IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Confirmation No.: 2444
Serial No.: 18/244,078 Group No.:
Filing or 371(c) Date: September 08, 2023 Examiner:
Entitled: USE OF MDMA FOR TREATMENT OF STRESS-RELATED DISORDERS

THIRD-PARTY PRE-ISSUANCE SUBMISSION

Examiner:

The following documents, which are also identified in the Form PTO/SB/429 filed herewith, are submitted for your consideration as being of potential relevance to the examination of the present application

1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392
2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-206
3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022)
4. EROWID (2021) "Like a Happy Smiley Speed MDMA, Escitalopram & Divalproex" Retrieved 29 May 2021. URL: https://www.erowid.org/experiences/exp.php?ID=89532
5. EROWID (2021) "Unexpectedly Hard Tripping... All Good, Too" Retrieved 7 July 2021. URL: https://www.erowid.org/experiences/exp.php?ID=108919
6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182
7. FEDUCCIA (2019) "MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms?" *Progress in Neuropsychopharmacology & Biological Psychiatry*. Vol. 84: 221-228
8. MITCHELL (2021) "MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study" *Nature Medicine*. Vol 27: 1025-1033
9. KIYATKIN (2012) "Environmental Conditions Modulate Neurotoxic Effects of Psychomotor Stimulant Drugs of Abuse" *International Review of Neurobiology*. 102: 147–171

Attached hereto is a claim chart providing a concise description of the relevance of each reference in the document list of the elements of the presently pending claims.

U.S.S.N. 18/244,078 Pending Claims	References
1. A method of treating a stress-related disease or disorder in a subject comprising administering to the subject a therapeutically effective amount of a composition comprising R(?)-3,4-methylenedioxymethamphetamine (R(?)-MDMA) to lessen avoidance behavior, thereby treating the stress-related disease or disorder in the subject.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…" 1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **abstract** "**The use of (±)-3,4-methylenedioxymethamphetamine ((±)-MDMA) as an adjunct to psychotherapy in the treatment of psychiatric and behavioral disorders dates back over 50 years**. Only in recent years have controlled and peer-reviewed preclinical and clinical studies lent support to (±)-MDMA's hypothesized clinical utility. However, the clinical utility of (±)-MDMA is potentially mitigated by a range of demonstrated adverse effects. One potential solution could lie in the individual S(+) and R(−) enantiomers that comprise (±)-MDMA. **Individual enantiomers of racemic compounds have been employed in psychiatry to improve a drug's therapeutic index.** Although no research has explored the individual effects of either S(+)-MDMA or R(−)- MDMA in humans in a controlled manner, preclinical research has examined similarities and differences between the two molecules and the racemic compound. This review addresses information related to the pharmacodynamics, neurotoxicity, physiological effects, and behavioral effects of S(+)-MDMA and R(−)-MDMA that might guide preclinical and clinical research. The current preclinical evidence suggests that **R(−)-MDMA may provide an improved therapeutic index, maintaining the therapeutic effects of (±)-MDMA with a reduced side effect profile**, and that future investigations should investigate the therapeutic potential of R(−)-MDMA." 2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-206 From **abstract** "**S,R(+/−)-3,4-methylenedioxymethamphetamine (SR-MDMA)** is an amphetamine derivative with prosocial and putative therapeutic effects. Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions. However, its potential for adverse effects such as hyperthermia and neurotoxicity may limit its clinical viability. We investigated the hypothesis that one of the two enantiomers of SR-MDMA, **R-MDMA, would retain the prosocial and therapeutic effects but with fewer adverse effects**. Using male Swiss Webster and C57BL/6 mice, the prosocial effects of R-MDMA were measured using a social interaction test, and the therapeutic-like effects were assessed using a Pavlovian fear conditioning and extinction paradigm relevant to PTSD. Locomotor activity and body temperature were tracked after administration, and neurotoxicity was evaluated postmortem. **R-MDMA**

	significantly increased murine social interaction and facilitated extinction of conditioned freezing. Yet, unlike racemic MDMA, it did not increase locomotor activity, produce signs of neurotoxicity, or increase body temperature. A key pharmacological difference between R-MDMA and racemic MDMA is that R-MDMA has much lower potency as a dopamine releaser. Pretreatment with a selective dopamine D1 antagonist prevented SR-MDMA-induced hyperthermia, suggesting that differential dopamine signaling may explain some of the observed differences between the treatments. Together, these results indicate that the prosocial and therapeutic effects of SR-MDMA may be separable from the stimulant, thermogenic, and potential neurotoxic effects. To what extent these findings translate to humans will require further investigation, but **these data suggest that R-MDMA could be a more viable therapeutic option for the treatment of PTSD and other disorders** for which SR-MDMA is currently being investigated." From **page 12** "**The primary findings of the present study are that R-MDMA** increases social interaction and **facilitates extinction of a conditioned fear response** in a manner similar to racemic MDMA, yet even when administered at high repeated doses, it does not produce hyperthermia or evidence of neurotoxicity in mice."
2. The method of claim 1, wherein the stress-related disease or disorder is mood/depressive disorder, bipolar disorder, anxiety disorder, psychotic or delirium disorder, schizophrenia, schizoaffective disorder, personality disorder, abuse or neglect disorder, tic disorder, neurocognitive disorder, neurodevelopmental disorder, learning disorder, disruptive mood regulation disorder, intermittent explosive disorder, antisocial personality disorder, conduct disorder, behavioral	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic**

and psychological symptoms of dementia, depression, treatment resistant depression, anxiety, post-traumatic stress disorder (PTSD), or any combination thereof.	**compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
3. The method of claim 1, wherein the stress-related disease or disorder is selected from the group consisting of depression, anxiety, post-traumatic stress disorder (PTSD), and any combination thereof.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic**

	compound." From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
4. The method of claim 1, wherein R(?)-MDMA has antidepressant and anxiolytic effects.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators**… Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin…" From **[0174]** "In some embodiments, a compound of the present invention is used to increase neuronal plasticity. **In some embodiments, the compounds used to** increase neuronal plasticity have, for example, anti-addictive properties, **antidepressant properties, anxiolytic properties**, or a combination thereof. In some embodiments, decreased neuronal plasticity is associated with a neuropsychiatric disease. In some embodiments, the neuropsychiatric disease is a mood or anxiety disorder. In some embodiments, the neuropsychiatric disease includes, for example, migraine, cluster headache, post-traumatic stress disorder (PTSD), schizophrenia, anxiety, depression, and addiction (e.g., substance abuse disorder). In some embodiments, brain disorders include, for example, migraines, addiction (e.g., substance use disorder), depression, and anxiety."
5. The method of claim 1, wherein said therapeutically	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022)

effective amount comprises between about 1 mg/kg and 20 mg/kg R(?)-MDMA.	From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
6. The method of claim 1, wherein said therapeutically effective amount comprises between about 25 mg and 350 mg R(?)-MDMA.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, **30, 40, 50, 60, 70, 80, 90, 100, 200, 300**, 400, 500, 600, 700, 800, 900 or 1000 **mg**." From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**"

	From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
7. The method of claim 1, wherein said therapeutically effective amount comprises about 5 mg/kg R(?)-MDMA.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg. Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, **300, 400**, 500, 600, 700, 800, 900 or 1000 **mg**." From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present

	invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
8. The method of claim 1, wherein the administering comprises intracutaneous, subcutaneous, intravenous, intraarterial, intradermal, transdermal, oral, sublingual, buccal, or nasal route of administration.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0053]** "**"Administering" refers to oral administration**, administration as a suppository, topical contact, parenteral, **intravenous**, intraperitoneal, intramuscular, intralesional, **intranasal** or **subcutaneous** administration, intrathecal administration, or the implantation of a slow-release device e.g., a mini-osmotic pump, to the subject." From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are**

	hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example, 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
9. The method of claim 1, comprising administering R(?)-MDMA as a single dose.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0155]** "**The compounds of the present invention can be administered at any suitable frequency, interval and duration**. For example, the compound of the present invention can be administered once an hour, or two, three or more times an hour, once a day, or two, three, or more times per day, or once every 2, 3, 4, 5, 6, or 7 days, so as to provide the preferred dosage level. When the compound of the present invention is administered more than once a day, representative intervals include 5, 10, 15,

	20, 30, 45 and 60 minutes, as well as 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 hours. **The compound of the present invention can be administered once**, twice, or three or more times, for an hour, for 1 to 6 hours, for 1 to 12 hours, for 1 to 24 hours, for 6 to 12 hours, for 12 to 24 hours, for a single day, for 1 to 7 days, for a single week, for 1 to 4 weeks, for a month, for 1 to 12 months, for a year or more, or even indefinitely." From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
10. The method of claim 1, comprising administering R(?)-MDMA in repeated doses.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0155]** "**The compounds of the present invention can be administered at any suitable frequency, interval and duration**. For example, the compound of the present invention can be administered once an hour, or two, three or more times an hour, once a day, or two, three, or more times per day, or once every 2, 3, 4, 5, 6, or 7 days, so as to provide the preferred dosage level. When the compound of the present invention is administered more than once a day, representative intervals include 5, 10, 15, 20, 30, 45 and 60 minutes, as well as 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 hours. **The compound of the present invention can be administered once, twice, or three or more times, for an hour, for 1 to 6 hours, for 1 to 12 hours, for 1 to 24 hours, for 6 to 12 hours, for 12 to 24 hours, for a single day, for 1 to 7 days, for a single week, for 1 to 4 weeks, for a month, for 1 to 12 months, for a year or more, or even indefinitely.**" From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**"

