

SPIRO-LACTAM NMDA RECEPTOR MODULATORS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to and the benefit of U.S. Provisional Patent Application No. 62/718,067, filed on August 13, 2018, and U.S. Provisional Patent Application
5 No. 62/624,218, filed on January 31, 2018; the contents of each of which are hereby incorporated by reference herein in their entirety.

BACKGROUND

An N-methyl-d-aspartate (“NMDA”) receptor is a postsynaptic, ionotropic receptor that is responsive to, *inter alia*, the excitatory amino acids glutamate and glycine and the synthetic compound NMDA. The NMDA receptor controls the flow of both divalent and monovalent
10 ions into the postsynaptic neural cell through a receptor associated channel (Foster *et al.*, Nature 1987, 329:395-396; Mayer *et al.*, Trends in Pharmacol. Sci. 1990, 11:254-260). The NMDA receptor has been implicated during development in specifying neuronal architecture and synaptic connectivity, and may be involved in experience-dependent synaptic modifications. In addition, NMDA receptors are also thought to be involved in long term
15 potentiation and central nervous system disorders.

The NMDA receptor plays a major role in the synaptic plasticity that underlies many higher cognitive functions, such as memory acquisition, retention and learning, as well as in certain cognitive pathways and in the perception of pain (Collingridge *et al.*, The NMDA Receptor, Oxford University Press, 1994). In addition, certain properties of NMDA receptors
20 suggest that they may be involved in the information-processing in the brain that underlies consciousness itself.

The NMDA receptor has drawn particular interest since it appears to be involved in a broad spectrum of CNS disorders. For instance, during brain ischemia caused by stroke or traumatic injury, excessive amounts of the excitatory amino acid glutamate are released from
25 damaged or oxygen deprived neurons. This excess glutamate binds to the NMDA receptors which opens their ligand-gated ion channels; in turn the calcium influx produces a high level of intracellular calcium which activates a biochemical cascade resulting in protein degradation and cell death. This phenomenon, known as excitotoxicity, is also thought to be responsible for the neurological damage associated with other disorders ranging from hypoglycemia and

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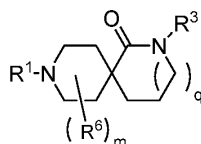
cardiac arrest to epilepsy. In addition, there are preliminary reports indicating similar involvement in the chronic neurodegeneration of Huntington's, Parkinson's and Parkinson's related conditions such as dyskinesia and L-dopa induced dyskinesia and Alzheimer's diseases. Activation of the NMDA receptor has been shown to be responsible for post-stroke
5 convulsions, and, in certain models of epilepsy, activation of the NMDA receptor has been shown to be necessary for the generation of seizures. Neuropsychiatric involvement of the NMDA receptor has also been recognized since blockage of the NMDA receptor Ca^{++} channel by the animal anesthetic PCP (phencyclidine) produces a psychotic state in humans similar to schizophrenia (reviewed in Johnson, K. and Jones, S., 1990). Further, NMDA receptors have
10 also been implicated in certain types of spatial learning.

The NMDA receptor is believed to consist of several protein chains embedded in the postsynaptic membrane. The first two types of subunits discovered so far form a large extracellular region, which probably contains most of the allosteric binding sites, several transmembrane regions looped and folded so as to form a pore or channel, which is permeable
15 to Ca^{++} , and a carboxyl terminal region. The opening and closing of the channel is regulated by the binding of various ligands to domains (allosteric sites) of the protein residing on the extracellular surface. The binding of the ligands is thought to affect a conformational change in the overall structure of the protein which is ultimately reflected in the channel opening, partially opening, partially closing, or closing.

20 A need continues to exist in the art for novel and more specific and/or potent compounds that are capable of modulating NMDA receptors, and provide pharmaceutical benefits. In addition, a need continues to exist in the medical arts for orally deliverable forms of such compounds.

SUMMARY

The present disclosure includes compounds that can be NMDA modulators. More
25 specifically, the present disclosure provides a compound represented by:



or a pharmaceutically acceptable salt and/or stereoisomer thereof, wherein

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R^1 is independently selected from the group consisting of H, $-C_1-C_6$ alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-O-C_1-C_6$ alkyl, and $-S(O)_w-C_1-C_6$ alkyl, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P ;

q is 0, 1, 2, or 3;

5 w is 0, 1 or 2;

R^6 , if present, is independently, for each occurrence, selected from the group consisting of H, $-C_1-C_6$ alkyl, hydroxyl, and halogen, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P ;

m is 0, 1, 2, 3, or 4;

10 R^3 is selected from the group consisting of H, $-C_1-C_6$ alkyl, $-C(O)-R^{31}$, and $-C(O)-O-R^{32}$, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P ;

R^{31} is selected from the group consisting of H, $-C_1-C_6$ alkyl, and $-C_3-C_6$ cycloalkyl, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P , and C_3-C_6 cycloalkyl is optionally substituted by one, two or three substituents each independently selected from R^Q ;

15 R^{32} is selected from the group consisting of $-C_1-C_6$ alkyl, and $-C_3-C_6$ cycloalkyl, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P , and C_3-C_6 cycloalkyl is optionally substituted by one, two or three substituents each independently selected from R^Q ;

R^P is independently, for each occurrence, selected from the group consisting of $-C(O)NR^aR^b$, $-NR^aR^b$, hydroxyl, $-SH$, and halogen;

R^Q is independently, for each occurrence, selected from the group consisting of $-C(O)NR^aR^b$, $-NR^aR^b$, $-C_1-C_3$ alkyl, hydroxyl, and halogen; and

25 R^a and R^b are each independently, for each occurrence, selected from the group consisting of H, $-C_1-C_3$ alkyl, phenyl, and benzyl, wherein each C_1-C_3 alkyl, phenyl, and benzyl is optionally substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C_1-C_3 alkyl, and halogen.

Also provided herein are pharmaceutically acceptable compositions comprising a disclosed compound, and a pharmaceutically acceptable excipient. Such compositions can be suitable for administration to a patient orally, parenterally, topically, intravaginally, intrarectally, sublingually, ocularly, transdermally, or nasally.

In one aspect, a method of treating a condition selected from the group consisting of

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autism, anxiety, depression, bipolar disorder, attention deficit disorder, attention deficit hyperactivity disorder (ADHD), schizophrenia, a psychotic disorder, a psychotic symptom, social withdrawal, obsessive-compulsive disorder, phobia, post-traumatic stress disorder or syndrome, a behavior disorder, an impulse control disorder, a substance abuse disorder, a sleep disorder, a cognitive impairment disorder such as a memory disorder or a learning disorder, urinary incontinence, multiple system atrophy, progressive supra-nuclear palsy, Friedrich's ataxia, Down's syndrome, fragile X syndrome, tuberous sclerosis, olivio-ponto-cerebellar atrophy, Rett syndrome, cerebral palsy, drug-induced optic neuritis, ischemic retinopathy, diabetic retinopathy, glaucoma, dementia, AIDS dementia, Alzheimer's disease, Huntington's chorea, spasticity, myoclonus, muscle spasm, Tourette's syndrome, epilepsy, cerebral ischemia, stroke, a brain tumor, traumatic brain injury, cardiac arrest, myelopathy, spinal cord injury, peripheral neuropathy, fibromyalgia, acute neuropathic pain, and chronic neuropathic pain, in a patient in need thereof is provided. Such methods may comprise administering to a patient a therapeutically effective amount of a disclosed compound, or a pharmaceutically acceptable salt, a stereoisomer, and/or an N-oxide thereof, or a pharmaceutical composition including a disclosed compound, or a pharmaceutically acceptable salt, a stereoisomer, and/or an N-oxide thereof.

In various embodiments, a method of this disclosure includes treating depression. In some embodiments, a method of this disclosure includes treating schizophrenia. In certain embodiments, a method of this disclosure includes treating Alzheimer's disease. In various embodiments, a method of this disclosure includes treating attention deficit disorder. In some embodiments, a method of this disclosure includes treating anxiety. In certain embodiments, a method of this disclosure includes treating a migraine. In various embodiments, a method of this disclosure includes treating neuropathic pain. In some embodiments, a method of this disclosure includes treating traumatic brain injury. In certain embodiments, a method of this disclosure includes treating a neurodevelopment disorder related to a synaptic dysfunction. In various embodiments, a method of this disclosure includes treating a cognitive impairment disorder. Such methods may comprise administering to a patient a therapeutically effective amount of a disclosed compound, or a pharmaceutically acceptable salt, a stereoisomer, and/or an N-oxide thereof, or a pharmaceutical composition including a disclosed compound, or a pharmaceutically acceptable salt, a stereoisomer, and/or an N-oxide thereof.

