

METHODS OF TREATING NEUROPSYCHIATRIC DISORDERS WITH NON-HALLUCINOGENIC TRYPTAMINES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/605,996, filed December 4, 2023, and U.S. Provisional Application No. 63/679,450, filed August 5, 2024, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments comprising such compounds, and methods of using such compounds for the treatment of conditions, diseases, or disorders that would benefit from promoting neuronal growth and/or improving neuronal structure.

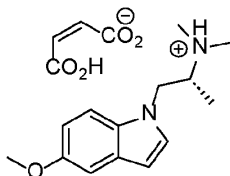
BACKGROUND

[0003] Altered synaptic connectivity and plasticity has been observed in the brains of individuals with neurological diseases and disorders. Psychoplastogens promote neuronal growth and improve neuronal architecture through mechanisms involving the activation of AMPA receptors, the tropomyosin receptor kinase B (TrkB), and the mammalian target of rapamycin (mTOR). Modulators of these biological targets, such as, for example, ketamine, scopolamine, N,N-dimethyltryptamine (DMT), and rapastinel have demonstrated psychoplastogenic properties. For example, ketamine is capable of rectifying deleterious changes in neuronal structure that are associated with neurological diseases and disorders. Such structural alterations include, for example, the loss of dendritic spines and synapses in the prefrontal cortex (PFC) as well as reductions in dendritic arbor complexity. Furthermore, pyramidal neurons in the PFC exhibit top-down control over areas of the brain controlling motivation, fear, and reward. Psychedelic psychoplastogens have demonstrated antidepressant, anxiolytic, and anti-addictive effects of in the clinic.

SUMMARY

[0004] Due to the limitations of psychedelic psychoplastogens, including dissociative effects and strain on clinical resources, new non-hallucinogenic therapeutic options are needed to treat neuropsychiatric disorders.

[0005] In one aspect, provided herein is a method of treating a neuropsychiatric disease in an individual in need thereof, comprising administering to the individual about 1mg to about 500 mg of Compound 1 calculated by free base:



Compound 1.

In some embodiments, the neuropsychiatric disease is depression, addiction, anxiety, post-traumatic stress disorder, bipolar disorder, schizophrenia, or substance use disorder. In some embodiments, the neuropsychiatric disease is depression, or anxiety. In some embodiments, the neuropsychiatric disease is depression. In some embodiments, the neuropsychiatric disease is treatment resistant depression, major depressive disorder, suicidal ideation, or combinations thereof. In some embodiments, the neuropsychiatric disease is major depressive disorder.

[0006] In one embodiment, Compound 1 is administered to the individual orally. In some embodiments, Compound 1 is administered to the individual at a dose of about 1 mg to about 500 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 1 mg to about 250 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 1 mg to about 10 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 2 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 6 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 10 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual a dose of about 10 mg to about 30 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 20 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 30 mg to about 100 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 60 mg to about 90 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 50 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 60 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 75 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 80 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 90 mg calculated by

free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 100 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 100 mg to about 250 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 100 mg, about 150 mg, or about 250 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 100 mg to about 240 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 120 mg to about 180 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 120 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 150 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 160 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 180 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 200 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 220 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 240 mg to about 500 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 240 mg to about 360 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 240 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 250 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 300 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 350 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 360 mg calculated by free base. In some embodiments, Compound 1 is administered once per day. In some embodiments, Compound 1 is administered once every 2 days. In some embodiments, Compound 1 is administered 3 times per week.

[0007] In one embodiment, administering Compound 1 to the individual does not cause hallucinations, dissociative effects, or psychomimetic effects. In some embodiments, Compound 1 is non-hallucinogenic, non-dissociative, and non-psychomimetic. In some embodiments, administering Compound 1 to the individual does not cause hallucinations, dissociative effects, or psychomimetic effects as determined by a Clinician-Administered Dissociative States Scale (CDSS), a Bond-Lader Visual Analog Scale (VAS), a Bowdle VAS, or a Revised Mystical Experience Questionnaire (MEQ-30), or a combination thereof.

[0008] In one embodiment, Compound 1 achieves a $C_{\max}$ under about 10 hours after administering the compound to the individual. In some embodiments, Compound 1 achieves a $C_{\max}$ under about 5 hours after administering the compound to the individual. In some embodiments, Compound 1 achieves a $C_{\max}$ at about 2 hours after administering the compound to the individual. In some embodiments, Compound 1 achieves a CSF/Plasma Ratio of about 0.10 to about 0.50, or of about 0.15 to about 0.30, or of about 0.20. In some embodiments, Compound 1 is administered to an individual in amount such that Compound 1 achieves a $C_{\max}$ of about 10 ng/mL to about 1,000 ng/mL in the individual. In some embodiments, Compound 1 is administered to an individual in amount such that Compound 1 achieves a $C_{\max}$ of about 25 ng/mL to about 500 ng/mL in the individual. In some embodiments, Compound 1 is administered to an individual in amount such that Compound 1 achieves a $C_{\max}$ of about 50 ng/mL to about 250 ng/mL in the individual. In some embodiments, Compound 1 is administered to an individual in amount such that Compound 1 achieves a $C_{\max}$ of about 75 ng/mL to about 125 ng/mL in the individual. In some embodiments, Compound 1 is administered to an individual in amount such that Compound 1 achieves a $C_{\max}$ of about 100 ng/mL in the individual.

[0009] In one aspect, disclosed herein is a pharmaceutical composition comprising about 1 mg to about 500 mg of Compound 1 calculated by free base. In some embodiments, disclosed herein is a pharmaceutical composition comprising 1 mg to 500 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 1 mg to about 250 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 1 mg to about 10 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 2 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 6 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 10 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 10 mg to about 30 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 20 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 30 mg to about 100 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 60 mg to about 90 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 75 mg of Compound 1 calculated by free base. In

some embodiments, the pharmaceutical composition comprises about 90 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 100 mg to about 250 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 100 mg, about 150 mg, or about 250 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 100 mg to about 240 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 120 mg to about 180 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 120 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 180 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 250 mg to about 500 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 240 mg to about 500 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 240 mg to about 360 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 240 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 360 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition further comprises at least one pharmaceutically acceptable excipient.

[0010] In one embodiment, described herein is a method of promoting neuronal growth in an individual comprising administering to the mammal Compound 1. In another embodiment, described herein is a method of improving neuronal structure comprising administering to the individual Compound 1. In another embodiment, described herein is a method of modulating the activity of 5-hydroxytryptamine receptor 2A (5-HT_{2A}) receptor in an individual comprising administering to the individual Compound 1. In another embodiment, described herein is a method of treating a disease or disorder in an individual that is mediated by the action of 5-hydroxytryptamine (5-HT) at 5-hydroxytryptamine receptor 2A (5-HT_{2A}) comprising administering to the individual Compound 1. In another embodiment, described herein is a method of treating a disease or disorder in an individual that is mediated by the loss of synaptic connectivity, plasticity, or a combination thereof comprising administering to the individual Compound 1. In some

embodiments, the disease or disorder is neurological disease or disorder. In some embodiments, the disease or disorder is depression, addiction, anxiety, post-traumatic stress disorder, bipolar disorder, schizophrenia, or substance use disorder. In some embodiments, the neuropsychiatric disease is depression. In some embodiments, the disease or disorder is treatment resistant depression, major depressive disorder, suicidal ideation, or combinations thereof. In some embodiments, the disease or disorder is major depressive disorder

[0011] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF DRAWINGS

[0012] **FIG. 1A-1C** illustrates that Compound 1 promotes structural plasticity in vitro. **FIG. 1A** illustrates the processes for a rat cortical neurite outgrowth assay. **FIG. 1B** illustrates an increase in neurite differentiation for Compound 1 treated cortical neurons compared to control. **FIG. 1C** illustrates changes in neurite length with Compound 1 treatment.

[0013] **FIG. 2A-2E** illustrate that Compound 1 produced rapid and enduring antidepressant-like effects. **FIG. 2A** illustrates rapid antidepressant-like activity after a single IP injection of Compound 1 24 hours before testing in a rat forced swim test. **FIG. 2B** illustrates that antidepressant-like effects of Compound 1 were durable and remained observable 7-days post administration in a rat forced swim test. **FIG. 2C** illustrates that antidepressant-like effects of Compound 1 were observed 24 hours after oral administration in a rat forced swim test. * $p < 0.05$ one-way ANOVA. Dunnett's post-hoc test. **FIG. 2D** illustrates that antidepressant like effects of Compound 1 were observed 30 minutes after administration in a mouse tail suspension test. **FIG. 2E** illustrates Compound 1 reversed a stress-induced social deficit in mouse chronic social defeat. C57BL/6 mice exposed to aggressors for 10 days were assessed for social preference of a novel conspecific. Stress susceptible mice (left bars) and were administered vehicle, ketamine, psilocybin, or Compound 1 and assessed a second time for their social preference (right bars). * $p < 0.05$ one-way ANOVA. Dunnett's post-hoc test for **FIG. A-D**. * $p < 0.05$ two-model ANOVA Sidak's multiple comparison test (pre vs post dose) for **FIG. E**.

[0014] **FIG. 3** illustrates that Compound 1 achieves high plasma and brain levels following oral administration in multiple species.