	From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
11. The method of claim 1, further comprising administering a therapeutic agent.	2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-206 From **abstract** "S,R(+/−)-3,4-methylenedioxymethamphetamine **(SR-MDMA) is an amphetamine derivative with prosocial and putative therapeutic effects.** Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions." From **page 3** "**SR-MDMA is a racemic mixture of two enantiomers: R-MDMA** and S-MDMA." 4. EROWID (2021) "Like a Happy Smiley Speed MDMA, Escitalopram & Divalproex" Retrieved 29 May 2021. URL: https://www.erowid.org/experiences/exp.php?ID=89532 From **webpage** "I'd been prescribed to **Lexapro (SSRI) for about 2 or 3 months** and had just been put on the Depakote (as a mood stabilizer) about a week **prior to my experience with the MDMA**… …While waiting to pick up the drugs, I took advantage of the supertechnology that I keep in my pocket (known commonly as a smart phone) and **used google to look up the effects of MDMA when mixed with** both **Lexapro** and Depekote. From my research, I deduced that Depekote, when mixed with MDMA, has very few, if any, harmful effects, and that **Lexapro mixed with MDMA could produce a less intense roll,** …

	…12:00AM -- **My anxiety dissipates**. My mind and body begin to feel waves of calm and mild euphoria. I convince myself this is a placebo effect and that I'm just excited for the drug to actually kick in. 12:30AM -- The euphoria of both mind and body have set in, almost fully. **I feel no anxiety.** I feel completely comfortable in my own skin. This euphoria I feel is not near comparable in magnitude to the euphoria I've felt with opiates, but it still feels nice. I feel willing and ready to open myself up--**something I struggle with when sober due to severe Generalized Anxiety and Social Phobia**…. …***MDMA** -- (1 tablet on Night 1; 1 tablet on Night 2) brought me up, but was underwhelming. I honestly expected a deeper, more psychedelic experience than I got. Included feelings of mild euphoria. ***Lexapro** -- (30mg on Day 1; missed dose on Day 2) **SSRI/anti-depressant prescribed to inhibit the reuptake of serotin for sufferers of long-term/chronic depression**. Seemed to inhibit many effects of the MDMA"
12. The method of claim 11, wherein the therapeutic agent is a selective serotonin reuptake inhibitor (SSRI).	2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-206 From **abstract** "S,R(+/−)-3,4-methylenedioxymethamphetamine **(SR-MDMA) is an amphetamine derivative with prosocial and putative therapeutic effects.** Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions." From **page 3** "**SR-MDMA is a racemic mixture of two enantiomers: R-MDMA** and S-MDMA." 4. EROWID (2021) "Like a Happy Smiley Speed MDMA, Escitalopram & Divalproex" Retrieved 29 May 2021. URL: https://www.erowid.org/experiences/exp.php?ID=89532 From **webpage** "I'd been prescribed to **Lexapro (SSRI) for about 2 or 3 months** and had just been put on the Depakote (as a mood stabilizer) about a week **prior to my experience with the MDMA**… …While waiting to pick up the drugs, I took advantage of the supertechnology that I keep in my pocket (known commonly as a smart phone) and **used google to look up the effects of MDMA when mixed with** both **Lexapro** and Depekote. From my research, I deduced that Depekote, when mixed with MDMA, has very few, if any, harmful effects, and that **Lexapro mixed with**

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13. The method of claim 12, wherein the SSRI is fluoxetine, paroxetine, sertraline, escitalopram or citalopram.	2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-206 From **abstract** "S,R(+/−)-3,4-methylenedioxymethamphetamine **(SR-MDMA) is an amphetamine derivative with prosocial and putative therapeutic effects.** Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions." From **page 3** "**SR-MDMA is a racemic mixture of two enantiomers: R-MDMA** and S-MDMA." 4. EROWID (2021) "Like a Happy Smiley Speed MDMA, Escitalopram & Divalproex" Retrieved 29 May 2021. URL: https://www.erowid.org/experiences/exp.php?ID=89532 From **webpage** "I'd been prescribed to **Lexapro (SSRI) for about 2 or 3 months** and had just been put on the Depakote (as a mood stabilizer) about a week **prior to my experience with the MDMA**… …While waiting to pick up the drugs, I took advantage of the supertechnology that I keep in my pocket (known commonly as a smart phone) and **used google to look up the effects of MDMA when mixed with** both **Lexapro** and Depekote. From my research, I deduced that Depekote, when mixed with

	MDMA, has very few, if any, harmful effects, and that **Lexapro mixed with MDMA could produce a less intense roll,** … …12:00AM -- **My anxiety dissipates**. My mind and body begin to feel waves of calm and mild euphoria. I convince myself this is a placebo effect and that I'm just excited for the drug to actually kick in. 12:30AM -- The euphoria of both mind and body have set in, almost fully. **I feel no anxiety.** I feel completely comfortable in my own skin. This euphoria I feel is not near comparable in magnitude to the euphoria I've felt with opiates, but it still feels nice. I feel willing and ready to open myself up--**something I struggle with when sober due to severe Generalized Anxiety and Social Phobia**…. …***MDMA** -- (1 tablet on Night 1; 1 tablet on Night 2) brought me up, but was underwhelming. I honestly expected a deeper, more psychedelic experience than I got. Included feelings of mild euphoria. ***Lexapro** -- (30mg on Day 1; missed dose on Day 2) **SSRI/anti-depressant prescribed to inhibit the reuptake of serotin for sufferers of long-term/chronic depression**. Seemed to inhibit many effects of the MDMA"
14. The method of claim 13, comprising administering the therapeutic agent prior to, concurrently with or after R(?)-MDMA.	2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-206 From **abstract** "S,R(+/−)-3,4-methylenedioxymethamphetamine **(SR-MDMA) is an amphetamine derivative with prosocial and putative therapeutic effects.** Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions." From **page 3** "**SR-MDMA is a racemic mixture of two enantiomers: R-MDMA** and S-MDMA." 4. EROWID (2021) "Like a Happy Smiley Speed MDMA, Escitalopram & Divalproex" Retrieved 29 May 2021. URL: https://www.erowid.org/experiences/exp.php?ID=89532 From **webpage** "I'd been prescribed to **Lexapro (SSRI) for about 2 or 3 months** and had just been put on the Depakote (as a mood stabilizer) about a week **prior to my experience with the MDMA**… …While waiting to pick up the drugs, I took advantage of the supertechnology that I keep in my pocket (known commonly as a smart phone) and **used google to look up the effects of MDMA when mixed with** both **Lexapro** and

	Depekote. From my research, I deduced that Depekote, when mixed with MDMA, has very few, if any, harmful effects, and that **Lexapro mixed with MDMA could produce a less intense roll,** … …12:00AM -- **My anxiety dissipates**. My mind and body begin to feel waves of calm and mild euphoria. I convince myself this is a placebo effect and that I'm just excited for the drug to actually kick in. 12:30AM -- The euphoria of both mind and body have set in, almost fully. **I feel no anxiety.** I feel completely comfortable in my own skin. This euphoria I feel is not near comparable in magnitude to the euphoria I've felt with opiates, but it still feels nice. I feel willing and ready to open myself up--**something I struggle with when sober due to severe Generalized Anxiety and Social Phobia**…. …***MDMA** -- (1 tablet on Night 1; 1 tablet on Night 2) brought me up, but was underwhelming. I honestly expected a deeper, more psychedelic experience than I got. Included feelings of mild euphoria. ***Lexapro** -- (30mg on Day 1; missed dose on Day 2) **SSRI/anti-depressant prescribed to inhibit the reuptake of serotin for sufferers of long-term/chronic depression**. Seemed to inhibit many effects of the MDMA"
15. The method of claim 1, wherein the subject is also undergoing psychotherapy treatment.	2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-206 From **page 2** "The first of these trials found that just **two SR-MDMA-paired psychotherapy sessions significantly reduced the symptoms of post-traumatic stress disorder (PTSD)**, with a sustained clinical response in 83% of SR-MDMA-treated patients compared to just 25% of those treated with placebo-paired psychotherapy (Mithoefer et al., 2011)." From **abstract** "S,R(+/−)-3,4-methylenedioxymethamphetamine **(SR-MDMA) is an amphetamine derivative with prosocial and putative therapeutic effects.** Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions." From **page 3** "**SR-MDMA is a racemic mixture of two enantiomers: R-MDMA** and S-MDMA." 1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 383** "**Extinction principles are employed to treat anxiety,**

