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(72) Inventor; and

(71) Applicant: DWULET, Gregory [US/US]; 2728 Valencia Street, Bellingham, Washington 98226 (US).

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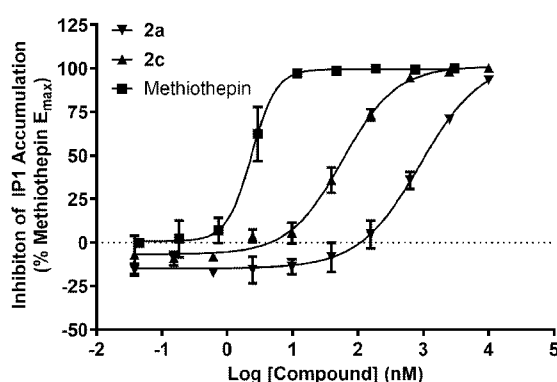
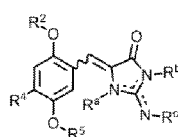


FIG. 1



Formula (1)

(57) Abstract: The present disclosure relates in some aspects to novel compounds containing an amino-phenylmethylene-imidazolone (i.e., amino-phenylmethylenidene-imidazolone) core structure. In some aspects, the disclosure further relates to methods of synthesizing the compounds, compositions containing the compounds, and methods of using such compounds, including their administration to subjects. In aspects, features of the compounds include neuromodulatory activity, for example, antagonism of serotonin receptors. In some aspects, the compounds are useful as therapeutic agents, e.g., antipsychotic agents



SUBSTITUTED AMINO-PHENYLMETHYLENE-IMIDAZOLONES

Gregory E. Dwulet

CROSS-REFERENCE

[01] Priority is claimed under PCT Art. 8(1) and Rule 4.10 to U.S. Prov. App. Nos. 63/527,013, filed July 15, 2023, and 63/655,031, filed June 2, 2024, both fully incorporated by reference for all purposes.

FIELD OF THE INVENTION

[02] This disclosure relates in some aspects to novel compounds containing an amino-phenylmethylene-imidazolone (i.e., amino-phenylmethyldene-imidazolone) core structure. In some aspects, the disclosure further relates to methods of synthesizing the compounds, compositions containing the compounds, and methods of using such compounds, including their administration to subjects. In aspects, features of the compounds include neuromodulatory activity, for example, antagonism of serotonin receptors. In some aspects, the compounds are useful as therapeutic agents, e.g., antipsychotic agents.

BACKGROUND OF THE INVENTION

[03] Current FDA-approved 5-HT_{2A} receptor antagonists include medications like clozapine, olanzapine, and risperidone, which are used to treat schizophrenia and bipolar disorder. These drugs often come with significant side effects, such as weight gain, metabolic issues, and an increased risk of diabetes. Additional side effects can include sedation and extrapyramidal symptoms, which may limit their long-term use.

[04] There therefore exists an ongoing need for the development of novel therapeutic compounds with 5-HT_{2A} receptor antagonist activity that are effective across a broad range of disease indications, particularly chronic mental health conditions and disorders of the central nervous system (e.g., schizophrenia, psychosis, depression). Provided herein are compounds, compositions, methods, uses, and kits to meet these needs and others, having such advantages and improvements as will become readily apparent through the disclosure below.

INCORPORATION BY REFERENCE

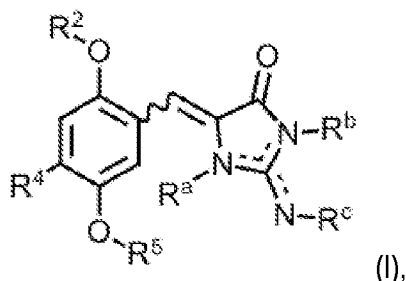
[05] Each cited patent, publication, and non-patent literature is incorporated by reference in its entirety, as if each was incorporated by reference individually, and as if each is fully set forth herein. However, no such citation is as an admission that a cited reference comes from an area that is 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 is part of the common general knowledge in the art.

BRIEF SUMMARY OF THE INVENTION

[06] The following presents a simplified summary of some embodiments of the invention in order to provide a basic understanding of the invention. 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 the scope of the

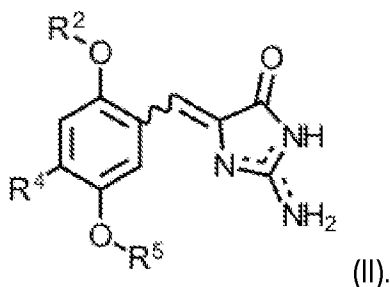
invention. Its sole purpose is to present some embodiments of the invention in a simplified form as a prelude to the more detailed description that is presented later.

[07] In a first aspect, provided is compound of Formula (I),

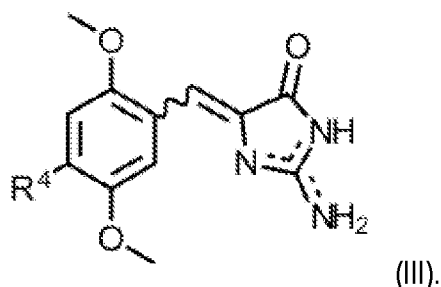


or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, wherein: R^a , R^b , and R^c are each independently H, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl; R^2 and R^5 are each independently H or C_1 - C_6 alkyl; R^4 is halogen or H; and $\sim$ is a single or double bond.

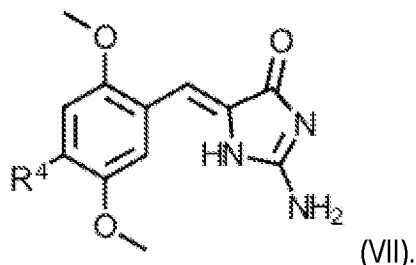
[08] In some embodiments, the compound has the structure of Formula (II),



[09] In some embodiments, the compound has the structure of Formula (III),



[10] In some embodiments, the compound has the structure of Formula (VII),



[11] In some embodiments, R^a is H. In some embodiments, R^a is C_1 - C_6 alkyl. In some embodiments, R^a is methyl.

[12] In some embodiments, R^b is H. In some embodiments, R^b is C_1 - C_6 alkyl. In some embodiments, R^b

is methyl. In some embodiments, R^b is ethyl. In some embodiments, R^b is C_1 - C_6 haloalkyl.

[13] In some embodiments, R^c is H. In some embodiments, R^c is C_1 - C_6 alkyl. In some embodiments, R^c is methyl.

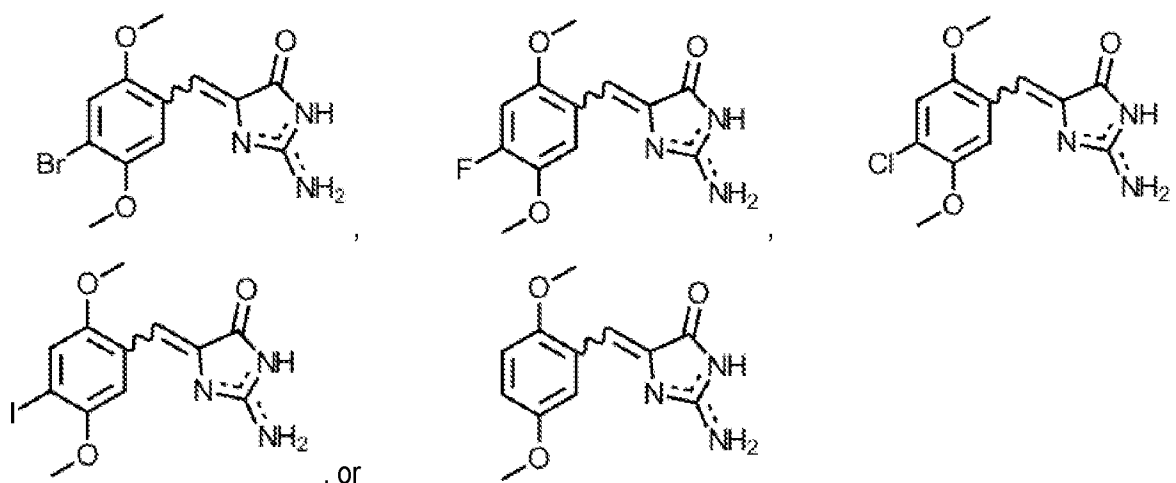
[14] In some embodiments, R^2 is C_1 - C_6 alkyl. In some embodiments, R^2 is methyl.

[15] In some embodiments, R^5 is C_1 - C_6 alkyl. In some embodiments, R^5 is methyl.

[16] In some embodiments, R^4 is halo. In some embodiments, R^4 is bromo. In some embodiments, R^4 is chloro. In some embodiments, R^4 is iodo. In some embodiments, R^4 is H.

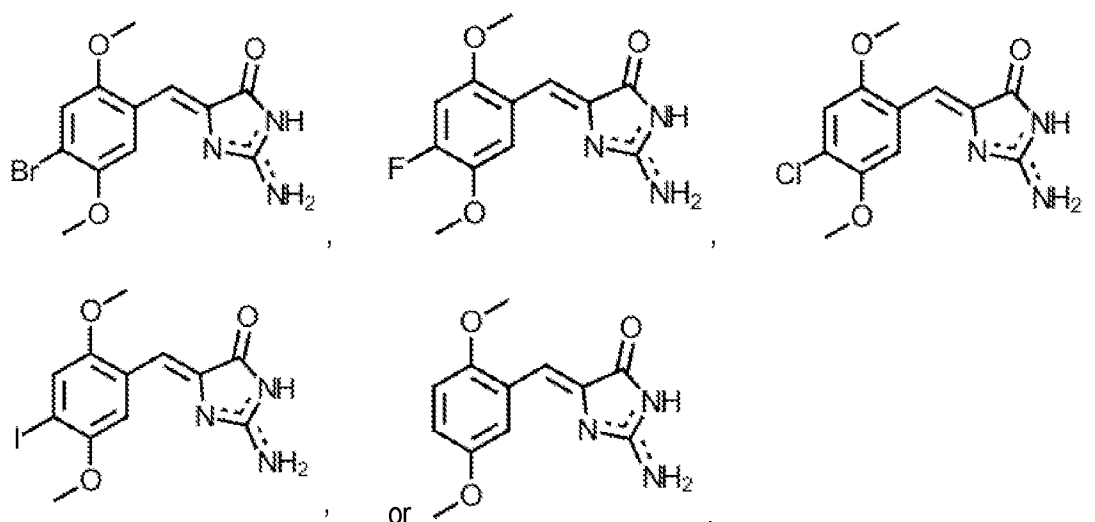
[17] In another aspect, provided is a compound selected from **Table 1**, **Table 2**, or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof. In some embodiments, the compound has *E* geometry.

[18] In some embodiments, the compound has the structure of:



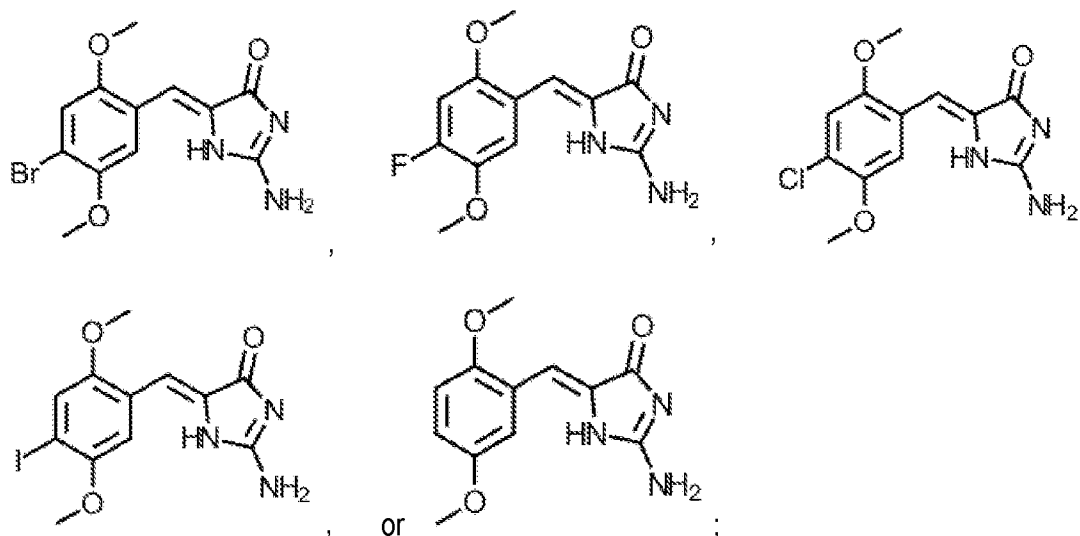
or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof.

[19] In some embodiments, the compound has the structure of:

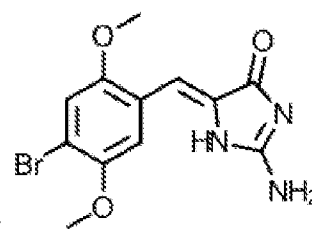


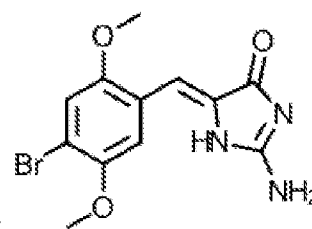
or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof.

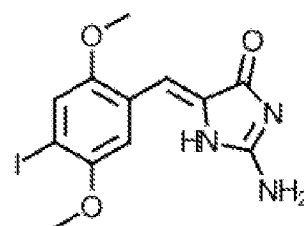
[20] In some embodiments, the compound has the structure of:

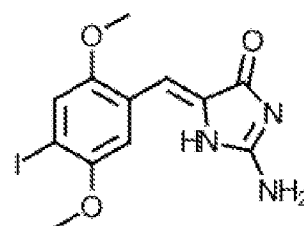


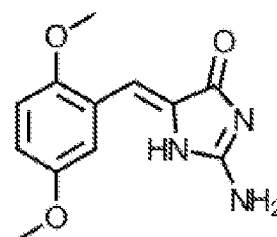
or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof.

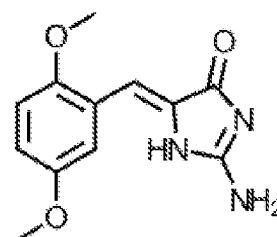


[21] In another aspect, provided is a compound having the structure of , or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof.



[22] In another aspect, provided is a compound having the structure of , or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof.



[23] In another aspect, provided is a compound having the structure of , or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof.

[24] In another aspect, provided is a pharmaceutical composition comprising a therapeutically effective amount of the compound of any disclosed embodiment, or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

[25] In another aspect, provided is a method of modulating neurotransmission in a subject, comprising administering to the subject the compound or pharmaceutical composition of any disclosed embodiment.

[26] In some embodiments, modulating neurotransmission comprises antagonizing the 5-HT_{2A} receptor.

[27] In another aspect, provided is a compound or pharmaceutical composition of any disclosed embodiment for use in the treatment of a medical condition.

[28] In another aspect, provided is the use of the compound or pharmaceutical composition of any disclosed embodiment for the manufacture of a medicament for the treatment of a medical condition.

[29] In another aspect, 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 compound or pharmaceutical composition of any disclosed embodiment. 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 mental, behavioral, or neurodevelopmental disorder. In some embodiments, the medical condition is a neurodegenerative disorder, a pain disorder, or a movement disorder. In some embodiments, the medical condition is schizophrenia or a primary psychotic disorder. In some embodiments, the medical condition is schizophrenia, schizoaffective disorder, schizophreniform disorder, schizotypal disorder, acute and transient psychotic disorder, delusional disorder, paraphrenia, postpartum psychosis, major depressive disorder with psychotic features, a substance-induced psychotic disorder, or a psychotic disorder due to another condition.

[30] 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.

[31] 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.

BRIEF DESCRIPTION OF THE FIGURES

[32] 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:

[33] **FIG. 1** shows dose-response curves for **2a** and **2c** in the IP-One assay in antagonist mode with methiothepin (mesylate salt) as the positive control.

DETAILED DESCRIPTION OF THE INVENTION

[34] 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.

[35] 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 embodiments, applications, and details of the invention illustrated herein can be made by those skilled in the art without departing from the spirit of the invention, or the scope of the invention as set forth in the appended claims.

