IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Mind Medicine, Inc.	Confirmation No.: 4343
Serial No.:	18/186,764	Group No.:
Filing or 371(c) Date:	20 March 2023	Examiner:

Entitled: MDMA ENANTIOMERS

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. PETERS (2005) "Drug Testing in Blood: Validated Negative-Ion Chemical Ionization Gas Chromatographic–Mass Spectrometric Assay for Enantioselective Measurement of the Designer Drugs MDEA, MDMA, and MDA and Its Application to Samples from a Controlled Study with MDMA" *Clinical Chemistry*. Vol. 51(10): 1811-1822
4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "RYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021)
5. EROWID (2020) "MDMA Dosage by Erowid" Retrieved 24 May 2020. URL: https://www.erowid.org/chemicals/mdma/mdma_dose.shtml
6. EROWID (2017) "MDA Dosage by Erowid" Retrieved 6 September 2017. https://www.erowid.org/chemicals/mda/mda_dose.shtml
7. PIZARRO (2004) "Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites in human samples including the catechol-type metabolite (3,4-dihydroxymethamphetamine)" *Drug Metabolism and Disposition*. Vol. 32(9): 1001-1007

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

U.S.S.N. 18/186,764 Pending Claims	References
1. A composition for use in psychotherapeutic treatment comprising an R(−) enantiomer of MDMA or MDA.	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." ***From the application of interest 18/186,764 paragraph [0006]*** *"**MDMA has two enantiomers, S(+)-MDMA and R(−)-MDMA**."* 4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, prodrugs, **stereoisomers**, or tautomers thereof." From **[0087]** "**Certain compounds described herein may exist in particular geometric or stereoisomeric forms**. A particular enantiomer of a compound described herein may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to **provide the pure desired enantiomers**. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-

	active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent **recovery of the pure enantiomers**." From [0090] "**Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.** The compounds or compositions described herein may contain an enantiomeric excess of at least 50%, 75%, 90%, 95%, or 99% of one form of the compound, e.g., the S-enantiomer. In other words, such compounds or compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. From [0091] "**Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer and may also be referred to as "optically enriched."** "Optically enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. **In other embodiments, the compound is made up of at least about** 95%, 98%, or **99% by weight of a preferred enantiomer.** Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses…" From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
2. The composition of claim 1, wherein said R(−) enantiomer of MDMA or MDA is present in an amount of 10-1000 mg.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 18** "The composition of claim 8, wherein the composition comprises 0.1 mg to 1 mg, 1 mg to 10 mg, **10 mg to 100 mg, 10 mg to 50 mg, 50 mg to 100 mg, 20 mg to 80 mg, 20 mg to 50 mg, 50 mg to 100 mg, 50 mg to 80 mg, or 10 mg to 80 mg** of one or more **phenethylamines** or amphetamines or an amount of a plant or mushroom extract or plant or mushroom to provide an equivalent dose." From **[0150]** "In one embodiment, **the dose of the phenethylamines,** amphetamines, erinacines, hericenones, cannabinoids one or more adversive compounds such as niacin, capsaicin, ipecac, apomorphine, bittering agents, or an amount of a mushroom or plant extract or mushroom or plant having

	an equivalent amount of about **0.1 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg, 1 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg**." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**..." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, prodrugs, **stereoisomers**, or tautomers thereof." From **[0087]** "**Certain compounds described herein may exist in particular geometric or stereoisomeric forms**. A particular enantiomer of a compound described herein may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to **provide the pure desired enantiomers**. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent **recovery of the pure enantiomers**." From [0090] "**Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.** The compounds or compositions described herein may contain an enantiomeric excess of at least 50%, 75%, 90%, 95%, or 99% of one form of the compound, e.g., the S-enantiomer. In other words, such compounds or compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. From [0091] "**Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer and may also be referred to as "optically enriched."** "Optically enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. **In other embodiments, the compound is made up of at least about** 95%, 98%, or **99% by weight of a preferred enantiomer.** Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses…"

From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."

7. PIZARRO (2004) "Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites in human samples including the catechol-type metabolite (3,4-dihydroxymethamphetamine)" *Drug Metabolism and Disposition*. Vol. 32(9): 1001-1007

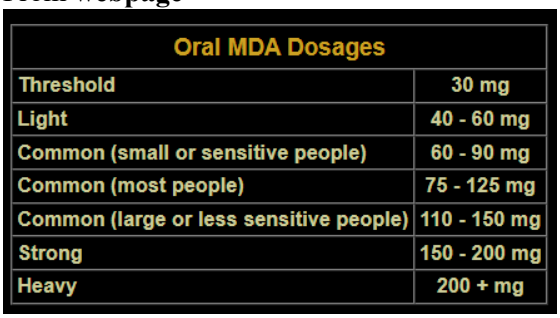
From page **1001** "**3,4-Methylenedioxymethamphetamine (MDMA**; "ecstasy") is a designer drug commonly misused in large segments of young populations. **MDMA is usually formulated in tablets of its racemate (1:1 mixture of its enantiomers) in doses ranging from 50 to 200 mg**. MDMA has an enantioselective metabolism, the (S)-enantiomer being metabolized faster than the **(R)-enantiomer**. Different pharmacologic properties have been attributed to each enantiomer. The carbon responsible for MDMA chirality is preserved along its metabolic disposition. **An analytical method has been developed to determine MDMA enantiomers and those from its major metabolites, 3,4-methylenedioxyamphetamine (MDA),** 3,4-dihydroxymethamphetamine (HHMA), and 4-hydroxy-3-methoxymethamphetamine (HMMA)."

5. EROWID (2020) "MDMA Dosage by Erowid" Retrieved 24 May 2020. URL: https://www.erowid.org/chemicals/mdma/mdma_dose.shtml

From **webpage**

Oral MDMA Dosages	
Threshold	30 mg
Light	40 - 75 mg
Common (small or sensitive people)	60 - 90 mg
Common (most people)	75 - 125 mg
Common (large or less sensitive people)	110 - 150 mg
Strong	150 - 200 mg
Heavy	200 + mg

From **webpage** "**Chemical analysis of ecstasy tablets has found from 0 - 120 mg of MDMA as well as a variety of the above substances.** Trying to calculate dosages from tablets containing unknown quantities of MDMA can

	be difficult, but **a high quality tablet of street ecstasy (those containing MDMA alone) generally contains between 80 and 120 mg of MDMA**. **Some unusual tablets (especially in Europe) contain 150mg or more**. The chart below shows what are considered recreational/therapeutic dosages for pure MDMA HCl (the most common crystalline form), measured in milligrams." 6. EROWID (2017) "MDA Dosage by Erowid" Retrieved 6 September 2017. https://www.erowid.org/chemicals/mda/mda_dose.shtml From **webpage**  **Oral MDA Dosages** **Threshold** 30 mg **Light** 40 - 60 mg **Common (small or sensitive people)** 60 - 90 mg **Common (most people)** 75 - 125 mg **Common (large or less sensitive people)** 110 - 150 mg **Strong** 150 - 200 mg **Heavy** 200 + mg From **webpage** "Erowid's current view is that **the required dose of MDA vs MDMA are very similar, but result in slightly different effects** (MDA is more physically stimulating while MDMA is more empathogenic at the same dose)."
3. The composition of claim 1, wherein said R(−) enantiomer of MDMA or MDA includes a prodrug bound thereto.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable

	salts, hydrates, solvates, **prodrugs**, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
4. The composition of claim 3, wherein said prodrug is an amino acid chosen from the group consisting of lysine, alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0178]** "**amino acids are selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine**, ornithine, citrulline, taurine, selenocysteine, pyrrolysine, aminobutyric acid, gama-aminobutryic acid, 3-aminopropanoic acid, dehydroalanine, delta-carboxyglutamic acid, N-formylmethionine."
5. The composition of claim 1, wherein said composition is in a continual slow-release formulation.	***From the application of interest 18/186,764 paragraph [0029]*** *"Using the R(−) enantiomer allows for daily use of MDMA or MDA. The compositions are particularly useful in* ***continual slow-release formulations, such as transdermal patches, that can provide a low dose over a long period of time****. The compositions can also be administered in an intranasal spray."* 4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0108]** "The pharmaceutically acceptable compositions of this disclosure may also be **administered topically**, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract can be administered using a rectal suppository formulation (see above) or a suitable enema formulation. **Topically transdermal patches may also be used**." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof."

6. The composition of claim 1, wherein said composition is in an intranasal spray form.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0110]** "The pharmaceutically acceptable compositions of this disclosure may also be **administered by nasal aerosol or inhalation.** Such compositions are prepared according to techniques known in the art of pharmaceutical formulation and may **be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, or other conventional solubilizing or dispersing agents…**" From **[0104]** "The compositions described herein may be **administered** orally, parenterally, **by inhalation spray**, topically, rectally, **nasally**, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques…" From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof."
7. The composition of claim 1, wherein said composition is in a liquid dosage form chosen from the group consisting of suspensions, solutions, emulsions, elixirs, tinctures, sprays, syrups, gels, magmas, liniments, lotions, ointments, pastes, drops, and inhalants.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0144]** "Another embodiment is a method for manufacturing a dosage form comprising formulating a composition as described herein comprising **sprays**, capsules, tablets, **elixirs, emulsions**, lozenges, **suspensions, syrups**, pills, **lotions**, epidermal patches, suppositories, inhalers, or injectables. Any methods known to the art for formulating extracts or active principal ingredients into lotions, soaps, etc. may be utilized." From **[0109]** "For **topical applications**, the pharmaceutically acceptable compositions may be formulated in a suitable **ointment** containing the active component suspended or dissolved in one or more carriers..." From **[0110]** "The pharmaceutically acceptable compositions of this disclosure may also be administered by nasal aerosol or **inhalation**..."
8. The composition of claim 1, wherein said composition is in an oral dosage form chosen from the group consisting of capsules,	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0144]** "Another embodiment is a method for manufacturing a dosage form comprising formulating a composition as described herein comprising

films, lozenge, patch, powder, tablets, pellets, pills, and troches.	sprays, **capsules, tablets**, elixirs, emulsions, **lozenges**, suspensions, syrups, **pills**, lotions, **epidermal patches**, suppositories, inhalers, or injectables. Any methods known to the art for formulating extracts or active principal ingredients into lotions, soaps, etc. may be utilized." From **claim 21** "The composition of claim 1, wherein the composition is a **powder admixture**, liquid, suspension, or emulsion."
9. A method of treating an individual for a medical condition, including the steps of: administering an effective amount of a composition of an R(−) enantiomer of MDMA or MDA; and treating the individual.	7. PIZARRO (2004) "Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites in human samples including the catechol-type metabolite (3,4-dihydroxymethamphetamine)" *Drug Metabolism and Disposition*. Vol. 32(9): 1001-1007 From page **1001** "**3,4-Methylenedioxymethamphetamine (MDMA**; "ecstasy") is a designer drug commonly misused in large segments of young populations. **MDMA is usually formulated in tablets of its racemate (1:1 mixture of its enantiomers) in doses ranging from 50 to 200 mg**. MDMA has an enantioselective metabolism, the (S)-enantiomer being metabolized faster than the **(R)-enantiomer**. Different pharmacologic properties have been attributed to each enantiomer. The carbon responsible for MDMA chirality is preserved along its metabolic disposition. **An analytical method has been developed to determine MDMA enantiomers and those from its major metabolites, 3,4-methylenedioxyamphetamine (MDA),** 3,4-dihydroxymethamphetamine (HHMA), and 4-hydroxy-3-methoxymethamphetamine (HMMA)." 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." 4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021)

