^8 together form a heteroalkanediyl moiety.

28. The compound as claimed in claim 27, or isotopologue or pharmaceutically acceptable salt thereof, wherein the heteroalkanediyl moiety is OCH_2CH_2 or OCH_2O.

29. Use of the compound as claimed in any one of claims 1 to 28 for the treatment of neuropsychiatric, neurodegenerative, neuroinflammatory and pain disorders.

30. Use of the compound as claimed in any one of claims 1 to 28 as a medicament in the treatment of neuropsychiatric, neurodegenerative, neuroinflammatory and pain disorders.

31. Use of the compound as claimed in any one of claims 1 to 28 in the manufacture of a medicament for the treatment of neuropsychiatric, neurodegenerative, neuroinflammatory and pain disorders.

32. The use as claimed in any one of claims 29 to 31, wherein the neuropsychiatric, neurodegenerative, neuroinflammatory and pain disorders comprise depression, drug (*e.g.* tobacco, opiate, and cocaine) addiction, alcoholism, post-traumatic stress disorder (PTSD), and neuropathic pain syndromes including cluster headaches and chemotherapy induced peripheral neuropathy.

33. Use of the compound as claimed in any one of claims 1 to 28 for the treatment of compulsive disorders, anxiety disorders, fear disorders and aggressiveness in an animal.

34. The use as claimed in claim 33, wherein the animal is selected from the group consisting of a dog, a cat, a pig, a mouse and a rat.

35. Use of the compound as claimed in any one of claims 1 to 28 for inducing contraction of a ureter in an animal.

36. The use as claimed in claim 35, wherein the animal is selected from the group consisting of a dog, a cat, a pig, a mouse and a rat.

37. A method of treating neuropsychiatric, neurodegenerative, neuroinflammatory and pain disorders in a patient comprising administering to said patient an effective amount of the compound as claimed in any one of claims 1 to 28.

38. A method of treating vascular disorders such as hypertension, hypotension, cardiovascular disease, stroke, and stroke recovery in a patient comprising administering to said patient an effective amount of the compound as claimed in any one of claims 1 to 28.

39. A method of modulating inflammation mediated by circulating platelet cells in a patient

comprising administering to said patient an effective amount of the compound as claimed in any one of claims 1 to 28.

40. A method of modulating gut motility in a patient comprising administering to said patient an effective amount of the compound as claimed in any one of claims 1 to 28.

41. A method of inducing contraction of a ureter in an animal comprising administering to said animal an effective amount of the compound as claimed in any one of claims 1 to 28.

42. A method of treating compulsive disorders, anxiety disorders, fear disorders and aggressiveness in an animal comprising administering to said animal an effective amount of the compound as claimed in any one of claims 1 to 28.

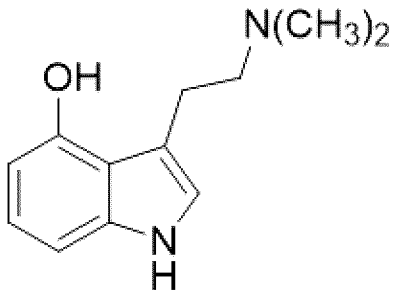


FIGURE 1

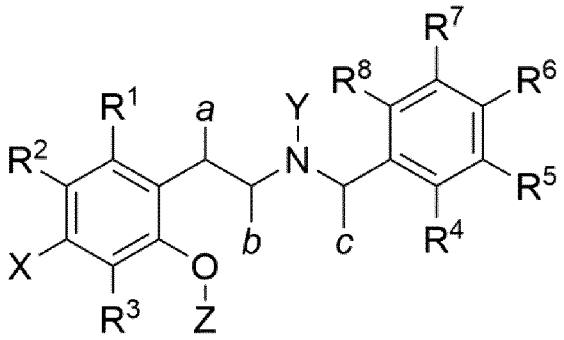


FIGURE 2

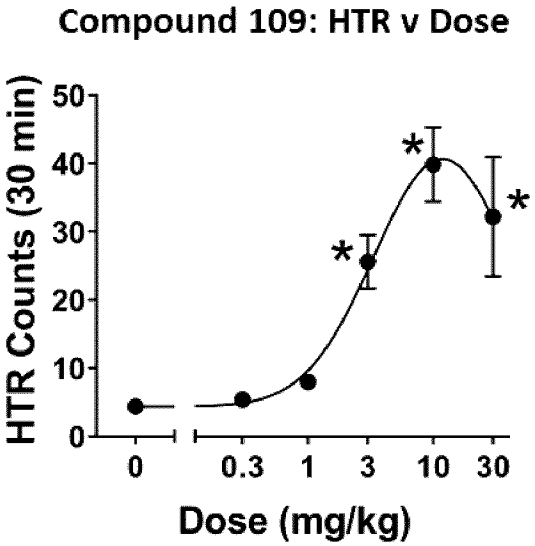

Compound 109: HTR v Dose
HTR Counts (30 min)
50
40
30
20
10
0
0
0.3
1
3
10
30
Dose (mg/kg)
*
*
*