A. General Definitions and Terms

[36] As used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an active agent” includes reference to a combination of two or more active agents, and reference to “an excipient” includes reference to a combination of two or more excipients. While the term “one or more” may be used, its absence (or its replacement by the singular) does not signify the singular only, but simply underscores the possibility of multiple agents or ingredients in particular embodiments. The terms “comprising,” “including,” “such as,” and “having” are inclusive and not exclusive (i.e., there may be other elements in addition to the recited elements). The term “or” is used herein to mean, and is used interchangeably with, the term “and/or,” unless context clearly indicates otherwise.

[37] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as concentration, reaction conditions, and so forth, used to describe and claim certain embodiments of the disclosure are to be understood as being modified in some instances by the term “about.” Accordingly, in

some embodiments (equivalently and as shorthand, “in embodiments”), the numerical parameters set forth in the description and claims are approximations that can vary depending upon the desired properties sought to be obtained by a particular embodiment. In some embodiments, “about” refers to plus or minus five percent ($\pm 5\%$) of the recited unit of measure. The term “substantially,” where it is applied to modify a feature or limitation herein, will be read in the context of the disclosure and in light of the knowledge in the art to provide the appropriate certainty, e.g., by using a standard that is 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 art. Where no such certainty can be established from the context, the term may be understood as also meaning “about,” e.g., within $\pm 1\%$, within $\pm 5\%$, or within $\pm 10\%$.

[38] Where “about” is used to modify one number in a series or range, it is 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.”

[39] In some embodiments, the 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 some embodiments of the disclosure are approximations, the numerical values set forth in the specific examples are reported as precisely as practicable. The numerical values presented in some embodiments may contain certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

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

[41] Unless defined otherwise, all technical and scientific terms herein have the meaning as commonly understood by one of ordinary skill in the art to which this invention belongs, who as a shorthand may be referred to simply as “one of skill.” Further definitions that may assist a reader in understanding the disclosed embodiments follow; however, it will be appreciated that such definitions are not intended to limit the scope of the invention, which shall be properly interpreted and understood by reference to the full specification (as well as any plain meaning known to one of skill) in view of the language used in the claims. Terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[42] Generally, the nomenclature used and procedures performed herein are those known in fields relating to one or more aspects of the invention, such as biology, pharmacology, neuroscience, organic chemistry, synthetic chemistry, and/or medicinal chemistry, and are those that will be well known and commonly employed in such fields. Standard techniques and procedures will be those generally performed

according to conventional methods in the art.

[43] The term “alkyl” includes straight or branched radicals having any degree or level of saturation, i.e., groups having exclusively single carbon-carbon bonds, groups having one or more double carbon-carbon bonds, groups having one or more triple carbon-carbon bonds and groups having mixtures of single, double and triple carbon-carbon bonds. “Alkyl” includes all possible structural isomers. For example, the term “butyl” encompasses *n*-butyl, *sec*-butyl, isobutyl, and *tert*-butyl. Where a specific level of saturation is intended, the expressions “alkanyl,” “alkenyl,” and “alkynyl” can also be used. In some embodiments, an alkyl group comprises from 1 to 10 carbon atoms, from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, or from 1 to 3 carbon atoms. For any alkyl, the alkyl may be optionally substituted at one or more positions.

[44] A “halogen” (or equivalently, “halo”) refers to fluorine, chlorine, bromine, and iodine.

[45] An “effective amount” or “a therapeutically effective amount” refers to an amount of an active agent that is sufficient to provide the desired therapeutic effect at a reasonable benefit/risk ratio. The effective amount can vary depending upon the subject and the disease condition being treated or health benefit sought, the weight and age of the subject, the severity of the disease condition or degree of health benefit sought, the manner of administration, and the like, all of which can readily be determined by one of ordinary skill in the art.

[46] “Therapeutic effect” or “therapeutic efficacy” means the responses(s) in a mammal, and preferably a human, after treatment that are judged to be desirable and beneficial. Depending on the 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 may therefore differ, but would be readily understood by those of ordinary skill. Measures of therapeutic effect includes any outcome measure, endpoint, effect measure, or measure of effect within clinical or medical practice or research which is used to assess the effect, both positive and negative, of an intervention or treatment, whether patient-reported (e.g., questionnaires), based on other patient data (e.g., patient monitoring), gathered through laboratory tests such as blood work, urine samples, etc., through medical examination by a doctor or other medical professional, or by digital tools or means, e.g., electronic tools such as online tools, smartphones, wireless devices, biosensors, or health apps.

[47] “Optionally substituted” unless otherwise specified means that a group may be unsubstituted, or substituted by one or more of the substituents listed for that group. Likewise, when a group is described as being “unsubstituted or substituted” if substituted, the substituent(s) may be selected from one or more of the indicated substituents. When there are more than one substituents, the substituents may be the same or different. In some embodiments, an optionally substituted group has one substituent. In another embodiment, an optionally substituted group has two substituents. In another embodiment, an optionally substituted group has three substituents. In another embodiment, an optionally substituted group has four

substituents. If no substituents are indicated for an “optionally substituted” or “substituted” group, it is meant that the indicated “optionally substituted” or “substituted” group may be substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amino group, a di-substituted amino group, and a tri-substituted amino group.

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

B. Compounds

[49] The serotonin 2A (5-HT_{2A}) receptor is the primary excitatory G-protein-coupled receptor in the serotonin (5-HT) receptor family, and is integral in modulating various physiological and psychological functions (Nichols DE & Nichols CD. *Chem. Rev.* 2008;108(5):1614–1641; Zhang et al. *Front. Pharmacol.* 2015;6:225; Carhart-Harris et al. *J. Psychopharmacol. (Oxf.)* 2017;31(9):1091–1120). The 5-HT_{2A} receptor is highly expressed in the mammalian brain, particularly in the cortex, where it is the most abundant 5-HT receptor (Andrade R. *Neuropharmacology* 2011;61(3):382–386). Given its involvement in numerous fundamental processes, including the regulation of mood, cognition, perception, and behavior, the 5-HT_{2A} receptor is a significant target for pharmacological intervention (Sriram K & Insel PA. *Mol. Pharmacol.* 2018;93(4):251–258).

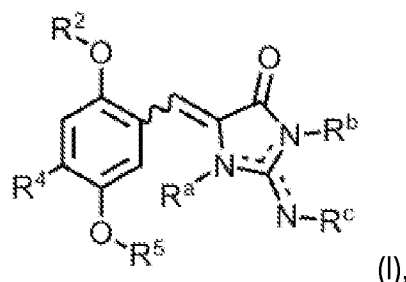
[50] Activation of the 5-HT_{2A} receptor mediates the hallucinogenic effects of psychedelic compounds, such as lysergic acid diethylamide (LSD) and psilocin. Psychedelic 5-HT_{2A} receptor agonists are under investigation for their potential to treat various medical conditions, including mental health disorders (Vollenweider FX & Preller KH. *Nat. Rev. Neurosci.* 2020;21(11):611–624). Additionally, some 5-HT_{2A} receptor agonists (e.g., (R)-2,5-dimethoxy-4-iodoamphetamine) exert robust anti-inflammatory effects in mouse models of vascular and pulmonary inflammation (Nichols CD. *Neuropharmacology.* 2022;219:109232). 5-HT_{2A} receptor agonists can also increase neuroplasticity and metaplasticity, making them promising as potential therapeutics for treating neurodegenerative conditions and traumatic brain injuries, among other conditions (see, e.g., Olson DE. *Biochemistry.* 2022;61(3):127–136; Nardou et al. *Nature.* 2023;618(7966):790–798; Kozłowska et al. *J Neurochem.* 2022;162(1):89–108; Khan et al. *Front. Neurol.* 2021;12:685085.).

[51] Similarly, 5-HT_{2A} receptor antagonists are useful therapeutics and research tools. 5-HT_{2A} receptor antagonism is a defining characteristic of many atypical antipsychotic medications used to treat schizophrenia, bipolar disorder, and depressive disorders (Casey et al. *Biochem Pharmacol.* 2022;200:115028). As research tools, 5-HT_{2A} receptor antagonists—particularly those with high selectivity

for the 5-HT_{2A} receptor, such as ketanserin—can be used to study psychedelic 5-HT_{2A} receptor agonists by mitigating or blocking their hallucinogenic effects (Vollenweider et al. NeuroReport. 1998;9(17):3897). Radiolabeled ketanserin has been used in neuroimaging studies to visualize and quantify the distribution of 5-HT_{2A} receptors in the brain, and [³H]ketanserin is an invaluable tool for radioligand binding assays used to identify new drugs that target the 5-HT_{2A} receptor (Paterson et al. Med Res Rev. 2013;33(1):54–111).

[52] In one aspect, provided herein are novel compounds having an amino-phenylmethylene-imidazolone (APMI) core structure.

[53] In some embodiments, the compound has the structure of Formula (I),



or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, wherein:

R^a, R^b, and R^c are each independently H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

R² and R⁵ are each independently H or C₁-C₆ alkyl;

R⁴ is H or halogen; and

 is a single or double bond.

[54] In some embodiments of Formula (I), R^a, R^b, and R^c are each independently H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments, R^a is H. In some embodiments, R^a is C₁-C₆ alkyl. In some embodiments, R^a is methyl. In some embodiments, R^a is ethyl. In some embodiments, R^a is propyl (i.e., *n*-propyl or isopropyl). In some embodiments, R^a is C₁-C₆ haloalkyl. In some embodiments, R^a is C₁-C₆ fluoroalkyl. In some embodiments, R^a is fluoromethyl (e.g., -CH₂F, -CHF₂, -CF₃). In some embodiments, R^a is fluoroethyl. In some embodiments, R^a is -CH₂CF₃.

[55] In some embodiments of Formula (I), R^b is H. In some embodiments, R^b is C₁-C₆ alkyl. In some embodiments, R^b is methyl. In some embodiments, R^b is ethyl. In some embodiments, R^b is propyl. In some embodiments, R^b is C₁-C₆ haloalkyl. In some embodiments, R^b is C₁-C₆ fluoroalkyl. In some embodiments, R^b is fluoromethyl. In some embodiments, R^b is fluoroethyl. In some embodiments, R^b is -CH₂CF₃.

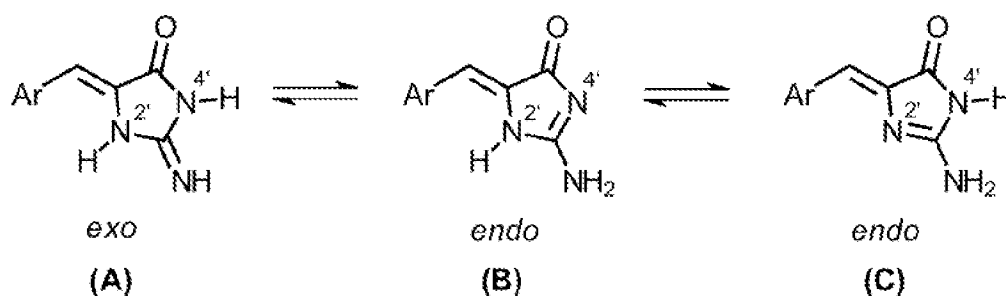
[56] In some embodiments of Formula (I), R^c is H. In some embodiments, R^c is C₁-C₆ alkyl. In some embodiments, R^c is methyl. In some embodiments, R^c is ethyl. In some embodiments, R^c is propyl (i.e., *n*-propyl or isopropyl). In some embodiments, R^c is C₁-C₆ haloalkyl. In some embodiments, R^c is C₁-C₆ fluoroalkyl. In some embodiments, R^c is fluoromethyl. In some embodiments, R^c is fluoroethyl. In some embodiments, R^c is -CH₂CF₃.

[57] In some embodiments of Formula (I), R^2 is H or C_1 - C_6 alkyl. In some embodiments, R^2 is H. In some embodiments, R^2 is C_1 - C_6 alkyl. In some embodiments, R^2 is methyl. In some embodiments, R^2 is ethyl. In some embodiments, R^2 is propyl.

[58] In some embodiments of Formula (I), R^4 is H or halo. In some embodiments of Formula (I), R^4 is H. In some embodiments, R^4 is halo. In some embodiments, R^4 is F, Cl, Br or I. In some embodiments, R^4 is F. In some embodiments, R^4 is Br. In some embodiments, R^4 is Cl. In some embodiments, R^4 is I.

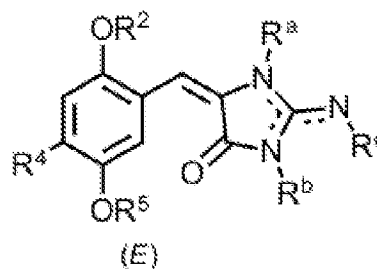
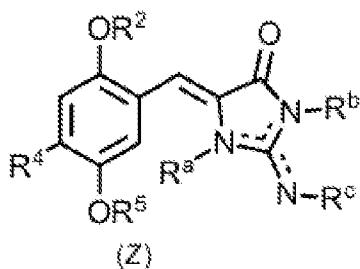
[59] In some embodiments of Formula (I), R^5 is H or C_1 - C_6 alkyl. In some embodiments, R^5 is H. In some embodiments, R^5 is C_1 - C_6 alkyl. In some embodiments, R^5 is methyl. In some embodiments, R^5 is ethyl. In some embodiments, R^5 is propyl.

[60] Multiple tautomeric compounds may be possible for a disclosed compound, depending, e.g., on the substitution pattern of the imidazolone ring. For example, in a compound wherein the imidazolone ring is unsubstituted (i.e., wherein R^a , R^b , and R^c are each H), the tautomeric forms may include include:



[61] Early investigators of acylguanidine chemistry concluded that in glycohydrazide, *endo* tautomer **B** is preferred because of conjugation of the endocyclic C=N with the carbonyl (Kenyon GL & Rowley GL. J. Am. Chem. Soc. 1971;93(21):5552-5560). However, in disclosed compounds, both *endo* tautomers (**B** and **C**) are fully conjugated in an extended π -system with the phenyl ring. All tautomeric forms are encompassed by the present disclosure, regardless of which form is depicted in any particular chemical structure or scheme herein. It will also be understood that tautomeric forms may exist in equilibrium. In some embodiments, a disclosed compound exists predominantly in tautomeric form **A**. In some embodiments, a disclosed compound exists predominantly in tautomeric form **B**. In some embodiments, a disclosed compound exists predominantly in tautomeric form **C**. In some embodiments, a disclosed compound exists in multiple tautomeric forms. In some embodiments, multiple tautomeric forms may be in equilibrium with each other. For consistency, disclosed compounds may be depicted herein as *endo* tautomer **C**, but it will be readily understood that such a disclosure will include all possible tautomeric forms, and a disclosure of a compound genus (e.g., Formula (I), any other Formula herein) will include all possible tautomeric forms of the compounds within the scope of the genus, regardless of which tautomeric form is depicted.

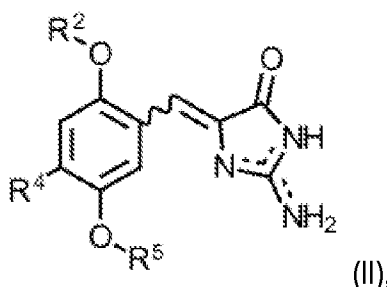
[62] Disclosed compounds may exhibit geometric isomerism around the carbon-carbon double bond that connects the imidazolinone and phenyl rings, as shown below.



[63] The disclosure includes both *E* and *Z* geometric isomers. In some embodiments, the synthesis of a disclosed compound results in the selective formation of one isomer. In embodiments wherein the particular synthesis used for a disclosed compound results in the formation of a mixture of *E* and *Z* isomers, the isomers can be separated and obtained in pure form if desired, using standard techniques in the art. Such techniques include, for example, chromatography (e.g., column chromatography, high-performance liquid chromatography, preparative thin-layer chromatography), selective crystallization, and selective derivatization. Both *E* and *Z* isomers are encompassed by the present disclosure, as are mixtures of *E* and *Z* isomers, regardless of which isomer is depicted in any particular chemical structure or scheme herein. In some embodiments, a disclosed compound has *E* geometry. In some embodiments, a disclosed compound has *Z* geometry. In some embodiments, a compound of Formula (I) has *E* geometry. In some embodiments, a compound of Formula (I) has *Z* geometry.

[64] In some embodiments, a disclosed composition comprising a disclosed compound comprises the compound in a mixture of *E* and *Z* isomers. In some embodiments, the composition comprises less than about 1% of the *E* isomer, or about 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or greater than about 99% of the *E* isomer. In some embodiments, the composition comprises less than about 1% of the *Z* isomer, or about 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or greater than about 99% of the *Z* isomer. In some embodiments, the composition comprises the *E* and *Z* isomers in an *E/Z* ratio of between about 1:100 and 100:1.