DETAILED DESCRIPTION

This disclosure is generally directed to compounds that are capable of modulating NMDA receptors, for example, NMDA receptor antagonists, agonists, or partial agonists, and compositions and/or methods of using the disclosed compounds. In some embodiments, compounds described herein bind to NMDA receptors expressing certain NR2 subtypes. In some embodiments, the compounds described herein bind to one NR2 subtype and not another. It should be appreciated that the disclosed compounds may modulate other protein targets and/or specific NMDA receptor subtype.

The term “alkyl,” as used herein, refers to a saturated straight-chain or branched hydrocarbon, such as a straight-chain or branched group of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as C₁-C₆ alkyl, C₁-C₄ alkyl, and C₁-C₃ alkyl, respectively. For example, “C₁-C₆ alkyl” refers to a straight-chain or branched saturated hydrocarbon containing 1-6 carbon atoms. Examples of a C₁-C₆ alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, isopentyl, and neopentyl. In another example, “C₁-C₄ alkyl” refers to a straight-chain or branched saturated hydrocarbon containing 1-4 carbon atoms. Examples of a C₁-C₄ alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, *sec*-butyl and *tert*-butyl. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 3-methyl-2-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, *t*-butyl, pentyl, isopentyl, neopentyl, and hexyl.

The term “cycloalkyl,” as used herein, refers to a monocyclic saturated or partially unsaturated hydrocarbon ring (carbocyclic) system, for example, where each ring is either completely saturated or contains one or more units of unsaturation, but where no ring is aromatic. A cycloalkyl can have 3-6 or 4-6 carbon atoms in its ring system, referred to herein as C₃-C₆ cycloalkyl or C₄-C₆ cycloalkyl, respectively. Exemplary cycloalkyl groups include, but are not limited to, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, cyclobutyl, and cyclopropyl.

The terms “halo” and “halogen,” as used herein, refer to fluoro (F), chloro (Cl), bromo (Br), and/or iodo (I).

The terms “hydroxy” and “hydroxyl,” as used herein, refer to the radical -OH.

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The term "amino acid," as used herein, includes any one of the following alpha amino acids: isoleucine, alanine, leucine, asparagine, lysine, aspartate, methionine, cysteine, phenylalanine, glutamate, threonine, glutamine, tryptophan, glycine, valine, proline, arginine, serine, histidine, and tyrosine. An amino acid also can include other art-recognized amino acids such as beta amino acids.

The term "compound," as used herein, refers to the compound itself and its pharmaceutically acceptable salts, hydrates, and N-oxides including its various stereoisomers and its isotopically-labelled forms, unless otherwise understood from the context of the description or expressly limited to one particular form of the compound, i.e., the compound itself, a specific stereoisomer and/or isotopically-labelled compound, or a pharmaceutically acceptable salt, a hydrate, or an N-oxide thereof. It should be understood that a compound can refer to a pharmaceutically acceptable salt, or a hydrate, or an N-oxide of a stereoisomer of the compound and/or an isotopically-labelled compound.

The term "moiety," as used herein, refers to a portion of a compound or molecule.

The compounds of the disclosure can contain one or more chiral centers and/or double bonds and therefore, can exist as stereoisomers, such as geometric isomers, and enantiomers or diastereomers. The term "stereoisomers," when used herein, consists of all geometric isomers, enantiomers and/or diastereomers of the compound. For example, when a compound is shown with specific chiral center(s), the compound depicted without such chirality at that and other chiral centers of the compound are within the scope of the present disclosure, i.e., the compound depicted in two-dimensions with "flat" or "straight" bonds rather than in three dimensions, for example, with solid or dashed wedge bonds. Stereospecific compounds may be designated by the symbols "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom. The present disclosure encompasses all the various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers can be designated "(±)" in nomenclature, but a skilled artisan will recognize that a structure can denote a chiral center implicitly. It is understood that graphical depictions of chemical structures, e.g., generic chemical structures, encompass all stereoisomeric forms of the specified compounds, unless indicated otherwise.

Individual enantiomers and diastereomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by

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resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns, or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures also can be resolved into their component enantiomers by well-known methods, such as chiral-phase gas chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations. See, for example, Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

Geometric isomers, resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a cycloalkyl or heterocycloalkyl, can also exist in the compounds of the present disclosure. The symbol $\equiv$ denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the “Z” or “E” configuration, where the terms “Z” and “E” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the “E” and “Z” isomers.

Substituents around a carbon-carbon double bond alternatively can be referred to as “cis” or “trans,” where “cis” represents substituents on the same side of the double bond and “trans” represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as “cis” or “trans.” The term “cis” represents substituents on the same side of the plane of the ring and the term “trans” represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated “cis/trans.”

The disclosure also embraces isotopically-labeled compounds which are identical to those compounds recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found

in nature. Examples of isotopes that can be incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^2H (“D”), ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. For example, a compound described herein can have one or more H atoms replaced with deuterium.

5 Certain isotopically-labeled compounds (*e.g.*, those labeled with ^3H and ^{14}C) can be useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^3H) and carbon-14 (*i.e.*, ^{14}C) isotopes can be particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^2H) can afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo*
10 half-life or reduced dosage requirements) and hence can be preferred in some circumstances. Isotopically-labeled compounds can generally be prepared by following procedures analogous to those disclosed herein, for example, in the Examples section, by substituting an isotopically-labeled reagent for a non-isotopically-labeled reagent.

 The phrases “pharmaceutically acceptable” and “pharmacologically acceptable,” as
15 used herein, refer to compounds, molecular entities, compositions, materials, and/or dosage forms that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA Office of Biologics standards.

20 The phrases “pharmaceutically acceptable carrier” and “pharmaceutically acceptable excipient,” as used herein, refer to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. Pharmaceutical acceptable carriers can include phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types
25 of wetting agents. The compositions also can include stabilizers and preservatives.

 The phrase “pharmaceutical composition,” as used herein, refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers. The pharmaceutical compositions can also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

30 The terms “individual,” “patient,” and “subject,” as used herein, are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and more preferably,

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humans. The compounds described in the disclosure can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, for example, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like). The mammal treated in the methods described in the disclosure is preferably a mammal in which treatment, for example, of pain or depression, is desired.

The term “treating,” as used herein, includes any effect, for example, lessening, reducing, modulating, ameliorating, or eliminating, that results in the improvement of the condition, disease, disorder, and the like, including one or more symptoms thereof. Treating can be curing, improving, or at least partially ameliorating the disorder.

The term “disorder” refers to and is used interchangeably with, the terms “disease,” “condition,” or “illness,” unless otherwise indicated.

The term “modulation,” as used herein, refers to and includes antagonism (*e.g.*, inhibition), agonism, partial antagonism, and/or partial agonism.

The phrase “therapeutically effective amount,” as used herein, refers to the amount of a compound (*e.g.*, a disclosed compound) that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. The compounds described in the disclosure can be administered in therapeutically effective amounts to treat a disease. A therapeutically effective amount of a compound can be the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in lessening of a symptom of a disease such as depression.

As used herein, the term “pharmaceutically acceptable salt” refers to any salt of an acidic or a basic group that may be present in a compound of the present disclosure, which salt is compatible with pharmaceutical administration. As is known to those of skill in the art, “salts” of the compounds of the present disclosure may be derived from inorganic or organic acids and bases.

Examples of salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride,

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hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present disclosure compounded
5 with a suitable cation such as Na^+ , NH_4^+ , and NW_4^+ (where W can be a C_{1-4} alkyl group), and the like. For therapeutic use, salts of the compounds of the present disclosure can be pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

10 Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that can be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate,
15 bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

20 Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts.

 Compounds included in the present compositions that include a basic or acidic moiety
25 can also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure can contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

 The compounds disclosed herein can exist in a solvated form as well as an unsolvated
30 form with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the disclosure embrace both solvated and unsolvated forms.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure pertains.

Throughout the description, where compositions and kits are described as having,
5 including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions and kits of the present disclosure that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present disclosure that consist essentially of, or consist of, the recited processing steps.

10 In the application, where an element or component is said to be included in and/or selected from a list of recited elements or components, it should be understood that the element or component can be any one of the recited elements or components, or the element or component can be selected from a group consisting of two or more of the recited elements or components.

15 Further, it should be understood that elements and/or features of a composition or a method described herein can be combined in a variety of ways without departing from the spirit and scope of the present disclosure, whether explicit or implicit herein. For example, where reference is made to a particular compound, that compound can be used in various embodiments of compositions of the present disclosure and/or in methods of the present
20 disclosure, unless otherwise understood from the context. In other words, within this application, embodiments have been described and depicted in a way that enables a clear and concise application to be written and drawn, but it is intended and will be appreciated that embodiments can be variously combined or separated without parting from the present teachings and disclosure(s). For example, it will be appreciated that all features described and
25 depicted herein can be applicable to all aspects of the disclosure(s) described and depicted herein.

The articles “a” and “an” are used in this disclosure to refer to one or more than one (i.e., to at least one) of the grammatical object of the article, unless the context is inappropriate. By way of example, “an element” means one element or more than one element.

