



(51) International Patent Classification:

C07C 217/60 (2006.01) A61P 25/24 (2006.01)
A61K 31/137 (2006.01) A61P 25/28 (2006.01)
A61P 25/22 (2006.01)

(21) International Application Number:

PCT/US2024/041007

(22) International Filing Date:

05 August 2024 (05.08.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/530,686 03 August 2023 (03.08.2023) US

(71) Applicant: **ARCADIA MEDICINE, INC.** [US/US]; 2261
Market Street #4519, San Francisco, California 94114 (US).

(72) Inventors: **FRERICHS, Quintin**; c/o Arcadia Medicine,
Inc., 2261 Market Street #4519, San Francisco, California
94114 (US). **OBIDIN, Nikita**; c/o Arcadia Medicine, Inc.,

2261 Market Street #4519, San Francisco, California 94114
(US).

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

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

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, CV,
GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST,

(54) Title: CRYSTALLINE POLYMORPHS OF 4-BROMO-2,5-DIMETHOXYPHENETHYLAMINE (2C-B)

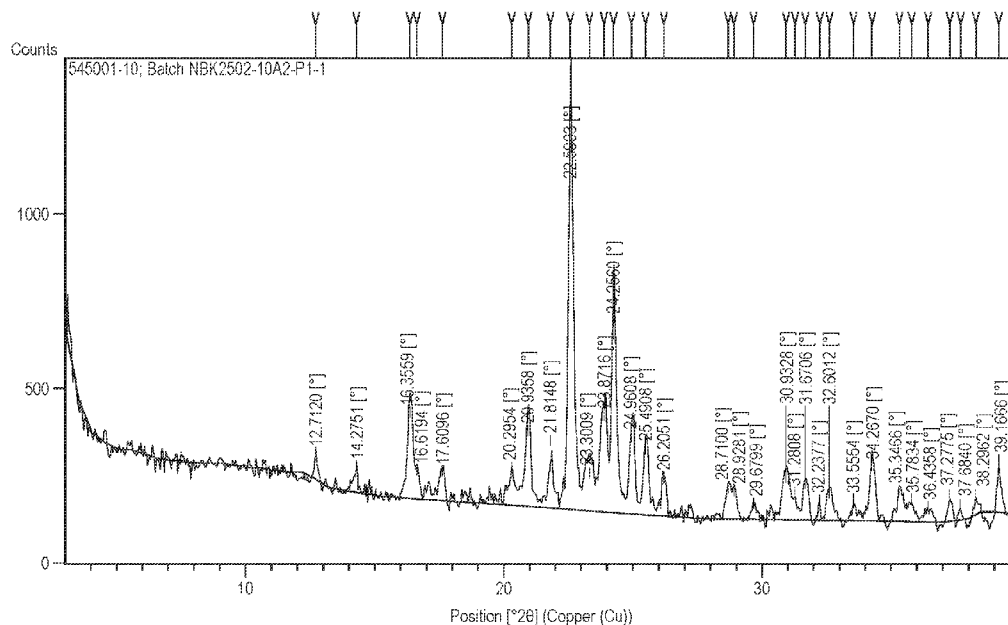


FIG. 1

(57) Abstract: The disclosure relates in some aspects to solid forms of 4-bromo-2,5-dimethoxyphenethylamine (2C-B), such as crystalline polymorphs. In some aspects, the disclosure relates to crystalline Polymorph 1 of 2C-B hydrobromide (HBr). In other aspects, the disclosure provides methods of making the solid forms, compositions comprising the solid forms, and methods of using such solid forms, including their administration to subjects, for example to modulate neurotransmission, increase neuroplasticity or neurogenesis, or treat a medical condition, such as a mental, behavioral, or neurodevelopmental disorder, a neurodegenerative disorder, or a pain disorder.

SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

CRYSTALLINE POLYMORPHS OF 4-BROMO-2,5-DIMETHOXYPHENETHYLAMINE (2C-B)

INVENTORS: Quintin Frerichs, Nikita Obidin

CROSS-REFERENCE

[01] Priority is claimed under PCT Art. 8(1) and Rule 4.10 to U.S. Prov. App. No. 63/530,686, filed August 3, 2023, and incorporated by reference for all purposes as if fully set forth herein.

FIELD OF THE INVENTION

[02] This disclosure relates in some aspects to solid forms of 4-bromo-2,5-dimethoxyphenethylamine (2C-B), such as crystalline polymorphs. In some aspects, the disclosure relates to crystalline Polymorph 1 of 2C-B hydrobromide (HBr). In other aspects are provided methods of making the solid forms, compositions comprising the solid forms, and methods of using such solid forms, including their administration to subjects.

BACKGROUND OF THE INVENTION

[03] 4-Bromo-2,5-dimethoxyphenethylamine (2C-B) is a member of the “2C” or “2C-x” family of compounds, and known for having both psychedelic and entactogenic effects. Structurally, 2C-x compounds are substituted phenethylamines characterized by methoxy groups on the 2 and 5 positions of the benzene ring, and an additional substituent at the 4 position. With 2C-B, the 4-substituent is bromine, hence 2C-“B.”

[04] 2C-B was first synthesized by Alexander (“Sasha”) Shulgin in 1974, and its synthesis and effects were described by Sasha and his wife Ann in their book PIHKAL: A Chemical Love Story, published in 1991 (“Phenethylamines I Have Known and Loved”). In PIHKAL, providing commentary on the hundreds of trip reports they had collected, they remarked: “The vast majority are positive, ranging from the colorful to the ecstatic.” 2C-B has since been used both recreationally and to treat a variety of disorders and conditions, and has attracted attention for its therapeutic potential in the recent years of the “psychedelic renaissance.”

[05] Crystalline forms of compounds can have different physical and/or chemical properties, and these may vary in ways relevant for drug delivery. In some cases, a single compound can exist as one or more unique crystalline forms called polymorphs. Different polymorphic forms of a compound may have varying properties related to, or that effect, for example, particle size, filtration rates, hygroscopicity, ability to micronize, stability, dissolution rates, dispersibility in powders, and bioavailability. Providing a pharmaceutical agent as a specific polymorph may optimize any one or more of these properties, and may improve the therapeutic utility of the agent, for example if the agent has intrinsic barriers to drug delivery, such as low solubility, slow gastrointestinal dissolution, low permeability, or susceptibility to first-pass metabolism.

[06] Applicant herein describes novel polymorphic forms of 2C-B, that can render it more suitable as a pharmaceutical agent, such as for use in pharmacotherapy or psychedelic-assisted therapy, and that have such other benefits and advantages as will become apparent from the description below.

INCORPORATION BY REFERENCE

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

BRIEF SUMMARY OF THE INVENTION

[08] The following is a simplified summary of some embodiments of the invention in order to provide a basic understanding thereof. This summary is not an extensive overview of the invention. It is not intended to identify key or critical elements of the invention or to delineate its full scope. Its sole purpose is to present some embodiments and aspects of the invention in a simplified form as a prelude to the detailed description.

[09] In one aspect is provided a crystalline polymorph of 4-bromo-2,5-dimethoxyphenethylamine (2C-B) hydrobromide (HBr) (Polymorph 1), characterized by one or more X-ray powder diffraction (XRPD) peaks at about 20.9, 24.3, 26.2, and 31.7 °2θ (Cu Kα1 radiation).

[10] In some embodiments, the disclosed polymorph is characterized by two or more XRPD peaks at about 20.9, 24.3, 26.2, and 31.7 °2θ. In some embodiments, the two or more XRPD peaks are at about 26.2 and 31.7 °2θ. In some embodiments, the two or more XRPD peaks are at about 24.3 and 26.2 °2θ. In some embodiments, the two or more XRPD peaks are at about 24.3 and 31.7 °2θ. In some embodiments, the disclosed polymorph is characterized by three or more XRPD peaks at about 20.9, 24.3, 26.2, and 31.7 °2θ. In some embodiments, the three or more XRPD peaks are at about 24.3, 26.2, and 31.7 °2θ. In some embodiments, the three or more XRPD peaks are at about 20.9, 26.2, and 31.7 °2θ. In some embodiments, the disclosed polymorph is characterized by XRPD peaks at about 20.9, 24.3, 26.2, and 31.7 °2θ.

[11] In another aspect is provided a crystalline polymorph characterized by any combination of XRPD peaks selected from **Table 1**. In some embodiments, the disclosed polymorph is characterized by at least one, two, three, four, five, six, seven, eight, nine, or ten XRPD peaks selected from **Table 1**. Also provided is a polymorph having an XRPD diffractogram that is characterized by peak locations, d-spacings, heights, and areas that are substantially similar to that of **Table 1**. Also provided is a disclosed polymorph having an XRPD diffractogram that is substantially similar to that shown in **FIG. 1**.

[12] In some embodiments, the XRPD peak at 24.3 °2θ has a relative peak area compared to the XRPD peak at 20.9 °2θ that is between about 1.5 and 2.5. In some embodiments, the XRPD peak at 24.3 °2θ has a relative peak area compared to the XRPD peak at 20.9 °2θ that is about 2.0. In some embodiments, provided is a disclosed polymorph wherein the XRPD peak at 24.3 °2θ has a relative peak area compared to the XRPD peak at 26.2 °2θ that is between about 2.0 and 5.0. In embodiments, the XRPD peak at 24.3 °2θ has a relative peak area compared to the XRPD peak at 26.2 °2θ that is about 3.5. In embodiments, the XRPD peak at 24.3 °2θ has a relative peak area compared to the XRPD peak at 31.7 °2θ that is between

about 3.0 and 6.0. In embodiments, the XRPD peak at $24.3^{\circ}2\theta$ has a relative peak area compared to the XRPD peak at $26.2^{\circ}2\theta$ that is about 4.5. In embodiments, a disclosed polymorph is further characterized by the absence of one or more XRPD peaks at about 27.2 and $30.3^{\circ}2\theta$. In embodiments, a disclosed polymorph is characterized by the absence of an XRPD peak at about $27.2^{\circ}2\theta$. In embodiments, a disclosed polymorph is characterized by the absence of an XRPD peak at about $30.3^{\circ}2\theta$. In embodiments, a disclosed polymorph is further characterized by the absence of XRPD peaks at 27.2 and $30.3^{\circ}2\theta$.

[13] In some embodiments, the disclosed polymorph is further characterized by a solubility curve in isopropyl alcohol (IPA) that is substantially similar to that shown in **FIG. 15**. In some embodiments, the disclosed polymorph is further characterized by a solubility curve in IPA:water (98:2) that is substantially similar to that shown in **FIG. 16**. In some embodiments, the disclosed polymorph is further characterized by a solubility curve in acetonitrile:water (95:5) that is substantially similar to that shown in **FIG. 17**.

[14] In some embodiments, the disclosed polymorph has a chemical purity of greater than about 95%, 96%, 97%, 98%, or 99%.

[15] In some embodiments, the XRPD peak at about $20.9^{\circ}2\theta$ is at $20.9 \pm 0.5^{\circ}$, 0.4° , 0.3° , 0.2° , 0.1° , 0.05° , or $0.01^{\circ}2\theta$. In some embodiments, the XRPD peak at about $24.3^{\circ}2\theta$ is at $24.3 \pm 0.5^{\circ}$, 0.4° , 0.3° , 0.2° , 0.1° , 0.05° , or $0.01^{\circ}2\theta$. In some embodiments, the XRPD peak at about $26.2^{\circ}2\theta$ is at $26.2 \pm 0.5^{\circ}$, 0.4° , 0.3° , 0.2° , 0.1° , 0.05° , or $0.01^{\circ}2\theta$. In some embodiments, the XRPD peak at about $31.7^{\circ}2\theta$ is at $31.7 \pm 0.5^{\circ}$, 0.4° , 0.3° , 0.2° , 0.1° , 0.05° , or $0.01^{\circ}2\theta$.

[16] In another aspect is provided a pharmaceutical composition comprising crystalline 2C-B, and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the crystalline 2C-B comprises the polymorph of any one of the disclosed embodiments. In some embodiments, the composition is suitable for oral, buccal, sublingual, intranasal, injectable, subcutaneous, intravenous, intraocular, topical, or transdermal administration. In some embodiments, the pharmaceutical composition is in unit dosage form. In some embodiments, the pharmaceutical composition comprises crystalline 2C-B in a total amount of between about 0.1 mg and 100 mg. In some embodiments, the pharmaceutical composition comprises crystalline 2C-B in a total amount of between about 1 mg and 50 mg or between about 10 mg and 50 mg.

[17] In some embodiments, the polymorphic purity of the crystalline 2C-B is at least 90%, at least 95%, at least 99%, at least 99.5%, or at least 99.9%.

[18] In some embodiments, the pharmaceutical composition further comprises a therapeutically effective amount of an additional active compound, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, provided is a pharmaceutical composition wherein the additional active compound is selected from the group consisting of amino acids, antioxidants, anti-inflammatory agents, analgesics, antineuropathic and antinociceptive agents, antimigraine agents, anxiolytics, antidepressants, antipsychotics, anti-PTSD agents, dissociatives, cannabinoids, immunostimulants, anti-cancer agents, antiemetics, orexigenics, antiulcer agents, antihistamines, antihypertensives, anticonvulsants, antiepileptics,

bronchodilators, neuroprotectants, nootropics, empathogens, psychedelics, plasticity-inducing agents, monoamine oxidase inhibitors, tryptamines, terpenes, phenethylamines, sedatives, stimulants, serotonergic agents, NMDA modulators, NMDA antagonists, and vitamins. In some embodiments, the additional active compound is a tryptamine, a phenethylamine, an ergoline, an ergot alkaloid, a lysergamide, or a cannabinoid. In some embodiments, the phenethylamine is MDMA or a salt thereof.

[19] In some embodiments, the phenethylamine is a pure or substantially pure individual enantiomer of MDMA or a salt thereof. In some embodiments, the phenethylamine is a non-racemic mixture of MDMA or a salt thereof, comprising an enantiomeric excess of R-MDMA or an enantiomeric excess of S-MDMA. In some embodiments, the non-racemic mixture of MDMA or a salt thereof comprises an enantiomeric excess of R-MDMA, wherein the R-MDMA in enantiomeric excess comprises R-MDMA to S-MDMA in a molar ratio of about 4:1 to 12:1, 5:1 to 10:1, 6:1 to 12:1, 7:1 to 11:1, or 8:1 to 10:1. In some embodiments, the non-racemic mixture of MDMA or a salt thereof comprises an enantiomeric excess of R-MDMA, wherein the R-MDMA in enantiomeric excess comprises R-MDMA to S-MDMA in a molar ratio of about 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, or 12:1. In some embodiments, the non-racemic mixture of MDMA or a salt thereof comprises an enantiomeric excess of R-MDMA, wherein the R-MDMA in enantiomeric excess comprises R-MDMA to S-MDMA in a molar ratio of about 9:1. In some embodiments, the non-racemic mixture of MDMA or a salt thereof comprises an enantiomeric excess of R-MDMA, wherein the R-MDMA in enantiomeric excess comprises, on a molar basis: 90% $\pm$ 5% R-MDMA and 10% $\pm$ 5% S-MDMA; 90% $\pm$ 2.5% R-MDMA and 10% $\pm$ 2.5% S-MDMA; 90% $\pm$ 2% R-MDMA and 10% $\pm$ 2% S-MDMA; 90% $\pm$ 1% R-MDMA and 10% $\pm$ 1% S-MDMA; 90% $\pm$ 0.1% R-MDMA and 10% $\pm$ 0.1% S-MDMA; or 90% $\pm$ 0.05% R-MDMA and 10% $\pm$ 0.05% S-MDMA.

[20] In another aspect is provided a method of modulating neurotransmission in a subject, comprising administering to the subject the polymorph of any of the disclosed embodiments. In some embodiments, modulating neurotransmission comprises agonizing the 5-HT_{2A} receptor.

[21] Also provided is a method of increasing neuroplasticity or neurogenesis in a subject, comprising administering to the subject the polymorph of any of the disclosed embodiments. In some embodiments, increasing neuroplasticity or neurogenesis comprises increasing neuritogenesis, spinogenesis, or synaptogenesis.

[22] Also provided is a method of treating a medical condition in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the polymorph of any of the disclosed embodiments. In some embodiments, the medical condition is a disorder linked to dysregulation or inadequate functioning of serotonergic neurotransmission. In some embodiments, the medical condition is a neurodevelopmental disorder, schizophrenia or another primary psychotic disorder, catatonia, a mood disorder, an anxiety or fear-related disorder, an obsessive-compulsive or related disorder, a disorder specifically associated with stress, a dissociative disorder, a feeding or eating disorder, an elimination disorder, a disorder of bodily distress or bodily experience, a disorder due to substance use or addictive behavior, an impulse control disorder, a disruptive behavior or dissocial disorder, a personality disorder, a

paraphilic disorder, a factitious disorder, a neurocognitive disorder, a mental or behavioral disorder associated with pregnancy, childbirth or the puerperium, a sleep-wake disorder, or a sexual dysfunction.

[23] In some embodiments, the medical condition is a depressive disorder. In some embodiments, the depressive disorder is major depressive disorder (MDD) or treatment resistant depression (TRD). In some embodiments, the medical condition is an anxiety disorder. In some embodiments, the anxiety disorder is generalized anxiety disorder (GAD). In some embodiments, the medical condition is a trauma-related disorder. In some embodiments, the trauma related disorder is post-traumatic stress disorder (PTSD) or complex post-traumatic stress disorder (cPTSD). In some embodiments, the medical condition is autism, autism spectrum disorder (ASD), or social anxiety in autistic subjects. In some embodiments, the medical condition is a neurodegenerative disorder or a pain disorder. In some embodiments, the polymorph is administered together with one or more sessions of psychotherapy.

[24] Also provided is a polymorph of any of the disclosed embodiments for use in the treatment of a medical condition. Also provided is the use of a polymorph of any of the disclosed embodiments for the manufacture of a medicament for the treatment of a medical condition. Also provided is a pharmaceutical composition of any of the disclosed embodiments for use in the treatment of a medical condition. Also provided is the use of a pharmaceutical composition of any of the disclosed embodiments for the manufacture of a medicament for the treatment of a medical condition.

[25] The foregoing has outlined broadly and in summary certain pertinent features of the disclosure so that the detailed description of the invention that follows may be better understood, and so that the present contribution to the art can be more fully appreciated. Hence, this summary is to be considered as a brief and general synopsis of only some of the objects and embodiments disclosed herein, is provided solely for the benefit and convenience of the reader, and is not intended to limit in any manner the scope, or range of equivalents, to which the claims are lawfully entitled. Additional features of the invention are described hereinafter. It should be appreciated by those in the art that all disclosed specific compositions and methods are only exemplary, and may be readily utilized as a basis for modifying or designing other compositions and methods for carrying out the same purposes. Such equivalent compositions and methods will be appreciated to be also within the scope and spirit of the invention as set forth in the claims.

BRIEF DESCRIPTION OF THE FIGURES

[26] To further clarify various aspects of the invention, a more particular description is rendered by reference to certain exemplary embodiments illustrated in the figures. It will be appreciated that these figures depict only illustrated embodiments of the invention and should not be considered limiting of its scope. They are merely provided as exemplary illustrations of certain concepts of some embodiments of the invention. These figures, and the elements depicted therein, are not necessarily drawn to consistent scale or to any scale. Certain aspects of the invention are therefore further described and explained with additional specificity and detail, but still by way of example only, with reference to the accompanying figures in which:

- [27] **FIG. 1** shows an exemplary XRPD diffractogram of a sample comprising 2C-B HBr Polymorph 1;
- [28] **FIG. 2** shows an exemplary XRPD diffractogram of 2C-B HBr;
- [29] **FIG. 3** shows exemplary XRPD diffractograms of batches of 2C-B HBr and 2C-B HCl used as starting materials in the synthesis of disclosed solid forms;
- [30] **FIG. 4** shows XRPD spectra of the 2C-B HBr starting material before DVS (**FIG. 4A**) and after DVS (**FIG. 4B**).
- [31] **FIG. 5** shows an exemplary thermogravimetric analysis (TGA) curve of a sample comprising 2C-B HBr starting material;
- [32] **FIG. 6** shows an exemplary differential scanning calorimetry (DSC) thermogram of a sample comprising 2C-B HBr starting material;
- [33] **FIG. 7** shows an exemplary Fourier-transform infrared (FT-IR) spectrum of a sample comprising 2C-B HBr starting material;
- [34] **FIG. 8** shows optical microscope images used for baseline morphological analysis of 2C-B HBr starting material at 2.5X (top), 5X (middle), and 10X (bottom) magnification;
- [35] **FIG. 9** shows an exemplary dynamic vapor sorption (DVS) profile of a sample comprising 2C-B HBr starting material;
- [36] **FIG. 10** shows an exemplary DVS isotherm plot of a sample comprising 2C-B HBr starting material;
- [37] **FIG. 11A** and **FIG. 11B** shows the heating and cooling cycles used to synthesize 2C-B HBr Polymorph 1 from the 2C-B HBr starting material, for two exemplary samples (vials);
- [38] **FIG. 12** shows exemplary XRPD spectra of 2C-B HBr obtained by crystallization from EtOH, MeOH, MeCN, and MeCN:Water, which show the same form as the 2C-B HBr starting material;
- [39] **FIG. 13** shows exemplary XRPD spectra of the new polymorphic form of 2C-B HBr (i.e., 2C-B HBr Polymorph 1) obtained by crystallization from IPA (**FIG. 13A** and **FIG. 13B**) or IPA:water (**FIG. 13C**).
- [40] **FIG. 14** shows a comparison between exemplary XRPD spectra of 2C-B starting material (**FIG. 14A**) and 2C-B Polymorph 1 (**FIG. 14B**). The solid boxes indicate peaks present in 2C-B Polymorph 1 that are absent in the 2C-B HBr starting material, and the hashed boxes indicate peaks present in the starting material that are absent in 2C-B Polymorph 1;
- [41] **FIG. 15** shows an exemplary solubility curve of 2C-B HBr Polymorph 1 in IPA;
- [42] **FIG. 16** shows an exemplary solubility curve of 2C-B HBr Polymorph 1 in IPA:water (98:2); and
- [43] **FIG. 17** shows an exemplary solubility curve of 2C-B HBr Polymorph 1 in MeCN:water (95:5).

DETAILED DESCRIPTION OF THE INVENTION

[44] While various aspects and features of certain embodiments are summarized above, the following detailed description illustrates several exemplary embodiments in further detail to enable one of skill in the art to practice such embodiments, and to make and use the full scope of the invention claimed. The described examples are provided for illustrative purposes and are not intended to limit the scope of the

invention or its applications. The scope of the invention includes all embodiments and formulations thereof, not only those expressly described below, and it will be understood that many modifications, substitutions, changes, and variations in the described examples, embodiments, applications, and details of the invention can be made by those skilled in the art without departing from the spirit of the invention, or the scope of the invention as described in the claims. The headings within this document are being utilized only to expedite its review by a reader. They should not be construed as limiting the invention in any manner.

A. General Definitions and Terms

[45] The singular forms “a,” “an,” and “the” include plural referents unless context clearly indicates otherwise. Thus, “a compound” includes reference to not only one but also to two or more compounds, and “an excipient” includes reference to not only one but also to two or more excipients. While the term “one or more” also may be used, its absence (or its replacement by the singular “a” or “an”) does not signify the singular only, but simply provides emphasis to the possibility of multiples in some particular embodiments.

[46] “Or” means, and is interchangeable with, “and/or” unless context clearly indicates otherwise.

[47] The terms “comprising,” “including,” “such as,” and “having” are inclusive and not exclusive (i.e., they do not limit lists to recited elements), and are interchangeable with the phrase “including but not limited to.”

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

[49] In embodiments, the numerical parameters are approximations that can vary depending upon the desired properties sought to be obtained by a particular embodiment.

[50] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as amounts, ratios, concentrations, reaction conditions, temperatures, XRPD peak locations, XRPD peak areas, and so forth, should be understood as being modified in some instances by the term “about,” even where not so stated explicitly. In alternative embodiments, such numbers should be understood as not being modified by the term “about.” In embodiments, “about” refers to plus or minus five percent ($\pm 5\%$) of the recited unit of measure. In other embodiments, “about” refers to plus or minus ten percent ($\pm 10\%$) of the recited unit of measure. In other embodiments, such as when referring to a non-racemic mixture of R:S-MDMA in a ratio of “about” a specific ratio, such as about 9:1, “about” will refer to any of $\pm 10\%$, $\pm 5\%$, $\pm 2.5\%$, $\pm 2\%$, $\pm 1.5\%$, $\pm 1\%$, $\pm 0.5\%$, $\pm 0.25\%$, $\pm 0.1\%$, or $\pm 0.05\%$. Where “about” is used to modify one number in a series or range, it will be understood to modify all numbers in the series or range, including, for a range, both the upper and lower bounds of the range. Thus, the term “about 1, 2, or 3” is understood to mean “about 1, about 2, or about 3” and the term “about 1 to 10” means “about 1 to about 10.”

[51] When used in the context of XRPD signal values, the term “about” can indicate a peak value ± 0.50 ,

± 0.40 , ± 0.30 , ± 0.20 , ± 0.15 , ± 0.10 , ± 0.05 , or ± 0.01 °2 θ . In some embodiments (equivalently, as shorthand, “in embodiments”), when used in the context of XRPD signal values, “about” indicates a peak value at ± 0.50 °2 θ . In embodiments, “about” indicates a peak value at ± 0.40 °2 θ . In embodiments, “about” indicates a peak value at ± 0.30 °2 θ . In embodiments, “about” indicates a peak value at ± 0.20 °2 θ . In embodiments, “about” indicates a peak value at ± 0.15 °2 θ . In embodiments, “about” indicates a peak value at ± 0.10 °2 θ . In embodiments, “about” indicates a peak value at ± 0.05 °2 θ . In embodiments, “about” indicates a peak value at ± 0.01 °2 θ . In some embodiments, “about” indicates a peak value at exactly the disclosed peak value.

[52] The term “substantially,” where it is used to modify a feature or limitation, must be read in the context of the disclosure and in light of the knowledge in the art to provide the appropriate certainty, such as by using a standard recognized in the art for measuring the meaning of “substantially” as a term of degree, or by ascertaining the scope as would one of skill in the relevant art. Thus, “substantially,” and like terms of degree such as “approximately,” mean a reasonable amount of deviation of the modified term such that the end result is not significantly changed, and such terms of degree should be construed as including a deviation of the modified term that would not negate the meaning of the modified term.

[53] The term “substantially similar” when referring to an XRPD pattern or another data set means that a pattern or data set that is not necessarily identical to those depicted herein, but that falls within the limits of experimental error or deviations, when considered by one of skill, would be encompassed. One of skill will be able to determine if two data sets (e.g., two XRPD diffractograms) are substantially similar. In some embodiments, “substantially similar,” when referring to an analytical spectrum such as an XRPD pattern, means that the spectrum resembles a reference spectrum in both the peak locations and their relative intensities, allowing for variability appropriate in the art. For example, two spectra may be regarded as “substantially similar” when the two spectra share defining characteristics sufficient to differentiate them from a spectrum obtained for a different solid form. In embodiments, spectra or characterization data that are substantially similar to those of a reference crystalline form are understood by those of skill to correspond to the same crystalline form as the particular reference. In analyzing whether spectra or characterization data are substantially similar, one of skill will understand that particular characterization data points may vary to a reasonable extent while still describing a given solid form, for example due to experimental error and routine sample-to-sample analysis.

[54] A comprehensive list of abbreviations used by organic chemists of ordinary skill is in the first issue of each volume of the Journal of Organic Chemistry, and typically presented in a table entitled Standard List of Abbreviations; the list as of the date of this filing is incorporated by reference as if fully set forth herein.

[55] Unless defined otherwise, all technical and scientific terms herein have the meaning as commonly understood by one having ordinary skill in the art to which this invention belongs (“one of skill”).

[56] Generally, the nomenclature used and procedures performed herein are those known in fields relating to one or more aspects of the invention, e.g., organic chemistry, synthetic chemistry, medicinal

chemistry, physical chemistry, neuroscience, crystallography, and/or pharmaceutical sciences, and that will be well known and commonly employed in such fields. Standard techniques and procedures are those generally performed according to conventional methods in the art.

[57] Further definitions to assist a reader in understanding the embodiments are below and throughout; however, it will be appreciated that such definitions are not intended to limit the scope of the invention, which is properly interpreted and understood by reference to the full specification (as well as any plain meaning known to one of skill in the relevant art) in view of the language used in the claims. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[58] The terms “powder X-ray diffraction pattern,” “PXRD pattern,” “X-ray powder diffraction pattern,” and “XRPD pattern” are used interchangeably herein and refer to the experimentally observed diffractogram or parameters derived therefrom. Powder X-ray diffraction patterns are typically characterized by peak positions (i.e., peak locations), peak areas, and absolute and/or relative peak intensities.

[59] The term “peak” refers to relative signal intensities within a given X-ray diffraction pattern. Factors which can affect the relative peaks are sample thickness and preferred orientation. The term “peak positions” refers to X-ray reflection positions as measured and observed in powder X-ray diffraction experiments.

[60] The terms “XRPD peak,” “XRPD signal” and “XRPD peak/signal” are used interchangeably herein.

[61] The term “2 theta value,” “2 theta,” “2 θ ,” and “2 θ ” refer to the XRPD peak position in degrees based on the experimental setup of the X-ray diffraction experiment and is a common abscissa unit in diffraction patterns. Reference herein to specific 2 θ values for a specific polymorphic form is intended to mean the 2 θ values (in degrees) as measured using the X-ray diffraction experimental conditions as described herein.

[62] The term “polymorph” or “solid form” refers to crystalline forms of a compound and includes other solid state molecular forms including pseudo-polymorphs, such as hydrates and solvates. Without being bound by theory, different crystalline polymorphs have different crystal structures due to a different packing of the molecules in the lattice, and this results in a different crystal symmetry and/or different unit cell parameters which directly influences physical properties, including X-ray diffraction characteristics.

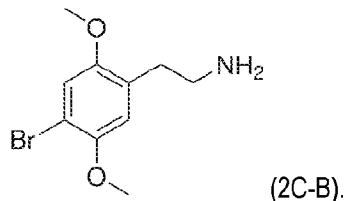
[63] The term “amorphous” refers to any solid substance which lacks order in three dimensions, or exhibits order in less than three dimensions, order only over short distances (e.g., less than 10 Å), or both. Thus, amorphous substances include partially crystalline materials and crystalline mesophases with, e.g., one- or two-dimensional translational order (liquid crystals), orientational disorder (orientationally disordered crystals), or conformational disorder (conformationally disordered crystals). Amorphous solids may be characterized by known techniques, including powder X-ray diffraction (PXRD) crystallography, solid state nuclear magnetic resonance (ssNMR) spectroscopy, differential scanning calorimetry (DSC), or some combination of these techniques. Amorphous solids give diffuse PXRD patterns, typically comprised of one or two broad peaks (i.e., peaks having base widths of about 5° 2 θ or greater).

[64] Still additional definitions and abbreviations are provided elsewhere herein.

B. Solid Forms

[65] In a first aspect are provided solid forms of 4-bromo-2,5-dimethoxyphenethylamine (2C-B).

[66] 2C-B has the following chemical structure:



[67] In some embodiments, the 2C-B is in salt form. Generally, salt forms of 2C-B are prepared by reacting the free base forms of 2C-B with a stoichiometric or superstoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media (e.g., ether, ethyl acetate, ethanol, isopropanol, or acetonitrile) are preferred.