[65] In some embodiments, the compound has the structure of Formula (II),



wherein R^2 , R^4 , and R^5 are as defined for Formula (I).

[66] In some embodiments of Formula (II), R^2 is H or C_1 - C_6 alkyl. In some embodiments, R^2 is H. In some embodiments, R^2 is C_1 - C_6 alkyl. In some embodiments, R^2 is methyl. In some embodiments, R^2 is ethyl. In some embodiments, R^2 is propyl (i.e., *n*-propyl or isopropyl).

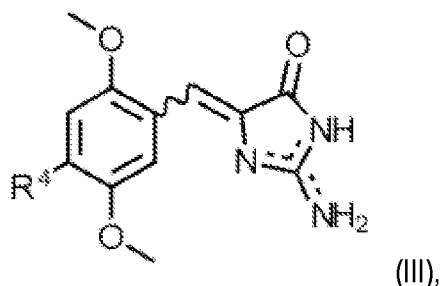
[67] In some embodiments of Formula (II), R^4 is H or halo. In some embodiments, R^4 is H. In some

embodiments, R^4 is halo. In some embodiments, R^4 is F, Cl, Br or I. In some embodiments, R^4 is F. In some embodiments, R^4 is Br. In some embodiments, R^4 is Cl. In some embodiments, R^4 is I.

[68] In some embodiments of Formula (II), R^5 is H or C_1 - C_6 alkyl. In some embodiments, R^5 is H. In some embodiments, R^5 is C_1 - C_6 alkyl. In some embodiments, R^5 is methyl. In some embodiments, R^5 is ethyl. In some embodiments, R^5 is propyl.

[69] In some embodiments, a compound of Formula (II) has *E* geometry. In some embodiments, a compound of Formula (II) has *Z* geometry.

[70] In some embodiments, the compound has the structure of Formula (III),

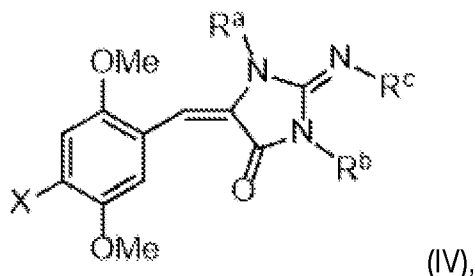


wherein R^4 is as defined for Formula (I).

[71] In some embodiments of Formula (III), R^4 is H or halo. In some embodiments, R^4 is H. In some embodiments, R^4 is halo. In some embodiments, R^4 is F, Cl, Br or I. In some embodiments, R^4 is F. In some embodiments, R^4 is Br. In some embodiments, R^4 is Cl. In some embodiments, R^4 is I.

[72] In some embodiments, a compound of Formula (III) has *E* geometry. In some embodiments, a compound of Formula (III) has *Z* geometry.

[73] In some embodiments, the compound has the structure of Formula (IV)



or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, wherein R^a , R^b , and R^c are each independently H, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl; and X is H or halo.

[74] In some embodiments of Formula (IV), R^a , R^b , and R^c are each independently H, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl. In some embodiments, R^a is H. In some embodiments, R^a is C_1 - C_6 alkyl. In some embodiments, R^a is methyl. In some embodiments, R^a is ethyl. In some embodiments, R^a is propyl (i.e., *n*-propyl or isopropyl). In some embodiments, R^a is C_1 - C_6 haloalkyl. In some embodiments, R^a is C_1 - C_6 fluoroalkyl. In some embodiments, R^a is fluoromethyl (e.g., $-CH_2F$, $-CHF_2$, $-CF_3$). In some embodiments, R^a is fluoroethyl. In some embodiments, R^a is $-CH_2CF_3$.

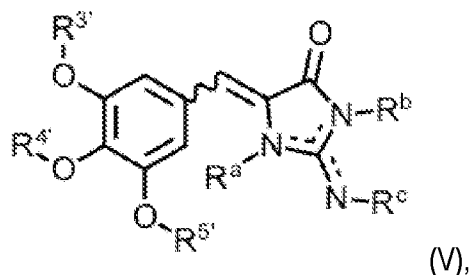
[75] In some embodiments of Formula (IV), R^b is H. In some embodiments, R^b is C_1 - C_6 alkyl. In some embodiments, R^b is methyl. In some embodiments, R^b is ethyl. In some embodiments, R^b is propyl (i.e., *n*-propyl or isopropyl). In some embodiments, R^b is C_1 - C_6 haloalkyl. In some embodiments, R^b is C_1 - C_6 fluoroalkyl. In some embodiments, R^b is fluoromethyl. In some embodiments, R^b is fluoroethyl. In some embodiments, R^b is $-CH_2CF_3$.

[76] In some embodiments of Formula (IV), R^c is H. In some embodiments, R^c is C_1 - C_6 alkyl. In some embodiments, R^c is methyl. In some embodiments, R^c is ethyl. In some embodiments, R^c is propyl (i.e., *n*-propyl or isopropyl). In some embodiments, R^c is C_1 - C_6 haloalkyl. In some embodiments, R^c is C_1 - C_6 fluoroalkyl. In some embodiments, R^c is fluoromethyl. In some embodiments, R^c is fluoroethyl. In some embodiments, R^c is $-CH_2CF_3$.

[77] In some embodiments of Formula (IV), X is H. In some embodiments, X is halo. In some embodiments, X is F, Cl, Br or I. In some embodiments, X is F. In some embodiments, X is Br. In some embodiments, X is Cl. In some embodiments, X is I.

[78] In some embodiments, a compound of Formula (IV) has *E* geometry. In some embodiments, a compound of Formula (IV) has *Z* geometry.

[79] In another aspect, provided is a compound of Formula (V),



or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, wherein:

R^a , R^b , and R^c are each independently H, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

$R^{3'}$, $R^{4'}$, and $R^{5'}$ are each independently H or C_1 - C_6 alkyl; and

is a single or double bond.

[80] In some embodiments of Formula (V), R^a , R^b , and R^c are each independently H, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl. In some embodiments, R^a is H. In some embodiments, R^a is C_1 - C_6 alkyl. In some embodiments, R^a is methyl. In some embodiments, R^a is ethyl. In some embodiments, R^a is propyl (i.e., *n*-propyl or isopropyl). In some embodiments, R^a is C_1 - C_6 haloalkyl. In some embodiments, R^a is C_1 - C_6 fluoroalkyl. In some embodiments, R^a is fluoromethyl (e.g., $-CH_2F$, $-CHF_2$, $-CF_3$). In some embodiments, R^a is fluoroethyl. In some embodiments, R^a is $-CH_2CF_3$.

[81] In some embodiments of Formula (V), R^b is H. In some embodiments, R^b is C_1 - C_6 alkyl. In some embodiments, R^b is methyl. In some embodiments, R^b is ethyl. In some embodiments, R^b is propyl (i.e.,

n-propyl or isopropyl). In some embodiments, R^b is C₁-C₆ haloalkyl. In some embodiments, R^b is C₁-C₆ fluoroalkyl. In some embodiments, R^b is fluoromethyl. In some embodiments, R^b is fluoroethyl. In some embodiments, R^b is -CH₂CF₃.

[82] In some embodiments of Formula (V), R^c is H. In some embodiments, R^c is C₁-C₆ alkyl. In some embodiments, R^c is methyl. In some embodiments, R^c is ethyl. In some embodiments, R^c is propyl (i.e., *n*-propyl or isopropyl). In some embodiments, R^c is C₁-C₆ haloalkyl. In some embodiments, R^c is C₁-C₆ fluoroalkyl. In some embodiments, R^c is fluoromethyl. In some embodiments, R^c is fluoroethyl. In some embodiments, R^c is -CH₂CF₃.

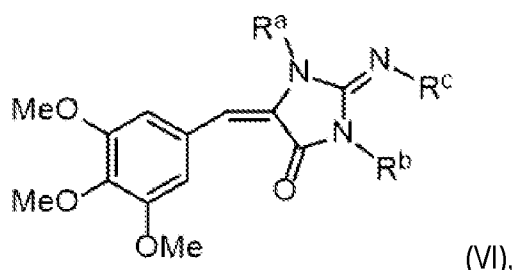
[83] In some embodiments of Formula (V), R³ is H or C₁-C₆ alkyl. In some embodiments, R³ is H. In some embodiments, R³ is C₁-C₆ alkyl. In some embodiments, R⁵ is methyl. In some embodiments, R³ is ethyl. In some embodiments, R³ is propyl.

[84] In some embodiments of Formula (V), R⁴ is H or C₁-C₆ alkyl. In some embodiments, R⁴ is H. In some embodiments, R⁴ is C₁-C₆ alkyl. In some embodiments, R⁴ is methyl. In some embodiments, R⁴ is ethyl. In some embodiments, R⁴ is propyl.

[85] In some embodiments of Formula (V), R⁵ is H or C₁-C₆ alkyl. In some embodiments, R⁵ is H. In some embodiments, R⁵ is C₁-C₆ alkyl. In some embodiments, R⁵ is methyl. In some embodiments, R⁵ is ethyl. In some embodiments, R⁵ is propyl.

[86] In some embodiments, a compound of Formula (V) has *E* geometry. In some embodiments, a compound of Formula (V) has *Z* geometry.

[87] In some embodiments, the compound has the structure of Formula (VI),



or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, wherein R^a, R^b, and R^c are each independently H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl.

[88] In some embodiments of Formula (VI), R^a, R^b, and R^c are each independently H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments, R^a is H. In some embodiments, R^a is C₁-C₆ alkyl. In some embodiments, R^a is methyl. In some embodiments, R^a is ethyl. In some embodiments, R^a is propyl (i.e., *n*-propyl or isopropyl). In some embodiments, R^a is C₁-C₆ haloalkyl. In some embodiments, R^a is C₁-C₆ fluoroalkyl. In some embodiments, R^a is fluoromethyl (e.g., -CH₂F, -CHF₂, -CF₃). In some embodiments, R^a is fluoroethyl. In some embodiments, R^a is -CH₂CF₃.

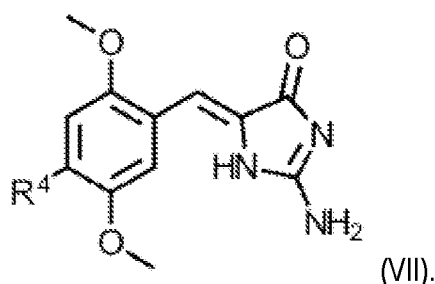
[89] In some embodiments of Formula (VI), R^b is H. In some embodiments, R^b is C₁-C₆ alkyl. In some

embodiments, R^b is methyl. In some embodiments, R^b is ethyl. In some embodiments, R^b is propyl (i.e., *n*-propyl or isopropyl). In some embodiments, R^b is C_1 - C_6 haloalkyl. In some embodiments, R^b is C_1 - C_6 fluoroalkyl. In some embodiments, R^b is fluoromethyl. In some embodiments, R^b is fluoroethyl. In some embodiments, R^b is $-CH_2CF_3$.

[90] In some embodiments of Formula (VI), R^c is H. In some embodiments, R^c is C_1 - C_6 alkyl. In some embodiments, R^c is methyl. In some embodiments, R^c is ethyl. In some embodiments, R^c is propyl (i.e., *n*-propyl or isopropyl). In some embodiments, R^c is C_1 - C_6 haloalkyl. In some embodiments, R^c is C_1 - C_6 fluoroalkyl. In some embodiments, R^c is fluoromethyl. In some embodiments, R^c is fluoroethyl. In some embodiments, R^c is $-CH_2CF_3$.

[91] In some embodiments, a compound of Formula (VI) has *E* geometry. In some embodiments, a compound of Formula (VI) has *Z* geometry.

[92] In some embodiments, the compound has the structure of Formula (VII),



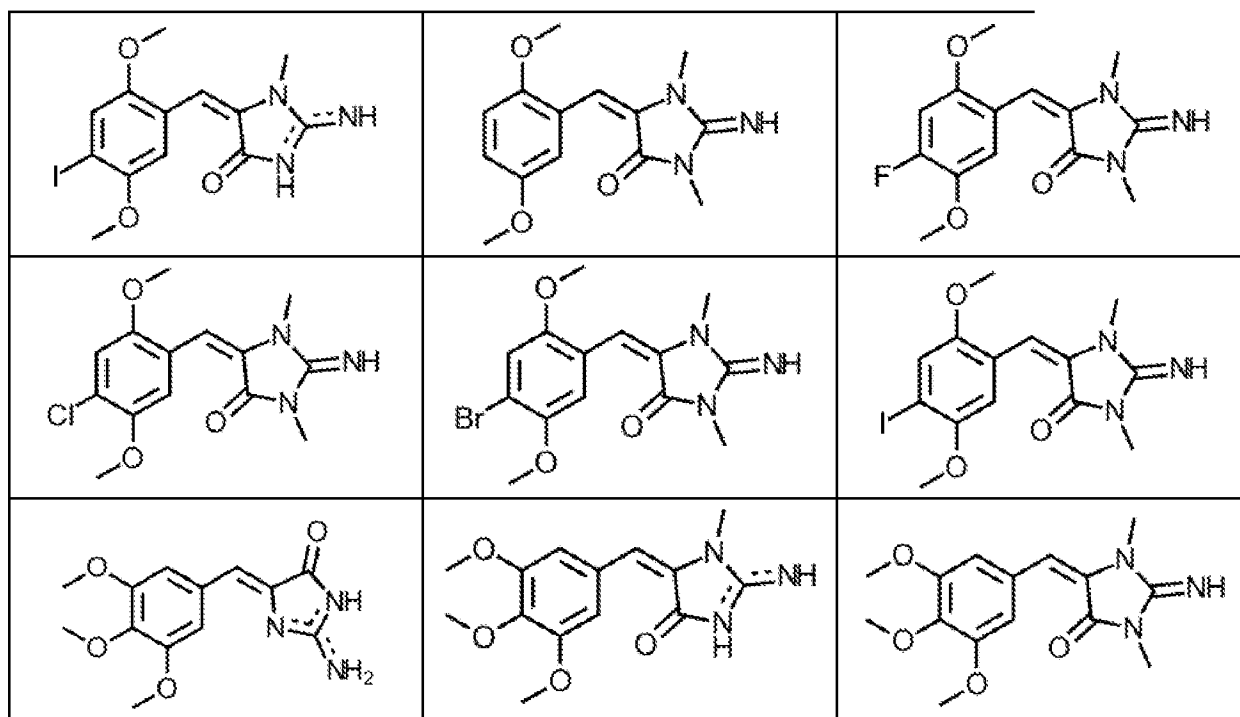
or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, wherein R^4 is halogen or H. In some embodiments, R^4 is H. In some embodiments, R^4 is halo. In some embodiments, R^4 is F, Cl, Br or I. In some embodiments, R^4 is F. In some embodiments, R^4 is Br. In some embodiments, R^4 is Cl. In some embodiments, R^4 is I.

[93] In some embodiments, the compound is selected from **Table 1**.

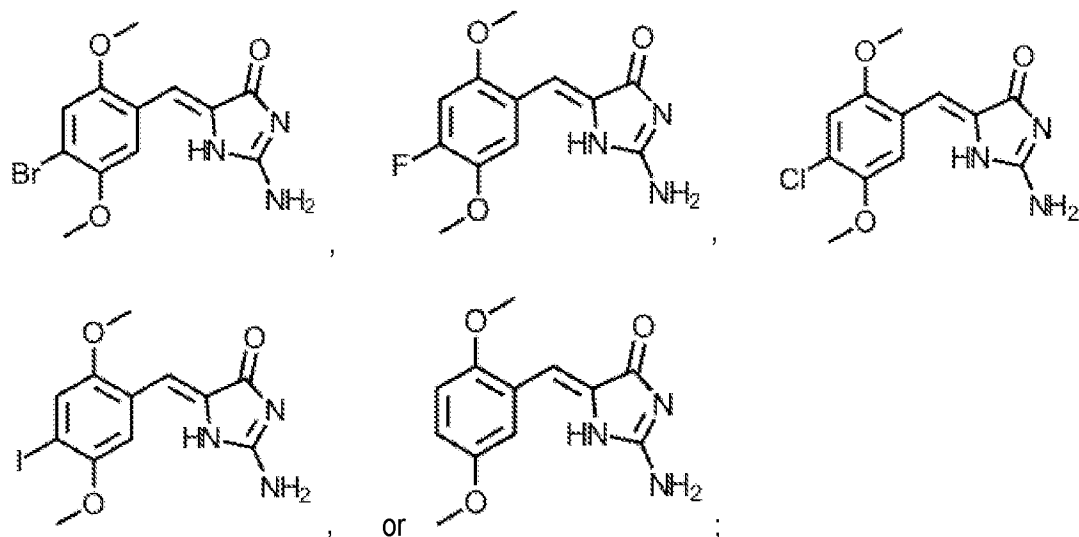
Table 1. Exemplary compounds

[94] In some embodiments, the compound is selected from **Table 2**.