30 The term “and/or” is used in this disclosure to mean either “and” or “or” unless indicated otherwise.

It should be understood that the expression “at least one of” includes individually each of the recited objects after the expression and the various combinations of two or more of the recited objects unless otherwise understood from the context and use. The expression “and/or” in connection with three or more recited objects should be understood to have the same
5 meaning unless otherwise understood from the context.

The use of the term “include,” “includes,” “including,” “have,” “has,” “having,” “contain,” “contains,” or “containing,” including grammatical equivalents thereof, should be understood generally as open-ended and non-limiting, for example, not excluding additional unrecited elements or steps, unless otherwise specifically stated or understood from the context.

10 Where the use of the term “about” is before a quantitative value, the present disclosure also include the specific quantitative value itself, unless specifically stated otherwise. As used herein, the term “about” refers to a $\pm 10\%$ variation from the nominal value unless otherwise indicated or inferred from the context.

Where a percentage is provided with respect to an amount of a component or material in
15 a composition, the percentage should be understood to be a percentage based on weight, unless otherwise stated or understood from the context.

Where a molecular weight is provided and not an absolute value, for example, of a polymer, then the molecular weight should be understood to be an average molecule weight, unless otherwise stated or understood from the context.

20 It should be understood that the order of steps or order for performing certain actions is immaterial so long as the present disclosure remain operable. Moreover, two or more steps or actions can be conducted simultaneously.

At various places in the present specification, substituents are disclosed in groups or in ranges. It is specifically intended that the description include each and every individual
25 subcombination of the members of such groups and ranges. For example, the term “C₁₋₆ alkyl” is specifically intended to individually disclose C₁, C₂, C₃, C₄, C₅, C₆, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₃-C₆, C₃-C₅, C₃-C₄, C₄-C₆, C₄-C₅, and C₅-C₆ alkyl. By way of other examples, an integer in the range of 0 to 40 is specifically intended to individually disclose 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,
30 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, and 40, and an integer in the range of 1 to 20 is specifically intended to individually disclose 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,

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16, 17, 18, 19, and 20. Additional examples include that the phrase “optionally substituted with 1-5 substituents” is specifically intended to individually disclose a chemical group that can include 0, 1, 2, 3, 4, 5, 0-5, 0-4, 0-3, 0-2, 0-1, 1-5, 1-4, 1-3, 1-2, 2-5, 2-4, 2-3, 3-5, 3-4, and 4-5 substituents.

5 The use of any and all examples, or exemplary language herein, for example, “such as” or “including,” is intended merely to illustrate better the present disclosure and does not pose a limitation on the scope of the disclosure unless claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the present disclosure.

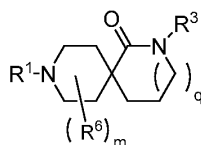
10 Further, if a variable is not accompanied by a definition, then the variable is defined as found elsewhere in the disclosure unless understood to be different from the context. In addition, the definition of each variable and/or substituent, for example, C₁-C₆ alkyl, R², R^b, w and the like, when it occurs more than once in any structure or compound, can be independent of its definition elsewhere in the same structure or compound.

15 Definitions of the variables and/or substituents in formulae and/or compounds herein encompass multiple chemical groups. The present disclosure includes embodiments where, for example, i) the definition of a variable and/or substituent is a single chemical group selected from those chemical groups set forth herein, ii) the definition is a collection of two or more of the chemical groups selected from those set forth herein, and iii) the compound is defined by a
20 combination of variables and/or substituents in which the variables and/or substituents are defined by (i) or (ii).

 Various aspects of the disclosure are set forth herein under headings and/or in sections for clarity; however, it is understood that all aspects, embodiments, or features of the disclosure described in one particular section are not to be limited to that particular section but rather can
25 apply to any aspect, embodiment, or feature of the present disclosure.

Compounds

Disclosed compounds include a compound represented by:



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or a pharmaceutically acceptable salt and/or stereoisomer thereof, wherein

R^1 is independently selected from the group consisting of H, $-C_1-C_6$ alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-O-C_1-C_6$ alkyl, and $-S(O)_w-C_1-C_6$ alkyl, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P ;

5 q is 0, 1, 2, or 3;

w is 0, 1 or 2;

R^6 , if present, is independently, for each occurrence, selected from the group consisting of H, $-C_1-C_6$ alkyl, hydroxyl, and halogen, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P ;

10 m is 0, 1, 2, 3, or 4;

R^3 is selected from the group consisting of H, $-C_1-C_6$ alkyl, $-C(O)-R^{31}$, and $-C(O)-O-R^{32}$, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P ;

15 R^{31} is selected from the group consisting of H, $-C_1-C_6$ alkyl, and $-C_3-C_6$ cycloalkyl, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P , and C_3-C_6 cycloalkyl is optionally substituted by one, two or three substituents each independently selected from R^Q ;

20 R^{32} is selected from the group consisting of $-C_1-C_6$ alkyl, and $-C_3-C_6$ cycloalkyl, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P , and C_3-C_6 cycloalkyl is optionally substituted by one, two or three substituents each independently selected from R^Q ;

R^P is independently, for each occurrence, selected from the group consisting of $-C(O)NR^aR^b$, $-NR^aR^b$, hydroxyl, $-SH$, and halogen;

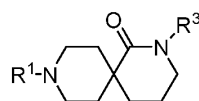
25 R^Q is independently, for each occurrence, selected from the group consisting of $-C(O)NR^aR^b$, $-NR^aR^b$, $-C_1-C_3$ alkyl, hydroxyl, and halogen; and

R^a and R^b are each independently, for each occurrence, selected from the group consisting of H, $-C_1-C_3$ alkyl, phenyl, and benzyl, wherein each C_1-C_3 alkyl, phenyl, and benzyl is optionally substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C_1-C_3 alkyl, and halogen.

30 In some embodiments, m is 0. In various embodiments, m is 1. In certain embodiments, m is 2. In particular embodiments, m is 3. In certain embodiments, R^6 is F.

In particular embodiments, the compound can have the formula:

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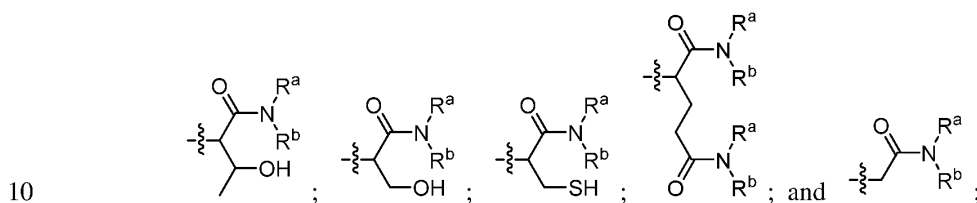
wherein the variables R^1 and R^3 are as defined herein.

In certain embodiments, R^1 may be $-C(O)-C_1-C_6$ alkyl, $-C(O)-C_1-C_4$ alkyl, $-C(O)-C_1-C_3$ alkyl, $-C(O)-C_1-C_2$ alkyl. For example, R^1 may be $-C(O)-CH_3$ or $-C(O)CH(CH_3)_2$.

5 In various embodiments, R^a and R^b may be H.

In certain embodiments, R^3 may be H.

In various embodiments, R^3 may be $-C_1-C_6$ alkyl optionally substituted by one, two or three substituents independently selected from R^P . For example, R^3 may be selected from the group consisting of:



wherein R^a and R^b are each independently selected for each occurrence from the group consisting of H, $-C_1-C_3$ alkyl, phenyl, and benzyl, wherein each C_1-C_3 alkyl, phenyl, and benzyl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C_1-C_3 alkyl, and halogen.

15 In certain embodiments, R^1 is $-C(O)-C_1-C_6$ alkyl and R^3 is H. In particular embodiments, R^1 is $-C(O)-C_1-C_4$ alkyl and R^3 is H. In various embodiments, R^1 is $-C(O)-C_1-C_3$ alkyl and R^3 is H. In some embodiments, R^1 is $-C(O)-C_1-C_2$ alkyl and R^3 is H. In certain embodiments, R^1 is $-C(O)-CH_3$ and R^3 is H.

20 In certain embodiments of compounds of the present disclosure, R^1 and R^3 independently can be an amino acid or a derivative of an amino acid, for example, an alpha "amino amide" represented by $H_2N-CH(\text{amino acid side chain})-C(O)NH_2$. In certain embodiments, the nitrogen atom of the amino group of the amino acid or the amino acid derivative is a ring nitrogen in a chemical formula described herein. In such embodiments, the carboxylic acid of the amino acid or the amide group of an amino amide (amino acid derivative) is not within the ring structure, i.e., not a ring atom. In certain embodiments, the

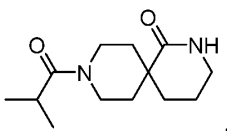
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carboxylic acid group of the amino acid or the amino acid derivative forms an amide bond with a ring nitrogen in a chemical formula disclosed herein, thereby providing an amino amide, where the amino group of the amino amide is not within the ring structure, i.e., not a ring atom. In certain embodiments, R^1 , R^2 , and R^3 independently can be an alpha amino acid, an alpha
5 amino acid derivative, and/or another amino acid or amino acid derivative such as a beta amino acid or a beta amino acid derivative, for example, a beta amino amide.