FIGURE 3

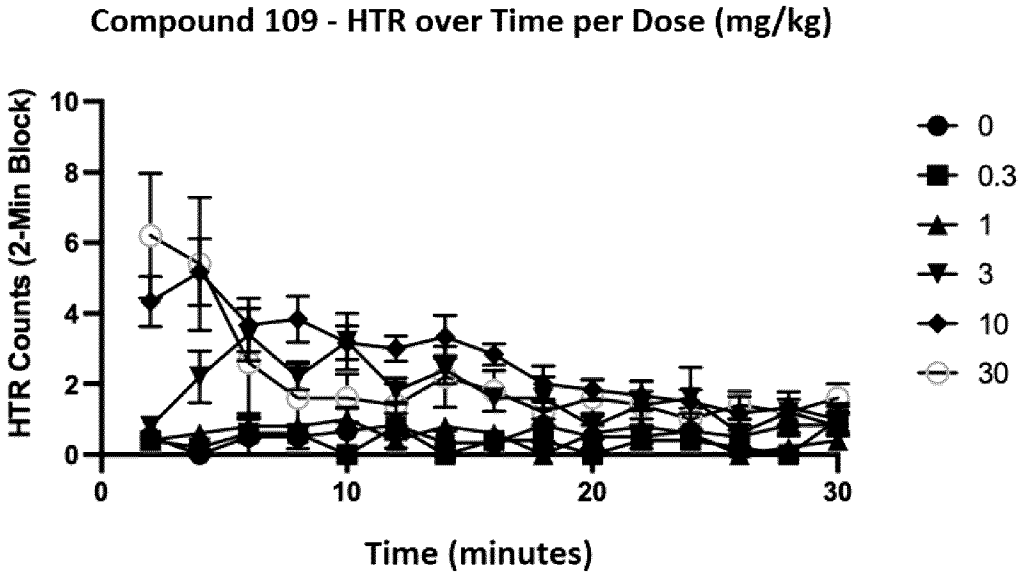

Compound 109 - HTR over Time per Dose (mg/kg)
HTR Counts (2-Min Block)
10
8
6
4
2
0
0
10
20
30
Time (minutes)
0
0.3
1
3
10
30

FIGURE 4

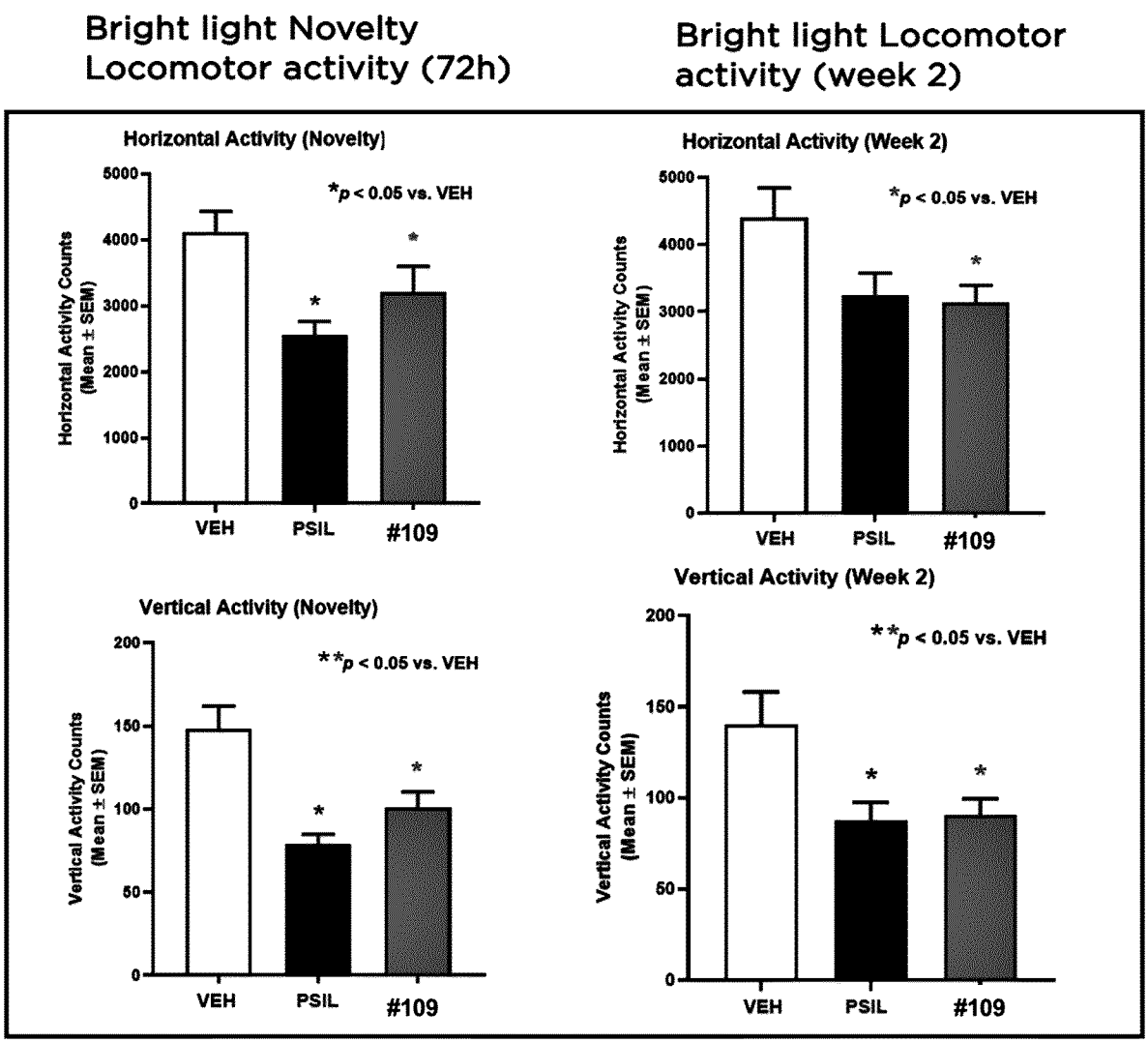

Bright light Novelty Locomotor activity (72h)
Bright light Locomotor activity (week 2)
Horizontal Activity (Novelty)
*p < 0.05 vs. VEH
Horizontal Activity Counts (Mean ± SEM)
5000
4000
3000
2000
1000
0
VEH
PSIL
#109
Horizontal Activity (Week 2)
*p < 0.05 vs. VEH
Horizontal Activity Counts (Mean ± SEM)
Vertical Activity (Novelty)
**p < 0.05 vs. VEH
Vertical Activity Counts (Mean ± SEM)
200
150
100
50
0
Vertical Activity (Week 2)
**p < 0.05 vs. VEH
Vertical Activity Counts (Mean ± SEM)