[68] In some embodiments, the 2C-B is 2C-B hydrobromide (i.e., 2C-B HBr).

[69] In some embodiments, the 2C-B is in solid form.

[70] In some embodiments, the 2C-B is a solid form of 2C-B HBr.

[71] In some embodiments, the solid form is a crystalline form of 2C-B HBr.

[72] In some embodiments, the solid form is a polymorph of 2C-B HBr.

[73] In some embodiments, the solid form is a crystalline polymorph of 2C-B HBr.

[74] In some embodiments, the crystalline polymorph of 2C-B HBr, which may be referred to herein as 2C-B HBr Polymorph 1, is characterized by one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, or thirty-two X-ray powder diffraction (XRPD) peaks at about 12.7, 14.3, 16.4, 16.6, 17.6, 20.3, 20.9, 21.8, 22.6, 23.3, 23.9, 24.3, 25.0, 25.5, 26.2, 28.7, 28.9, 29.7, 30.9, 31.3, 31.7, 32.2, 32.6, 33.6, 33.6, 34.5, 35.6, 36.4, 37.3, 37.7, 38.3, and 39.2 °2θ (Cu Kα1 radiation).

[75] In some embodiments, 2C-B HBr Polymorph 1 is characterized by at least one, two, three, four, five, six, seven, eight, nine, or ten XRPD peaks at about 12.7, 14.3, 16.4, 16.6, 17.6, 20.3, 20.9, 21.8, 22.6, 23.3, 23.9, 24.3, 25.0, 25.5, 26.2, 28.7, 28.9, 29.7, 30.9, 31.3, 31.7, 32.2, 32.6, 33.6, 33.6, 34.5, 35.6, 36.4, 37.3, 37.7, 38.3, and 39.2 °2θ (Cu Kα1 radiation).

[76] In some embodiments, 2C-B HBr Polymorph 1 is characterized by one or more XRPD peaks at about 20.9, 24.3, 26.2, and 31.7 °2θ (Cu Kα1 radiation). In embodiments, 2C-B HBr Polymorph 1 is characterized by two or more XRPD peaks at about 20.9, 24.3, 26.2, and 31.7 °2θ (Cu Kα1 radiation). In embodiments, 2C-B HBr Polymorph 1 is characterized by three or more XRPD peaks at about 20.9, 24.3, 26.2, and 31.7 °2θ (Cu Kα1 radiation). In embodiments, 2C-B HBr Polymorph 1 is characterized by XRPD peaks at about 20.9 and 24.3 °2θ (Cu Kα1 radiation). In embodiments, 2C-B HBr Polymorph 1 is characterized by XRPD peaks at about 20.9 and 26.2 °2θ (Cu Kα1 radiation). In embodiments, 2C-B HBr

Polymorph 1 is characterized by XRPD peaks at about 20.9 and 31.7 °2 θ (Cu K α 1 radiation). In embodiments, 2C-B HBr Polymorph 1 is characterized by XRPD peaks at about 24.3 and 26.2 °2 θ (Cu K α 1 radiation). In embodiments, 2C-B HBr Polymorph 1 is characterized by XRPD peaks at about 24.3 and 31.7 °2 θ (Cu K α 1 radiation). In embodiments, 2C-B HBr Polymorph 1 is characterized by XRPD peaks at about 26.2 and 31.7 °2 θ (Cu K α 1 radiation). In embodiments, 2C-B HBr Polymorph 1 is characterized by XRPD peaks at about 20.9, 24.3, and 26.2 °2 θ (Cu K α 1 radiation). In embodiments, 2C-B HBr Polymorph 1 is characterized by XRPD peaks at about 20.9, 24.3, and 31.7 °2 θ (Cu K α 1 radiation). In embodiments, 2C-B HBr Polymorph 1 is characterized by XRPD peaks at about 20.9, 26.2, and 31.7 °2 θ (Cu K α 1 radiation). In embodiments, 2C-B HBr Polymorph 1 is characterized by XRPD peaks at about 24.3, 26.2, and 31.7 °2 θ (Cu K α 1 radiation). In embodiments, 2C-B HBr Polymorph 1 is characterized by XRPD peaks at about 20.9, 24.3, 26.2, and 31.7 °2 θ (Cu K α 1 radiation).

[77] In some embodiments, 2C-B HBr Polymorph 1 is characterized by an XRPD peak at about 12.7 °2 θ (12.7° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 14.3 °2 θ (14.3° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 16.4 °2 θ (16.4° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 16.6 °2 θ (16.6° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 17.6 °2 θ (17.6° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 20.3 °2 θ (20.3° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 20.9 °2 θ (20.9° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 21.8 °2 θ (21.8° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 22.6 °2 θ (22.6° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 23.3 °2 θ (23.3° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 23.9 °2 θ (23.9° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 24.3 °2 θ (24.3° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 25.0 °2 θ (25.0° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 25.5 °2 θ (25.5° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 26.2 °2 θ (26.2° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 28.7 °2 θ (28.7° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 28.9 °2 θ (28.9° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ). In embodiments, the polymorph is characterized by an XRPD peak at about 29.7 °2 θ (29.7° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2 θ).

0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 30.9 °2θ (30.9° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 31.3 °2θ (31.3° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 31.7 °2θ (31.7° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 32.2 °2θ (32.2° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 32.6 °2θ (32.6° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 33.6 °2θ (33.6° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 34.5 °2θ (34.5° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 35.6 °2θ (35.6° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 36.4 °2θ (36.4° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 37.3 °2θ (37.3° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 37.7 °2θ (37.7° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 38.3 °2θ (38.3° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ). In embodiments, the polymorph is characterized by an XRPD peak at about 39.2 °2θ (39.2° ± 0.5°, 0.4°, 0.3°, 0.2°, 0.1°, 0.05°, or 0.01° 2θ).

[78] In some embodiments, 2C-B HBr Polymorph 1 is characterized by the XRPD peak at 24.3 °2θ having a relative peak area compared to the XRPD peak at 20.9 °2θ that is between about 1.0 and 3.0. In some embodiments, the XRPD peak at 24.3 °2θ has a relative peak area compared to the XRPD peak at 20.9 °2θ that is between about 1.5 and 2.5. In some embodiments, the XRPD peak at 24.3 °2θ has a relative peak area compared to the XRPD peak at 20.9 °2θ that is about 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5. In some embodiments, the XRPD peak at 24.3 °2θ has a relative peak area compared to the XRPD peak at 20.9 °2θ that is about 2.0.

[79] In some embodiments, 2C-B HBr Polymorph 1 is characterized by the XRPD peak at 24.3 °2θ having a relative peak area compared to the XRPD peak at 26.2 °2θ that is between about 2.0 and 6.0. In some embodiments, the XRPD peak at 24.3 °2θ has a relative peak area compared to the XRPD peak at 26.2 °2θ that is between about 2.0 and 5.0. In some embodiments, the XRPD peak at 24.3 °2θ has a relative peak area compared to the XRPD peak at 26.2 °2θ that is between about 3.0 and 5.0. In some embodiments, the XRPD peak at 24.3 °2θ has a relative peak area compared to the XRPD peak at 26.2 °2θ that is between about 3.0 and 4.0. In some embodiments, the XRPD peak at 24.3 °2θ has a relative peak area compared to the XRPD peak at 26.2 °2θ that is about 3.5.

[80] In some embodiments, 2C-B HBr Polymorph 1 is characterized by the XRPD peak at 24.3 °2θ having a relative peak area compared to the XRPD peak at 31.7 °2θ that is between about 3.0 and 6.0. In

some embodiments, the XRPD peak at $24.3^{\circ}2\theta$ has a relative peak area compared to the XRPD peak at $31.7^{\circ}2\theta$ that is between about 3.0 and 5.0. In some embodiments, the XRPD peak at $24.3^{\circ}2\theta$ has a relative peak area compared to the XRPD peak at $31.7^{\circ}2\theta$ that is between about 4.0 and 6.0. In some embodiments, the XRPD peak at $24.3^{\circ}2\theta$ has a relative peak area compared to the XRPD peak at $31.7^{\circ}2\theta$ that is between about 4.0 and 5.0. In some embodiments, the XRPD peak at $24.3^{\circ}2\theta$ has a relative peak area compared to the XRPD peak at $31.7^{\circ}2\theta$ that is about 4.5.

[81] In some embodiments, 2C-B HBr Polymorph 1 is characterized by the absence of one or more XRPD peaks at about 27.2 and $30.3^{\circ}2\theta$ (Cu K α 1 radiation). In some embodiments, 2C-B HBr Polymorph 1 is characterized by the absence of an XRPD peak at about $27.2^{\circ}2\theta$ (Cu K α 1 radiation). In some embodiments, 2C-B HBr Polymorph 1 is characterized by the absence of an XRPD peak at about $30.3^{\circ}2\theta$ (Cu K α 1 radiation). In some embodiments, 2C-B HBr Polymorph 1 is characterized by the absence of XRPD peaks at about 27.2 and $30.3^{\circ}2\theta$ (Cu K α 1 radiation). In some embodiments, 2C-B HBr Polymorph 1 is characterized by the absence of an XRPD peak at about $27.2^{\circ}2\theta$ ($27.2^{\circ} \pm 0.5^{\circ}$, 0.4° , 0.3° , 0.2° , 0.1° , 0.05° , or $0.01^{\circ} 2\theta$). In some embodiments, 2C-B HBr Polymorph 1 is characterized by the absence of an XRPD peak at about $30.3^{\circ}2\theta$ ($30.3^{\circ} \pm 0.5^{\circ}$, 0.4° , 0.3° , 0.2° , 0.1° , 0.05° , or $0.01^{\circ} 2\theta$).

[82] In some embodiments, 2C-B HBr Polymorph 1 has an XRPD diffractogram as shown in **FIG. 1**. In some embodiments, 2C-B HBr Polymorph 1 has an XRPD diffractogram that is substantially similar to that shown in **FIG. 1**. In some embodiments, 2C-B HBr Polymorph 1 is characterized by at least one, two, three, four, five, six, seven, eight, nine, or ten XRPD peaks selected from XRPD diffractogram shown in **FIG. 1**.

[83] In some embodiments, 2C-B HBr Polymorph 1 has an XRPD peak list as shown in **Table 1**. In some embodiments, 2C-B HBr Polymorph 1 has an XRPD peak list that is substantially similar to that shown in **Table 1**. In some embodiments, 2C-B HBr Polymorph 1 is characterized by at least one, two, three, four, five, six, seven, eight, nine, or ten XRPD peaks selected from the peak list shown in **Table 1**.

Table 1. XRPD signals of a sample comprising 2C-B HBr Polymorph 1.

No.	Pos. [$^{\circ}2\theta$]	d-spacing [$\text{\AA}$]	Height [cts]	Area [cts $^{\circ}2\theta$]	Backgr.[cts]
1	12.7120	6.95805	59.76	7.17	241.15
2	14.2751	6.19950	62.55	9.21	202.97
3	16.3559	5.41517	231.74	41.58	185.88
4	16.6194	5.32990	67.23	14.10	184.54
5	17.6096	5.03237	69.58	18.34	179.52
6	20.2954	4.37208	95.65	11.48	165.89
7	20.9358	4.23977	203.33	49.60	162.63
8	21.8148	4.07087	179.81	13.35	158.17
9	22.5903	3.93284	911.58	226.53	154.24
10	23.3009	3.81449	93.30	39.12	150.63
11	23.8716	3.72457	260.08	80.79	147.73

12	24.2560	3.66640	534.43	99.60	145.78
13	24.9608	3.56446	205.52	57.46	142.21
14	25.4908	3.49154	176.01	38.27	139.52
15	26.2051	3.39795	95.44	28.90	135.89
16	28.7100	3.10693	74.48	24.88	126.56
17	28.9281	3.08400	66.93	8.03	126.32
18	29.6799	3.00757	33.60	9.74	125.51
19	30.9328	2.88855	108.86	44.56	124.15
20	31.2808	2.85720	64.29	3.98	123.77
21	31.6706	2.82292	93.24	21.92	123.35
22	32.2377	2.77455	43.62	5.07	122.73
23	32.6012	2.74443	66.30	23.88	122.34
24	33.5554	2.66854	49.62	6.60	121.31
25	34.2670	2.61474	145.66	39.48	120.53
26	35.3466	2.53731	77.51	23.49	119.36
27	35.7834	2.50733	50.59	10.06	118.89
28	36.4358	2.46392	33.02	13.52	118.18
29	37.2775	2.41020	65.64	8.37	120.70
30	37.6840	2.38512	32.16	3.69	124.51
31	38.2962	2.34839	45.75	5.49	139.68
32	39.1666	2.29819	136.89	16.43	146.52

[84] For comparison, an exemplary peak list from an XRPD spectrum of a sample comprising 2C-B HBr starting material is provided in Table 2.

Table 2. XRPD signals of a sample comprising 2C-B HBr starting material.

No.	Pos. [°2 θ]	d-spacing [Å]	Height [cts]	Area [cts*°2 θ]	Backgr.[cts]
1	5.5600	15.88202	2354.82	294.00	2657.67
2	11.1014	7.96367	7486.77	1350.16	1980.76
3	12.8090	6.90560	3005.85	474.31	1812.55
4	16.0063	5.53266	1465.73	303.18	1610.14
5	16.6656	5.31524	25401.25	5254.12	1585.61
6	17.0534	5.19522	4222.59	349.37	1571.18
7	20.3035	4.37035	14438.73	2986.58	1624.80
8	20.6526	4.29726	2981.94	740.16	1652.09
9	22.6066	3.93005	9375.49	1113.64	3239.79
10	23.1665	3.83631	15207.30	3096.58	3084.46
11	23.7774	3.73911	21246.34	3965.76	2830.63
12	24.5346	3.62540	5377.74	645.33	2516.00

13	25.1455	3.53869	4955.52	588.62	2262.17
14	25.4382	3.49863	8946.48	1214.48	2140.55
15	25.7373	3.45865	4551.17	546.14	2016.28
16	26.7425	3.33088	419.78	50.37	1740.60
17	27.1919	3.27684	7362.99	889.18	1713.08
18	27.9478	3.18991	810.16	97.22	1666.79
19	28.6376	3.11463	1612.68	464.41	1624.55
20	28.9615	3.08052	2397.06	601.22	1604.71
21	29.4273	3.03281	841.51	100.98	1576.19
22	30.3043	2.94701	16397.16	3249.51	1522.48
23	31.2667	2.85846	4138.56	861.17	1463.55
24	32.5700	2.74699	2442.41	739.68	1402.17
25	33.6326	2.66259	4900.04	2239.52	1367.18
26	34.4529	2.60105	526.72	65.17	1340.17
27	35.6326	2.51760	2044.72	619.24	1323.44
28	36.4510	2.46292	2781.03	776.75	1323.44
29	36.8586	2.43662	1250.79	150.09	1323.44
30	37.4309	2.40067	1012.42	121.49	1323.44
31	38.3306	2.34637	1977.92	381.84	1323.44
32	39.3551	2.28761	880.78	402.55	1323.44

[85] In some embodiments, disclosed solid forms (e.g., crystalline polymorphs, such as 2C-B HBr Polymorph 1) exhibit advantageous properties. In embodiments, 2C-B HBr Polymorph 1 has one or more improved properties compared to another form of 4-bromo-2,5-dimethoxyphenethylamine (e.g., freebase 2C-B, a 2C-B salt, a 2C-B solid form, amorphous 2C-B, a 2C-B crystalline form, or another polymorph of 2C-B). In embodiments, 2C-B HBr Polymorph 1 has one or more improved properties compared to freebase 2C-B. In embodiments, 2C-B HBr Polymorph 1 has one or more improved properties compared to a 2C-B salt. In embodiments, 2C-B HBr Polymorph 1 has one or more improved properties compared to a 2C-B salt, wherein the 2C-B salt is formed from a mineral acid (e.g., hydrochloric acid, hydrobromic acid) or an organic acid (e.g., tartaric acid, acetic acid). In embodiments, 2C-B HBr Polymorph 1 has one or more improved properties compared to a 2C-B salt, wherein the 2C-B salt is formed from an acid selected from galactaric (mucic) acid, naphthalene-1,5-disulfonic acid, citric acid, sulfuric acid, d-glucuronic acid, ethane-1,2-disulfonic acid, lactobionic acid, p-toluenesulfonic acid, D-glucoheptonic acid, thiocyanic acid, (-)-L-pyroglutamic acid, glycolic acid, methanesulfonic acid, L-malic acid, tartaric acid (e.g., L-tartaric acid), dodecylsulfuric acid, hippuric acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic (xinafoic) acid, D-gluconic acid, benzenesulfonic acid, D,L-lactic acid, oxalic acid, oleic acid, glycerophosphoric acid, succinic acid, malonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, glutaric acid, L-aspartic acid,

cinnamic acid, maleic acid, adipic acid, phosphoric acid, sebacic acid, ethanesulfonic acid, (+)-camphoric acid, glutamic acid, acetic acid, fumaric acid, hydroxybenzoic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, or a combination thereof. In embodiments, 2C-B HBr Polymorph 1 has one or more improved properties compared to a 2C-B solid form. In embodiments, 2C-B HBr Polymorph 1 has one or more improved properties compared to amorphous 2C-B. In embodiments, 2C-B HBr Polymorph 1 has one or more improved properties compared to a 2C-B crystalline form.

[86] In embodiments, 2C-B HBr Polymorph 1 has one or more improved properties compared to another 2C-B polymorph. In embodiments, Polymorph 1 has one or more improved properties compared to another 2C-B polymorph, where the other 2C-B polymorph is any of a 2C-B freebase, 2C-B HCl, 2C-B besylate, 2C-B citrate, 2C-B esylate, 2C-B fumarate, 2C-B gentisate, 2C-B gluconate, 2C-B glycolate, 2C-B sulfate, 2C-B phosphate, 2C-B xinafoate, 2C-B lactate, 2C-B malate, 2C-B maleate, 2C-B malonate, 2C-B mesylate, 2C-B mucate, 2C-B succinate, 2C-B tartrate, 2C-B tosylate, 2C-B aspartate, or a 2C-B glutamate polymorph.

[87] In some embodiments, an improved property is a physical property, such as any of melting point, glass transition temperature, flowability, stability, such as thermal stability, mechanical stability, and stability against polymorphic transition, and shelf life. In some embodiments, an improved property is a chemical property. In some embodiments, an improved property is a thermal property. In some embodiments, an improved property is a hygroscopic property, such as solubility in water and/or organic solvents. In some embodiments, an improved property is reactivity or compatibility with excipients and/or delivery vehicles. In embodiments, an improved property is a pharmacokinetic property, such as any of bioavailability, absorption, distribution, metabolism, excretion, toxicity including cytotoxicity, dissolution rate, and half-life. Other such properties that can be improved will be known in view of the disclosure and ordinary skill in the art.

[88] Solid forms (e.g., crystalline polymorphs, such as 2C-B HBr Polymorph 1) may be characterized by a variety of analytical techniques that investigate physical structure, thermal properties, stability, and chemical purity. In addition to visual assessment, analytical tools may include X-ray diffraction techniques (e.g., single-crystal X-ray diffraction, powder X-Ray diffraction), thermogravimetric analysis, dynamic scanning calorimetry, microscopy (e.g., optical microscopy, electron microscopy, scanning electron microscopic, transmission electron microscopy), infrared spectroscopy (e.g., Fourier-transform infrared spectroscopy), dynamic vapor sorption, chromatography (e.g., high-performance liquid chromatography), and nuclear magnetic resonance spectroscopy (e.g., ^1H NMR, ^{13}C NMR, solid-state NMR).

[89] Generally, disclosed solid forms (e.g., crystalline polymorphs, such as 2C-B HBr Polymorph 1) are administered as part of a pharmaceutical composition. In embodiments, solid forms are included in or formulated as a pharmaceutical composition in purified form. Terms such as “purified” and “substantially pure” refer herein to material that is substantially or essentially free components that otherwise accompany the material when the material is synthesized, manufactured, or produced. A “purified,” or “substantially pure” preparation of a solid form may be defined as a preparation having a chromatographic purity (of the desired

solid form) of greater than 90%, more preferably greater than 95%, more preferably greater than 96%, more preferably greater than 97%, more preferably greater than 98%, more preferably greater than 99%, more preferably greater than 99.5%, and most preferably greater than 99.9%, as determined by area normalization of an HPLC profile or other similar detection method. A substantially pure solid form may be substantially free of other active compounds not intended to be administered to a subject. In embodiments, a substantially pure solid form is substantially free of any other solid forms of 2C-B, such as other polymorphs and/or salts of 2C-B. In this context “substantially free” can mean that no active compound(s) or solid form(s) other than the active compound and solid form intended to be administered to a subject are detectable by HPLC, XRPD, or other similar detection method, or are below a desired threshold of detection such as above.

C. Pharmaceutical Compositions

[90] In some aspects, provided herein are compositions, such as pharmaceutical compositions, comprising a disclosed solid form, such as a disclosed crystalline polymorph of 2C-B HBr (e.g., Polymorph 1). “Pharmaceutical compositions” are compositions that include a disclosed solid form together in an amount (for example, in a unit dosage form) with a pharmaceutically acceptable carrier, diluent, or excipient. Some embodiments will not have a single carrier, diluent, or excipient alone, but will include multiple carriers, diluents, and/or excipients. Compositions can be prepared by standard pharmaceutical formulation techniques such as disclosed in, e.g., Remington: The Science & Practice of Pharmacy (2020) 23th ed., Academic Press., Cambridge, Mass.; The Merck Index (1996) 12th ed., Merck Pub. Group, Whitehouse, N.J.; Pharm. Principles of Solid Dosage Forms (1993), Technomic Pub. Co., Inc., Lancaster, Pa.; and Ansel & Stoklosa, Pharm. Calculations (2001) 11th ed., Lippincott Williams & Wilkins, Baltimore, Md.; & Poznansky et al. Drug Delivery Systems (1980), R.L. Juliano, ed., Oxford, N.Y., pp. 253-315).

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

[92] When any reference is made in embodiments herein to administration or use of a “solid form” or a “polymorph,” such as in a disclosed method of such administration or use (e.g., “a disclosed solid form is administered,” “a disclosed solid form is used to treat,” and the like), such reference also will include, unless context clearly indicates otherwise, reference to the administration or use of a composition, such as a pharmaceutical composition, comprising the solid form or the polymorph, such as a disclosed composition.

[93] In embodiments, a disclosed composition includes mixtures of 2C-B HBr Polymorph 1 described in various embodiments herein, together with another form of 2C-B (e.g., amorphous 2C-B, another crystalline form of 2C-B). In embodiments, the mixture can be described by its polymorphic purity. “Polymorphic purity” can be defined as the percent of a particular polymorph (e.g., 2C-B HBr Polymorph 1) relative to the total molar quantity of the substance (e.g., 2C-B). For example, a 90% polymorphic purity means that 2C-B HBr

Polymorph 1 accounts for 90% of the total molar quantity of 2C-B. Polymorphic purity can be determined by methods known in the art, including XRPD, Raman spectroscopy, IR spectroscopy, and differential scanning calorimetry (Thomas et al. Chem Comm. 2012;48(85):10559; Yu et al. Pharm Science & Tech Today. 1998;1(3):118-127). In embodiments, the polymorphic purity of crystalline 2C-B HBr Polymorph 1 in a disclosed composition is at least 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 100% for 2C-B HBr Polymorph 1. In embodiments, the polymorphic purity of the crystalline 2C-B is at least 90%, at least 95%, at least 99%, at least 99.5%, or at least 99.9% for 2C-B HBr Polymorph 1. In embodiments, the polymorphic purity of the crystalline 2C-B is at least 90%. In embodiments, the polymorphic purity of the crystalline 2C-B is at least 95%. In embodiments, the polymorphic purity of the crystalline 2C-B is at least 99%. In embodiments, the polymorphic purity of the crystalline 2C-B is at least 99.5%. In embodiments, the polymorphic purity of the crystalline 2C-B is at least 99.9%.

[94] Also provided are compositions (e.g., pharmaceutical compositions) comprising a therapeutically effective amount of crystalline 2C-B HBr in the form 2C-B HBr Polymorph 1, as described in embodiments herein. In some embodiments, "crystalline 2C-B HBr in the form Polymorph 1" refers to crystalline 2C-B HBr that comprises a detectable amount of 2C-B HBr Polymorph 1. In embodiments, "crystalline 2C-B HBr in the form Polymorph 1" refers to crystalline 2C-B HBr that comprises 2C-B HBr Polymorph 1 and has a polymorphic purity of at least 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 100% for 2C-B HBr Polymorph 1. In embodiments, "crystalline 2C-B HBr in the form Polymorph 1" refers to crystalline 2C-B HBr that comprises 2C-B HBr Polymorph 1 and has a polymorphic purity of at least 90%, at least 95%, at least 99%, at least 99.5%, or at least 99.9% for 2C-B HBr Polymorph 1.

[95] In some embodiments, the total amount of 2C-B HBr Polymorph 1 in a disclosed pharmaceutical composition ranges from about 1% to 100% by weight. In some embodiments, the total amount of 2C-B HBr Polymorph 1 in a disclosed pharmaceutical composition is at least 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 100% by weight. In some embodiments, the total amount of 2C-B HBr Polymorph 1 in a disclosed pharmaceutical composition is at least 90%, at least 95%, at least 99%, at least 99.5%, or at least 99.9% for 2C-B HBr Polymorph 1.

[96] In some embodiments, a disclosed pharmaceutical composition (or for shorthand, a "disclosed composition") comprises 2C-B HBr Polymorph 1 in amount providing a dose (in a milligram dose amount based on the kilogram weight of the patient) of, e.g., 0.25 mg/kg or less (including a dose of 0.10 mg/kg or less, 0.05 mg/kg or less, 0.01 mg/kg or less, and 0.005 mg/kg or less), at least 0.50 mg/kg, at least 0.55 mg/kg, at least 0.60 mg/kg, at least 0.65 mg/kg, at least 0.70 mg/kg, at least 0.75 mg/kg, at least 0.80 mg/kg, at least 0.85 mg/kg, at least 0.90 mg/kg, at least 0.95 mg/kg, at least 1.0 mg/kg, at least 1.1 mg/kg, at least

1.2 mg/kg, at least 1.3 mg/kg, or at least 1.4 mg/kg, at least 1.5 mg/kg, at least 1.6 mg/kg, at least 1.7 mg/kg, at least 1.8 mg/kg, at least 1.9 mg/kg, at least 2.0 mg/kg, at least 2.1 mg/kg, at least 2.2 mg/kg, at least 2.3 mg/kg, at least 2.4 mg/kg, at least 2.5 mg/kg, at least 2.6 mg/kg, at least 2.7 mg/kg, at least 2.8 mg/kg, at least 2.9 mg/kg, or at least 3.0 mg/kg, as well as amounts within these ranges.

[97] In some embodiments, pharmaceutical compositions comprising a disclosed solid form can be administered by a variety of routes including oral, mucosal (e.g., buccal, sublingual), rectal, transdermal, subcutaneous, intravenous, intramuscular, inhaled, and intranasal. In some embodiments, the disclosed solid forms employed in disclosed methods are effective as oral, mucosal (e.g., buccal, sublingual), rectal, transdermal, subcutaneous, intravenous, intramuscular, inhaled, and intranasal compositions. Such compositions can be prepared in a manner as described herein or as otherwise known in the pharmaceutical arts (see, e.g., Remington, 2020).

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

[99] Unit dosage forms include capsules, troches, cachets, lozenges, tablets, ampules and vials, which may include a composition in a freeze-dried or lyophilized state; a sterile liquid carrier, for example, can be added prior to administration or delivery in vivo.

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

may be administered as a single capsule or in multiple capsule dosage form. In some embodiments, the pharmaceutical composition is administered in two, three, four, or more capsules or tablets.

[101] Oral solid dosage forms can comprise excipients such as fillers, diluents, lubricants, surfactants, glidants, binders, dispersing agents, suspending agents, disintegrants, viscosity-increasing agents, film-forming agents, granulation aid, flavoring agents, sweetener, coating agents, solubilizing agents, and combinations thereof. Oral solid dosage forms can comprise additives such as any one or more of a compatible carrier, complexing agent, ionic dispersion modulator, disintegrating agent, surfactant, lubricant, colorant, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, and anti-foaming agent, as well as combinations thereof.

[102] Also provided are solid dosage form preparations which are intended to be converted, generally shortly before use, into liquid dosage form preparations, such as for oral, intravenous, intramuscular, subcutaneous, or other liquid dosage form administration. In some embodiments, a composition comprises a disclosed solid form and at least one dispersing agent or suspending agent for oral administration. The composition may be a powder and/or granules for suspension, whereupon admixture with water a substantially uniform suspension is obtained. A disclosed solid form also can be formulated as an oral liquid dosage form, such as tinctures, drops, emulsions, syrups, elixirs, suspensions, and solutions, and the like.

[103] In some embodiments, a disclosed composition comprises particles of 2C-B. In embodiments, the composition comprises particles of 2C-B hydrobromide (i.e., 2C-B HBr). In embodiments, the composition comprises particles of 2C-B in solid form. In embodiments, the composition comprises particles of a solid form of 2C-B HBr. In embodiments, the composition comprises particles of a crystalline form of 2C-B HBr. In embodiments, the composition comprises particles of a polymorph of 2C-B HBr. In embodiments, the composition comprises particles of a crystalline polymorph of 2C-B HBr. In embodiments, the composition comprises particles of 2C-B HBr Polymorph 1.

[104] In some embodiments, the particles have desirable bulk properties and processability for preparing dosage forms suitable for administration to a subject. In embodiments, the particles have a specified particle size. "Particle size" as used herein (e.g., to describe the size of 2C-B particles) refers to any of the diameter, radius, length, width, or any linear dimension of a particle. For a spherical particle, particle size may refer to the diameter of the particle. For a non-spherical particle, particle size can refer to the measurement of any major and minor axes, the particle's equivalent diameter (e.g., the diameter of a sphere that has the same volume or surface area as the particle), and other definitions known to and used by those of skill to define the size of a particle. In embodiments, "particle size" refers to mean particle size. Hence, in some embodiments, "particle size" refers to the mean particle size (e.g., the mathematical average of the distribution of particle sizes). In embodiments, "particle size" refers to a particle size range centered on the mean particle size, plus or minus a number of standard deviations (e.g., ± 1 , ± 2 , ± 3 , ± 4 , ± 5 standard deviations). In embodiments, "particle size" refers to a particle size range centered on the mean particle size,

plus or minus a percentage value (e.g., $\pm 1\%$, $\pm 5\%$, $\pm 10\%$, $\pm 20\%$, $\pm 30\%$, $\pm 40\%$, $\pm 50\%$). In embodiments, “particle size” refers to the median particle size of a distribution of particle sizes, and may include for example the D50, DV50, D(V,0.5), or x50. In embodiments, “particle size distribution” refers to any of the D10, D50, D90, and D99. Examples of techniques for measuring particle size and particle size distribution are known in the art, and include as examples, sieve analysis, light scattering techniques (e.g., static light scattering, dynamic light scattering, nanoparticle tracking analysis), laser diffraction analysis, and microscopy (e.g., optical microscopy, electron microscopy).