In certain embodiments, a disclosed compound is selected from the compounds delineated in the Examples or in Table 1 herein, for example, Compounds AA-AH, and includes a pharmaceutically acceptable salt and/or a stereoisomer thereof.

10 In particular embodiments, a disclosed compound is:



or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

The compounds of the present disclosure and formulations thereof may have a plurality of chiral centers. Each chiral center may be independently *R*, *S*, or any mixture of *R* and *S*. For
15 example, in some embodiments, a chiral center may have an *R*:*S* ratio of between about 100:0 and about 50:50 ("racemate"), between about 100:0 and about 75:25, between about 100:0 and about 85:15, between about 100:0 and about 90:10, between about 100:0 and about 95:5, between about 100:0 and about 98:2, between about 100:0 and about 99:1, between about 0:100 and 50:50, between about 0:100 and about 25:75, between about 0:100 and about 15:85,
20 between about 0:100 and about 10:90, between about 0:100 and about 5:95, between about 0:100 and about 2:98, between about 0:100 and about 1:99, between about 75:25 and 25:75, and about 50:50. Formulations of the disclosed compounds comprising a greater ratio of one or more isomers (i.e., *R* and/or *S*) may possess enhanced therapeutic characteristic relative to racemic formulations of a disclosed compounds or mixture of compounds. In some instances,
25 chemical formulas contain the descriptor "*-(R)-*" or "*-(S)-*" that is further attached to solid wedge or dashed wedge. This descriptor is intended to show a methine carbon (CH) that is attached to three other substituents and has either the indicated *R* or *S* configuration.

Disclosed compounds may provide for efficient cation channel opening at the NMDA receptor, e.g., may bind or associate with the glutamate site or glycine site or other modulatory

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site of the NMDA receptor to assist in opening the cation channel. The disclosed compounds may be used to regulate (turn on or turn off) the NMDA receptor through action as an agonist or antagonist.

The compounds described herein, in some embodiments, may bind to a specific N-methyl-D-aspartate (NMDA) receptor subtypes. For example, a disclosed compound may bind to one NMDA subtype and not another. In various embodiments, a disclosed compound may bind to one, or more than one NMDA subtype, and/or may have substantially less (or substantial no) binding activity to certain other NMDA subtypes. For example, in some embodiments, a disclosed compound (e.g., compound A) binds to NR2A with substantially no binding to NR2D. In some embodiments, a disclosed compound (e.g., compound B) binds to NR2B and NR2D with substantially lower binding to NR2A and NR2C.

The compounds as described herein may bind to NMDA receptors. A disclosed compound may bind to the NMDA receptor resulting in agonist-like activity (facilitation) over a certain dosing range and/or may bind to the NMDA receptor resulting in antagonist-like activity (inhibition) over a certain dosing range. In some embodiments, a disclosed compound may possess a potency that is 10-fold or greater than the activity of existing NMDA receptor modulators.

The disclosed compounds may exhibit a high therapeutic index. The therapeutic index, as used herein, refers to the ratio of the dose that produces a toxicity in 50% of the population (i.e., TD_{50}) to the minimum effective dose for 50% of the population (i.e., ED_{50}). Thus, the therapeutic index = $(TD_{50})/(ED_{50})$. In some embodiments, a disclosed compound may have a therapeutic index of at least about 10:1, at least about 50:1, at least about 100:1, at least about 200:1, at least about 500:1, or at least about 1000:1.

Compositions

In other aspects of this disclosure, a pharmaceutical formulation or a pharmaceutical composition including a disclosed compound and a pharmaceutically acceptable excipient are provided. In some embodiments, a pharmaceutical composition includes a racemic mixture or a varied stereoisomeric mixture of one or more of the disclosed compounds.

A formulation can be prepared in any of a variety of forms for use such as for administering an active agent to a patient, who may be in need thereof, as are known in the pharmaceutical arts. For example, the pharmaceutical compositions of the present disclosure can be formulated for administration in solid or liquid form, including those adapted for the

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following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets (e.g., those targeted for buccal, sublingual, and/or systemic absorption), boluses, powders, granules, and pastes for application to the tongue; (2) parenteral administration by, for example, subcutaneous, intramuscular, intraperitoneal, intravenous or
5 epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical administration, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginal or intrarectal administration, for example, as a pessary, cream or foam; (5) sublingual administration; (6) ocular administration; (7) transdermal administration; or (8) nasal administration.

10 For example, pharmaceutical compositions of the disclosure can be suitable for delivery to the eye, i.e., ocularly. Related methods can include administering a therapeutically effective amount of a disclosed compound or a pharmaceutical composition including a disclosed compound to a patient in need thereof, for example, to an eye of the patient, where administering can be topically, subconjunctivally, subtenonally, intravitreally, retrobulbarly,
15 peribulbarly, intracomerally, and/or systemically.

Amounts of a disclosed compound as described herein in a formulation may vary according to factors such as the disease state, age, sex, and weight of the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose
20 may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to
25 produce the desired therapeutic effect in association with the required pharmaceutical carrier.

The specification for the dosage unit forms are dictated by and directly dependent on (a) the unique characteristics of the compound selected and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

30 Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a

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solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use
5 of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin.

The compounds can be administered in a time release formulation, for example in a
10 composition which includes a slow release polymer. The compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic
15 copolymers (PLG). Many methods for the preparation of such formulations are generally known to those skilled in the art.

Sterile injectable solutions can be prepared by incorporating the compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by
20 incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

25 In accordance with an alternative aspect, a compound may be formulated with one or more additional compounds that enhance the solubility of the compound.

Methods

Methods for treating a condition in a patient in need thereof by administering a therapeutically effective amount of a compound described herein or a composition including
30 such a compound are provided. In some embodiments, the condition may be a mental condition. For example, a mental illness may be treated. In some embodiments, a nervous system condition may be treated. For example, a condition that affects the central nervous

system, the peripheral nervous system, and/or the eye may be treated. In some embodiments, neurodegenerative diseases may be treated.

In some embodiments, the methods include administering a compound to treat patients suffering from autism, anxiety, depression, bipolar disorder, attention deficit disorder, attention deficit hyperactivity disorder (ADHD), schizophrenia, a psychotic disorder, a psychotic symptom, social withdrawal, obsessive-compulsive disorder (OCD), phobia, post-traumatic stress syndrome, a behavior disorder, an impulse control disorder, a substance abuse disorder (e.g., a withdrawal symptom, opiate addiction, nicotine addiction, and ethanol addition), a sleep disorder, a memory disorder (e.g., a deficit, loss, or reduced ability to make new memories), a learning disorder, urinary incontinence, multiple system atrophy, progressive supra-nuclear palsy, Friedrich's ataxia, Down's syndrome, fragile X syndrome, tuberous sclerosis, olivoponto-cerebellar atrophy, cerebral palsy, drug-induced optic neuritis, ischemic retinopathy, diabetic retinopathy, glaucoma, dementia, AIDS dementia, Alzheimer's disease, Huntington's chorea, spasticity, myoclonus, muscle spasm, infantile spasm, Tourette's syndrome, epilepsy, cerebral ischemia, stroke, a brain tumor, traumatic brain injury, cardiac arrest, myelopathy, spinal cord injury, peripheral neuropathy, acute neuropathic pain, and chronic neuropathic pain.

In some embodiments, the present disclosure provides methods of treating a cognitive impairment disorder, for example, a dysfunction in learning and/or memory such as that seen in age-related cognitive decline, Lewy body dementia, AIDS dementia, HIV dementia, vascular dementia, mild cognitive impairment in Huntington's disease, Huntington's disease dementia, mild cognitive impairment in Parkinson's disease, Parkinson's disease dementia, mild cognitive impairment in Alzheimer's disease, Alzheimer's dementia, frontotemporal dementia, cognitive impairment associated with schizophrenia (CIAS), and cognitive impairment associated with seizures, stroke, cerebral ischemia, hypoglycemia, cardiac arrest, migraine, multiple sclerosis, traumatic brain injury, and/or Down's syndrome.

In certain embodiments, methods for treating schizophrenia are provided. For example, paranoid type schizophrenia, disorganized type schizophrenia (i.e., hebephrenic schizophrenia), catatonic type schizophrenia, undifferentiated type schizophrenia, residual type schizophrenia, post-schizophrenic depression, and simple schizophrenia may be treated using the methods and compositions provided herein. Psychotic disorders such as schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders, and psychotic

disorders with delusions or hallucinations may also be treated using the compositions provided herein.