FIGURE 5

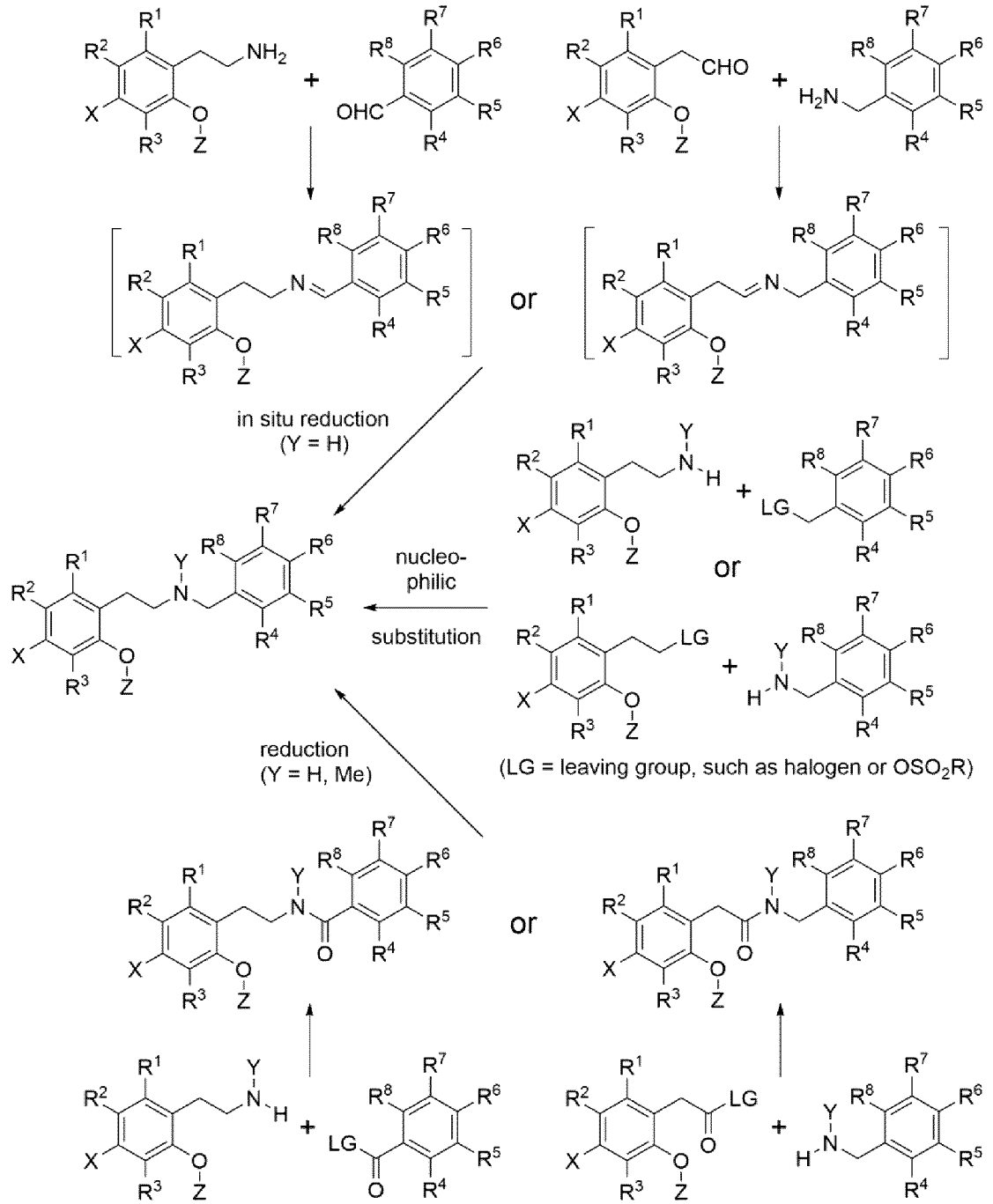

in situ reduction
(Y = H)
nucleo-
philic
substitution
reduction
(Y = H, Me)
or
(LG = leaving group, such as halogen or OSO2R)
(LG = leaving group, such as halogen, 1/2 O, or derived from activating agent)