	From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, prodrugs, **stereoisomers**, or tautomers thereof." From **[0087]** "**Certain compounds described herein may exist in particular geometric or stereoisomeric forms**. A particular enantiomer of a compound described herein may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to **provide the pure desired enantiomers**. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent **recovery of the pure enantiomers**." From [0090] "**Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.** The compounds or compositions described herein may contain an enantiomeric excess of at least 50%, 75%, 90%, 95%, or 99% of one form of the compound, e.g., the S-enantiomer. In other words, such compounds or compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. From [0091] "**Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer and may also be referred to as "optically enriched."** "Optically enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. **In other embodiments, the compound is made up of at least about** 95%, 98%, or **99% by weight of a preferred enantiomer.** Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses…" From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable

	salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
10. The method of claim 9, wherein said administering step is further defined as administering 10-1000 mg of the R(−) enantiomer of MDMA or MDA.	7. PIZARRO (2004) "Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites in human samples including the catechol-type metabolite (3,4-dihydroxymethamphetamine)" *Drug Metabolism and Disposition*. Vol. 32(9): 1001-1007 From page **1001** "**3,4-Methylenedioxymethamphetamine (MDMA**; "ecstasy") is a designer drug commonly misused in large segments of young populations. **MDMA is usually formulated in tablets of its racemate (1:1 mixture of its enantiomers) in doses ranging from 50 to 200 mg**. MDMA has an enantioselective metabolism, the (S)-enantiomer being metabolized faster than the **(R)-enantiomer**. Different pharmacologic properties have been attributed to each enantiomer. The carbon responsible for MDMA chirality is preserved along its metabolic disposition. **An analytical method has been developed to determine MDMA enantiomers and those from its major metabolites, 3,4-methylenedioxyamphetamine (MDA),** 3,4-dihydroxymethamphetamine (HHMA), and 4-hydroxy-3-methoxymethamphetamine (HMMA)." 4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 18** "The composition of claim 8, wherein the composition comprises 0.1 mg to 1 mg, 1 mg to 10 mg, **10 mg to 100 mg, 10 mg to 50 mg, 50 mg to 100 mg, 20 mg to 80 mg, 20 mg to 50 mg, 50 mg to 100 mg, 50 mg to 80 mg, or 10 mg to 80 mg** of one or more **phenethylamines** or amphetamines or an amount of a plant or mushroom extract or plant or mushroom to provide an equivalent dose." From **[0150]** "In one embodiment, **the dose of the phenethylamines,** amphetamines, erinacines, hericenones, cannabinoids one or more adversive compounds such as niacin, capsaicin, ipecac, apomorphine, bittering agents, or an amount of a mushroom or plant extract or mushroom or plant having an equivalent amount of about **0.1 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg, 1 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg**."

	From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, prodrugs, **stereoisomers**, or tautomers thereof." From **[0087]** "**Certain compounds described herein may exist in particular geometric or stereoisomeric forms**. A particular enantiomer of a compound described herein may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to **provide the pure desired enantiomers**. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent **recovery of the pure enantiomers**." From [0090] "**Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.** The compounds or compositions described herein may contain an enantiomeric excess of at least 50%, 75%, 90%, 95%, or 99% of one form of the compound, e.g., the S-enantiomer. In other words, such compounds or compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. From [0091] "**Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer and may also be referred to as "optically enriched."** "Optically enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. **In other embodiments, the compound is made up of at least about** 95%, 98%, or **99% by weight of a preferred enantiomer.** Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses…" From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable

salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."

3. PETERS (2005) "Drug Testing in Blood: Validated Negative-Ion Chemical Ionization Gas Chromatographic–Mass Spectrometric Assay for Enantioselective Measurement of the Designer Drugs MDEA, MDMA, and MDA and Its Application to Samples from a Controlled Study with MDMA" *Clinical Chemistry*. Vol. 51(10): 1811-1822

From **page 1811** "**Background:** The enantiomers of the designer drugs **3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA),** and 3,4-methylenedioxyethylamphetamine (MDEA) differ in their pharmacologic and toxicologic potency. The aim of this study was to develop an assay for **measuring these enantiomers in small plasma volumes and to analyze samples from a controlled study with MDMA**.

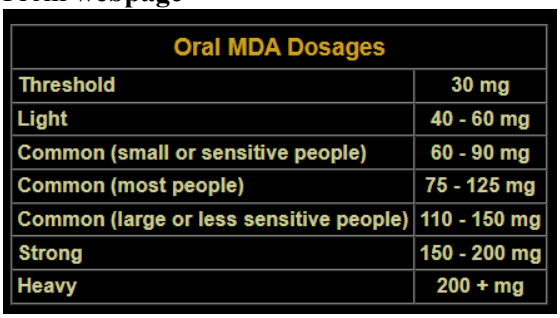
Methods: The analytes were extracted from < or = 0.2 mL of plasma by mixed-mode solid-phase extraction. After derivatization with S-(-)-heptafluorobutyrylprolyl chloride, the resulting diastereomers were separated by gas chromatography (HP-5MS) within 17 min and detected by mass spectrometry in the negative-ion chemical ionization mode. The method was fully validated and applied to samples from a controlled study in which **a single dose of racemic MDMA (75 mg) was administered**.

5. EROWID (2020) "MDMA Dosage by Erowid" Retrieved 24 May 2020. URL: https://www.erowid.org/chemicals/mdma/mdma_dose.shtml

From **webpage**

Oral MDMA Dosages	
Threshold	30 mg
Light	40 - 75 mg
Common (small or sensitive people)	60 - 90 mg
Common (most people)	75 - 125 mg
Common (large or less sensitive people)	110 - 150 mg
Strong	150 - 200 mg
Heavy	200 + mg

From **webpage** "**Chemical analysis of ecstasy tablets has found from 0 - 120 mg of MDMA as well as a variety of the above substances.** Trying to calculate dosages from tablets containing unknown quantities of MDMA can

	be difficult, but **a high quality tablet of street ecstasy (those containing MDMA alone) generally contains between 80 and 120 mg of MDMA**. **Some unusual tablets (especially in Europe) contain 150mg or more**. The chart below shows what are considered recreational/therapeutic dosages for pure MDMA HCl (the most common crystalline form), measured in milligrams." 6. EROWID (2017) "MDA Dosage by Erowid" Retrieved 6 September 2017. https://www.erowid.org/chemicals/mda/mda_dose.shtml From **webpage**  **Oral MDA Dosages** **Threshold** 30 mg **Light** 40 - 60 mg **Common (small or sensitive people)** 60 - 90 mg **Common (most people)** 75 - 125 mg **Common (large or less sensitive people)** 110 - 150 mg **Strong** 150 - 200 mg **Heavy** 200 + mg From **webpage** "Erowid's current view is that **the required dose of MDA vs MDMA are very similar, but result in slightly different effects** (MDA is more physically stimulating while MDMA is more empathogenic at the same dose)."
11. The method of claim 9, wherein said administering step is further defined as administering the R(−) enantiomer of MDMA or MDA daily.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0159]** "In one embodiment, the compositions described herein can be **administered as dosage forms in various regimens, including one dose per day (QD)**, two doses per day (BID), three doses per day (TID), or four times per day (QID) to achieve a total daily dosage. In another embodiment, any of the foregoing doses comprise **a total daily dosage**." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects."

12. The method of claim 9, further including the step of preventing or reducing side effects of neurotoxicity, hyperthermia, and dependence/addiction experienced with racemic MDMA or MDA.	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)… **This suggests that the neurotoxicity of (±)- MDMA is driven by S(+)-MDMA,** but because they did not account for the lower potency of R(−)-MDMA relative to (±)- MDMA, it is not clear if neurotoxicity would occur at a higher, behaviorally equivalent dose of R(−)-MDMA…**Another key difference between R(−)-MDMA and S(+)- MDMA is that R(−)-MDMA does not produce hyperthermia** (Fantegrossi et al. 2003; Frau et al. 2013; Curry et al. 2017). Hyperthermia can be dangerous, and sometimes fatal, following ingestion of MDMA (Henry et al. 1992)… Thus, **the lack of hyperthermia following R(−)-MDMA administration may play a role in the decreased risk for neurotoxicity**." 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." From **page 384** "he one **human study of the behavioral effects** of the enantiomers of (±)-MDMA concluded that S(+)-MDMA was the active enantiomer because no dose of R(−)-MDMA produced even Bnominal^ intoxication, pupil dilation, or jaw clenching (Anderson et al. 1978). **The lack of intoxication following R(−)-MDMA could indicate lower abuse liability**, although further controlled studies would be necessary. Interestingly, as with the previously discussed preclinical studies, (±)-MDMA produced intoxication at doses lower than would be expected from the results of either enantiomer alone…**another study in nonhuman**

	primates suggests that R(−)-MDMA may have lower abuse liability than (±)- MDMA or S(+)-MDMA. Wang and Woolverton (2007), examining self-administration rates of rhesus macaques with a history of cocaine self-administration under a progressive ratio (PR) schedule of reinforcement, found that **R(−)- MDMA did not act as a reinforcer in three out of the five monkeys and the average maximum number of injections was significantly lower for R(−)-MDMA (4.7 injections) than for S(+)-MDMA (10) and (±)-MDMA (9).**"
13. The method of claim 9, wherein the R(−) enantiomer of MDMA or MDA includes a prodrug bound thereto.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
14. The method of claim 13, wherein the prodrug is an amino acid chosen from the group consisting of lysine, alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine,	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof."

isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine.	From **[0178]** "**amino acids are selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine**, ornithine, citrulline, taurine, selenocysteine, pyrrolysine, aminobutyric acid, gama-aminobutryic acid, 3-aminopropanoic acid, dehydroalanine, delta-carboxyglutamic acid, N-formylmethionine."
15. The method of claim 9, wherein the composition is in a continual slow-release formulation.	***From the application of interest 18/186,764 paragraph [0029]*** *"Using the R(−) enantiomer allows for daily use of MDMA or MDA. The compositions are particularly useful in* ***continual slow-release formulations, such as transdermal patches, that can provide a low dose over a long period of time****. The compositions can also be administered in an intranasal spray."* 4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0108]** "The pharmaceutically acceptable compositions of this disclosure may also be **administered topically**, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract can be administered using a rectal suppository formulation (see above) or a suitable enema formulation. **Topically transdermal patches may also be used**." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof."
16. The method of claim 9, wherein the composition is in an intranasal spray form.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0110]** "The pharmaceutically acceptable compositions of this disclosure may also be **administered by nasal aerosol or inhalation.** Such compositions are prepared according to techniques known in the art of pharmaceutical formulation and may **be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, or other conventional solubilizing or dispersing agents…**" From **[0104]** "The compositions described herein may be **administered** orally, parenterally, **by inhalation spray**, topically, rectally, **nasally**, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-

	articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques…" From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof."
17. The method of claim 9, wherein the composition is in a liquid dosage form chosen from the group consisting of suspensions, solutions, emulsions, elixirs, tinctures, sprays, syrups, gels, magmas, liniments, lotions, ointments, pastes, drops, and inhalants.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "RYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0144]** "Another embodiment is a method for manufacturing a dosage form comprising formulating a composition as described herein comprising **sprays**, capsules, tablets, **elixirs, emulsions**, lozenges, **suspensions, syrups**, pills, **lotions**, epidermal patches, suppositories, inhalers, or injectables. Any methods known to the art for formulating extracts or active principal ingredients into lotions, soaps, etc. may be utilized." From **[0109]** "For **topical applications**, the pharmaceutically acceptable compositions may be formulated in a suitable **ointment** containing the active component suspended or dissolved in one or more carriers..." From **[0110]** "The pharmaceutically acceptable compositions of this disclosure may also be administered by nasal aerosol or **inhalation**..."
18. The method of claim 9, wherein the composition is in an oral dosage form chosen from the group consisting of capsules, films, lozenge, patch, powder, tablets, pellets, pills, and troches.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0144]** "Another embodiment is a method for manufacturing a dosage form comprising formulating a composition as described herein comprising sprays, **capsules, tablets**, elixirs, emulsions, **lozenges**, suspensions, syrups, **pills**, lotions, **epidermal patches**, suppositories, inhalers, or injectables. Any methods known to the art for formulating extracts or active principal ingredients into lotions, soaps, etc. may be utilized." From **claim 21** "The composition of claim 1, wherein the composition is a **powder admixture**, liquid, suspension, or emulsion."
19. The method of claim 9, wherein said treating step is further defined as treating a condition or disorder chosen from the group consisting of post-traumatic stress disorder, social anxiety,	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 24** "The composition of claim 1, wherein the composition is effective to **treat, alleviate, prevent or ameliorate serotonin (5-hydroxytryptamine, 5-HT) receptor disorders, psychiatric and mood disorders comprising depression, anxiety, major depressive disorder, treatment resistant depression, persistent depression, manic depression**

autism spectrum disorder, substance use disorder, depression, anxiety disorder, anxiety with life-threatening disease, personality disorder, schizophrenia, obsessive compulsive disorder, couple therapy, enhancement of any psychotherapy by inducing feelings of well-being connectivity, trust, love, empathy, openness, and pro-sociality, and enhancing therapeutic bond in any psychotherapy of patients or neurotic/healthy subjects.	**or bipolar disorder, depressive psychosis, perinatal depression, premenstrual dysphoric disorder, seasonal depressions, situational depression, panic disorder, obsessive compulsive disorder, post-traumatic stress disorder,** attention deficit/hyperactivity disorder, sleep disorders, eating disorders, **schizophrenia**, **personality disorders, substance abuse disorders (drug abuse, addiction, alcoholism)**; neuronal injuries or physical neurodegeneration (e.g., physical injury, head trauma, spinal cord trauma, concussion, peripheral neuron trauma, paralysis, ischemia, hypoxia, stroke; organophosphates, lead, heavy metals, nerve agents, other toxic compounds, prions, amyloid plaque, neurotoxic viruses, stress); neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, frontotemporal dementia, Huntington's disease, adrenal leukodystrophy, Alexander's disease, Alper's disease, Alzheimer's disease, amyotrophic lateral sclerosis, balo concentric sclerosis, Canavan disease, Charcot-Marie-Tooth disease, childhood ataxia with central nervous system hypomyelination, chronic idiopathic peripheral neuropathy, frontotemporal dementia, Huntington's disease, Krabbe disease, monomelic amyotrophy, multiple sclerosis (MS), neurodegeneration, neuromyelitis optica, neuropathic pain, neurosarcoidosis, Parkinson's disease, Pelizaeus-Merzbacher disease, primary lateral sclerosis, progressive supranuclear palsy, radicular pain, radiculopathic pain, Schilder's disease, sciatic pain, sciatica, subacute necrotizing myelopathy, transverse myelitis, or Zellweger syndrome); congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder**; cognitive enhancement, intelligence enhancement, creativity enhancement, memory improvement, learning enhancement and improvement, spiritual enhancement, "mind expansion," IQ improvement, EQ improvement, balance enhancement, athleticism, motor skill enhancement, special navigation, clairvoyance, psychic enhancement, **or general improvement of mental health.**" From **[0064]** "As used herein, **"mental health"** refers to a subject's **emotional, psychological, and social well-being**. Mental health disorders or problems refer to disorders affecting cognition, mood, behavior, and homeostasis. Mental health disorders may be caused by biological factors (genetic or neurochemistry), stress, trauma, or abuse, or associated with injury." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the

	popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects."
20. A method of reducing neurotoxicity of MDMA and MDA, including the steps of: administering an effective amount of a composition of an R(−) enantiomer of MDMA or MDA to an individual; and reducing neurotoxicity of MDMA or MDA while treating the individual.	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)… **This suggests that the neurotoxicity of (±)- MDMA is driven by S(+)-MDMA,** but because they did not account for the lower potency of R(−)-MDMA relative to (±)- MDMA, it is not clear if neurotoxicity would occur at a higher, behaviorally equivalent dose of R(−)-MDMA…Another key difference between R(−)-MDMA and S(+)- MDMA is that R(−)-MDMA does not produce hyperthermia (Fantegrossi et al. 2003; Frau et al. 2013; Curry et al. 2017). Hyperthermia can be dangerous, and sometimes fatal, following ingestion of MDMA (Henry et al. 1992)… Thus, **the lack of hyperthermia following R(−)-MDMA administration may play a role in the decreased risk for neurotoxicity**."
21. The method of claim 20, wherein said administering step is further defined as administering 10-1000 mg of the R(−) enantiomer of MDMA or MDA.	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)… **This suggests that the neurotoxicity of (±)- MDMA is driven by S(+)-MDMA,** but because they did not account for the lower potency of R(−)-MDMA relative to (±)- MDMA, it is not clear if neurotoxicity would occur at a higher, behaviorally equivalent dose of R(−)-MDMA…Another key difference between R(−)-MDMA and S(+)- MDMA is that R(−)-MDMA does not produce hyperthermia (Fantegrossi et al. 2003; Frau et al. 2013; Curry et al. 2017). Hyperthermia can be dangerous, and sometimes fatal, following ingestion of MDMA (Henry et al. 1992)… Thus, **the lack of hyperthermia following R(−)-MDMA administration may play a role in the decreased risk for neurotoxicity**." From **page 378** "A second double blind study of (±)-MDMA-assisted psychotherapy, using similar methods, was conducted in Switzerland with a similar patient population of 12 individuals. It compared **125 mg (±)-MDMA to 25 mg (±)-MDMA** as an active placebo and found a clinically, but not statistically, significant effect of high- versus low-dose (±)-MDMA on CAPS scores (Oehen et al. 2013)."

3. PETERS (2005) “Drug Testing in Blood: Validated Negative-Ion Chemical Ionization Gas Chromatographic–Mass Spectrometric Assay for Enantioselective Measurement of the Designer Drugs MDEA, MDMA, and MDA and Its Application to Samples from a Controlled Study with MDMA” *Clinical Chemistry*. Vol. 51(10): 1811-1822

From **page 1811** “**Background:** The enantiomers of the designer drugs **3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA),** and 3,4-methylenedioxyethylamphetamine (MDEA) differ in their pharmacologic and toxicologic potency. The aim of this study was to develop an assay for **measuring these enantiomers in small plasma volumes and to analyze samples from a controlled study with MDMA**.

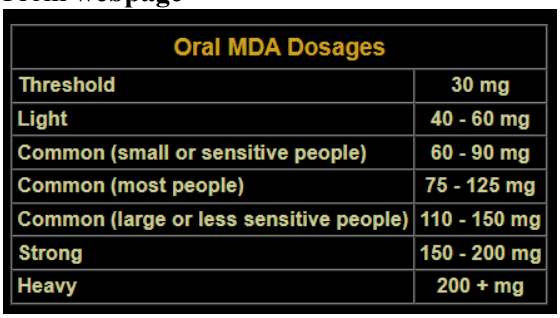
Methods: The analytes were extracted from < or = 0.2 mL of plasma by mixed-mode solid-phase extraction. After derivatization with S-(-)-heptafluorobutyrylprolyl chloride, the resulting diastereomers were separated by gas chromatography (HP-5MS) within 17 min and detected by mass spectrometry in the negative-ion chemical ionization mode. The method was fully validated and applied to samples from a controlled study in which **a single dose of racemic MDMA (75 mg) was administered**.

5. EROWID (2020) “MDMA Dosage by Erowid” Retrieved 24 May 2020. URL: https://www.erowid.org/chemicals/mdma/mdma_dose.shtml

From **webpage**

Oral MDMA Dosages	
Threshold	30 mg
Light	40 - 75 mg
Common (small or sensitive people)	60 - 90 mg
Common (most people)	75 - 125 mg
Common (large or less sensitive people)	110 - 150 mg
Strong	150 - 200 mg
Heavy	200 + mg

From **webpage** “**Chemical analysis of ecstasy tablets has found from 0 - 120 mg of MDMA as well as a variety of the above substances.** Trying to calculate dosages from tablets containing unknown quantities of MDMA can be difficult, but **a high quality tablet of street ecstasy (those containing MDMA alone) generally contains between 80 and 120 mg of MDMA**. **Some unusual tablets (especially in Europe) contain 150mg or more**. The chart below shows what are considered recreational/therapeutic dosages for pure MDMA HCl (the most common crystalline form), measured in milligrams.”

	6. EROWID (2017) "MDA Dosage by Erowid" Retrieved 6 September 2017. https://www.erowid.org/chemicals/mda/mda_dose.shtml From **webpage**  **Oral MDA Dosages** **Threshold** 30 mg **Light** 40 - 60 mg **Common (small or sensitive people)** 60 - 90 mg **Common (most people)** 75 - 125 mg **Common (large or less sensitive people)** 110 - 150 mg **Strong** 150 - 200 mg **Heavy** 200 + mg From **webpage** "Erowid's current view is that **the required dose of MDA vs MDMA are very similar, but result in slightly different effects** (MDA is more physically stimulating while MDMA is more empathogenic at the same dose)."
22. The method of claim 20, wherein said administering step is further defined as administering the R(−) enantiomer of MDMA or MDA daily.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0159]** "In one embodiment, the compositions described herein can be **administered as dosage forms in various regimens, including one dose per day (QD)**, two doses per day (BID), three doses per day (TID), or four times per day (QID) to achieve a total daily dosage. In another embodiment, any of the foregoing doses comprise **a total daily dosage**." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From [0091] "**Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer and may also be referred to as "optically enriched."** "Optically enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. **In other embodiments, the compound is made up of at least about** 95%, 98%, or **99% by weight of a preferred enantiomer.**

	Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses…"
23. The method of claim 20, wherein the R(−) enantiomer of MDMA or MDA includes a prodrug bound thereto.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
24. The method of claim 23, wherein the prodrug is an amino acid chosen from the group consisting of lysine, alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine,	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0178]** "**amino acids are selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine**, ornithine, citrulline, taurine, selenocysteine, pyrrolysine, aminobutyric acid, gama-aminobutryic

tryptophan, tyrosine, and valine.	acid, 3-aminopropanoic acid, dehydroalanine, delta-carboxyglutamic acid, N-formylmethionine."
25. A method of reducing hyperthermia of MDMA and MDA, including the steps of: administering an effective amount of a composition of an R(−) enantiomer of MDMA or MDA to an individual; and reducing hyperthermia of MDMA or MDA while treating the individual.	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)… **This suggests that the neurotoxicity of (±)- MDMA is driven by S(+)-MDMA,** but because they did not account for the lower potency of R(−)-MDMA relative to (±)- MDMA, it is not clear if neurotoxicity would occur at a higher, behaviorally equivalent dose of R(−)-MDMA…**Another key difference between R(−)-MDMA and S(+)- MDMA is that R(−)-MDMA does not produce hyperthermia** (Fantegrossi et al. 2003; Frau et al. 2013; Curry et al. 2017). Hyperthermia can be dangerous, and sometimes fatal, following ingestion of MDMA (Henry et al. 1992)… Thus, **the lack of hyperthermia following R(−)-MDMA administration may play a role in the decreased risk for neurotoxicity**."
26. The method of claim 25, wherein said administering step is further defined as administering 10-1000 mg of the R(−) enantiomer of MDMA or MDA.	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)… **This suggests that the neurotoxicity of (±)- MDMA is driven by S(+)-MDMA,** but because they did not account for the lower potency of R(−)-MDMA relative to (±)- MDMA, it is not clear if neurotoxicity would occur at a higher, behaviorally equivalent dose of R(−)-MDMA…**Another key difference between R(−)-MDMA and S(+)- MDMA is that R(−)-MDMA does not produce hyperthermia** (Fantegrossi et al. 2003; Frau et al. 2013; Curry et al. 2017). Hyperthermia can be dangerous, and sometimes fatal, following ingestion of MDMA (Henry et al. 1992)… Thus, **the lack of hyperthermia following R(−)-MDMA administration may play a role in the decreased risk for neurotoxicity**." From **page 378** "A second double blind study of (±)-MDMA-assisted psychotherapy, using similar methods, was conducted in Switzerland with a similar patient population of 12 individuals. It compared **125 mg (±)-MDMA to 25 mg (±)-MDMA** as an active placebo and found a clinically,

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From **page 1811** "**Background:** The enantiomers of the designer drugs **3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA),** and 3,4-methylenedioxyethylamphetamine (MDEA) differ in their pharmacologic and toxicologic potency. The aim of this study was to develop an assay for **measuring these enantiomers in small plasma volumes and to analyze samples from a controlled study with MDMA**.

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asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine.	**(MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0178]** "**amino acids are selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine**, ornithine, citrulline, taurine, selenocysteine, pyrrolysine, aminobutyric acid, gama-aminobutryic acid, 3-aminopropanoic acid, dehydroalanine, delta-carboxyglutamic acid, N-formylmethionine."
30. A method of reducing physical dependence or abuse liability of MDMA and MDA, including the steps of: administering an effective amount of a composition of an R(−) enantiomer of MDMA or MDA to an individual; and reducing the physical dependence or abuse liability of MDMA or MDA while treating the individual.	1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 384** "he one **human study of the behavioral effects** of the enantiomers of (±)-MDMA concluded that S(+)-MDMA was the active enantiomer because no dose of R(−)-MDMA produced even Bnominal^ intoxication, pupil dilation, or jaw clenching (Anderson et al. 1978). **The lack of intoxication following R(−)-MDMA could indicate lower abuse liability**, although further controlled studies would be necessary. Interestingly, as with the previously discussed preclinical studies, (±)-MDMA produced intoxication at doses lower than would be expected from the results of either enantiomer alone…**another study in nonhuman primates suggests that R(−)-MDMA may have lower abuse liability than (±)- MDMA or S(+)-MDMA.** Wang and Woolverton (2007), examining self-administration rates of rhesus macaques with a history of cocaine self-administration under a progressive ratio (PR) schedule of reinforcement, found that **R(−)- MDMA did not act as a reinforcer in three out of the five monkeys and the average maximum number of injections was significantly lower for R(−)-MDMA (4.7 injections) than for S(+)-MDMA (10) and (±)-MDMA (9).**"
31. The method of claim 30, wherein said administering step is further defined as administering 10-1000 mg of the R(−) enantiomer of MDMA or MDA.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 18** "The composition of claim 8, wherein the composition comprises 0.1 mg to 1 mg, 1 mg to 10 mg, **10 mg to 100 mg, 10 mg to 50 mg, 50 mg to 100 mg, 20 mg to 80 mg, 20 mg to 50 mg, 50 mg to 100 mg, 50 mg to 80 mg, or 10 mg to 80 mg** of one or more **phenethylamines** or amphetamines or an amount of a plant or mushroom extract or plant or mushroom to provide an equivalent dose." From **[0150]** "In one embodiment, **the dose of the phenethylamines,** amphetamines, erinacines, hericenones, cannabinoids one or more adverse compounds such as niacin, capsaicin, ipecac, apomorphine, bittering agents, or an amount of a mushroom or plant extract or mushroom or plant having an equivalent amount of about **0.1 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg, 1 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60**

	mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, prodrugs, **stereoisomers**, or tautomers thereof." From **[0087]** "**Certain compounds described herein may exist in particular geometric or stereoisomeric forms**. A particular enantiomer of a compound described herein may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to **provide the pure desired enantiomers**. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent **recovery of the pure enantiomers**." From [0090] "**Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.** The compounds or compositions described herein may contain an enantiomeric excess of at least 50%, 75%, 90%, 95%, or 99% of one form of the compound, e.g., the S-enantiomer. In other words, such compounds or compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. From [0091] "**Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer and may also be referred to as "optically enriched."** "Optically enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. **In other embodiments, the compound is made up of at least about** 95%, 98%, or **99% by weight of a preferred enantiomer.** Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses…"

	From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
32. The method of claim 30, wherein said administering step is further defined as administering the R(−) enantiomer of MDMA or MDA daily.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0159]** "In one embodiment, the compositions described herein can be **administered as dosage forms in various regimens, including one dose per day (QD)**, two doses per day (BID), three doses per day (TID), or four times per day (QID) to achieve a total daily dosage. In another embodiment, any of the foregoing doses comprise **a total daily dosage**." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects."
33. The method of claim 30, wherein the R(−) enantiomer of MDMA or MDA includes a prodrug bound thereto.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the

	popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
34. The method of claim 33, wherein the prodrug is an amino acid chosen from the group consisting of lysine, alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0178]** "**amino acids are selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine**, ornithine, citrulline, taurine, selenocysteine, pyrrolysine, aminobutyric acid, gama-aminobutryic acid, 3-aminopropanoic acid, dehydroalanine, delta-carboxyglutamic acid, N-formylmethionine."

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/186,764	**01/12/2024 05:27:56 PM Z ET**	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	63942996	FILING DATE	03/20/2023
CUSTOMER #	–	FIRST NAMED INVENTOR	
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 16

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
third-party-preissuance-submission.pdf		3	Third-Party Submission Under 37 CFR 1.290	66 KB
Concise-description-generated.pdf		2	Concise Description of Relevance	35 KB
Third-party-notification-request.pdf		1	Request for Notification of Non-compliant Third-Party Submission	14 KB
Claims_Chart.pdf		33	-	521 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-33)	33	Concise Description of Relevance	428 KB
Claims_Chart-	(1-33)	33	Concise Description of	428 KB

3P.RELEVANCE.pdf			Relevance	
Claims_Chart-3P.RELEVANCE.pdf	(1-33)	33	Concise Description of Relevance	428 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-33)	33	Concise Description of Relevance	428 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-33)	33	Concise Description of Relevance	428 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-33)	33	Concise Description of Relevance	428 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-33)	33	Concise Description of Relevance	428 KB
1_PITTS.pdf		16	-	2409 KB
1_PITTS-NPL.pdf	(1-16)	16	Non Patent Literature	2359 KB
2_CURRY.pdf		26	-	3467 KB
2_CURRY-NPL.pdf	(1-26)	26	Non Patent Literature	3451 KB
3_PETERS.pdf		12	-	347 KB
3_PETERS-NPL.pdf	(1-12)	12	Non Patent Literature	343 KB
5_EROWID_MDMA.pdf		1	-	305 KB
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6_EROWID_MDA.pdf		1	-	217 KB
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7_PIZARRO.pdf		7	-	1493 KB

7_PIZARRO-NPL.pdf	(1-7)	7	Non Patent Literature	1484 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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Claims_Chart-3P.RELEVANCE.pdf	F749C099D9AE1ABB9A4012F10B7BE808CBA32F266324A5D039F9533CAF3A6475068D158161666C0A93D6978259FE6BC97D1785D1E2D0CE18381229AB9B65A420
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7_PIZARRO-NPL.pdf	9A891090F4B02B11B0B18CE17A10A5F03E7EB6A838ABEF3E963D35FC1BC752460D4A3308E54D680C08AFE7C7F11A32ABB7F52E46C87990192D243AC56FBD3D75

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/186,764	**01/12/2024 05:27:56 PM Z ET**	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	63942996	AUTHORIZED BY	-
CUSTOMER #	–	FILING DATE	03/20/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0642	**E20241BH28435866**	**Sisi Li**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2818	DOCUMENT FEE FOR THIRD-PARTY SUBMISSIONS (SEE 37 CFR 1.290(F))	72.00	1	72.00
			TOTAL AMOUNT:	**$72.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Mind Medicine, Inc.	Confirmation No.: 6704
Serial No.:	18/186,494	Group No.:
Filing or 371(c) Date:	20 March 2023	Examiner:

Entitled: MDMA ENANTIOMERS

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. PETERS (2005) "Drug Testing in Blood: Validated Negative-Ion Chemical Ionization Gas Chromatographic–Mass Spectrometric Assay for Enantioselective Measurement of the Designer Drugs MDEA, MDMA, and MDA and Its Application to Samples from a Controlled Study with MDMA" *Clinical Chemistry*. Vol. 51(10): 1811-1822
4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "RYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021)
5. EROWID (2020) "MDMA Dosage by Erowid" Retrieved 24 May 2020. URL: https://www.erowid.org/chemicals/mdma/mdma_dose.shtml
6. EROWID (2017) "MDA Dosage by Erowid" Retrieved 6 September 2017. https://www.erowid.org/chemicals/mda/mda_dose.shtml
7. PIZARRO (2004) "Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites in human samples including the catechol-type metabolite (3,4-dihydroxymethamphetamine)" *Drug Metabolism and Disposition*. Vol. 32(9): 1001-1007