Paranoid schizophrenia may be characterized where delusions or auditory hallucinations are present, but thought disorder, disorganized behavior, or affective flattening are not.

- 5 Delusions may be persecutory and/or grandiose, but in addition to these, other themes such as jealousy, religiosity, or somatization may also be present. Disorganized type schizophrenia may be characterized where thought disorder and flat affect are present together. Catatonic type schizophrenia may be characterized where the patient may be almost immobile or exhibit agitated, purposeless movement. Symptoms can include catatonic stupor and waxy flexibility.
- 10 Undifferentiated type schizophrenia may be characterized where psychotic symptoms are present but the criteria for paranoid, disorganized, or catatonic types have not been met. Residual type schizophrenia may be characterized where positive symptoms are present at a low intensity only. Post-schizophrenic depression may be characterized where a depressive episode arises in the aftermath of a schizophrenic illness where some low-level schizophrenic
- 15 symptoms may still be present. Simple schizophrenia may be characterized by insidious and progressive development of prominent negative symptoms with no history of psychotic episodes.

- In some embodiments, methods are provided for treating psychotic symptoms that may be present in other mental disorders, including, but not limited to, bipolar disorder, borderline
- 20 personality disorder, drug intoxication, and drug-induced psychosis. In certain embodiments, methods for treating delusions (e.g., "non-bizarre") that may be present in, for example, delusional disorder are provided.

- Also provided are methods for treating social withdrawal in conditions including, but not limited to, social anxiety disorder, avoidant personality disorder, and schizotypal
- 25 personality disorder.

- In some embodiments, the disclosure provides methods for treating a neurodevelopmental disorder related to synaptic dysfunction in a patient in need thereof, where the methods generally include administering to the patient a therapeutically effective amount of a disclosed compound, or a pharmaceutical composition including a disclosed compound. In
- 30 certain embodiments, the neurodevelopmental disorder related to synaptic dysfunction can be Rett syndrome also known as cerebroatrophic hyperammonemia, MECP2 duplication syndrome (e.g., a MECP2 disorder), CDKL5 syndrome, fragile X syndrome (e.g., a FMR1

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disorder), tuberous sclerosis (e.g., a TSC1 disorder and/or a TSC2 disorder), neurofibromatosis (e.g., a NF1 disorder), Angelman syndrome (e.g., a UBE3A disorder), the PTEN hamartoma tumor syndrome, Phelan-McDermid syndrome (e.g., a SHANK3 disorder), or infantile spasms. In particular embodiments, the neurodevelopmental disorder can be caused by mutations in the
5 neuroigin (e.g., a NLGN3 disorder and/or a NLGN2 disorder) and/or the neurexin (e.g., a NRXN1 disorder).

In some embodiments, methods are provided for treating neuropathic pain. The neuropathic pain may be acute or chronic. In some cases, the neuropathic pain may be associated with a condition such as herpes, HIV, traumatic nerve injury, stroke, post-ischemia,
10 chronic back pain, post-herpetic neuralgia, fibromyalgia, reflex sympathetic dystrophy, complex regional pain syndrome, spinal cord injury, sciatica, phantom limb pain, diabetic neuropathy such as diabetic peripheral neuropathy ("DPN"), and cancer chemotherapeutic-induced neuropathic pain. Methods for enhancing pain relief and for providing analgesia to a patient are also provided.

Further methods of the disclosure include a method of treating autism and/or an autism spectrum disorder in a patient in need thereof, comprising administering an effective amount of a compound to the patient. In an embodiment, a method for reducing the symptoms of autism in a patient in need thereof is provided, comprising administering an effective amount of a
15 disclosed compound to the patient. For example, upon administration, the compound may decrease the incidence of one or more symptoms of autism such as eye contact avoidance, failure to socialize, attention deficit, poor mood, hyperactivity, abnormal sound sensitivity, inappropriate speech, disrupted sleep, and perseveration. Such decreased incidence may be measured relative to the incidence in the untreated individual or an untreated individual(s).
20

Also provided herein is a method of modulating an autism target gene expression in a
25 cell comprising contacting a cell with an effective amount of a compound described herein. The autism gene expression may be for example, selected from ABAT, APOE, CHRNA4, GABRA5, GFAP, GRIN2A, PDYN, and PENK. In some embodiments, a method of modulating synaptic plasticity in a patient suffering from a synaptic plasticity related disorder is provided, comprising administering to the patient an effective amount of a compound.

30 In some embodiments, a method of treating Alzheimer's disease, or e.g., treatment of memory loss that e.g., accompanies early stage Alzheimer's disease, in a patient in need thereof is provided, comprising administering a compound. Also provided herein is a method of

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modulating an Alzheimer's amyloid protein (e.g., beta amyloid peptide, e.g. the isoform A β ₁₋₄₂), in-vitro or in-vivo (e.g. in a cell) comprising contacting the protein with an effective amount of a compound is disclosed. For example, in some embodiments, a compound may block the ability of such amyloid protein to inhibit long-term potentiation in hippocampal slices
5 as well as apoptotic neuronal cell death. In some embodiments, a disclosed compound may provide neuroprotective properties to a Alzheimer's patient in need thereof, for example, may provide a therapeutic effect on later stage Alzheimer's –associated neuronal cell death.

In certain embodiments, the disclosed methods include treating a psychosis or a pseudobulbar affect (“PBA”) that is induced by another condition such as a stroke, amyotrophic
10 lateral sclerosis (ALS or Lou Gehrig's disease), multiple sclerosis, traumatic brain injury, Alzheimer's disease, dementia, and/or Parkinson's disease. Such methods, as with other methods of the disclosure, include administration of a therapeutically effective amount of a disclosed compound to a patient in need thereof.

In various embodiments, a method of treating depression comprising administering a
15 compound described herein is provided. In some embodiments, the treatment may relieve depression or a symptom of depression without affecting behavior or motor coordination and without inducing or promoting seizure activity. Exemplary depression conditions that are expected to be treated according to this aspect include, but are not limited to, major depressive disorder, dysthymic disorder, psychotic depression, postpartum depression, premenstrual
20 syndrome, premenstrual dysphoric disorder, seasonal affective disorder (SAD), bipolar disorder (or manic depressive disorder), mood disorder, and depressions caused by chronic medical conditions such as cancer or chronic pain, chemotherapy, chronic stress, and post traumatic stress disorders. In addition, patients suffering from any form of depression often experience anxiety. Various symptoms associated with anxiety include fear, panic, heart palpitations,
25 shortness of breath, fatigue, nausea, and headaches among others. Anxiety or any of the symptoms thereof may be treated by administering a compound as described herein.

Also provided herein are methods of treating a condition in treatment-resistant patients, e.g., patients suffering from a mental or central nervous system condition that does not, and/or has not, responded to adequate courses of at least one, or at least two, other compounds or
30 therapeutics. For example, provided herein is a method of treating depression in a treatment resistant patient, comprising a) optionally identifying the patient as treatment resistant and b) administering an effective dose of a compound to said patient.

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In some embodiments, a compound described herein may be used for acute care of a patient. For example, a compound may be administered to a patient to treat a particular episode (e.g., a severe episode) of a condition described herein.

Also provided herein are combination therapies comprising a compound in combination
5 with one or more other active agents. For example, a compound may be combined with one or more antidepressants, such as tricyclic antidepressants, MAO-I's, SSRI's, and double and triple uptake inhibitors and/or anxiolytic drugs. Exemplary drugs that may be used in combination with a compound include Anafranil, Adapin, Aventyl, Elavil, Norpramin, Pamelor, Pertofrane, Sinequan, Surmontil, Tofranil, Vivactil, Parnate, Nardil, Marplan, Celexa, Lexapro, Luvox,
10 Paxil, Prozac, Zoloft, Wellbutrin, Effexor, Remeron, Cymbalta, Desyrel (trazodone), and Ludiomill. In another example, a compound may be combined with an antipsychotic medication. Non-limiting examples of antipsychotics include butyrophenones, phenothiazines, thioxanthenes, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, amisulpride, asenapine, paliperidone, iloperidone, zotepine, sertindole, lurasidone, and aripiprazole. It
15 should be understood that combinations of a compound and one or more of the above therapeutics may be used for treatment of any suitable condition and are not limited to use as antidepressants or antipsychotics.