[0015] **FIG. 4A-4B.** illustrates that Compound 1 does not produce head twitches in rodents. **FIG. 4A** illustrates the number of head twitches in mice after administration of psilocybin, DOI, or Compound 1. **FIG. 4B** illustrates the number of head shakes in rats after administration of DOI or Compound 1.

[0016] **FIG. 5A-5F** illustrate that Compound 1 promotes structural plasticity in the PFC in vivo at behaviorally relevant doses. **FIG. 5A** illustrates an in vivo dendritic spinogenesis assay. **FIG. 5B** illustrates Golgi stained layer V PFC pyramidal neurons treated with 3, 10, or 30mg/kg Compound 1. **FIG. 5C** and **5D** illustrate Compound 1 dose dependently induces spinogenesis in vivo. **FIG. 5E** and **5F** illustrate psilocybin (PSI) and ketamine induce spinogenesis in vivo.

[0017] **FIG. 6A-6F** illustrate that Compound 1 increases functional plasticity in the PFC in vivo at behaviorally relevant doses. **FIG. 6A** illustrates an ex vivo functional plasticity assay. **FIG. 6B** illustrates pEPSC traces from layer V PFC pyramidal neurons treated with Vehicle or Compound 1. **FIG. 6C** illustrates the cumulative mean frequency of EPSCs recorded from mPFC layer-V pyramidal neurons in rat brain slices treated with Vehicle or Compound 1. **FIG. 6D** illustrates the peak amplitude of EPSCs recorded from mPFC layer-V pyramidal neurons in rat brain slices treated with Vehicle or Compound 1. **FIG. 6E** illustrates the cumulative mean frequency of EPSCs recorded from mPFC layer-V pyramidal neurons in rat brain slices treated with Compound 1, DMT, ketamine, and psilocybin as a % of control. **FIG. 6F** illustrates the peak amplitude of EPSCs recorded from mPFC layer-V pyramidal neurons in rat brain slices treated with Compound 1, DMT, ketamine, and psilocybin as a % of control.

[0018] **FIG. 7** illustrates the study schematic of the human clinical trial.

[0019] **FIG. 8** illustrates the sample characteristics of subjects enrolled in the clinical trial.

[0020] **FIG. 9** illustrates the TEAEs by preferred term of subjects enrolled in the clinical trial.

[0021] **FIGs. 10A-10B** illustrate CADSS total score over time in subjects of the SAD cohort (**FIG. 10A**) and MAD cohort (**FIG. 10B**) respectively.

[0022] **FIGs. 11A-11C** illustrate bond and ladder (B&L) visual analogue scale mean value over time in subjects of the SAD cohort (**FIG. 11A**) and MAD cohort (**FIG. 11B**) respectively. **FIG. 11C** illustrates the B&L visual analogue scale.

[0023] **FIGs. 12A-12D** illustrate summary pharmacokinetics of Compound 1 in plasma of subjects of the SAD (**FIG. 12A**), Food Effect (**FIG. 12B**) and MAD cohorts (**FIGs. 12C** and **12D**).

[0024] **FIG. 13** illustrates the CSF/Plasma ratio of Compound 1.

[0025] **FIG. 14A** and **FIG. 14B** illustrate the change in slow wave activity (SWA) in delta (**FIG. 14A**) and theta (**FIG. 14B**) bands as the magnitude of change from baseline before and after administering Compound 1.

DETAILED DESCRIPTION

[0026] The present disclosure provides a non-hallucinogenic compound useful for the treatment of a variety of neurological diseases and disorders, such as major depressive disorder, as well as increasing neuronal plasticity.

[0027] Psychedelic compounds promote structural and functional neural plasticity in key circuits, elicit therapeutic responses in multiple neuropsychiatric disorders, and produce beneficial neurological effects that can last for months following a single administration. Compounds capable of modifying neural circuits that control motivation, anxiety, and drug-seeking behavior have potential for treating neurological diseases and disorders that are mediated by the loss of synaptic connectivity and/or plasticity. Moreover, such compounds are likely to produce sustained therapeutic effects because, for example, of the potential to treat the underlying pathological changes in circuitry.

[0028] Slow wave activity (SWA) in the brain has been proposed as a measure of cortical synaptic strengthening, which plays a role in memory consolidation and neural plasticity. Certain psychedelics, including ketamine, show an increase in SWA characterized by oscillations in the delta (0.5-4 Hz) and theta (4-8 Hz) frequency bands (Duncan et al., 2013). Surprisingly, Compound 1 was discovered to increase magnitude of change from baseline in both delta and theta frequency band absolute power, indicating Compound 1 increases neural plasticity (FIG. 14A and FIG. 14B). In some embodiments, administering Compound 1 increases slow wave activity (e.g., delta band power or theta band power), by at least about 10pp, at least about 20pp, at least about 30pp, at least about 40pp, at least about 50pp, at least about 60pp, at least about 70pp, at least about 80pp, at least about 90pp, or at least about 100pp between 1 to 24 hours after administering Compound 1. As used here, “pp” means “percentage points”. For example, 50% and 54% differ by 4pp. In some embodiments, administering Compound 1 increases slow wave activity by 10pp-20pp. In some embodiments, administering Compound 1 increases slow wave activity by 15pp-25pp. In some embodiments, administering Compound 1 increases slow wave activity by 20pp-30pp. In some embodiments, administering Compound 1 increases slow wave activity by 25pp-35pp. In some embodiments, administering Compound 1 increases slow wave activity by 30pp-40pp. In some embodiments, administering Compound 1 increases slow wave activity by 35pp-45pp. In some embodiments, administering Compound 1 increases slow wave activity by 40pp-50pp. In some embodiments, administering Compound 1 increases slow wave activity by 55pp-65pp. In some embodiments, administering Compound 1 increases slow wave activity by 60pp-70pp. In some embodiments, administering Compound 1 increases slow wave activity by 65pp-75pp. In some embodiments, administering Compound 1 increases slow wave activity by 70pp-80pp. In some

embodiments, administering Compound 1 increases slow wave activity by 75pp-85pp. In some embodiments, administering Compound 1 increases slow wave activity by 80pp-90pp. In some embodiments, administering Compound 1 increases slow wave activity by 95pp-95pp. In some embodiments, administering Compound 1 increases slow wave activity by 90pp-100pp. In some embodiments, the slow wave activity is Delta band power. In some embodiments, the slow wave activity is Theta band power.

[0029] In some embodiments, 5-HT_{2A} antagonists abrogate the neuritogenesis and spinogenesis effects of hallucinogenic compounds with 5-HT_{2A} agonist activity, e.g., DMT, LSD, and DOI, demonstrating the correlation of 5-HT_{2A} agonism and the promotion of neural plasticity (Ly et al., 2018; Dunlap et al., 2020). However, the hallucinogenic and dissociative potential of such compounds has limited the use of these compounds in the clinic for neurological diseases, such as, for example, neuropsychiatric diseases. (Ly et al., 2018)

Certain Terminology

[0030] Unless otherwise stated, the following terms used in this application have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. The use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0031] The term “about” or “approximately” can mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.*, the limitations of the measurement system. For example, “about” can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, “about” can mean a range of up to 20%, up to 15%, up to 10%, up to 5%, or up to 1% of a given value.

[0032] The term “comprising” (and related terms such as “comprise” or “comprises” or “having” or “including”) is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, “consist of” or “consist essentially of” the described features.

[0033] The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[0034] The term “modulate” as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target. In some embodiments, “modulate” means to interact with a target either directly or indirectly so as to decrease or inhibit receptor activity. In some embodiments, modulation is an increase or decrease in the amount, quality, or effect of a particular activity, function or molecule. By way of illustration and not limitation, agonists, partial agonists, antagonists, and allosteric modulators (e.g., a positive allosteric modulator) of a G protein-coupled receptor (e.g., 5HT_{2A}) are modulators of the receptor.

[0035] The term “modulator” as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist, antagonist, or combinations thereof. In some embodiments, a modulator is an antagonist. Receptor antagonists are inhibitors of receptor activity. Antagonists mimic ligands that bind to a receptor and prevent receptor activation by a natural ligand. Preventing activation may have many effects. If a natural agonist binding to a receptor leads to an increase in cellular function, an antagonist that binds and blocks this receptor decreases the function of the receptor.

[0036] The term “agonism,” as used herein, generally refers to the activation of a receptor or enzyme by a modulator, or agonist, to produce a biological response.

[0037] The term “agonist,” as used herein, generally refers to a modulator that binds to a receptor or enzyme and activates the receptor to produce a biological response. By way of example only, a “5HT_{2A} agonist” can be used to refer to a compound that exhibits an EC₅₀ with respect to 5HT_{2A} activity of no more than about 100 μM. In some embodiments, the term “agonist” includes full agonists or partial agonists. “Full agonist” refers to a modulator that binds to and activates a receptor with the maximum response that an agonist can elicit at the receptor. “Partial agonist” refers to a modulator that binds to and activates a given receptor, but has partial efficacy, that is, less than the maximal response, at the receptor relative to a full agonist.

[0038] The term “positive allosteric modulator,” as used herein, generally refers to a modulator that binds to a site distinct from the orthosteric binding site and enhances or amplifies the effect of an agonist.

[0039] The term “antagonism,” as used herein, generally refers to the inactivation of a receptor or enzyme by a modulator, or antagonist. Antagonism of a receptor, for example, is when a molecule binds to the receptor and blocks function of the receptor.