	phobia, and PTSD in the clinical setting through exposure therapy. Here, patients are repeatedly exposed to a fear eliciting stimulus in a safe setting." From **page 385** "**Increasing evidence supports the efficacy of (±)-MDMA as an adjunct to psychotherapy for the treatment of psychiatric disorders** that have heretofore been resistant to existing pharmacological approaches." From **abstract** "**The use of (±)-3,4-methylenedioxymethamphetamine ((±)-MDMA) as an adjunct to psychotherapy in the treatment of psychiatric and behavioral disorders dates back over 50 years**. Only in recent years have controlled and peer-reviewed preclinical and clinical studies lent support to (±)-MDMA's hypothesized clinical utility. However, the clinical utility of (±)-MDMA is potentially mitigated by a range of demonstrated adverse effects. One potential solution could lie in the individual S(+) and R(−) enantiomers that comprise (±)-MDMA. **Individual enantiomers of racemic compounds have been employed in psychiatry to improve a drug's therapeutic index.** Although no research has explored the individual effects of either S(+)-MDMA or R(−)- MDMA in humans in a controlled manner, preclinical research has examined similarities and differences between the two molecules and the racemic compound. This review addresses information related to the pharmacodynamics, neurotoxicity, physiological effects, and behavioral effects of S(+)-MDMA and R(−)-MDMA that might guide preclinical and clinical research. The current preclinical evidence suggests that **R(−)-MDMA may provide an improved therapeutic index, maintaining the therapeutic effects of (±)-MDMA with a reduced side effect profile**, and that future investigations should investigate the therapeutic potential of R(−)-MDMA."
16. The method of claim 15, wherein the psychotherapy treatment is cognitive processing therapy (CPT), cognitive behavioral therapy (CBT), prolonged exposure therapy (PET), brief eclectic psychotherapy (BEP), narrative exposure therapy (NAT), or eye-movement desensitization and reprocessing (EMDR).	2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-206 From **page 2** "The first of these trials found that just **two SR-MDMA-paired psychotherapy sessions significantly reduced the symptoms of post-traumatic stress disorder (PTSD)**, with a sustained clinical response in 83% of SR-MDMA-treated patients compared to just 25% of those treated with placebo-paired psychotherapy (Mithoefer et al., 2011)." From **abstract** "S,R(+/−)-3,4-methylenedioxymethamphetamine **(SR-MDMA) is an amphetamine derivative with prosocial and putative therapeutic effects.** Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions." From **page 3** "**SR-MDMA is a racemic mixture of two enantiomers: R-MDMA** and S-MDMA."

	1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 383** "**Extinction principles are employed to treat anxiety, phobia, and PTSD in the clinical setting through exposure therapy**. Here, patients are repeatedly exposed to a fear eliciting stimulus in a safe setting." From **page 385** "**Increasing evidence supports the efficacy of (±)-MDMA as an adjunct to psychotherapy for the treatment of psychiatric disorders** that have heretofore been resistant to existing pharmacological approaches." From **abstract** "**The use of (±)-3,4-methylenedioxymethamphetamine ((±)-MDMA) as an adjunct to psychotherapy in the treatment of psychiatric and behavioral disorders dates back over 50 years**. Only in recent years have controlled and peer-reviewed preclinical and clinical studies lent support to (±)-MDMA's hypothesized clinical utility. However, the clinical utility of (±)-MDMA is potentially mitigated by a range of demonstrated adverse effects. One potential solution could lie in the individual S(+) and R(−) enantiomers that comprise (±)-MDMA. **Individual enantiomers of racemic compounds have been employed in psychiatry to improve a drug's therapeutic index.** Although no research has explored the individual effects of either S(+)-MDMA or R(−)- MDMA in humans in a controlled manner, preclinical research has examined similarities and differences between the two molecules and the racemic compound. This review addresses information related to the pharmacodynamics, neurotoxicity, physiological effects, and behavioral effects of S(+)-MDMA and R(−)-MDMA that might guide preclinical and clinical research. The current preclinical evidence suggests that **R(−)-MDMA may provide an improved therapeutic index, maintaining the therapeutic effects of (±)-MDMA with a reduced side effect profile**, and that future investigations should investigate the therapeutic potential of R(−)-MDMA." 5. EROWID (2021) "Unexpectedly Hard Tripping... All Good, Too" Retrieved 7 July 2021. URL: https://www.erowid.org/experiences/exp.php?ID=108919 From **webpage** "**Had plenty of other drugs during that time, plenty of : mdma/pills**… …I was at a **CBT therapy session** the night before and cried heavily, and the lady reminded me tears wash away cortisol so could help relax me…" 8. MITCHELL (2021) "MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study" *Nature Medicine*. Vol 27: 1025-1033

	From **pages 1025-1026** "Likewise, **although evidenced-based trauma-focused psychotherapies such as prolonged exposure and cognitive behavioral therapy are considered to be the gold standard treatments for PTSD**8, many participants fail to respond or continue to have significant symptoms, and dropout rates are high9,10. Novel cost-effective therapeutics are therefore desperately needed11. The substituted amphetamine 3,4-methylenedioxymethamphetamine (MDMA) induces serotonin release by binding primarily to presynaptic serotonin transporters12. **MDMA has been shown to enhance fear memory extinction, modulate fear memory reconsolidation (possibly through an oxytocin-dependent mechanism), and bolster social behavior in animal models13,14. Pooled analysis of six phase 2 trials of MDMA-assisted therapy for PTSD have now shown promising safety and efficacy findings**15."
17. A method of activating 5-HT.sub.2A and 5-HT.sub.2C receptors in a subject comprising administering to the subject a composition comprising an effective amount of R(?)-3,4-methylenedioxymethamphetamine (R(?)-MDMA), thereby activating 5-HT.sub.2A and 5-HT.sub.2C receptors in the subject.	1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 386** "Although the mechanism underlying this synergy is not known, it may result from the distinct pharmacological effects of R(−)-MDMA and S(+)-MDMA that each contribute to the behavioral effects of (±)-MDMA. **R(−)-MDMA is a more potent 5-HT2A receptor agonist**, while S(+)-MDMA is a more potent 5-HT releaser."
18. The method of claim 17, wherein R(?)-MDMA is a partial agonist of 5-HT.sub.2A.	1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 380** "Additionally, **R(−)-MDMA more potently activates 5-HT2A second messenger signaling**, with S(+)-MDMA having very little effect and **R(−)-MDMA acting as a weak partial agonist** (Nash et al. 1994)."
19. The method of claim 17, wherein R(?)-MDMA induces neurite growth.	6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182 From **page 3171** "**Nearly all psychedelic compounds tested were capable of robustly promoting neuritogenesis**, with comparable effects being produced

	by tryptamines (N,N-dimethyltryptamine [DMT] and psilocin), amphetamines (2,5-dimethoxy-4-iodoamphetamine [DOI] and **MDMA**), and ergolines (lysergic acid diethylamide [LSD]).”
20. A method of decreasing side effects of 3,4-methylenedioxy-methamphetamine (MDMA) treatment comprising administering to the subject a therapeutically effective amount of a composition comprising R(?)-3,4-methylenedioxymethamphetamine (R(?)-MDMA) to lessen avoidance behavior in the subject, thereby decreasing side effects of MDMA treatment.	1. PITTS (2017) “(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA” *Psychopharmacology*. Vol. 235(2): 377-392 From **page 383** “**The fear response to the conditioned stimulus can be diminished, or extinguished, by repeatedly presenting it in the absence of the unconditioned stimulus**. **Extinction principles are employed to treat anxiety, phobia, and PTSD in the clinical setting through exposure therapy.** Here, patients are repeatedly exposed to a fear eliciting stimulus in a safe setting. It has been hypothesized that individuals with PTSD persistently experience powerful fear responses to reminders of trauma because of impairments in fear extinction processes, as many PTSD patients are resistant to exposure therapy… Notably, **R(−)-MDMA** did not reduce fear behavior during the fear extinction session, but **significantly reduced conditioned fear when retention of extinction was assessed the following day.”** 8. MITCHELL (2021) “MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study” *Nature Medicine*. Vol 27: 1025-1033 From **pages 1025-1026** “Likewise, **although evidenced-based trauma-focused psychotherapies such as prolonged exposure and cognitive behavioral therapy are considered to be the gold standard treatments for PTSD**8, many participants fail to respond or continue to have significant symptoms, and dropout rates are high9,10. Novel cost-effective therapeutics are therefore desperately needed11. The substituted amphetamine 3,4-methylenedioxymethamphetamine (MDMA) induces serotonin release by binding primarily to presynaptic serotonin transporters12. **MDMA has been shown to enhance fear memory extinction, modulate fear memory reconsolidation (possibly through an oxytocin-dependent mechanism), and bolster social behavior in animal models13,14. Pooled analysis of six phase 2 trials of MDMA-assisted therapy for PTSD have now shown promising safety and efficacy findings**15.”
21. The method of claim 20, wherein the subject has a stress-related disease or	1. PITTS (2017) “(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA” *Psychopharmacology*. Vol. 235(2): 377-392 From **page 383** “**The fear response to the conditioned stimulus can be**