EXAMPLES

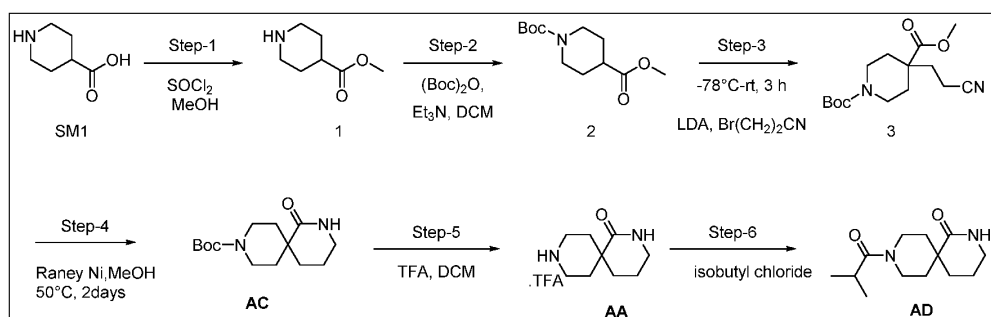
The following examples are provided for illustrative purposes only, and are not intended to limit the scope of the disclosure.

20 The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that
25 reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are
30 readily prepared by standard methods from known materials. At least some of the compounds identified as "intermediates" herein can be compounds of the disclosure.

- The following abbreviations may be used herein and have the indicated definitions: Ac is acetyl ($-\text{C}(\text{O})\text{CH}_3$), AIDS is acquired immune deficiency syndrome, Boc and BOC are *tert*-butoxycarbonyl, Boc_2O is di-*tert*-butyl dicarbonate, Bn is benzyl, Cbz is carboxybenzyl, DCM is dichloromethane, DIPEA is *N,N*-diisopropylethylamine, DMF is *N,N*-dimethylformamide,
- 5 DMSO is dimethyl sulfoxide, ESI is electrospray ionization, EtOAc is ethyl acetate, h is hour, HATU is 2-(7-*aza-1H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, HIV is human immunodeficiency virus, HPLC is high performance liquid chromatography, LCMS is liquid chromatography/mass spectrometry, LDA is lithium diisopropylamide,
- 10 LiHMDS is lithium hexamethyldisilazane, Ms is mesyl or methanesulfonyl, NMDAR is *N*-methyl-*D*-aspartate receptor, NMR is nuclear magnetic resonance, Pd/C is palladium on carbon, RT is room temperature (e.g., from about 20 °C to about 25 °C), SM is starting material, TEA is triethylamine, TLC is thin layer chromatography, TFA is trifluoroacetic acid, THF is tetrahydrofuran, TMS is trimethylsilyl, and Ts is tosyl or *para*-toluenesulfonyl.

A. SYNTHESIS OF COMPOUNDS

15 Synthesis of AC, AA, AD:



Synthesis of methyl piperidine-4-carboxylate (1):

- To a stirred solution of piperidine-4-carboxylic acid (20.0 g, 155 mmol) in MeOH (200 mL), thionyl chloride (20 mL) was added at 0 °C and the reaction mixture was stirred at RT for
- 20 16 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford 1 (28.4 g, crude) as a thick oil (HCl salt). The crude was used as such for next step without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.40 – 9.33 (m, 1H), 3.62 (s, 3H), 3.12– 3.05 (m, 2H), 2.89 – 2.80 (m, 2H), 2.69 – 2.60 (m, 1H), 2.02 – 1.90 (m, 2H), 1.78 (m, 2H).

Synthesis of 1-(*tert*-butyl) 4-methyl piperidine-1,4-dicarboxylate (2):

To a stirred solution of **1** (28.0 g, 155 mmol) in DCM (300 mL), Et₃N (65 mL, 467 mmol) was added at 0 °C and stirred for 15 min. Boc₂O (41 mL, 187 mmol) was added drop wise at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was quenched with ice-cold water (500 mL) and extracted with DCM (3 x 350 mL). The combined organic layer was washed with brine (150 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography with 20-30% EtOAc/*n*-hexane to afford **2** (35.6 g, 94%) as a thick oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.85 (t, *J* = 3.4 Hz, 2H), 3.61 (s, 3H), 2.82 (s, 2H), 2.54 – 2.44 (m, 1H), 1.85 – 1.74 (m, 2H), 1.44 – 1.41 (m, 2H), 1.43 (d, *J* = 32.1 Hz, 9H).

Synthesis of 1-(*tert*-butyl) 4-methyl 4-(2-cyanoethyl)piperidine-1,4-dicarboxylate (3):

To a stirred solution of **2** (20.0 g, 82.2 mmol) in THF (200 mL), LDA (60 mL, 122 mmol) was added at -78 °C and stirred for 1 h. 3-bromopropanenitrile (8 mL, 98.0 mmol) was added to the reaction mixture at -78 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was quenched with saturated aqueous NH₄Cl (250 mL) and extracted with EtOAc (2 x 250 mL). The combined organic layer was washed with brine (150 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography using 30% EtOAc/hexane to afford **3** (8.1 g, 33%). LCMS (ESI): *m/z* 197 [M⁺-Boc].

Synthesis of *tert*-butyl 1-oxo-2,9-diazaspiro[5.5]undecane-9-carboxylate (AC):

To a stirred solution of compound **3** (4.0 g, 13.5 mmol) in MeOH (50 mL), Raney- Ni (1.0 g) and 7N NH₃ in MeOH (5 mL) was added at RT and stirred for 7 h at 50 °C under H₂ atmosphere (50 psi) in an autoclave. After consumption of the starting material (by TLC), the reaction mixture was filtered through celite and washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using 80% EtOAc/hexane to afford **AC** (2.2 g, 61%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) : δ 7.30 (d, *J* = 3.8 Hz, 1H), 3.63 – 3.57 (m, 2H), 3.08 – 2.92 (m, 4H), 1.85 – 1.61 (m, 6H), 1.38 – 1.31 (m, 11H). LCMS (ESI) : *m/z* 169 [M⁺-Boc]. HPLC: 99.4%.

Synthesis of 2,9-diazaspiro[5.5]undecan-1-one (AA):

To a stirred solution of **AC** (0.3 g, 1.10 mmol) in DCM (5 mL), TFA (0.6 mL) was added at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford **AA** (300 mg) TFA salt as a thick

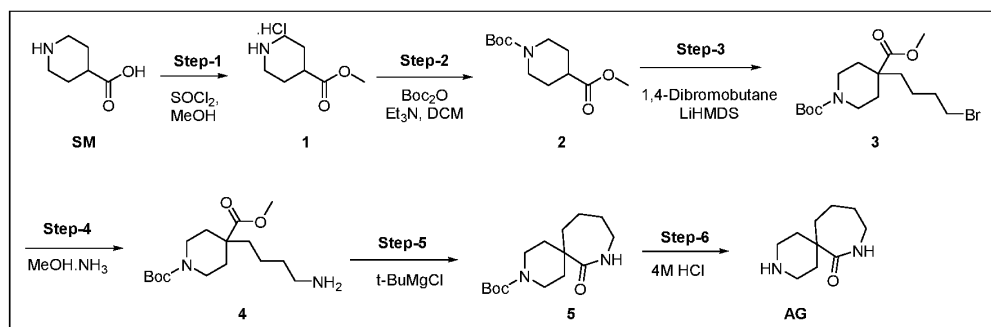
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oil. ^1H NMR (400 MHz, DMSO- d_6) δ 8.55 – 8.45 (m, 1H), 7.45 (s, 1H), 3.29 – 3.20 (m, 2H), 3.1-3.06 (m, 4H), 2.09-2.00 (m, 2H), 1.68 – 1.58 (m, 4H), 1.59 – 1.48 (m, 2H). LCMS (ESI) : m/z 169 [M^+ +1]. HPLC: 99.2%.

Synthesis of 9-isobutyryl-2,9-diazaspiro[5.5]undecan-1-one (AD):

- 5 To a stirred solution of **AA** (0.2 g, 1.19 mmol) in DCM (2 mL), DIPEA (0.66 mL, 3.57 mmol) was added followed by addition of isobutyryl chloride (0.19 mL, 1.78 mmol) at -78 °C and stirred for same temperature for 15 min. After consumption of the starting material (by TLC), reaction mixture was evaporated under reduced pressure. The residue was purified by column chromatography followed Prep HPLC to afford **AD** (0.07 g, 25%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 7.35 (s, 1H), 3.98 (m, 1H), 3.74 (m, 1H), 3.27 – 3.20 (m, 1H), 3.10 – 3.00 (m, 2H), 2.99 – 2.93 (m, 1H), 2.84 – 2.78 (m, 1H), 1.87 – 1.78 (m, 1H), 1.81 – 1.62 (m, 5H), 1.38 (t, J = 16.2 Hz, 2H), 0.98 (t, J = 6.7 Hz, 6H). LCMS (ESI): m/z 239 [M^+ +1]. HPLC: 99.7%.

Synthesis of AG



15

Synthesis of methyl piperidine-4-carboxylate hydrochloride (1):

- To a stirring solution of piperidine-4-carboxylic acid (SM) (50 g, 0.387 mol) in methanol (500 mL) was added thionyl chloride (50.6 mL, 0.696 mol) drop wise at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 h. After consumption of the starting material (by TLC), volatiles were concentrated under reduced pressure to afford crude compound 1 (71.5 g) as an off-white solid.