[0040] The term “antagonist” or “neutral antagonist,” as used herein, generally refers to a modulator that binds to a receptor or enzyme and blocks a biological response. An antagonist may have no activity in the absence of an agonist or inverse agonist but can block the activity of either, causing no change in the biological response.

[0041] The terms “administer,” “administering,” “administration,” and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein. In some embodiments, the compounds and compositions described herein are administered orally.

[0042] The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered, which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case is optionally determined using techniques, such as a dose escalation study.

[0043] The terms “enhance” or “enhancing,” as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term “enhancing” refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An “enhancing-effective amount,” as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[0044] The term “subject,” “individual,” or “patient” encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one embodiment, the mammal is a human.

[0045] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition,

relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

[0046] The term “pharmaceutically acceptable,” as used herein, generally refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material is administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0047] The term “pharmaceutically acceptable salt,” as used herein, generally refers to a form of a therapeutically active agent that consists of a cationic form of the therapeutically active agent in combination with a suitable anion, or in alternative embodiments, an anionic form of the therapeutically active agent in combination with a suitable cation. Handbook of Pharmaceutical Salts: Properties, Selection and Use. International Union of Pure and Applied Chemistry, Wiley-VCH 2002. S.M. Berge, L.D. Bighley, D.C. Monkhouse, J. Pharm. Sci. 1977, 66, 1-19. P. H. Stahl and C. G. Wermuth, editors, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Weinheim/Zürich: Wiley-VCH/VHCA, 2002. Pharmaceutical salts typically are more soluble and more rapidly soluble in stomach and intestinal juices than non-ionic species and so are useful in solid dosage forms. Furthermore, because their solubility often is a function of pH, selective dissolution in one or another part of the digestive tract is possible and this capability can be manipulated as one aspect of delayed and sustained release behaviors. Also, because the salt-forming molecule can be in equilibrium with a neutral form, passage through biological membranes can be adjusted.

Neuropsychiatric Disease and Disorders

[0048] Neuronal plasticity has been attributed to many neurological diseases and disorders. For example, during development and in adulthood, changes in dendritic spine number and morphology (e.g., lengths, crossings, density) accompany synapse formation, maintenance and elimination; these changes are thought to establish and remodel connectivity within neuronal circuits. Furthermore, dendritic spine structural plasticity is coordinated with synaptic function and plasticity. For example, spine enlargement is coordinated with long-term potentiation in neuronal circuits, whereas long-term depression is associated with spine shrinkage.

[0049] In addition, dendritic spines undergo experience-dependent morphological changes in live animals, and even subtle changes in dendritic spines can affect synaptic function, synaptic plasticity, and patterns of connectivity in neuronal circuits. For example, disease-specific

disruptions in dendritic spine shape, size, and/or number accompany neurological diseases and disorders, such as, for example, neurodegenerative (e.g., Alzheimer's disease or Parkinson's disease) and neuropsychiatric (e.g., depression or schizophrenia) diseases and disorders, suggesting that dendritic spines may serve as a common substrate in diseases that involve deficits in information processing.

[0050] In some embodiments, disclosed herein are methods of treating a neuropsychiatric disease or disorder with Compound 1. In some embodiments, provided herein is a method of treating a mood disorder with Compound 1. In some embodiments, provided herein is a method of treating depression (e.g., clinical depression, persistent depressive disorder, bipolar disorder, postpartum depression, suicidal ideation, major depressive disorder, seasonal depression, treatment resistant depression, and the like) with Compound 1. In some embodiments, the depression is major depressive disorder.

[0051] In some embodiments, Compound 1 improves dendritic spine number and dendritic spine morphology that is lost in neurological diseases and disorders.

5-HT_{2A}

[0052] 5-HT_{2A} agonism has been correlated with the promotion of neural plasticity (Ly et al., 2018). In some embodiments, 5-HT_{2A} antagonists abrogate the neuritogenesis and spinogenesis effects of hallucinogenic compounds with 5-HT_{2A} agonist activity, e.g., DMT, LSD, and DOI. Furthermore, DMT and other psychedelic compounds promote increased dendritic arbor complexity, dendritic spine density, and synaptogenesis through a 5-HT_{2A}-dependent process.

[0053] Compound 1 is a non-hallucinogenic compound that demonstrate similar or improved therapeutic potential as hallucinogenic 5-HT_{2A} agonists. In some embodiments, Compound 1 provides better therapeutic potential than hallucinogenic 5-HT_{2A} agonists for neurological or neuropsychiatric diseases or disorders. In some embodiments, Compound 1 is a 5-HT_{2A} modulator and promotes neural plasticity (e.g., cortical structural plasticity and neurite outgrowth). In some embodiments, Compound 1 promotes neural plasticity. In some embodiments, provided herein is a method of treating a neuropsychiatric disease or disorder characterized by decreased neural plasticity, decreased cortical structural plasticity, decreased 5-HT_{2A} receptor content, decreased dendritic arbor complexity, loss of dendritic spines, decreased dendritic branch content, decreased spinogenesis, decreased neuritogenesis, retraction of neurites, or any combination thereof. In some embodiments, promotion of neural plasticity includes, for example, increased dendritic spine growth, increased synthesis of synaptic proteins, strengthened synaptic responses, increased dendritic arbor complexity, increased dendritic branch content, increased spinogenesis, increased

neuritogenesis, or any combination thereof. In some embodiments, increased neural plasticity includes, for example, increased cortical structural plasticity in the anterior parts of the brain.

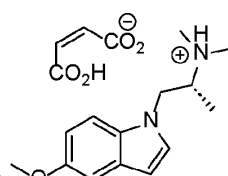
[0054] In some embodiments, Compound 1 is a 5-HT_{2A} agonist. In some embodiments, Compound 1 is a 5-HT_{2A} agonist and promotes neural plasticity (e.g., cortical structural plasticity), such as increases neurite outgrowth. In some embodiments, Compound 1 provides (significant) 5-HT_{2A} agonism and promotes neural plasticity (e.g., cortical structural plasticity), such as increases neurite outgrowth. In some embodiments, Compound 1 promotes neural plasticity (e.g., cortical structural plasticity), and has a low potential for hallucinogenic activity (e.g., is non-hallucinogenic). In some embodiments, Compound 1 does not elicit dissociative side-effects.

[0055] In some embodiments, Compound 1 is used to treat neurological diseases. In some embodiments, the neurological diseases comprise decreased neural plasticity, decreased cortical structural plasticity, decreased 5-HT_{2A} receptor content, decreased dendritic arbor complexity, loss of dendritic spines, decreased dendritic branch content, decreased spinogenesis, decreased neuritogenesis, retraction of neurites, or any combination thereof.

[0056] In some embodiments, Compound 1 is used for increasing neuronal plasticity. In some embodiments, Compound 1 is used for treating a brain disorder. In some embodiments, Compound 1 is used for increasing at least one of translation, transcription, or secretion of neurotrophic factors.

[0057] Non-limiting examples of experiments or assays to demonstrate the increased neuronal plasticity of Compound 1 include: a phenotypic assay, a dendritogenesis assay, a spinogenesis assay, a synaptogenesis assay, a Sholl analysis, a concentration-response experiment, a 5-HT_{2A} agonist assay, a 5-HT_{2A} antagonist assay, a 5-HT_{2A} binding assay, or a 5-HT_{2A} blocking experiment (e.g., ketanserin blocking experiments).

Compound 1



[0058] Disclosed herein is Compound 1 having the structure of ((R)-1-(5-methoxy-1H-indol-1-yl)-N,N-dimethylpropan-2-amine, maleate salt). Individual stereoisomers are obtained by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns or the separation of diastereomers by either non-chiral or chiral chromatographic columns or crystallization and recrystallization in a proper solvent or a mixture of solvents. In certain embodiments, Compound 1 is prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair

of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure individual enantiomers. In some embodiments, resolution of individual enantiomers is carried out using covalent diastereomeric derivatives of Compound 1. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of stereoisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981. In some embodiments, stereoisomers are obtained by stereoselective synthesis.

[0059] In further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

Synthesis of Compounds

[0060] Compound 1 was synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein, for example those published in US Patent Application Number 17/570,997 which is hereby incorporated by reference for such disclosure. For example, a solution of (R)-1-(5-methoxy-1H-indol-1-yl)-N,N-dimethylpropan-2-amine is cooled in an ice bath and a solution of maleic acid is added dropwise while stirring. The ice bath may be removed and the reaction allowed to stir at room temperature. The mixture is then concentrated and triturated to yield Compound 1.

[0061] Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed.

[0062] Compound 1 was prepared using standard organic chemistry techniques such as those described in, for example, March's Advanced Organic Chemistry, 6th Edition, John Wiley and Sons, Inc.

Pharmaceutical compositions

[0063] In some embodiments, provided herein is a pharmaceutical composition comprising Compound 1. In some embodiments, the pharmaceutical composition further comprises at least one pharmaceutically acceptable excipient.