FIGURE 6

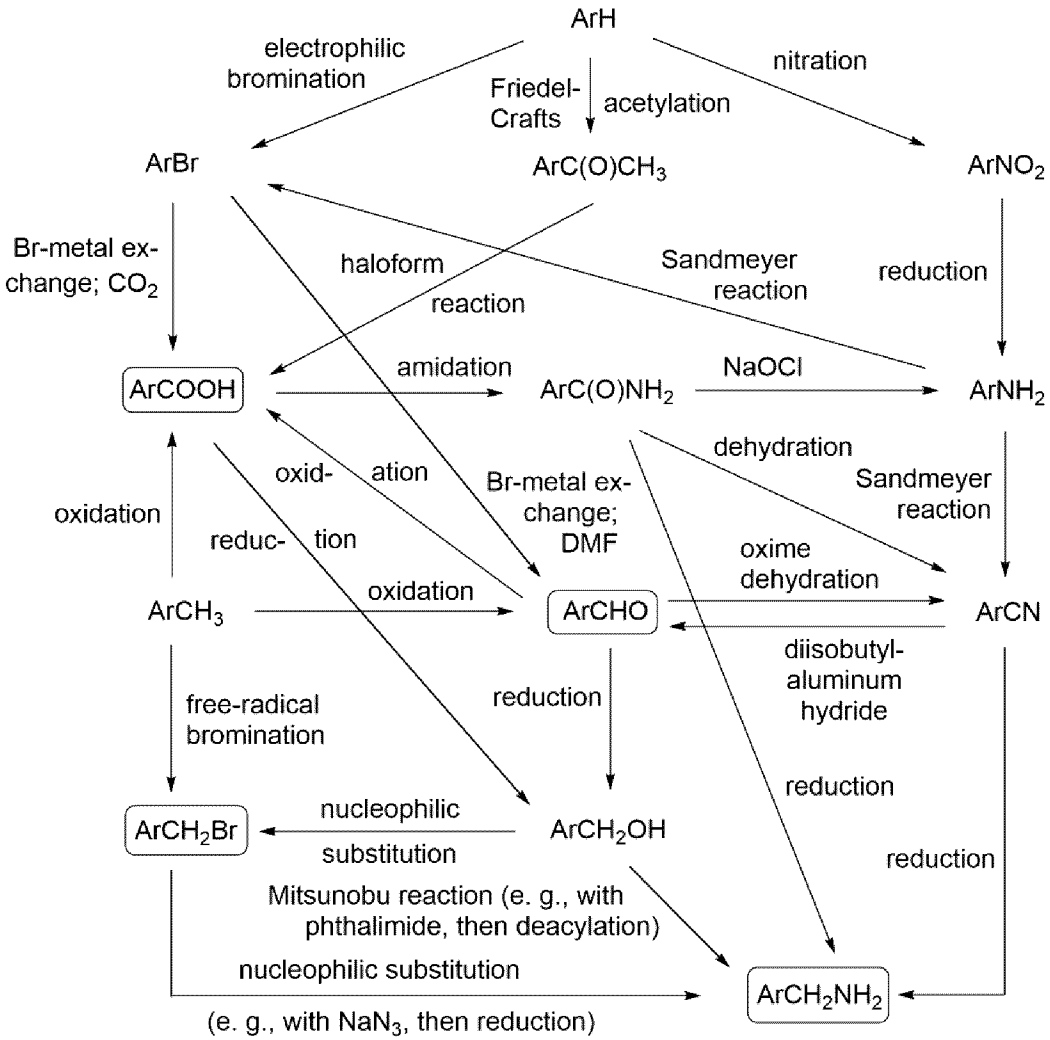

ArH
electrophilic bromination
Friedel-Crafts acetylation
nitration
ArBr
ArC(O)CH3
ArNO2
Br-metal ex-change; CO2
haloform reaction
Sandmeyer reaction
reduction
ArCOOH
amidation
ArC(O)NH2
NaOCl
ArNH2
dehydration
oxid- ation
Br-metal ex-change; DMF
Sandmeyer reaction
oxidation
reduc- tion
oxime dehydration
ArCH3
oxidation
ArCHO
ArCN
diisobutyl-aluminum hydride
free-radical bromination
reduction
reduction
ArCH2Br
nucleophilic substitution
ArCH2OH
reduction
Mitsunobu reaction (e. g., with phthalimide, then deacylation)
nucleophilic substitution
(e. g., with NaN3, then reduction)
ArCH2NH2