- ^1H NMR (500 MHz, DMSO- d_6) δ 9.14 (br s, 1H), 8.96 (br s, 1H), 3.62 (s, 3H), 3.19 (br d, J = 12.8 Hz, 2H), 2.98 - 2.82 (m, 2H), 2.71 - 2.65 (m, 1H), 1.99 - 1.94 (m, 2H), 1.84 - 1.69 (m, 2H). LCMS (ESI): m/z 287.3 [$2M+H$] $^+$.

25

Synthesis of 1-(*tert*-butyl) 4-methyl piperidine-1,4-dicarboxylate (2):

To a stirring solution of compound **1** (71.5 g, 0.496 mol) in CH₂Cl₂ (700 mL) was added Et₃N (139 mL, 0.595 mol) at 0 °C and stirred for 10 min. Boc₂O (81 mL, 0.595 mol) was added at 0 °C and the reaction mixture was stirred at room temperature for 16 h. After consumption of the starting material (by TLC), the reaction was quenched with water (1 L) and extracted with CH₂Cl₂ (2 x 1 L). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by column chromatography on SiO₂ by eluting with 20% EtOAc/ hexane to obtain compound **2** (95 g, 78%) as colorless liquid.

¹H NMR (500 MHz, DMSO-d₆) δ 3.83 (br d, *J* = 13.3 Hz, 2H), 3.61 (s, 3H), 2.82 (br s, 2H), 2.57 - 2.51 (m, 1H), 1.83 - 1.76 (m, 2H), 1.44 - 1.41 (m, 2H), 1.39 (s, 9H). LCMS (ESI): *m/z* 266.3 [M+Na]⁺.

Synthesis of 1-(*tert*-butyl) 4-methyl 4-(4-bromobutyl)piperidine-1,4-dicarboxylate (3):

To a stirring solution of compound **2** (10 g, 0.041 mol) in THF (80 mL) was added LiHMDS (1.0 M solution in THF, 62 mL, 0.062 mol) drop wise at -78 °C under nitrogen atmosphere.

After stirring for 40 min, 1,4-dibromobutane (24.5 mL, 0.205 mol) in THF (20 mL) was added drop wise. The reaction mixture was brought to room temperature and stirred for 3 h. After consumption of the starting material (by TLC), the reaction was quenched with water (100 mL) and extracted with EtOAc (2 x 500 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by column chromatography on SiO₂ by eluting with 10% EtOAc/ hexane to afford compound **3** (10 g, 65%) colorless liquid.

¹H NMR (400 MHz, DMSO-d₆) δ 3.75 - 3.66 (m, 2H), 3.64 (s, 3H), 3.50 (t, *J* = 6.7 Hz, 2H), 2.82 (br s, 2H), 2.01 - 1.90 (m, 2H), 1.78 - 1.68 (m, 2H), 1.55 - 1.45 (m, 2H), 1.38 (s, 9H), 1.35 - 1.20 (m, 4H). LCMS (ESI): *m/z* 278.6 [M-Boc+H]⁺.

Synthesis of 1-(*tert*-butyl) 4-methyl 4-(4-aminobutyl)piperidine-1,4-dicarboxylate (4):

A mixture of compound **3** (5 g, 0.013 mol) and methanolic ammonia (7M solution, 50 mL) was taken in to a sealed tube under nitrogen atmosphere. The reaction mixture was stirred at 90 °C for 3 h. After consumption of the starting material (by TLC), cooled to room temperature and volatiles were evaporated under reduced pressure. The crude was purified by column chromatography on SiO₂ by eluting with 10% MeOH/ CH₂Cl₂ to afford compound **4** (3.5 g, 84%) colorless liquid.

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¹H NMR (500 MHz, DMSO-d₆) δ 3.70 (d, *J* = 13.3 Hz, 2H), 3.65 (s, 3H), 3.31 (br s, 2H), 2.82 (br s, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 1.94 (d, *J* = 13.3 Hz, 2H), 1.54 - 1.43 (m, 4H), 1.38 (s, 9H), 1.35 - 1.27 (m, 2H), 1.21 - 1.12 (m, 2H). LCMS (ESI): *m/z* 315.3 [M+H]⁺.

Synthesis of *tert*-butyl 7-oxo-3,8-diazaspiro[5.6]dodecane-3-carboxylate (5):

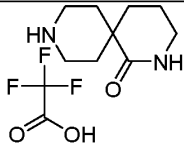
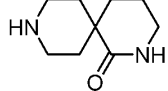
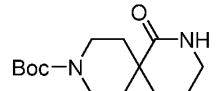
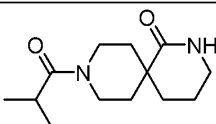
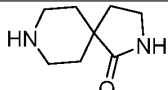
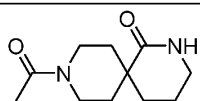
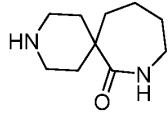
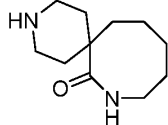
- 5 To a stirring solution of compound **4** (3 g, 9.55 mmol) in THF (30 mL) was added *t*-BuMgCl (1M solution in THF, 38 mL, 38.0 mmol) dropwise at 0 °C and the reaction mixture was stirred at room temperature for 10 h. After consumption of the starting material (by TLC), the reaction was quenched with cold water (100 mL) and extracted with 10% MeOH/ CH₂Cl₂ (2 x 500 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under
10 reduced pressure. The crude was purified by column chromatography on SiO₂ by eluting with 5% MeOH/ CH₂Cl₂ to afford mixture of compound **5** (1.2 g, 44%) as an off-white solid. LCMS (ESI): *m/z* 183.2 [M-Boc+H]⁺.

Synthesis of 3,8-diazaspiro[5.6]dodecan-7-one (AG):

- To a stirring solution of compound **5** (50 mg, 0.177 mmol) in CH₂Cl₂ (1 mL) was added HCl
15 (4M solution in 1,4-dioxane, 1 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 h. After consumption of the starting material (by TLC), volatiles were evaporated under reduced pressure. The crude was diluted with saturated aqueous NaHCO₃ (5 mL) in a round bottom flask and subjected to lyophilization for 48 h. Resultant solid product was triturated with 5% MeOH/ CH₂Cl₂ followed by diethyl ether and
20 dried under vacuum to afford **AG** (32 mg) as an off-white solid.
¹H NMR (400 MHz, DMSO-d₆) δ 7.47 (br s, 1H), 3.41 (br s, 1H), 3.14 - 3.03 (m, 2H), 3.00 - 2.91 (m, 2H), 2.89 - 2.79 (m, 2H), 2.07 (br d, *J* = 14.4 Hz, 2H), 1.66 (br d, *J* = 4.1 Hz, 2H), 1.55 - 1.40 (m, 6H). LCMS (ESI): *m/z* 183.0 [M+H]⁺. HPLC: 95.86%.

- Following the above procedures, the following compounds and stereoisomers thereof
25 were or are prepared. It will be appreciated by a person of skill in the art that for structures shown additional diastereomers and/or enantiomers may be envisioned and are included herein.

Table 1

Compound	Structure
AA	
AB	
AC	
AD	
AE	
AF	
AG	
AH	

B. NMDAR AGONIST ASSAYS

Assays were conducted as described by Moskal et al., "GLYX-13: a monoclonal antibody-derived peptide that acts as an N-methyl-D-aspartate receptor modulator," Neuropharmacology, 49, 1077-87, 2005. These studies were designed to determine if the test compounds act to facilitate NMDAR activation in NMDAR2A, NMDAR2B, NMDAR2C or NMDAR2D expressing HEK cell membranes as measured by increases in [³H]MK-801 binding.

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In the assay, 300 µg of NMDAR expressing HEK cell membrane extract protein was preincubated for 15 minutes at 25° C in the presence of saturating concentrations of glutamate (50 µM) and varying concentrations of test compound (1×10^{-15} M – 1×10^{-7} M), or 1 mM glycine. Following the addition of 0.3 µCi of [³H]MK-801 (22.5 Ci/mmol), reactions were again
 5 incubated for 15 minutes at 25 ° C (nonequilibrium conditions). Bound and free [³H]MK-801 were separated via rapid filtration using a Brandel apparatus.

In analyzing the data, the DPM (disintegrations per minute) of [³H]MK-801 remaining on the filter were measured for each concentration of test compound or for 1 mM glycine. The DPM values for each concentration of a ligand (N=2) were averaged. The baseline value was
 10 determined from the best fit curve of the DPM values modeled using the GraphPad program and the log(agonist) vs. response(three parameters) algorithm was then subtracted from all points in the dataset. The % maximal [³H]MK-801 binding was then calculated relative to that of 1 mM glycine: all baseline subtracted DPM values were divided by the average value for 1 mM glycine. The EC₅₀ and % maximal activity were then obtained from the best fit curve of
 15 the % maximal [³H]MK-801 binding data modelled using the GraphPad program and the log(agonist) vs. response(three parameters) algorithm.