[0064] In some embodiments, Compound 1 is formulated into a pharmaceutical composition. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds

into preparations that are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

[0065] In some embodiments, Compound 1 is administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition. Administration of Compound 1 can be affected by any method that enables delivery of the compounds to the site of action. These methods include, though are not limited to delivery via enteral routes (including oral, gastric or duodenal feeding tube, rectal suppository and rectal enema), parenteral routes (injection or infusion, including intraarterial, intracardiac, intradermal, intraduodenal, intramedullary, intramuscular, intraosseous, intraperitoneal, intrathecal, intravascular, intravenous, intravitreal, epidural and subcutaneous), inhalational, transdermal, transmucosal, sublingual, buccal and topical (including epicutaneous, dermal, enema, eye drops, ear drops, intranasal, vaginal) administration, although the most suitable route may depend upon the condition and disorder of the recipient.

[0066] In some embodiments, Compound 1, is formulated for oral administration. In some embodiments, pharmaceutical compositions suitable for oral administration are presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. In some embodiments, the active ingredient is presented as a bolus, electuary or paste.

[0067] Pharmaceutical compositions which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The pharmaceutical composition may be a capsule comprising a capsule shell, such as a hydroxypropyl methylcellulose (HPMC, Hypromellose) capsule shell. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. In some embodiments,

the tablets are coated or scored and are formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or Dragee coatings for identification or to characterize different combinations of active compound doses.

[0068] In some embodiments, provided herein is a pharmaceutical composition comprising Compound 1. In some embodiments, provided herein is a pharmaceutical composition comprising an effective amount of Compound 1. In some embodiments, the pharmaceutical composition is formulated for oral administration. In some embodiments, the pharmaceutical composition is a capsule or a tablet. In some embodiments, the pharmaceutical composition is a capsule. In some embodiments, the pharmaceutical composition is a tablet. In some embodiments, the pharmaceutical composition comprises about 1 mg to about 500 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises 1 mg to 500 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 1 mg to about 10 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 2 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 6 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 10 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 10 mg to about 30 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 20 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 30 mg to about 100 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 60 mg to about 90 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises 60 mg to 90 mg of Compound 1 calculated by free base. In some

embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises 60 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 75 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises 75 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 90 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises 90 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 100 mg to about 250 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 100 mg, about 150 mg, or about 250 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 100 mg to about 240 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 120 mg to about 180 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises 120 mg to 180 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 120 of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises 120 of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises 150 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 180 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises 180 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 250 mg to about 500 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 240 mg to about 500 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 240 mg to about 360 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises 240 mg to 360 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 240 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises 240 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1 calculated by free base. In

some embodiments, the pharmaceutical composition comprises 300 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises about 360 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition comprises 360 mg of Compound 1 calculated by free base. In some embodiments, the pharmaceutical composition further comprises at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is a tablet or capsule further comprising hypromellose and/or titanium dioxide. In some embodiments, the pharmaceutical composition is a capsule further comprising hypromellose and titanium dioxide. In some embodiments, multiple pharmaceutical compositions are administered in combination to achieve a target dose. For example, one pharmaceutical composition comprising 50mg of Compound 1 calculated by free base and three pharmaceutical compositions comprising 10mg of Compound 1 calculated by free base may be combined to equal a total administered dose of 80 mg of Compound 1 calculated by free base.

[0069] It should be understood that in addition to the ingredients particularly mentioned above, the compounds and compositions described herein may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Methods of Treatment, Dosing and Treatment Regimens

[0070] Compound 1 is useful for promoting neuronal growth and/or improving neuronal structure.

[0071] Compound 1 is a non-hallucinogenic psychoplastogens that useful for treating one or more diseases or disorders associated with loss of synaptic connectivity and/or plasticity.

[0072] In some embodiments, provided herein is a method of promoting neural plasticity (e.g., cortical structural plasticity) in an individual by administering Compound 1 to the individual. In some embodiments, provided herein are methods of modulating 5-HT_{2A} in an individual by administering Compound 1 to the individual. In some embodiments, provided herein are methods of agonizing 5-HT_{2A} in an individual by administering Compound 1 to the individual. In some embodiments, the individual has or is diagnosed with a brain disorder or other conditions described herein.

[0073] In some embodiments, provided herein is a method of promoting neuronal growth in an individual in need thereof, comprising administering to the individual in need thereof Compound 1.

[0074] In some embodiments, provided herein is a method of improving neuronal structure in an individual in need thereof, comprising administering to the individual in need thereof Compound 1.

[0075] In some embodiments, provided herein is a method of modulating the activity of 5-hydroxytryptamine receptor 2A (5-HT_{2A}) receptor in an individual in need thereof, comprising administering to the individual in need thereof Compound 1.

[0076] In some embodiments, provided herein is a method of treating a disease or disorder in an individual in need thereof that is mediated by the action of 5-hydroxytryptamine (5-HT) at 5-hydroxytryptamine receptor 2A (5-HT_{2A}), comprising administering to the individual in need thereof Compound 1.

[0077] In some embodiments, provided herein is a method of treating a disease or disorder in an individual in need thereof that is mediated by the loss of synaptic connectivity, plasticity, or a combination thereof, comprising administering to the individual in need thereof Compound 1.

[0078] In some embodiments, provided herein is a method of treating a neurological disease or disorder in an individual in need thereof, comprising administering to the individual in need thereof Compound 1.

[0079] In some embodiments, an individual administered Compound 1 does not have a hallucinogenic event. In some embodiments, administering Compound 1 to the individual does not cause hallucinations, dissociative effects, or psychomimetic effects. In some embodiments, Compound 1 is non-hallucinogenic, non-dissociative, and non-psychomimetic. In some embodiments, administering Compound 1 to the individual does not cause hallucinations, dissociative effects, or psychomimetic effects as determined by a Clinician-Administered Dissociative States Scale (CADSS), a Bond-Lader Visual Analog Scale (VAS), a Bowdle VAS, or a Revised Mystical Experience Questionnaire (MEQ-30), or a combination thereof. In some embodiments, the CADSS value is less than 5, or is less than 3, or is less than 2, or is less than 1. In some embodiments, the CADSS value is less than 5, or is less than 3, or is less than 2, or is less than 1 at any point after administering Compound 1. In some embodiments, the Bond-Lader VAS value is between 25-75, or is between 30-70, or is between 35-65 for each measure on the scale. In some embodiments, the Bond-Lader VAS value is between 25-75, or is between 30-70, or is between 35-65 for each measure on the scale at any point after administering Compound 1.

[0080] In some embodiments, described herein are methods for treating a disease or disorder, wherein the disease or disorder is a neurological diseases and disorder.

[0081] In some embodiments, Compound 1 is used to treat neurological diseases. In some embodiments, Compound 1 has, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof.

[0082] In some embodiments, the neurological disease is a neuropsychiatric disease. In some embodiments, the neuropsychiatric disease is a mood or anxiety disorder. In some embodiments,

the neurological disease is a migraine, headaches (e.g., cluster headache), post-traumatic stress disorder (PTSD), anxiety, depression, neurodegenerative disorder, Alzheimer's disease, Parkinson's disease, psychological disorder, treatment resistant depression, suicidal ideation, major depressive disorder, bipolar disorder, schizophrenia, stroke, traumatic brain injury, and addiction (e.g., substance use disorder). In some embodiments, the neurological disease is a migraine or cluster headache. In some embodiments, the neurological disease is a neurodegenerative disorder, Alzheimer's disease, or Parkinson's disease. In some embodiments, the neurological disease is a psychological disorder, treatment resistant depression, suicidal ideation, major depressive disorder, bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), addiction (e.g., substance use disorder), depression, or anxiety. In some embodiments, the neuropsychiatric disease is a psychological disorder, treatment resistant depression, suicidal ideation, major depressive disorder, bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), addiction (e.g., substance use disorder), depression, or anxiety. In some embodiments, the neuropsychiatric disease or neurological disease is post-traumatic stress disorder (PTSD), addiction (e.g., substance use disorder), schizophrenia, depression, or anxiety. In some embodiments, the neuropsychiatric disease or neurological disease is addiction (e.g., substance use disorder). In some embodiments, the neuropsychiatric disease or neurological disease is depression. In some embodiments, the neuropsychiatric disease or neurological disease is anxiety. In some embodiments, the neuropsychiatric disease or neurological disease is post-traumatic stress disorder (PTSD). In some embodiments, the neurological disease is stroke or traumatic brain injury. In some embodiments, the neuropsychiatric disease or neurological disease is schizophrenia. In some embodiments, the neuropsychiatric disease is depression, addiction, anxiety, post-traumatic stress disorder, bipolar disorder, schizophrenia, or substance use disorder. In some embodiments, the neuropsychiatric disease is depression. In some embodiments, the depression is treatment resistant depression, major depressive disorder, suicidal ideation, or combinations thereof. In some embodiments, the depression is major depressive disorder.

[0083] In some embodiments, Compound 1 is useful for the modulation of a 5-hydroxytryptamine (5-HT) receptor. In some embodiments, the 5-HT receptor modulated by Compound 1 is 5-hydroxytryptamine receptor 2A (5-HT_{2A}).

[0084] In some embodiments, Compound 1 is used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from inhibition or reduction of 5-HT_{2A} activity.

[0085] In some embodiments, Compound 1 is used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from promoting neuronal growth and/or improving neuronal structure.