disorder.	**diminished, or extinguished, by repeatedly presenting it in the absence of the unconditioned stimulus**. **Extinction principles are employed to treat anxiety, phobia, and PTSD in the clinical setting through exposure therapy.** Here, patients are repeatedly exposed to a fear eliciting stimulus in a safe setting. It has been hypothesized that individuals with PTSD persistently experience powerful fear responses to reminders of trauma because of impairments in fear extinction processes, as many PTSD patients are resistant to exposure therapy… Notably, **R(−)-MDMA** did not reduce fear behavior during the fear extinction session, but **significantly reduced conditioned fear when retention of extinction was assessed the following day."** 8. MITCHELL (2021) "MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study" *Nature Medicine*. Vol 27: 1025-1033 From **pages 1025-1026** "Likewise, **although evidenced-based trauma-focused psychotherapies such as prolonged exposure and cognitive behavioral therapy are considered to be the gold standard treatments for PTSD**8, many participants fail to respond or continue to have significant symptoms, and dropout rates are high9,10. Novel cost-effective therapeutics are therefore desperately needed11. The substituted amphetamine 3,4-methylenedioxymethamphetamine (MDMA) induces serotonin release by binding primarily to presynaptic serotonin transporters12. **MDMA has been shown to enhance fear memory extinction, modulate fear memory reconsolidation (possibly through an oxytocin-dependent mechanism), and bolster social behavior in animal models13,14. Pooled analysis of six phase 2 trials of MDMA-assisted therapy for PTSD have now shown promising safety and efficacy findings**15."
22. The method of claim 21, wherein the stress-related disease or disorder is mood/depressive disorder, bipolar disorder, anxiety disorder, psychotic or delirium disorder, schizophrenia, schizoaffective disorder, personality disorder, abuse or	1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 383** "**The fear response to the conditioned stimulus can be diminished, or extinguished, by repeatedly presenting it in the absence of the unconditioned stimulus**. **Extinction principles are employed to treat anxiety, phobia, and PTSD in the clinical setting through exposure therapy.** Here, patients are repeatedly exposed to a fear eliciting stimulus in a safe setting. It has been hypothesized that individuals with PTSD persistently experience powerful fear responses to reminders of trauma because of impairments in fear extinction processes, as many PTSD patients are resistant to exposure therapy…

neglect disorder, tic disorder, neurocognitive disorder, neurodevelopmental disorder, learning disorder, disruptive mood regulation disorder, intermittent explosive disorder, antisocial personality disorder, conduct disorder, behavioral and psychological symptoms of dementia, depression, treatment resistant depression, anxiety, post-traumatic stress disorder (PTSD), or any combination thereof.	Notably, **R(−)-MDMA** did not reduce fear behavior during the fear extinction session, but **significantly reduced conditioned fear when retention of extinction was assessed the following day."** 8. MITCHELL (2021) "MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study" *Nature Medicine*. Vol 27: 1025-1033 From **pages 1025-1026** "Likewise, **although evidenced-based trauma-focused psychotherapies such as prolonged exposure and cognitive behavioral therapy are considered to be the gold standard treatments for PTSD**8, many participants fail to respond or continue to have significant symptoms, and dropout rates are high9,10. Novel cost-effective therapeutics are therefore desperately needed11. The substituted amphetamine 3,4-methylenedioxymethamphetamine (MDMA) induces serotonin release by binding primarily to presynaptic serotonin transporters12. **MDMA has been shown to enhance fear memory extinction, modulate fear memory reconsolidation (possibly through an oxytocin-dependent mechanism), and bolster social behavior in animal models13,14. Pooled analysis of six phase 2 trials of MDMA-assisted therapy for PTSD have now shown promising safety and efficacy findings**15."
23. The method of claim 22, wherein the stress-related disease or disorder is PTSD.	1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 383** "**The fear response to the conditioned stimulus can be diminished, or extinguished, by repeatedly presenting it in the absence of the unconditioned stimulus**. **Extinction principles are employed to treat anxiety, phobia, and PTSD in the clinical setting through exposure therapy.** Here, patients are repeatedly exposed to a fear eliciting stimulus in a safe setting. It has been hypothesized that individuals with PTSD persistently experience powerful fear responses to reminders of trauma because of impairments in fear extinction processes, as many PTSD patients are resistant to exposure therapy… Notably, **R(−)-MDMA** did not reduce fear behavior during the fear extinction session, but **significantly reduced conditioned fear when retention of extinction was assessed the following day."** 8. MITCHELL (2021) "MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study" *Nature*

	Medicine. Vol 27: 1025-1033 From **pages 1025-1026** "Likewise, **although evidenced-based trauma-focused psychotherapies such as prolonged exposure and cognitive behavioral therapy are considered to be the gold standard treatments for PTSD**8, many participants fail to respond or continue to have significant symptoms, and dropout rates are high9,10. Novel cost-effective therapeutics are therefore desperately needed11. The substituted amphetamine 3,4-methylenedioxymethamphetamine (MDMA) induces serotonin release by binding primarily to presynaptic serotonin transporters12. **MDMA has been shown to enhance fear memory extinction, modulate fear memory reconsolidation (possibly through an oxytocin-dependent mechanism), and bolster social behavior in animal models13,14. Pooled analysis of six phase 2 trials of MDMA-assisted therapy for PTSD have now shown promising safety and efficacy findings**15."
24. The method of claim 20, wherein the side effects are cardiovascular effects, hyperthermia, neurotoxicity or a combination thereof.	1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 382** "Few studies have assessed the toxicity of the individual enantiomers, **but there is some compelling evidence from rodent studies that the neurotoxicity of (±)-MDMA is driven by the S(+) enantiomer, and that R(−)-MDMA has substantially lower or potentially no neurotoxicity.** Reactive gliosis, which is a reliable marker of neurotoxicity (O'Callaghan and Miller 1993), is evident 48 h following a high-dose regimen of (±)-MDMA in mice (Frau et al. 2013; Curry et al. 2017)… **Thus, the lack of hyperthermia following R(−)-MDMA administration may play a role in the decreased risk for neurotoxicity**…R(−)-MDMA's low efficacy as a DA releaser, compared to (±)-MDMA or S(+)-MDMA (Hiramatsu and Cho 1990; Acquas et al. 2007; Murnane et al. 2010), may also decrease its potential for neurotoxicity…**Thus, the lack of DA release by R(−)-MDMA presents a viable explanation for the lack of observed neurotoxicity following administration of this enantiomer in mice and rats**." From **page 386** "Critically, even at higher doses, R(−)- MDMA is well tolerated in mice, with no evidence of neurotoxicity or other adverse effects (Curry et al. 2017), suggesting **R(−)-MDMA alone is also a promising therapeutic."** 8. MITCHELL (2021) "MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study" *Nature Medicine*. Vol 27: 1025-1033 From **pages 1025-1026** "Likewise, **although evidenced-based trauma-focused psychotherapies such as prolonged exposure and cognitive**

	behavioral therapy are considered to be the gold standard treatments for PTSD8, many participants fail to respond or continue to have significant symptoms, and dropout rates are high9,10. Novel cost-effective therapeutics are therefore desperately needed11. The substituted amphetamine 3,4-methylenedioxymethamphetamine (MDMA) induces serotonin release by binding primarily to presynaptic serotonin transporters12. **MDMA has been shown to enhance fear memory extinction, modulate fear memory reconsolidation (possibly through an oxytocin-dependent mechanism), and bolster social behavior in animal models13,14. Pooled analysis of six phase 2 trials of MDMA-assisted therapy for PTSD have now shown promising safety and efficacy findings**15."
25. The method of claim 24, wherein the cardiovascular effects are increased blood pressure, increased heart rate or a combination thereof.	1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 385-386** "This is particularly problematic **because (±)-MDMA significantly increases blood pressure above hypertensive thresholds in both PTSD patients** and healthy subjects (Mithoefer et al. 2011; Vizeli and Liechti 2017). **While the specific cardiovascular effects of R(−)-MDMA have not been assessed in humans or animals, pharmacogenetic studies suggest that (±)-MDMA's cardiovascular effects may be mediated primarily by its S(+) enantiomer.** The acute hypertensive effects of (±)-MDMA are significantly exacerbated in individuals with reduced rates of CYP2C19-dependent metabolism, which has been demonstrated to be highly enantioselective for S(+)-MDMA across multiple metabolic pathways (Meyer et al. 2008; Vizeli et al 2017). While further research is needed, **R(−)-MDMA may be a safer treatment for PTSD patients with contraindicating comorbid disorders**."
26. The method of claim 24, wherein neurotoxicity comprises mood disorder, cognition disorder and/or psychomotor deficits.	1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 383** "**The fear response to the conditioned stimulus can be diminished, or extinguished, by repeatedly presenting it in the absence of the unconditioned stimulus**. **Extinction principles are employed to treat anxiety, phobia, and PTSD in the clinical setting through exposure therapy.** Here, patients are repeatedly exposed to a fear eliciting stimulus in a safe setting. It has been hypothesized that individuals with PTSD persistently experience powerful fear responses to reminders of trauma because of impairments in fear extinction processes, as many PTSD patients are resistant to exposure therapy… Notably, **R(−)-MDMA** did not reduce fear behavior during the fear extinction session, but **significantly reduced conditioned fear when retention of**