[105] In embodiments, the particle size of the 2C-B is between about 1 μm and 10 μm (i.e., between about 1 μm and about 10 μm). In embodiments, the particle size is greater than about 10 μm . In embodiments, the particle size is between about 1 μm and 2000 μm . In embodiments, the particle size is between about 10 μm and 2000 μm . In embodiments, the particle size is between about 10 μm and 500 μm . In embodiments, the particle size is between about 10 μm and 100 μm , between about 10 μm and 200 μm , between about 10 μm and 300 μm , between about 10 μm and 400 μm , between about 10 μm and 500 μm , between about 50 μm and 100 μm , between about 50 μm and 200 μm , between about 50 μm and 300 μm , between about 50 μm and 400 μm , or between about 50 μm and 500 μm . In embodiments, the particle size is between about 500 μm and 2000 μm . In embodiments, the particle size is between about 500 μm and 1000 μm , between about 500 μm and 1500 μm , between about 100 μm and 2000 μm , or greater than about 2000 μm .

[106] In some embodiments, the particle size of the 2C-B is less than about 1 μm . In embodiments, the particle size of the 2C-B is between about 100 nm and 1000 nm. In embodiments, the particle size of the 2C-B is between about 100 nm and 200 nm, between about 100 nm and 500 nm, between about 100 nm and 800 nm, or between about 100 nm and 1000 nm. In embodiments, the particle size is less than about 100 nm. In embodiments, the particle size is less than about 50 nm. In embodiments, the particle size is less than about 10 nm. In embodiments, the particle size is less than about 1 nm.

[107] In some embodiments, the particle size of the 2C-B is between about 10 pm and 1000 pm. In embodiments, the particle size is between about 10 pm and 100 pm, between about 100 pm and 150 pm, between about 150 pm and 200 pm, between about 200 pm and 250 pm, between about 250 pm and 300 pm, between about 350 pm and 400 pm, between about 400 pm and 450 pm, between about 50 pm and 150 pm, between about 150 pm and 250 pm, between about 250 pm and 450 pm, between about 200 pm and 450 pm, between about 100 pm and 300 pm, between about 300 pm and 450 pm, or between about 400 pm and 450 pm. In embodiments, the particle size is between about 50 pm and 400 pm. In embodiments, the particle size is between about 75 pm and 200 pm. In embodiments, the particle size is between about 100 pm and 200 pm. In some embodiments, the 2C-B particles have a D90 of between about 1 μm and 10 μm . In embodiments, the particles have a D90 of greater than about 10 μm . In embodiments, the particles have a D90 of between about 1 μm and 2000 μm . In embodiments, the particles have a D90 of between about 10 μm and 2000 μm . In embodiments, the particles have a D90 of between about 10 μm and 500 μm . In

embodiments, the particles have a D90 of between about 10 μm and 100 μm , between about 10 μm and 200 μm , between about 10 μm and 300 μm , between about 10 μm and 400 μm , between about 10 μm and 500 μm , between about 50 μm and 100 μm , between about 50 μm and 200 μm , between about 50 μm and 300 μm , between about 50 μm and 400 μm , or between about 50 μm and 500 μm . In embodiments, the particles have a D90 of between about 500 μm and 2000 μm . In embodiments, the particles have a D90 of between about 500 μm and 1000 μm , between about 500 μm and 1500 μm , between about 100 μm and 2000 μm , or greater than about 2000 μm .

[108] In some embodiments, the 2C-B particles have a D90 of less than about 1 μm . In embodiments, the particle size of the 2C-B is between about 100 nm and 1000 nm. In embodiments, the particle size of the 2C-B is between about 100 nm and 200 nm, between about 100 nm and 500 nm, between about 100 nm and 800 nm, or between about 100 nm and 1000 nm. In embodiments, the particles have a D90 of less than about 100 nm. In embodiments, the particles have a D90 of less than about 50 nm. In embodiments, the particles have a D90 of less than about 10 nm. In embodiments, the particles have a D90 of less than about 1 nm. In some embodiments, the 2C-B particles have a D90 of between about 10 pm to about 1000 pm. In embodiments, the particles have a D90 of between about 10 pm and 100 pm, between about 100 pm and 150 pm, between about 150 pm and 200 pm, between about 200 pm and 250 pm, between about 250 pm and 300 pm, between about 350 pm and 400 pm, between about 400 pm and 450 pm, between about 50 pm and 150 pm, between about 150 pm and 250 pm, between about 250 pm and 450 pm, between about 200 pm and 450 pm, between about 100 pm and 300 pm, between about 300 pm and 450 pm, or between about 400 pm and 450 pm. In embodiments, the particles have a D90 of between about 50 pm and 400 pm. In embodiments, the particles have a D90 of between about 75 pm and 200 pm. In embodiments, the particles have a D90 of between about 100 pm and 200 pm.

[109] In some embodiments, the 2C-B particles have a D50 of between about 1 μm and 10 μm . In embodiments, the particles have a D50 of greater than about 10 μm . In embodiments, the particles have a D50 of between about 1 μm and 2000 μm . In embodiments, the particles have a D50 of between about 10 μm and 2000 μm . In embodiments, the particles have a D50 of between about 10 μm and 500 μm . In embodiments, the particles have a D50 of between about 10 μm and 100 μm , between about 10 μm and 200 μm , between about 10 μm and 300 μm , between about 10 μm and 400 μm , between about 10 μm and 500 μm , between about 50 μm and 100 μm , between about 50 μm and 200 μm , between about 50 μm and 300 μm , between about 50 μm and 400 μm , or between about 50 μm and 500 μm . In embodiments, the particles have a D50 of between about 500 μm and 2000 μm . In embodiments, the particles have a D50 of between about 500 μm and 1000 μm , between about 500 μm and 1500 μm , between about 100 μm and 2000 μm , or greater than about 2000 μm .

[110] In some embodiments, the 2C-B particles have a D50 of less than about 1 μm . In embodiments, the particle size of the 2C-B is between about 100 nm and 1000 nm. In embodiments, the particle size of the

2C-B is between about 100 nm and 200 nm, between about 100 nm and 500 nm, between about 100 nm and 800 nm, or between about 100 nm and 1000 nm. In embodiments, the particles have a D50 of less than about 100 nm. In embodiments, the particles have a D50 of less than about 50 nm. In embodiments, the particles have a D50 of less than about 10 nm. In embodiments, the particles have a D50 of less than about 1 nm. In some embodiments, the 2C-B particles have a D50 of between about 10 pm to about 1000 pm. In embodiments, the particles have a D50 of between about 10 pm and 100 pm, between about 100 pm and 150 pm, between about 150 pm and 200 pm, between about 200 pm and 250 pm, between about 250 pm and 300 pm, between about 350 pm and 400 pm, between about 400 pm and 450 pm, between about 50 pm and 150 pm, between about 150 pm and 250 pm, between about 250 pm and 450 pm, between about 200 pm and 450 pm, between about 100 pm and 300 pm, between about 300 pm and 450 pm, or between about 400 pm and 450 pm. In embodiments, the particles have a D50 of between about 50 pm and 400 pm. In embodiments, the particles have a D50 of between about 75 pm and 200 pm. In embodiments, the particles have a D50 of between about 100 pm and 200 pm.

[111] In some embodiments, the 2C-B particles have a D10 of between about 1 μm and 10 μm . In embodiments, the particles have a D10 of greater than about 10 μm . In embodiments, the particles have a D10 of between about 1 μm and 2000 μm . In embodiments, the particles have a D10 of between about 10 μm and 2000 μm . In embodiments, the particles have a D10 of between about 10 μm and 500 μm . In embodiments, the particles have a D10 of between about 10 μm and 100 μm , between about 10 μm and 200 μm , between about 10 μm and 300 μm , between about 10 μm and 400 μm , between about 10 μm and 500 μm , between about 50 μm and 100 μm , between about 50 μm and 200 μm , between about 50 μm and 300 μm , between about 50 μm and 400 μm , or between about 50 μm and 500 μm . In embodiments, the particles have a D10 of between about 500 μm and 2000 μm . In embodiments, the particles have a D10 of between about 500 μm and 1000 μm , between about 500 μm and 1500 μm , between about 100 μm and 2000 μm , or greater than about 2000 μm .

[112] In some embodiments, the 2C-B particles have a D10 of less than about 1 μm . In embodiments, the particle size of the 2C-B is between about 100 nm and 1000 nm. In embodiments, the particle size of the 2C-B is between about 100 nm and 200 nm, between about 100 nm and 500 nm, between about 100 nm and 800 nm, or between about 100 nm and 1000 nm. In embodiments, the particles have a D10 of less than about 100 nm. In embodiments, the particles have a D10 of less than about 50 nm. In embodiments, the particles have a D10 of less than about 10 nm. In embodiments, the particles have a D10 of less than about 1 nm. In some embodiments, the 2C-B particles have a D10 of between about 10 pm to about 1000 pm. In embodiments, the particles have a D10 of between about 10 pm and 100 pm, between about 100 pm and 150 pm, between about 150 pm and 200 pm, between about 200 pm and 250 pm, between about 250 pm and 300 pm, between about 350 pm and 400 pm, between about 400 pm and 450 pm, between about 50 pm and 150 pm, between about 150 pm and 250 pm, between about 250 pm and 450 pm, between about 200

pm and 450 pm, between about 100 pm and 300 pm, between about 300 pm and 450 pm, or between about 400 pm and 450 pm. In embodiments, the particles have a D10 of between about 50 pm and 400 pm. In embodiments, the particles have a D10 of between about 75 pm and 200 pm. In embodiments, the particles have a D10 of between about 100 pm and 200 pm.

[113] In some embodiments, where a disclosed composition comprises 2C-B HBr Polymorph 1 and one or more additional active agents, the composition comprises one or more additional active agent(s) in specified particle size(s), such as disclosed in embodiments herein for 2C-B particles. In some such embodiments, the particle sizes of the 2C-B HBr Polymorph 1 and the additional active agent(s) are substantially similar or identical (e.g., within about $\pm 1\%$, $\pm 5\%$, $\pm 10\%$, $\pm 20\%$, $\pm 30\%$, $\pm 40\%$, $\pm 50\%$). In other such embodiments, the particle sizes of the 2C-B and the additional active agent(s) are different. In one exemplary embodiment, a disclosed composition comprises 2C-B HBr (e.g., as 2C-B HBr Polymorph 1) and MDMA, and the particle sizes of the 2C-B HBr and the MDMA are substantially identical. In another embodiment, the particle sizes of the 2C-B HBr and the MDMA are substantially similar. In another embodiment, the particle sizes of the 2C-B HBr and the MDMA are different (comprising, e.g., particles of 2C-B HBr that are between about 1 μm and 2000 μm ; and particles of MDMA that are between about 50 pm and 400 pm). In some embodiments, where a disclosed composition comprises 2C-B HBr Polymorph 1 and one or more additional active agents, the composition comprises the additional active agent(s) not in any specified particle size(s).

[114] In some embodiments, a composition comprising 2C-B (e.g., 2C-B HBr, such as 2C-B HBr Polymorph 1), and optionally any additional active agents, is prepared by a process comprising milling (e.g., screen milling, ball milling). In embodiments, the milling is conducted under an inert atmosphere. In embodiments, the inert atmosphere is substantially free of moisture. In embodiments, the inert atmosphere comprises substantially dry nitrogen gas. In embodiments, the inert atmosphere comprises substantially dry argon gas. In embodiments, the milling is conducted at ambient temperature. In embodiments, the milling is conducted at a temperature greater than ambient temperature. In embodiments, the milling is conducted at between about 50 °C and 70 °C. In embodiments, coarse particles are prepared for milling by heating them to a temperature greater than ambient temperature. In embodiments, coarse particles are prepared for milling by heating them to a temperature of between about 50 °C and 70 °C.

[115] Dosage forms can further comprise supplementary active compounds. These include preservatives, antioxidants, and antimicrobial agents including biocides and biostats such as antibacterial, antiviral and antifungal agents. Preservatives can be used to inhibit microbial growth or increase stability of an agent thereby prolonging the shelf life of the composition. Suitable preservatives are known in the art and include EDTA, EGTA, benzalkonium chloride or benzoic acid or benzoates, such as sodium benzoate. Antioxidants include vitamin A, vitamin C (ascorbic acid), vitamin E, tocopherols, other vitamins or provitamins, and compounds such as alpha lipoic acid. Other supplementary active compounds include colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

D. Pharmaceutical Combinations

[116] It will be readily appreciated that the disclosed compositions are not limited to combinations of a single compound or solid form (e.g., 2C-HBr Polymorph 1), or (when formulated as a pharmaceutical composition) limited to a single carrier, diluent, and/or excipient alone, but also may include combinations of multiple compounds (including additional active compounds), combinations of multiple solid (or non-solid) forms, and/or combinations of multiple carriers, diluents, and excipients. Pharmaceutical compositions (interchangeably, unless context dictates otherwise, with pharmaceutical “formulations”) thus may comprise a disclosed solid form together with one or more other solid (or non-solid) forms, one or more other active compounds, and/or one or more other pharmaceutically-acceptable carriers, diluents, and/or excipients.

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

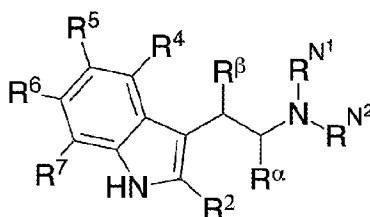
[118] “Therapeutic effects” that may be increased or added in embodiments include, but are not limited to, antioxidant, anti-inflammatory, analgesic, antineuropathic, antinociceptive, antimigraine, anxiolytic, antidepressant, antipsychotic, anti-PTSD, dissociative, immunostimulant, anti-cancer, antiemetic,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

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

[120] In some embodiments, a disclosed pharmaceutical composition comprises an additional active compound. In embodiments, the additional active compound is selected from the group consisting of: amino acids, antioxidants, anti-inflammatory agents, analgesics, antineuropathic and antinociceptive agents, antimigraine agents, anxiolytics, antidepressants, antipsychotics, anti-PTSD agents, dissociatives, cannabinoids, immunostimulants, anti-cancer agents, antiemetics, orexigenics, antiulcer agents, anti-

histamines, antihypertensives, anticonvulsants, antiepileptics, bronchodilators, neuroprotectants, nootropics, empathogens, psychedelics, plasticity-inducing agents (e.g., psychoplastogens, neuroplastogens), monoamine oxidase inhibitors, tryptamines, terpenes, phenethylamines, sedatives, stimulants, serotonergic agents, and vitamins. In embodiments, the additional active compound acts to increase a therapeutic effect, provide an additional therapeutic effect, decrease an unwanted effect, increase stability or shelf-life, improve bioavailability, induce synergy, increase plasticity (e.g., neural plasticity), or alter PK or PD. In embodiments, the additional therapeutic effect is an antioxidant, anti-inflammatory, analgesic, antineuropathic, antinociceptive, antimigraine, anxiolytic, antidepressant, antipsychotic, anti-PTSD, dissociative, immunostimulant, anti-cancer, antiemetic, orexigenic, antiulcer, antihistamine, antihypertensive, anticonvulsant, antiepileptic, bronchodilator, neuroprotective, empathogenic, psychedelic, sedative, or stimulant effect.

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



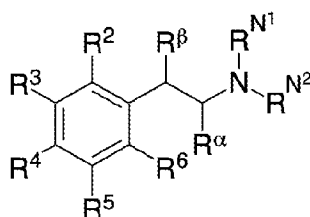
[122] In embodiments, R^{N1} , R^{N2} , R^α , R^β , R^2 , R^4 , R^5 , R^6 , and R^7 are each independently hydrogen (H), deuterium (D), halogen (F, Cl, Br, or I), OH, phosphoryloxy, or any of alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, all of which may be optionally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

[123] In some embodiments, the additional active compound is a tryptamine selected from the group consisting of psilocybin, psilocin, psilocetin, DBT, DET, DiPT, α ,O-DMS, DMT, 2, α -DMT, α ,N-DMT, DPT, EiPT, AET, 4-HO-DBT, 4-HO-DET, 4-HO-DiPT, 4-HO-TMT, 4-HO-DMT, 5-HO-DMT (i.e., bufotenine), 4-HO-DPT, 4-HO-MET, 4-HO-MiPT, 4-HO-MPT, 4-HO-pyr-T, ibogaine, MBT, 4,5-MDO-DiPT, 5,6-MDO-DiPT, 4,5-MDO-DMT, 5,6-MDO-DMT, 5,6-MDO-MiPT, 2-Me-DET, 5-Br-DMT, 5-Cl-DMT, 5-F-DMT, 4,5-MDO-DMT, 4,5-MDO-DiPT, 2-Me-DMT, melatonin, 5-MeO-DET, 5-MeO-DiPT, 5-MeO-DALT, 5-MeO-DMT, 4-MeO-MiPT, 5-MeO-MiPT, 5,6-MeO-MiPT, 5-MeO-NMT, 5-MeO-pyr-T, 5-MeO-TMT, 5-MeS-DMT, MiPT, α -MT (i.e., AMT), NET, NMT, pyr-T, tryptamine, or α ,N,O-TMS, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a combination thereof. As known to one of skill, the systematic naming

of tryptamines, such as those listed herein, involves the use of prefixes and suffixes to indicate substitutions on the indole ring and/or the side chain of the tryptamine core structure. For example, EiPT stands for ethyl isopropyl tryptamine, also known as N-ethyl-N-isopropyltryptamine (i.e., N-ethyl-N-[2-(1H-indol-3-yl)ethyl]propan-2-amine). Examples of these tryptamines and others that may in embodiments be included in a disclosed composition as an additional active compound are known to those of skill, and include the compounds disclosed in Shulgin & Shulgin, *TiHKAL: The Continuation*, Transform Press (1997) ("TiHKAL").

[124] In some embodiments, the tryptamine is a "complex tryptamine" or other indolamine, including such examples as iboga alkaloids such as ibogaine, and its analogs, metabolites, and derivatives. In some embodiments, the tryptamine is a beta-carboline, such as beta-carboline, harmaline, harmine, harmane, harmalol, tetrahydroharmine, 9-methyl- β -carboline, pinoline, and 6-MeO-THH.

[125] In some embodiments, the additional active compound is a phenethylamine. As will be appreciated in the art, phenethylamines are compounds having the general structure below, wherein R^{N1} , R^{N2} , R^α , R^β , and each of R^2 - R^6 are as taught herein and as generally understood in the art:



[126] In some embodiments, R^{N1} , R^{N2} , R^α , R^β , and each of R^2 - R^6 are independently H, D, halogen, or any of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, all of which may be optionally substituted. In some embodiments, R^3 and R^4 are joined together to form an optionally substituted heterocyclyl, such as a dioxole (as with MDMA), a furan, a tetrahydrofuran, a thiophene, a pyrrole, a pyridine, a pyrrolidine, an ethylene oxide, an ethylenimine, a trimethylene oxide, a pyran, a piperidine, an imidazole, a thiazole, a dioxane, a morpholine, or a pyrimidine. In embodiments, R^3 and R^4 are joined together to form an optionally substituted aryl, such as a phenyl. In embodiments, the phenethylamine comprises a quaternary ammonium cation wherein each of R^{N1} , R^{N2} , and an additional R^{N3} are independently an alkyl group or an aryl group, and with all other substituents as above. In embodiments, the phenethylamine is a quaternary salt, in which an additional R^{N3} is connected to the nitrogen to which R^{N1} and R^{N2} are bound; wherein R^{N3} is alkyl, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, all of which may be optionally substituted.

[127] In some embodiments, the additional active compound is a phenethylamine selected from the group consisting of mescaline, α -ethylmescaline, escaline, symbescaline, metaescaline, allylescaline, methallylescaline, asymbescaline, cyclopropylmescaline, phenescaline, 4-desoxymescaline, isomescaline, proscaline, metaproscaline, isoproscaline, thiomescaline, thioescaline, thioproscaline, thiobuscaline, a thiomescaline analog (e.g., 3-TM, 4-TM), buscaline, a thioisomescaline (e.g., 2-TIM, 3-TIM, 4-TIM), Aleph (i.e., DOT), a thiometaescaline (e.g., 3-TME, 4-TME, 5-TME), a thiotrisescaline (e.g., 3-T-TRIS, 4-T-TRIS), a

thiosymbescaline (e.g., 3-TSB, 4-TSB), Aleph-2, Aleph-4, Aleph-6, Aleph-7, Ariadne, Beatrice (i.e., MDO-D, MDOM), BIS-TOM, BOB, BOD, BOH, BOHD, BOM, 4-Br-3,5-DMA, 2-Br-4,5-MDA, MDEA, 3C-BZ, a 2C-X compound (e.g., 2C-B, 2C-B-AN, 2C-B-FLY, 2C-B-BUTTERFLY, 2C-B-FLY-NBOMe, 2C-B-FLY-NB2EtO5Cl, 2C-Bn, 2C-Bu, 2C-B-5-HEMIFLY, 2C-C, 2C-C-3, 2C-CN, 2C-CP, 2C-D, 2C-E, 2C-EF, 2C-F, 2C-G, 2C-G-1, 2C-G-2, 2C-G-3, 2C-G-4, 2C-G-5, 2C-G-6, 2C-G-N, 2C-H, 2C-I, 2CB-Ind, 2C-iP, 2C-N, 2C-NH₂, 2C-PYR, 2C-PIP, 2C-O, 2C-O-4, 2C-MOM, 2C-P, 2C-Ph, 2C-Se, 2C-T, 2C-T-2, 2C-T-3, 2C-T-4, 2C-T-5, 2C-T-6, 2C-T-7, 2C-T-8, 2C-T-9, 2C-T-10, 2C-T-11, 2C-T-12, 2C-T-13, 2C-T-14, 2C-T-15, 2C-T-16, 2C-T-17, 2C-T-18, 2C-T-19, 2C-T-21, 2C-T-21.5, 2C-T-22, 2C-T-23, 2C-T-24, 2C-T-25, 2C-T-27, 2C-T-28, 2C-T-30, 2C-T-31, 2C-T-32, 2C-T-33, 2C-DFM, 2C-TFM, 2C-TFE, 2C-YN, 2C-V, 2C-AL, CPM, psi-2C-T-4, 2C-Se), 3C-BZ, 3C-E, 4-D, beta-D, 2,4-DMA, 2,5-DMA, 3,4-DMA, DMCPA, DME, DMMDA, DMMDA-2, DMPEA, DOAM, DOB, DOBU, DOC, DOEF, DOET, DOI, DOM (i.e., STP), psi-DOM, DON, DOPR, EEE, EEM, EME, EMM, ETHYL-J, ETHYL-K, F-2, F-22, FLEA, GANESHA, a GANESHA analog (e.g., G-3, G-4, G-5, G-N), HOT-2, HOT-7, HOT-17, IDNNA, IRIS, BDB, LOPHOPHINE, 4-MA (i.e., PMA), MADAM-6, MDA, MDMA, MDAL, MDBU, MDBZ, MDCPM, MDDM, MDE, MDHOET, MDIP, MDMC, MDMEO, MDMEOET, MDMP, MDOH, MDPEA, MDPH, MDPL, MDPR, MEDA, MEE, MEM, MEPEA, META-DOB, META-DOT, METHYL-DMA, METHYL-DOB, METHYL-J (i.e., MBDB), METHYL-K, METHYL-MA (i.e., PMMA), METHYL-MMDA-2, MMDA, MMDA-2, MMDA-3a, MMDA-3b, MME, MPM, ORTHO-DOT, PEA, PROPYNYL, tetramethoxy-amphetamine, 3-TASB, 4-TASB, 5-TASB, 3-TE, 4-TE, TMA, TMA-2, TMA-3, TMA-4, TMA-5, TMA-6, 2T-MMDA-3a, 4T-MMDA-2, TMPEA, 2-TOET, 5-TOET, 2-TOM, 5-TOM, TOMSO, 4-MTA, MDAL, 5-methyl-MDA, 5-APB, 6-APB, and DiFMDA, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a combination thereof. As known in the art, the systematic naming of phenethylamines, such as those herein, involves the use of prefixes and suffixes to indicate substitutions on the phenyl ring and/or side chain of the phenethylamine core structure. For example, MDBZ stands for methylenedioxybenzylamphetamine (i.e., 3,4-methylenedioxy-N-benzylamphetamine). Examples of these phenethylamines and others that may in embodiments be included in a disclosed composition as an additional active compound are known to those of skill, and include the compounds disclosed in Shulgin & Shulgin, PiHKAL: A Chemical Love Story, Transform Press (1991) ("PiHKAL"); and Shulgin AT, The Shulgin Index Vol.1: Psychedelic Phenethylamines & Related Compounds, Transform Press (2011).

[128] In some embodiments, the additional active compound is MDMA. In embodiments, the MDMA is a fumarate salt. In embodiments, the MDMA is a malonate salt. In embodiments, the MDMA is a maleate salt. In embodiments, the MDMA is a malate salt. In embodiments, the MDMA is a phosphate salt. In embodiments, the MDMA is a tartrate salt. In embodiments, the MDMA is a galactarate salt. In embodiments, the MDMA is a succinate salt. In embodiments, the MDMA is a tosylate salt. In embodiments, the MDMA is a hydrochloride salt. In embodiments, the MDMA is a hydrobromide salt.

[129] In some embodiments, the MDMA is a pure or substantially pure individual enantiomer of MDMA or

a salt thereof, i.e., R-MDMA or S-MDMA, wherein the individual enantiomer is present in an amount of at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5%, at least about 99.9%, or up to and including 100% by weight of the enantiomer, relative to the other enantiomer. In embodiments, the MDMA is racemic MDMA. In embodiments, MDMA is a non-racemic mixture of MDMA or a salt (or salts, i.e., mixed salts) thereof, comprising an enantiomeric excess of R-MDMA, or an enantiomeric excess of S-MDMA. For example, wherein the non-racemic MDMA comprises an enantiomeric excess of R-MDMA, in some embodiments the enantiomeric excess of R-MDMA is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%. In embodiments, the enantiomeric excess of R-MDMA is about 10%-95%, 20%-95%, 30%-95%, 40%-95%, 50%-95%, 55%-95%, 60%-90%, 65%-90%, 70%-85%, or 75%-85%, wherein each range is inclusive. In embodiments, the enantiomeric excess of R-MDMA is about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%. In embodiments, the enantiomeric excess of R-MDMA is about 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, or 85%. In embodiments, the enantiomeric excess of R-MDMA is about 79% to 81%, 79.1% to 80.9%, 79.2% to 80.8%, 79.3% to 80.7%, 79.4% to 80.6%, 79.5% to 80.5%, 79.6% to 80.4%, 79.7% to 80.3%, 79.8% to 80.2%, or 79.9% to 80.1%. In embodiments, the enantiomeric excess of R-MDMA is about 79.5%, 79.6%, 79.7%, 79.8%, 79.9%, 80%, 80.1%, 80.2%, 80.3%, 80.4%, or 80.5%. In embodiments, the R-MDMA in enantiomeric excess comprises R-MDMA to S-MDMA in a ratio of about 4:1 to 12:1, 5:1 to 10:1, 6:1 to 12:1, 7:1 to 11:1, or 8:1 to 10:1. In embodiments, the R-MDMA in enantiomeric excess comprises R-MDMA to S-MDMA in a ratio of about 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, or 12:1. In embodiments, the R-MDMA in enantiomeric excess comprises R-MDMA to S-MDMA in a ratio of 9:1. In embodiments, the enantiomeric excess of R-MDMA is within 0.05%, within 0.1%, within 1%, within 2%, within 2.5%, or within 5% of 80%.

[130] In some embodiments, the non-racemic mixture comprises R-MDMA and S-MDMA, on a molar basis, as any of: 90% $\pm$ 5% R-MDMA and 10% $\pm$ 5% S-MDMA; 90% $\pm$ 2.5% R-MDMA and 10% $\pm$ 2.5% S-MDMA; 90% $\pm$ 2% R-MDMA and 10% $\pm$ 2% S-MDMA; 90% $\pm$ 1% R-MDMA and 10% $\pm$ 1% S-MDMA; 90% $\pm$ 0.1% R-MDMA and 10% $\pm$ 0.1% S-MDMA; or 90% $\pm$ 0.05% R-MDMA and 10% $\pm$ 0.05% S-MDMA.

[131] In some embodiments, the non-racemic mixture comprises 90% $\pm$ 0.1% R-MDMA and 10% $\pm$ 0.1% S-MDMA. In embodiments, the non-racemic mixture comprises 90% $\pm$ 0.05% R-MDMA and 10% $\pm$ 0.05% S-MDMA. In some embodiments, the non-racemic mixture comprises 90% $\pm$ 1% R-MDMA and 10% $\pm$ 1% S-MDMA. In embodiments, the non-racemic mixture comprises 90% $\pm$ 2.5% R-MDMA and 10% $\pm$ 2.5% S-MDMA. In embodiments, the non-racemic mixture comprises 90% $\pm$ 5% R-MDMA and 10% $\pm$ 5% S-MDMA. In embodiments, the non-racemic mixture comprises $x\%$ $\pm$ 5% R-MDMA and $y\%$ $\pm$ 5% S-MDMA, $x\%$ $\pm$ 2.5% R-MDMA and $y\%$ $\pm$ 2.5% S-MDMA, $x\%$ $\pm$ 1% R-MDMA and $y\%$ $\pm$ 1% S-MDMA, $x\%$ $\pm$ 0.1% R-MDMA and $y\%$ $\pm$ 0.1% S-MDMA, or $x\%$ $\pm$ 0.05% R-MDMA and $y\%$ $\pm$ 0.05% S-MDMA, wherein x and y

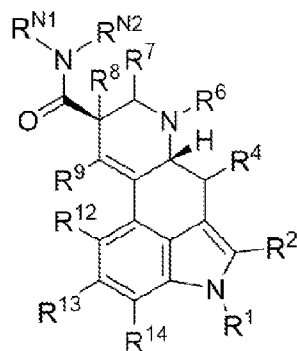
when combined equal about 100, and wherein x and y can be any two numbers that equal about 100.

[132] In some embodiments, x and y represent a non-racemic mixture of R-MDMA and S-MDMA as disclosed herein, such as in a ratio of about 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, or 12:1.

[133] For example, in embodiments, a disclosed composition comprises MDMA as a non-racemic mixture (e.g., R-MDMA to S-MDMA in a ratio of about 9:1) in an amount between about 50 mg and 300 mg, 100 mg and 300 mg, 150 mg and 300 mg, 200 mg and 300 mg, 200 and 250 mg, 62 mg and 285 mg, 62 mg and 235 mg, 141 mg and 285 mg, or between about 141 mg and 235 mg.

[134] In embodiments, the R-MDMA is a fumarate salt. In embodiments, the R-MDMA is a malonate salt. In embodiments, the R-MDMA is a maleate salt. In embodiments, the R-MDMA is a malate salt. In embodiments, the R-MDMA is a phosphate salt. In embodiments, the R-MDMA is a tartrate salt. In embodiments, the R-MDMA is a galactarate salt. In embodiments, the R-MDMA is a succinate salt. In embodiments, the R-MDMA is a tosylate salt. In embodiments, the R-MDMA is a hydrochloride salt. In embodiments, the R-MDMA is a hydrobromide salt. In some embodiments, the S-MDMA is a fumarate salt. In embodiments, the S-MDMA is a malonate salts. In embodiments, the S-MDMA is a maleate salt. In embodiments, the S-MDMA is a malate salt. In embodiments, the S-MDMA is a phosphate salt. In embodiments, the S-MDMA is a tartrate salt. In embodiments, the S-MDMA is a galactarate salt. In embodiments, the S-MDMA is a succinate salt. In embodiments, the S-MDMA is a tosylate salt. In embodiments, the S-MDMA is a hydrochloride salt. In embodiments, the S-MDMA is a hydrobromide salt.