[95] **Table 2. Exemplary compounds**

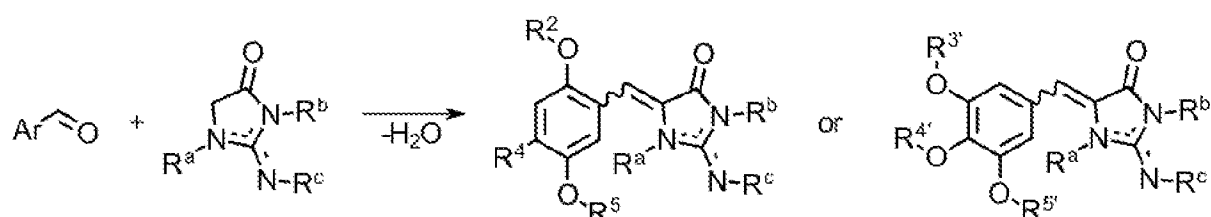


[96] In some embodiments, the compound has the structure of:



or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof.

[97] Disclosed compounds can be chemically synthesized according to standard techniques known to one of skill, including the following general procedures. In some embodiments, a disclosed compound can be synthesized by condensation of suitable benzaldehyde and imidazolinone precursors:



[98] Suitable reaction conditions for such a condensation may include thermal conditions (e.g., heating

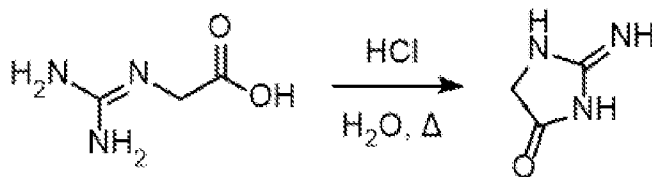
the aryl aldehyde and imidazolinone in the absence of solvent, such as to a temperature of greater than about 150 °C), and acid- or base-catalyzed Knoevenagel condensation conditions. In one example, a disclosed compound is synthesized by Knoevenagel condensation of an aryl aldehyde and an imidazolinone in glacial acetic acid. In some embodiments, a disclosed compound is synthesized by Knoevenagel condensation of an aryl aldehyde and an imidazolinone in glacial acetic acid heated above reflux temperatures (e.g., in a pressure reactor). Suitable catalysts for the Knoevenagel condensation include, e.g., ammonium acetate, piperidine.

[99] Chlorinated, brominated, and iodinated compounds of Formula (I) (i.e., wherein R^4 is Cl, Br, or I) can be produced by halogenation of the corresponding 4-unsubstituted compound (i.e., wherein R^4 is H), according to standard techniques. For example, a compound wherein R^4 is Cl may be synthesized by reacting the corresponding compound in which R^4 is H with a chlorinating agent (e.g., NCS, Cl_2) in a suitable solvent (e.g., CH_2Cl_2). A compound wherein R^4 is Br may be synthesized by reacting the corresponding compound in which R^4 is H with a brominating agent (e.g., NBS, Br_2) in a suitable solvent (e.g., CH_2Cl_2 , glacial acetic acid). A compound wherein R^4 is Br may be synthesized by reacting the corresponding compound in which R^4 is H with an iodinating agent (e.g., I_2/Ag_2SO_4 , ICl) in a suitable solvent (e.g., EtOH, glacial acetic acid). In such embodiments, the imidazolone exocyclic amine (i.e., $N-R^c$) may first be protected. Suitable protecting groups are known to those of skill.

[100] A fluorinated compounds of Formula (I) (i.e., wherein R^4 is F) can be synthesized by: (1) converting 2,5-dimethoxyaniline to an aryldiazonium intermediate with fluoroboric acid, followed by pyrolysis to yield 2,5-dimethoxyfluorobenzene; (2) converting 2,5-dimethoxyfluorobenzene to 4-fluoro-2,5-dimethoxybenzaldehyde using a Vilsmeier–Haack reaction; and (3) condensation with a suitable imidazolinone precursor.

[101] Alternatively, a compound wherein R^4 is halogen can be synthesized using a halogenated benzaldehyde precursor. Many suitable benzaldehyde precursors are commercially available, including 4-bromo-2,5-dimethoxybenzaldehyde. If such a precursor is not commercially available, it can be readily synthesized according to standard techniques known to one of skill. For example, 4-bromo-2,5-dimethoxybenzaldehyde can be synthesized by bromination of 2,5-dimethoxybenzaldehyde (see, e.g., Example 1).

[102] Many suitable imidazolinone precursors are commercially available. For example, creatinine (2-amino-1-methyl-5H-imidazol-4-one) is inexpensive and widely available and can be used directly in the synthesis of a disclosed compound wherein R^a is methyl, and R^b and R^c are both H). Creatinine can also be further derivatized (e.g., by alkylation, to produce compounds wherein one or both of R^b and R^c are alkyl or haloalkyl). Imidazolinone precursors can also be synthesized through a cyclization reaction of glycohydrazide, as reported in Bengelsdorf I. J. Am. Chem. Soc. 1952;75(13):3138-3140 (see also Example 1) as follows:



[103] Subsequent alkylation of one or more of the amines can be conducted according to methods known to those of skill in the art (e.g., to install a C₁-C₆ alkyl or C₁-C₆ haloalkyl).

[104] While the reaction schemes depict exemplary reaction conditions, including exemplary reagents and/or solvents, suitable alternatives are also embraced by the present disclosure. For example, while HCl is depicted as an exemplary acid in the synthesis of glycohydrazide, other acids (e.g., mineral acids, organic acids) and other reaction conditions may be suitable for the same purpose, as will be known to one of skill. Likewise, adaptation of this exemplary procedure for the synthesis of disclosed compounds with different structural features by modifying precursor compounds and/or reaction conditions is within the capabilities of the person of skill.

[105] The individual compounds of the disclosed compositions will be understood to also encompass pharmaceutically acceptable salts of such compounds. The term "pharmaceutically acceptable salt" refers to a salt prepared from pharmaceutically acceptable non-toxic acids or bases, and which may be synthesized by conventional chemical methods. Generally, such salts are prepared by reacting the free acid or base forms of these agents with the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. For therapeutic use, salts of the compounds are those wherein the counter-ion is pharmaceutically acceptable. One of ordinary skill in the art can select from among a wide variety of available counterions those that are pharmaceutically acceptable. In specific applications, the selection of a given anion or cation for preparation of a salt may result in increased or decreased solubility of that salt. Exemplary salts include 2-hydroxyethanesulfonate, 2-naphthalenesulfonate, 2-napsylate, 3-hydroxy-2-naphthoate, 3-phenylpropionate, 4-acetamidobenzoate, acefyllinate, acetate, aceturate, adipate, alginate, aminosalicylate, amsonate, ascorbate, aspartate, benzenesulfonate, benzoate, besylate, bicarbonate, bisulfate, bitartrate, borate, butyrate, camphocarbonate, camphorate, camphorsulfonate, camsylate, carbonate, cholate, citrate, clavulinate, cyclopentanepropionate, cypionate, d-aspartate, d-camsylate, d-lactate, decanoate, dichloroacetate, digluconate, dodecylsulfate, edentate, edetate, edisylate, estolate, esylate, ethanesulfonate, ethyl sulfate, fumarate, furate, fusidate, galactarate (mucate), galacturonate, gallate, gentisate, gluceptate, glucoheptanoate, gluconate, glucuronate, glutamate, glutarate, glycerophosphate, glycolate, glycolylarsanilate, hemisulfate, heptanoate (enanthate), heptanoate, hexafluorophosphate, hexanoate, hexylresorcinate, hippurate, hybenzate, hydrabamine, hydrobromide, hydrobromide/bromide, hydrochloride, hydroiodide, hydroxide, hydroxybenzoate, hydroxynaphthoate, iodide, isethionate, isothionate, l-aspartate, l-camsylate, l-lactate, lactate, lactobionate, laurate, laurylsulphonate, malate, maleate, malonate, mandelate, meso-tartrate, mesylate,

methanesulfonate, methylbromide, methylnitrate, methylsulfate, mucate, myristate, napadisilate, naphthylate, napsylate, nicotinate, nitrate, octanoate, oleate, orotate, oxalate, p-toluenesulfonate, palmitate, pamoate, pantothenate, pectinate, persulfate, phenylpropionate, phosphate, phosphateldiphosphate, picrate, pivalate, polygalacturonate, potassium, propionate, pyrophosphate, saccharate, salicylate, salicylsulfate, sodium, stearate, subacetate, succinate, sulfate, sulfosalicylate, sulfosalicylate, suramate, tannate, tartrate, teoclate, terephthalate, thiocyanate, thiosalicylate, tosylate, tribrophenate, triethiodide, undecanoate, undecylenate, valerate, valproate, xinafoate, and the like. (Berge SM, Bighley LM, Monkhouse DC. *Pharmaceutical Salts*. Journal of Pharmaceutical Sciences. 1977;66(1):1-19.)

[106] Certain compounds disclosed herein may contain one or more ionizable groups, such as an amine that can be quaternized (e.g., to form an ammonium). All possible ionic forms of such molecules and salts thereof are included in the present disclosure.

[107] A compound described herein can exist in solid or liquid form. In the solid state, the compound may exist in crystalline or noncrystalline form, or as a mixture thereof. The skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed for crystalline or non-crystalline compounds. In crystalline solvates, solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve non-aqueous solvents such as, but not limited to, ethanol, isopropanol, DMSO, acetic acid, ethanamine, or ethyl acetate, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent incorporated into the crystalline lattice are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The subject matter described herein includes such solvates.

[108] The skilled artisan will further appreciate that certain compounds described herein that exist in crystalline form, including the various solvates thereof, may exhibit polymorphism (i.e. the capacity to occur in different crystalline structures). These different crystalline forms are typically known as "polymorphs." The subject matter disclosed herein includes such polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder diffraction patterns, which may be used for identification. The skilled artisan will appreciate that different polymorphs may be produced, for example, by changing or adjusting the reaction conditions or reagents, used in making the compound. For example, changes in temperature, pressure, or solvent may result in polymorphs. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate. In addition, one polymorph may spontaneously convert to another polymorph under certain conditions.

[109] The compounds described herein may contain one or more asymmetric centers and give rise to enantiomers, diastereomers, and other stereoisomeric forms. Each chiral center may be defined, in terms of absolute stereochemistry, as (R)– or (S)–. The invention includes all such possible isomers, as well as mixtures thereof, including racemic and optically pure forms. Optically active (R)– and (S)–, (–)– and (+)–, or (D)– and (L)–isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Various methods are known in the art for preparing optically active forms and determining activity. Such methods include standard tests described herein and other similar tests which are well known in the art. Examples of methods that can be used to obtain optical isomers of the compounds according to the present disclosure include selective crystallization, enzymatic resolution, asymmetric synthesis (including asymmetric chemical synthesis and asymmetric enzymatic synthesis), kinetic resolution, and chiral chromatography (including chiral liquid chromatography, gas chromatography, and high-performance liquid chromatography).

[110] The disclosure also includes compounds with at least one desired isotopic substitution of an atom, at an amount above the natural abundance of the isotope, i.e., an isotopically enriched compound (or “isotopolog”). Examples of isotopes that can be incorporated into such compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, and chlorine such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , and ^{36}Cl respectively. In one non-limiting embodiment, isotopically labeled compounds can be used in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. Further, substitution with heavier isotopes such as deuterium (^2H) can in embodiments afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. Isotopologs of a disclosed compound can generally be prepared by carrying out the procedures disclosed in the schemes or in the Examples by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[111] The invention also includes prodrugs of disclosed compounds. A “prodrug” is a precursor of a biologically active pharmaceutical agent, which may undergo a chemical or a metabolic conversion to become the biologically active agent. In some embodiments, a prodrug of a disclosed compound comprises a biologically labile group on a functional moiety (e.g., an amine) of the compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, or dephosphorylated to produce the active compound. Commonly used functional groups include esters, carbonates, carbamates, amides, phosphates, and sulfonamides. These functional groups can be attached to the drug molecule via a linker that is designed to be cleaved under specific physiological conditions, such as enzymatic hydrolysis or pH-dependent cleavage. The choice of functional group depends on

factors such as stability, ease of synthesis, enzymatic activity, and desired rate of prodrug conversion.

[112] An individual compound of the disclosure may be administered as part of a pharmaceutical composition or formulation, but will be prepared for inclusion in such composition or formulations as isolated or purified compounds. The terms “isolated,” “purified,” or “substantially pure,” as used herein, refer to material that is substantially or essentially free from components that normally accompany the material when the material is synthesized, manufactured, or otherwise produced. An “isolated,” “purified,” or “substantially pure” preparation of a compound is accordingly defined as a preparation having a chromatographic purity (of the desired compound) 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.

[113] Preferably the substantially pure compound used in the invention is substantially free of any other active compounds which are not intended to be administered to a subject. In this context “substantially free” can be taken to mean that no active compound(s) other than the active compound intended to be administered to a subject are detectable by HPLC or other similar detection method, or are below a desired threshold of detection such as defined above.

C. Pharmaceutical Compositions

[114] In some aspects, provided herein are compositions, such as pharmaceutical compositions, comprising a disclosed compound. “Pharmaceutical compositions” are compositions that comprise a disclosed compound together in an amount (for example, in a unit dosage form) with a pharmaceutically acceptable carrier, diluent, or excipient. Some embodiments include multiple carriers, diluents, and/or excipients. Compositions can be prepared by standard pharmaceutical formulation techniques such as disclosed in, e.g., Adejare A. *Remington: The Science and Practice of Pharmacy*. 23rd ed. Cambridge, MA: Academic Press; 2020.; Budavari S, O'Neil M, Smith A. *The Merck Index*. 12th ed. Whitehouse, NJ: Merck Publishing Group; 1996.; Carstensen JT. *Pharmaceutical Principles of Solid Dosage Forms*. Lancaster, PA: Technomic Pub. Co., Inc.; 1993.; Ansel HC, Stoklosa MJ. *Pharmaceutical Calculations*. 11th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001.; and Poznansky MJ, Cleland LG. *Drug Delivery Systems*. NY: by RL Juliano Oxford University Press; 1980:253-315.

[115] “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.

[116] In some embodiments, a pharmaceutical composition comprising a disclosed compound 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, a disclosed

compound employed in the methods of this invention is effective as an oral, mucosal (e.g., buccal, sublingual), rectal, transdermal, subcutaneous, intravenous, intramuscular, inhaled, and intranasal compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

[117] A disclosed composition may be formulated in a unit dosage form, each dosage containing a therapeutically effective amount of a disclosed compound, for example in the dosage 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.

[118] 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. Unit dosage forms also include ampules and vials with liquid compositions disposed therein. Unit dosage forms further include compounds for transdermal administration, such as “patches” that contact the epidermis (including the mucosa) of a subject for an extended or brief period of time.

[119] In some embodiments, the disclosed compositions are formulated in a pharmaceutically acceptable oral dosage form. Oral dosage forms include oral liquid dosage forms (such as tinctures, drops, emulsions, syrups, elixirs, suspensions, and solutions, and the like) and oral solid dosage forms. The disclosed pharmaceutical compositions also may be prepared as formulations suitable for intramuscular, subcutaneous, intraperitoneal, or intravenous injection, comprising physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, liposomes, and sterile powders for reconstitution into sterile injectable solutions or dispersions.

[120] 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 formulation is in the form of a powder. In still other embodiments, the pharmaceutical formulation is in the form of a tablet, including a fast-melt tablet. Additionally, pharmaceutical formulations may be administered as a single capsule or in multiple capsule dosage form. In some embodiments, the pharmaceutical formulation is administered in two, three, four, or more capsules or tablets.