FIGURE 7

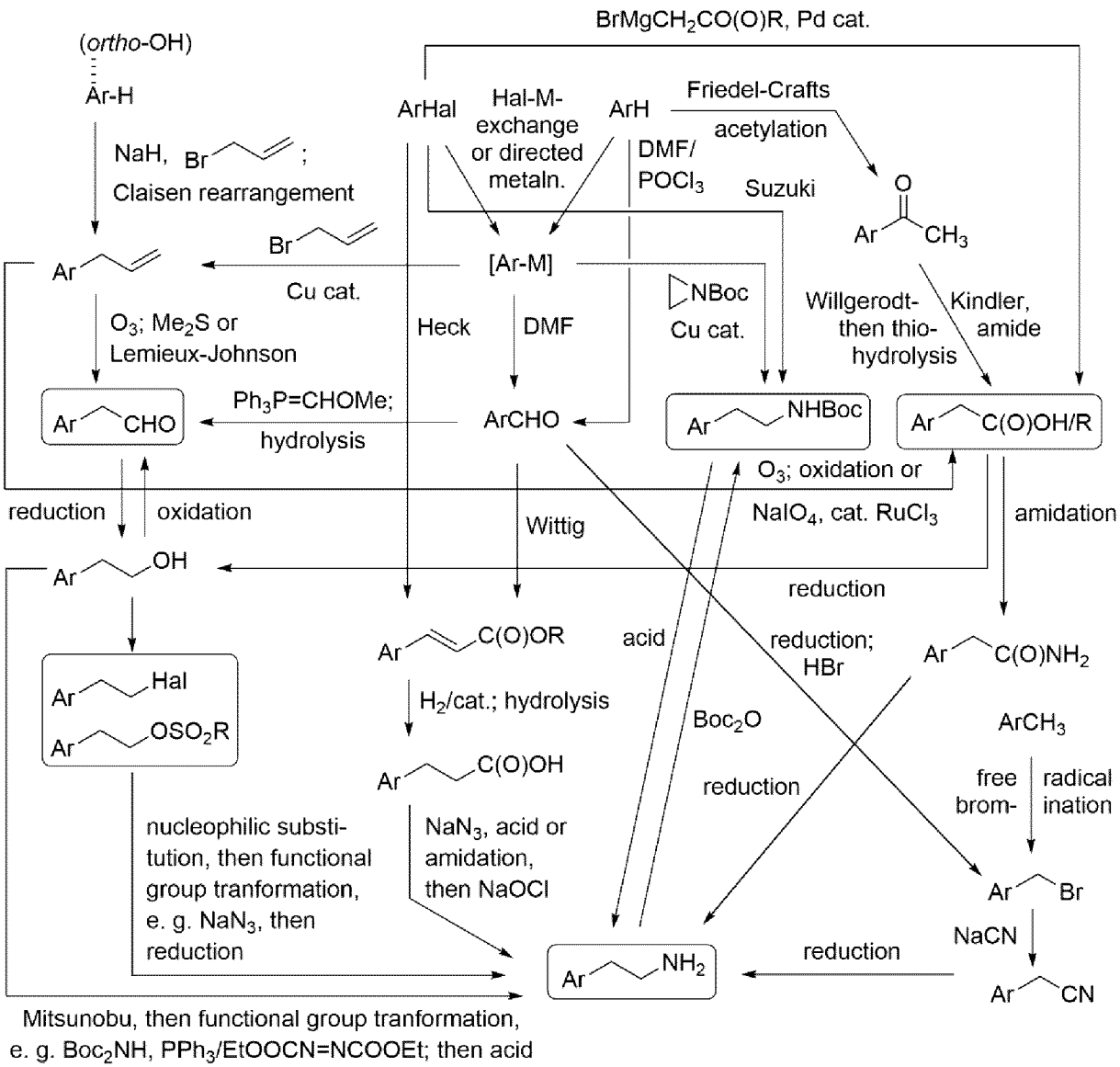

BrMgCH2CO(O)R, Pd cat.
(ortho-OH)
Ar-H
ArHal
Hal-M-exchange or directed metaln.
ArH
Friedel-Crafts acetylation
NaH, Br ;
Claisen rearrangement
DMF/POCl3
Suzuki
Ar CH3
O
Br
Ar
Cu cat.
[Ar-M]
NBoc
Cu cat.
Willgerodt-then thio-hydrolysis
Kindler, amide
O3; Me2S or Lemieux-Johnson
Heck
DMF
Ar CHO
Ph3P=CHOMe; hydrolysis
ArCHO
Ar NHBoc
Ar C(O)OH/R
O3; oxidation or NaIO4, cat. RuCl3
reduction
oxidation
Wittig
amidation
Ar OH
reduction
Ar C(O)OR
acid
reduction; HBr
Ar C(O)NH2
Ar Hal
Ar OSO2R
H2/cat.; hydrolysis
Boc2O
ArCH3
Ar C(O)OH
reduction
free brom-
radical ination
nucleophilic substi-tution, then functional group tranformation, e. g. NaN3, then reduction
NaN3, acid or amidation, then NaOCl
Ar Br
NaCN
Ar NH2
reduction
Ar CN
Mitsunobu, then functional group tranformation,
e. g. Boc2NH, PPh3/EtOOCN=NCOOEt; then acid