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



[136] In some embodiments, R^{N1} , R^{N2} , R^1 , R^2 , R^4 , R^6 , R^7 , R^8 , R^9 , R^{12} , R^{13} , and R^{14} are each independently H, deuterium, halogen, or any of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, all of which may be optionally substituted. Additionally, any two of R^{N1} , R^{N2} , R^1 , R^2 , R^4 , R^6 , R^7 , R^8 , R^9 , R^{12} , R^{13} , and R^{14} and the intervening atoms can be taken together to form a cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, all of which may be optionally substituted. In some embodiments, the lysergamide is a quaternary salt, in

which an additional R^{6A} is connected to the nitrogen to which R⁶ is bound; wherein R^{6A} is alkyl, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, all of which may be optionally substituted.

[137] In some embodiments, the additional active compound is a lysergamide selected from the group consisting of LSD, ETH-LAD, PARGY-LAD, AL-LAD, PRO-LAD, IP-LAD, CIP-LAD, BU-LAD, FLUOROETH-LAD, ALD, ALD-52, N-acetyl-LSD, 1P-LSD, 1B-LSD, 1V-LSD, 1cP-LSD, 1D-LSD, 1P-AL-LAD, 1cP-AL-LAD, 1P-ETH-LAD, LA-SS-Az, LSZ, LSD-Pip, and MIPLA, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a combination thereof.

[138] Other tryptamines, phenethylamines, and lysergamides useful as additional active compounds for purposes of the invention and thus contemplated for inclusion therein will be as generally known in the art (see, e.g., PiHKAL; TiHKAL; Grob & Grigsby, Handbook of Medical Hallucinogens, 2021; Luethi & Liechti, Arch. Toxicol., 2020; 94, 1085-1133; Nichols, Pharmacol Rev., 2016; 68(2), 264-355; Glennon, Pharmacol Biochem Behav., 1999; 64, 251-256; each of which is incorporated by reference as if fully set forth herein).

[139] In some embodiments, the additional active compound is a cannabinoid. Herein, "cannabinoid" includes all naturally occurring phytocannabinoids. Naturally-occurring phytocannabinoids, such as from *Cannabis* plants, include THC and CBD as well as cannabinal (CBN), cannabigerol (CBG), cannabinodiol (or cannabidinodiol) (CBDL, CBND), cannabichromene (CBC), cannabielsoin (CBE), cannabicyclol (CBL), cannabicitran (CBT), cannabivarin (CBV), cannabidivarin (CBDV), tetrahydrocannabivarin (THCV), cannabichromevarin (CBCV), cannabigerovarin (CBGV), and cannabigerol monomethyl ether (CBGM). The term "cannabinoid" also includes cannabinoid acids. "Cannabinoid acids" refers generally to a heterogeneous group of naturally-occurring compounds found within the cannabis plant that are the carboxylic acid precursors of their corresponding "neutral" cannabinoid, which are also included (e.g., Burstein, S. Bioorg. Med. Chem. 2014;22(10):2830-2843). Examples of cannabinoid acids include cannabichromenonic acid (CBCA), cannabichromevarinic acid (CBCVA), cannabidiolic acid (CBDA), cannabidiolic acid monomethyl ether (CBDMA), CBDPA (cannabidiphorolic acid), CBDVA (cannabidivarinic acid), CBFA (cannabifuranic acid), CBEA (cannabielsoinic acid), CBGA (cannabigerolic acid), CBGVA (cannabigerovarinic acid), CBLA (cannabicyclolic acid), CBNA (cannabinolic acid), CBNDA (cannabinodiolic acid), CBTA (cannabitrilic acid), THCA (tetrahydrocannabinolic acid, including Δ^8 and Δ^9 THCA), THCPA (tetrahydrocannabipgorolic acid), and THCVA (tetrahydrocannabivarinic acid). "Neutral cannabinoids" refer to the decarboxylated form of a given cannabinoid acid; i.e., the cannabinoid where the additional carboxyl group is removed.

E. Dose and Dosage

[140] In some embodiments, pharmaceutical compositions comprise a therapeutically effective amount or an effective amount of a disclosed solid form (e.g., 2C-B HBr Polymorph 1), such as for administration to a subject. Administration of disclosed pharmaceutical compositions in a "therapeutically effective amount," or an "effective amount" to a subject means administration of an amount of composition sufficient to achieve the desired effect. When an "effective amount" means an amount effective in treating the stated disorder or

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

[141] In embodiments, where a disclosed composition comprises a solid form of 2C-B HBr (e.g., 2C-B HBr Polymorph 1), the composition comprises the solid form in an amount so that a single dose is (in a milligram dose amount based on the kilogram weight of the patient), e.g., 0.25 mg/kg or less (including a dose of 0.10 mg/kg or less, 0.05 mg/kg or less, 0.01 mg/kg or less, and 0.005 mg/kg or less), at least 0.50 mg/kg, at least 0.55 mg/kg, at least 0.60 mg/kg, at least 0.65 mg/kg, at least 0.70 mg/kg, at least 0.75 mg/kg, at least 0.80 mg/kg, at least 0.85 mg/kg, at least 0.90 mg/kg, at least 0.95 mg/kg, at least 1.0 mg/kg, at least 1.1 mg/kg, at least 1.2 mg/kg, at least 1.3 mg/kg, or at least 1.4 mg/kg, at least 1.5 mg/kg, at least 1.6 mg/kg, at least 1.7 mg/kg, at least 1.8 mg/kg, at least 1.9 mg/kg, or at least 2.0 mg/kg, as well as amounts within these ranges. In other embodiments, the composition comprises the solid form in an amount so that a single dose is, e.g., between about 0.01 mg/kg and 0.1 mg/kg, such as about 0.01 mg/kg, about 0.02 mg/kg, about 0.03 mg/kg, about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg about 0.08 mg/kg about 0.09 mg/kg, and about 0.1 mg/kg, as well as ranges between these values. In some embodiments, a single dose is between about 0.1 mg/kg and 1.0 mg/kg, such as about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg about 0.8 mg/kg about 0.9 mg/kg, and about 1.0 mg/kg, as well as ranges between these values. In other embodiments, the composition comprises between about 0.25 mg/kg and 3.0 mg/kg, such as between about 0.25 mg/kg and 2.5 mg/kg, 0.25 mg/kg and 2.0 mg/kg, 0.25 mg/kg and 1.5 mg/kg, 0.25 mg/kg and 1.0 mg/kg, 0.25 mg/kg and 0.75 mg/kg, 0.25 mg/kg and 0.50 mg/kg, 0.50 mg/kg and 2.5 mg/kg, 0.50 mg/kg and 2.0 mg/kg, 0.50 mg/kg and 1.5 mg/kg, or 0.50 mg/kg and 1.0 mg/kg, as well as ranges between these values.

[142] In some embodiments, where a disclosed composition comprises a solid form of 2C-B HBr (e.g., 2C-B HBr Polymorph 1), such as where a composition is an oral solid dosage form comprising Polymorph 1, the composition comprises the solid form in an amount so that a single dose is (whether or not such dose is present in a unit dosage form), between about 0.1 mg to 100 mg. In embodiments, a single dose is about 0.1 mg to 50 mg. In embodiments, a single dose is about 1 mg to 100 mg. In embodiments, a single dose is about 1 mg to 50 mg. In embodiments, a single dose is about 1 mg to 25 mg. In embodiments, a single dose is about 10 mg to 100 mg. In embodiments, a single dose is about 10 mg to 50 mg. In embodiments, a single dose is about 10 mg to 25 mg. In embodiments, a single dose is less than 5 mg. In embodiments, a single dose is about 5 mg to 10 mg. In embodiments, a single dose is about 10 mg to 15 mg. In embodiments, a

single dose is about 15 mg to 25 mg. In embodiments, a single dose is about 25 mg to 35 mg. In embodiments, a single dose is about 35 mg to 45 mg. In embodiments, a single dose is greater than 45 mg.

[143] In embodiments, a single dose is, e.g., 10 mg or less (including 7.5 mg or less, 5 mg or less, 2.5 mg or less, 1 mg or less, and 0.5 mg or less), at least 10 mg, at least 15 mg, at least 20 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, and at least 95 mg, as well as amounts within these ranges. In some other embodiments, a single dose is at least 100 mg.

[144] In some embodiments, where a disclosed composition comprises a solid form of 2C-B HBr (e.g., 2C-B HBr Polymorph 1), the composition comprises the solid form in an amount so that a single dose is (whether or not such dose is present in a unit dosage form) between about 0.1 mg and 1.0 mg, such as about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, and about 1.0 mg, as well as ranges between these values. In some embodiments, a single dose is between about 1 mg and 10 mg, such as about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, and about 10 mg, as well as ranges between these values. In some embodiments, a single dose is between about 10 mg and 100 mg.

[145] In some embodiments, where a disclosed composition comprises a solid form of 2C-B HBr (e.g., 2C-B HBr Polymorph 1), the composition comprises the solid form in an amount so that a single dose is (whether or not such dose is present in a unit dosage form), e.g., between about 10 mg and 150 mg, such as between about 10 mg and 150 mg, 10 mg and 100 mg, 10 mg and 75 mg, 10 mg and 50 mg, 10 mg and 40 mg, 10 mg and 30 mg, 10 mg and 20 mg, 20 mg and 150 mg, 20 mg and 100 mg, 20 mg and 75 mg, 20 mg and 50 mg, 20 mg and 40 mg, 20 mg and 30 mg, 30 mg and 150 mg, 30 mg and 100 mg, 30 mg and 75 mg, 30 mg and 50 mg, or 30 mg and 40 mg.

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

[147] In embodiments, where a disclosed composition comprises an additional active compound, the composition comprises the additional active compound in an amount so that a single dose is (in a milligram

dose amount based on the kilogram weight of the patient), e.g., between about 0.25 mg/kg and 3.0 mg/kg, such as between about 0.25 mg/kg and 2.5 mg/kg, 0.25 mg/kg and 2.0 mg/kg, 0.25 mg/kg and 1.5 mg/kg, 0.25 mg/kg and 1.0 mg/kg, 0.25 mg/kg and 0.75 mg/kg, 0.25 mg/kg and 0.50 mg/kg, 0.50 mg/kg and 2.5 mg/kg, 0.50 mg/kg and 2.0 mg/kg, 0.50 mg/kg and 1.5 mg/kg, or 0.50 mg/kg and 1.0 mg/kg.

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

[149] In embodiments, where a disclosed composition comprises an additional active compound, such as a phenethylamine or a tryptamine, the composition comprises the additional active compound in an amount so that a single dose is (whether or not such dose is present in a unit dosage form), e.g., between about 10 mg and 300 mg, such as between about 10 mg and 250 mg, 10 mg and 200 mg, 10 mg and 150 mg, 10 mg and 100 mg, 10 mg and 75 mg, 10 mg and 50 mg, 10 mg and 40 mg, 10 mg and 30 mg, 10 mg and 20 mg, 20 mg and 300 mg, 20 mg and 250 mg, 20 mg and 200 mg, 20 mg and 150 mg, 20 mg and 100 mg, 20 mg and 75 mg, 20 mg and 50 mg, 20 mg and 40 mg, 20 mg and 30 mg, 30 mg and 300 mg, 30 mg and 250 mg, 30 mg and 200 mg, 30 mg and 150 mg, 30 mg and 100 mg, 30 mg and 75 mg, 30 mg and 50 mg, 30 mg and 40 mg, 50 mg and 200 mg, 50 mg and 250 mg, 50 mg and 300 mg, 50 mg and 150 mg, 50 mg and 100 mg, 50 mg and 75 mg, 100 mg and 300 mg, 100 mg and 250 mg, 100 mg and 200 mg, or 100 mg and 150 mg.

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

[151] In embodiments, where a disclosed composition comprises an additional active compound, such as

an ergoline or lysergamide, such as LSD, the composition comprises the ergoline or lysergamide in an amount so that a single dose is (in a $\mu\text{g/kg}$ dose amount based on the kg weight of the patient), e.g., 1 $\mu\text{g/kg}$ or less (including a dose of about 0.5 $\mu\text{g/kg}$ or less, about 0.25 $\mu\text{g/kg}$ or less, about 0.1 $\mu\text{g/kg}$ or less, about 0.05 $\mu\text{g/kg}$ or less, about 0.005 $\mu\text{g/kg}$ or less, about 0.001 $\mu\text{g/kg}$ or less, and about 0.0005 $\mu\text{g/kg}$ or less), or at least about 1 $\mu\text{g/kg}$ or more, including 1.0 $\mu\text{g/kg}$, 1.1 $\mu\text{g/kg}$, 1.2 $\mu\text{g/kg}$, 1.3 $\mu\text{g/kg}$, 1.4 $\mu\text{g/kg}$, 1.5 $\mu\text{g/kg}$, 1.6 $\mu\text{g/kg}$, 1.7 $\mu\text{g/kg}$, 1.8 $\mu\text{g/kg}$, 1.9 $\mu\text{g/kg}$, 2.0 $\mu\text{g/kg}$, 2.1 $\mu\text{g/kg}$, 2.2 $\mu\text{g/kg}$, 2.3 $\mu\text{g/kg}$, 2.4 $\mu\text{g/kg}$, 2.5 $\mu\text{g/kg}$, 2.6 $\mu\text{g/kg}$, 2.7 $\mu\text{g/kg}$, 2.8 $\mu\text{g/kg}$, 2.9 $\mu\text{g/kg}$, 3.0 $\mu\text{g/kg}$, 3.1 $\mu\text{g/kg}$, 3.2 $\mu\text{g/kg}$, 3.3 $\mu\text{g/kg}$, 3.4 $\mu\text{g/kg}$, 3.5 $\mu\text{g/kg}$, 3.6 $\mu\text{g/kg}$, 3.7 $\mu\text{g/kg}$, 3.8 $\mu\text{g/kg}$, 3.9 $\mu\text{g/kg}$, 4.0 $\mu\text{g/kg}$, 4.1 $\mu\text{g/kg}$, 4.2 $\mu\text{g/kg}$, 4.3 $\mu\text{g/kg}$, 4.4 $\mu\text{g/kg}$, 4.5 $\mu\text{g/kg}$, 4.6 $\mu\text{g/kg}$, 4.7 $\mu\text{g/kg}$, 4.8 $\mu\text{g/kg}$, 4.9 $\mu\text{g/kg}$, 5.0 $\mu\text{g/kg}$, as well as amounts within these ranges. In embodiments, a single dose may be greater than 5.0 $\mu\text{g/kg}$, including 7.5 $\mu\text{g/kg}$, 10.0 $\mu\text{g/kg}$, or greater than 10 $\mu\text{g/kg}$.

[152] In some embodiments, wherein a pharmaceutical composition comprises R-MDMA, S-MDMA, or a non-racemic mixture thereof (such as a mixture comprising R-MDMA and S-MDMA in a R:S ratio of about 9:1), the composition comprises MDMA in an amount so that a single dose is (whether or not such dose is in a unit dosage form), e.g., 5 mg or less, at least 5 mg, at least 10 mg, at least 15 mg, at least 20 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, at least 100 mg, at least 105 mg, at least 110 mg, at least 115 mg, at least 120 mg, at least 125 mg, at least 130 mg, at least 135 mg, at least 140 mg, at least 145 mg, at least 150 mg, at least 155 mg, at least 160 mg, at least 165 mg, at least 170 mg, at least 175 mg, at least 180 mg, at least 185 mg, at least 190 mg, at least 195 mg, at least 200 mg, at least 205 mg, at least 210 mg, at least 215 mg, at least 220 mg, at least 225 mg, at least 230 mg, at least 235 mg, at least 240 mg, at least 245 mg, at least 250 mg, at least 255 mg, at least 260 mg, at least 265 mg, at least 270 mg, at least 275 mg, at least 280 mg, at least 285 mg, at least 290 mg, at least 295 mg, at least 300 mg, at least 305 mg, at least 310 mg, at least 315 mg, at least 320 mg, or at least 325 mg, as well as amounts within these ranges.

[153] In some embodiments, wherein a pharmaceutical composition comprises R-MDMA, S-MDMA, or a non-racemic mixture thereof (such as a mixture comprising R-MDMA and S-MDMA in a R:S ratio of about 9:1), the composition comprises MDMA in an amount so that a single dose is (whether or not such dose is in a unit dosage form), e.g., between about 25 mg and 325 mg, 25 mg and 175 mg, 50 mg and 150 mg, or 62 mg to 62.5 mg and 125 mg. In some embodiments, the composition comprises between about 50 mg to 300 mg, 75 mg to 300 mg, 100 mg to 300 mg, or 140 mg to 285 mg of R-MDMA, S-MDMA, or a non-racemic mixture thereof. In some embodiments, the composition comprises between about 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, or 75 mg of R-MDMA, S-MDMA, or a non-racemic mixture thereof.

[154] It will be readily appreciated that dosages may vary depending upon whether the treatment is therapeutic or prophylactic, the onset, progression, severity, frequency, duration, probability of or

susceptibility of the symptom to which treatment is directed, clinical endpoint desired, previous, simultaneous or subsequent treatments, general health, age, gender, and race of the subject, bioavailability, potential adverse systemic, regional or local side effects, the presence of other disorders or diseases in the subject, and other factors that will be appreciated by the skilled artisan (e.g., medical or familial history).

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

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

[157] In embodiments, for example where a composition is prepared in single unit dosage form, suggested dose amounts may be known by reference to the format of the preparation itself. In embodiments, for example where a composition is prepared in multiple dosage form, suggested dose amounts may be known by reference to the means of administration or by reference to the packaging and labeling, package insert(s), marketing materials, training materials, or other information available to those of skill or the public.

F. Kits

[158] Another aspect of this disclosure provides pharmaceutical kits (as shorthand, "kits") containing a disclosed pharmaceutical composition, suggested administration guidelines or prescribing information therefor, and a suitable container. Individual unit dosage forms can be included in multi-dose kits or containers. pharmaceutical compositions also can be packaged in single or multiple unit dosage forms for uniformity of dosage and ease of administration. Kits may comprise suitable packaging. Kits may comprise one or more containers comprising any solid form described herein, along with any additional active compounds. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit. The kits may be in unit dosage forms, bulk packages (e.g., multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a solid form as disclosed herein and/or an additional pharmaceutically active compound useful for a disease detailed herein to provide effective

treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (e.g., hospital pharmacies and compounding pharmacies).

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

G. Methods of Use

[160] In some aspects, provided are methods of using a disclosed solid form (e.g., 2C-B HBr Polymorph 1) and compositions thereof. In some embodiments, a disclosed solid form is used to modulate neurotransmission. In embodiments, a disclosed solid form is used to treat a condition, such as a disease or a disorder. In embodiments, a disclosed solid form is used in the manufacture of a medicament for the therapeutic and/or the prophylactic treatment of a condition, such as a disease or a disorder. In embodiments, a disclosed solid form is administered as part of therapy. In embodiments, a disclosed solid form is administered along with psychotherapy, psychological support, or patient monitoring. In embodiments, a disclosed solid form is administered in a therapeutically effective amount to a subject having a condition, such as a disease or a disorder. In embodiments, the condition is a mental health disorder. In embodiments, the condition is a neurodegenerative disorder. In embodiments, the condition is a pain disorder. In embodiments, a disclosed solid form is administered to a subject that is healthy.

[161] Herein, the terms “subject,” “user,” “patient,” and “individual” are used interchangeably, and refer to any mammal, including murines, simians, mammalian farm animals, mammalian sport animals, and mammalian pets, such as canines and felines, although preferably humans. Such terms will be understood to include one who has an indication for which a solid form, composition, or method described herein may be efficacious, or who otherwise may benefit therefrom. Disclosed methods can be modified to treat multiple patients, including couples and groups. Hence, in some embodiments, these terms will be understood to also mean two or more individuals. In general, all of the disclosed solid forms, compositions, and methods will be appreciated to work for all individuals, although individual variation is to be expected, and will be understood.

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

3. Modulating Neurotransmission

[163] In embodiments, a disclosed solid form modulates neurotransmission in a subject, such as following administration of a therapeutically effective amount to said subject. In embodiments, modulating

neurotransmission by administering a disclosed solid form to a subject treats a disease or disorder in the subject. In embodiments, modulating neurotransmission comprises regulating levels of monoamines in, for example, the CNS and peripheral tissues. In embodiments, modulating neurotransmission by administering a disclosed solid form to a subject treats a disease or disorder in the subject.

[164] In embodiments, modulating neurotransmission contributes to the therapeutic effects of a disclosed solid form in a subject. In embodiments, modulating neurotransmission by administering a disclosed solid form to a subject treats a disease or disorder in the subject. In some embodiments, modulating neurotransmission comprises modulating any of serotonergic neurotransmission, dopaminergic neurotransmission, and noradrenergic neurotransmission.

[165] Neurotransmission refers to the transfer of information between neurons. Information is emitted by a neuron when an action potential occurs, resulting in the release of neurotransmitters into a synapse. Neurotransmission can thus be quantified by measuring parameters of action potential firing in a population of neurons. In embodiments, neurotransmission is quantified by measuring the general action potential firing activity (Obien et al. *Front Neurosci.* 2015;8:423; Morin et al. *J Biosci Bioeng.* 2005;100(2):131-143). General action potential firing activity parameters include spike rate, burst rate, and/or spike contrast. In embodiments, neurotransmission is quantified by measuring burst structure. Burst structure parameters include burst spike number, burst duration, and/or burst amplitude. In embodiments, neurotransmission is quantified by measuring oscillatory behavior. Oscillatory behavior is measured as the standard deviation of spike rate, burst rate, and/or burst amplitude. In embodiments, neurotransmission is quantified by measuring the synchronicity of activity of a neuron population. Synchronicity is measured as the coefficient of variation in spike rate, burst rate, and/or burst duration across a neuron population. Synchronicity is also measured as synchronicity share, synchronicity distance, and/or spike simplex.

[166] In embodiments, administration of a disclosed solid form modulates spike rate. Spike rate is the number of action potentials per second. In embodiments, administration of a disclosed solid form modulates burst rate. Neurons may send out a series of action potentials in rapid succession, known as a burst. Burst rate is the number of bursts per second. In embodiments, a disclosed solid form modulates spike contrast. Spike contrast is a measure of variability in neuronal activity, measured as the difference between the number of spikes occurring in the first half and second half of a recording duration (e.g., 700 milliseconds). In embodiments, a disclosed solid form modulates burst spike number. Burst spike number is the number of spikes per burst. In embodiments, a disclosed solid form modulates burst duration. Burst duration is the mean duration of detected bursts. In embodiments, neurotransmission is measured as the burst amplitude. To obtain burst amplitude, an integral function with a decay is calculated over the timestamps of bursts. The burst amplitude is the peak value of the integral, which increases with highly frequent and numerous spiking.

[167] In embodiments, administration of a disclosed solid form modulates oscillatory behavior. Oscillatory behavior is a measure of variability in a parameter, measured as the standard deviation of a parameter over

time within the experimental episode. In embodiments, administration of a disclosed solid form modulates the synchronicity of activity in a neuron population. Synchronicity is a measure of the relative variability in activity across a neuron population. In embodiments, administration of a disclosed solid form modulates synchronicity share. Synchronicity share is the average number of units involved in population bursts, higher values reflecting a higher degree of synchronicity in bursts occurring amongst populations of neurons. In embodiments, administration of a disclosed solid form modulates synchronicity distances. Synchronicity distances are defined as the average distance of burst starts within a population burst from the population burst center, lower values reflecting a stronger synchronicity of a network. In embodiments, administration of a disclosed solid form modulates spike simplex. Spike simplex is a measure of connectivity and complexity in a neuronal network, higher values reflecting higher synchronicity among neurons.

b. Modulating Neuroplasticity

[168] In embodiments, administration of a disclosed solid form increases neuroplasticity. Neuroplasticity, also known as neural plasticity or brain plasticity, refers to the brain's ability to change and adapt in response to experiences, learning, and environmental factors. Without being bound by theory, neuroplasticity occurs through several mechanisms, including synaptic plasticity, which involves the strengthening or weakening of connections (synapses) between neurons. Synaptic plasticity is often associated with learning and memory processes. Another form of plasticity is called structural plasticity, which involves changes in the physical structure of neurons, such as the growth of new dendritic branches or the formation of new synapses. In embodiments, increasing neuroplasticity contributes to the therapeutic effects of administering a disclosed solid form to a subject. In embodiments, increasing neuroplasticity refers to increasing synaptic plasticity. In embodiments, increasing neuroplasticity refers to increasing structural plasticity. In embodiments, increasing neuroplasticity by administering a disclosed solid form to a subject treats a disease or disorder in the subject.

[169] Neuroplasticity can be defined in terms of neuritogenesis, spinogenesis, and synaptogenesis in neurons. Neuritogenesis refers to the process by which neurons generate and extend their neurites (i.e., to form axons and dendrites). Neuritogenesis is a critical step in neural development and the formation of neuronal circuits. Spinogenesis refers to the formation of dendritic spines, which are small protrusions on the dendrites of neurons. Dendritic spines are crucial for synaptic connections and play a vital role in synaptic transmission and plasticity. Synaptogenesis refers to the formation of synapses, which is crucial for the establishment and refinement of neural circuits, and is a fundamental process underlying learning, memory, and information processing in the brain. In embodiments, administration of a disclosed solid form increases neuritogenesis. Neuritogenesis can be measured in terms of total neurite length, maximum neurite length, number of neurite nodes, and/or number of neurite extremities. In embodiments, administration of a disclosed solid form increases total neurite length. In embodiments, a disclosed solid form increases maximum neurite length. In embodiments, administration of a disclosed solid form increases the number of neurite nodes. In embodiments, administration of a disclosed solid form increases the number of neurite

extremities. In embodiments, administration of a disclosed solid form increases dendritogenesis. In embodiments, administration of a disclosed solid form increases spinogenesis. In embodiments, administration of a disclosed solid form increases synaptogenesis. In embodiments, administration of a disclosed solid form increases the number of dendritic branches, the number of dendritic crossings, the density of dendritic spines, the density of synapses (i.e., number of synapses per neuron), or total dendritic length. These factors can be measured using a Sholl analysis and other techniques known to those of skill in the art (see, e.g., Ly et al. ACS Pharmacol Transl Sci. 2020;4(2):452-460).

c. Treatment

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

[171] In embodiments, a disclosed solid form is administered to a subject by one or more routes of administration, including, e.g., oral, mucosal, rectal, subcutaneous, intravenous, intramuscular, intranasal, inhaled, ocular, intraocular, topical, and transdermal routes. When administered through one or more of such routes, the solid form is useful in methods for treating a patient in need of such treatment.

[172] In some embodiments are provided methods of treating and/or preventing a condition in a mammal, the method comprising administering to the mammal a therapeutically effective amount of a disclosed solid form. In embodiments, “treating” or “treatment” refers to treating a disease or disorder in a mammal, and preferably in a human, and includes causing a desired biological or pharmacological effect, such as: (a) preventing a disorder from occurring in a subject who may be predisposed to the disorder but has not yet been diagnosed with it; (b) inhibiting a disorder, i.e. arresting its development; (c) relieving a disorder, i.e., causing regression thereof; (d) protecting from or relieving a symptom or pathology caused by or related to a disorder; (e) reducing, decreasing, inhibiting, ameliorating, or preventing the onset, severity, duration, progression, frequency or probability of one or more symptoms or pathologies associated with a disorder; and (f) preventing or inhibiting of a worsening or progression of symptoms or pathologies associated with a disorder or comorbid with a disorder. In embodiments, treatment includes prevention. In other embodiments, treatment does not include prevention. Other such measurements, benefits, and surrogate or clinical endpoints, alone or in combination, will be understood in view of the disclosure and the knowledge in the art.

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

i. Mental, Behavioral, or Neurodevelopmental Disorders

[174] In embodiments, a disclosed solid form is used to treat a mental, behavioral, or neurodevelopmental

disorder. In embodiments, a disclosed solid form is administered, such as in a therapeutically effective amount, to a subject having a mental, behavioral, or neurodevelopmental disorder, thereby treating said mental, behavioral, or neurodevelopmental disorder. In some methods herein, the disclosed compositions, when administered in a therapeutically effective amount, provide beneficial therapeutic effects for the treatment of a mental, behavioral, or neurodevelopmental disorder.

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

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

[177] In embodiments, a disclosed solid form is used to treat a mental health disorder in a subject. In embodiments, a subject has a mental health disorder. In embodiments, a subject is at risk of a mental health disorder. The diagnosis of a mental health disorder and determining that a subject is at risk of a neurodevelopmental disorder will be known to those in the art. In embodiments, a disclosed solid form is administered, such as in a therapeutically effective amount, to a subject having a mental health disorder, thereby treating said mental health disorder. In some methods herein, the disclosed compositions, when

administered in a therapeutically effective amount, provide beneficial therapeutic effects for the treatment of a mental health disorder. In embodiments, a disclosed solid form is used to reduce the symptoms of a mental health disorder. The symptoms of the mental health disorder to be treated shall be able to be determined by one of skill in the art, by reference to the general understanding of the art regarding that disorder.

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

[179] In embodiments, a disclosed solid form is used to treat a neurodevelopmental disorder in a subject. In embodiments, a subject has a neurodevelopmental disorder. In embodiments, a subject is at risk of a neurodevelopmental disorder. The diagnosis of a neurodevelopmental disorder and determining that a subject is at risk of a neurodevelopmental disorder will be known to those in the art. Examples of a neurodevelopmental disorder, treatable using a disclosed solid form, include a disorder of intellectual development, a developmental speech or language disorder, autism, autism spectrum disorder (ASD), social anxiety in autistic subjects, a developmental learning disorder, a developmental motor coordination disorder, attention deficit hyperactivity disorder, or stereotypic movement disorder.

[180] In embodiments, a disclosed solid form is used to treat schizophrenia or another primary psychotic disorder. In embodiments, a subject has schizophrenia or another primary psychotic disorder. In embodiments, a subject is at risk of schizophrenia or another primary psychotic disorder. The diagnosis of schizophrenia or another primary psychotic disorder and determining that a subject is at risk of schizophrenia or another primary psychotic disorder will be known to those in the art. Examples of a psychotic disorder, treatable using a disclosed solid form, include schizophrenia, schizoaffective disorder, schizotypal disorder, acute and transient psychotic disorder, delusional disorder, or a substance-induced psychotic disorder.

[181] In embodiments, a disclosed solid form is used to treat catatonia. In embodiments, a subject has catatonia. In embodiments, a subject is at risk of catatonia. The diagnosis of catatonia and determining that a subject is at risk of catatonia will be known to those in the art. In embodiments, catatonia is associated with another mental disorder. In embodiments, catatonia is induced by substances or medications.

[182] In embodiments, a disclosed solid form is used to treat a mood disorder. In embodiments, a subject has a mood disorder. In embodiments, a subject is at risk of a mood disorder. The diagnosis of a mood disorder and determining that a subject is at risk of a mood disorder will be known to those in the art.

Examples of a mood disorder, treatable using a disclosed solid form, include depressive episodes, manic episodes, mixed episodes, and hypomanic episodes. In embodiments, the mood disorder is a bipolar or related disorder (e.g., bipolar type I disorder, bipolar type II disorder, cyclothymic disorder), a depressive disorder, or a substance-induced mood disorder. In embodiments, the mood disorder is a depressive disorder. In embodiments, the depressive disorder is single-episode depressive disorder, major depressive episode disorder, persistent depressive disorder (dysthymia), disruptive mood dysregulation disorder, premenstrual dysphoric disorder, postpartum depression, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, seasonal affective disorder, mixed depressive and anxiety disorder, or an unspecified depressive disorder. In embodiments, the depressive disorder is major depressive disorder (MDD) or treatment resistant depression (TRD).