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

U.S.S.N. 18/186,494 Pending Claims	References
1. A composition for use in psychotherapeutic treatment comprising an R(−) enantiomer of MDMA or MDA.	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." ***From the application of interest 18/186,764 paragraph [0006]*** *"**MDMA has two enantiomers, S(+)-MDMA and R(−)-MDMA**."* 4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, prodrugs, **stereoisomers**, or tautomers thereof." From **[0087]** "**Certain compounds described herein may exist in particular geometric or stereoisomeric forms**. A particular enantiomer of a compound described herein may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to **provide the pure desired enantiomers**. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-

	active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent **recovery of the pure enantiomers**." From [0090] "**Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.** The compounds or compositions described herein may contain an enantiomeric excess of at least 50%, 75%, 90%, 95%, or 99% of one form of the compound, e.g., the S-enantiomer. In other words, such compounds or compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. From [0091] "**Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer and may also be referred to as "optically enriched."** "Optically enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. **In other embodiments, the compound is made up of at least about** 95%, 98%, or **99% by weight of a preferred enantiomer.** Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses…" From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
2. The composition of claim 1, wherein said R(−) enantiomer of MDMA or MDA is present in an amount of 10-1000 mg.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 18** "The composition of claim 8, wherein the composition comprises 0.1 mg to 1 mg, 1 mg to 10 mg, **10 mg to 100 mg, 10 mg to 50 mg, 50 mg to 100 mg, 20 mg to 80 mg, 20 mg to 50 mg, 50 mg to 100 mg, 50 mg to 80 mg, or 10 mg to 80 mg** of one or more **phenethylamines** or amphetamines or an amount of a plant or mushroom extract or plant or mushroom to provide an equivalent dose." From **[0150]** "In one embodiment, **the dose of the phenethylamines,** amphetamines, erinacines, hericenones, cannabinoids one or more adversive compounds such as niacin, capsaicin, ipecac, apomorphine, bittering agents, or an amount of a mushroom or plant extract or mushroom or plant having

	an equivalent amount of about **0.1 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg, 1 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg**." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**..." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, prodrugs, **stereoisomers**, or tautomers thereof." From **[0087]** "**Certain compounds described herein may exist in particular geometric or stereoisomeric forms**. A particular enantiomer of a compound described herein may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to **provide the pure desired enantiomers**. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent **recovery of the pure enantiomers**." From [0090] "**Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.** The compounds or compositions described herein may contain an enantiomeric excess of at least 50%, 75%, 90%, 95%, or 99% of one form of the compound, e.g., the S-enantiomer. In other words, such compounds or compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. From [0091] "**Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer and may also be referred to as "optically enriched."** "Optically enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. **In other embodiments, the compound is made up of at least about** 95%, 98%, or **99% by weight of a preferred enantiomer.** Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses…"

From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."

7. PIZARRO (2004) "Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites in human samples including the catechol-type metabolite (3,4-dihydroxymethamphetamine)" *Drug Metabolism and Disposition*. Vol. 32(9): 1001-1007

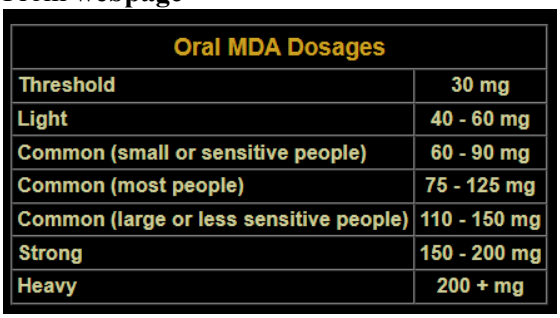
From page **1001** "**3,4-Methylenedioxymethamphetamine (MDMA**; "ecstasy") is a designer drug commonly misused in large segments of young populations. **MDMA is usually formulated in tablets of its racemate (1:1 mixture of its enantiomers) in doses ranging from 50 to 200 mg**. MDMA has an enantioselective metabolism, the (S)-enantiomer being metabolized faster than the **(R)-enantiomer**. Different pharmacologic properties have been attributed to each enantiomer. The carbon responsible for MDMA chirality is preserved along its metabolic disposition. **An analytical method has been developed to determine MDMA enantiomers and those from its major metabolites, 3,4-methylenedioxyamphetamine (MDA),** 3,4-dihydroxymethamphetamine (HHMA), and 4-hydroxy-3-methoxymethamphetamine (HMMA)."

5. EROWID (2020) "MDMA Dosage by Erowid" Retrieved 24 May 2020. URL: https://www.erowid.org/chemicals/mdma/mdma_dose.shtml

From **webpage**

Oral MDMA Dosages	
Threshold	30 mg
Light	40 - 75 mg
Common (small or sensitive people)	60 - 90 mg
Common (most people)	75 - 125 mg
Common (large or less sensitive people)	110 - 150 mg
Strong	150 - 200 mg
Heavy	200 + mg

From **webpage** "**Chemical analysis of ecstasy tablets has found from 0 - 120 mg of MDMA as well as a variety of the above substances.** Trying to calculate dosages from tablets containing unknown quantities of MDMA can

	be difficult, but **a high quality tablet of street ecstasy (those containing MDMA alone) generally contains between 80 and 120 mg of MDMA**. **Some unusual tablets (especially in Europe) contain 150mg or more**. The chart below shows what are considered recreational/therapeutic dosages for pure MDMA HCl (the most common crystalline form), measured in milligrams." 6. EROWID (2017) "MDA Dosage by Erowid" Retrieved 6 September 2017. https://www.erowid.org/chemicals/mda/mda_dose.shtml From **webpage**  **Oral MDA Dosages** **Threshold** 30 mg **Light** 40 - 60 mg **Common (small or sensitive people)** 60 - 90 mg **Common (most people)** 75 - 125 mg **Common (large or less sensitive people)** 110 - 150 mg **Strong** 150 - 200 mg **Heavy** 200 + mg From **webpage** "Erowid's current view is that **the required dose of MDA vs MDMA are very similar, but result in slightly different effects** (MDA is more physically stimulating while MDMA is more empathogenic at the same dose)."
3. The composition of claim 1, wherein said R(−) enantiomer of MDMA or MDA includes a prodrug bound thereto.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable

	salts, hydrates, solvates, **prodrugs**, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
4. The composition of claim 3, wherein said prodrug is an amino acid chosen from the group consisting of lysine, alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0178]** "**amino acids are selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine**, ornithine, citrulline, taurine, selenocysteine, pyrrolysine, aminobutyric acid, gama-aminobutryic acid, 3-aminopropanoic acid, dehydroalanine, delta-carboxyglutamic acid, N-formylmethionine."
5. The composition of claim 1, wherein said composition is in a continual slow-release formulation.	***From the application of interest 18/186,764 paragraph [0029]*** *"Using the R(−) enantiomer allows for daily use of MDMA or MDA. The compositions are particularly useful in* ***continual slow-release formulations, such as transdermal patches, that can provide a low dose over a long period of time****. The compositions can also be administered in an intranasal spray."* 4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0108]** "The pharmaceutically acceptable compositions of this disclosure may also be **administered topically**, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract can be administered using a rectal suppository formulation (see above) or a suitable enema formulation. **Topically transdermal patches may also be used**." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof."

6. The composition of claim 1, wherein said composition is in an intranasal spray form.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0110]** "The pharmaceutically acceptable compositions of this disclosure may also be **administered by nasal aerosol or inhalation.** Such compositions are prepared according to techniques known in the art of pharmaceutical formulation and may **be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, or other conventional solubilizing or dispersing agents…**" From **[0104]** "The compositions described herein may be **administered** orally, parenterally, **by inhalation spray**, topically, rectally, **nasally**, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques…" From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof."
7. The composition of claim 1, wherein said composition is in a liquid dosage form chosen from the group consisting of suspensions, solutions, emulsions, elixirs, tinctures, sprays, syrups, gels, magmas, liniments, lotions, ointments, pastes, drops, and inhalants.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0144]** "Another embodiment is a method for manufacturing a dosage form comprising formulating a composition as described herein comprising **sprays**, capsules, tablets, **elixirs, emulsions**, lozenges, **suspensions, syrups**, pills, **lotions**, epidermal patches, suppositories, inhalers, or injectables. Any methods known to the art for formulating extracts or active principal ingredients into lotions, soaps, etc. may be utilized." From **[0109]** "For **topical applications**, the pharmaceutically acceptable compositions may be formulated in a suitable **ointment** containing the active component suspended or dissolved in one or more carriers..." From **[0110]** "The pharmaceutically acceptable compositions of this disclosure may also be administered by nasal aerosol or **inhalation**..."
8. The composition of claim 1, wherein said composition is in an oral dosage form chosen from the group consisting of capsules,	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0144]** "Another embodiment is a method for manufacturing a dosage form comprising formulating a composition as described herein comprising

films, lozenge, patch, powder, tablets, pellets, pills, and troches.	sprays, **capsules, tablets**, elixirs, emulsions, **lozenges**, suspensions, syrups, **pills**, lotions, **epidermal patches**, suppositories, inhalers, or injectables. Any methods known to the art for formulating extracts or active principal ingredients into lotions, soaps, etc. may be utilized." From **claim 21** "The composition of claim 1, wherein the composition is a **powder admixture**, liquid, suspension, or emulsion."
9. A method of treating an individual for a medical condition, including the steps of: administering an effective amount of a composition of an R(−) enantiomer of MDMA or MDA; and treating the individual.	7. PIZARRO (2004) "Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites in human samples including the catechol-type metabolite (3,4-dihydroxymethamphetamine)" *Drug Metabolism and Disposition*. Vol. 32(9): 1001-1007 From page **1001** "**3,4-Methylenedioxymethamphetamine (MDMA**; "ecstasy") is a designer drug commonly misused in large segments of young populations. **MDMA is usually formulated in tablets of its racemate (1:1 mixture of its enantiomers) in doses ranging from 50 to 200 mg**. MDMA has an enantioselective metabolism, the (S)-enantiomer being metabolized faster than the **(R)-enantiomer**. Different pharmacologic properties have been attributed to each enantiomer. The carbon responsible for MDMA chirality is preserved along its metabolic disposition. **An analytical method has been developed to determine MDMA enantiomers and those from its major metabolites, 3,4-methylenedioxyamphetamine (MDA),** 3,4-dihydroxymethamphetamine (HHMA), and 4-hydroxy-3-methoxymethamphetamine (HMMA)." 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." 4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021)

	From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, prodrugs, **stereoisomers**, or tautomers thereof." From **[0087]** "**Certain compounds described herein may exist in particular geometric or stereoisomeric forms**. A particular enantiomer of a compound described herein may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to **provide the pure desired enantiomers**. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent **recovery of the pure enantiomers**." From [0090] "**Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.** The compounds or compositions described herein may contain an enantiomeric excess of at least 50%, 75%, 90%, 95%, or 99% of one form of the compound, e.g., the S-enantiomer. In other words, such compounds or compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. From [0091] "**Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer and may also be referred to as "optically enriched."** "Optically enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. **In other embodiments, the compound is made up of at least about** 95%, 98%, or **99% by weight of a preferred enantiomer.** Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses…" From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable

	salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
10. The method of claim 9, wherein said administering step is further defined as administering 10-1000 mg of the R(−) enantiomer of MDMA or MDA.	7. PIZARRO (2004) "Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites in human samples including the catechol-type metabolite (3,4-dihydroxymethamphetamine)" *Drug Metabolism and Disposition*. Vol. 32(9): 1001-1007 From page **1001** "**3,4-Methylenedioxymethamphetamine (MDMA**; "ecstasy") is a designer drug commonly misused in large segments of young populations. **MDMA is usually formulated in tablets of its racemate (1:1 mixture of its enantiomers) in doses ranging from 50 to 200 mg**. MDMA has an enantioselective metabolism, the (S)-enantiomer being metabolized faster than the **(R)-enantiomer**. Different pharmacologic properties have been attributed to each enantiomer. The carbon responsible for MDMA chirality is preserved along its metabolic disposition. **An analytical method has been developed to determine MDMA enantiomers and those from its major metabolites, 3,4-methylenedioxyamphetamine (MDA),** 3,4-dihydroxymethamphetamine (HHMA), and 4-hydroxy-3-methoxymethamphetamine (HMMA)." 4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 18** "The composition of claim 8, wherein the composition comprises 0.1 mg to 1 mg, 1 mg to 10 mg, **10 mg to 100 mg, 10 mg to 50 mg, 50 mg to 100 mg, 20 mg to 80 mg, 20 mg to 50 mg, 50 mg to 100 mg, 50 mg to 80 mg, or 10 mg to 80 mg** of one or more **phenethylamines** or amphetamines or an amount of a plant or mushroom extract or plant or mushroom to provide an equivalent dose." From **[0150]** "In one embodiment, **the dose of the phenethylamines,** amphetamines, erinacines, hericenones, cannabinoids one or more adversive compounds such as niacin, capsaicin, ipecac, apomorphine, bittering agents, or an amount of a mushroom or plant extract or mushroom or plant having an equivalent amount of about **0.1 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg, 1 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg**."