	extinction was assessed the following day." From **page 382** "Few studies have assessed the toxicity of the individual enantiomers, **but there is some compelling evidence from rodent studies that the neurotoxicity of (±)-MDMA is driven by the S(+) enantiomer, and that R(−)-MDMA has substantially lower or potentially no neurotoxicity.** Reactive gliosis, which is a reliable marker of neurotoxicity (O'Callaghan and Miller 1993), is evident 48 h following a high-dose regimen of (±)-MDMA in mice (Frau et al. 2013; Curry et al. 2017)… **Thus, the lack of hyperthermia following R(−)-MDMA administration may play a role in the decreased risk for neurotoxicity**…R(−)-MDMA's low efficacy as a DA releaser, compared to (±)-MDMA or S(+)-MDMA (Hiramatsu and Cho 1990; Acquas et al. 2007; Murnane et al. 2010), may also decrease its potential for neurotoxicity…**Thus, the lack of DA release by R(−)-MDMA presents a viable explanation for the lack of observed neurotoxicity following administration of this enantiomer in mice and rats**." 9. KIYATKIN (2012) "Environmental Conditions Modulate Neurotoxic Effects of Psychomotor Stimulant Drugs of Abuse" *International Review of Neurobiology*. 102: 147–171 From **page 147** "**Psychomotor stimulants** such as methamphetamine (METH), amphetamine, and **3,4-Metylenedioxymethamphetamine (MDMA** or ecstasy) **are** potent addictive **drugs with neurotoxic properties**."
27. The method of claim 20, wherein. R(?)-MDMA has antidepressant and anxiolytic effects	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators**… Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin…" From **[0174]** "In some embodiments, a compound of the present invention is used to increase neuronal plasticity. **In some embodiments, the compounds used to** increase neuronal plasticity have, for example, anti-addictive properties, **antidepressant properties, anxiolytic properties**, or a combination thereof. In some embodiments, decreased neuronal plasticity is associated with a neuropsychiatric disease. In some embodiments, the neuropsychiatric disease is a mood or anxiety disorder. In some embodiments, the neuropsychiatric disease includes, for example, migraine, cluster headache, post-traumatic stress disorder (PTSD), schizophrenia, anxiety, depression, and addiction (e.g., substance abuse disorder). In some embodiments, brain

	disorders include, for example, migraines, addiction (e.g., substance use disorder), depression, and anxiety."
28. The method of claim 20, wherein said therapeutically effective amount comprises between about 1 mg/kg and 20 mg/kg R(?)-MDMA.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**"
29. The method of claim 19, wherein the administering comprises intracutaneous,	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0053]** "**"Administering" refers to oral administration**, administration as a suppository, topical contact, parenteral, **intravenous**, intraperitoneal,

subcutaneous, intravenous, intraarterial, intradermal, transdermal, oral, sublingual, buccal, or nasal route of administration.	intramuscular, intralesional, **intranasal** or **subcutaneous** administration, intrathecal administration, or the implantation of a slow-release device e.g., a mini-osmotic pump, to the subject." From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"

30. A method for inducing neurite outgrowth in a subject comprising administering to the subject a therapeutically effective amount of a composition comprising R(?)-3,4-methylenedioxymethamphetamine (R(?)-MDMA) to lessen avoidance behavior in the subject, thereby inducing neurite outgrowth in the subject.	6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182 From **page 3171** "**Nearly all psychedelic compounds tested were capable of robustly promoting neuritogenesis**, with comparable effects being produced by tryptamines (N,N-dimethyltryptamine [DMT] and psilocin), amphetamines (2,5-dimethoxy-4-iodoamphetamine [DOI] and **MDMA**), and ergolines (lysergic acid diethylamide [LSD])." 1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 383** "**The fear response to the conditioned stimulus can be diminished, or extinguished, by repeatedly presenting it in the absence of the unconditioned stimulus**. **Extinction principles are employed to treat anxiety, phobia, and PTSD in the clinical setting through exposure therapy.** Here, patients are repeatedly exposed to a fear eliciting stimulus in a safe setting. It has been hypothesized that individuals with PTSD persistently experience powerful fear responses to reminders of trauma because of impairments in fear extinction processes, as many PTSD patients are resistant to exposure therapy… Notably, **R(−)-MDMA** did not reduce fear behavior during the fear extinction session, but **significantly reduced conditioned fear when retention of extinction was assessed the following day."**
31. The method of claim 30, wherein neurite outgrowth comprises neurite number, neurite total length, number of neurite branch points per neuron or any combination thereof.	6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182 From **page 3171** "**Nearly all psychedelic compounds tested were capable of robustly promoting neuritogenesis**, with comparable effects being produced by tryptamines (N,N-dimethyltryptamine [DMT] and psilocin), amphetamines (2,5-dimethoxy-4-iodoamphetamine [DOI] and **MDMA**), and ergolines (lysergic acid diethylamide [LSD])." From **page 3171** "**This increase in arbor complexity appeared to result from large changes in both the number of dendritic branches and the total length of the arbors** (Figures 1F, 1H, S1F, and S1H). Psychedelics had a limited effect on the number of primary dendrites and did not alter the length of the longest dendrite (Figures 1G, 1I, S1G, and S1I)."
32. The method of claim 30, wherein the	6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182

neurite outgrowth comprises neurite outgrowth on prefrontal cortex neurons and/or hippocampal neurons.	From **page 3170** "**Atrophy of neurons in the prefrontal cortex (PFC) plays a key role in the pathophysiology of depression and related disorders**… A preponderance of evidence from a combination of human imaging, postmortem studies, and animal models suggests that **atrophy of neurons in the prefrontal cortex (PFC) plays a key role in the pathophysiology of depression and related disorders and is precipitated and/or exacerbated by stress** (Arnsten, 2009; Autry and Monteggia, 2012; Christoffel et al., 2011; Duman and Aghajanian, 2012; Duman et al., 2016; Izquierdo et al., 2006; Pittenger and Duman, 2008; Qiao et al., 2016; Russo and Nestler, 2013)." From **page 3171** "**Nearly all psychedelic compounds tested were capable of robustly promoting neuritogenesis**, with comparable effects being produced by tryptamines (N,N-dimethyltryptamine [DMT] and psilocin), amphetamines (2,5-dimethoxy-4-iodoamphetamine [DOI] and **MDMA**), and ergolines (lysergic acid diethylamide [LSD])." From **page 3171** "**This increase in arbor complexity appeared to result from large changes in both the number of dendritic branches and the total length of the arbors** (Figures 1F, 1H, S1F, and S1H). Psychedelics had a limited effect on the number of primary dendrites and did not alter the length of the longest dendrite (Figures 1G, 1I, S1G, and S1I)."
33. The method of claim 30, wherein said therapeutically effective amount comprises between about 1 mg/kg and 20 mg/kg R(?)-MDMA.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor**

	assay in agonist mode, whereas compounds, such as, for example, 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
34. The method of claim 30, wherein the subject has a stress-related disease or disorder.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900**

	or 1000 mg." From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
35. The method of	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-

claim 34, wherein the stress-related disease or disorder is mood/depressive disorder, bipolar disorder, anxiety disorder, psychotic or delirium disorder, schizophrenia, schizoaffective disorder, personality disorder, abuse or neglect disorder, tic disorder, neurocognitive disorder, neurodevelopmental disorder, learning disorder, disruptive mood regulation disorder, intermittent explosive disorder, antisocial personality disorder, conduct disorder, behavioral and psychological symptoms of dementia, depression, treatment resistant depression, anxiety, post-traumatic stress disorder (PTSD) or any combination thereof.	b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
36. The method of claim 35, wherein the stress-related disease or disorder is PTSD.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**"

	From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
37. A method of treating neuronal atrophy in a subject comprising administering to the subject a therapeutically effective amount of a composition comprising R(?)-3,4-methylenedioxymethamphetamine (R(?)-MDMA) to lessen avoidance behavior in the subject, thereby treating neuronal atrophy in the subject.	6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182 From **page 3170** "**Atrophy of neurons in the prefrontal cortex (PFC) plays a key role in the pathophysiology of depression and related disorders**… A preponderance of evidence from a combination of human imaging, postmortem studies, and animal models suggests that **atrophy of neurons in the prefrontal cortex (PFC) plays a key role in the pathophysiology of depression and related disorders and is precipitated and/or exacerbated by stress** (Arnsten, 2009; Autry and Monteggia, 2012; Christoffel et al., 2011; Duman and Aghajanian, 2012; Duman et al., 2016; Izquierdo et al., 2006; Pittenger and Duman, 2008; Qiao et al., 2016; Russo and Nestler, 2013)." From **page 3171** "**Nearly all psychedelic compounds tested were capable of robustly promoting neuritogenesis**, with comparable effects being produced by tryptamines (N,N-dimethyltryptamine [DMT] and psilocin), amphetamines (2,5-dimethoxy-4-iodoamphetamine [DOI] and **MDMA**), and ergolines (lysergic acid diethylamide [LSD])." From **page 3171** "**This increase in arbor complexity appeared to result from large changes in both the number of dendritic branches and the total length of the arbors** (Figures 1F, 1H, S1F, and S1H). Psychedelics had a limited effect on the number of primary dendrites and did not alter the length of the longest dendrite (Figures 1G, 1I, S1G, and S1I)."