[183] In embodiments, depression is assessed through the Patient Health Questionnaire-9 (PHQ-9) screening tool, Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale, Beck Depression Inventory (BDI-II), Zung Self-Rating Depression Scales (SDS), Major Depression Inventory (MDI), Center for Epidemiologic Studies Depression Scale (CED-D), Rome Depression Inventory (RDI), Hamilton Rating Scale for Depression (HRSD), and Carroll Rating Scale (CRS).

[184] In embodiments, a disclosed solid form is used to treat an anxiety or fear-related disorder. In embodiments, a subject has an anxiety or fear-related disorder. In embodiments, a subject is at risk of an anxiety or fear-related disorder. The diagnosis of an anxiety or fear-related disorder and determining that a subject is at risk of an anxiety or fear-related disorder will be known to those in the art. Examples of an anxiety or fear-related disorder, treatable using a disclosed solid form, include generalized anxiety disorder, panic disorder, agoraphobia, specific phobia, social anxiety disorder, separation anxiety disorder, selective mutism, or a substance-induced anxiety disorder.

[185] In embodiments, a disclosed solid form is used to treat an obsessive-compulsive or related disorder. In embodiments, a subject has an obsessive-compulsive or related disorder. In embodiments, a subject is at risk of an obsessive-compulsive or related disorder. The diagnosis of an obsessive-compulsive or related disorder and determining that a subject is at risk of obsessive-compulsive or related disorder will be known to those in the art. Examples of an obsessive-compulsive or related disorder, treatable using a disclosed solid form, include an obsessive-compulsive disorder, body dysmorphic disorder, olfactory reference disorder, hypochondriasis, hoarding disorder, a body-focused repetitive behavior disorder, or a substance-induced obsessive-compulsive disorder.

[186] In embodiments, a disclosed solid form is used to treat a disorder associated with stress. In embodiments, a subject has a disorder associated with stress. In embodiments, a subject is at risk of a disorder associated with stress. The diagnosis of a disorder associated with stress and determining that a subject is at risk of a disorder associated with stress will be known to those in the art. In embodiments, the disorder associated with stress has an identifiable stressor that is a causal factor, like exposure to a stressful

or traumatic event, or a series of such events or adverse experiences. Stressors may be within the normal range of life experiences (e.g., divorce, socioeconomic problems), or from a threatening or traumatizing experience. In general, the nature and duration of the symptoms that arise in response to the stressor can distinguish the disorder from everyday stress. Examples of a disorder associated with stress, treatable using a disclosed solid form, include post-traumatic stress disorder (PTSD), complex PTSD (cPTSD), prolonged grief disorder, adjustment disorder, reactive attachment disorder, or disinhibited social engagement disorder.

[187] In embodiments, a disclosed solid form is used to treat a dissociative disorder. In embodiments, a subject has a dissociative disorder. In embodiments, a subject is at risk of a dissociative disorder. The diagnosis of a dissociative disorder and determining that a subject is at risk of a dissociative disorder will be known to those in the art. Examples of a dissociative disorder, treatable using a disclosed solid form, include dissociative amnesia (including amnesia with dissociative fugue and without dissociative fugue), trance disorder, possession trance disorder, dissociative identity disorder, partial dissociative identity disorder, or depersonalization- derealization disorder.

[188] In embodiments, a disclosed solid form is used to treat a feeding or eating disorder. In embodiments, a subject has a feeding or eating disorder. In embodiments, a subject is at risk of a feeding or eating disorder. The diagnosis of a feeding or eating disorder and determining that a subject is at risk of a feeding or eating disorder will be known to those in the art. Examples of a feeding or eating disorder, treatable using a disclosed solid form, include anorexia nervosa (including anorexia with significantly low body weight, with dangerously low body weight, and anorexia in recovery with normal body weight), bulimia nervosa, binge eating disorder, avoidant-restrictive food intake disorder, pica, or rumination-regurgitation disorder.

[189] In embodiments, a disclosed solid form is used to treat an elimination disorder. In embodiments, a subject has an elimination disorder. In embodiments, a subject is at risk of an elimination disorder. The diagnosis of an elimination disorder and determining that a subject is at risk of an elimination disorder will be known to those in the art. Examples of an elimination disorder, treatable using a disclosed solid form, include enuresis (including nocturnal enuresis, diurnal enuresis, and nocturnal and diurnal enuresis) or encopresis (including both with constipation or overflow incontinence, and without constipation or overflow incontinence).

[190] In embodiments, a disclosed solid form is used to treat a disorder of bodily distress or bodily experience. In embodiments, a subject has a disorder of bodily distress or bodily experience. In embodiments, a subject is at risk of a disorder of bodily distress or bodily experience. The diagnosis of a disorder of bodily distress or bodily experience and determining that a subject is at risk of a disorder of bodily distress or bodily experience will be known to those in the art. Examples of a disorder of bodily distress or bodily experience, treatable using a disclosed solid form, include bodily distress disorder (including mild, moderate, and severe bodily distress disorder) or body integrity dysphoria.

[191] In embodiments, a disclosed solid form is used to treat a disorder due to substance use or addictive behaviors. In embodiments, a subject has a disorder due to substance use or addictive behaviors. In

embodiments, a subject is at risk of a disorder due to substance use or addictive behaviors. The diagnosis of a disorder due to substance use or addictive behaviors and determining that a subject is at risk of a disorder due to substance use or addictive behaviors will be known to those in the art. In embodiments, a disclosed solid form is used to treat disorders due to substance use (i.e., a substance use disorder, or SUD). In embodiments, the substance use disorder is associated with alcohol, cannabis, synthetic cannabinoids, opioids, sedatives, hypnotics or anxiolytics, cocaine, stimulants (e.g., amphetamines, methamphetamines, methcathinone, synthetic cathinones, caffeine), hallucinogens, nicotine, volatile inhalants, MDMA or MDA, dissociative drugs like ketamine and phencyclidine, or another substance (including medications and non-psychoactive substances). Examples of a substance use disorder, treatable using the solid form, include alcohol use disorder, cannabis use disorder, caffeine use disorder, phencyclidine use disorder, inhalants use disorder, opioids use disorder, sedatives use disorder, hypnotics use disorder, anxiolytics use disorder, stimulants use disorder, and tobacco use disorder. In embodiments, the substance use disorder is alcohol use disorder. In embodiments, the substance use disorder is cannabis use disorder. In embodiments, the substance use disorder is caffeine use disorder. In embodiments, the substance use disorder is phencyclidine use disorder. In embodiments, the substance use disorder is inhalant use disorder. In embodiments, the substance use disorder is opioids use disorder. In embodiments, the substance use disorder is sedatives use disorder. In embodiments, the substance use disorder is hypnotics use disorder. In embodiments, the substance use disorder is anxiolytics use disorder. In embodiments, the substance use disorder is stimulants use disorder. In embodiments, the substance use disorder is tobacco use disorder. In embodiments, the substance use disorder is alcohol use disorder, wherein said alcohol use disorder is selected from alcohol abuse, alcohol dependence, and alcoholism. In embodiments, the disorder is associated with another addictive behavior (e.g., gambling disorders, gaming disorder). In embodiments, a substance use disorder can be screened using a Screening to Brief Intervention (S2BI), Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), Brief Screener for Alcohol, Tobacco, and other Drugs (BSTAD), Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS), the Opioid Risk Tool - OUD (ORT-OUD) Chart, Drug Abuse Screen Test (DAST-10), and Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS).

[192] In embodiments, a disclosed solid form is used to treat an impulse control disorder. In embodiments, a subject has an impulse control disorder. In embodiments, a subject is at risk of an impulse control disorder. The diagnosis of an impulse control disorder and determining that a subject is at risk of an impulse control disorder will be known to those in the art. In embodiments, impulse control behaviors include fire-setting, stealing, inappropriate sexual behavior, and explosive outbursts. Examples of an impulse control disorder, treatable using a disclosed solid form, include pyromania, kleptomania, compulsive sexual behavior disorder, or intermittent explosive disorder.

[193] In embodiments, a disclosed solid form is used to treat a disruptive behavior disorder or a dissocial

disorder. In embodiments, a subject has a disruptive behavior disorder or a dissocial disorder. In embodiments, a subject is at risk of a disruptive behavior disorder or a dissocial disorder. The diagnosis of a disruptive behavior disorder or a dissocial disorder and determining that a subject is at risk of a disruptive behavior disorder or a dissocial disorder will be known to those in the art. Examples of a disruptive behavior disorder or a dissocial disorder, treatable using a disclosed solid form, include oppositional defiant disorder (including oppositional defiant disorder with chronic irritability-anger and oppositional defiant disorder without chronic irritability-anger) or conduct-dissocial disorder (including childhood-onset conduct-dissocial disorder and adolescent-onset conduct-dissocial disorder).

[194] In embodiments, a disclosed solid form is used to treat a personality disorder. In embodiments, a subject has a personality disorder. In embodiments, a subject is at risk of a personality disorder. The diagnosis of a personality disorder and determining that a subject is at risk of a personality disorder will be known to those in the art. In embodiments, a disclosed solid form is used to treat a mild, moderate, or severe personality disorders. In embodiments, a disclosed solid form is used to treat a prominent personality trait or patterns (e.g., negative affectivity, detachment, dissociality, disinhibition, anankastia, borderline pattern). Examples of a personality disorder, treatable using a disclosed solid form, include antisocial personality disorder, avoidant personality disorder, borderline personality disorder, dependent personality disorder, histrionic personality disorder, masochistic or sadistic behavior, narcissistic personality disorder, obsessive-compulsive personality disorder, paranoid personality disorder, psychopathy, sociopathy, schizoid personality disorder, or schizotypal personality disorder.

[195] In embodiments, a disclosed solid form is used to treat a paraphilic disorder. In embodiments, a subject has a paraphilic disorder. In embodiments, a subject is at risk of a paraphilic disorder. The diagnosis of a paraphilic disorder and determining that a subject is at risk of a paraphilic disorder will be known to those in the art. Examples of a paraphilic disorder, treatable using a disclosed solid form, include exhibitionistic disorder, voyeuristic disorder, pedophilic disorder, coercive sexual sadism disorder, frotteuristic disorder, other paraphilic disorders involving non-consenting individuals, or paraphilic disorders involving solitary behavior or consenting individuals.

[196] In embodiments, a disclosed solid form is used to treat a factitious disorder. In embodiments, a subject has a factitious disorder. In embodiments, a subject is at risk of a factitious disorder. The diagnosis of a factitious disorder and determining that a subject is at risk of a factitious disorder will be known to those in the art. Subjects with factitious disorders may seek treatment or otherwise present themselves or another person as ill, injured, or impaired. Examples of a factitious disorder, treatable using a disclosed solid form, include a factitious disorder imposed on self or a factitious disorder imposed on another.

[197] In embodiments, a disclosed solid form is used to treat a neurocognitive disorder. In embodiments, a subject has a neurocognitive disorder. In embodiments, a subject is at risk of a neurocognitive disorder. The diagnosis of a neurocognitive disorder and determining that a subject is at risk of a neurocognitive disorder

will be known to those in the art. Examples of a neurocognitive disorder, treatable using a disclosed solid form, include delirium, amnestic disorder, dementia, Alzheimer's disease, Parkinson's disease, cerebrovascular disease, or Lewy body disease. In embodiments, a neurocognitive disorder, treatable using the disclosed solid forms, is associated with a psychoactive substance (including medications and illicit or illegal substances). In embodiments, a disclosed solid form is used to treat delirium. In embodiments, the delirium is associated with another disease or disorder. In embodiments, the delirium is associated with a psychoactive substance (including medications and illicit or illegal substances). In embodiments, a disclosed solid form is used to treat mild neurocognitive disorder. In embodiments, a disclosed solid form is used to treat an amnestic disorder. In embodiments, the amnestic disorder is associated with another disease or disorder. In embodiments, the delirium is associated with a psychoactive substance (including medications and illicit or illegal substances). In embodiments, a disclosed solid form is used to treat dementia. In embodiments, the dementia is associated with Alzheimer's disease, Parkinson's disease, cerebrovascular disease, Lewy body disease, a psychoactive substance (including medications and illicit or illegal substances). In embodiments, a disclosed solid form is used to treat a behavioral or psychological disturbance associated with dementia. In embodiments, dementia is assessed using a Functional Activities Questionnaire (FAQ), Ascertain Dementia 8 (AD8), Mini-Cog, Mini-Mental State Exam (MMSE), the Montreal Cognitive Assessment (MoCA), and the Neuropsychiatric Inventory Questionnaire (NPI-Q).

[198] In embodiments, a disclosed solid form is used to treat a mental or behavioral disorder associated with pregnancy, childbirth, or the puerperium. In embodiments, a subject has a mental or behavioral disorder associated with pregnancy, childbirth, or the puerperium. In embodiments, a subject is at risk of a mental or behavioral disorder associated with pregnancy, childbirth, or the puerperium. The diagnosis of a mental or behavioral disorder associated with pregnancy, childbirth, or the puerperium and determining that a subject is at risk of a mental or behavioral disorder associated with pregnancy, childbirth, or the puerperium will be known to those in the art. In embodiments, the disorder includes psychotic symptoms. In embodiments, a disclosed solid form is used to treat mental or behavioral disorders associated with pregnancy, childbirth or the puerperium, with psychotic symptoms. In embodiments, a disclosed solid form is used to treat mental or behavioral disorders associated with pregnancy, childbirth or the puerperium, without psychotic symptoms.

[199] In embodiments, a disclosed solid form is used to treat a sleep-wake disorder. In embodiments, a subject has a sleep-wake disorder. In embodiments, a subject is at risk of a sleep-wake disorder. The diagnosis of a sleep-wake disorder and determining that a subject is at risk of a sleep-wake disorder will be known to those in the art. Examples of a sleep-wake disorder, treatable using a disclosed solid form, include an insomnia disorder, a hypersomnolence disorder, a sleep-related breathing disorder, a circadian rhythm sleep-wake disorder, or a parasomnia disorder.

[200] In embodiments, a disclosed solid form is used to treat sexual dysfunction. In embodiments, a subject has sexual dysfunction. In embodiments, a subject is at risk of sexual dysfunction. The diagnosis of

sexual dysfunction and determining that a subject is at risk of sexual dysfunction will be known to those in the art. Examples of a sexual dysfunction, treatable using the solid form, include hypoactive sexual desire dysfunction, sexual arousal dysfunction, orgasmic dysfunction, ejaculatory dysfunction, or sexual dysfunction associated with pelvic organ prolapse.

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

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

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

[204] In embodiments, the psychotherapy conducted with a disclosed solid form is conducted in widely spaced sessions. These sessions can be as frequently as weekly but are more often approximately monthly or less frequently. In most cases, a small number of sessions, on the order of one to three, is needed for a

patient to experience significant clinical progress, as indicated, for example, by a reduction in the symptoms of the mental health disorder being treated. In embodiments, psychotherapy comprises multiple sessions, during some of which a disclosed solid form is administered (“drug-assisted psychotherapy”); in others, the patient participates in psychosocial or behavioral therapy without concomitant administration of a drug, or without administration of the solid form.

[205] In embodiments, a disclosed solid form is administered together with standardized psychological treatment or support, such as any accepted modality of standard psychotherapy or counseling, whether once a week, twice a week, or as needed; whether in person or virtual (e.g., over telemedicine or by means of a web program or mobile app); and whether with a human therapist or a virtual or AI “therapist.” Herein, “therapist” refers to a person who treats a patient using a disclosed solid form or method, whether the person is a psychiatrist, clinical psychologist, clinical therapist, registered therapist, psychotherapist, or other trained clinician, counselor, facilitator, or guide, although it will be understood that certain requirements are appropriate to certain aspects of the drug-assisted therapy (e.g., prescribing, dispensing, or administering a drug, offering psychotherapeutic support). In embodiments, a “person” may also include an AI.

[206] In embodiments, a subject will participate in a disclosed treatment protocol or method, or be administered a disclosed solid form as part of a method, if the subject meets certain inclusion criteria, does not meet certain exclusion criteria, and/or does not meet any withdrawal criteria during such treatment.

[207] In embodiments, a personalized or precision medicine approach may be used, based on individual characteristics, including drug metabolism (e.g., CYP2D6 or CYP3A4) or individual genetic variation. The term “genetic variation” refers to a change in a gene sequence relative to a reference sequence (e.g., a commonly-found and/or wild-type sequence). Genetic variation may be recombination events or mutations such as substitution/deletion/insertion events like point and splice site mutations.

[208] In embodiments, the genetic variation is a variation in one or more cytochrome P450 (CYP or CYP450) enzymes that affects drug metabolism, such as 2C-B metabolism, e.g., CYP1A2, CYP2C9, CYP2D6, CYP2C19, CYP3A4 and CYP3A5. In embodiments, also including CYP1A1, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, and CYP51.

[209] In embodiments, a disclosed solid form is taken together with a compound that is metabolized by the same CYP enzyme(s) as 2C-B, so as to permit a lower dose to be taken, increase the effective bioavailability of one or both, or otherwise affect drug metabolism or PK. In embodiments, the dose of a disclosed solid form is adjusted, such as reduced, when administered to a subject known to be a poor metabolizer of 2C-B, or increased when administered to a subject known to be a rapid metabolizer of 2C-B. In embodiments, a patient is tested using means known to in the art to determine if the patient is a poor or rapid metabolizer.

[210] In embodiments, the genetic variation is a genetic variation in metabotropic glutamate receptor type 5 (mGluR5), which has been implicated in mood and anxiety symptoms in humans. In another embodiment, the genetic variation is one or more single nucleotide polymorphisms (SNPs) in the FKBP5 gene that are associated with elevated levels of FKBP51 protein relative to persons lacking such SNPs. The FKBP5 gene has been implicated in responses to stress and trauma, and such SNPs are correlated with susceptibility to certain depression, PTSD, and anxiety disorders. In embodiments, a genetic variation is an inclusion criteria for the administration of a disclosed solid form. In embodiments, a genetic variation is an exclusion criteria for the administration of a disclosed solid form. In embodiments, the mammal being treated has altered epigenetic regulation of a gene, the expression of which is associated with a mental health condition or susceptibility to a mental health treatment, such as the SIGMAR1 gene for the non-opioid sigma-1 receptor.

ii. Neurodegenerative Disorders

[211] In embodiments, a disclosed solid form is used to treat a neurodegenerative disorder. In embodiments, a disclosed solid form is administered, such as in a therapeutically effective amount, to a subject having a neurodegenerative disorder. In some methods herein, a disclosed solid form, when administered in a therapeutically effective amount, provides beneficial therapeutic effects for the treatment of a neurodegenerative disorder. The term “neurodegenerative disorder” refers to a class of progressive, chronic, and debilitating conditions characterized by the gradual loss of structure and function of neurons within the central or peripheral nervous systems, and which may involve the degeneration, impairment, or death of neuronal cells, leading to a decline in cognitive, motor, and/or sensory abilities. Neurodegenerative disorders can be classified according to primary clinical features, e.g., dementia, parkinsonism, or motor neuron disease, anatomic distribution of neurodegeneration, e.g., frontotemporal degenerations, extrapyramidal disorders, or spinocerebellar degenerations, or principal molecular abnormality (Dugger B, Dickson DW. *Pathology of Neurodegenerative Diseases*. Cold Spring Harbor Perspectives Biol. 2017;9(7):a028035). These disorders may involve various etiologies, including but not limited to, presence of pathogenic proteins, age, environmental stressors, and genetic predisposition (Armstrong R. *Folia Neuropathologica*. 2020;58(2);93-112). In embodiments, the neurodegenerative disorder is any of Alzheimer's disease, amyotrophic lateral sclerosis, Charcot's disease, chronic traumatic encephalopathy (CTE), corticobasal degeneration, dementias including vascular dementia, Huntington's disease, Lytico-Bodig disease, mild cognitive impairment, multiple sclerosis, motor neuron disease, neuromyelitis optica spectrum disorder, Parkinson's disease, Parkinsonisms, prion disease, progressive supranuclear palsy, and traumatic brain injury (TBI), including mild traumatic brain injury (mTBI).

iii. Pain Disorders

[212] In embodiments, a disclosed solid form is used to treat a pain disorder. In embodiments, a disclosed solid form is administered, such as in a therapeutically effective amount, to a subject having a pain disorder. In some methods herein, a disclosed solid form, when administered in a therapeutically effective amount,

provides beneficial therapeutic effects for the treatment of a pain disorder. A “pain disorder” refers to a class of medical conditions characterized by the experience of persistent or recurrent physical or psychological pain, either localized or widespread, that significantly impairs an individual's daily functioning and quality of life. These disorders may involve various etiologies, including but not limited to nociceptive, neuropathic, psychogenic, idiopathic or radicular origins. Pain can be assessed using the Pain, Enjoyment, and General Activity Scale (PEG), the Numeric Rating Scale (NRS), the Visual Analog Scale (VAS), Behavioral Pain Scale (BPS), and the Faces Pain Scale-Revised (FPS-R).

[213] In embodiments, a disclosed solid form is used to treat neuropathic pain. In embodiments, a disclosed solid form is used to treat psychogenic pain. In embodiments, a disclosed solid form is used to treat idiopathic pain. In embodiments, a disclosed solid form is used to treat radicular pain. Pain disorders may manifest as acute or chronic pain, and can affect different parts of the body, such as musculoskeletal, neurological, gastrointestinal, or visceral systems. Pain can be expressed as, for example, post-herpetic pain, trigeminal pain, occipital pain, or pudendal pain. In embodiments, a disclosed solid form is used to treat pain associated with chemotherapy (e.g., chemotherapy-associated neuropathy). In embodiments, a disclosed solid form is used to treat arthritis, back pain, central pain, chronic fatigue syndrome, cluster headaches, migraine headaches, phantom limb pain, complex regional pain syndrome, compression mononeuropathy, diabetic neuropathy, fibromyalgia, focal neuropathy, herniated disc pain, or sciatica.

H. Examples

[214] The following examples are included for illustrative purposes only and are not intended to be limiting.

EXAMPLE 1: Characterization of 2C-B HCl and 2C-B HBr Starting Materials

[215] The 2C-B HCl and 2C-B HBr starting materials were characterized for chemical purity, and by X-ray powder diffraction (XRPD), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FT-IR), optical microscopy (morphological image analysis), and dynamic vapor sorption (DVS).

[216] Chemical Purity:

Salt	HBr		HCl		
Batch No	NBK2445-12-P1 -1 (main batch)	NBK2445-12-P2 -1 (small batch)	NBK2445-19-P2 -1 (main batch)	NBK2445-18-P 1-1 (small batch)	0631413 (commercial batch)
Original Mass	5.60 g	1.70 g	5.25 g	0.87 g	5.00 g
CoA UPLC	99.26%	-	99.64%	99.22%	-
CoA QNMR	97.80%	-	97.40%	97.82%	-
OA UPLC	97.8%	94.9%	100%	99.4%	99.0%

[217] XRPD: As shown in **FIG. 3**, each batch of 2C-B HBr starting material showed the same polymorphic form, and each batch of 2C-B HCl starting material showed the same polymorphic form. The XRPD spectra

show that no change in polymorphic form was observed before and after subjecting the 2C-B HBr starting material to DVS analysis. However, the post-DVS XRPD spectrum of the 2C-B HBr starting material showed an increase in intensity compared to the pre-DVS XRPD spectrum (**FIG. 4**).

[218] TGA: 2C-B HCl starting material showed no mass loss prior to degradation commencing at ca. 205°C. The overall mass loss was ca. 60%, which occurred in 2 steps. 2C-B HBr starting material showed a slight mass loss prior to degradation commencing at ca. 230°C. The overall mass loss was ca. 52%, which occurred in 3 steps, as shown in **FIG. 5**.

[219] DSC: The DSC thermogram of 2C-B HCl starting material showed 2 endothermic events; the first event is very small at 200 °C with a ΔH of 0.10 J/g, and the second event showed a typical melting point profile at 238 °C with a ΔH of 121.28 J/g. The DSC thermogram of 2C-B HBr starting material showed 2 endothermic events, with a typical profile of 2 separate melting points: the first at 201 °C with a ΔH of 22.05 J/g, and the second at 212 °C with a ΔH of 48.19 J/g, as shown in **FIG. 6**.

[220] FT-IR: Baseline FT-IR spectra were obtained for 2C-B HCl and 2C-B HBr starting materials. **FIG. 7** shows an exemplary FT-IR spectrum of a sample comprising 2C-B HBr starting material.

[221] Optical Microscopy (Morphologi 4): Microscope images of 2C-B HCl and 2C-B HBr starting materials were obtained for baseline morphological characterization. **FIG. 8** shows optical microscope images used for baseline morphological analysis of 2C-B HBr starting material at 2.5X (**FIG. 8A**), 5X (**FIG. 8B**), and 10X (**FIG. 8C**) magnification.

[222] DVS: The first and second DVS profiles of 2C-B HCl starting material were similar to each other, with evidence of hysteresis between 40-80% P/Po in both cycles over sorption and desorption. The first and second DVS profiles of 2C-B HBr starting material DVS also were similar (**FIG. 9**), with a slight mass loss between the first and second sorption cycles (**FIG. 10**). The overall mass loss over both cycles was minimal.

EXAMPLE 2: Solubility Screening of 2C-B HCl and 2C-B HBr Starting Materials

[223] Initial screening of 2C-B HCl and 2C-B HBr starting materials was conducted at room temp. **Table 3** shows the measured solubilities of the 2C-B HCl and 2C-B HBr starting materials in various solvent systems.

Table 3. Measured solubilities of 2C-B HBr and 2C-B HCl starting materials.

Solvent	Solubility of 2C-B HBr (mg/mL)	Solubility of 2C-B HCl (mg/mL)
Toluene	<0.4	<1.0
TBME	<0.4	<1.0
THF	5.2	<1.0
EtOAc	2.5	<1.0
Isobutanol	8.3	4.5
IPA	15.0	4.7
EtOH	43.2	13.7

MeOH	177.8	71.2
MeCN	6.2	1.5
Water	87.3	58.4
MeCN:water (95:5)	43.6	6.2
THF:water (95:5)	94.2	9.8
IPA:water (98:2)	26.7	6.1

[224] On the basis of the initial solubility screening, five solvent systems were selected for crystallization experiments (conducted in quadruplicate) with the 2C-B HBr starting material: THF, IPA, MeCN, MeCN:water (95:5), and IPA:water (98:2). **Table 4** shows the results, including observed solubility properties.

Table 4. Results of solubility screening of 2C-B HBr starting material in THF, IPA, MeCN, MeCN:water (95:5), and IPA:water (98:2).

Block	Solvent	Observations	Solubility Curve
A	IPA	Samples 1 & 2 successful. Sample 3 did not dissolve on cycles 1 & 2, but did dissolve and crystallize on cycles 3 & 4. Sample 4 did not dissolve.	Yes
B	MeCN	No samples dissolved.	No
C	THF	No samples dissolved.	No
D	MeCN:water (95:5)	Sample 1 did not crystallize. Sample 2 dissolved and crystallized on cycles 1 & 2, but did not dissolve after that. Samples 3 and 4 dissolved and crystallized.	Yes

[225] From these, IPA, IPA:water, and MeCN:water were selected for further crystallization experiments, and for generating solubility curves. **Table 5** shows the results of these additional experiments. The solubility properties of 2C-B HBr starting material in all three solvent systems were sufficient to generate solubility curves and proceed with polymorph screening.

Table 5. Additional solubility screening (2C-B HBr starting material in IPA, IPA:water, MeCN:water).

Block	Solvent	Observations	Solubility curve
A	IPA	Sample 1 - variable cloud point (might need lower temp for this concentration). Sample 2 OK. Sample 3 did not dissolve on cycle 2, but cycle 3 was OK.	Yes
B	MeCN:water (95:5)	Samples 1-3 OK. Sample 4 did not dissolve on cycle 3	Yes
C	IPA:water (98:2)	Sample 1 - did not crystallize on cycle 2, but did on cycle 3. Samples 2-4 OK.	Yes

[226] The solubility and crystallization properties of 2C-B HBr starting material was then additionally tested at four different concentrations in IPA, with heating and cooling cycles as shown in FIG. 11A and FIG. 11B. Table 6 shows the results of these experiments; 2C-B HBr starting material was fully soluble and crystallized out of IPA solutions at concentrations of 25 and 50 mg/mL; and was fully soluble and crystallized out of IPA solutions on the third and fourth cycles (see FIG. 11A and FIG. 11B) at a concentration of 75 mg/mL.

Table 6. Solubility and crystallization properties of 2C-B HBr starting material in IPA.

Vial	Concentration (mg/mL)	Dissolve & Crystallized?
1	25	Yes
2	50	Yes
3	75	Cycles 3 & 4
4	100	No

EXAMPLE 3: Synthesis and Characterization of 2C-B HBr Polymorph 1

[227] 2C-B HBr starting material (50 mg, 0.146 mmol) was suspended in isopropanol (1.00 mL). The mixture was heated to 75 °C at 5 °C/min, held at 75 °C for 60 minutes then cooled to 10 °C at 0.3 °C/min. The mixture was held at 10 °C for 15 minutes, heated to 75 °C at 0.3 °C/min, held at 75 °C for 15 minutes and cooled to 10 °C at 0.3 °C/min. The heat/cool cycle was repeated once more, the mixture held at 10 °C for 15 minutes then warmed to 20 °C at 1 °C/min. The resulting suspension was passed through a filtration frit under vacuum to provide 2C-B HBr Polymorph 1 (9 mg, 0.026 mmol, 18% yield).

[228] XRPD characterization of 2C-B HBr Polymorph 1 produced according to this procedure is shown in FIG. 1 and Table 1. All data generated from EtOH, MeOH, MeCN, or MeCN:Water samples (Table 7) matched the same HBr form seen previously in the starting material (with lower intensities due to sample availability) (FIG. 12). In contrast, all data generated from IPA or IPA:water samples showed a new HBr form (i.e., 2C-B HBr Polymorph 1), as shown in FIG. 1, FIG. 13, Table 1, and below. FIG. 14 shows a comparison between 2C-B HBr starting material (A) and 2C-B HBr Polymorph 1 (B). The solid boxes indicate peaks present in 2C-B Polymorph 1 that are absent in the 2C-B HBr starting material, and the hashed boxes indicate peaks present in the starting material that are absent in 2C-B Polymorph 1.

Table 7. Mass, solvent, and isolation method of 2C-B HBr solid forms resulting from crystallization from various solvent systems, corresponding to XRPD data shown in FIG. 12.

Batch number	Mass (mg)	Solvent	Isolation Method
NBK2502-4G-P1-1	9	EtOH	Slow evaporation
NBK2502-4H-P1-1	26	MeOH	Slow evaporation
NBK2502-6B1-P1-1	7	MeCN	Crystallization & filtration
NBK2502-6D3-P1-1	36	MeCN:water	Crystallization & filtration
NBK2502-10A2-P1-1	9	IPA	Crystallization & filtration

NBK2502-10A3-P1-1	33	IPA	Crystallization & filtration
NBK2502-10B3-P1-1	68	MeCN:water	Crystallization & filtration
NBK2502-10B4-P1-1	80	MeCN:water	Crystallization & filtration
NBK2502-10C3-P1-1	40	IPA:water	Crystallization & filtration

[229] Solubility curves for 2C-B HBr Polymorph 1 were generated by testing its solubility at different concentrations and temperatures in IPA (**FIG. 15**) and IPA:water (98:2) (**FIG. 16**). For comparison, **FIG. 17** shows the solubility curve of 2C-B HBr Polymorph 1 in MeCN:water (95:5), which regenerated the polymorphic form of the 2C-B HBr starting material.