[0086] In one embodiment, Compound 1 is administered to the individual orally. In some embodiments, Compound 1 is administered to the individual at a dose of about 1 mg to about 250 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 1 mg to about 10 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 2 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 6 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 10 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual a dose of about 10 mg to about 30 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 20 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 30 mg to about 100 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 50 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 60 mg to about 90 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of 60 mg to 90 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 60 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of 60 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 75 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of 75 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 80 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 90 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of 90 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 100 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 100 mg to about 250 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 100 mg, about 150 mg, or about 250 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 120 mg to about 180 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of 120 mg to 180 mg calculated by free base. In some embodiments,

Compound 1 is administered to the individual at a dose of about 120 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of 120 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 150 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of 150 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 160 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 180 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of 180 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 200 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 220 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 240 mg to about 500 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 250 mg to about 500 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 240 mg to about 360 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of 240 mg to 360 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 240 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of 240 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 250 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 300 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of 300 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 350 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of about 360 mg calculated by free base. In some embodiments, Compound 1 is administered to the individual at a dose of 360 mg calculated by free base.

[0087] In some embodiments, the individual in need thereof is fasted prior to administering Compound 1. In some embodiments, the individual in need thereof is sated prior to administering Compound 1. In some embodiments, the individual in need thereof is fasted or sated prior to administering Compound 1.

[0088] In some embodiments, Compound 1 is administered once per day. In some embodiments, Compound 1 is administered once every 2 days. In some embodiments, Compound 1 is administered 3 times a week. In some embodiments, Compound 1 is administered 3 times in a 7

day period, wherein there is at least 1 day between each administration. In some embodiments, Compound 1 is administered for at least 3 days, or for at least 5 days, or for at least 7 days, or for at least 10 days, or for at least 14 days, or for at least 21 days, or for at least 28 days. In some embodiments, Compound 1 is administered once every 7 days. In some embodiments, Compound 1 does not accumulate in the individual. In some embodiments, Compound 1 is present in the individual in an amount lower than about 1ng/mL after 30 hours administering Compound 1. In some embodiments, Compound 1 is administered in an outpatient setting.

[0089] In some embodiments, Compound 1 achieves a C_{max} under about 10 hours after administering the compound to the individual. In some embodiments, Compound 1 achieves a C_{max} under about 5 hours after administering the compound to the individual. In some embodiments, Compound 1 achieves a C_{max} at about 2 hours after administering the compound to the individual. In some embodiments, Compound 1 achieves a CSF/Plasma Ratio of about 0.10 to about 0.50, or of about 0.15 to about 0.30, or of about 0.20. In some embodiments, administering Compound 1 produces a sustained therapeutic response for at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, or at least 7 days after administration. In some embodiments, Compound 1 is administered to an individual in amount such that Compound 1 achieves a C_{max} of about 10 ng/mL to about 1,000 ng/mL in the individual. In some embodiments, Compound 1 is administered to an individual in amount such that Compound 1 achieves a C_{max} of about 25 ng/mL to about 500 ng/mL in the individual. In some embodiments, Compound 1 is administered to an individual in amount such that Compound 1 achieves a C_{max} of about 50 ng/mL to about 250 ng/mL in the individual. In some embodiments, Compound 1 is administered to an individual in amount such that Compound 1 achieves a C_{max} of about 75 ng/mL to about 125 ng/mL in the individual. In some embodiments, Compound 1 is administered to an individual in amount such that Compound 1 achieves a C_{max} of about 100 ng/mL in the individual.

[0090] In some embodiments, administering Compound 1 to the individual does not cause cardiotoxicity. In some embodiments, Compound 1 is not cardiotoxic. In some embodiments, Compound 1 does not activate the 5-HT_{2B} receptor. In some embodiments, a risk of the individual developing any serious treatment-emergent adverse event (TEAE) is less than about 60%, or less than about 50%, or less than about 40%, or less than about 30%, or less than about 20%, or less than about 10%, or less than about 5%.

[0091] In some embodiments, administering Compound 1 to an individual increases neurite differentiation, neurite length, spinogenesis, or a combination thereof in the individual. In some embodiments, the increase is greater than 1.0 fold. In some embodiments, administering Compound 1 increases frequency and amplitude of layer V pyramidal neurons 24 hours after administration.

[0092] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once a day; or (ii) the compound is administered to the individual multiple times over the span of one day. In some embodiments, administering Compound 1 produces a therapeutic effect within about 48 hours, or within about 24 hours. In some embodiments, the therapeutic effect is an anti-depressive effect. In some embodiments, the individual experiences a therapeutic effect after a single administration of Compound 1.

[0093] In some embodiments, an individual administered Compound 1 has a diagnosis of major depressive disorder (MDD) that has been present for 12-week to 2 years and/or has a Hamilton Rating Scale for Depression, 17-item (HAM-D) total score of at least 22 prior to administering Compound 1. In some embodiments, an individual administered Compound 1 has a diagnosis of major depressive disorder (MDD) that has been present for 12-week to 2 years. In some embodiments, an individual administered Compound 1 has a Hamilton Rating Scale for Depression, 17-item (HAM-D) total score of at least 22 prior to administering Compound 1.

[0094] In some embodiments, an individual administered Compound 1 does not have: a) psychosis or a history of psychosis, b) seizures or a history of seizures, c) bipolar disorder, schizophrenia, and/or schizoaffective disorder or a history of bipolar disorder, schizophrenia, and/or schizoaffective disorder, d) a history of alcohol or drug dependence or use of psychedelics within the 12 months prior to administering Compound 1, or e) any combination of a) through d). In some embodiments, an individual administered Compound 1 does not have psychosis or a history of psychosis. In some embodiments, an individual administered Compound 1 does not have seizures or a history of seizures. In some embodiments, an individual administered Compound 1 does not have bipolar disorder, schizophrenia, and/or schizoaffective disorder, or a history of bipolar disorder, schizophrenia, and/or schizoaffective disorder. In some embodiments, an individual administered Compound 1 does not have a history of alcohol or drug dependence or use of psychedelics within the 12 months prior to administering Compound 1.

[0095] It is understood that the dosage regimen to treat, prevent, or ameliorate the disease(s) for which relief is sought, is modified in accordance with a variety of factors (e.g. the disease or disorder from which the subject suffers; the age, weight, sex, diet, and medical condition of the subject). Thus, in some embodiments, the dosage regimen actually employed varies and, in some embodiments, deviates from the dosage regimens set forth herein.

EXAMPLES

[0096] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1: Preclinical Pharmacology of Compound 1 that is a Novel Non-Hallucinogenic Neuroplastogen for Treating Neuropsychiatric Diseases

[0097] This example illustrates the preclinical pharmacology of Compound 1 disclosed herein.

[0098] Background

[0099] Cortical synaptic atrophy is a critical component of many neuropsychiatric disorders and treatments that promote structural neuroplasticity, in key brain areas, show efficacy in treating them. Psychedelic agents, including the dissociative anesthetic ketamine and the serotonergic psilocybin, have been reported to show efficacy in humans for treating multiple neuropsychiatric disorders. The clinical effects of these compounds are hypothesized to be due to their ability to promote rapid and enduring effects on structural neuroplasticity in key brain areas, and as such, these compounds have been classified as psychoplastogens. The dissociative experiences, hallucinations, and/or cardiotoxic properties of these compounds will limit their widespread clinical use. Bringing these transformative therapies to a greater patient population will require an orally bioavailable, non-hallucinogenic compound that maintains the rapid and enduring effects of psychoplastogens, or a “neuroplastogen”. To that end, we designed a novel isoptryptamine, Compound 1, that is a potent, orally active neuroplastogen, promoting rapid and enduring behavioral efficacy and structural plasticity without pro-hallucinogenic activity or cardiotoxicity. Here we present a deep the characterization of the neuroplastic and behavioral effects of Compound 1 compared to several first-generation psychoplastogens.

[00100] Results

- (a) Compound 1 is an orally active, brain penetrant, small molecule.
- (b) Compound 1 has a unique poly-pharmacological profile in traditional in vitro RLB binding/functional assays.
- (c) Compound 1 promotes structural plasticity in vitro.
- (d) Compound 1 is active in multiple behavioral models of antidepressant activity.
- (e) Compound 1 promotes structural and functional neuroplasticity in PFC layer V pyramidal neurons at the same doses that are active in behavioral assays.
- (f) Compound 1 does not have hallucinogenic properties.
- (g) Compound 1 is predicted to have rapid and enduring anti-depressant effects in humans without producing hallucinations.

(h) In a phenotypic screen of neurite outgrowth in neuronal cell cultures, Compound 1 produced significant increases in both neurite length and complexity.

(i) In vivo, Compound 1 demonstrated significant effects on promoting both structural and functional neuroplasticity on par with the 1st generation compounds after a single dose.

(j) Compound 1 in vivo behavioral data exhibited both rapid, within 24-hours, and enduring, up to 7 days, antidepressant-like activity after a single dose.

(k) In studies relevant to cardiotoxicity and hallucinations, no signal was identified for Compound 1.

(l) Importantly, Compound 1 met or exceeded the efficacy and endurance of first-generation psychoplastogens, including DMT, psilocybin, and ketamine.