	1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 383** "**The fear response to the conditioned stimulus can be diminished, or extinguished, by repeatedly presenting it in the absence of the unconditioned stimulus**. **Extinction principles are employed to treat anxiety, phobia, and PTSD in the clinical setting through exposure therapy.** Here, patients are repeatedly exposed to a fear eliciting stimulus in a safe setting. It has been hypothesized that individuals with PTSD persistently experience powerful fear responses to reminders of trauma because of impairments in fear extinction processes, as many PTSD patients are resistant to exposure therapy… Notably, **R(−)-MDMA** did not reduce fear behavior during the fear extinction session, but **significantly reduced conditioned fear when retention of extinction was assessed the following day."**
38. The method of claim 37, wherein administration of R(?)-MDMA induces neurite outgrowth.	6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182 From **page 3170** "**Atrophy of neurons in the prefrontal cortex (PFC) plays a key role in the pathophysiology of depression and related disorders**… A preponderance of evidence from a combination of human imaging, postmortem studies, and animal models suggests that **atrophy of neurons in the prefrontal cortex (PFC) plays a key role in the pathophysiology of depression and related disorders and is precipitated and/or exacerbated by stress** (Arnsten, 2009; Autry and Monteggia, 2012; Christoffel et al., 2011; Duman and Aghajanian, 2012; Duman et al., 2016; Izquierdo et al., 2006; Pittenger and Duman, 2008; Qiao et al., 2016; Russo and Nestler, 2013)." From **page 3171** "**Nearly all psychedelic compounds tested were capable of robustly promoting neuritogenesis**, with comparable effects being produced by tryptamines (N,N-dimethyltryptamine [DMT] and psilocin), amphetamines (2,5-dimethoxy-4-iodoamphetamine [DOI] and **MDMA**), and ergolines (lysergic acid diethylamide [LSD])." From **page 3171** "**This increase in arbor complexity appeared to result from large changes in both the number of dendritic branches and the total length of the arbors** (Figures 1F, 1H, S1F, and S1H). Psychedelics had a limited effect on the number of primary dendrites and did not alter the length of the longest dendrite (Figures 1G, 1I, S1G, and S1I)."

	1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 383** "**The fear response to the conditioned stimulus can be diminished, or extinguished, by repeatedly presenting it in the absence of the unconditioned stimulus**. **Extinction principles are employed to treat anxiety, phobia, and PTSD in the clinical setting through exposure therapy.** Here, patients are repeatedly exposed to a fear eliciting stimulus in a safe setting. It has been hypothesized that individuals with PTSD persistently experience powerful fear responses to reminders of trauma because of impairments in fear extinction processes, as many PTSD patients are resistant to exposure therapy… Notably, **R(−)-MDMA** did not reduce fear behavior during the fear extinction session, but **significantly reduced conditioned fear when retention of extinction was assessed the following day."**
39. The method of claim 38, wherein neurite outgrowth comprises increasing neurite number, neurite total length, number of neurite branch points per neuron or any combination thereof.	6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182 From **page 3171** "**Nearly all psychedelic compounds tested were capable of robustly promoting neuritogenesis**, with comparable effects being produced by tryptamines (N,N-dimethyltryptamine [DMT] and psilocin), amphetamines (2,5-dimethoxy-4-iodoamphetamine [DOI] and **MDMA**), and ergolines (lysergic acid diethylamide [LSD])." From **page 3171** "**This increase in arbor complexity appeared to result from large changes in both the number of dendritic branches and the total length of the arbors** (Figures 1F, 1H, S1F, and S1H). Psychedelics had a limited effect on the number of primary dendrites and did not alter the length of the longest dendrite (Figures 1G, 1I, S1G, and S1I)."
40. The method of claim 38, wherein the neurite outgrowth comprises neurite outgrowth on prefrontal cortex neurons and/or hippocampal neurons.	6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182 From **page 3170** "**Atrophy of neurons in the prefrontal cortex (PFC) plays a key role in the pathophysiology of depression and related disorders**… A preponderance of evidence from a combination of human imaging, postmortem studies, and animal models suggests that **atrophy of neurons in the prefrontal cortex (PFC) plays a key role in the pathophysiology of depression and related disorders and is precipitated and/or exacerbated by stress** (Arnsten, 2009; Autry and Monteggia, 2012; Christoffel et al., 2011; Duman and Aghajanian, 2012; Duman et al., 2016; Izquierdo et al., 2006; Pittenger and Duman, 2008; Qiao et al., 2016; Russo and Nestler, 2013)."

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41. The method of claim 37, wherein said therapeutically effective amount comprises between about 1 mg/kg and 20 mg/kg R(?)-MDMA.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention

	that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
42. The method of claim 37, wherein the subject has a stress related disorder.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor**

	assay in agonist mode, whereas compounds, such as, for example, 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
43. The method of claim 42, wherein the stress-related disease or disorder is mood/depressive disorder, bipolar disorder, anxiety disorder, psychotic or delirium disorder, schizophrenia, schizoaffective disorder, personality	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900**

disorder, abuse or neglect disorder, tic disorder, neurocognitive disorder, neurodevelopmental disorder, learning disorder, disruptive mood regulation disorder, intermittent explosive disorder, antisocial personality disorder, conduct disorder, behavioral and psychological symptoms of dementia, depression, treatment resistant depression, anxiety, post-traumatic stress disorder (PTSD) or any combination thereof or any combination thereof.	**or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
44. The method of	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-

claim 43, wherein the stress-related disease or disorder is PTSD.	b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
45. A method of inducing structural neuroplasticity in a subject comprising administering to the subject a therapeutically effective amount of a composition comprising R(?)-3,4-methylenedioxymethamphetamine (R(?)-MDMA), thereby inducing structural neuroplasticity in the subject.	6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182 From **page 3171** "**Nearly all psychedelic compounds tested were capable of robustly promoting neuritogenesis**, with comparable effects being produced by tryptamines (N,N-dimethyltryptamine [DMT] and psilocin), amphetamines (2,5-dimethoxy-4-iodoamphetamine [DOI] and **MDMA**), and ergolines (lysergic acid diethylamide [LSD])." 1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 383** "**The fear response to the conditioned stimulus can be diminished, or extinguished, by repeatedly presenting it in the absence of the unconditioned stimulus**. **Extinction principles are employed to treat anxiety, phobia, and PTSD in the clinical setting through exposure therapy.** Here, patients are repeatedly exposed to a fear eliciting stimulus in a safe setting. It has been hypothesized that individuals with PTSD persistently experience powerful fear responses to reminders of trauma because of impairments in fear extinction processes, as many PTSD patients are resistant to exposure therapy… Notably, **R(−)-MDMA** did not reduce fear behavior during the fear extinction session, but **significantly reduced conditioned fear when retention of extinction was assessed the following day."** 3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators**… Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-

	DET, L-MDMA, **R-MDMA**, Ketanserin…" From **[0174]** "In some embodiments, a compound of the present invention is used to increase neuronal plasticity. **In some embodiments, the compounds used to increase neuronal plasticity** have, for example, anti-addictive properties, **antidepressant properties, anxiolytic properties**, or a combination thereof. In some embodiments, decreased neuronal plasticity is associated with a neuropsychiatric disease. In some embodiments, the neuropsychiatric disease is a mood or anxiety disorder. In some embodiments, the neuropsychiatric disease includes, for example, migraine, cluster headache, post-traumatic stress disorder (PTSD), schizophrenia, anxiety, depression, and addiction (e.g., substance abuse disorder). In some embodiments, brain disorders include, for example, migraines, addiction (e.g., substance use disorder), depression, and anxiety."
46. The method of claim 45, wherein administration of R(?)-MDMA induces neurite outgrowth.	6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182 From **page 3171** "**Nearly all psychedelic compounds tested were capable of robustly promoting neuritogenesis**, with comparable effects being produced by tryptamines (N,N-dimethyltryptamine [DMT] and psilocin), amphetamines (2,5-dimethoxy-4-iodoamphetamine [DOI] and **MDMA**), and ergolines (lysergic acid diethylamide [LSD])." From **page 3171** "**This increase in arbor complexity appeared to result from large changes in both the number of dendritic branches and the total length of the arbors** (Figures 1F, 1H, S1F, and S1H). Psychedelics had a limited effect on the number of primary dendrites and did not alter the length of the longest dendrite (Figures 1G, 1I, S1G, and S1I)."
47. The method of claim 46, wherein neurite outgrowth comprises increasing neurite number, neurite total length, number of neurite branch points per neuron or a combination thereof.	6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182 From **page 3171** "**Nearly all psychedelic compounds tested were capable of robustly promoting neuritogenesis**, with comparable effects being produced by tryptamines (N,N-dimethyltryptamine [DMT] and psilocin), amphetamines (2,5-dimethoxy-4-iodoamphetamine [DOI] and **MDMA**), and ergolines (lysergic acid diethylamide [LSD])." From **page 3171** "**This increase in arbor complexity appeared to result from large changes in both the number of dendritic branches and the total length of the arbors** (Figures 1F, 1H, S1F, and S1H). Psychedelics had a limited effect on the number of primary dendrites and did not alter the length of the longest dendrite (Figures 1G, 1I, S1G, and S1I)."