FIGURE 8

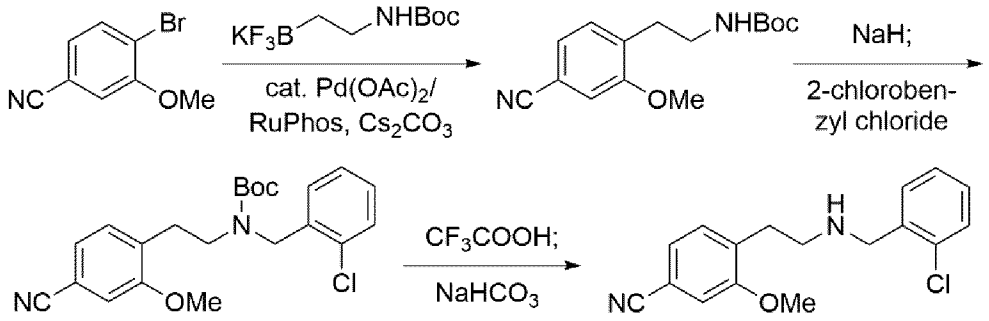


FIGURE 9a

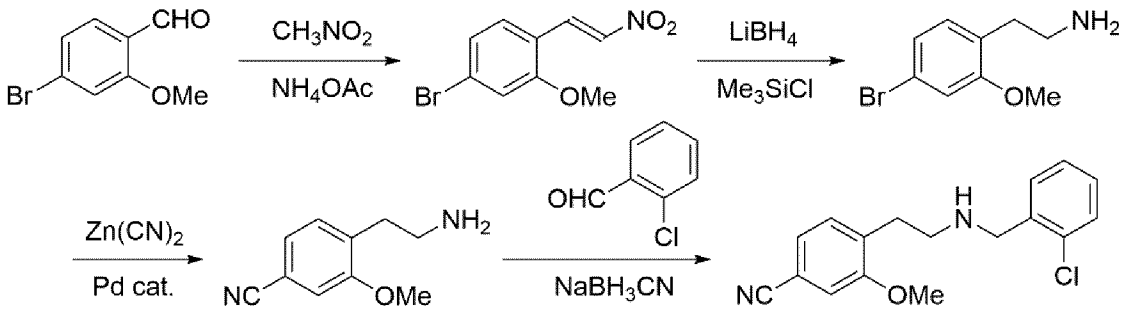


FIGURE 9b

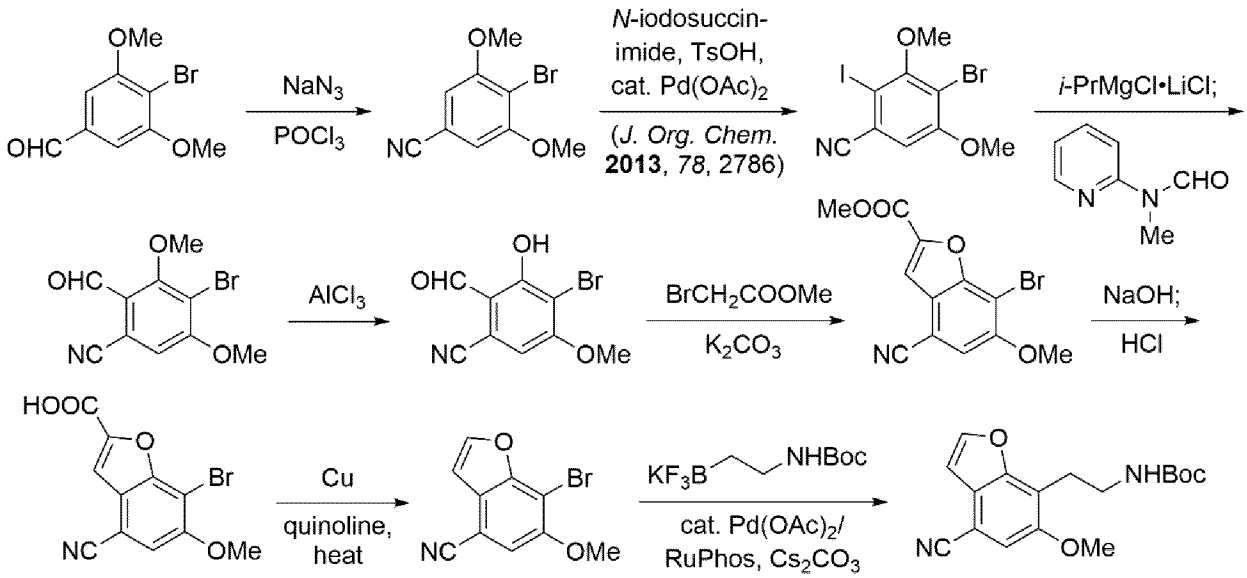

OMe
Br
OHC
OMe
NaN3
POCl3
NC
N-iodosuccin-
imide, TsOH,
cat. Pd(OAc)2
(J. Org. Chem.
2013, 78, 2786)
I
i-PrMgCl•LiCl;
N
CHO
Me
AlCl3
OH
BrCH2COOMe
K2CO3
MeOOC
O
NaOH;
HCl
HOOC
Cu
quinoline,
heat
KF3B
NHBoc
cat. Pd(OAc)2/
RuPhos, Cs2CO3