[121] An oral solid dosage form may contain pharmaceutically acceptable 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. An oral solid dosage form also can comprise one or more pharmaceutically acceptable additives such as a compatible carrier, complexing agent, ionic dispersion modulator, disintegrating agent, surfactant, lubricant, colorant, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, alone or in combination, as well as supplementary active compound(s).

[122] Supplementary active compounds include preservatives, antioxidants, 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 the active ingredient thereby prolonging the shelf life of the formulation. 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.

[123] In some embodiments, a disclosed composition is formulated as an oral liquid dosage form. Oral liquid dosage forms include tinctures, drops, emulsions, syrups, elixirs, suspensions, and solutions, and the like. These oral liquid dosage forms may be formulated with any pharmaceutically acceptable excipient known to those of skill in the art for the preparation of liquid dosage forms, and with solvents, diluents, carriers, excipients, and the like chosen as appropriate to the solubility and other properties of the active agents and other ingredients. Solvents may be, for example, water, glycerin, simple syrup, alcohol, medium chain triglycerides (MCT), and combinations thereof.

[124] A liquid dosage form for oral administration may be in the form of a pharmaceutically acceptable emulsion, syrup, elixir, suspension, or solution, which may comprise an inactive diluent, such as water. Pharmaceutical formulations may be prepared as liquid suspensions or solutions using a sterile liquid, such as but not limited to, an oil, water, an alcohol, and combinations of these pharmaceutically suitable surfactants, suspending agents, emulsifying agents, may be added for oral or parenteral administration. Liquid formulations also may be prepared as single dose or multi-dose beverages. Suspensions may

include oils. Such oils include peanut oil, sesame oil, cottonseed oil, corn oil, and olive oil. Suitable oils also include carrier oils such as MCT and long chain triglyceride (LCT) oils. Suspension preparation may also contain esters of fatty acids such as ethyl oleate, isopropyl myristate, fatty acid glycerides, and acetylated fatty acid glycerides. Suspension formulations may include alcohols, (such as ethanol, isopropyl alcohol, hexadecyl alcohol), glycerol, and propylene glycol. Ethers, such as poly(ethylene glycol), petroleum hydrocarbons such as mineral oil and petrolatum, and water may also be used in suspension formulations. Suspension can thus include an aqueous liquid or a non-aqueous liquid, an oil-in-water liquid emulsion, or a water-in-oil emulsion.

[125] In some embodiments, formulations are provided comprising a disclosed composition and at least one dispersing agent or suspending agent for oral administration to a subject. The formulation may be a powder and/or granules for suspension, and upon admixture with water, a substantially uniform suspension is obtained. The aqueous dispersion can comprise amorphous and non-amorphous particles consisting of multiple effective particle sizes such that a compound is absorbed in a controlled manner over time.

[126] Dosage forms for oral administration can be aqueous suspensions selected from the group including pharmaceutically acceptable aqueous oral dispersions, emulsions, solutions, and syrups. (Swarbrick J, Boylan JC. *Encyclopedia of Pharmaceutical Technology*. 2nd ed. CRC Press; 2002:754-757). In addition to the disclosed compounds, the liquid dosage forms may comprise additives, such as one or more (a) disintegrating agents, (b) dispersing agents, (c) wetting agents, (d) preservatives, (e) viscosity enhancing agents, (f) sweetening agents, or (g) flavoring agents.

[127] A disclosed composition may also be prepared as a formulation suitable for intramuscular, subcutaneous, intraperitoneal, or intravenous injection, comprising physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, liposomes, and sterile powders for reconstitution into sterile injectable solutions or dispersions.

D. Pharmaceutical Combinations

[128] It should be readily appreciated that the disclosed compositions are not limited to combinations of a single compound, or (when formulated as a pharmaceutical composition) limited to a single carrier, diluent, and/or excipient alone, but may also include combinations of multiple compounds (including additional active compounds), and/or multiple carriers, diluents, and excipients. Pharmaceutical compositions of this invention thus may comprise a disclosed compound together with one or more other active agents in combination, together with one or more pharmaceutically-acceptable carriers, diluents, and/or excipients, and additionally with one or more other active compounds.

[129] In some embodiments, a formulation of the invention is prepared so as 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 or pharmacodynamics), modulate a desired system or pathway (e.g., a neurotransmitter

system), or provide synergistic effects.

[130] “Therapeutic effects” that may be increased or added in embodiments of the invention 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.

[131] “Synergistic effects” should be understood to 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 et al. *Front Pharmacol.* 2019;10:1222), or the equation of Loewe additivity (Loewe S & Muischnek H. *Archiv für experimentelle Pathologie und Pharmakologie.* 1926;114:313-326). A synergistic effect also may be calculated using methods such as the Sigmoid-Emax equation (Holford NHG & Sheiner LB. *Clin Pharmacokinet.* 1981;6:429-453) and the median-effect equation (Chou TC & Talalay P. *Adv Enzyme Regul.* 1984;22:27-55). Each method referred to above may be applied to experimental data to aid in assessing the effects of the drug combination.

[132] In some embodiments, a disclosed pharmaceutical composition comprises an additional active compound. In some 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, antihistamines, antihypertensives, anticonvulsants, antiepileptics, bronchodilators, neuroprotectants, nootropics, empathogens, psychedelics, plasticity-inducing agents (e.g., psychoplastogens), monoamine oxidase inhibitors, tryptamines, terpenes, phenethylamines, sedatives, stimulants, serotonergic agents, NMDA modulators, NMDA antagonists, and vitamins. In some 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 pharmacokinetics or pharmacodynamics. In some 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.

[133] In some embodiments, the additional active agent compound is a 5-HT_{2A} receptor agonist. In some embodiments, the additional active agent compound is a tryptamine, phenethylamine, or lysergamide, such compounds being generally known in the art (Shulgin A, Shulgin A. *PiHKAL: A Chemical Love Story*. Berkeley, CA: Transform Press; 1991; Shulgin A, Shulgin A. *TiHKAL: The Continuation*. Berkeley, CA: Transform Press; 1997; Grob CS, Grigsby J. *Handbook of Medical Hallucinogens*. New York, NY: Guilford Press; 2021; Nichols DE. *Psychedelics*. *Pharmacological Reviews*. 2016;68(2):264-355; Glennon RA. *Arylalkylamine Drugs of Abuse: An Overview of Drug Discrimination Studies*. *Pharmacology Biochemistry and Behavior*. 1999;64:251-256; each of which is incorporated by reference as if fully set forth herein).

E. Dose and Dosage

[134] In some embodiments, a pharmaceutical composition comprises a therapeutically effective amount or an effective amount of a disclosed compound, such as for administration to a subject. Administration of pharmaceutical compositions in a “therapeutically effective amount,” or an “effective amount” to a subject means administration of an amount of composition sufficient to achieve a 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.

[135] In some embodiments, where a pharmaceutical composition includes a disclosed compound, it may be present in an amount so that a single dose is (in a milligram dosage amount calculated based on the kilogram weight of the patient) 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 some embodiments, where a pharmaceutical composition includes a disclosed compound, it may be present in an amount so that a single dose is less than about 0.01 mg/kg, such as between about 0.001 and 0.01 mg/kg. In some embodiments, where a pharmaceutical composition includes a disclosed compound, it may be present in an amount so that a single dose is greater than about 1.0 mg/kg, such as between about 1 and 10 mg/kg.

[136] In some embodiments, where a pharmaceutical composition includes a disclosed compound, it may be present in an amount so that a single dose is 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, such as about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg, as well as ranges between these values. In some embodiments, where a pharmaceutical composition includes a disclosed compound, it may be present in an amount so that a single dose is greater than about 100 mg.

[137] 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).

[138] 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.

[139] 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 or formulation 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.

F. Kits

[140] Another aspect of this disclosure provides pharmaceutical kits containing a pharmaceutical composition or formulation of the invention, suggested administration guidelines or prescribing information therefore, and a suitable container. Individual unit dosage forms can be included in multi-dose kits or containers. pharmaceutical formulations also can be packaged in single or multiple unit dosage forms for uniformity of dosage and ease of administration.

[141] Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. 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 compound 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).

[142] Preferably, information pertaining to dosing and proper administration (if needed) will be printed onto a multi-dose kit directly (e.g., on a blister pack or other interior packaging holding the compositions or formulations of the invention); however, kits of the invention can further contain package inserts and other printed instructions (e.g., on exterior packaging) for administering the disclosed compositions and for their appropriate therapeutic use.

G. Methods of Use

[143] In some aspects, provided herein are methods of using disclosed compounds. In some embodiments, a disclosed compound is used to modulate neurotransmission. In some embodiments, a disclosed compound is used to treat a medical condition, such as a disease or a disorder. In some embodiments, a disclosed compound is used in the manufacture of a medicament for the therapeutic and/or the prophylactic treatment of a condition, such for the treatment of a disease or a disorder. In some embodiments, a disclosed compound is administered in a therapeutically effective amount to a subject having a condition, such as a disease or a disorder. In some embodiments, the condition is a mental health disorder. In some embodiments, the condition is a neurodegenerative disorder. In some embodiments, the condition is a pain disorder.

[144] As used herein, the terms “subject,” “user,” “patient,” and “individual” are used interchangeably, and refer to any mammal, preferably a human. Such terms will be understood to include one who has an indication for which a compound, composition, or method described herein may be efficacious.

[145] In some embodiments, a disclosed compound or composition is orally, mucosally, rectally, subcutaneously, intravenously, intramuscularly, intranasally, by inhalation or transdermally administered to a subject. In some embodiments, when administered through one or more such routes, the compound or composition is useful in methods for treating a subject in need of such treatment.

a. Modulating Neurotransmission

[146] In some embodiments, a disclosed compound modulates neurotransmission in a subject, such as

following administration of a therapeutically effective amount to said subject. In some embodiments, modulating neurotransmission by administering a disclosed compound to a subject treats a disease or disorder in the subject.

[147] In some embodiments, a disclosed compound modulates monoaminergic neurotransmission by binding to and agonizing, partially agonizing, or antagonizing a monoamine receptor (e.g., any of a serotonin, dopamine, and/or norepinephrine receptor). In some embodiments, a disclosed compound modulates monoaminergic neurotransmission by binding to and agonizing, partially agonizing, or antagonizing a monoamine transporter (e.g., any of a serotonin, dopamine, and/or norepinephrine transporter).

[148] In some embodiments, a disclosed compound modulates monoaminergic neurotransmission. In some embodiments, a disclosed compound modulates serotonergic neurotransmission. In some embodiments, a disclosed compound modulates dopaminergic neurotransmission. In some embodiments, a disclosed compound modulates norepinephrine neurotransmission. In some embodiments, a disclosed compound modulates monoaminergic neurotransmission by binding to and agonizing, partially agonizing, or antagonizing a monoamine transporter (e.g., any of SERT, DAT, and/or NET).

[149] In some embodiments, a disclosed compound antagonizes serotonin receptors, such as serotonin-2 (5-HT₂) receptors. The 5-HT₂ receptor family consists of the three distinct receptor subtypes: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. 5-HT_{2A} and 5-HT_{2C} receptors are more highly expressed in the brain than the 5-HT_{2B} subtype. Antagonism of the 5-HT_{2A} receptor may provide therapeutic value through a variety of mechanisms, and is a common feature of many antipsychotic (e.g., atypical antipsychotic) drugs.

b. Treatment

[150] In embodiments, disclosed are methods of treating and/or preventing a condition in a subject, the method comprising administering to the subject a therapeutically effective amount of a disclosed compound or pharmaceutical composition. In some embodiments, “treating” or “treatment” refers to treating a disease or disorder in a subject, 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. Other such measurements, benefits, and surrogate or clinical endpoints, alone or in combination, will be understood to one of ordinary skill based on the teachings herein and the knowledge in the art.

[151] In some embodiments, a disclosed compound is used to treat a central nervous system (CNS)

disorder. Broadly, CNS disorders include diseases of the nervous system (e.g., movement disorders, inflammatory disorders, neurodegenerative disorders) as well as mental, behavioral, and neurodevelopmental disorders, such as those characterized by the DSM-5, Merck Manual, ICD-11, or other such diagnostic resources known to those of skill.

i. Mental, Behavioral, or Neurodevelopmental Disorders

[152] In some embodiments, a disclosed compound or composition is used to treat a mental, behavioral, or neurodevelopmental disorder. In some embodiments, a disclosed compound or composition 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 embodiments, a disclosed compound or composition, when administered in a therapeutically effective amount, provides beneficial therapeutic effects for the treatment of a mental, behavioral, or neurodevelopmental disorder.

[153] 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.

[154] A mental, behavioral, or neurodevelopmental disorder where otherwise undefined, will be understood to 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.

[155] In some embodiments, a disclosed compound or composition is used to treat a mental health disorder. In some embodiments, a disclosed compound or composition 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 embodiments, a disclosed compound or composition, when administered in a therapeutically effective amount, provides beneficial therapeutic effects for the treatment of a mental health disorder. In some embodiments, the compounds and compositions of the invention are 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.

[156] In some embodiments, measures of therapeutic efficacy include reports by a subject or an observer. In some 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.

[157] In some embodiments, a disclosed compound is used to treat a neurodevelopmental disorder in a subject. In some embodiments, a subject has a neurodevelopmental disorder. In some 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 the disclosed compounds, include a disorder of intellectual development, a developmental speech or language disorder, autism spectrum disorder, a developmental learning disorder, a developmental motor coordination disorder, attention deficit hyperactivity disorder, or stereotypic movement disorder.

[158] In some embodiments, a disclosed compound is used to treat schizophrenia or another primary psychotic disorder. In some embodiments, a subject has schizophrenia or another primary psychotic disorder. In some 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, and may include a diagnostic and/or assessment tool such as the Mini International Neuropsychiatric Interview,

Positive and Negative Syndrome Scale, Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Negative Symptoms, Brief Psychiatric Rating Scale, Clinical Global Impressions Scale, . Examples of a psychotic disorder, treatable using the disclosed compounds, include schizophrenia, schizoaffective disorder, schizophreniform disorder, schizotypal disorder, acute and transient psychotic disorder, delusional disorder, paraphrenia, postpartum psychosis, major depressive disorder with psychotic features, a substance-induced psychotic disorder, or a psychotic disorder due to another condition. In some embodiments, the schizophrenia is paranoid schizophrenia, disorganized (i.e., hebephrenic) schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, or residual schizophrenia.

[159] In some embodiments, a disclosed compound is used to treat a mood disorder. In some embodiments, a subject has a mood disorder. In some 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 the disclosed compounds, include depressive episodes, manic episodes, mixed episodes, and hypomanic episodes. In some 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 some embodiments, the mood disorder is a depressive disorder. In some embodiments, the depressive disorder is single-episode depressive disorder, major depressive episode disorder, persistent depressive disorder (formally known as 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 some 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).

[160] In some embodiments, a disclosed compound is used to treat an anxiety or fear-related disorder. In some embodiments, a subject has an anxiety or fear-related disorder. In some 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 the disclosed compounds, include generalized anxiety disorder, panic disorder, agoraphobia, specific phobia, social anxiety disorder, separation anxiety disorder, selective mutism, or a substance-induced anxiety disorder.

[161] In some embodiments, a disclosed compound is used to treat an obsessive-compulsive or related disorder. In some embodiments, a subject has an obsessive-compulsive or related disorder. In some

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 the disclosed compounds, 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.

[162] In some embodiments, a disclosed compound is used to treat a disorder associated with stress. In some embodiments, a subject has a disorder associated with stress. In some 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. Examples of a disorder associated with stress, treatable using the disclosed compounds, include post-traumatic stress disorder, complex post-traumatic stress disorder, prolonged grief disorder, adjustment disorder, reactive attachment disorder, or disinhibited social engagement disorder.

[163] In some embodiments, a disclosed compound is used to treat a dissociative disorder. In some embodiments, a subject has a dissociative disorder. In some 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 the disclosed compounds, 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.

[164] In some embodiments, a disclosed compound is used to treat a feeding or eating disorder. In some embodiments, a subject has a feeding or eating disorder. In some 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 the disclosed compounds, include anorexia nervosa (including anorexia with significantly low body weight, anorexia with dangerously low body weight, or anorexia in recovery with normal body weight), bulimia nervosa, binge eating disorder, avoidant-restrictive food intake disorder, pica, or rumination-regurgitation disorder.