48. The method of claim 46, wherein the neurite outgrowth comprises neurite outgrowth on prefrontal cortex neurons and/or hippocampal neurons.	6. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports*. Vol. 23(11): 3170-3182 From **page 3170** "**Atrophy of neurons in the prefrontal cortex (PFC) plays a key role in the pathophysiology of depression and related disorders**… A preponderance of evidence from a combination of human imaging, postmortem studies, and animal models suggests that **atrophy of neurons in the prefrontal cortex (PFC) plays a key role in the pathophysiology of depression and related disorders and is precipitated and/or exacerbated by stress** (Arnsten, 2009; Autry and Monteggia, 2012; Christoffel et al., 2011; Duman and Aghajanian, 2012; Duman et al., 2016; Izquierdo et al., 2006; Pittenger and Duman, 2008; Qiao et al., 2016; Russo and Nestler, 2013)." From **page 3171** "**Nearly all psychedelic compounds tested were capable of robustly promoting neuritogenesis**, with comparable effects being produced by tryptamines (N,N-dimethyltryptamine [DMT] and psilocin), amphetamines (2,5-dimethoxy-4-iodoamphetamine [DOI] and **MDMA**), and ergolines (lysergic acid diethylamide [LSD])." From **page 3171** "**This increase in arbor complexity appeared to result from large changes in both the number of dendritic branches and the total length of the arbors** (Figures 1F, 1H, S1F, and S1H). Psychedelics had a limited effect on the number of primary dendrites and did not alter the length of the longest dendrite (Figures 1G, 1I, S1G, and S1I)."
49. The method of claim 45, wherein said therapeutically effective amount comprises between about 1 mg/kg and 20 mg/kg R(?)-MDMA.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover,

	compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
50. The method of claim 52, wherein the subject has a stress-related disease or disorder.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.**

	Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"

51. The method of claim 50, wherein the stress-related disease or disorder is mood/depressive disorder, bipolar disorder, anxiety disorder, psychotic or delirium disorder, schizophrenia, schizoaffective disorder, personality disorder, abuse or neglect disorder, tic disorder, neurocognitive disorder, neurodevelopmental disorder, learning disorder, disruptive mood regulation disorder, intermittent explosive disorder, antisocial personality disorder, conduct disorder, behavioral and psychological symptoms of dementia, depression, treatment resistant depression, anxiety, post-traumatic stress disorder (PTSD) or any combination thereof.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
52. The method of claim 51, wherein the stress-related disease or disorder is PTSD.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that**

	does not activate the sensor in agonist mode is a non-hallucinogenic compound." From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
53. A method of increasing brain-derived neurotrophic factor (BDNF) levels in a subject comprising administering to the subject a therapeutically effective amount of a composition comprising R(?)-3,4-methylenedioxymethamphetamine (R(?)-MDMA) to lessen avoidance behavior, thereby increasing BDNF levels in the subject.	7. FEDUCCIA (2019) "MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms?" *Progress in Neuropsychopharmacology & Biological Psychiatry*. Vol. 84: 221-228 From **page 225** "**Given MDMA's strong propensity to release** 5-HT and NE, **BDNF** involvement in MDMA-driven memory reconsolidation and fear extinction is plausible and has been demonstrated in rodents. **After extinction training with MDMA, expression of the early-response gene Fos and Bdnf in the amygdala of mice was increased**; however, MDMA without training failed to show these effects. Direct infusion of MDMA (1 μg) into the basolateral amygdala (BLA) also enhanced extinction training which was blocked by disrupting of BDNF signaling in this region, suggesting that **MDMA augments fear extinction learning in the amygdala through a BDNF-dependent mechanism** (Young et al., 2015)… In rats, high doses of MDMA (20 mg/kg, s.c. repeated for 4 days), although not in range with human therapeutic doses (approximately 1–3 mg/kg), improved spatial learning and reference memory processes in the Morris water maze compared to saline treated animals. **An increase in glutamate and BDNF expression accompanied by an enhancement of spine densities in the CA1 region of the hippocampus was reported for the MDMA trained group**."

	2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-206 From **page 2** "The first of these trials found that just **two SR-MDMA-paired psychotherapy sessions significantly reduced the symptoms of post-traumatic stress disorder (PTSD)**, with a sustained clinical response in 83% of SR-MDMA-treated patients compared to just 25% of those treated with placebo-paired psychotherapy (Mithoefer et al., 2011)." From **abstract** "S,R(+/−)-3,4-methylenedioxymethamphetamine **(SR-MDMA) is an amphetamine derivative with prosocial and putative therapeutic effects.** Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions." From **page 3** "**SR-MDMA is a racemic mixture of two enantiomers: R-MDMA** and S-MDMA."
54. The method of claim 53, wherein increasing BDNF levels comprises increasing cerebral cortex and hippocampal BDNF levels.	7. FEDUCCIA (2019) "MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms?" *Progress in Neuropsychopharmacology & Biological Psychiatry*. Vol. 84: 221-228 From **page 225** "**Given MDMA's strong propensity to release** 5-HT and NE, **BDNF** involvement in MDMA-driven memory reconsolidation and fear extinction is plausible and has been demonstrated in rodents. **After extinction training with MDMA, expression of the early-response gene Fos and Bdnf in the amygdala of mice was increased**; however, MDMA without training failed to show these effects. Direct infusion of MDMA (1 μg) into the basolateral amygdala (BLA) also enhanced extinction training which was blocked by disrupting of BDNF signaling in this region, suggesting that **MDMA augments fear extinction learning in the amygdala through a BDNF-dependent mechanism** (Young et al., 2015)… In rats, high doses of MDMA (20 mg/kg, s.c. repeated for 4 days), although not in range with human therapeutic doses (approximately 1–3 mg/kg), improved spatial learning and reference memory processes in the Morris water maze compared to saline treated animals. **An increase in glutamate and BDNF expression accompanied by an enhancement of spine densities in the CA1 region of the hippocampus was reported for the MDMA trained group**." 2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-

	206 From **page 2** "The first of these trials found that just **two SR-MDMA-paired psychotherapy sessions significantly reduced the symptoms of post-traumatic stress disorder (PTSD)**, with a sustained clinical response in 83% of SR-MDMA-treated patients compared to just 25% of those treated with placebo-paired psychotherapy (Mithoefer et al., 2011)." From **abstract** "S,R(+/−)-3,4-methylenedioxymethamphetamine **(SR-MDMA) is an amphetamine derivative with prosocial and putative therapeutic effects.** Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions." From **page 3** "**SR-MDMA is a racemic mixture of two enantiomers: R-MDMA** and S-MDMA."
55. The method of claim 53, wherein increasing BDNF levels increases neuronal survival and synaptic plasticity.	7. FEDUCCIA (2019) "MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms?" *Progress in Neuropsychopharmacology & Biological Psychiatry*. Vol. 84: 221-228 From **page 225** "**MDMA may play a role in facilitating synaptic plasticity in the hippocampus** and amygdala through cholinergic signaling." From **page 225** "**Given MDMA's strong propensity to release** 5-HT and NE, **BDNF** involvement in MDMA-driven memory reconsolidation and fear extinction is plausible and has been demonstrated in rodents. **After extinction training with MDMA, expression of the early-response gene Fos and Bdnf in the amygdala of mice was increased**; however, MDMA without training failed to show these effects. Direct infusion of MDMA (1 μg) into the basolateral amygdala (BLA) also enhanced extinction training which was blocked by disrupting of BDNF signaling in this region, suggesting that **MDMA augments fear extinction learning in the amygdala through a BDNF-dependent mechanism** (Young et al., 2015)… In rats, high doses of MDMA (20 mg/kg, s.c. repeated for 4 days), although not in range with human therapeutic doses (approximately 1–3 mg/kg), improved spatial learning and reference memory processes in the Morris water maze compared to saline treated animals. **An increase in glutamate and BDNF expression accompanied by an enhancement of spine densities in the CA1 region of the hippocampus was reported for the MDMA trained group**." 2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-

	206 From **page 2** "The first of these trials found that just **two SR-MDMA-paired psychotherapy sessions significantly reduced the symptoms of post-traumatic stress disorder (PTSD)**, with a sustained clinical response in 83% of SR-MDMA-treated patients compared to just 25% of those treated with placebo-paired psychotherapy (Mithoefer et al., 2011)." From **abstract** "S,R(+/−)-3,4-methylenedioxymethamphetamine **(SR-MDMA) is an amphetamine derivative with prosocial and putative therapeutic effects.** Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions." From **page 3** "**SR-MDMA is a racemic mixture of two enantiomers: R-MDMA** and S-MDMA."
56. The method of claim 53, wherein said therapeutically effective amount comprises between about 1 mg/kg and 20 mg/kg R(?)-MDMA.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From [0154] "**The compound of the present invention can be present in any suitable amount**, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. **Suitable dosage ranges for the compound of the present invention include from about** 0.1 mg to about 10,000 mg, or **about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg.** Suitable dosages for the compound of the present invention include about 1 mg, 5, 10, 20, 30, 40, 50, 60, **70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg."** From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode

	or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…" 7. FEDUCCIA (2019) "MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms?" *Progress in Neuropsychopharmacology & Biological Psychiatry*. Vol. 84: 221-228 From **page 225** "**MDMA may play a role in facilitating synaptic plasticity in the hippocampus** and amygdala through cholinergic signaling." From **page 225** "**Given MDMA's strong propensity to release** 5-HT and NE, **BDNF** involvement in MDMA-driven memory reconsolidation and fear extinction is plausible and has been demonstrated in rodents. **After extinction training with MDMA, expression of the early-response gene Fos and Bdnf in the amygdala of mice was increased**; however, MDMA without training failed to show these effects. Direct infusion of MDMA (1 μg) into the basolateral amygdala (BLA) also enhanced extinction training which was blocked by disrupting of BDNF signaling in this region, suggesting that **MDMA augments fear extinction learning in the amygdala through a BDNF-dependent mechanism** (Young et al., 2015)… In rats, high doses of