[00101] FIG. 1 illustrates that Compound 1 promotes structural plasticity in vitro. Compound 1 treatment increases neuronal differentiation in vitro. Isolated rat cortical neurons treated for 72 hrs (FIG. 1A) in culture showed an increase in neurite differentiation (FIG. 1B) compared to control. Changes in neurite length upon Compound 1 treatment showed an increase in a concentration dependent manner (FIG. 1C). (**p < 0.01, ***p < 0.001 using one-way ANOVA followed by post-hoc Fisher's LSD)

[00102] FIG. 2A-2E illustrate that Compound 1 produced rapid and enduring antidepressant-like effects. Compound 1 produced rapid and enduring antidepressant-like activity in a rat model of depression. FIG. 2A illustrates that the rat forced swim test revealed rapid antidepressant-like activity after a single IP injection 24 hours before testing. FIG. 2B illustrates that antidepressant-like effects were durable and remained observable 7-days post administration. FIG. 2C illustrates that antidepressant-like effects were observed 24 hours after oral administration. *p<0.05 one-way ANOVA. Dunnett's post-hoc test.

[00103] Compound 1 produced rapid antidepressant-like activity in two mouse models of depression. FIG. 2D illustrates that the mouse tail suspension test showed antidepressant-like activity 30 minutes after treatment. FIG. 2E illustrates Compound 1 reversed a stress-induced social deficit in mouse chronic social defeat. C57BL/6 mice exposed to aggressors for 10 days were assessed for social preference of a novel conspecific. Stress susceptible mice (left bars) and were administered vehicle, ketamine, psilocybin, or Compound 1 and assessed a second time for their social preference (right bars). *p<0.05 one-way ANOVA. Dunnett's post-hoc test for A-D. *p<0.05 two-model ANOVA Sidak's multiple comparison test (pre vs post dose) for E.

[00104] FIG. 3 illustrates that Compound 1 achieves high plasma and brain levels following oral administration in multiple species. Compound 1 has a unique poly-pharmacological profile. At exposures relevant for neuroplasticity and behavioral efficacy, Compound 1 appears to bind an

array of targets relevant to neuropsychiatric disorders. In traditional radioligand binding/functional assays, Compound 1 was found to engage 5-HT_{2C}, 5-HT_{1D}, 5-HT₃, Sigma-1 receptors, and MAO-A. Importantly, antagonist experiments indicate that 5HT_{2A/2C} receptors play an important role in the proplastic effects of Compound 1 and it does not activate 5HT_{2B}.

[00105] FIG. 4A and 4B illustrate that Compound 1 does not produce head twitches in rodents. Compound 1 did not produce a significant number of head twitches when administered to mice at high doses (10 or 30mg/kg, IP) (FIG. 4A). Similarly, therapeutic and supratherapeutic doses of Compound 1 did not produce a significant number of head shakes in rats (FIG. 4B).

[00106] FIG. 5A-5F illustrate that Compound 1 promotes structural plasticity in the PFC in vivo at behaviorally relevant doses. FIG. 5A illustrates in vivo dendritic spinogenesis assay. FIG. 5B illustrates Golgi stained layer V PFC pyramidal neurons. FIGS. 5C-5D illustrate Compound 1 - induced spinogenesis in vivo. FIGS. 5E-5F illustrate psilocybin and ketamine induced spinogenesis in vivo. Compound 1, at behaviorally relevant and efficacious doses, increased dendritic spine density in layer-V PFC pyramidal neurons of rat brain 24 hours following a single dose (FIG. 5A) as shown by Golgi-impregnated neurons (FIG. 5B). Compound 1 treatment induced changes are quantified as spine density (# of spines/ dendritic length)(FIGS. 5C-5D). Changes in Compound 1 induced spine density are similar to ketamine and psilocybin (FIGS. 5E-5F). *p<0.05, ** p<0.01 using two-way ANOVA followed by Tukey's post-hoc test.

[00107] FIG. 6A-6F illustrate that Compound 1 increases functional plasticity in the PFC in vivo at behaviorally relevant doses. FIG. 6A illustrates ex vivo functional plasticity assay. FIG. 6B illustrates pEPSC traces from layer V PFC pyramidal neurons. FIGS. 6C-6D illustrate that Compound 1 induced functional plasticity ex vivo. FIG. 6E-6F illustrate DMT, psilocybin, and ketamine induced functional plasticity ex vivo. Compound 1 altered excitatory post-synaptic potentials (EPSCs) in mPFC layer V pyramidal neurons 24 hours after a single in vivo administration of a behaviorally relevant dose. FIG. 6B illustrates raw traces from layer V cells following administration of Compound 1 or Vehicle. Compound 1 increased the cumulative mean frequency (FIGS. 6C, 6E) and the peak amplitude (FIGS. 6D, 6F) of EPSCs recorded from mPFC layer-V pyramidal neurons in rat brain slices. In measures of cumulative mean frequency, the effect of Compound 1 was similar to DMT, ketamine, and psilocybin tested independently at behaviorally relevant doses relative to controls (FIGS. 6C, 6E). In measures of peak amplitude, Compound 1 responses were similar to DMT, but both differed from ketamine and psilocybin (FIGS. 6D, 6F), indicating potential nuances in neuroplastic mechanisms. *p <0.05, Mann-Whitney U-test.

[00108] Citation of References

1. Ly et al., 2018, Cell Reports 23, 3170–3182

2. Olson, Journal of Experimental Neuroscience 12, 1–4

Example 2: Use of Compound 1 for Treatment of Major Depressive Disorder (MDD)

[00109] This example illustrates a Phase I study to evaluate the safety, tolerability, and pharmacokinetic profile of neuroplastogen Compound 1 disclosed herein.

[00110] Background

[00111] Psychedelic compounds have demonstrated preliminary efficacy across a range of neuropsychiatric conditions, with effects that are believed to be mediated by their rapid and enduring impact on brain structural neuroplasticity. However, the dissociative experiences and hallucinations produced by these compounds will likely limit their widespread clinical use.

[00112] In an attempt to discover and develop a non- hallucinogenic, non-dissociative plastogenic compound that could be used to treat neuropsychiatric conditions with high unmet need, we synthesized Compound 1, and are examining its safety, tolerability, and pharmacokinetic (PK) profiles in a combined single- and multiple-ascending dose study in healthy volunteers. Compound 1 is a non-hallucinogenic and non-dissociative isotryptamine neuroplastogen currently undergoing initial human testing to treat those diagnosed with major depressive disorder (MDD) and other associated neuropsychiatric conditions. Preclinical data suggested that in efficacious doses, Compound 1 increased dendritic spine density in rat brain layer-V PFC pyramidal neurons and rapid and enduring antidepressant-like effects after a single dose. Recent Phase 1 data found Compound 1 to be safe and well tolerated in recently reported research, with no serious adverse events reported. In addition, researchers did not observe significant abnormalities among crucial safety indicators, including vital signs, electrocardiogram (ECG) readings, and laboratory analysis.

[00113] Neuroplastogens are a novel class of potentially disease-modifying therapeutics for psychiatric and neurological conditions. These compounds promote rapid and sustained neuroplasticity in selective neural circuits resulting in fast-acting therapeutic effects.

Neuroplastogens are chemical entities inspired by compounds that are proving to be beneficial across a range of therapeutic areas including mood, anxiety, cognitive, and neurodegenerative disorders in addition to other synaptopathies with differentiated profiles.

[00114] Methods

[00115] This 3-part inpatient study was being conducted in male and female healthy volunteers (HVs) aged 18 to 55. Part A is a randomized, double-blind, placebo- controlled single ascending dose (SAD) study to investigate the safety, tolerability, and PK of single- ascending oral doses of Compound 1 (8 participants per cohort). Part B is a standard, open-label, crossover design study to investigate the effect of food on the PK of Compound 1. In Part B, HVs received a single oral dose of Compound 1 on 2 separate occasions, one in a fed state and the other in a fasted state. The 2

treatments (fasted and fed) are separated by a 7-day washout period. Part C is a randomized, double-blind, placebo- controlled multiple ascending dose (MAD) study in which participants (8 per cohort) received multiple oral doses of either Compound 1 or placebo once a day for up to 7 days. Safety monitoring included clinical and laboratory assessments, serial 12-lead ECGs, vital signs, and emergence of suicidality (Columbia Suicide Severity Rating Scale - C-SSRS) or psychotic symptoms (Brief Psychiatric Rating Scale - BPRS). Pharmacodynamic assessments included clinical measures of psychedelic and psychotomimetic effects (Mystical Experience Questionnaire 30 – MEQ-30, Clinician-Administered Dissociative States Scale - CADSS), neuroendocrine effects, and serial quantitative resting state EEG. Non-compartmental PK analysis of plasma Compound 1 was performed up to 30h post-dose in the SAD and on Days 1 and 7 in the MAD. PK analysis of CSF concentrations of Compound 1 was performed in selected cohorts.

[00116] Brief Summary of Results

- (a) Compound 1 has been safe and well-tolerated in 62 healthy volunteers dosed to date.
- (b) No serious adverse events have been reported.
- (c) No clinically significant abnormalities in laboratory tests, vital signs, ECGs, or other safety measures (e.g., C-SSRS, EEG) have been observed.
- (d) All Treatment emergent adverse events (TEAE) have been mild in severity, and none have resulted in study drug discontinuation or withdrawal from the study.
- (e) The most common TEAEs to date include mild dizziness (n=8), mild headache (n=10), and mild nausea (n=10). These were dose-related, time-limited, and resolved without intervention.
- (f) No psychomimetic, hallucinatory, or dissociative effects have been observed, as reflected by no change over time on a robust battery of measures, including Clinician-Administered Dissociative States Scale (CADSS), Bond-Lader Visual Analogue Scales (VAS) (Mood Rating Scale) (B&L VAS), Bowdle VAS, and Mystical Experience Questionnaire (MEQ-30).
- (g) Data demonstrate that Compound 1 is orally bioavailable, achieves plasma exposures within the predicted therapeutic range, and achieves measurable levels within the Cerebrospinal fluid (CSF).
- (h) Pharmacokinetics demonstrate dose-proportionality across cohorts, limited food effect, and no accumulation over 7 days of administration.