[165] In some embodiments, a disclosed compound is used to treat a disorder due to substance use or addictive behaviors. In some embodiments, a subject has a disorder due to substance use or addictive behaviors. In some 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, and may include a diagnostic and/or assessment tool such as 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). In some embodiments, a disclosed compound is used to treat disorders due to substance use (i.e., a substance use disorder, or SUD). In some 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 disclosed compounds, 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 some embodiments, the substance use disorder is alcohol use disorder, wherein said alcohol use disorder is selected from alcohol abuse, alcohol dependence, and alcoholism.

[166] In some embodiments, a disclosed compound is used to treat an impulse control disorder. In some embodiments, a subject has an impulse control disorder. In some 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 some embodiments, impulse control behaviors include fire-setting, stealing, inappropriate sexual behavior, and explosive outbursts. Examples of an impulse control disorder, treatable using the disclosed compounds, include pyromania, kleptomania, compulsive sexual behavior disorder, or intermittent explosive disorder.

[167] In some embodiments, a disclosed compound is used to treat a disruptive behavior disorder or a dissocial disorder. In some embodiments, a subject has a disruptive behavior disorder or a dissocial disorder. In some 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 the disclosed compounds, 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).

[168] In some embodiments, a disclosed compound is used to treat a personality disorder. In some embodiments, a subject has a personality disorder. In some 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 some embodiments, a disclosed compound is used to treat a mild, moderate, or severe personality disorder. In some embodiments, a disclosed compound 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 the disclosed compounds, 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.

[169] In some embodiments, a disclosed compound is used to treat a neurocognitive disorder. In some embodiments, a subject has a neurocognitive disorder. In some 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 the disclosed compounds, include delirium, amnestic disorder, dementia, Alzheimer's disease, Parkinson's disease, cerebrovascular disease, or Lewy body disease. In some embodiments, a neurocognitive disorder, treatable using the disclosed compounds, is associated with a psychoactive substance (including medications and illicit or illegal substances). In some embodiments, a disclosed compound is used to treat delirium. In some embodiments, the delirium is associated with another disease or disorder. In some embodiments, the delirium is associated with a psychoactive substance (including medications and illicit or illegal substances). In some embodiments, a disclosed compound is used to treat dementia. In some 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 some embodiments, a disclosed compound is used to treat a behavioral or psychological disturbance associated with dementia. In some 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).

[170] In some embodiments, a disclosed compound is used to treat a sleep-wake disorder. In some embodiments, a subject has a sleep-wake disorder. In some 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 the disclosed compounds, include an insomnia disorder, a hypersomnolence disorder, a sleep-related breathing disorder, a circadian rhythm sleep-wake disorder, or a parasomnia disorder.

ii. Neurodegenerative Disorders

[171] In some embodiments, a disclosed compound or composition is used to treat a neurodegenerative disorder. In some embodiments, a disclosed compound or composition is administered, such as in a therapeutically effective amount, to a subject having a neurodegenerative disorder, thereby treating said neurodegenerative disorder. In some methods herein, a disclosed compound or composition, when

administered in a therapeutically effective amount, provides beneficial therapeutic effects for the treatment of a neurodegenerative disorder.

[172] 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 in Biology. 2017:9(7);a028035). The diagnosis of a neurodegenerative disorder and determining that a subject is at risk of a neurodegenerative disorder will be known to those in the art. Examples of a neurodegenerative disorder, treatable using the disclosed compounds, include Alzheimer's disease, amyotrophic lateral sclerosis or Charcot's disease, chronic traumatic encephalopathy, corticobasal degeneration, dementias including vascular dementia, Huntington's disease, Lytico-Bodig disease, cognitive impairment, multiple sclerosis, a motor neuron disease, neuromyelitis optica spectrum disorder, Parkinson's disease or parkinsonisms, prion diseases, progressive supranuclear palsy, and traumatic brain injury.

iii. Pain Disorders

[173] In some embodiments, a disclosed compound or composition is used to treat a pain disorder. In some embodiments, a disclosed compound or composition is administered, such as in a therapeutically effective amount, to a subject having a pain disorder, thereby treating said pain disorder. In some methods herein, a disclosed compound or composition, when administered in a therapeutically effective amount, provides beneficial therapeutic effects for the treatment of a pain disorder.

[174] 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. In some embodiments, a compound is used to treat neuropathic pain. In some embodiments, a compound is used to treat psychogenic pain. In some embodiments, a compound is used to treat idiopathic pain. In some embodiments, a compound is used to treat radicular pain.

[175] The diagnosis of a neurodegenerative disorder and determining that a subject is at risk of a neurodegenerative disorder will be known to those in the art. Examples of a neurodegenerative disorder, treatable using the disclosed compounds, include both acute or chronic pain. In some embodiments, a disclosed compound is used to treat pain associated with chemotherapy (e.g., chemotherapy associated neuropathy). In some embodiments, a disclosed compound is used to treat arthritis, back pain, central pain, chronic fatigue syndrome, cluster headaches, migraine headaches, phantom limb pain, complex regional pain syndrome, neuropathic pain, compression mononeuropathy, inflammatory pain, diabetic neuropathy, fibromyalgia, focal neuropathy, herniated disc pain, or sciatica.

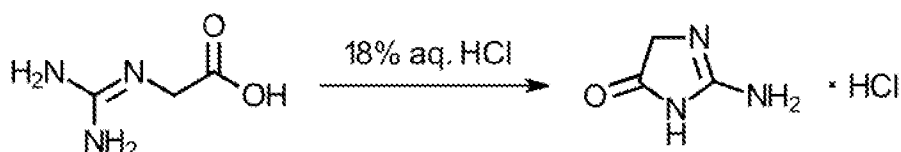
H. Examples

[176] The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

Example 1: Synthesis of Disclosed Compounds

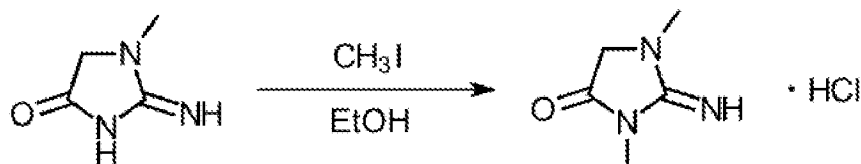
[364] Materials and General Procedures: All chemicals and solvents were analytical or reagent grade and purchased from either Sigma-Aldrich or Fisher Scientific and used as-received without further purification. All manipulations were performed under air in standard laboratory glassware. ^1H and ^{13}C NMR spectra were obtained using a JNM-ECZ400S (400 MHz for ^1H) or Magitrek SpinsolveTM benchtop NMR (43 MHz for ^1H) spectrometer. Chemical shifts are reported in ppm relative to residual nondeuterated solvent. High-resolution mass spectral analysis was performed using a Bruker Maxis 3G Ultra-High Resolution Time of Flight (UHR-TOF) tandem mass spectrometer, and ESI spectra were recorded on an AB Sciex Triple QuadTM 5500 instrument with a capillary voltage of 5.5 kV and an ESI mode positive ion trap detector. All MS data are reported in the form of m/z . High-performance liquid chromatography was conducted using an Agilent 1260 HPLC system with a HALO[®] C18 reverse phase column (2.1 x 50 mm, 2.7 μm); the column temperature was 40 $^\circ\text{C}$, flow rate 1 mL/min, injection volume 0.5 μL , solvent system gradient of 90:10 to 5:95 A:B (A: 0.05% trifluoroacetic acid in water; B: 0.05% trifluoroacetic acid in acetonitrile). All compounds were >95% pure by HPLC.

[365] *Glycocyamidine:*



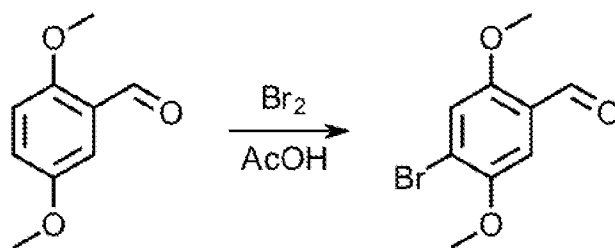
[366] Glycocyamidine (4.99 g, 42.6 mmol) was cyclized according to literature procedures to give glycocyamidine hydrochloride (3.62 g, 26.7 mmol, 63% yield). The spectral data agreed with those previously reported in the literature (Bengelsdorf, IS. J. Am. Chem. Soc. 1953;75(13):3138–3140).

[367] *2-Imino-1,3-dimethylimidazolidin-4-one:*



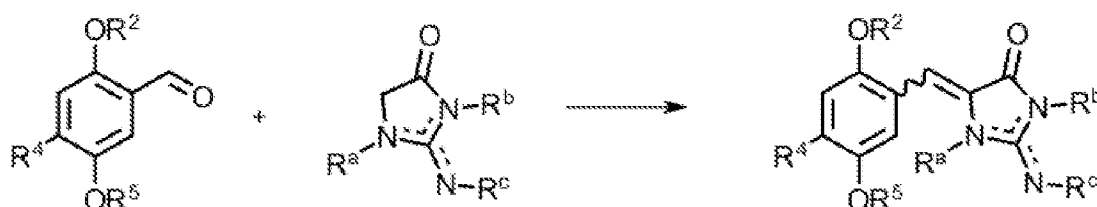
[368] Creatinine (1.28 g, 11.3 mmol) was methylated according to literature procedures to give 2-imino-1,3-dimethylimidazolidin-4-one hydrochloride (1.55 g, 6.1 mmol, 54% yield). The spectral data agreed with those previously reported in the literature (Kenyon GL & Rowley GL. J. Am. Chem. Soc. 1971;93(21):5552–5560; Nuthakki et al. Bioorg Chem. 2021;107:104568).

[369] *4-Bromo-2,5-dimethoxybenzaldehyde:*



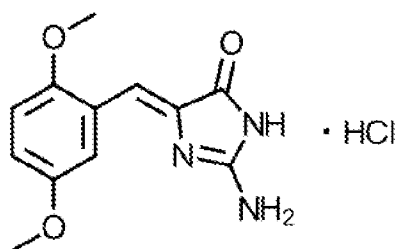
[370] 2,5-Dimethoxybenzaldehyde (1.12 g, 6.74 mmol) was brominated according to literature procedures to give 4-bromo-2,5-dimethoxybenzaldehyde (0.73 g, 2.97 mmol, 44% yield). The spectral data agreed with those previously reported in the literature (Hathaway et al. *Synth. Commun.* **1998**;28(24):4629–4637).

[371] *General synthetic procedure for disclosed compounds:*



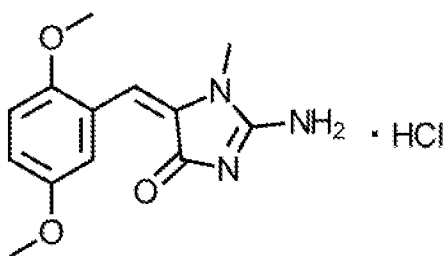
[372] The aryl aldehyde (1 equiv.), imidazozone (1.1 equiv.), and NH_4OAc (1.1 equiv) were dissolved in glacial acetic acid (5 mL per mmol aldehyde) in a 68 mL round-bottom pressure flask with a PTFE cap. Upon dissolution, the resulting solutions were generally clear and light yellow in color. The flask was sealed and placed into a 128 °C oil bath. As the reaction proceeded, the solution darkened to a clear, dark orange/brown color. After 12-20 h, the flask was removed from the oil bath and the reaction was allowed to cool to room temperature. Deionized water (10 mL per mmol aldehyde) was added, and the mixture was slowly basified to pH > 8 with saturated aqueous NaHCO_3 , resulting in the formation of a precipitate. The precipitate was collected by vacuum filtration, washed with excess ice-cold deionized water, and dried with suction to give the crude freebase product, which was typically a fluffy yellow-to-orange solid. The solid was dissolved or suspended in MeOH (5 mL per mmol crude product) and 1.25-1.5 equiv. of HCl was added as a 0.82 M solution of HCl in MeOH. The resulting solution was stirred for 30 min at room temperature. Solvents and volatiles (e.g., excess HCl) were removed by rotary evaporation to yield the crude product as the hydrochloride salt, which was purified by trituration with excess CH_2Cl_2 or recrystallization from boiling EtOH/DMF (7:3). Structural characterization of the APMIs was conducted by NMR spectroscopy and UHR-TOF high-resolution mass spectrometry (HRMS). Unfortunately, the solubility of the APMIs in common solvents (e.g., H_2O , MeOH, EtOH, iPrOH, acetone, DMSO, THF, EtOAc, CH_2Cl_2 , CHCl_3 , and mixtures thereof) was too low to obtain ^{13}C NMR spectra of certain compounds.

[373] (Z)-2-amino-4-[(2,5-dimethoxyphenyl)methylene]-2-imidazolin-5-one (**2a**):



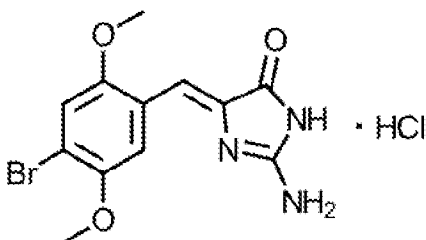
[374] Yield: 85%, pale yellow solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.19 (s, 2H), 7.20 (s, 1H), 7.04 (m, 3H), 6.86 (s, 1H), 3.83 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (15 MHz, $\text{DMSO-}d_6$): δ 174.4, 163.4, 153.3, 151.7, 138.9, 125.0, 116.0, 113.8, 112.0, 103.5, 56.3, 55.7. HRMS (ESI-TOF): m/z calculated for $\text{C}_{12}\text{H}_{14}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 248.1035; found 248.1033.

[375] (E)-2-amino-5-[(2,5-dimethoxyphenyl)methylene]-1-methyl-2-imidazolin-4-one (**2b**):



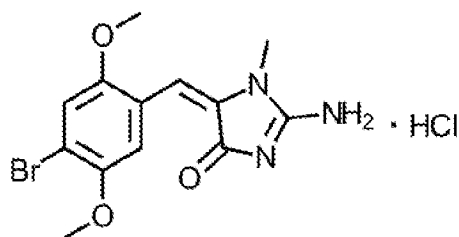
[376] Yield: 60%, orange solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 7.80 (br s, 2H), 6.91 (m, 2H), 6.83 (dd, 1H, $J = 9$ Hz, 3 Hz), 3.77 (s, 3H), 3.70 (s, 3H), 3.15 (s, 3H). HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_3\text{Br}$ $[\text{M}+\text{H}]^+$ 340.0291; found 340.02923.

[377] (Z)-2-amino-4-[(4-bromo-2,5-dimethoxyphenyl)methylene]-2-imidazolin-5-one (**2c**):



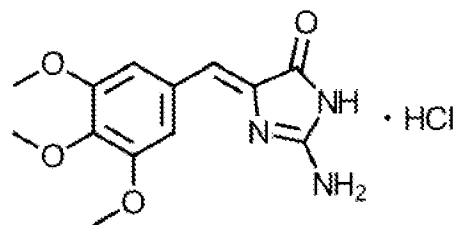
[378] Yield: 71%, yellow solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.44 (br s, 1H), 7.36 (s, 1H), 7.27 (s, 1H), 6.80 (s, 1H), 3.94 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (15 MHz, $\text{DMSO-}d_6$): δ 172.7, 161.1, 151.7, 149.5, 140.6, 124.7, 115.7, 114.5, 110.0, 102.8, 56.8, 56.4. HRMS (ESI-TOF): m/z calculated for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_3\text{Br}$ $[\text{M}+\text{H}]^+$ 326.0135; found 326.0137.

[379] (E)-2-amino-5-[(4-bromo-2,5-dimethoxyphenyl)methylene]-1-methyl-2-imidazolin-4-one (**2d**):



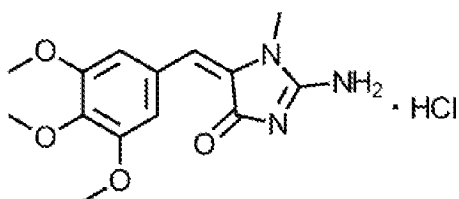
[380] Yield: 45%, orange solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.59 (br s, 2H), 7.94 (s, 1H), 7.32 (s, 1H), 6.80 (s, 1H), 3.83 (s, 3H), 3.78 (s, 3H). HRMS (ESI-TOF): m/z calculated for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_3\text{Br}$ $[\text{M}+\text{H}]^+$ 326.0135; found 326.0137.