	From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, prodrugs, **stereoisomers**, or tautomers thereof." From **[0087]** "**Certain compounds described herein may exist in particular geometric or stereoisomeric forms**. A particular enantiomer of a compound described herein may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to **provide the pure desired enantiomers**. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent **recovery of the pure enantiomers**." From [0090] "**Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.** The compounds or compositions described herein may contain an enantiomeric excess of at least 50%, 75%, 90%, 95%, or 99% of one form of the compound, e.g., the S-enantiomer. In other words, such compounds or compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. From [0091] "**Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer and may also be referred to as "optically enriched."** "Optically enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. **In other embodiments, the compound is made up of at least about** 95%, 98%, or **99% by weight of a preferred enantiomer.** Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses…" From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable

salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."

3. PETERS (2005) "Drug Testing in Blood: Validated Negative-Ion Chemical Ionization Gas Chromatographic–Mass Spectrometric Assay for Enantioselective Measurement of the Designer Drugs MDEA, MDMA, and MDA and Its Application to Samples from a Controlled Study with MDMA" *Clinical Chemistry*. Vol. 51(10): 1811-1822

From **page 1811** "**Background:** The enantiomers of the designer drugs **3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA),** and 3,4-methylenedioxyethylamphetamine (MDEA) differ in their pharmacologic and toxicologic potency. The aim of this study was to develop an assay for **measuring these enantiomers in small plasma volumes and to analyze samples from a controlled study with MDMA**.

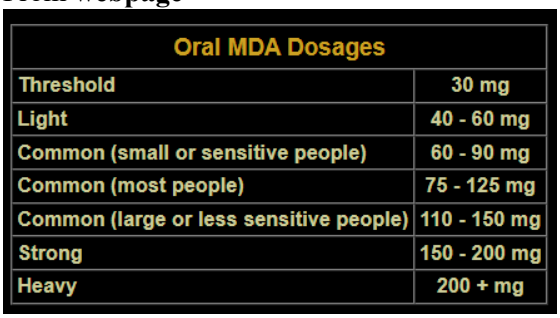
Methods: The analytes were extracted from < or = 0.2 mL of plasma by mixed-mode solid-phase extraction. After derivatization with S-(-)-heptafluorobutyrylprolyl chloride, the resulting diastereomers were separated by gas chromatography (HP-5MS) within 17 min and detected by mass spectrometry in the negative-ion chemical ionization mode. The method was fully validated and applied to samples from a controlled study in which **a single dose of racemic MDMA (75 mg) was administered**.

5. EROWID (2020) "MDMA Dosage by Erowid" Retrieved 24 May 2020. URL: https://www.erowid.org/chemicals/mdma/mdma_dose.shtml

From **webpage**

Oral MDMA Dosages	
Threshold	30 mg
Light	40 - 75 mg
Common (small or sensitive people)	60 - 90 mg
Common (most people)	75 - 125 mg
Common (large or less sensitive people)	110 - 150 mg
Strong	150 - 200 mg
Heavy	200 + mg

From **webpage** "**Chemical analysis of ecstasy tablets has found from 0 - 120 mg of MDMA as well as a variety of the above substances.** Trying to calculate dosages from tablets containing unknown quantities of MDMA can

	be difficult, but **a high quality tablet of street ecstasy (those containing MDMA alone) generally contains between 80 and 120 mg of MDMA**. **Some unusual tablets (especially in Europe) contain 150mg or more**. The chart below shows what are considered recreational/therapeutic dosages for pure MDMA HCl (the most common crystalline form), measured in milligrams." 6. EROWID (2017) "MDA Dosage by Erowid" Retrieved 6 September 2017. https://www.erowid.org/chemicals/mda/mda_dose.shtml From **webpage**  **Oral MDA Dosages** **Threshold** 30 mg **Light** 40 - 60 mg **Common (small or sensitive people)** 60 - 90 mg **Common (most people)** 75 - 125 mg **Common (large or less sensitive people)** 110 - 150 mg **Strong** 150 - 200 mg **Heavy** 200 + mg From **webpage** "Erowid's current view is that **the required dose of MDA vs MDMA are very similar, but result in slightly different effects** (MDA is more physically stimulating while MDMA is more empathogenic at the same dose)."
11. The method of claim 9, wherein said administering step is further defined as administering the R(−) enantiomer of MDMA or MDA daily.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0159]** "In one embodiment, the compositions described herein can be **administered as dosage forms in various regimens, including one dose per day (QD)**, two doses per day (BID), three doses per day (TID), or four times per day (QID) to achieve a total daily dosage. In another embodiment, any of the foregoing doses comprise **a total daily dosage**." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects."

12. The method of claim 9, further including the step of preventing or reducing side effects of neurotoxicity, hyperthermia, and dependence/addiction experienced with racemic MDMA or MDA.	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)… **This suggests that the neurotoxicity of (±)- MDMA is driven by S(+)-MDMA,** but because they did not account for the lower potency of R(−)-MDMA relative to (±)- MDMA, it is not clear if neurotoxicity would occur at a higher, behaviorally equivalent dose of R(−)-MDMA…**Another key difference between R(−)-MDMA and S(+)- MDMA is that R(−)-MDMA does not produce hyperthermia** (Fantegrossi et al. 2003; Frau et al. 2013; Curry et al. 2017). Hyperthermia can be dangerous, and sometimes fatal, following ingestion of MDMA (Henry et al. 1992)… Thus, **the lack of hyperthermia following R(−)-MDMA administration may play a role in the decreased risk for neurotoxicity**." 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." From **page 384** "he one **human study of the behavioral effects** of the enantiomers of (±)-MDMA concluded that S(+)-MDMA was the active enantiomer because no dose of R(−)-MDMA produced even Bnominal^ intoxication, pupil dilation, or jaw clenching (Anderson et al. 1978). **The lack of intoxication following R(−)-MDMA could indicate lower abuse liability**, although further controlled studies would be necessary. Interestingly, as with the previously discussed preclinical studies, (±)-MDMA produced intoxication at doses lower than would be expected from the results of either enantiomer alone…**another study in nonhuman**

	primates suggests that R(−)-MDMA may have lower abuse liability than (±)- MDMA or S(+)-MDMA. Wang and Woolverton (2007), examining self-administration rates of rhesus macaques with a history of cocaine self-administration under a progressive ratio (PR) schedule of reinforcement, found that **R(−)- MDMA did not act as a reinforcer in three out of the five monkeys and the average maximum number of injections was significantly lower for R(−)-MDMA (4.7 injections) than for S(+)-MDMA (10) and (±)-MDMA (9).**"
13. The method of claim 9, wherein the R(−) enantiomer of MDMA or MDA includes a prodrug bound thereto.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
14. The method of claim 13, wherein the prodrug is an amino acid chosen from the group consisting of lysine, alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine,	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof."

isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine.	From **[0178]** "**amino acids are selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine**, ornithine, citrulline, taurine, selenocysteine, pyrrolysine, aminobutyric acid, gama-aminobutryic acid, 3-aminopropanoic acid, dehydroalanine, delta-carboxyglutamic acid, N-formylmethionine."
15. The method of claim 9, wherein the composition is in a continual slow-release formulation.	***From the application of interest 18/186,764 paragraph [0029]*** *"Using the R(−) enantiomer allows for daily use of MDMA or MDA. The compositions are particularly useful in* ***continual slow-release formulations, such as transdermal patches, that can provide a low dose over a long period of time****. The compositions can also be administered in an intranasal spray."* 4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0108]** "The pharmaceutically acceptable compositions of this disclosure may also be **administered topically**, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract can be administered using a rectal suppository formulation (see above) or a suitable enema formulation. **Topically transdermal patches may also be used**." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof."
16. The method of claim 9, wherein the composition is in an intranasal spray form.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0110]** "The pharmaceutically acceptable compositions of this disclosure may also be **administered by nasal aerosol or inhalation.** Such compositions are prepared according to techniques known in the art of pharmaceutical formulation and may **be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, or other conventional solubilizing or dispersing agents…**" From **[0104]** "The compositions described herein may be **administered** orally, parenterally, **by inhalation spray**, topically, rectally, **nasally**, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-

	articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques…" From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof."
17. The method of claim 9, wherein the composition is in a liquid dosage form chosen from the group consisting of suspensions, solutions, emulsions, elixirs, tinctures, sprays, syrups, gels, magmas, liniments, lotions, ointments, pastes, drops, and inhalants.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "RYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0144]** "Another embodiment is a method for manufacturing a dosage form comprising formulating a composition as described herein comprising **sprays**, capsules, tablets, **elixirs, emulsions**, lozenges, **suspensions, syrups**, pills, **lotions**, epidermal patches, suppositories, inhalers, or injectables. Any methods known to the art for formulating extracts or active principal ingredients into lotions, soaps, etc. may be utilized." From **[0109]** "For **topical applications**, the pharmaceutically acceptable compositions may be formulated in a suitable **ointment** containing the active component suspended or dissolved in one or more carriers..." From **[0110]** "The pharmaceutically acceptable compositions of this disclosure may also be administered by nasal aerosol or **inhalation**..."
18. The method of claim 9, wherein the composition is in an oral dosage form chosen from the group consisting of capsules, films, lozenge, patch, powder, tablets, pellets, pills, and troches.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0144]** "Another embodiment is a method for manufacturing a dosage form comprising formulating a composition as described herein comprising sprays, **capsules, tablets**, elixirs, emulsions, **lozenges**, suspensions, syrups, **pills**, lotions, **epidermal patches**, suppositories, inhalers, or injectables. Any methods known to the art for formulating extracts or active principal ingredients into lotions, soaps, etc. may be utilized." From **claim 21** "The composition of claim 1, wherein the composition is a **powder admixture**, liquid, suspension, or emulsion."
19. The method of claim 9, wherein said treating step is further defined as treating a condition or disorder chosen from the group consisting of post-traumatic stress disorder, social anxiety,	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 24** "The composition of claim 1, wherein the composition is effective to **treat, alleviate, prevent or ameliorate serotonin (5-hydroxytryptamine, 5-HT) receptor disorders, psychiatric and mood disorders comprising depression, anxiety, major depressive disorder, treatment resistant depression, persistent depression, manic depression**