[00117] Conclusions

- (a) Data from the ongoing Phase I study support the continued clinical development of Compound 1.

- (b) Clear demonstration of Compound 1's lack of psychomimetic, hallucinatory, or dissociative effects – in keeping with results from pre-clinical studies – provides “proof of platform” for growing library of non-hallucinogenic neuroplastogens.
- (c) Promotion of neuroplasticity plays a critical role in the efficacy and time to onset of antidepressant activity across different modalities (SSRIs, ketamine, ECT), and, as described herein, preclinical data demonstrated that Compound 1 produces rapid and durable increases in structural and functional neuroplasticity in prefrontal cortex (PFC) layer V pyramidal neurons.
- (d) Measurable CSF drug concentrations and observed increases in low frequency EEG bands coinciding with neuroendocrine effects support the conclusion that Compound 1 reaches the CNS and demonstrates central target engagement with no dissociative, hallucinatory or psychotomimetic effects.
- (e) Given its emerging clinical and preclinical profile, Compound 1 has the potential to address significant unmet needs within MDD and related neuropsychiatric disorders as a novel, fast-acting, outpatient oral pharmacotherapy.

[00118] Results

[00119] FIG. 7 illustrates the study schematic of the human clinical trial.

[00120] FIG. 8 illustrates the sample characteristics of subjects enrolled in the clinical trial.

[00121] FIG. 9 illustrates the TEAEs by preferred term of subjects enrolled in the clinical trial.

[00122] FIGs. 10A and 10B illustrate CADSS total score over time in subjects of the SAD cohort (**FIG. 10A**) and MAD cohort (**FIG. 10B**) respectively.

[00123] FIGs. 11A-11C illustrate bond and ladder (B&L) visual analogue scale mean value over time in subjects of the SAD cohort (**FIG. 11A**) and MAD cohort (**FIG. 11B**) respectively. **FIG. 5C** illustrates the B&L visual analogue scale.

[00124] FIGs. 12A-12D illustrate summary pharmacokinetics of Compound 1 in plasma of subjects of the SAD, Food Effect and MAD cohorts.

[00125] FIG. 13 illustrates the CSF/Plasma ratio of Compound 1.

1. Citation of Reference(Bond & Lader 1974)

Example 3: Effects of Compound 1 on Delta and Theta power as measured with EEG

[00126] EEG data represent electrical voltage differences between pairs of recording electrodes placed on the scalp. These electrical signals are caused by the summated electrical activity of excitatory and inhibitory postsynaptic potentials impinging on cortical pyramidal cell. Because of the insulating effects of the skull, scalp, and CSF, and the small intensity of the currents, extensive temporal and spatial summation of activity is necessary before neuronal electrical activity can be detected on the scalp.

[00127] Resting-state EEG recordings with open and closed eyes for 4 min in each eye state were performed. Each recording employed alternating periods with eyes open and closed with a duration of 64-seconds for each period. Subjects were positioned in a semi-recumbent position facing a featureless wall and were instructed not to stare, not to move their head and eyes, and to suppress eye blinks.

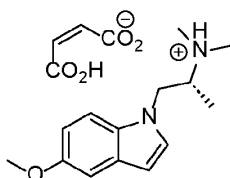
[00128] EEG was continuously recorded before and after administering Compound 1 using a 40-channel recording system (Refa-40, TMSi B.V., the Netherlands). Electrodes were placed according to the international 10-20 system (32-lead cap, TMSi B.V.). The results of the EEG study are shown in **FIG. 14A** and **FIG. 14B**. **FIG. 14A** shows an increase in Delta wave power post treatment with Compound 1. 20mg of Compound 1 increased Delta wave power by >26pp 305 minutes after administration. 60mg of Compound 1 increased Delta wave power by >26pp 101 to 305 minutes after administration. 120 mg of Compound 1 increased Delta wave power by >26pp at 63 minutes after administration, by >58pp 101 to 213 minutes after administration, and by >26pp 305 minutes after administration. Placebo control did not significantly increase Delta wave power at any timepoint. **FIG. 14B** shows an increase in Theta wave power post treatment with Compound 1. 2mg of Compound 1 increased Theta wave power by >26pp 488 minutes after administration. 6mg of Compound 1 increased Theta wave power by >26pp 63, 213, and 305 minutes after administration. 20mg of Compound 1 increased Theta wave power by >26pp 63 and 213 minutes after administration. 60 mg of Compound 1 increased Theta wave power by >26pp 63 minutes after administration, by > 58pp 101 minutes after administration, and by >26pp 213 and 305 minutes after administration. 120mg of Compound 1 increased Theta wave power by >58pp 63, 101, and 213 minutes after administration, and >26pp 305 and 488 minutes after administration. Placebo control increased Theta wave power by >26pp 101 minutes after administration.

[00129] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

We Claim:

1. A method of treating a neuropsychiatric disease or disorder in an individual in need thereof, comprising administering to the individual about 1 mg to about 500 mg of Compound 1 calculated by free base:



Compound 1.

2. The method of claim 1, wherein Compound 1 is administered to the individual daily.
3. The method of claim 1, wherein Compound 1 is administered once every 2 days.
4. The method of claim 1, wherein Compound 1 is administered 3 times a week.
5. The method of claim 1, wherein Compound 1 is administered for at least 3 days, or for at least 5 days, or for at least 7 days, or for at least 10 days, or for at least 14 days, or for at least 21 days, or for at least 28 days.
6. The method of claim 1, wherein Compound 1 is administered once every 7 days.
7. The method of any one of claims 1-6, wherein Compound 1 is administered orally.
8. The method of any one of claims 1-7, comprising administering about 50 mg to about 360 mg of Compound 1 calculated by free base.
9. The method of any one of claims 1-7, comprising administering about 1 mg to about 10 mg of Compound 1 calculated by free base.
10. The method of claim 9, comprising administering about 2 mg of Compound 1 calculated by free base.
11. The method of claim 9, comprising administering about 6 mg of Compound 1 calculated by free base.
12. The method of claim 9, comprising administering about 10 mg of Compound 1 calculated by free base.
13. The method of any one of claims 1-7, comprising administering about 10 mg to about 30 mg of Compound 1 calculated by free base.
14. The method of claim 13, comprising administering about 20 mg of Compound 1 calculated by free base.
15. The method of any one of claims 1-7, comprising administering about 30 mg to about 100 mg of Compound 1 calculated by free base.

16. The method of claim 15, comprising administering about 50 mg of Compound 1 calculated by free base.
17. The method of claim 15, comprising administering about 100 mg of Compound 1 calculated by free base.
18. The method of any one of claims 1-7, comprising administering about 60 mg to about 90 mg of Compound 1 calculated by free base.
19. The method of claim 18, comprising administering about 60 mg of Compound 1 calculated by free base.
20. The method of claim 18, comprising administering about 75 mg of Compound 1 calculated by free base.
21. The method of claim 18, comprising administering about 80 mg of Compound 1 calculated by free base.
22. The method of claim 18, comprising administering about 90 mg of Compound 1 calculated by free base.
23. The method of any one of claims 1-7, comprising administering about 100 mg to about 250 mg of Compound 1 calculated by free base.
24. The method of claim 23, comprising administering about 100 mg of Compound 1 calculated by free base.
25. The method of claim 23, comprising administering about 150 mg of Compound 1 calculated by free base.
26. The method of claim 23, comprising administering about 160 mg of Compound 1 calculated by free base.
27. The method of claim 23, comprising administering about 200 mg of Compound 1 calculated by free base.
28. The method of claim 23, comprising administering about 220 mg of Compound 1 calculated by free base.
29. The method of claim 23, comprising administering about 250 mg of Compound 1 calculated by free base.
30. The method of any one of claims 1-7, comprising administering about 120 mg to about 180 mg of Compound 1 calculated by free base.
31. The method of claim 30, comprising administering about 120 mg of Compound 1 calculated by free base.
32. The method of claim 30, comprising administering about 150 mg of Compound 1 calculated by free base.