EXAMPLE 4: Thermal and Physical Characterization of 2C-B HBr Polymorph 1

[230] 2C-B HBr Polymorph 1 is prepared and characterized as described herein, e.g., in Examples 2-3. Following isolation of the polymorph, the polymorph is characterized by TGA, DSC, FT-IR, morphological analysis (e.g., optical microscopy), and/or DVS. Results are compared to a comparator solid form, such as the 2C-B HBr starting material described in Examples 2-3, or another solid form of 2C-B. Results may show that 2C-B HBr Polymorph 1 differs in chemical and/or physical properties relative to a comparator solid form.

EXAMPLE 5: Single Crystal X-Ray Diffraction Study of 2C-B HBr Polymorph 1

[231] Crystals of 2C-B HBr Polymorph 1 are prepared and characterized as described herein, e.g., in Examples 2-4. A sample is examined by optical microscopy to choose single crystals of sufficient size and quality for single-crystal X-Ray Diffraction (XRD). A suitable crystal is selected and mounted. Diffraction data is collected and the structure is solved. Unit cell parameters and other measurements are obtained, for example: crystal system (e.g., monoclinic, orthorhombic, cubic), space group (e.g., C2, Cm, Cc, P23, Pmm2, P4, etc.), a (Å), b (Å), c (Å), α (°), β (°), γ (°), volume (Å³), Z , ρ_{calc} (gcm⁻³), μ (mm⁻¹), and $F(000)$.

EXAMPLE 6: In Vivo Pharmacokinetics (PK) of 2C-B HBr Polymorph 1

[232] Purpose: The aim of this experiment is to evaluate the in vivo PK of 2C-B HBr Polymorph 1 compared to another 2C-B form (e.g., amorphous 2C-B or another crystalline 2C-B form) in a mouse model.

[233] Methods: Mice (C57BL6/j) are supplied by Charles River UK (Margate, Kent UK). Mice are housed in groups of up to 3 upon arrival in the animal facility under a normal phase 12 h light-dark cycle. Relative humidity is controlled, and prolonged periods below 40% RH or above 70% RH are avoided. The mice are housed in polypropylene cages with sawdust-coated floors, red house, red tunnel, sizzlenest, and nestlet. Animals have free access to standard maintenance diet and tap water ad libitum. Animals are acclimatized to the facility for approximately 3-7 days prior to procedures. Body weights are recorded upon arrival and during the acclimatization period.

[234] Suitable doses of 2C-B HBr Polymorph 1 and comparator solid forms (e.g., another solid form of 2C-B, such as amorphous 2C-B, freebase 2C-B, crystalline 2C-B HBr of another polymorphic form) are administered to the mice by oral gavage. Following a single dose, mice are terminally bled by cardiac puncture to a timed schedule to obtain blood samples. Blood samples are taken at 15, 30, 45, 60, 120, 240,

360, and/or 480 min. Blood samples are held on wet ice and spun within 30 minutes of collection in a cooled centrifuge. Plasma samples are aliquoted and analyzed by LC-MS for the presence of 2C-B.

[235] Results: PK-PD type curves are generated to demonstrate the activity of 2C-B HBr Polymorph 1, as compared to control and another form of 2C-B. PK parameters that can be determined according to this assay include $C_{\max}$, $T_{\max}$, $t_{1/2}$, AUC, and bioavailability. Results are expected to show that 2C-B HBr Polymorph 1 exhibits one or more advantageous properties as described in embodiments herein.

EXAMPLE 7: Chemical Stability of 2C-B HBr Polymorph 1

[236] Solid-state chemical stability is assessed using a temperature/humidity control chamber. Samples of 2C-B HBr Polymorph 1 and any comparators (e.g., different solid forms of 2C-B) are placed in the chamber and exposed to various temperatures and humidities, for example 25° C/60% RH, 40° C/75% RH, 70° C/75% RH. In some experiments, the samples are alternatively or additionally irradiated with a Xenon lamp. The exposure and/or irradiation is provided continuously or intermittently for a specified time period, such as one day, one week, two weeks, one month, two months, three months, or 6 months. Any changes in polymorphic state, crystallinity, thermal properties (e.g., thermal phase transition temperatures and/or enthalpies), physical properties (e.g., density), purity, and/or weight of the resultant samples after the exposure and/or irradiation are evaluated by any of XRPD, thermogravimetry/differential thermal analysis, thermogravimetric analysis, differential scanning calorimetry, solubility testing, chromatography (e.g., HPLC), and microbalance analysis. Results are expected to show that 2C-B HBr Polymorph 1 exhibits improved stability compared to a comparator solid form. The improvement in stability may be an improvement of chemical stability (e.g., decreased chemical decomposition, such as oxidative degradation), physical stability (e.g., retention of crystallinity or polymorphic state), and any other chemical, physical, or thermal property disclosed herein or otherwise known to one of skill.

EXAMPLE 8: Photostability of 2C-B HBr Polymorph 1

[237] Photostability experiments are performed with 2C-B HBr Polymorph 1 and comparator solid forms in both the solid phase and as an aqueous solution. For solid-phase experiments, a specified amount of the solid form is placed into a glass vial at an amount sufficient to achieve a specified depth of the solid phase in the vial (e.g., 3 mm above the bottom of the vial). For solution-phase experiments, solutions of a suitable concentration (e.g., 0.2 mg/mL) are prepared by dissolving the solid form in water that has been purged with nitrogen for 30 minutes to prevent oxidative degradation. Duplicate vials are prepared for each sample, where one is exposed to light and the other to act as a control, with the control vial being wrapped in foil for the duration of the experiment. The samples are exposed to light (at a wavelength of between about 300 nm and 800 nm) at an irradiance level of, for example 500 W/m², for the equivalent of 1 week of bright sunlight. Observations are made before and after the exposure for each sample. Purity analysis using HPLC is performed before and after exposure for all samples. X-ray powder diffraction spectra are collected for solid form samples before and after exposure. Experiments may be repeated to compare photostability in clear

glass to amber glass vials. The experiments also may be repeated to compare photostability in the presence or absence of nitrogen (e.g., where each vial is backfilled with either air or nitrogen prior to being capped).

[238] It is anticipated that the purity and stability of the solid samples after light exposure will not change when compared to pre-exposure. It is also anticipated that the XRPD analysis will also find that the samples will not change form after the photostability experiments. Results may show that 2C-B HBr Polymorph 1 is more photostable in the solid and/or solution phase, relative to a comparator solid form. The improved photostability may result in greater retention of chemical purity post-exposure, and/or reduced or no change in polymorphic form, relative to a comparator solid form.

EXAMPLE 9: Forced Oxidative Degradation of 2C-B HBr Polymorph 1

[239] A forced degradation experiment is conducted to assess the stability of 2C-B HBr Polymorph 1 and comparator solid forms (e.g., another solid form of 2C-B) to oxidative degradation. Forced degradation of 2C-B HBr Polymorph 1 is performed in H₂O₂, for example 0.3 % H₂O₂ to test the oxidative stability of 2C-B HBr Polymorph 1. An appropriate volume of H₂O₂ is added to pre-weighed samples of the 2C-B HBr Polymorph 1 in an amber vial (or other vial shielded from light) at varying concentrations, for example 0.1 to 1.0 mg/mL. The samples are stored at 25 °C and the purity of each sample is assessed periodically thereafter by HPLC. For example, the samples may be assessed at 0, 1, 6, and 24 hours using HPLC.

[240] Results may show that the rate of degradation in H₂O₂ is slower for 2C-B HBr Polymorph 1 relative to a comparator solid form, demonstrating that 2C-B HBr Polymorph 1 may have a superior shelf-life stability and resistance to oxidative degradation.

C. Exemplary Aspects and Embodiments

[241] Among the various exemplary and non-limiting aspects and embodiments herein are the following.

[242] In one exemplary aspect, provided is a crystalline polymorph of 4-bromo-2,5-dimethoxy-phenethylamine (2C-B) hydrobromide (Polymorph 1), characterized by one or more X-ray powder diffraction (XRPD) peaks selected from the group consisting of 20.9, 24.3, 26.2, and 31.7 °2θ (Cu Kα1 radiation). In embodiments (equivalently, and as shorthand, “in embodiments”), Polymorph 1 is characterized by two or more XRPD peaks selected from the group consisting of 20.9, 24.3, 26.2, and 31.7 °2θ (Cu Kα1 radiation). In embodiments, Polymorph 1 is characterized by three or more XRPD peaks selected from the group consisting of 20.9, 24.3, 26.2, and 31.7 °2θ (Cu Kα1 radiation). In embodiments, Polymorph 1 is characterized by XRPD peaks at 20.9, 24.3, 26.2, and 31.7 °2θ (Cu Kα1 radiation).

[243] In another aspect, provided is a crystalline polymorph of 2C-B HBr (Polymorph 1), characterized by at least one, two, three, four, five, six, seven, eight, nine, or ten XRPD peaks selected from **Table 1**.

[244] In another aspect, provided is a crystalline polymorph of 2C-B HBr (Polymorph 1), characterized by at least one, two, three, four, five, six, seven, eight, nine, or ten XRPD peaks as shown in disclosed Figures.

[245] In another aspect, provided is a crystalline polymorph of 2C-B HBr (Polymorph 1), having an XRPD diffractogram that is substantially similar to that shown in the disclosed Figures.

[246] In another aspect, provided is a crystalline polymorph of 2C-B HBr (Polymorph 1), having an XRPD diffractogram that is characterized by a peak list substantially similar to that of **Table 1**.

[247] In embodiments, Polymorph 1 is further characterized by the absence of one or more XRPD peaks selected from the group consisting of 27.2 and 30.3 °2 θ (Cu K α 1 radiation). In embodiments, Polymorph 1 is further characterized by the absence of XRPD peaks at 27.2 and 30.3 °2 θ (Cu K α 1 radiation). In embodiments, Polymorph 1 has a solubility curve that is substantially similar to that of the disclosed Figures.

[248] Also provided is a pharmaceutical composition comprising crystalline 2C-B, and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the crystalline 2C-B comprises the polymorph of the disclosed embodiments. In embodiments, the composition is suitable for oral, buccal, sublingual, intranasal, injectable, subcutaneous, intravenous, intraocular, topical, or transdermal administration. In embodiments, the composition is provided in unit dosage form. In embodiments, the composition comprises crystalline 2C-B in a total amount of between about 0.1 and 100 mg. In embodiments, the composition comprises crystalline 2C-B in a total amount of between about 1 and 50 mg.

[249] In embodiments, the polymorphic purity of the crystalline 2C-B in a disclosed pharmaceutical composition is at least 90%, at least 95%, at least 99%, at least 99.5%, or at least 99.9%. In embodiments, the polymorphic purity of the crystalline 2C-B in a disclosed pharmaceutical composition is at least 90%. In embodiments, the polymorphic purity of the crystalline 2C-B in a disclosed pharmaceutical composition is at least 95%. In embodiments, the polymorphic purity of the crystalline 2C-B in a disclosed pharmaceutical composition is at least 99%. In embodiments, the polymorphic purity of the crystalline 2C-B in a disclosed pharmaceutical composition is at least 99.5%. In embodiments, the polymorphic purity of the crystalline 2C-B in a disclosed pharmaceutical composition is at least 99.9%.

[250] In embodiments, the pharmaceutical composition further comprises a therapeutically effective amount of an additional active compound, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In embodiments, the additional active compound is selected from the group consisting of amino acids, antioxidants, anti-inflammatory agents, analgesics, antineuropathic and antinociceptive agents, anti-migraine agents, anxiolytics, antidepressants, antipsychotics, anti-PTSD agents, dissociatives, cannabinoids, immunostimulants, anti-cancer agents, antiemetics, orexigenics, antiulcer agents, antihistamines, anti-hypertensives, anticonvulsants, antiepileptics, bronchodilators, neuroprotectants, nootropics, empathogens, psychedelics, plasticity-inducing agents (e.g., “psychoplastogens” or “neuroplastogens”), monoamine oxidase inhibitors, tryptamines, terpenes, phenethylamines, sedatives, stimulants, serotonergic agents, NMDA modulators, NMDA antagonists, and vitamins. In embodiments, the additional active compound is a tryptamine, a phenethylamine, an ergoline, an ergot alkaloid, or a lysergamide.

[251] In embodiments, the phenethylamine is MDMA or a salt thereof. In embodiments, the phenethylamine is a pure or substantially pure individual enantiomer of MDMA or a salt thereof. In embodiments, the phenethylamine is a non-racemic mixture of MDMA or a salt thereof, comprising an

enantiomeric excess of R-MDMA, or an enantiomeric excess of S-MDMA.

[252] In embodiments, the non-racemic mixture of MDMA or a salt thereof ("or a salt thereof," in reference to a composition of more than one enantiomer, such as a non-racemic mixture, should be understood to also include mixtures of salts, for example non-racemic mixtures of R-MDMA and S-MDMA mixed salts where the R-MDMA salt and the S-MDMA salt are different salts) comprises an enantiomeric excess of R-MDMA, wherein the R-MDMA in enantiomeric excess comprises R-MDMA to S-MDMA in a ratio of about 4:1 to 12:1, 5:1 to 10:1, 6:1 to 12:1, 7:1 to 11:1, or 8:1 to 10:1. In embodiments, the non-racemic mixture of MDMA or a salt thereof comprises an enantiomeric excess of R-MDMA, wherein the R-MDMA in enantiomeric excess comprises R-MDMA to S-MDMA in a ratio of about 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, or 12:1. In embodiments, the non-racemic mixture of MDMA or a salt thereof comprises an enantiomeric excess of R-MDMA, wherein the R-MDMA in enantiomeric excess comprises R-MDMA to S-MDMA in a ratio of about 9:1. In embodiments, the non-racemic mixture of MDMA or a salt thereof comprises an enantiomeric excess of R-MDMA, and comprises $90\% \pm 0.1\%$ R-MDMA and $10\% \pm 0.1\%$ S-MDMA.

[253] Also provided is a method of modulating neurotransmission in a subject, comprising administering to the subject the polymorph or pharmaceutical composition of any of the disclosed embodiments. In embodiments, modulating neurotransmission comprises agonizing the 5-HT_{2A} receptor.

[254] Also provided is a method of increasing neural plasticity in a subject, comprising administering to the subject the polymorph or pharmaceutical composition of any of the disclosed embodiments.

[255] In another aspect, provided is the polymorph or pharmaceutical composition of any of the disclosed embodiments, for use in the treatment of a medical condition.

[256] In another aspect, provided is the polymorph or pharmaceutical composition of any of the disclosed embodiments, for the manufacture of a medicament for the treatment of a medical condition.

[257] Also provided is a method of treating a medical condition in a subject in need of such treatment, the method comprising administering to the subject a therapeutically effective amount of the polymorph or pharmaceutical composition of any of the disclosed embodiments. In embodiments, the medical condition is a disorder linked to dysregulation or inadequate functioning of serotonergic neurotransmission. In embodiments, the medical condition is a mental, behavioral, or neurodevelopmental disorder. In embodiments, the medical condition is a neurodegenerative disorder, or a pain disorder. In embodiments, the medical condition is a neurodevelopmental disorder, schizophrenia or another primary psychotic disorder, catatonia, a mood disorder, an anxiety or fear-related disorders, an obsessive-compulsive or related disorder, a disorder specifically associated with stress, a dissociative disorder, a feeding or eating disorder, an elimination disorder, a disorder of bodily distress or bodily experience, a disorder due to substance use or addictive behavior, an impulse control disorder, a disruptive behavior or dissocial disorder, a personality disorder, a paraphilic disorder, a factitious disorder, a neurocognitive disorder, a mental or behavioral disorder associated with pregnancy, childbirth or the puerperium, a sleep-wake disorder, or a sexual

dysfunction. In embodiments, the medical condition is an anxiety disorder. In embodiments, the anxiety disorder is generalized anxiety disorder (GAD). In embodiments, the medical condition is a trauma related disorder. In embodiments, the trauma related disorder is PTSD or complex post-traumatic stress disorder (cPTSD). In embodiments, the medical condition is autism spectrum disorder (ASD). In embodiments, the polymorph or composition is administered together with one or more sessions of psychotherapy.

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

CLAIMS

The invention claimed is:

1. A crystalline polymorph of 4-bromo-2,5-dimethoxyphenethylamine (2C-B) hydrobromide (Polymorph 1), characterized by one or more X-ray powder diffraction (XRPD) peaks at about 20.9, 24.3, 26.2, and 31.7 °2 θ (Cu K α 1 radiation).
2. The polymorph of claim 1, characterized by two or more XRPD peaks at about 20.9, 24.3, 26.2, and 31.7 °2 θ .
3. The polymorph of claim 2, wherein the two or more XRPD peaks are at about 26.2 and 31.7 °2 θ .
4. The polymorph of claim 2, wherein the two or more XRPD peaks are at about 24.3 and 26.2 °2 θ .
5. The polymorph of claim 2, wherein the two or more XRPD peaks are at about 24.3 and 31.7 °2 θ .
6. The polymorph of claim 2, characterized by three or more XRPD peaks at about 20.9, 24.3, 26.2, and 31.7 °2 θ .
7. The polymorph of claim 6, wherein the three or more XRPD peaks are at about 24.3, 26.2, and 31.7 °2 θ .
8. The polymorph of claim 6, wherein the three or more XRPD peaks are at about 20.9, 26.2, and 31.7 °2 θ .
9. The polymorph of claim 6, characterized by XRPD peaks at about 20.9, 24.3, 26.2, and 31.7 °2 θ .
10. The polymorph of claim 1, characterized by any combination of XRPD peaks selected from **Table 1**.
11. The polymorph of claim 10, characterized by at least one, two, three, four, five, six, seven, eight, nine, or ten XRPD peaks selected from **Table 1**.
12. The polymorph of claim 10, having an XRPD diffractogram that is characterized by peak locations, d-spacings, heights, and areas that are substantially similar to that of **Table 1**.
13. The polymorph of claim 1, having an XRPD diffractogram that is substantially similar to that shown in **FIG. 1**.
14. The polymorph of claim 1, wherein the XRPD peak at 24.3 °2 θ has a relative peak area compared to the XRPD peak at 20.9 °2 θ that is between about 1.5 and 2.5.
15. The polymorph of claim 14, wherein the XRPD peak at 24.3 °2 θ has a relative peak area compared to the XRPD peak at 20.9 °2 θ that is about 2.0.

16. The polymorph of claim 1, wherein the XRPD peak at $24.3^{\circ}2\theta$ has a relative peak area compared to the XRPD peak at $26.2^{\circ}2\theta$ that is between about 2.0 and 5.0.
17. The polymorph of claim 16, wherein the XRPD peak at $24.3^{\circ}2\theta$ has a relative peak area compared to the XRPD peak at $26.2^{\circ}2\theta$ that is about 3.5.
18. The polymorph of claim 1, wherein the XRPD peak at $24.3^{\circ}2\theta$ has a relative peak area compared to the XRPD peak at $31.7^{\circ}2\theta$ that is between about 3.0 and 6.0.
19. The polymorph of claim 18, wherein the XRPD peak at $24.3^{\circ}2\theta$ has a relative peak area compared to the XRPD peak at $26.2^{\circ}2\theta$ that is about 4.5.
20. The polymorph of claim 1, further characterized by the absence of one or more XRPD peaks at about 27.2 and $30.3^{\circ}2\theta$.
21. The polymorph of claim 20, characterized by the absence of an XRPD peak at about $27.2^{\circ}2\theta$.
22. The polymorph of claim 20, characterized by the absence of an XRPD peak at about $30.3^{\circ}2\theta$.
23. The polymorph of claim 20, further characterized by the absence of XRPD peaks at 27.2 and $30.3^{\circ}2\theta$.
24. The polymorph of claim 1, further characterized by a solubility curve in isopropyl alcohol (IPA) that is substantially similar to that shown in **FIG. 15**.
25. The polymorph of claim 1, further characterized by a solubility curve in IPA:water (98:2) that is substantially similar to that shown in **FIG. 16**.
26. The polymorph of claim 1, further characterized by a solubility curve in acetonitrile:water (95:5) that is substantially similar to that shown in **FIG. 17**.
27. The polymorph of claim 1, having a chemical purity of greater than about 95%, 96%, 97%, 98%, or 99%.
28. The polymorph of claim 1, wherein the XRPD peak at about $20.9^{\circ}2\theta$ is at $20.9 \pm 0.5^{\circ}$, 0.4° , 0.3° , 0.2° , 0.1° , 0.05° , or $0.01^{\circ}2\theta$.
29. The polymorph of claim 1, wherein the XRPD peak at about $24.3^{\circ}2\theta$ is at $24.3 \pm 0.5^{\circ}$, 0.4° , 0.3° , 0.2° , 0.1° , 0.05° , or $0.01^{\circ}2\theta$.
30. The polymorph of claim 1, wherein the XRPD peak at about $26.2^{\circ}2\theta$ is at $26.2 \pm 0.5^{\circ}$, 0.4° , 0.3° , 0.2° , 0.1° , 0.05° , or $0.01^{\circ}2\theta$.
31. The polymorph of claim 1, wherein the XRPD peak at about $31.7^{\circ}2\theta$ is at $31.7 \pm 0.5^{\circ}$, 0.4° , 0.3° , 0.2° , 0.1° , 0.05° , or $0.01^{\circ}2\theta$.

32. A pharmaceutical composition comprising crystalline 2C-B, and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the crystalline 2C-B comprises the polymorph of any one of claims 1-31.
33. The pharmaceutical composition of claim 32, wherein the composition is suitable for oral, buccal, sublingual, intranasal, injectable, subcutaneous, intravenous, intraocular, topical, or transdermal administration.
34. The pharmaceutical composition of claim 32, in unit dosage form.
35. The pharmaceutical composition of claim 32, comprising crystalline 2C-B in a total amount of between about 0.1 mg and 100 mg.
36. The pharmaceutical composition of claim 35, comprising crystalline 2C-B in a total amount of between about 1 mg and 50 mg or between about 10 mg and 50 mg.
37. The pharmaceutical composition of claim 32, wherein the polymorphic purity of the crystalline 2C-B is at least 90%, at least 95%, at least 99%, at least 99.5%, or at least 99.9%.
38. The pharmaceutical composition of claim 32, further comprising a therapeutically effective amount of an additional active compound, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.
39. The pharmaceutical composition of claim 38, wherein the additional active compound is selected from the group consisting of amino acids, antioxidants, anti-inflammatory agents, analgesics, antineuropathic and antinociceptive agents, antimigraine agents, anxiolytics, antidepressants, antipsychotics, anti-PTSD agents, dissociatives, cannabinoids, immunostimulants, anti-cancer agents, antiemetics, orexigenics, antiulcer agents, antihistamines, antihypertensives, anticonvulsants, antiepileptics, bronchodilators, neuroprotectants, nootropics, empathogens, psychedelics, plasticity-inducing agents, monoamine oxidase inhibitors, tryptamines, terpenes, phenethylamines, sedatives, stimulants, serotonergic agents, NMDA modulators, NMDA antagonists, and vitamins.
40. The pharmaceutical composition of claim 38, wherein the additional active compound is a tryptamine, a phenethylamine, an ergoline, an ergot alkaloid, a lysergamide, or a cannabinoid.
41. The pharmaceutical composition of claim 40, wherein the phenethylamine is MDMA or a salt thereof.
42. The pharmaceutical composition of claim 41, wherein the phenethylamine is a pure or substantially pure individual enantiomer of MDMA or a salt thereof.
43. The pharmaceutical composition of claim 41, wherein the phenethylamine is a non-racemic mixture of MDMA or a salt thereof, comprising an enantiomeric excess of R-MDMA or an enantiomeric excess of S-MDMA.

44. The pharmaceutical composition of claim 43, wherein the non-racemic mixture of MDMA or a salt thereof comprises an enantiomeric excess of R-MDMA, wherein the R-MDMA in enantiomeric excess comprises R-MDMA to S-MDMA in a molar ratio of about 4:1 to 12:1, 5:1 to 10:1, 6:1 to 12:1, 7:1 to 11:1, or 8:1 to 10:1.
45. The pharmaceutical composition of claim 44, wherein the non-racemic mixture of MDMA or a salt thereof comprises an enantiomeric excess of R-MDMA, wherein the R-MDMA in enantiomeric excess comprises R-MDMA to S-MDMA in a molar ratio of about 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, or 12:1.
46. The pharmaceutical composition of claim 45, wherein the non-racemic mixture of MDMA or a salt thereof comprises an enantiomeric excess of R-MDMA, wherein the R-MDMA in enantiomeric excess comprises R-MDMA to S-MDMA in a molar ratio of about 9:1.
47. The pharmaceutical composition of claim 46, wherein the non-racemic mixture of MDMA or a salt thereof comprises an enantiomeric excess of R-MDMA, wherein the R-MDMA in enantiomeric excess comprises, on a molar basis:
- 90% $\pm$ 5% R-MDMA and 10% $\pm$ 5% S-MDMA;
 - 90% $\pm$ 2.5% R-MDMA and 10% $\pm$ 2.5% S-MDMA;
 - 90% $\pm$ 2% R-MDMA and 10% $\pm$ 2% S-MDMA;
 - 90% $\pm$ 1% R-MDMA and 10% $\pm$ 1% S-MDMA;
 - 90% $\pm$ 0.1% R-MDMA and 10% $\pm$ 0.1% S-MDMA; or
 - 90% $\pm$ 0.05% R-MDMA and 10% $\pm$ 0.05% S-MDMA.
48. A method of modulating neurotransmission in a subject, comprising administering to the subject the polymorph of any one of claims 1-31.
49. The method of claim 48, wherein modulating neurotransmission comprises agonizing the 5-HT_{2A} receptor.
50. A method of increasing neuroplasticity or neurogenesis in a subject, comprising administering to the subject the polymorph of any one of claims 1-31.
51. The method of claim 50, wherein increasing neuroplasticity or neurogenesis comprises increasing neuritogenesis, spinogenesis, or synaptogenesis.
52. A method of treating a medical condition in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the polymorph of any one of claims 1-31.
53. The method of claim 52, wherein the medical condition is a disorder linked to dysregulation or inadequate functioning of serotonergic neurotransmission.

54. The method of claim 52, wherein the medical condition is a neurodevelopmental disorder, schizophrenia or another primary psychotic disorder, catatonia, a mood disorder, an anxiety or fear-related disorder, an obsessive-compulsive or related disorder, a disorder specifically associated with stress, a dissociative disorder, a feeding or eating disorder, an elimination disorder, a disorder of bodily distress or bodily experience, a disorder due to substance use or addictive behavior, an impulse control disorder, a disruptive behavior or dissocial disorder, a personality disorder, a paraphilic disorder, a factitious disorder, a neurocognitive disorder, a mental or behavioral disorder associated with pregnancy, childbirth or the puerperium, a sleep-wake disorder, or a sexual dysfunction.
55. The method of claim 52, wherein the medical condition is a depressive disorder.
56. The method of claim 55, wherein the depressive disorder is major depressive disorder (MDD) or treatment resistant depression (TRD)
57. The method of claim 52, wherein the medical condition is an anxiety disorder.
58. The method of claim 57, wherein the anxiety disorder is generalized anxiety disorder (GAD).
59. The method of claim 52, wherein the medical condition is a trauma-related disorder.
60. The method of claim 59, wherein the trauma related disorder is post-traumatic stress disorder (PTSD) or complex post-traumatic stress disorder (cPTSD).
61. The method of claim 52, wherein the medical condition is autism, autism spectrum disorder (ASD), or social anxiety in autistic subjects.
62. The method of claim 52, wherein the medical condition is a neurodegenerative disorder or a pain disorder.
63. The method of claim 52, wherein the polymorph is administered together with one or more sessions of psychotherapy.
64. The polymorph of any one of claims 1-31 for use in the treatment of a medical condition.
65. Use of the polymorph of any one of claims 1-31 for the manufacture of a medicament for the treatment of a medical condition.
66. The pharmaceutical composition of claim 32 for use in the treatment of a medical condition.
67. Use of the pharmaceutical composition of claim 32 for the manufacture of a medicament for the treatment of a medical condition.