FIGURE 10

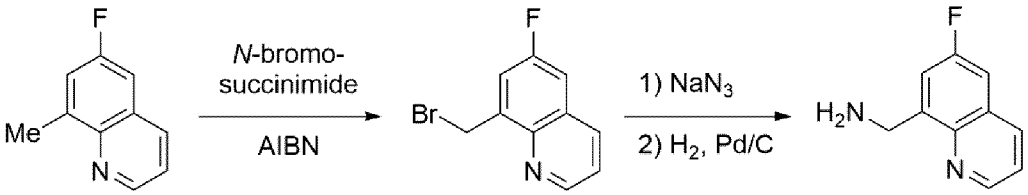


FIGURE 11

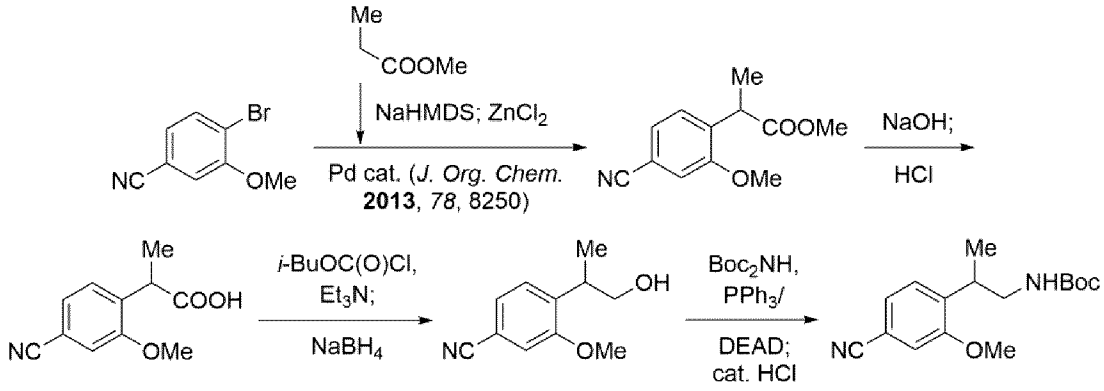


FIGURE 12a

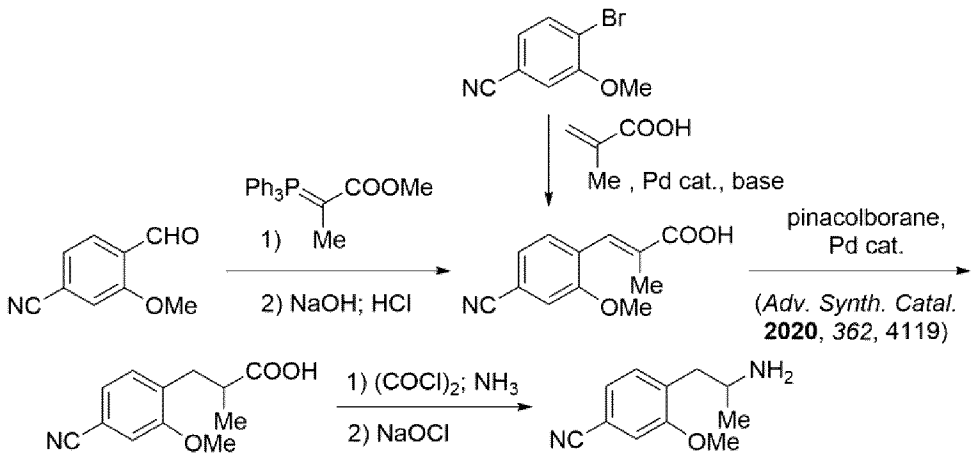


FIGURE 12b

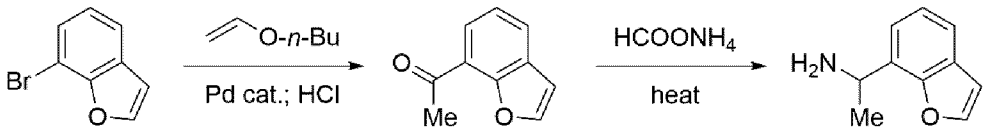


FIGURE 12c

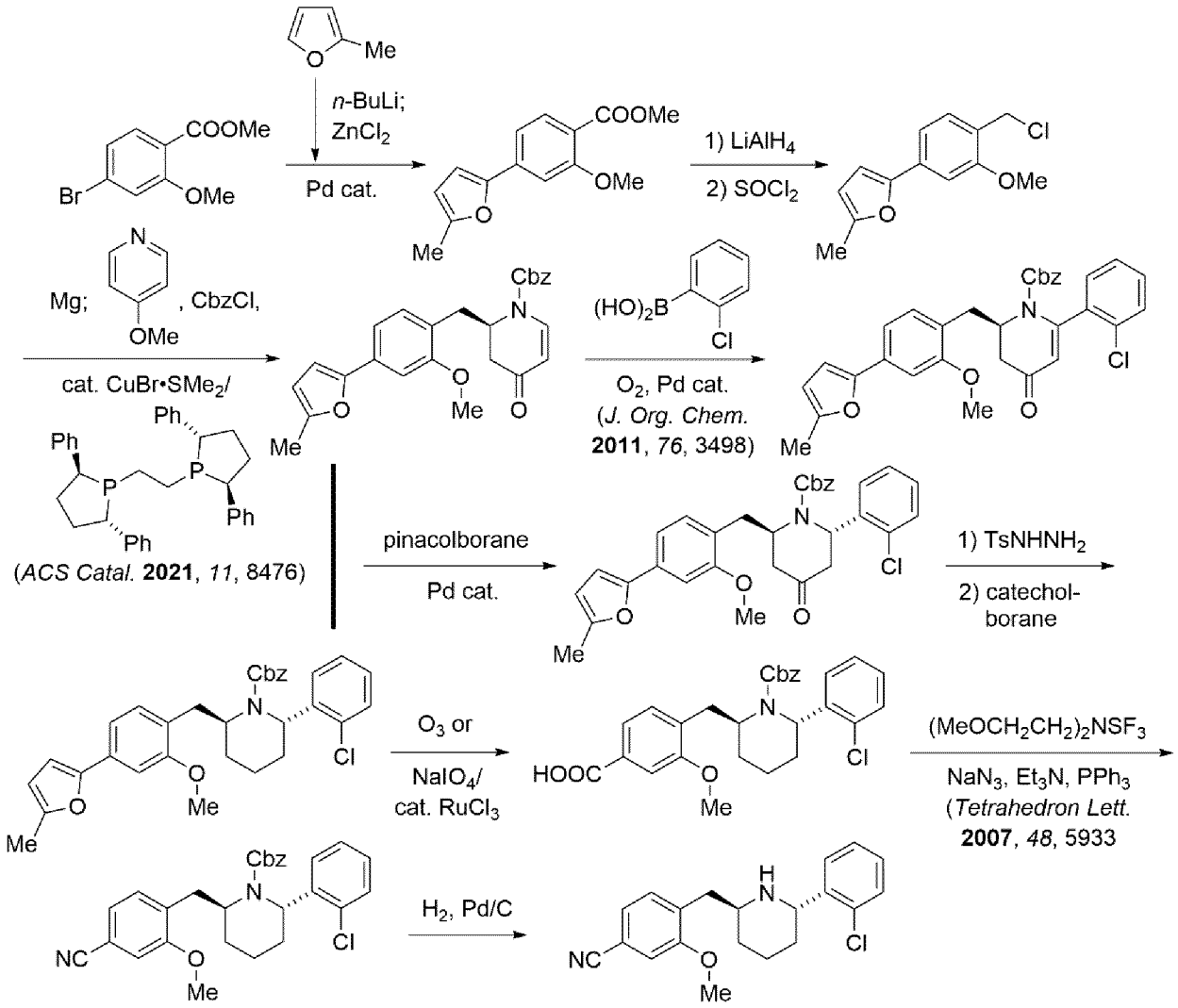

Me
n-BuLi;
ZnCl2
COOMe
Br
OMe
Pd cat.
COOMe
OMe
Me
1) LiAlH4
2) SOCl2
Cl
OMe
Me
Mg;
N
OMe
, CbzCl,
cat. CuBr•SMe2/
Ph
Ph
P
P
Ph
Ph
(ACS Catal. 2021, 11, 8476)
Cbz
N
O
Me
O
Me
(HO)2B
Cl
O2, Pd cat.
(J. Org. Chem.
2011, 76, 3498)
Cbz
N
Cl
O
Me
O
Me
pinacolborane
Pd cat.
Cbz
N
Cl
O
Me
O
Me
1) TsNHNH2
2) catechol-
borane
Cbz
N
Cl
O
Me
Me
O3 or
NaIO4/
cat. RuCl3
Cbz
N
Cl
HOOC
O
Me
(MeOCH2CH2)2NSF3
NaN3, Et3N, PPh3
(Tetrahedron Lett.
2007, 48, 5933
Cbz
N
Cl
NC
O
Me
H2, Pd/C
H
N
Cl
NC
O
Me

FIGURE 13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2023/050003

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07C 323/36*** (2006.01), ***A61K 31/36*** (2006.01), ***A61K 31/40*** (2006.01), ***A61K 31/42*** (2006.01), ***A61K 31/137*** (2006.01), ***A61K 31/277*** (2006.01) (more IPCs on the last page)

CPC: **C07C 323/36** (2020.01), A61K 31/36 (2020.01), A61K 31/40 (2020.01), A61K 31/42 (2020.01), A61K 31/137 (2020.01), A61K 31/277 (2020.01) (more CPCs on the last page)

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)
C07C323/36,A61K31/36,A61K31/40,A61K31/42,A61K31/137,A61K31/277,A61K31/343,A61K31/381,A61K31/404,A61K31/421,A61K31/505, A61K31/4184, C07C217/60,C07D209/04,C07D235/06,C07D239/26,C07D261/08,C07D263/32,C07D-307/79,C07D-317/50,C07D333/28,C07D333/54