33. The method of claim 30, comprising administering about 180 mg of Compound 1 calculated by free base.
34. The method of any one of claims 1-7, comprising administering about 240 mg to 360 mg of Compound 1 calculated by free base.
35. The method of claim 34, comprising administering about 240 mg of Compound 1 calculated by free base.
36. The method of claim 34, comprising administering about 250 mg of Compound 1 calculated by free base.
37. The method of claim 34, comprising administering about 300 mg of Compound 1 calculated by free base.
38. The method of claim 34, comprising administering about 350 mg of Compound 1 calculated by free base.
39. The method of claim 34, comprising administering about 360 mg of Compound 1 calculated by free base.
40. The method of any one of claims 1-39, wherein the neuropsychiatric disease comprises depression, addiction, anxiety, post-traumatic stress disorder, bipolar disorder, schizophrenia, or substance use disorder.
41. The method of any one of claims 1-39, wherein the neuropsychiatric disease comprises depression.
42. The method of any one of claims 1-39, wherein the neuropsychiatric disease is treatment resistant depression, major depressive disorder, suicidal ideation, or combinations thereof.
43. The method of any one of claims 1-39, wherein the neuropsychiatric disease comprises a major depressive disorder.
44. The method of any one of claims 1-43, wherein the individual demonstrates decreased depressive symptoms at the end of treatment compared to baseline, as measured by Montgomery-Åsberg Depression Rating Scale (MADRS).
45. The method of claim 44, wherein the MADRS score is reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%.
46. The method of any one of claims 1-45, wherein the individual demonstrates decreased depressive symptoms at the end of treatment compared to baseline, as measured by Clinician-Administered Dissociative States Scale (CADSS), Hamilton Rating Scale for Depression (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Clinical Global Impression – Improvement (CGI-I), Clinical Global Impression – Severity (CGI-S), 36-item short form survey (SF-36), speech

characteristics, Patient health questionnaire – 9 questions (PHQ-9), EuroQol Standardized Health Questionnaire (5-level) (EQ-5D-5L), or Cambridge Neuropsychological Test Automated Battery (CANTAB), including Psychomotor Vigilance Test (PVT), Cognition Kit N-Back test (N-Back), paired associates learning (PAL) or emotional bias task (EBT).

47. The method of any one of claims 1-46, wherein the individual demonstrates increased slow wave activity after administering Compound 1 compared to baseline prior to administering Compound 1, as measured by quantitative electroencephalographic (qEEG).

48. The method of claim 47, wherein the slow wave activity (e.g., delta band power or theta band power) is increased by at least about 10pp, at least about 20pp, at least about 30pp, at least about 40pp, at least about 50pp, at least about 60pp, at least about 70pp, at least about 80pp, at least about 90pp, or at least about 100pp between 0 to 24 hours after administering Compound 1.

49. The method of any one of claims 1-48, wherein the administering does not cause hallucinations, dissociative effects, or psychomimetic effects.

50. The method of claim 49, wherein the administering does not cause hallucinations, dissociative effects, or psychomimetic effects as determined by a Clinician-Administered Dissociative States Scale (CDSS), a Bond-Lader Visual Analog Scale (VAS), a Bowdle VAS, or a Revised Mystical Experience Questionnaire (MEQ-30), or a combination thereof.

51. The method of claim 50, wherein the CADSS value is less than 5, or is less than 3, or is less than 2, or is less than 1.

52. The method of claim 50 or 51, wherein the CADSS value is less than 5, or is less than 3, or is less than 2, or is less than 1 at any point after administering Compound 1.

53. The method of claim 50, wherein the Bond-Lader VAS value is between 25-75, or is between 30-70, or is between 35-65 for each measure on the scale.

54. The method of claim 50 or 53, wherein the Bond-Lader VAS value is between 25-75, or is between 30-70, or is between 35-65 for each measure on the scale at any point after administering Compound 1.

55. The method of any one of claims 1-54, wherein the administering does not cause cardiotoxicity.

56. The method of any one of claims 1-55, wherein a risk of the individual developing any serious treatment-emergent adverse event (TEAE) after the administering is less than about 60%, or less than about 50%, or less than about 40%, or less than about 30%, or less than about 20%, or less than about 10%, or less than about 5%.

57. The method of any one of claims 1-56, wherein the individual is fasted prior to the administering of Compound 1.

58. The method of any one of claims 1-56, wherein the individual is sated prior to the administering of Compound 1.
59. The method of any one of claims 1-56, wherein the individual is fasted or sated prior to the administering of Compound 1.
60. The method of any one of claims 1-59, wherein the individual has a diagnosis of major depressive disorder (MDD) that has been present for 12-week to 2 years.
61. The method of any one of claims 1-60, wherein the individual has a Hamilton Rating Scale for Depression, 17-item (HAM-D) total score of at least 22 prior to administering Compound 1.
62. The method of any one of claims 1-61, wherein the individual does not have psychosis or a history of psychosis.
63. The method of any one of claims 1-62, wherein the individual does not have seizures or a history of seizures.
64. The method of any one of claims 1-63, wherein the individual does not have bipolar disorder, schizophrenia, and/or a schizoaffective disorder.
65. The method of any one of claims 1-64, wherein the individual does not have a history of alcohol or drug dependence or use of psychedelics within the 12 months prior to administering Compound 1.
66. A pharmaceutical composition comprising about 1 mg to about 500 mg of Compound 1 calculated by free base.
67. The pharmaceutical composition of claim 66, wherein the composition comprises about 50 mg to about 200 mg of Compound 1 calculated by free base.
68. The pharmaceutical composition of claim 66, wherein the composition comprises about 2 mg, about 10 mg, or about 50 mg of Compound 1 calculated by free base.
69. The pharmaceutical composition of claim 66, wherein the composition comprises about 50 mg, about 100 mg, or about 200 mg of Compound 1 calculated by free base.
70. The pharmaceutical composition of claim 66, wherein the composition comprises about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 240 mg, about 300 mg, or about 360 mg of Compound 1 calculated by free base.
71. The pharmaceutical composition of claim 66, wherein the composition comprises about 100 mg, about 150 mg, or about 250 mg of Compound 1 calculated by free base.
72. The pharmaceutical composition of claim 66, wherein the composition comprises about 1 mg to about 10 mg of Compound 1 calculated by free base.
73. The pharmaceutical composition of claim 72, wherein the composition comprises about 2 mg of Compound 1 calculated by free base.

74. The pharmaceutical composition of claim 72, wherein the composition comprises about 6 mg of Compound 1 calculated by free base.
75. The pharmaceutical composition of claim 72, wherein the composition comprises about 10 mg of Compound 1 calculated by free base.
76. The pharmaceutical composition of claim 66, wherein the composition comprises about 10 mg to about 30 mg of Compound calculated by free base.
77. The pharmaceutical composition of claim 76, wherein the composition comprises about 20 mg of Compound 1 calculated by free base.
78. The pharmaceutical composition of claim 66, wherein the composition comprises about 30 mg to about 100 mg of Compound 1 calculated by free base.
79. The pharmaceutical composition of claim 78, wherein the composition comprises about 50 mg of Compound 1 calculated by free base.
80. The pharmaceutical composition of claim 78, wherein the composition comprises about 100 mg of Compound 1 calculated by free base.
81. The pharmaceutical composition of claim 66, wherein the composition comprises about 60 mg to 90 mg of Compound 1 calculated by free base.
82. The pharmaceutical composition of claim 81, wherein the composition comprises about 60 mg of Compound 1 calculated by free base.
83. The pharmaceutical composition of claim 81, wherein the composition comprises about 75 mg of Compound 1 calculated by free base.
84. The pharmaceutical composition of claim 81, wherein the composition comprises about 90 mg of Compound 1 calculated by free base.
85. The pharmaceutical composition of claim 66, wherein the composition comprises about 100 mg to about 250 mg of Compound 1 calculated by free base.
86. The pharmaceutical composition of claim 85, wherein the composition comprises about 100 mg of Compound 1 calculated by free base.
87. The pharmaceutical composition of claim 85, wherein the composition comprises about 150 mg of Compound 1 calculated by free base.
88. The pharmaceutical composition of claim 85, wherein the composition comprises about 160 mg of Compound 1 calculated by free base.
89. The pharmaceutical composition of claim 85, wherein the composition comprises about 200 mg of Compound 1 calculated by free base.
90. The pharmaceutical composition of claim 85, wherein the composition comprises about 220 mg of Compound 1 calculated by free base.

91. The pharmaceutical composition of claim 85, wherein the composition comprises about 250 mg of Compound 1 calculated by free base.
92. The pharmaceutical composition of claim 66, wherein the composition comprises about 120 mg to 180 mg of Compound 1 calculated by free base.
93. The pharmaceutical composition of claim 92, wherein the composition comprises about 120 mg of Compound 1 calculated by free base.
94. The pharmaceutical composition of claim 92, wherein the composition comprises about 150 mg of Compound 1 calculated by free base.
95. The pharmaceutical composition of claim 92, wherein the composition comprises about 180 mg of Compound 1 calculated by free base.
96. The pharmaceutical composition of claim 66, wherein the composition comprises about 250 mg to 500 mg of Compound 1 calculated by free base.
97. The pharmaceutical composition of claim 66, wherein the composition comprises about 240 mg to 360 mg of Compound 1 calculated by free base.
98. The pharmaceutical composition of claim 97, wherein the composition comprises about 240 mg of Compound 1 calculated by free base.
99. The pharmaceutical composition of claim 97, wherein the composition comprises about 300 mg of Compound 1 calculated by free base.
100. The pharmaceutical composition of claim 97, wherein the composition comprises about 360 mg of Compound 1 calculated by free base.
101. The pharmaceutical composition of any one of claims 66-100, wherein the pharmaceutical composition is a tablet or a capsule.
102. The pharmaceutical composition of claim 101, wherein the pharmaceutical composition is a capsule.
103. The pharmaceutical composition of claim 101, wherein the pharmaceutical composition is a tablet.
104. The pharmaceutical composition of any one of claims 66-103, wherein the composition further comprises at least one pharmaceutically acceptable excipient.
105. The pharmaceutical composition of any one of claims 66-104, wherein the composition further comprises hypromellose and titanium dioxide.