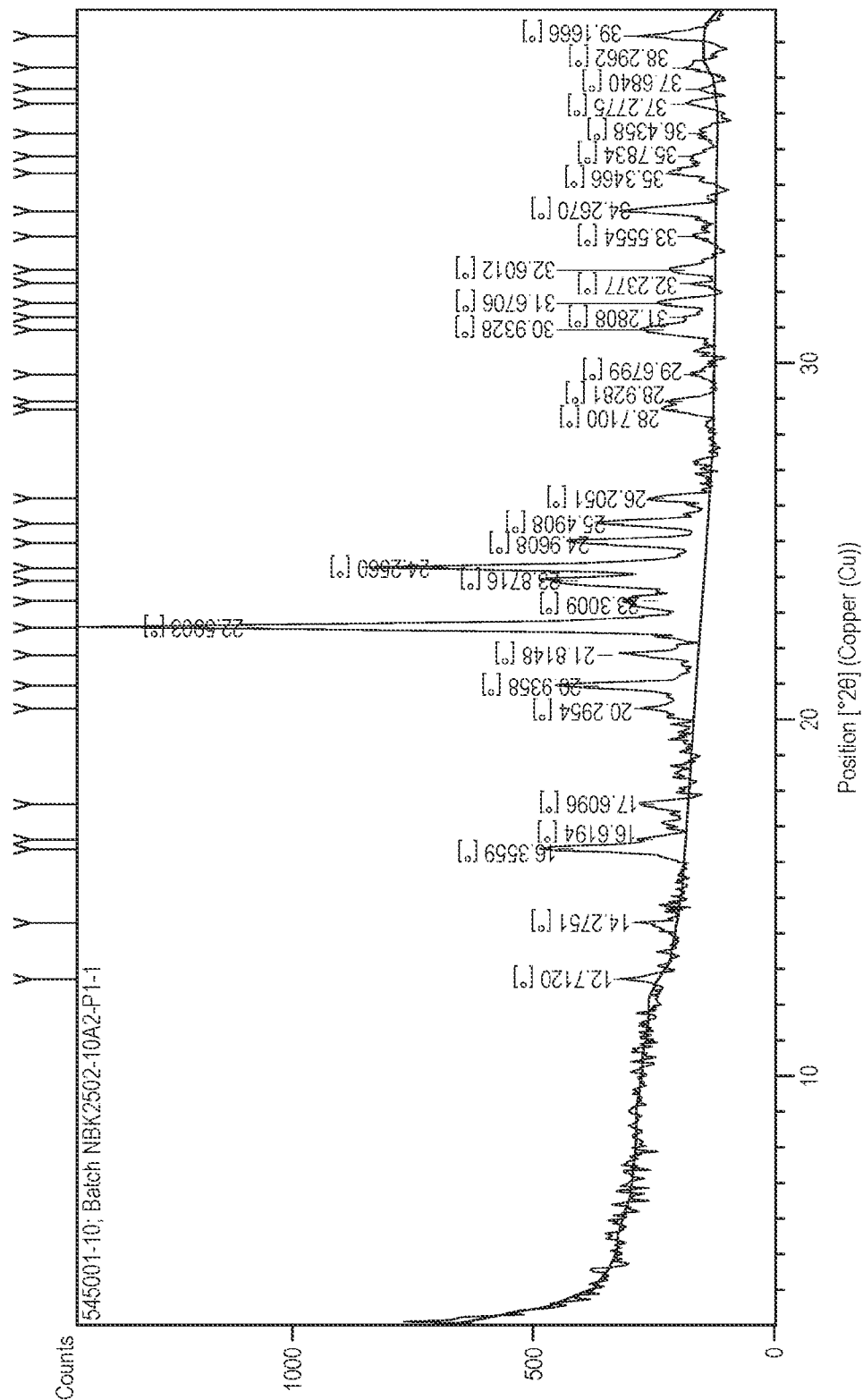


FIG. 1

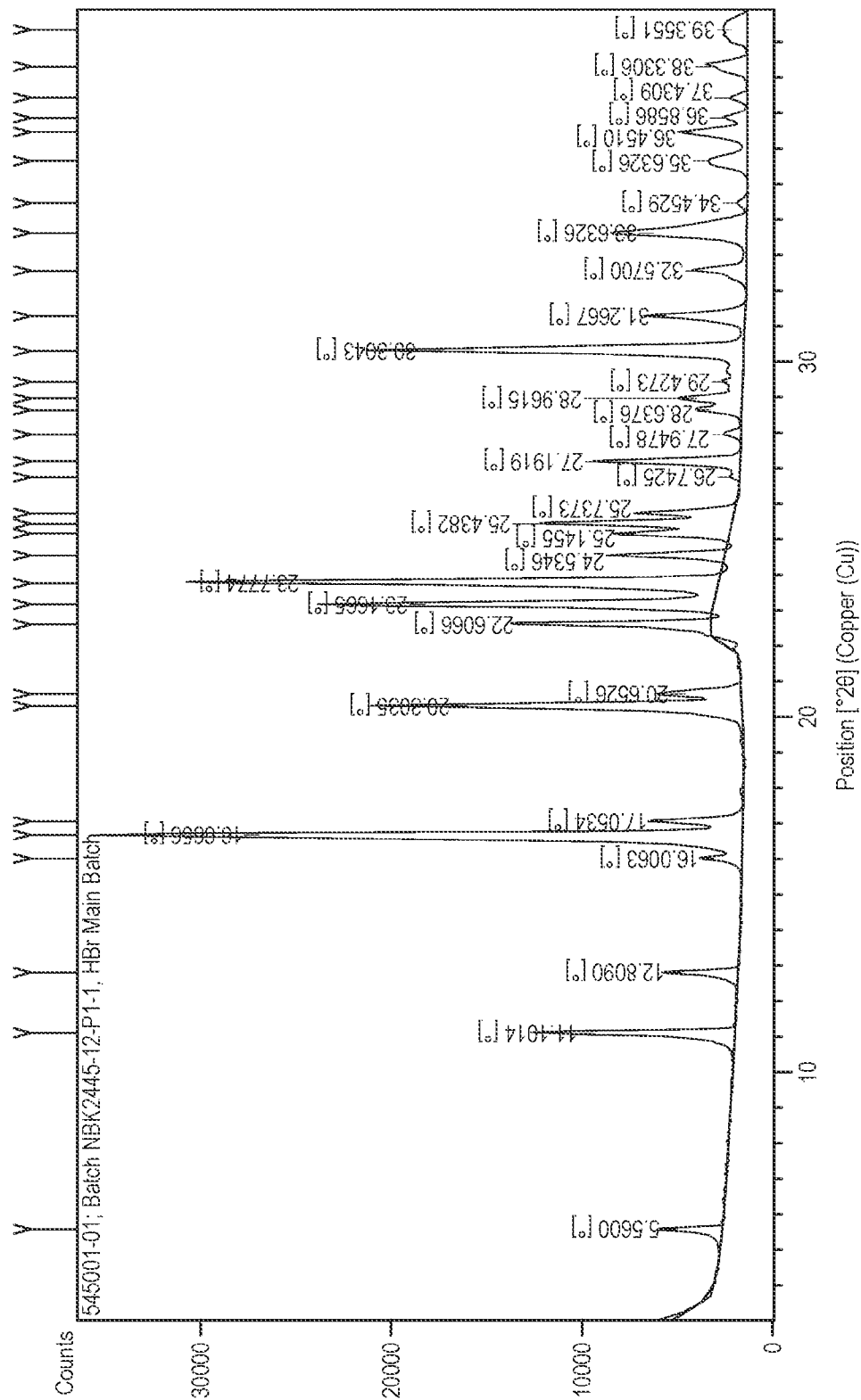


FIG. 2

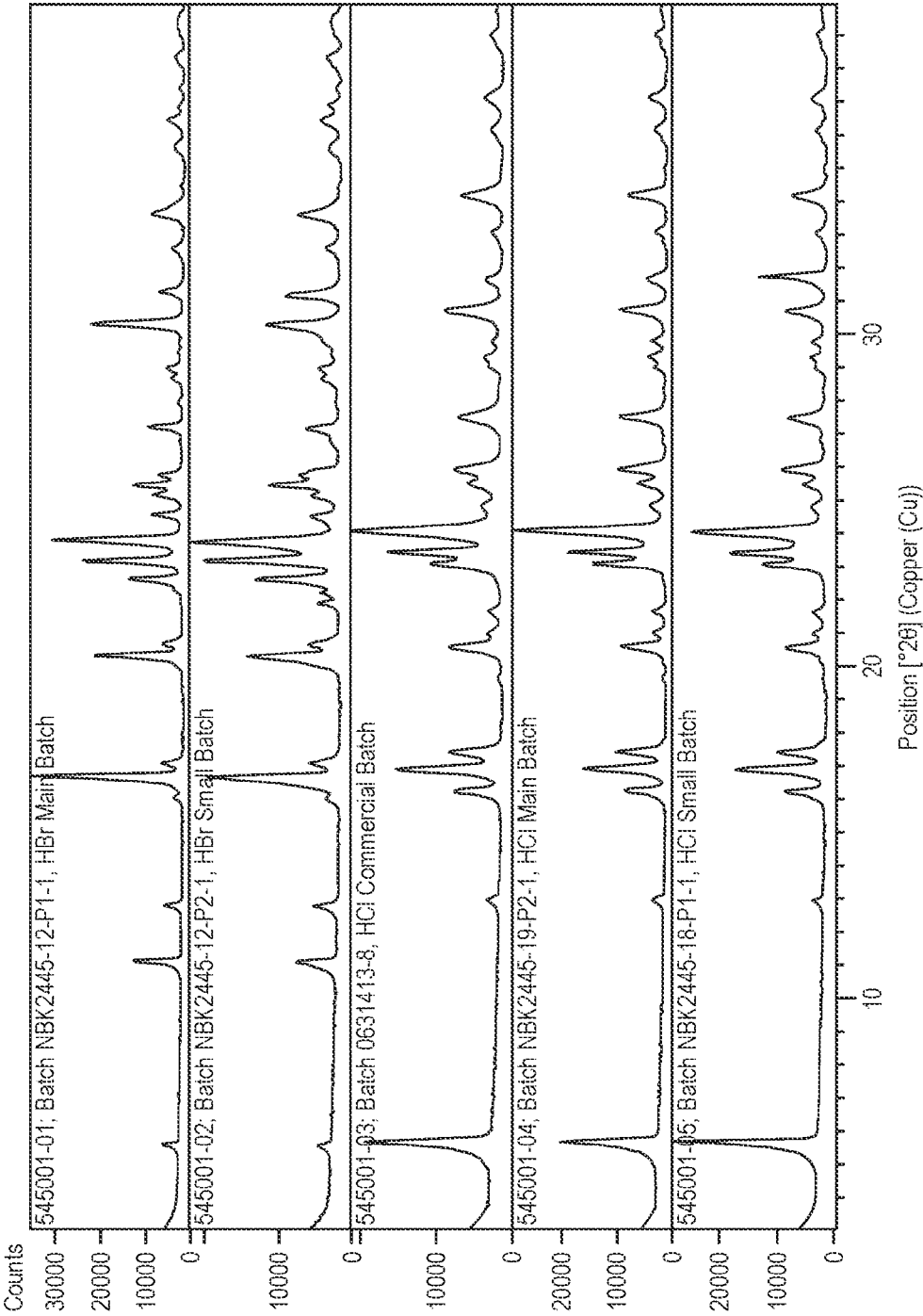
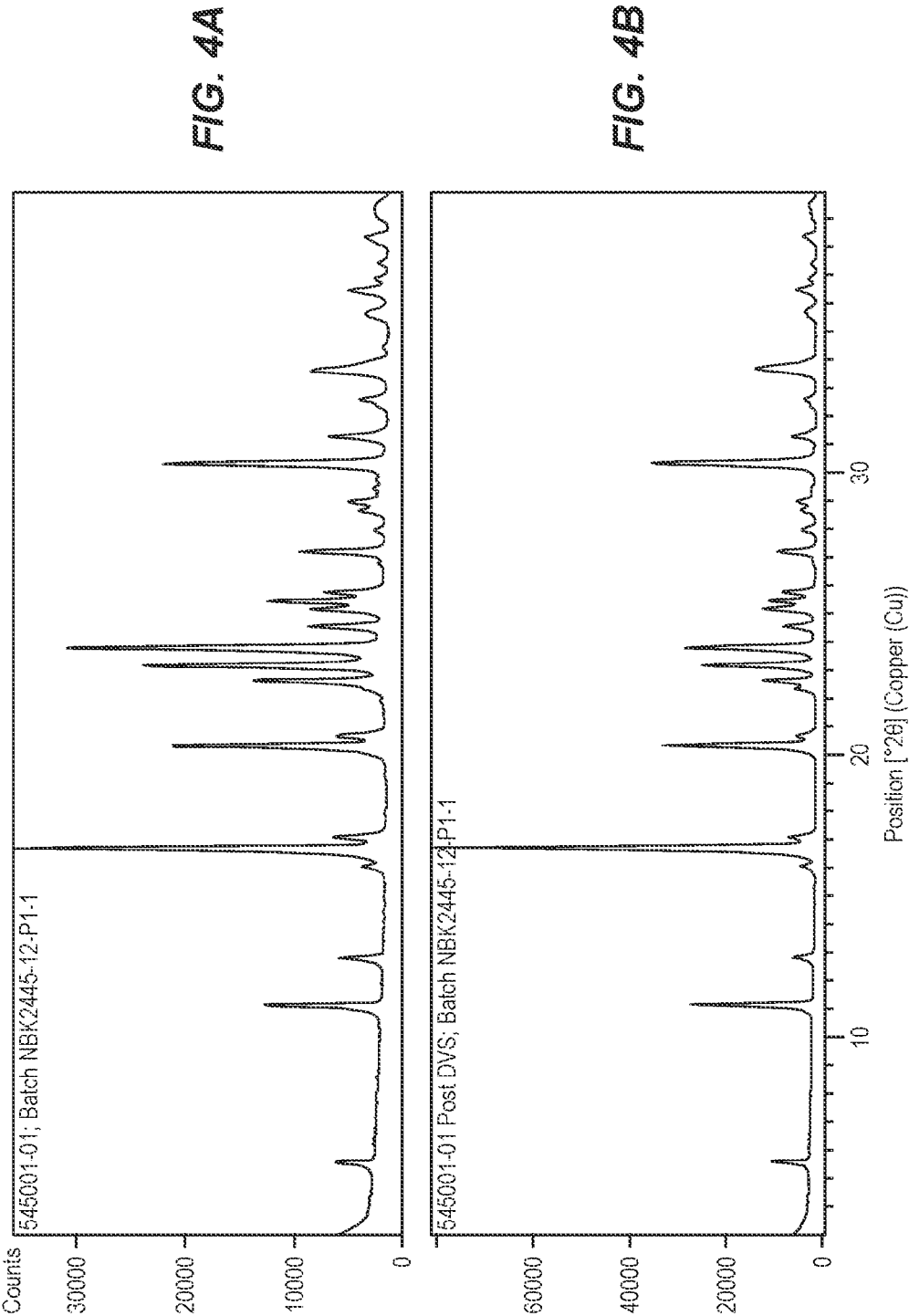


FIG. 3



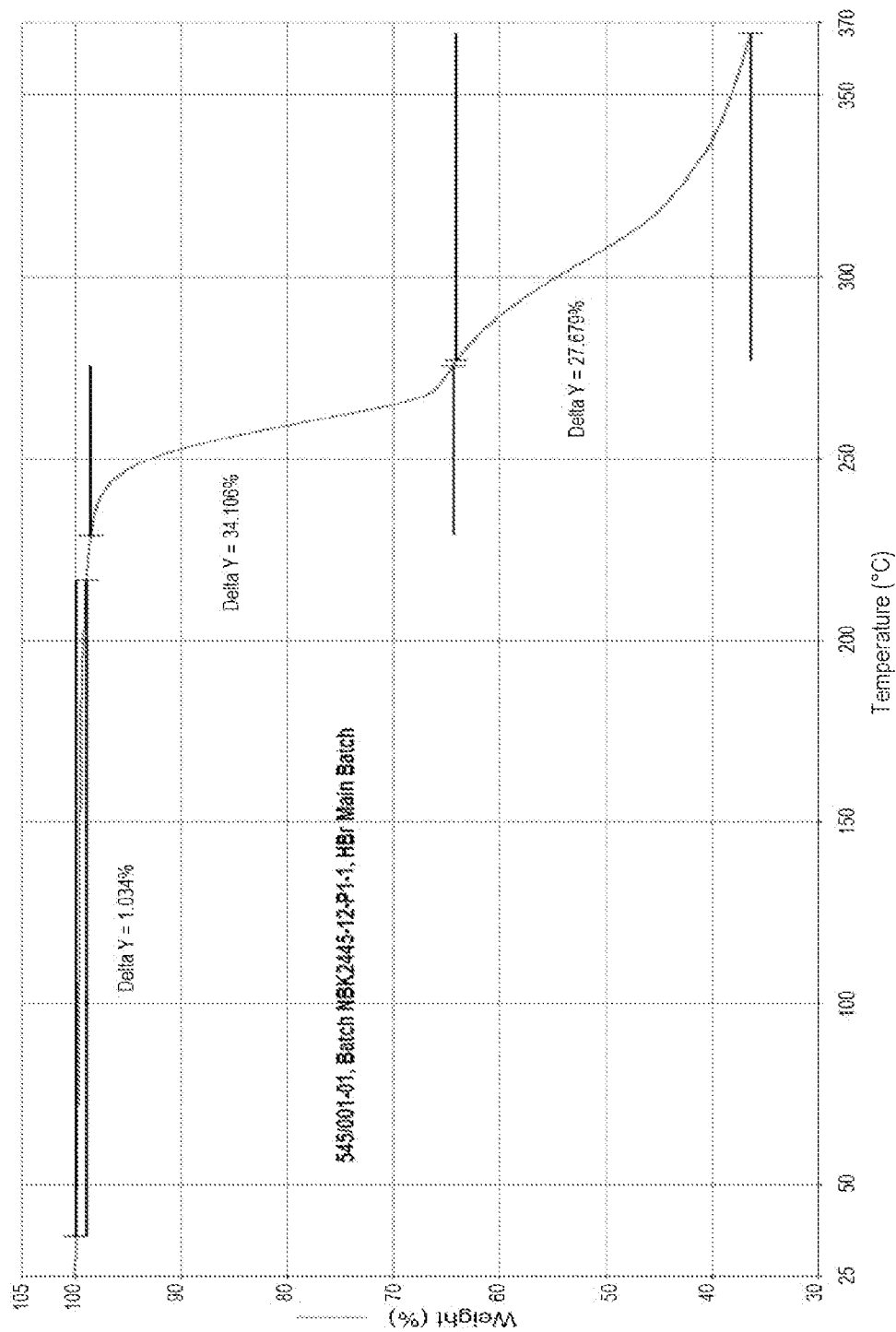


FIG. 5

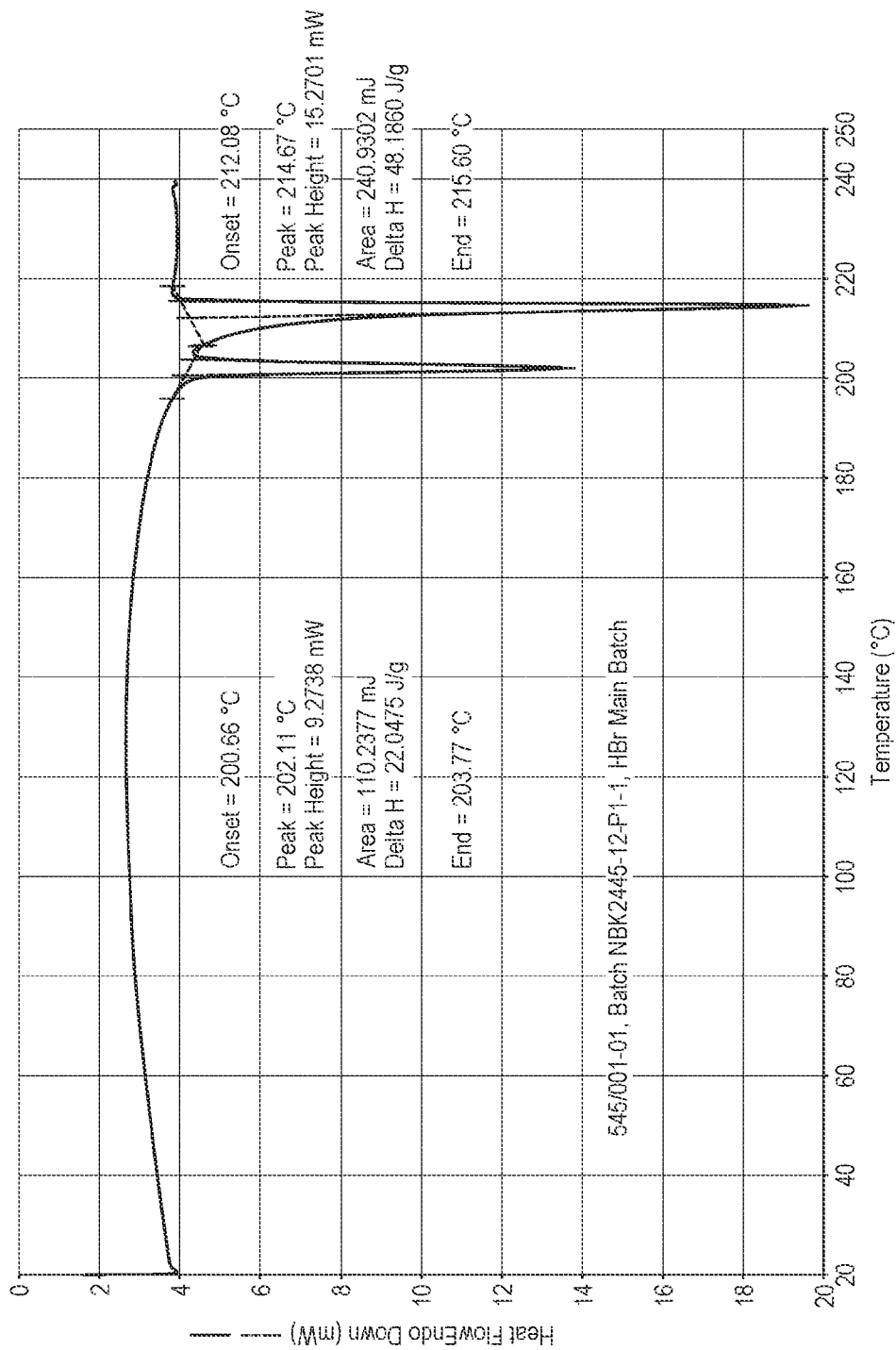


FIG. 6

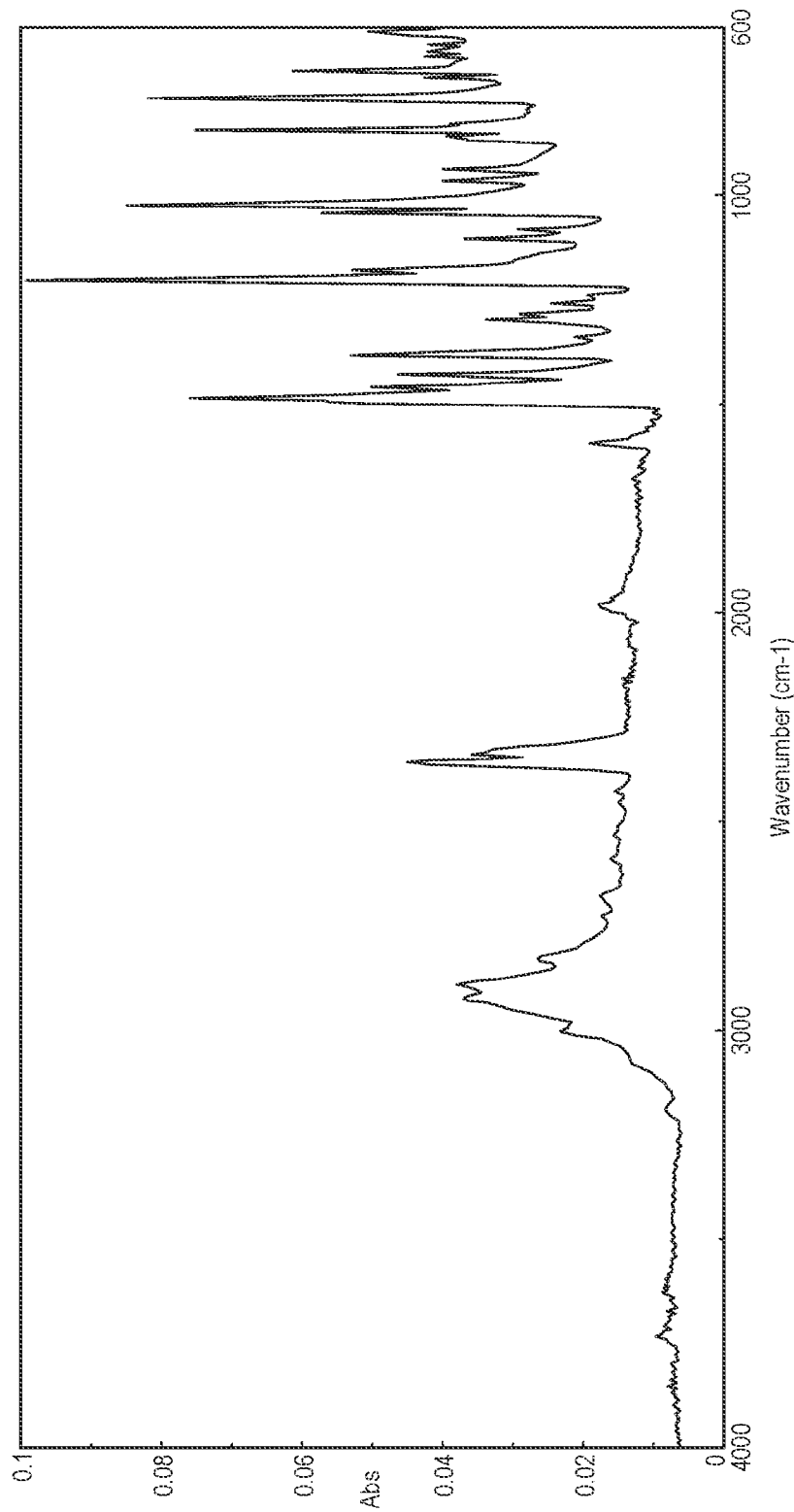


FIG. 7

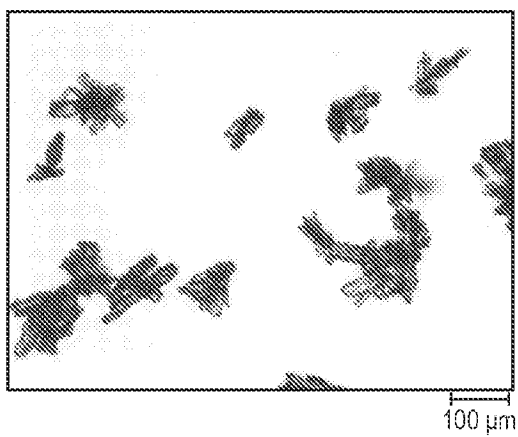
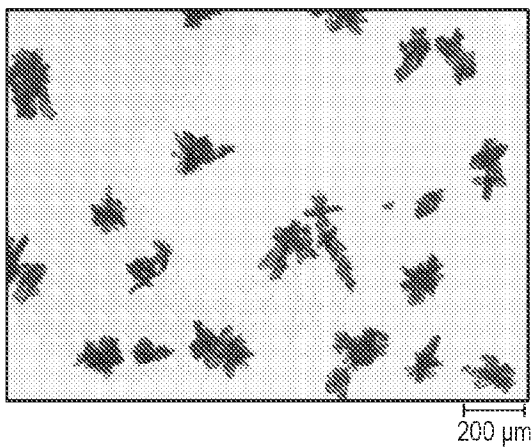
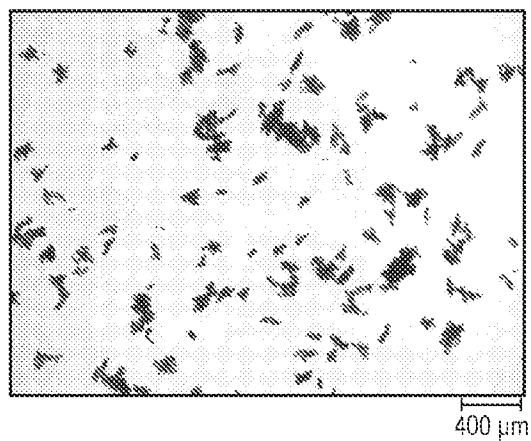