	MDMA (20 mg/kg, s.c. repeated for 4 days), although not in range with human therapeutic doses (approximately 1–3 mg/kg), improved spatial learning and reference memory processes in the Morris water maze compared to saline treated animals. **An increase in glutamate and BDNF expression accompanied by an enhancement of spine densities in the CA1 region of the hippocampus was reported for the MDMA trained group**." 2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-206 From **page 2** "The first of these trials found that just **two SR-MDMA-paired psychotherapy sessions significantly reduced the symptoms of post-traumatic stress disorder (PTSD)**, with a sustained clinical response in 83% of SR-MDMA-treated patients compared to just 25% of those treated with placebo-paired psychotherapy (Mithoefer et al., 2011)." From **abstract** "S,R(+/−)-3,4-methylenedioxymethamphetamine **(SR-MDMA) is an amphetamine derivative with prosocial and putative therapeutic effects.** Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions." From **page 3** "**SR-MDMA is a racemic mixture of two enantiomers: R-MDMA** and S-MDMA."
57. The method of claim 53, wherein the subject has a stress-related disease or disorder.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor

	assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…" 7. FEDUCCIA (2019) "MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms?" *Progress in Neuropsychopharmacology & Biological Psychiatry*. Vol. 84: 221-228 From **page 225** "**MDMA may play a role in facilitating synaptic plasticity in the hippocampus** and amygdala through cholinergic signaling." From **page 225** "**Given MDMA's strong propensity to release** 5-HT and NE, **BDNF** involvement in MDMA-driven memory reconsolidation and fear extinction is plausible and has been demonstrated in rodents. **After extinction training with MDMA, expression of the early-response gene Fos and Bdnf in the amygdala of mice was increased**; however, MDMA without training failed to show these effects. Direct infusion of MDMA (1 μg) into the basolateral amygdala (BLA) also enhanced extinction training which was blocked by disrupting of BDNF signaling in this region, suggesting that **MDMA augments fear extinction learning in the amygdala through a**

	BDNF-dependent mechanism (Young et al., 2015)… In rats, high doses of MDMA (20 mg/kg, s.c. repeated for 4 days), although not in range with human therapeutic doses (approximately 1–3 mg/kg), improved spatial learning and reference memory processes in the Morris water maze compared to saline treated animals. **An increase in glutamate and BDNF expression accompanied by an enhancement of spine densities in the CA1 region of the hippocampus was reported for the MDMA trained group**." 2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-206 From **page 2** "The first of these trials found that just **two SR-MDMA-paired psychotherapy sessions significantly reduced the symptoms of post-traumatic stress disorder (PTSD)**, with a sustained clinical response in 83% of SR-MDMA-treated patients compared to just 25% of those treated with placebo-paired psychotherapy (Mithoefer et al., 2011)." From **abstract** "S,R(+/−)-3,4-methylenedioxymethamphetamine **(SR-MDMA) is an amphetamine derivative with prosocial and putative therapeutic effects.** Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions." From **page 3** "**SR-MDMA is a racemic mixture of two enantiomers: R-MDMA** and S-MDMA."
58. The method of claim 57, wherein the stress-related disease or disorder is mood/depressive disorder, bipolar disorder, anxiety disorder, psychotic or delirium disorder, schizophrenia, schizoaffective disorder, personality disorder, abuse or neglect disorder, tic disorder, neurocognitive disorder, neurodevelopmental	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential

disorder, learning disorder, disruptive mood regulation disorder, intermittent explosive disorder, antisocial personality disorder, conduct disorder, behavioral and psychological symptoms of dementia, depression, treatment resistant depression, anxiety, post-traumatic stress disorder (PTSD) or any combination thereof.	of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…" 7. FEDUCCIA (2019) "MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms?" *Progress in Neuropsychopharmacology & Biological Psychiatry*. Vol. 84: 221-228 From **page 225** "**MDMA may play a role in facilitating synaptic plasticity in the hippocampus** and amygdala through cholinergic signaling." From **page 225** "**Given MDMA's strong propensity to release** 5-HT and NE, **BDNF** involvement in MDMA-driven memory reconsolidation and fear extinction is plausible and has been demonstrated in rodents. **After extinction training with MDMA, expression of the early-response gene Fos and Bdnf in the amygdala of mice was increased**; however, MDMA without training failed to show these effects. Direct infusion of MDMA (1 μg) into the basolateral amygdala (BLA) also enhanced extinction training which was blocked by disrupting of BDNF signaling in this region, suggesting that

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59. The method of claim 58, wherein the stress-related disease or disorder is PTSD.	7. FEDUCCIA (2019) "MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms?" *Progress in Neuropsychopharmacology & Biological Psychiatry*. Vol. 84: 221-228 From **page 225** "**MDMA may play a role in facilitating synaptic plasticity in the hippocampus** and amygdala through cholinergic signaling." From **page 225** "**Given MDMA's strong propensity to release** 5-HT and NE, **BDNF** involvement in MDMA-driven memory reconsolidation and fear extinction is plausible and has been demonstrated in rodents. **After extinction training with MDMA, expression of the early-response gene Fos and Bdnf in the amygdala of mice was increased**; however, MDMA without training failed to show these effects. Direct infusion of MDMA (1 μg) into the basolateral amygdala (BLA) also enhanced extinction training which was blocked by disrupting of BDNF signaling in this region, suggesting that

	MDMA augments fear extinction learning in the amygdala through a BDNF-dependent mechanism (Young et al., 2015)… In rats, high doses of MDMA (20 mg/kg, s.c. repeated for 4 days), although not in range with human therapeutic doses (approximately 1–3 mg/kg), improved spatial learning and reference memory processes in the Morris water maze compared to saline treated animals. **An increase in glutamate and BDNF expression accompanied by an enhancement of spine densities in the CA1 region of the hippocampus was reported for the MDMA trained group**." 2. CURRY (2018) "Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice" *Neuropharmacology*. Vol. 128: 196-206 From **page 2** "The first of these trials found that just **two SR-MDMA-paired psychotherapy sessions significantly reduced the symptoms of post-traumatic stress disorder (PTSD)**, with a sustained clinical response in 83% of SR-MDMA-treated patients compared to just 25% of those treated with placebo-paired psychotherapy (Mithoefer et al., 2011)." From **abstract** "S,R(+/−)-3,4-methylenedioxymethamphetamine **(SR-MDMA) is an amphetamine derivative with prosocial and putative therapeutic effects.** Ongoing clinical trials are investigating it as a **treatment for post-traumatic stress disorder (PTSD)** and other conditions." From **page 3** "**SR-MDMA is a racemic mixture of two enantiomers: R-MDMA** and S-MDMA."
60. A pharmaceutical composition comprising R(?)-MDMA and a pharmaceutically acceptable carrier.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0141]** "For preparing pharmaceutical compositions from the compounds of the present invention, **pharmaceutically acceptable carriers** can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules…" From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor**

	assay in agonist mode, whereas compounds, such as, for example, 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"
61. The pharmaceutical composition of claim 52, wherein the pharmaceutically acceptable carrier is saline or purified water.	3. U.S. Pat. No. 11414423 "Substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles for treating brain disorders" (Published August 16, 2022) From **[0145]** "**Liquid form preparations include** solutions, suspensions, and emulsions, for example, **water** or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution." From **[0141]** "For preparing pharmaceutical compositions from the compounds of the present invention, **pharmaceutically acceptable carriers** can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules,

	cachets, suppositories, and dispersible granules…" From **[0163]** "In some embodiments, **the compounds of the present invention have activity as 5-HT.sub.2A modulators. In some embodiments, the compounds of the present invention have activity as 5-HT.sub.2A modulators**…Hallucinogens (e.g., LSD and 5-MeO-DMT) activate a 5HT.sub.2A sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) do not (FIG. 15). Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, **which are hallucinogenic in animals (e.g., humans), activate the 5HT.sub.2A sensor assay in agonist mode, whereas compounds, such as, for example,** 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, **R-MDMA**, Ketanserin, BOL148, **which are non-hallucinogenic in animals (e.g., humans), do not activate the 5HT.sub.2A sensor assay in agonist mode** (FIG. 16, at 10 ?M of compound). In some embodiments, hallucinogenic potential of a compound of the present invention is determined in vitro. In some embodiments, hallucinogenic potential of a compound of the present invention is determined using a 5HT.sub.2A sensor assay. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the 5HT.sub.2A sensor assay is in an agonist mode. In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode has non-hallucinogenic potential. **In some embodiments, a compound of the present invention that does not activate the sensor in agonist mode is a non-hallucinogenic compound.**" From **[0161]** "In some embodiments, a compound of the **present invention is used to treat neurological diseases**. In some embodiments, the compounds have, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof. 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…"

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
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Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	65356627	FILING DATE	05/12/2023
CUSTOMER #	–	FIRST NAMED INVENTOR	
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 8

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
third-party-preissuance-submission.pdf		2	Third-Party Submission Under 37 CFR 1.290	51 KB
Concise-description-generated.pdf		2	Concise Description of Relevance	28 KB
Third-party-notification-request.pdf		1	Request for Notification of Non-compliant Third-Party Submission	14 KB
Claims_Chart.pdf		60	-	1017 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-60)	60	Concise Description of Relevance	859 KB
Claims_Chart-	(1-60)	60	Concise Description of	859 KB

3P.RELEVANCE.pdf			Relevance	
Claims_Chart-3P.RELEVANCE.pdf	(1-60)	60	Concise Description of Relevance	859 KB
2_SHEKUNOV.pdf		25	-	877 KB
2_SHEKUNOV-NPL.pdf	(1-25)	25	Non Patent Literature	845 KB
3_ANASTOS.pdf		6	-	1015 KB
3_ANASTOS-NPL.pdf	(1-6)	6	Non Patent Literature	1006 KB

Digest

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