[381] (Z)-2-amino-4-[(3,4,5-trimethoxyphenyl)methylene]-2-imidazolin-5-one (**3a**):



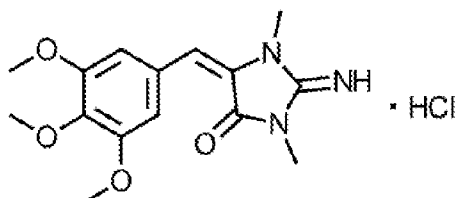
[382] Yield: 49%, yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.48 (s, 2H), 7.23 (s, 1H), 4.44 (s, 6H), 4.23 (s, 3H). ^{13}C NMR (15 MHz, $\text{DMSO}-d_6$): δ 173.1, 162.9, 152.2, 139.1, 136.7, 130.4, 109.4, 106.6, 59.49, 55.31. HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{16}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$ 278.1141; found 278.1137.

[383] (E)-2-amino-1-methyl-5-[(3,4,5-trimethoxyphenyl)methylene]-2-imidazolin-4-one (**3b**):



[384] Yield: 68%, orange solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.11 (s, 2H), 7.41 (s, 1H), 4.30 (s, 6H), 4.23 (s, 3H), 4.00 (s, 3H). HRMS (ESI-TOF): m/z calculated for $\text{C}_{14}\text{H}_{18}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$ 292.1292; found 292.1292.

[385] (E)-2-imino-1,3-dimethyl-5-[(3,4,5-trimethoxyphenyl)methylene]imidazolidin-4-one (**3c**):



[386] Yield: 83%, yellow solid. ^1H NMR (43 MHz, D_2O): δ 7.43 (s, 2H), 6.82 (s, 1H), 3.91 (s, 6H), 3.86 (s, 3H), 3.38 (s, 3H), 3.27 (s, 3H). HRMS (ESI-TOF): m/z calculated for $\text{C}_{15}\text{H}_{20}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$ 306.1448; found 306.1445.

[387] The final compounds were isolated from the reaction mixtures as freebases and converted to the

corresponding hydrochloride salts for storage and biological testing. Both the freebase and hydrochloride forms are non-hygroscopic solids that have bright yellow/orange colors similar to the characteristic colors of β -nitrostyrene intermediates used in the synthesis of psychedelic phenethylamines. *E/Z* geometries were tentatively assigned based on NOESY experiments and by correlation with established trends for the geometries of aplysinopsins (see Example 2).

Example 2: *E/Z* Geometries

[388] In principle, disclosed can also exist in two geometrically isomeric forms (*E* and *Z*) based on the stereochemistry of the double bond linking the aryl and imidazolone moieties. In aplysinopsin-type compounds, the presence or absence of an N2' substituent is the dominant factor that determines the stereochemical outcomes of the reaction of the aryl aldehyde with the imidazolone (Bialonska et al. Mar. Drugs 2009;7(2):166–183). For example, Guella and coworkers' crystallographic and NMR studies concluded that in N2'-methylated aplysinopsins, significant steric repulsion between the N2' methyl and the indole core in the rate-limiting transition state of condensation/elimination leads to the selective formation of the *E* isomer (*E:Z* ratio > 95:5) (Guella et al. Helv. Chim. Acta 1988;71(4):773–782). Similarly, in aplysinopsins lacking a N2' methyl (i.e., in which N2' is unsubstituted), steric repulsions between the imidazolone C=O and the indole core lead to the selective formation of the *Z* isomer (*Z:E* ratio > 95:5) (*id.*).

[389] It was hypothesized that the compounds herein would follow a similar trend, given that for each compound, the available spectroscopic and chromatographic data only indicated the presence of a single isomer. Trends in *E/Z* geometry were investigated and tentatively assigned by 2D Nuclear Overhauser Effect Spectroscopy (NOESY). NOESY spectra of **2d** in DMSO-*d*₆ showed an NOE correlation between the methylidene proton and the N2' methyl, suggesting that **2d** compound has *E* geometry. As expected, the NOESY spectra for compounds that are unsubstituted at N2' (e.g., **2c**) do not show any NOE correlations between the methylidene proton and any other peaks. For example, the NOESY spectra of **2c** in DMSO-*d*₆ show no NOE correlations between the methylidene proton and any other signals. Therefore, NOESY could not be used for assigning the geometry of these compounds.

[390] Based on the results of the NOESY experiments for the N2'-methylated compounds, and the agreement of these results with the reported trends of *E/Z* geometry in aplysinopsin-type compounds, the geometries of the compounds were assigned as follows: (*E*)-**2a**, (*Z*)-**2b**, (*E*)-**2c**, (*Z*)-**2d**, (*E*)-**3a**, (*Z*)-**3b**, (*Z*)-**3c**.

Example 3: *In Vitro* Radioligand Binding Affinity Assays

[364] Disclosed compounds were evaluated in a [³H]ketanserin competitive binding assay with cloned 5-HT_{2A} receptors stably expressed in HEK293 cells. The compounds were evaluated at concentrations from 0.4 nM to 10 μ M in duplicate, and dose-response curves were constructed to determine their binding constants (*K_i*).

[365] Methods: Using a multi-channel pipette, 1 μ L of serial diluted reference compound (ketanserin)

and test compounds were transferred to assay plates. Then 1 μL of the nonspecific binding compounds was transferred to the assay plate, according to the plate map, for nonspecific binding. Next, 100 μL of membrane stocks were distributed into the plate. To this, 100 μL of [^3H]ketanserin was added. The plates were sealed and shaken at 300 rpm. The Unifilter-96 GF/C filter plates were soaked with 50 μL of 0.3% PEI per well for at least 0.5 h at room temperature. When the binding assays completed, the reaction mixture was filtered through GF/B plates using Perkin Elmer Filtermate Harvester, and then each plate was washed 4 times with 250 μL cold wash buffer. The filter plates were dried for 1 h at 50 $^{\circ}\text{C}$. After drying, the bottom of the filter plate wells was sealed using Perkin Elmer Unifilter-96 backing seal tape. 50 μL of Perkin Elmer Microscint 20 cocktail was added. The top of filter plates was sealed with Perkin Elmer TopSeal-A sealing film. ^3H trapped on the filter was counted using a Perkin Elmer MicroBeta2 Reader. Data were analyzed with GraphPad Prism 5.0 (GraphPad software).

[366] **Results:** **2c** had the highest affinity for the 5-HT_{2A} receptor ($K_i = 19 \text{ nM}$), followed by **2a** ($K_i = 233 \text{ nM}$) (Table 3). **2b** displayed weak affinity ($K_i > 10 \text{ }\mu\text{M}$), and compounds based on the 3,4,5-trimethoxyphenyl core (**3a**, **3b**, and **3c**) had no measurable affinity at the maximum tested concentration of 10 μM . Notably, the binding affinity of **2c** is higher than any reported aplysinopsin.

Table 3. Radioligand binding assay results for control and test compounds

Compound	IC ₅₀ (nM)	K _i (nM)	Max Dose (nM)	%Inh @ MaxDose
Ketanserin (control)	1.65	0.64	100	99.23
2a	601.7	233.33	10000	94.94
2b	> 10000	> 3877.8	10000	31.66
2c	48.03	18.63	10000	97.12
2d	> 10000	> 3877.8	10000	19.13
3a	> 10000	> 3877.8	10000	6.61
3b	> 10000	> 3877.8	10000	-6.54
3c	> 10000	> 3877.8	10000	-0.35

Example 4: *In Vitro* IP-One Assays

[367] Having established that certain disclosed compounds exhibit significant 5-HT_{2A} receptor-binding affinity, their effects on receptor signaling were investigated. The canonical 5-HT_{2A} receptor signaling pathway involves activation of G_{αq} proteins that subsequently activate phospholipase C (PLC) (Nichols DE. Pharmacol. Ther. 2004;101(2):131–181). The hydrolysis of phosphatidylinositol membrane lipids by PLC triggers a metabolic signaling cascade that ultimately results in the generation of inositol-1,4,5-triphosphate (IP3), inositol diphosphate (IP2), and inositol monophosphate (IP1) (Kadamur et al. Annu. Rev. Physiol. 2013;75:127–154). Many studies use *in vitro* assays that focus on this pathway to characterize the agonist activity of compounds that target the 5-HT_{2A} receptor (Pottie E & Stove CP. J. Neurochem.

2022;162(1):39–59). The functional effects of **2a** and **2c** on 5-HT_{2A} G_{αq} signaling were therefore investigated using the homogeneous time-resolved fluorescence-based IP-One immunoassay (Cisbio Bioassays, Codolet, France), which quantifies IP1 accumulation resulting from administration of a test compound (*id.*).

[368] **Methods:** Cells were plated onto 384-well plates (7,500 cells per well) and treated with varying doses of test compounds or reference compounds (serotonin for the agonist assays; methiothepin mesylate salt for the antagonist assays).

[369] The standard curve was prepared according to the manufacturer's instructions, starting at 7,700 nM IP1 in stimulation buffer and diluted 4-fold to create 9 points in duplicate. Each point of the standard curve was added to an empty assay plate in a volume of 14 μL. 14 μL of stimulation buffer was added as a negative control.

[370] The plates were incubated for 1 h at 37 °C, lysed by addition of the supplied buffer containing d2-labeled IP1, followed by addition of terbium cryptate-labeled anti-IP1 antibody, according to the manufacturer's instructions. Plates were incubated for 1 h at room temperature and fluorescence signals were measured at 615 and 665 nm using an EnVision® Multimode Plate Reader (PerkinElmer). Data were analyzed with GraphPad Prism 5.0 (GraphPad software).

[371] **Results:** Surprisingly, there was no response for either **2c** or **2a** as agonists at concentrations assayed (from 0.4 nM to 10 μM) (**Table 4**). Rather, in antagonist mode, **2a** and **2c** blocked 5-HT-stimulated IP1 production in a concentration-dependent manner (**FIG. 1**), with potencies (IC₅₀) shown in **Table 5**.

Table 4. IP-One (Agonist) assay results for control and test compounds

Compound	EC ₅₀ (nM)	Max Dose (nM)	%Activity @ MaxDose
<i>Serotonin (control)</i>	7.904	5000	100.73
2a	>10,000	10000	-1.28
2c	>10,000	10000	3.06

Table 5. IP-One (Antagonist) assay results for control and test compounds

Compound	IC ₅₀ (nM)	Max Dose (nM)	%Inh @ MaxDose
<i>Methiothepin (control)</i>	2.439	3000	100.03
2a	887.4	10000	93.24
2c	57.66	10000	100.21

Example 5: Kinetic Solubility Assays

[372] **Methods (Solution Preparation):** Stock solutions of test compounds were prepared by dissolving each test compound in DMSO (10 mM). Standard solutions were prepared by first diluting the 10 mM stock

solutions prepared as described above to a final concentration of 300 μM in DMSO. 10 μL aliquots of each of the diluted stock solutions were transferred into vials, then mixed with 980 μL of methanol and 10 μL of pH 7.4 PBS buffer solution to obtain standard solutions with a final concentration of 3 μM .

[373] Methods (Assay Procedure): A stock solution of the positive control compound (progesterone) was prepared in DMSO (30 mM). Duplicate 30 μL aliquots of each stock solution were transferred into vials, then 970 μL of pH 7.4 PBS buffer solution was added to each vial. A stir stick was added to each vial and then the vials were sealed using a molded PTDE/SIL 96-Well Plate Cover. The plate was moved to a Thermomixer plate shaker and incubated at room temperature for 2 hours with shaking at 1100 rpm. After 2 hours of incubation, the stir sticks were removed using a magnet and all samples were vacuum filtered to remove any insoluble compound. 10 μL aliquots of each of the filtered samples were diluted with 980 μL of methanol and 10 μL of DMSO.

[374] Data Analysis: The filtered solutions were analyzed and quantified against the standard solutions using liquid chromatography-tandem mass spectrometry (LC-MS/MS) operating in multiple reaction monitoring (MRM) mode using a Shimadzu LC-30AD system coupled to a AB Sciex Triple Quad™ 5500 instrument with a capillary voltage of 5.5 kV and an ESI mode positive ion trap detector. The column was an XSelect Hss T3 2.5 μM (2.1 $\times$ 30 mm) XP column coupled with a preguard column. The chromatography conditions and MS parameters were:

[375] Mobile phase: 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B) (gradient from 5% B at 0 min, 100% B at 0.5 min, 100% B at 0.8 min, 5% B at 0.81 min, 5% B at 1.0 min). Injection volume: 20 μL . Flow rate: 1.00 mL/min. Column temperature: 40 $^{\circ}\text{C}$

[376] MS parameters. Ion source: Turbo spray. Ionization model: ESI. Scan type: MRM. Collision gas: 6 L/min. Curtain gas: 30 L/min. Nebulize gas: 50 L/min. Auxiliary gas: 50 L/min. Temperature: 500 $^{\circ}\text{C}$. Ionspray voltage: +5500 V (positive MRM)

[377] Results: Kinetic solubility assays confirmed that all of the APMIs were soluble above the maximum concentrations of the *in vitro* assays (10 μM), with kinetic solubilities ranging from ca. 20 μM to >300 μM at pH 7.4 (Table 6).

Table 6. Kinetic solubility values for control and test compounds

Compound	Solubility (μM) in pH 7.4 PBS
<i>Progesterone (control)</i>	18.58
2a	>300*
2b	>300*
2c	20.17
2d	56.03
3a	290.89
3b	>300*

3c	>300*
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*The upper limit of the assay was 300 μ M.

Example 6: *In Vitro* PAMPA-BBB Permeability Assays

[378] Disclosed compounds were also tested in a parallel artificial membrane permeability assay (PAMPA) to assess their permeabilities across the blood–brain barrier (BBB). The PAMPA assay is a high-throughput screening technique that simulates the passive diffusion of compounds across the blood-brain barrier to provide early-stage predictive data on the ability of a compound to reach the CNS through passive diffusion alone (Di, L.; Kerns, E. H.; Fan, K.; McConnell, O. J.; Carter, G. T. High Throughput Artificial Membrane Permeability Assay for Blood–Brain Barrier. *Eur. J. Med. Chem.* **2003**, 38 (3), 223–232).

[379] Methods (Solution Preparation): Stock solutions of controls (testosterone and methotrexate) and test compounds were prepared by dissolving the compounds in DMSO at a concentration of 10 mM, then diluting with pH 7.4 PBS buffer solution to a final concentration of 10 μ M.

[380] Methods (Assay Procedure): A 2% (w/v) solution of Porcine brain polar lipid extract was prepared in dodecane solvent, with sonication to ensure complete dissolution. 5 μ L of this solution was pipetted into the top compartment of each acceptor plate well. Immediately after application of the artificial membrane (i.e., within 10 min), 300 μ L of pH 7.4 PBS solution was added to each well of the acceptor plate. Then, 300 μ L of the test compound solutions was added to the bottom compartment of each well of the donor plate. The assay was conducted in triplicate. The acceptor plate was placed into the donor plate, ensuring good contact between the underside of the membrane and the test compound solutions in all wells. The plate lid was installed and the plate was incubated at 25 °C for 16 h. After incubation, 50 μ L aliquots from each well of the acceptor and donor plates were transferred into a 96-well plate. 200 μ L of methanol (containing 100 nM alprazolam, 200 nM caffeine, and 200 nM diclofenac as internal standards) was added into each well. The plate lid was reinstalled and the plate was vortexed at 750 rpm for 100 s. Each sample was then centrifuged at 3,220 g for 20 min.

[381] Results: The concentrations of compounds were determined by LC-MS/MS as described above. The effective permeabilities (P_e ; cm/s) were calculated. Results showed that although **2a** is predicted to have low BBB permeability ($P_e = 1.10 \times 10^{-6}$ cm s⁻¹), **2c** exhibited excellent permeability ($P_e = 6.03 \times 10^{-6}$ cm s⁻¹) (Table 7).