FIG. 8

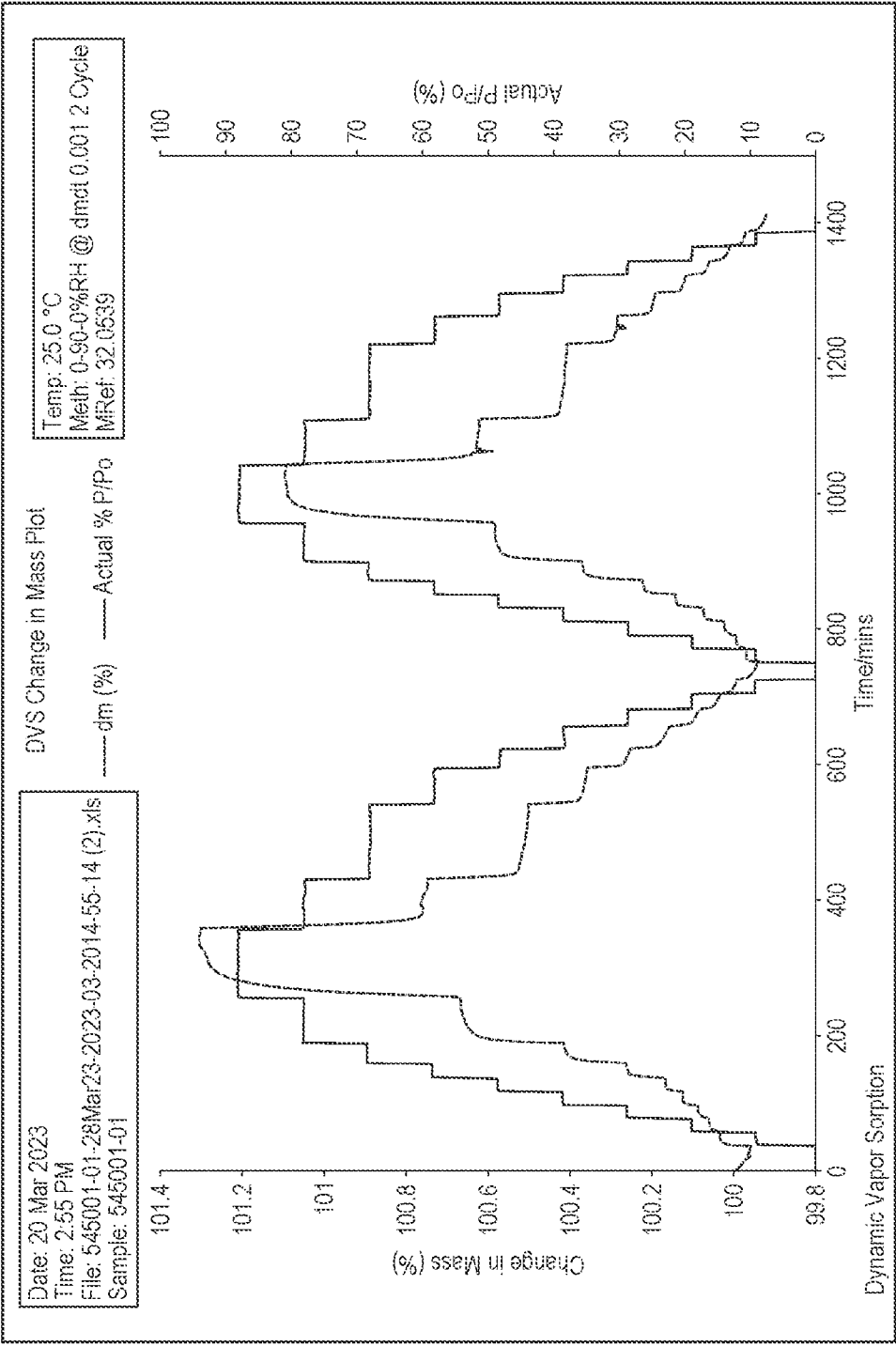


FIG. 9

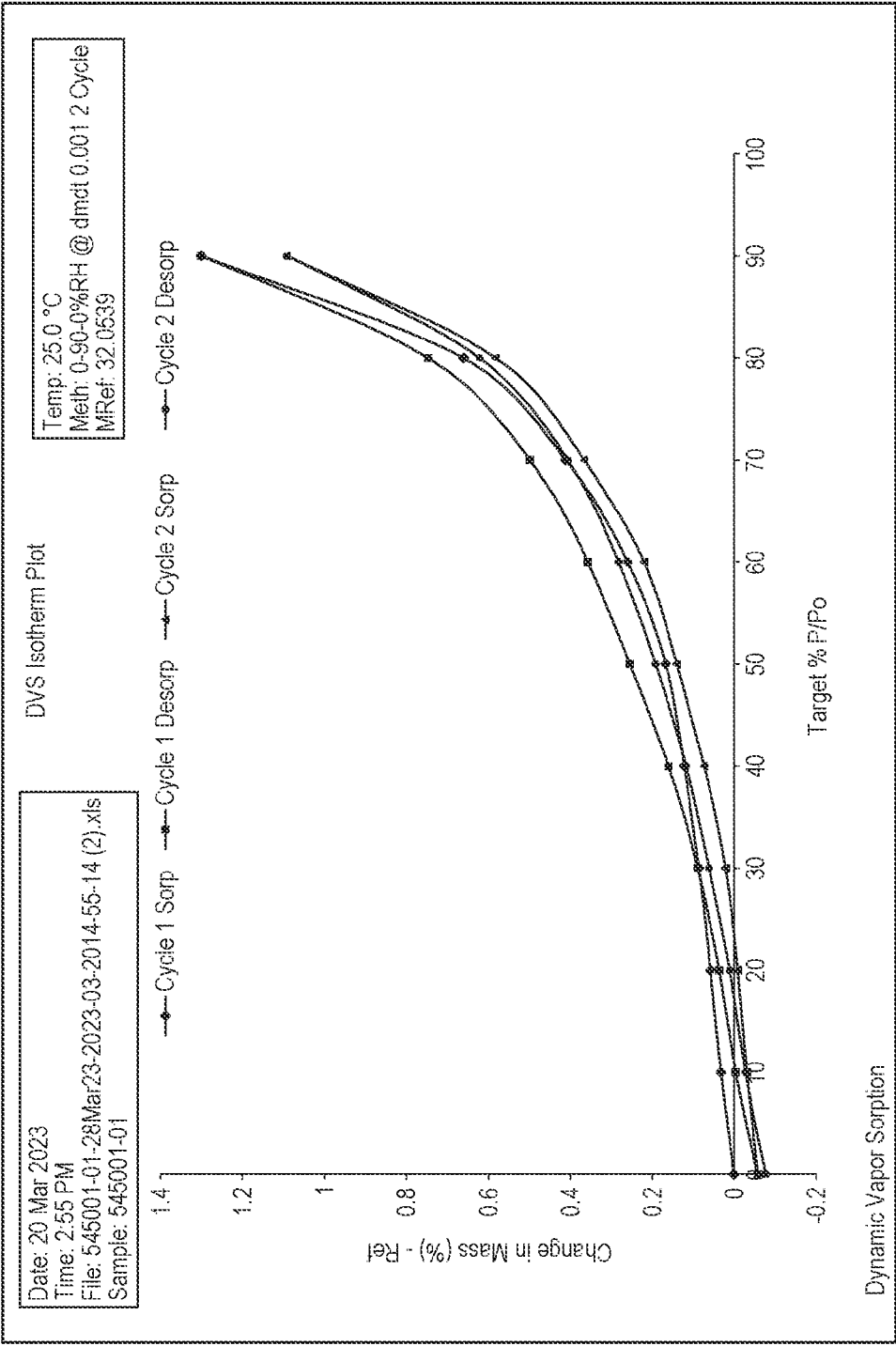


FIG. 10

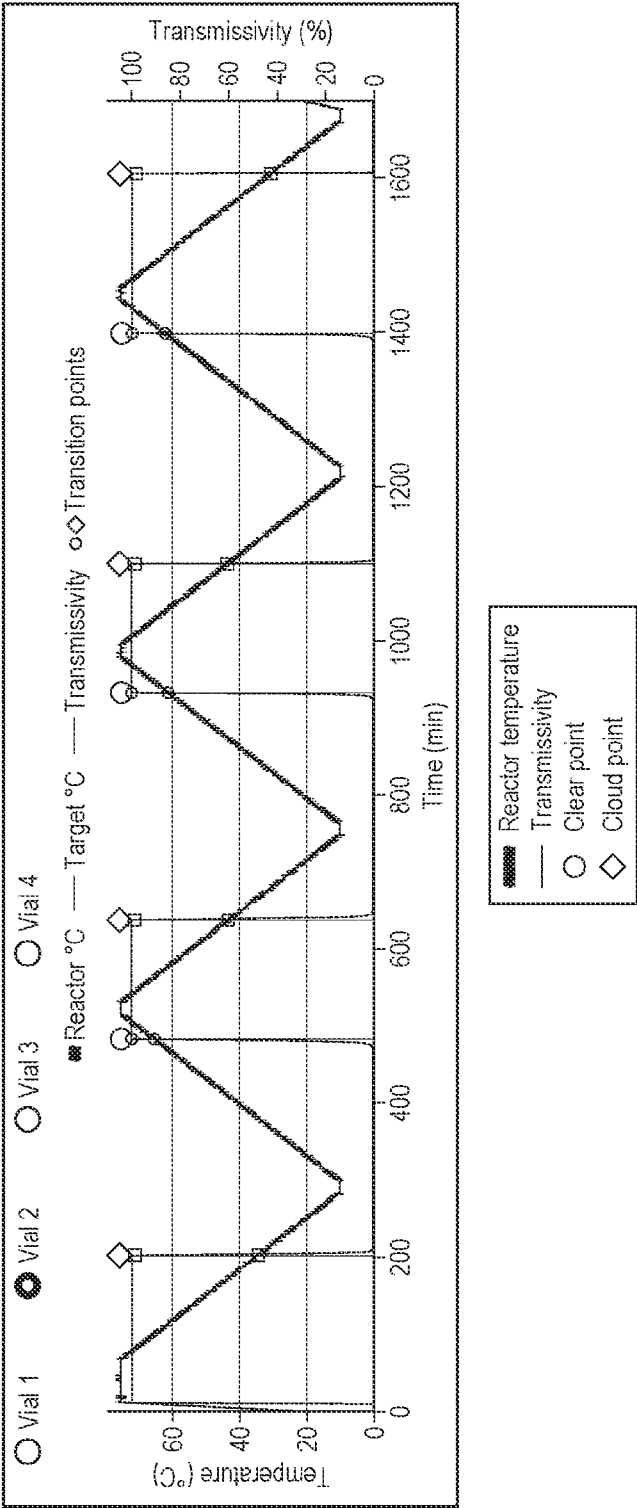


FIG. 11A

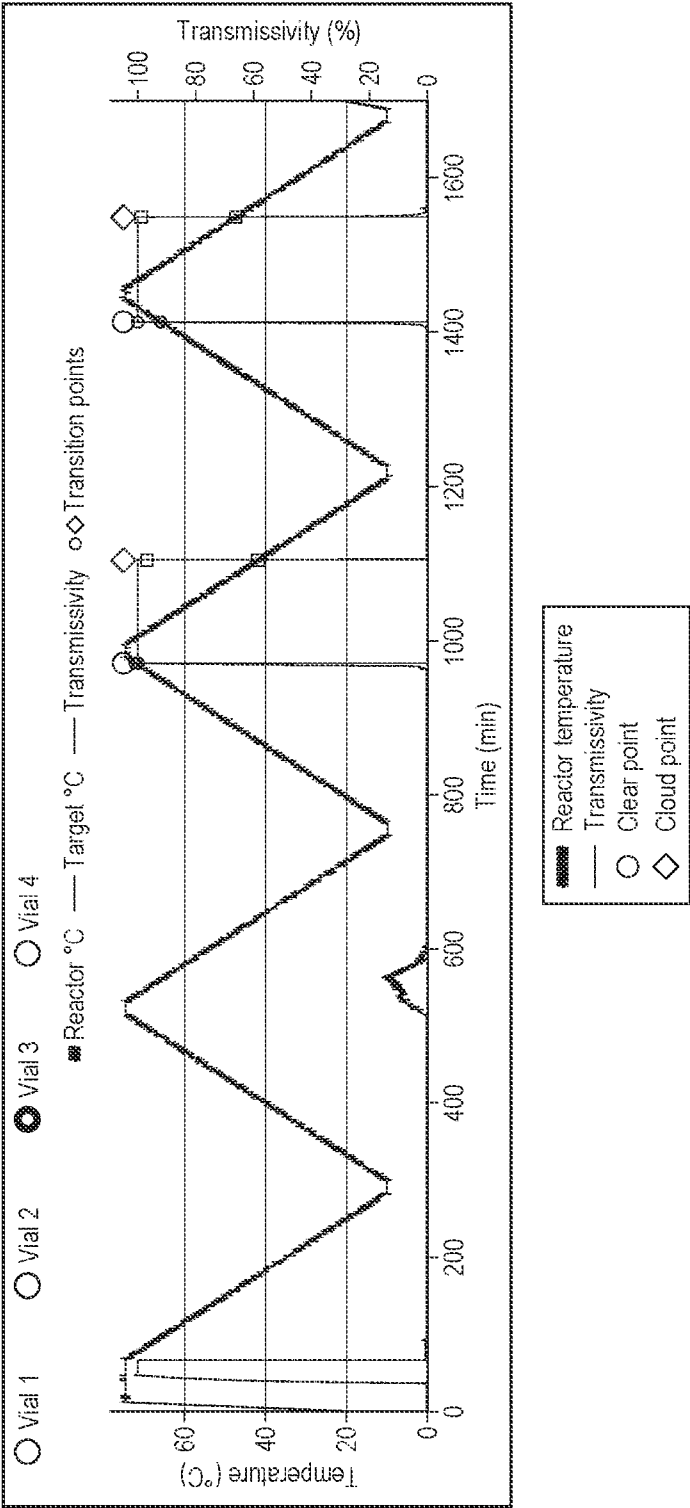


FIG. 11B

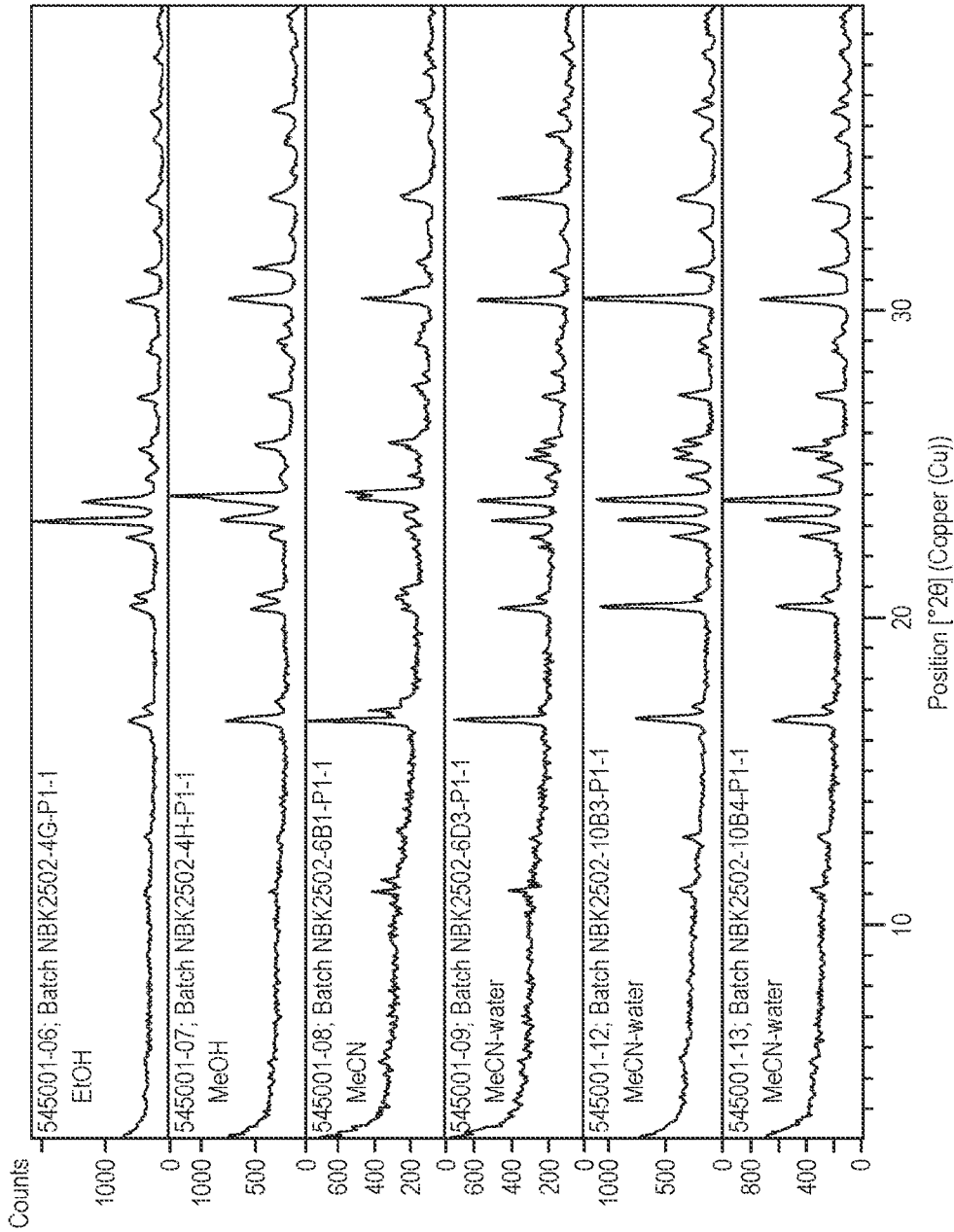
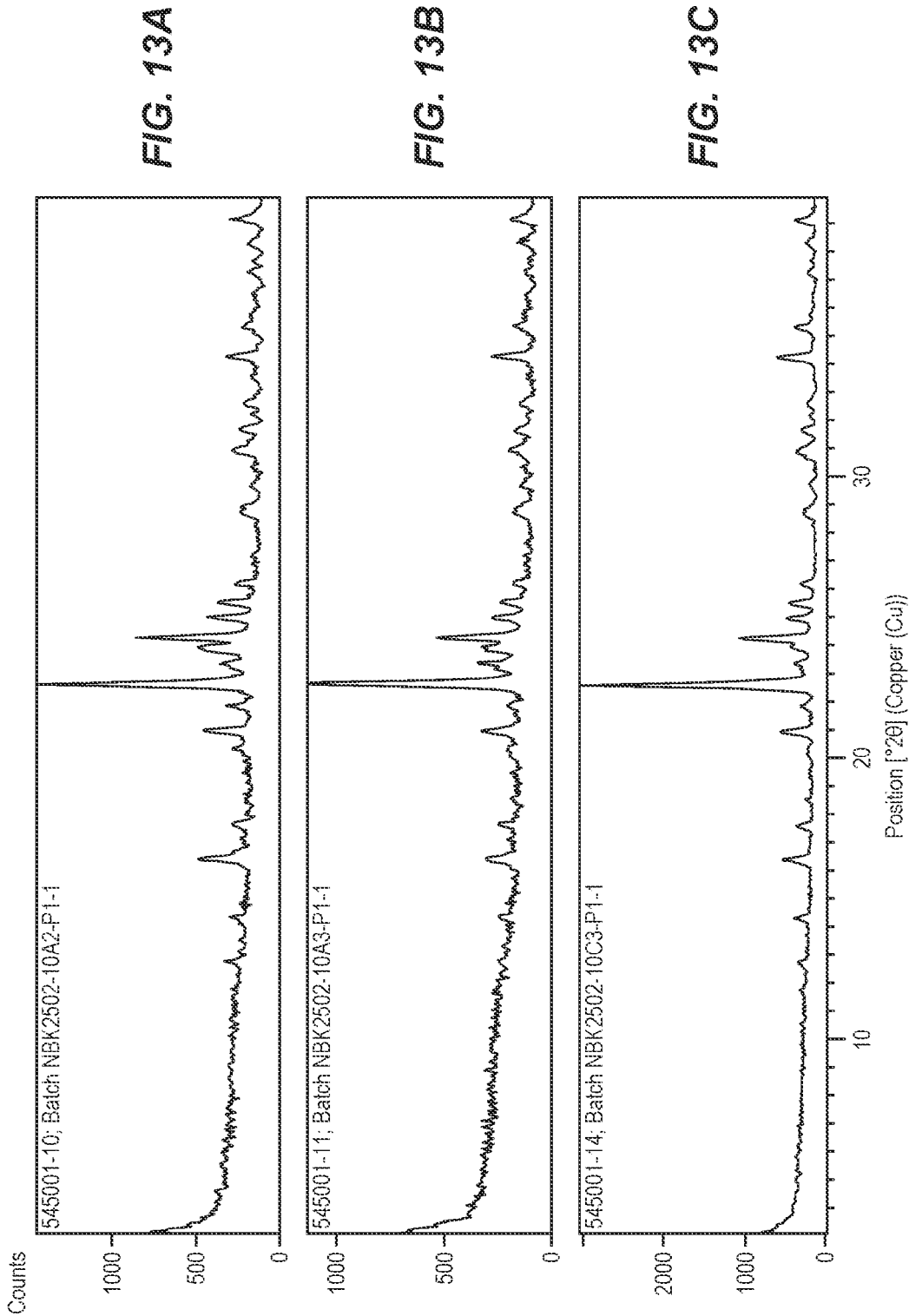
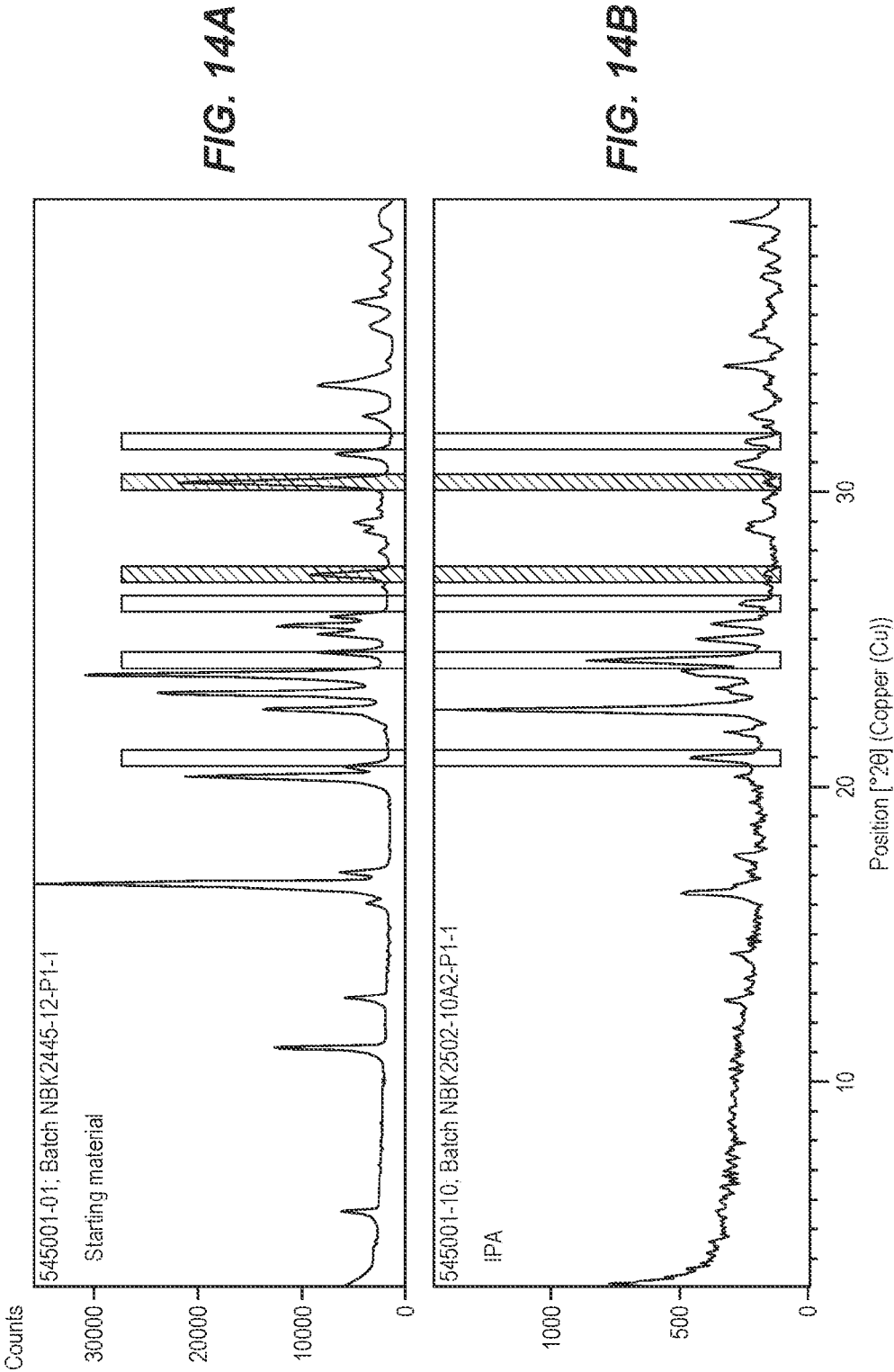


FIG. 12





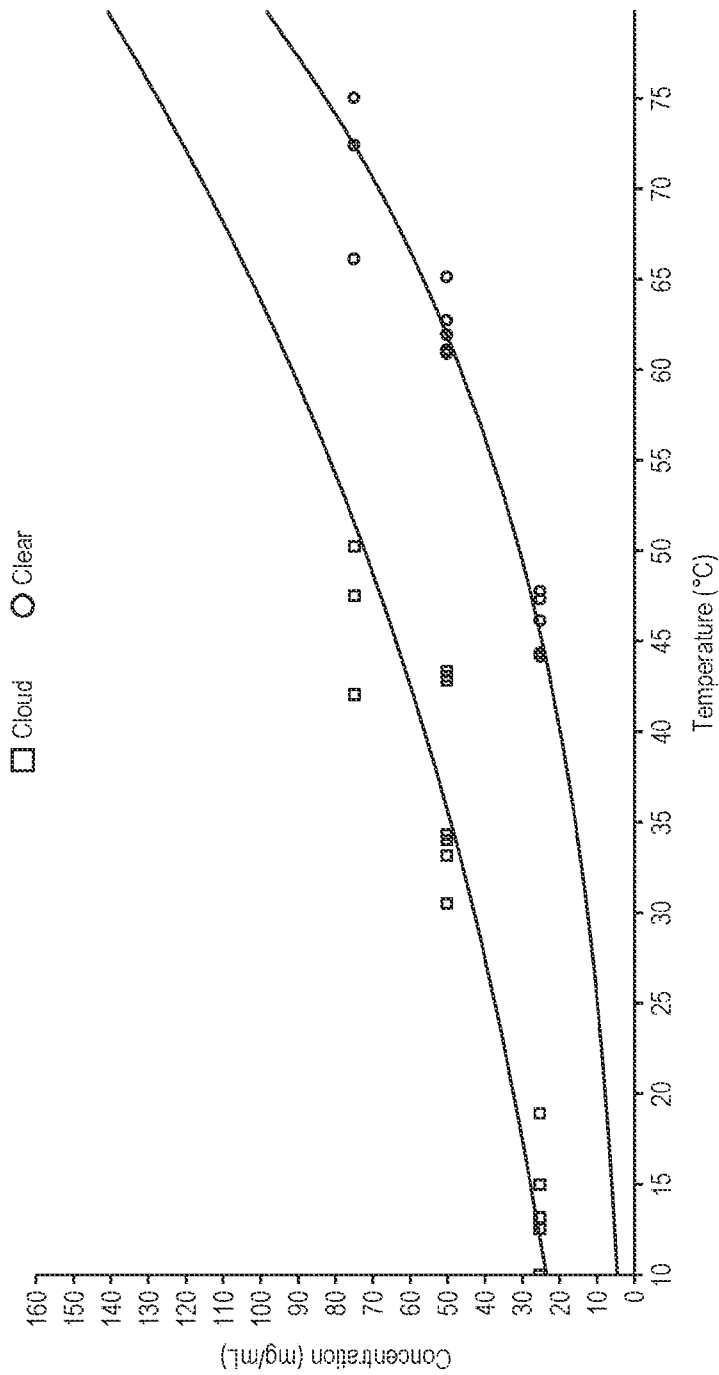


FIG. 15

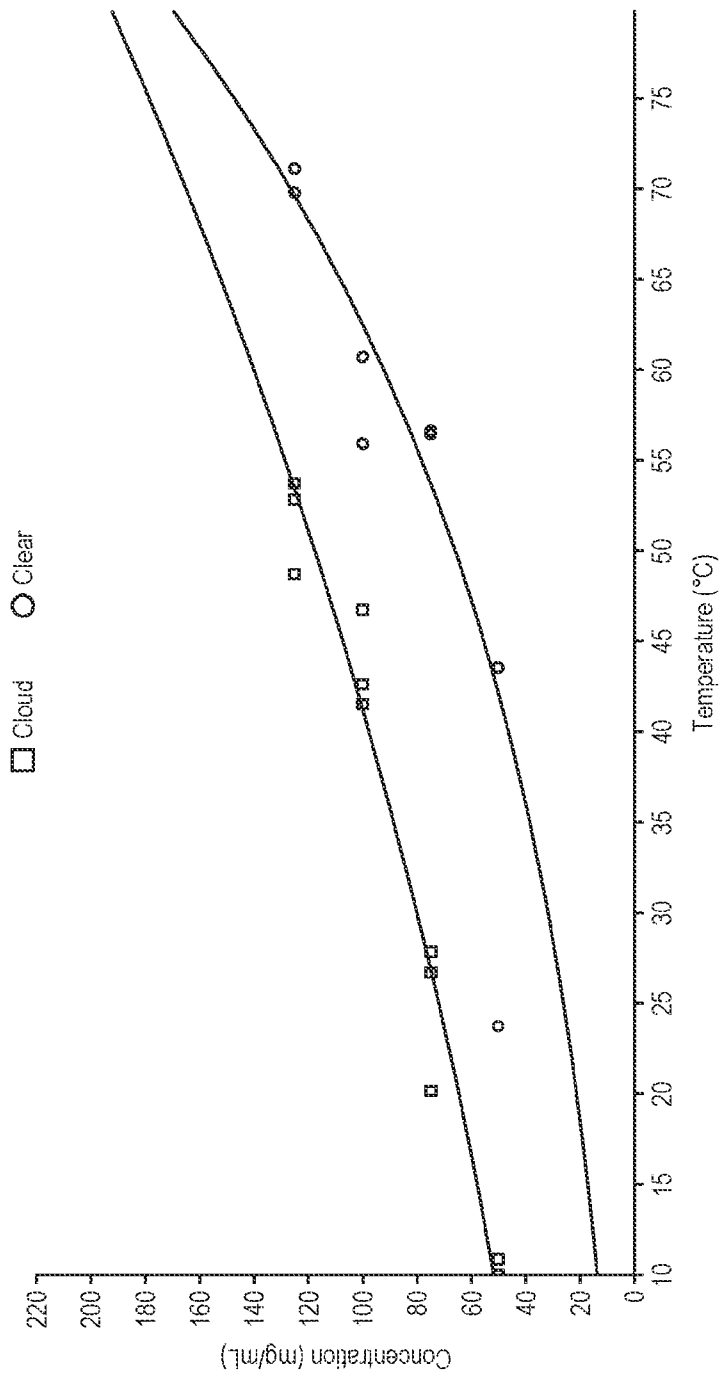


FIG. 16

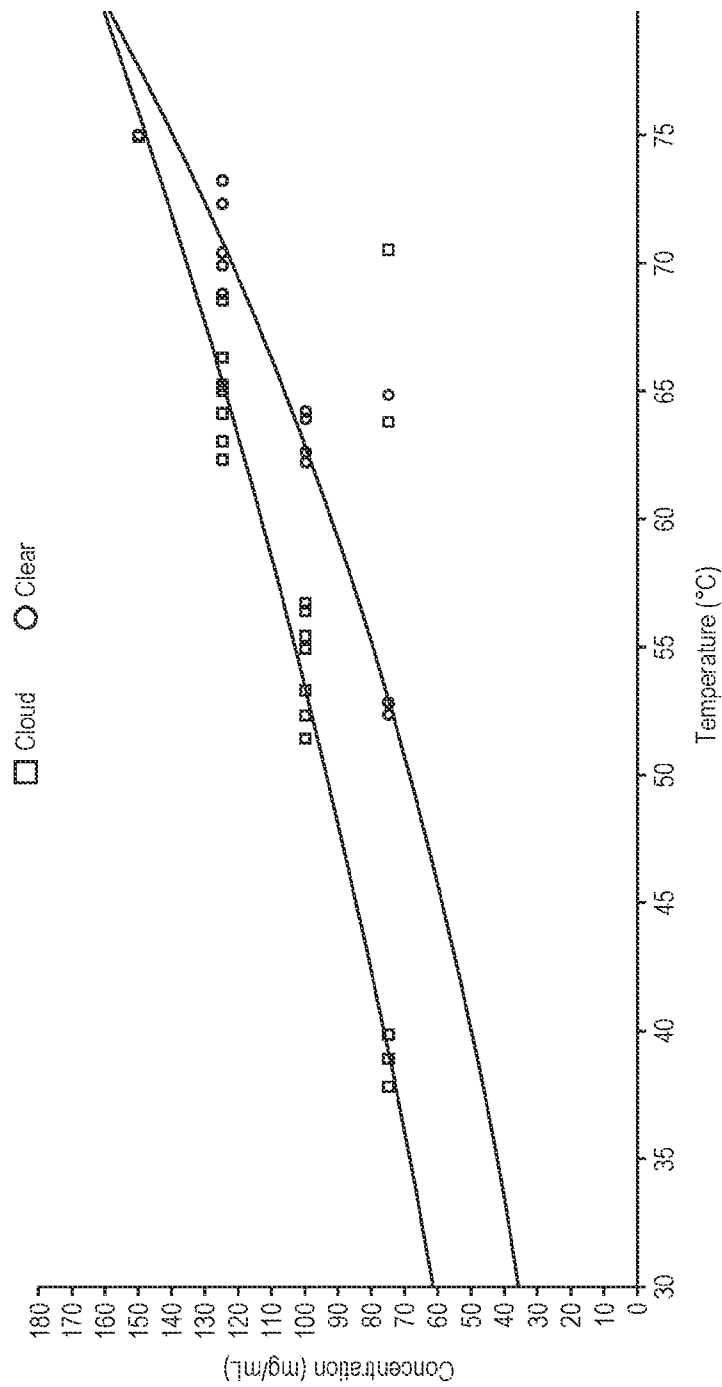


FIG. 17

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/041007

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. C07C 217/60; A61K 31/137 (2024.01)

ADD. A61P 25/22; A61P 25/24; A61P 25/28 (2024.01)

CPC - INV. C07C 217/60; A61K 31/137

ADD. A61P 25/22; A61P 25/24; A61P 25/28

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2023/087034 A1 (TERRAN BIOSCIENCES, INC) 19 May 2023; page 2, lines 14-15; page 31, lines 19-21	1-67
A	WO 2023/115002 A1 (TERRAN BIOSCIENCES INC) 22 June 2023; paragraphs [00104], [0092], [00364]	1-67
A	WO 2022/256720 A2 (ARCADIA MEDICINE INC) 08 December 2022; paragraphs [14], [90], [192], [293]	1-67
A	WO 2020/032080 A1 (KEIO UNIVERSITY) 13 February 2020; page 77, second paragraph, translation; page 84, second paragraph, translation	1-67
A	(ZWARTSEN, A et al.) Measuring inhibition of monoamine reuptake transporters by new psychoactive substances (NPS) in real-time using a high-throughput, fluorescence-based assay. Toxicology in Vitro, Vol. 45 (Pt 1), December 2017, published online 13 May 2017, doi: 10.1016/j.tiv.2017.05.010, pages 60-71; page 61, second column, fourth paragraph	1-67
A	(VILLALOBOS, CA et al.) 4-Bromo-2,5-dimethoxyphenethylamine (2C-B) and structurally related phenylethylamines are potent 5-HT2A receptor antagonists in Xenopus laevis oocytes. British Journal of Pharmacology, Vol. 141, No. 7, April 2004, published online 8 Mar 2004, doi: 10.1038/sj.bjp.0705722, pages 1167-1174; abstract; page 1169, first column, third paragraph	1-67
A	WO 2023/023351 A1 (TERRAN BIOSCIENCES INC) 23 February 2023; entire publication	1-67



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

"D" document cited by the applicant in the international application

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

28 October 2024 (28.10.2024)

Date of mailing of the international search report

NOV 20 2024

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

Telephone No. PCT Helpdesk: 571-272-4300