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
QUESTEL FAMPAT/ STN CAPLUS REGISTRY/ CPD INTELLECT/ SCOPUS: phenethylamine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ETTRUP et al., "Radiosynthesis and in vivo evaluation of a series of substituted 11C-phenethylamines as 5-HT2A agonist PET tracers." European Journal of Nuclear Medicine and Molecular Imaging, 38(4), pp. 681-693. 2011 (2011), [ISSN: 1619-7089]	1-4, 12, 16-17, 27-28 29-42
Y	https://doi.org/10.1007/s00259-010-1686-8; **D1**: p 663, figure 4.	35-36, 40-41
X	MÄRCHER RØRSTED et al. "25CN-NBOH: A Selective Agonist for in vitro and in vivo Investigations of the Serotonin 2A Receptor." ChemMedChem, 16(21), pp 3263-3270. 20 July 2021 (20-07-2021) [ISSN: 1860-7179]	1-4, 12, 16-17, 27-28 29-42
Y	https://doi.org/10.1002/cmdc.202100395 **D2**: pp. 3265-3267.	35-36, 40-41

☒ 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 06 April 2023 (06-04-2023)	Date of mailing of the international search report 06 April 2023 (06-04-2023)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Christine Bourque (819) 576-2951

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	CASALE et al., "Characterization of Eleven 2,5-Dimethoxy-N-(2-methoxy benzyl)phenethylamine (NBOMe) Derivatives and Differentiation from their 3- and 4-Methoxybenzyl Analogues - Part I), Microgram Journal, 9(2), pp. 84-109. January 2012 (01-01-2012). https://www.dea.gov/documents/2012/2012-01/2012-01-01/characterization-eleven-25-dimethoxy-n-2 **D3**: Compounds 7-9 and 25-33	1-4, 18-19, 29-34, 37, and 42 35-36, 40-41
X Y	POTTIE et al., "Synthesis and Functional Characterization of 2-(2,5-Dimethoxyphenyl)-N-(2-fluorobenzyl)ethanamine (25H-NBF) Positional Isomers." ACS Chemical Neuroscience, 12(9), pp 1667-1673. 28 April 2021 (28-04-2021) [ISSN: 1948-7193] https://doi.org/10.1021/acschemneuro.1c00124 **D4**: See compound 3.	1-4, 18-19, 29-34, 37, and 42 35-36, 40-41
X Y	HANSEN et al. "Synthesis and Structure–Activity Relationships of N-Benzyl Phenethylamines as 5-HT2A/2C Agonists" ACS Chem. Neuroscience. 5(3), pp. 243–249. 7 January 2014 (07-01-2014) [ISSN: 1948-7193] https://doi.org/10.1021/cn400216u **D5**: See entire document and supporting information for compounds 3a-3d, 4a-4d, 5a-5d, 6a-d, 10a-d, 11a-d, 12a-d.	1-4, 8, 12, 14-19, 21, 23, 25-34, 37, 42 35-36, 40-41
Y	BRUTA et al., "The role of serotonin and diet in the prevalence of irritable bowel syndrome: a systematic review." Translational Medicine Communications volume 6, Article number: 1 (9 pages), 5 January 2021 (05-01-2021) https://doi.org/10.1186/s41231-020-00081-y **D6**: see entire document.	35-36, 40-41
Y	HERNANDEZ et al., "Characterization of the 5-hydroxytryptamine receptors mediating contraction in the pig isolated intravesical ureter." British Journal of Pharmacology, 138 (1), pp. 137-144. 7 January 2003 (07-01-2003) https://doi.org/10.1038/sj.bjp.0705019 **D7**: see entire document.	35-36, 40-41
P,X	WO2022-192781 A1 KRUEGEL A. C., 15 September 2022 (15-09-2022) See compounds of formula IV and compounds 10, 20, 21, 50, 51, 52, 59, 60, and 64; paragraphs 0038, 0070, 0079,and 0086; EXAMPLES 9, 19-20, 48-50, 52, 57-58, and 62.	1-4, 18-19, 29-34, 37, 40, 42

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2023/050003

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the 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. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 1
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:

Claim 1 encompasses compounds that are not defined in clear and concise terms as required under PCT Article 6. In particular, claim 1 contains open ended proviso statements in the definition of variables R^1, R^2, and R^3. These open ended provisos contain the "if each of" statement, but are missing the "then" statement. Consequently, the search has been established for subject matter of these claims as if no if/then statement has been made in the definition of variables R^1, R^2, and R^3.

3. ☐ Claim Nos.:
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:

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 claim 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 claim Nos.:

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.

IPC:
A61K 31/343 (2006.01), ***A61K 31/381*** (2006.01), ***A61K 31/404*** (2006.01), ***A61K 31/421*** (2006.01), ***A61K 31/505*** (2006.01), ***A61K 31/4184*** (2006.01), ***A61P 13/02*** (2006.01), ***A61P 25/00*** (2006.01), ***C07C 217/60*** (2006.01), ***C07D 209/04*** (2006.01), ***C07D 235/06*** (2006.01), ***C07D 239/26*** (2006.01), ***C07D 261/08*** (2006.01), ***C07D 263/32*** (2006.01), ***C07D 307/79*** (2006.01), ***C07D 317/50*** (2006.01), ***C07D 333/28*** (2006.01), ***C07D 333/54*** (2006.01)

CPC:
A61K 31/343 (2020.01), A61K 31/381 (2020.01), A61K 31/404 (2020.01), A61K 31/421 (2020.01), A61K 31/505 (2020.01), A61K 31/4184 (2020.01), A61P 13/02 (2020.01), A61P 25/00 (2020.01), C07C 217/60 (2020.01), C07D 209/04 (2020.01), C07D 235/06 (2020.01), C07D 239/26 (2020.01), C07D 261/08 (2020.01), C07D 263/32 (2020.01), C07D 307/79 (2022.08), C07D 317/50 (2020.01), C07D 333/28 (2020.01), C07D 333/54 (2020.01)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2023/050003

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2022192781A1	15 September 2022 (15-09-2022)	None	