autism spectrum disorder, substance use disorder, depression, anxiety disorder, anxiety with life-threatening disease, personality disorder, schizophrenia, obsessive compulsive disorder, couple therapy, enhancement of any psychotherapy by inducing feelings of well-being connectivity, trust, love, empathy, openness, and pro-sociality, and enhancing therapeutic bond in any psychotherapy of patients or neurotic/healthy subjects.	**or bipolar disorder, depressive psychosis, perinatal depression, premenstrual dysphoric disorder, seasonal depressions, situational depression, panic disorder, obsessive compulsive disorder, post-traumatic stress disorder,** attention deficit/hyperactivity disorder, sleep disorders, eating disorders, **schizophrenia**, **personality disorders, substance abuse disorders (drug abuse, addiction, alcoholism)**; neuronal injuries or physical neurodegeneration (e.g., physical injury, head trauma, spinal cord trauma, concussion, peripheral neuron trauma, paralysis, ischemia, hypoxia, stroke; organophosphates, lead, heavy metals, nerve agents, other toxic compounds, prions, amyloid plaque, neurotoxic viruses, stress); neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, frontotemporal dementia, Huntington's disease, adrenal leukodystrophy, Alexander's disease, Alper's disease, Alzheimer's disease, amyotrophic lateral sclerosis, balo concentric sclerosis, Canavan disease, Charcot-Marie-Tooth disease, childhood ataxia with central nervous system hypomyelination, chronic idiopathic peripheral neuropathy, frontotemporal dementia, Huntington's disease, Krabbe disease, monomelic amyotrophy, multiple sclerosis (MS), neurodegeneration, neuromyelitis optica, neuropathic pain, neurosarcoidosis, Parkinson's disease, Pelizaeus-Merzbacher disease, primary lateral sclerosis, progressive supranuclear palsy, radicular pain, radiculopathic pain, Schilder's disease, sciatic pain, sciatica, subacute necrotizing myelopathy, transverse myelitis, or Zellweger syndrome); congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder**; cognitive enhancement, intelligence enhancement, creativity enhancement, memory improvement, learning enhancement and improvement, spiritual enhancement, "mind expansion," IQ improvement, EQ improvement, balance enhancement, athleticism, motor skill enhancement, special navigation, clairvoyance, psychic enhancement, **or general improvement of mental health.**" From **[0064]** "As used herein, **"mental health"** refers to a subject's **emotional, psychological, and social well-being**. Mental health disorders or problems refer to disorders affecting cognition, mood, behavior, and homeostasis. Mental health disorders may be caused by biological factors (genetic or neurochemistry), stress, trauma, or abuse, or associated with injury." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the

	popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects."
20. A method of reducing neurotoxicity of MDMA and MDA, including the steps of: administering an effective amount of a composition of an R(−) enantiomer of MDMA or MDA to an individual; and reducing neurotoxicity of MDMA or MDA while treating the individual.	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)… **This suggests that the neurotoxicity of (±)- MDMA is driven by S(+)-MDMA,** but because they did not account for the lower potency of R(−)-MDMA relative to (±)- MDMA, it is not clear if neurotoxicity would occur at a higher, behaviorally equivalent dose of R(−)-MDMA…Another key difference between R(−)-MDMA and S(+)- MDMA is that R(−)-MDMA does not produce hyperthermia (Fantegrossi et al. 2003; Frau et al. 2013; Curry et al. 2017). Hyperthermia can be dangerous, and sometimes fatal, following ingestion of MDMA (Henry et al. 1992)… Thus, **the lack of hyperthermia following R(−)-MDMA administration may play a role in the decreased risk for neurotoxicity**."
21. The method of claim 20, wherein said administering step is further defined as administering 10-1000 mg of the R(−) enantiomer of MDMA or MDA.	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)… **This suggests that the neurotoxicity of (±)- MDMA is driven by S(+)-MDMA,** but because they did not account for the lower potency of R(−)-MDMA relative to (±)- MDMA, it is not clear if neurotoxicity would occur at a higher, behaviorally equivalent dose of R(−)-MDMA…Another key difference between R(−)-MDMA and S(+)- MDMA is that R(−)-MDMA does not produce hyperthermia (Fantegrossi et al. 2003; Frau et al. 2013; Curry et al. 2017). Hyperthermia can be dangerous, and sometimes fatal, following ingestion of MDMA (Henry et al. 1992)… Thus, **the lack of hyperthermia following R(−)-MDMA administration may play a role in the decreased risk for neurotoxicity**." From **page 378** "A second double blind study of (±)-MDMA-assisted psychotherapy, using similar methods, was conducted in Switzerland with a similar patient population of 12 individuals. It compared **125 mg (±)-MDMA to 25 mg (±)-MDMA** as an active placebo and found a clinically, but not statistically, significant effect of high- versus low-dose (±)-MDMA on CAPS scores (Oehen et al. 2013)."

3. PETERS (2005) “Drug Testing in Blood: Validated Negative-Ion Chemical Ionization Gas Chromatographic–Mass Spectrometric Assay for Enantioselective Measurement of the Designer Drugs MDEA, MDMA, and MDA and Its Application to Samples from a Controlled Study with MDMA” *Clinical Chemistry*. Vol. 51(10): 1811-1822

From **page 1811** “**Background:** The enantiomers of the designer drugs **3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA),** and 3,4-methylenedioxyethylamphetamine (MDEA) differ in their pharmacologic and toxicologic potency. The aim of this study was to develop an assay for **measuring these enantiomers in small plasma volumes and to analyze samples from a controlled study with MDMA**.

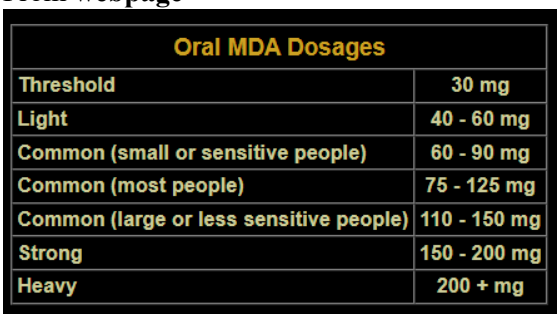
Methods: The analytes were extracted from < or = 0.2 mL of plasma by mixed-mode solid-phase extraction. After derivatization with S-(-)-heptafluorobutyrylprolyl chloride, the resulting diastereomers were separated by gas chromatography (HP-5MS) within 17 min and detected by mass spectrometry in the negative-ion chemical ionization mode. The method was fully validated and applied to samples from a controlled study in which **a single dose of racemic MDMA (75 mg) was administered**.

5. EROWID (2020) “MDMA Dosage by Erowid” Retrieved 24 May 2020. URL: https://www.erowid.org/chemicals/mdma/mdma_dose.shtml

From **webpage**

Oral MDMA Dosages	
Threshold	30 mg
Light	40 - 75 mg
Common (small or sensitive people)	60 - 90 mg
Common (most people)	75 - 125 mg
Common (large or less sensitive people)	110 - 150 mg
Strong	150 - 200 mg
Heavy	200 + mg

From **webpage** “**Chemical analysis of ecstasy tablets has found from 0 - 120 mg of MDMA as well as a variety of the above substances.** Trying to calculate dosages from tablets containing unknown quantities of MDMA can be difficult, but **a high quality tablet of street ecstasy (those containing MDMA alone) generally contains between 80 and 120 mg of MDMA**. **Some unusual tablets (especially in Europe) contain 150mg or more**. The chart below shows what are considered recreational/therapeutic dosages for pure MDMA HCl (the most common crystalline form), measured in milligrams.”

	6. EROWID (2017) "MDA Dosage by Erowid" Retrieved 6 September 2017. https://www.erowid.org/chemicals/mda/mda_dose.shtml From **webpage**  **Oral MDA Dosages** **Threshold** 30 mg **Light** 40 - 60 mg **Common (small or sensitive people)** 60 - 90 mg **Common (most people)** 75 - 125 mg **Common (large or less sensitive people)** 110 - 150 mg **Strong** 150 - 200 mg **Heavy** 200 + mg From **webpage** "Erowid's current view is that **the required dose of MDA vs MDMA are very similar, but result in slightly different effects** (MDA is more physically stimulating while MDMA is more empathogenic at the same dose)."
22. The method of claim 20, wherein said administering step is further defined as administering the R(−) enantiomer of MDMA or MDA daily.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0159]** "In one embodiment, the compositions described herein can be **administered as dosage forms in various regimens, including one dose per day (QD)**, two doses per day (BID), three doses per day (TID), or four times per day (QID) to achieve a total daily dosage. In another embodiment, any of the foregoing doses comprise **a total daily dosage**." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From [0091] "**Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer and may also be referred to as "optically enriched."** "Optically enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. **In other embodiments, the compound is made up of at least about** 95%, 98%, or **99% by weight of a preferred enantiomer.**

	Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses…"
23. The method of claim 20, wherein the R(−) enantiomer of MDMA or MDA includes a prodrug bound thereto.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
24. The method of claim 23, wherein the prodrug is an amino acid chosen from the group consisting of lysine, alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine,	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0178]** "**amino acids are selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine**, ornithine, citrulline, taurine, selenocysteine, pyrrolysine, aminobutyric acid, gama-aminobutryic

tryptophan, tyrosine, and valine.	acid, 3-aminopropanoic acid, dehydroalanine, delta-carboxyglutamic acid, N-formylmethionine."
25. A method of reducing hyperthermia of MDMA and MDA, including the steps of: administering an effective amount of a composition of an R(−) enantiomer of MDMA or MDA to an individual; and reducing hyperthermia of MDMA or MDA while treating the individual.	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)… **This suggests that the neurotoxicity of (±)- MDMA is driven by S(+)-MDMA,** but because they did not account for the lower potency of R(−)-MDMA relative to (±)- MDMA, it is not clear if neurotoxicity would occur at a higher, behaviorally equivalent dose of R(−)-MDMA…**Another key difference between R(−)-MDMA and S(+)- MDMA is that R(−)-MDMA does not produce hyperthermia** (Fantegrossi et al. 2003; Frau et al. 2013; Curry et al. 2017). Hyperthermia can be dangerous, and sometimes fatal, following ingestion of MDMA (Henry et al. 1992)… Thus, **the lack of hyperthermia following R(−)-MDMA administration may play a role in the decreased risk for neurotoxicity**."
26. The method of claim 25, wherein said administering step is further defined as administering 10-1000 mg of the R(−) enantiomer of MDMA or MDA.	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)… **This suggests that the neurotoxicity of (±)- MDMA is driven by S(+)-MDMA,** but because they did not account for the lower potency of R(−)-MDMA relative to (±)- MDMA, it is not clear if neurotoxicity would occur at a higher, behaviorally equivalent dose of R(−)-MDMA…**Another key difference between R(−)-MDMA and S(+)- MDMA is that R(−)-MDMA does not produce hyperthermia** (Fantegrossi et al. 2003; Frau et al. 2013; Curry et al. 2017). Hyperthermia can be dangerous, and sometimes fatal, following ingestion of MDMA (Henry et al. 1992)… Thus, **the lack of hyperthermia following R(−)-MDMA administration may play a role in the decreased risk for neurotoxicity**." From **page 378** "A second double blind study of (±)-MDMA-assisted psychotherapy, using similar methods, was conducted in Switzerland with a similar patient population of 12 individuals. It compared **125 mg (±)-MDMA to 25 mg (±)-MDMA** as an active placebo and found a clinically,

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From **page 1811** "**Background:** The enantiomers of the designer drugs **3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA),** and 3,4-methylenedioxyethylamphetamine (MDEA) differ in their pharmacologic and toxicologic potency. The aim of this study was to develop an assay for **measuring these enantiomers in small plasma volumes and to analyze samples from a controlled study with MDMA**.