Table 7. Permeability results for controls and test compounds

Compound	P_e (cm s ⁻¹)	-Log P_e	Recovery (%)
Methotrexate (control)	2.19×10^{-9}	>8.66	>98.26
Testosterone (control)	2.57×10^{-5}	4.59	75.18

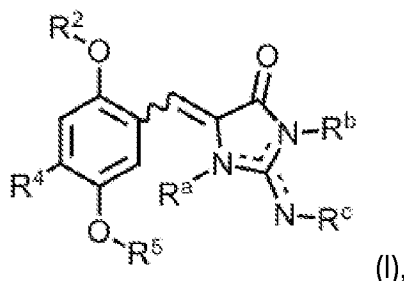
2a	1.10×10^{-6}	5.96	96.47
2b	2.29×10^{-6}	5.64	104.82
2c	6.03×10^{-6}	5.22	70.24
2d	9.33×10^{-6}	5.03	97.60
3a	1.86×10^{-7}	6.73	100.28
3b	5.62×10^{-7}	6.25	100.81
3c	3.09×10^{-5}	4.51	89.37

[382] 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 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 compositions, formulations, methods, or the like disclosed; many modifications and variations are possible in view of the above teachings. The embodiments were chosen and described in order to best explain the 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 utilize the invention and various embodiments with various modifications as are suited to the particular use contemplated, 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 compound of Formula (I),



or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, wherein:

R^a, R^b, and R^c are each independently H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

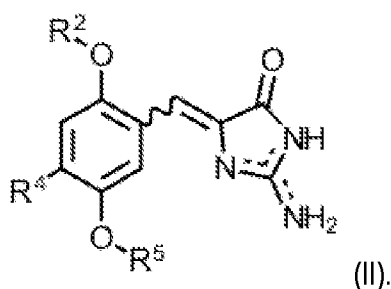
R² and R⁵ are each independently H or C₁-C₆ alkyl;

R⁴ is halogen or H; and

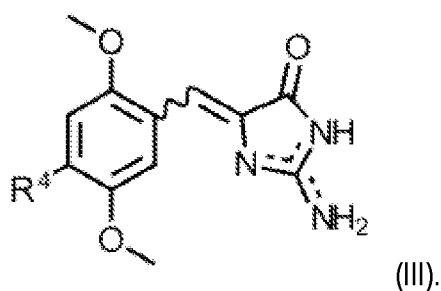
is a single or double bond.

2. The compound of claim 1, wherein R^a is H.
3. The compound of claim 1, wherein R^a is C₁-C₆ alkyl.
4. The compound of claim 3, wherein R^a is methyl.
5. The compound of claim 1, wherein R^b is H.
6. The compound of claim 1, wherein R^b is C₁-C₆ alkyl.
7. The compound of claim 6, wherein R^b is methyl.
8. The compound of claim 6, wherein R^b is ethyl.
9. The compound of claim 1, wherein R^b is C₁-C₆ haloalkyl.
10. The compound of claim 1, wherein R^c is H.
11. The compound of claim 1, wherein R^c is C₁-C₆ alkyl.
12. The compound of claim 6, wherein R^c is methyl.
13. The compound of claim 1, wherein R² is C₁-C₆ alkyl.
14. The compound of claim 13, wherein R² is methyl.
15. The compound of claim 1, wherein R⁵ is C₁-C₆ alkyl.
16. The compound of claim 15, wherein R⁵ is methyl.
17. The compound of claim 1, wherein R⁴ is halo.
18. The compound of claim 17, wherein R⁴ is bromo.
19. The compound of claim 17, wherein R⁴ is chloro.
20. The compound of claim 17, wherein R⁴ is iodo.
21. The compound of claim 1, wherein R⁴ is H.

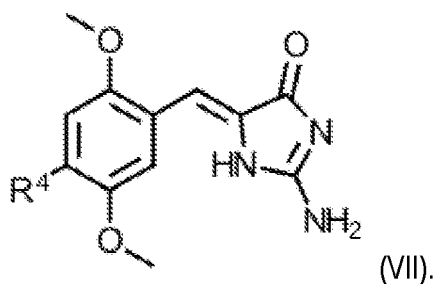
22. The compound of claim 1, having the structure of Formula (II),



23. The compound of claim 22, wherein R² is C₁-C₆ alkyl.
 24. The compound of claim 23, wherein R² is methyl.
 25. The compound of claim 22, wherein R⁵ is C₁-C₆ alkyl.
 26. The compound of claim 25, wherein R⁵ is methyl.
 27. The compound of claim 22, wherein R⁴ is halo.
 28. The compound of claim 27, wherein R⁴ is bromo.
 29. The compound of claim 27, wherein R⁴ is chloro.
 30. The compound of claim 27, wherein R⁴ is iodo.
 31. The compound of claim 27, wherein R⁴ is H.
 32. The compound of claim 1, having the structure of Formula (III),

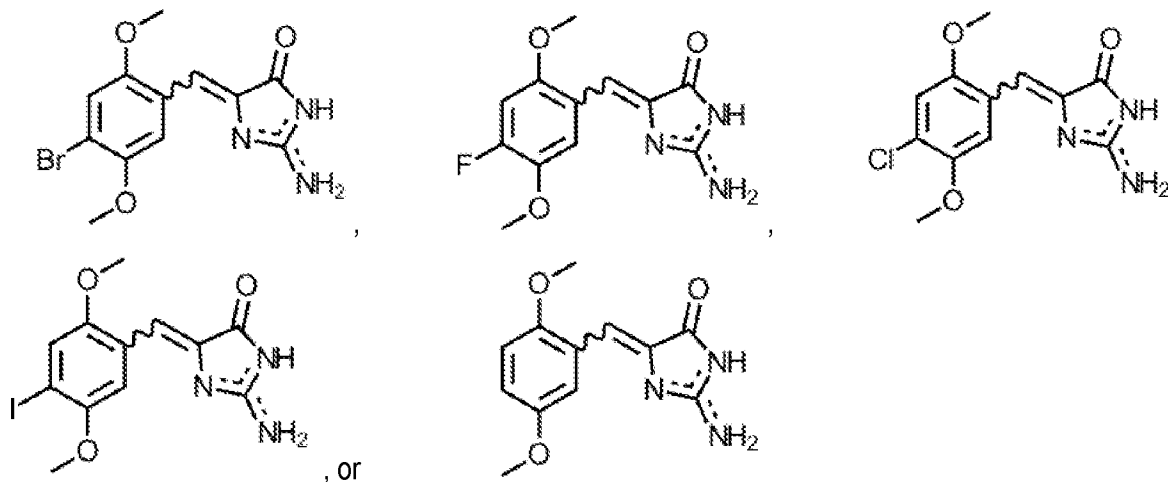


33. The compound of claim 32, wherein R⁴ is halo.
 34. The compound of claim 33, wherein R⁴ is bromo.
 35. The compound of claim 33, wherein R⁴ is chloro.
 36. The compound of claim 33, wherein R⁴ is iodo.
 37. The compound of claim 32, wherein R⁴ is H.
 38. The compound of claim 1, having the structure of Formula (VII),

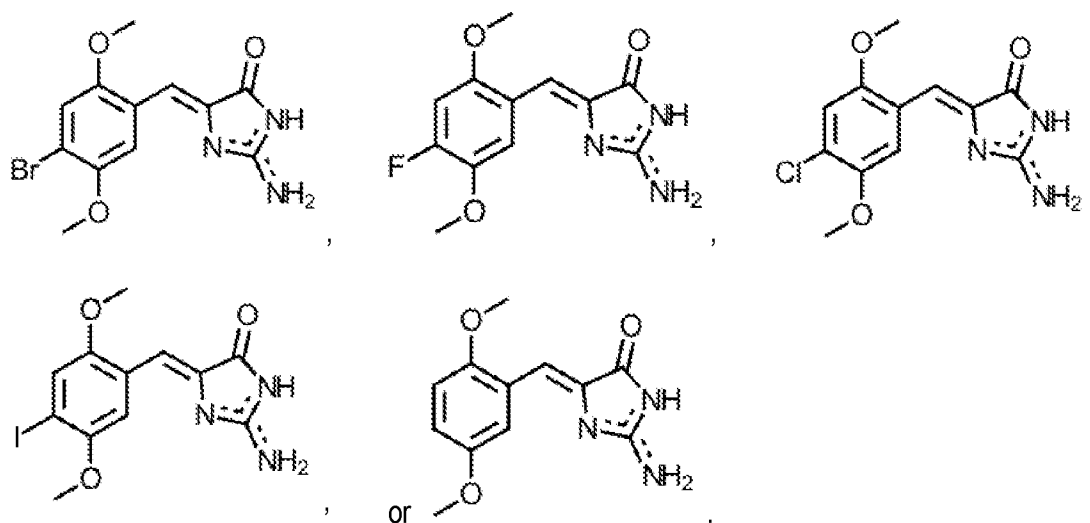


39. The compound of claim 38, wherein R⁴ is halo.

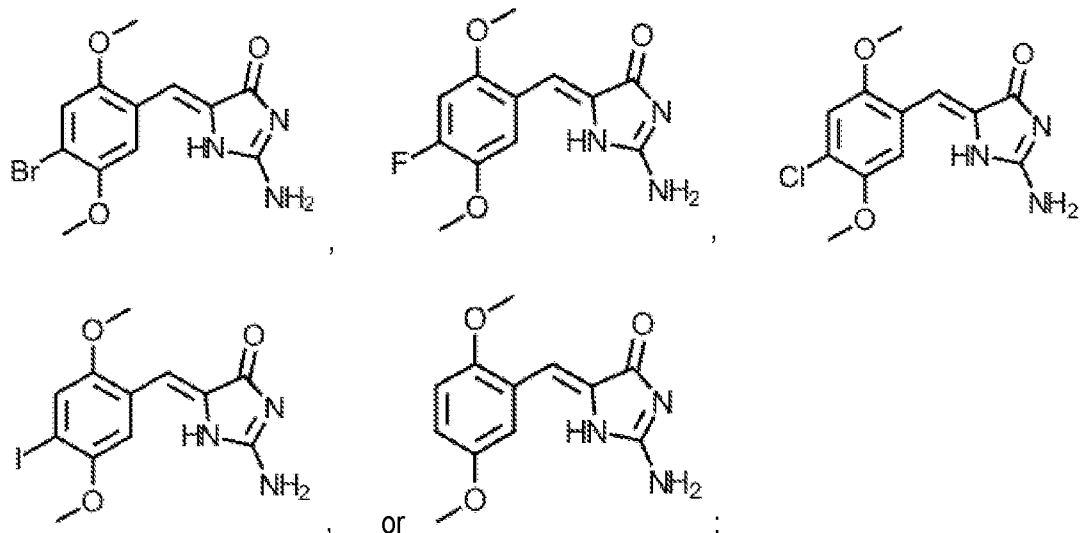
40. The compound of claim 39, wherein R⁴ is bromo.
41. The compound of claim 39, wherein R⁴ is chloro.
42. The compound of claim 39, wherein R⁴ is iodo.
43. The compound of claim 38, wherein R⁴ is H.
44. A compound selected from **Table 1**, **Table 2**, or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof.
45. The compound of claim 44, having the structure of:



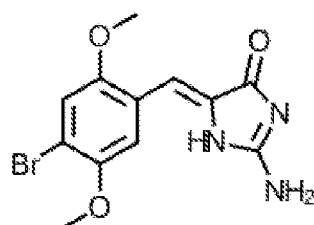
46. The compound of claim 45, having *E* geometry.
47. The compound of claim 46, having the structure of:

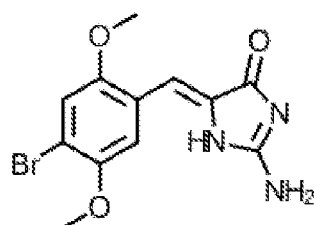


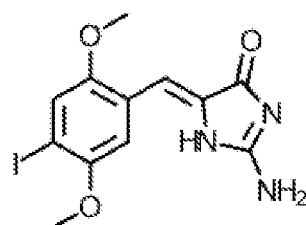
48. A compound having the structure of:

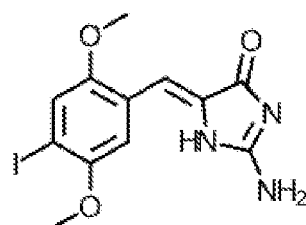


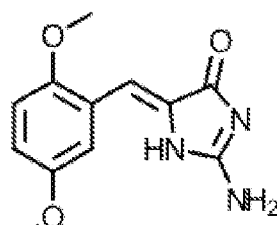
or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof.

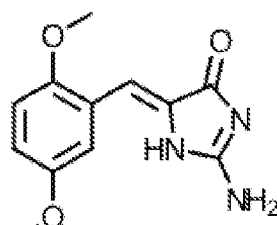


49. A compound having the structure of , or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof.



50. A compound having the structure of , or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof.



51. A compound having the structure of , or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof.
52. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1, or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.
53. A method of modulating neurotransmission in a subject, comprising administering to the subject

the compound of claim 1, or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, or the pharmaceutical composition of claim 52.

54. The method of claim 53, wherein modulating neurotransmission comprises antagonizing the 5-HT_{2A} receptor.
55. A compound of claim 1, or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, or the pharmaceutical composition of claim 52, for use in the treatment of a medical condition.
56. Use of the compound of claim 1, or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, or the pharmaceutical composition of claim 52, for the manufacture of a medicament for the treatment of a medical condition.
57. 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 compound of claim 1, or a pharmaceutically acceptable salt, tautomer, isotopic derivative, hydrate, or solvate thereof, or the pharmaceutical composition of claim 52.
58. The method of claim 57, wherein the medical condition is a disorder linked to dysregulation or inadequate functioning of serotonergic neurotransmission.
59. The method of claim 57, wherein the medical condition is a mental, behavioral, or neurodevelopmental disorder.
60. The method of claim 57, wherein the medical condition is a neurodegenerative disorder, a pain disorder, or a movement disorder.
61. The method of claim 57, wherein the medical condition is schizophrenia or a primary psychotic disorder.
62. The method of claim 57, wherein the medical condition is schizophrenia, schizoaffective disorder, schizophreniform disorder, schizotypal disorder, acute and transient psychotic disorder, delusional disorder, paraphrenia, postpartum psychosis, major depressive disorder with psychotic features, a substance-induced psychotic disorder, or a psychotic disorder due to another condition.

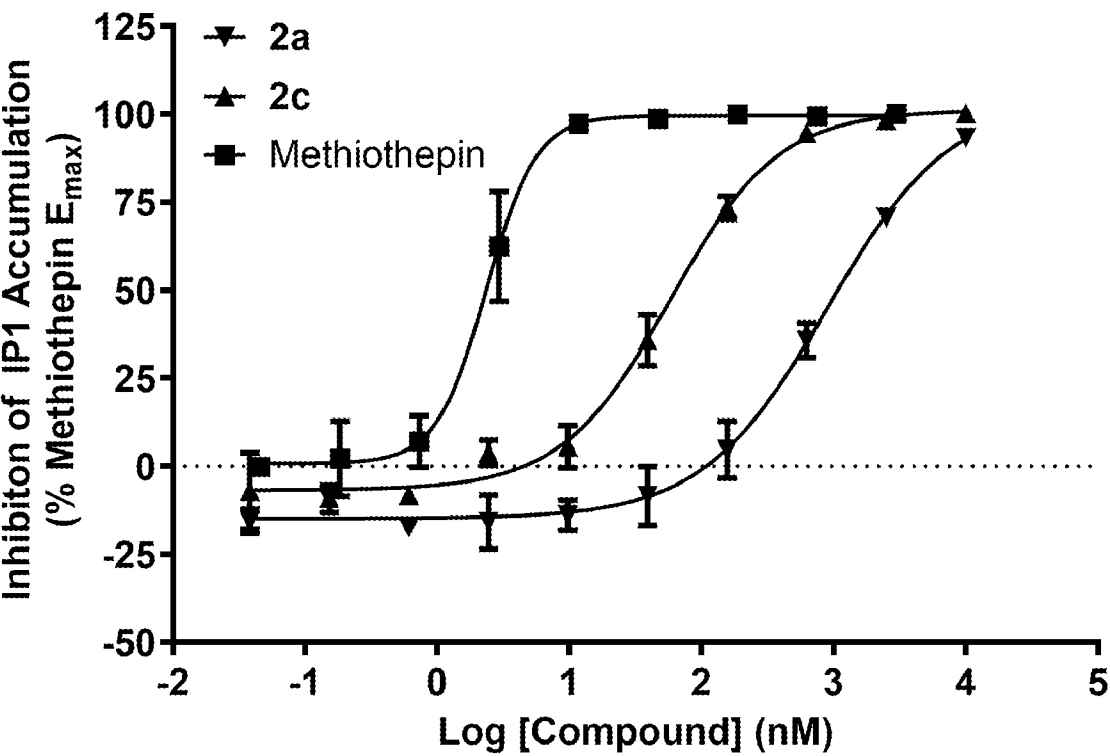


FIG. 1