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	6. EROWID (2017) "MDA Dosage by Erowid" Retrieved 6 September 2017. https://www.erowid.org/chemicals/mda/mda_dose.shtml From **webpage** **Oral MDA Dosages** Threshold: 30 mg Light: 40 - 60 mg Common (small or sensitive people): 60 - 90 mg Common (most people): 75 - 125 mg Common (large or less sensitive people): 110 - 150 mg Strong: 150 - 200 mg Heavy: 200 + mg From **webpage** "Erowid's current view is that **the required dose of MDA vs MDMA are very similar, but result in slightly different effects** (MDA is more physically stimulating while MDMA is more empathogenic at the same dose)."
27. The method of claim 25, wherein said administering step is further defined as administering the R(−) enantiomer of MDMA or MDA daily.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0159]** "In one embodiment, the compositions described herein can be **administered as dosage forms in various regimens, including one dose per day (QD)**, two doses per day (BID), three doses per day (TID), or four times per day (QID) to achieve a total daily dosage. In another embodiment, any of the foregoing doses comprise **a total daily dosage**." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." 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

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28. The method of claim 25, wherein the R(−) enantiomer of MDMA or MDA includes a prodrug bound thereto.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
29. The method of claim 28, wherein the prodrug is an amino acid chosen from the group consisting of lysine, alanine, arginine,	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine**

asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine.	**(MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0178]** "**amino acids are selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine**, ornithine, citrulline, taurine, selenocysteine, pyrrolysine, aminobutyric acid, gama-aminobutryic acid, 3-aminopropanoic acid, dehydroalanine, delta-carboxyglutamic acid, N-formylmethionine."
30. A method of reducing physical dependence or abuse liability of MDMA and MDA, including the steps of: administering an effective amount of a composition of an R(−) enantiomer of MDMA or MDA to an individual; and reducing the physical dependence or abuse liability of MDMA or MDA while treating the individual.	1. PITTS (2017) "(±)-MDMA and its enantiomers: potential therapeutic advantages of R(−)-MDMA" *Psychopharmacology*. Vol. 235(2): 377-392 From **page 384** "he one **human study of the behavioral effects** of the enantiomers of (±)-MDMA concluded that S(+)-MDMA was the active enantiomer because no dose of R(−)-MDMA produced even Bnominal^ intoxication, pupil dilation, or jaw clenching (Anderson et al. 1978). **The lack of intoxication following R(−)-MDMA could indicate lower abuse liability**, although further controlled studies would be necessary. Interestingly, as with the previously discussed preclinical studies, (±)-MDMA produced intoxication at doses lower than would be expected from the results of either enantiomer alone…**another study in nonhuman primates suggests that R(−)-MDMA may have lower abuse liability than (±)- MDMA or S(+)-MDMA.** Wang and Woolverton (2007), examining self-administration rates of rhesus macaques with a history of cocaine self-administration under a progressive ratio (PR) schedule of reinforcement, found that **R(−)- MDMA did not act as a reinforcer in three out of the five monkeys and the average maximum number of injections was significantly lower for R(−)-MDMA (4.7 injections) than for S(+)-MDMA (10) and (±)-MDMA (9).**"
31. The method of claim 30, wherein said administering step is further defined as administering 10-1000 mg of the R(−) enantiomer of MDMA or MDA.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 18** "The composition of claim 8, wherein the composition comprises 0.1 mg to 1 mg, 1 mg to 10 mg, **10 mg to 100 mg, 10 mg to 50 mg, 50 mg to 100 mg, 20 mg to 80 mg, 20 mg to 50 mg, 50 mg to 100 mg, 50 mg to 80 mg, or 10 mg to 80 mg** of one or more **phenethylamines** or amphetamines or an amount of a plant or mushroom extract or plant or mushroom to provide an equivalent dose." From **[0150]** "In one embodiment, **the dose of the phenethylamines,** amphetamines, erinacines, hericenones, cannabinoids one or more adverse compounds such as niacin, capsaicin, ipecac, apomorphine, bittering agents, or an amount of a mushroom or plant extract or mushroom or plant having an equivalent amount of about **0.1 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg, 1 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60**

	mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, prodrugs, **stereoisomers**, or tautomers thereof." From **[0087]** "**Certain compounds described herein may exist in particular geometric or stereoisomeric forms**. A particular enantiomer of a compound described herein may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to **provide the pure desired enantiomers**. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent **recovery of the pure enantiomers**." From [0090] "**Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.** The compounds or compositions described herein may contain an enantiomeric excess of at least 50%, 75%, 90%, 95%, or 99% of one form of the compound, e.g., the S-enantiomer. In other words, such compounds or compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. From [0091] "**Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer and may also be referred to as "optically enriched."** "Optically enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. **In other embodiments, the compound is made up of at least about** 95%, 98%, or **99% by weight of a preferred enantiomer.** Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses…"

	From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
32. The method of claim 30, wherein said administering step is further defined as administering the R(−) enantiomer of MDMA or MDA daily.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **[0159]** "In one embodiment, the compositions described herein can be **administered as dosage forms in various regimens, including one dose per day (QD)**, two doses per day (BID), three doses per day (TID), or four times per day (QID) to achieve a total daily dosage. In another embodiment, any of the foregoing doses comprise **a total daily dosage**." From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects."
33. The method of claim 30, wherein the R(−) enantiomer of MDMA or MDA includes a prodrug bound thereto.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **claim 8** "The composition of claim 1, wherein **the composition further comprises one or more phenethylamines** or amphetamines in pure form or extracts or isolates from plants comprising thereof." From **[0224]** "In another embodiment, **the compositions described herein comprises a phenethylamine or an amphetamine compound selected from**:… **N-methyl-3,4-methylenedioxy-amphetamine (MDMA)**… (R)-2,5-dimethoxy-4-iodoamphetamine (i.e., 2C-H) is structurally similar to the

	popular psychedelic drug 2C-B (which is similar to ecstasy and MDMA), but it does not itself have any psychoactive effects." From **claim 29** "The use of a pharmaceutical composition comprising one or more tryptamines, erinacines, hericenones, or pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, stereoisomers, or tautomers thereof, or combinations thereof and one or more pharmaceutically acceptable excipients, in the manufacture of **a medicament for treatment of serotonin (5-hydroxytryptamine, 5-HT) receptor disorders**, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, **autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement**, physical or motor neuron enhancement, **or general improvement of mental health**."
34. The method of claim 33, wherein the prodrug is an amino acid chosen from the group consisting of lysine, alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine.	4. U.S. Pat. App. Doc. No. 2021/0069170 A1 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published March 11, 2021) From **claim 9** "The composition of claim 8, wherein **the phenethylamines** or amphetamines **comprises** … **3,4-methylenedioxy-amphetamine (MDA)**, …pharmaceutically acceptable salts, hydrates, solvates, **prodrugs**, **stereoisomers**, or tautomers thereof." From **[0178]** "**amino acids are selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine**, ornithine, citrulline, taurine, selenocysteine, pyrrolysine, aminobutyric acid, gama-aminobutryic acid, 3-aminopropanoic acid, dehydroalanine, delta-carboxyglutamic acid, N-formylmethionine."

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/186,494	**01/12/2024 05:34:34 PM Z ET**	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	63943378	FILING DATE	03/20/2023
CUSTOMER #	–	FIRST NAMED INVENTOR	
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 16

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Third-party-notification-request.pdf		1	Request for Notification of Non-compliant Third-Party Submission	14 KB
Concise-description-generated.pdf		2	Concise Description of Relevance	35 KB
third-party-preissuance-submission.pdf		3	Third-Party Submission Under 37 CFR 1.290	66 KB
Claims_Chart.pdf		33	-	521 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-33)	33	Concise Description of Relevance	428 KB
Claims_Chart-	(1-33)	33	Concise Description of	428 KB

3P.RELEVANCE.pdf			Relevance	
Claims_Chart-3P.RELEVANCE.pdf	(1-33)	33	Concise Description of Relevance	428 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-33)	33	Concise Description of Relevance	428 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-33)	33	Concise Description of Relevance	428 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-33)	33	Concise Description of Relevance	428 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-33)	33	Concise Description of Relevance	428 KB
1_PITTS.pdf		16	-	2409 KB
1_PITTS-NPL.pdf	(1-16)	16	Non Patent Literature	2359 KB
2_CURRY.pdf		26	-	3467 KB
2_CURRY-NPL.pdf	(1-26)	26	Non Patent Literature	3451 KB
3_PETERS.pdf		12	-	347 KB
3_PETERS-NPL.pdf	(1-12)	12	Non Patent Literature	343 KB
5_EROWID_MDMA.pdf		1	-	305 KB
5_EROWID_MDMA-NPL.pdf	(1-1)	1	Non Patent Literature	297 KB
6_EROWID_MDA.pdf		1	-	217 KB
6_EROWID_MDA-NPL.pdf	(1-1)	1	Non Patent Literature	210 KB
7_PIZARRO.pdf		7	-	1493 KB

7_PIZARRO-NPL.pdf	(1-7)	7	Non Patent Literature	1484 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Third-party-notification-request.pdf	6341CD6839B3B9D4FF1C96120FB7E2DB3A8001D49619274003C775875B4F5F381E9F9C48AA2DA15B2DC5C1F82F3305D58576C337FF34BAD5C1D1BF3281122FF5
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Claims_Chart.pdf	A38C0BFA8142BEC8524F9084A17BB92FC2EECD126B2D45BD0D351B583D6021AEC6294314947E24703C3327D5DB534E3987A500A6EF38E4F31EE1E34A28974E2C
Claims_Chart-3P.RELEVANCE.pdf	25FBE5D23BA9F182127F1400A7090FEE05E493F23627B90805BA9DB4CE5566B0B4260C8393AFA099809A7C33BE247F9EF16F6609562744F9DBFD304393D2E04A
Claims_Chart-3P.RELEVANCE.pdf	56795386CA51BABA9594BF6EA5372984DDDF40B258DE92FC5BF8BC8AD721306947562F47441D5D838B1A213141372C2D018FE54C7796675EDA68433567474A35
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Claims_Chart-3P.RELEVANCE.pdf	CC7B4FE32CBD12F413D824C6A1688966A1C5DF3960DA227B2DF3C5276E361C9A8C077ECD024FB2A5FDDF73C2ACC0A109420E9361BAB6E630D38C9AFB8F7DDBE3
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7_PIZARRO-NPL.pdf	4BDADCBF143BBC4CED62EA9E402B09575014AD41DA0410BF23157028DE3708917E048883E5DE81220CAF384971BEE1781BBC5F9221E8B7D68DA154E1B57D42EC

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/186,494	**01/12/2024 05:34:34 PM Z ET**	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	63943378	AUTHORIZED BY	-
CUSTOMER #	–	FILING DATE	03/20/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0642	**E20241BH35086902**	**Sisi Li**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2818	DOCUMENT FEE FOR THIRD-PARTY SUBMISSIONS (SEE 37 CFR 1.290(F))	72.00	1	72.00
			TOTAL AMOUNT:	**$72.00**

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New Applications Under 35 U.S.C. 111

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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