The tables below summarize the results for the wild type NMDAR agonists NMDAR2A, NMDAR2B, NMDAR2C, and NMDAR2D, and whether the compound is not an agonist (-), is an agonist (+), or is a strong agonist (++), where column A is based on the %
 20 maximal [³H]MK-801 binding relative to 1 mM glycine (- = 0; < 100% = +; and > 100% = ++); and column B is based on log EC₅₀ values (0 = -; $\geq 1 \times 10^{-9}$ M (e.g., -8) = +; and $< 1 \times 10^{-9}$ M (e.g., -10) = ++). An “ND” indicates that the assay was not done.

Compound	NMDAR2A		NMDAR2B	
	A	B	A	B
AA	-	-	+	++
AD	+	++	+	++
AC	+	+	+	++
AG	+	++	+	++

Compound	NMDAR2C		NMDAR2D	
	A	B	A	B
AA	ND	ND	++	++
AD	+	++	+	++

C. PHARMACOKINETICS ASSAYS

Sprague Dawley rats were dosed intravenously using a normal saline formulation containing 2 mg/kg of the compounds identified in the below table. The table below

5 summarizes the results of the IV pharmacokinetics.

Compound	C _{max} (ng/mL)	AUC _{last} (hr*ng/ mL)	T _{1/2} (hr)	Cl (mL/min/ kg)	V _{ss} (L/kg)
AA	2663	1155	2	28.35	1.76
AD	3793	5276	6.37	6.22	0.92
AC	5665	845	0.12	39.46	0.31

In another experiment, Sprague Dawley rats were dosed per os (oral gavage) using a normal saline formulation containing 10 mg/kg of the compounds identified in the table below. Plasma, brain, and CSF samples were analyzed at various time points over a 24 hour period.

10 The table below summarizes the results of the oral pharmacokinetics, where the first three values (T_{max}, C_{max} and AUC_{last}) are plasma values.

Compound	T _{max} (hr)	C _{max} (ng/mL)	AUC _{last} (hr*ng/ mL)	CSF C _{max} (ng/mL)	Brain C _{max} (ng/mL)	%F
AA	2.11	325	1021	12	0	18
AD	0.33	8538	18448	4697	4833	70
AC	0.25	3633	1864	261	298	44

D: PORSOLT ASSAY

A non-clinical *in vivo* pharmacology study (Porsolt assay) was performed to measure antidepressant-like effects. The study allowed for the evaluation of the effects of each compound on the Porsolt forced swim test as assessed by the rats' response (reduced floating time) during a 5-minute swimming test.

Male 2-3 month old Sprague Dawley rats were used (Harlan, Indianapolis, IN). Rats were housed in Lucite cages with aspen wood chip bedding, maintained on a 12:12 light:dark cycle (lights on at 5 AM), and given ad libitum access to Purina lab chow (USA) and tap water throughout the study.

The Porsolt forced swim test adapted for use in rats was performed as described by Burgdorf et al., (The long-lasting antidepressant effects of rapastinel (GLYX-13) are associated with a metaplasticity process in the medial prefrontal cortex and hippocampus. *Neuroscience* 308:202-211, 2015). Animals were placed in a 46 cm tall × 20 cm in diameter clear glass tube filled to 30 cm with tap water (23 ± 1 °C) for 15 min on the first day (habituation) and 5 min on the subsequent test day. Animals were tested 1 h or 1 week post-dosing with the test compounds or vehicle control (0.5% sodium carboxymethyl cellulose in 0.9% sterile saline). Animals received a 15 min habituation session 1 day before the first 5 min test. Water was changed after every other animal. Animals were videotaped, and floating time as defined as the minimal amount of effort required to keep the animals head above water was scored offline by a blinded experimenter with high inter-rater reliability (Pearson's $r > .9$).

Compound	1 h post-dose			1 wk post-dose		
	Dose (mg/kg)	Significance vs. vehicle	% reduction in float time	Dose (mg/kg)	Significance vs. vehicle	% reduction in float time
AD	0.00001	No	25	0.00001	No	1
AD	0.001	Yes	47	0.001	No	41
AD	0.1	Yes	53	0.1	No	39
AD	10.0	Yes	39	10.0	No	37

E. MICROSOMAL STABILITY

Microsomal stability of disclosed compounds was investigated. The following table indicates the percent of compound remaining after 60 minutes.

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Compound	Microsomal (Human)	Microsomal (Rat)
AA	96%	91%
AD	100%	100%
AC	100%	96%

F. PLASMA STABILITY

Plasma stability of disclosed compounds was investigated. The following table indicates the percent of compound remaining after 60 minutes.

Compound	Plasma (Human)	Plasma (Rat)
AA	97%	84%
AD	98%	95%
AC	100%	100%

G. BENNETT NERVE INJURY ASSAY

5 The Bennett model of mechanical analgesia is used to assess the analgesic effects of compounds as measured by paw withdrawal threshold. Bennett GJ, Xie YK, "A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man," Pain 33:87-107, 1988. Sciatic nerve chronic constriction nerve injury surgery is performed on animals with testing for analgesic response once animals have recovered from surgery but still exhibit a low threshold of paw withdrawal after application of von Frey filaments. Vehicle animals receive the surgery and then receive vehicle rather than test compound. Animals were tested 1 hr, 24 h and 1 wk post-test compound or vehicle administration.

Male 2-3 month old Sprague Dawley rats were used. Harlan was the supplier for all studies. Rats were housed in Lucite cages with aspen wood chip bedding, maintained on a 12:12 light:dark cycle (lights on at 5 AM), and given ad libitum access to Purina lab chow (USA) and tap water throughout the study.

Rats were anesthetized using inhaled isoflurane (2.5%). Sciatic nerve chronic constriction nerve injury surgery was performed as previously described (Bennett and Xie, 1988). An incision (~1.5 cm in length) was made with a scalpel blade dorsally through skin on the right hind limb, parallel and posterior to femur. Using a small pointed hemostat, the biceps

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femoris and gluteus superficialis muscles were separated. Using curved blunt forceps, the common sciatic nerve was isolated and exposed. For the mechanical analgesia studies, the whole sciatic nerve was ligated. Using hemostats/forceps and chromic gut (5-0), the nerve was loosely ligated with a square knot; 3 ligatures, 1 mm apart were placed on the nerve. The
5 ligatures were tightened to the point that the suture did not slide up or down the nerve. This protocol resulted in a partial loss-of-function of the nerve. Testing occurred approximately 2 weeks post-surgery.

During testing, rats were acclimated to the surface of a suspended wire mesh grid (1 cm X 1 cm, with the wire being 0.3 cm in diameter) for 15-20 min. Starting from the smallest, each
10 Von Frey filament was pressed perpendicularly to the plantar surface of the affected (ipsilateral) hind paw until slightly bent and then held for 6 second. If an obvious hind paw withdrawal or a flinching behavior immediately after the withdrawal of the filament was not observed, the next larger filament was used in the same manner. In case of a response, a lower filament was used. This was repeated until six responses were collected.

15 For all studies, animals were baselined prior to study start to test for allodynia (defined as a paw withdrawal threshold under 5). A subset of animals was tested with gabapentin (150 mg/kg, PO) to ensure at least 50% analgesia. Once it was confirmed animals were ready for study initiation, animals were balanced across groups. All study investigators were blind to treatment conditions. Animals were dosed with 0.1, 1 or 10 mg/kg of test compound via oral
20 gavage (PO), control sets of animals were dosed with gabapentin (150 mg/kg, PO) or vehicle (0.5% Na-CMC in 0.9% sterile saline, PO). Testing occurred 1 h post-dosing with animals retested 24 hrs and 1 week post-dosing. The percent analgesia calculations for each animal were made using the following equation: $\% \text{ analgesia} = [(\log(x) - y) / ((\log(z) - y))] * 100$, where x = the paw withdrawal threshold for the drug-treated animal in grams, y = the average
25 of the log(x) values for the vehicle treated group, and z = the paw withdrawal threshold for naïve animals in grams (historical value of 15 used). The results for Compound AD, where the percentage of analgesia is measured at 1 hour, 24 hours, and 1 week after compound administration are as follows: for 0.1 mg/kg dose: 38.7% at 1 h, 34.5% at 24 h, and 19.7% at 1 wk; for 1 mg/kg dose: 24.1% at 1 h, 26.5% at 24 h, and 13.2% at 1 wk; and for 10 mg/kg dose:
30 61.2% at 1 h, 45.1% at 24 h, and 39.5% at 1 wk. The study had a gabapentin control group, where example (typical) gabapentin control values for 150 mg/kg dose are 77% at 1 h, 17% at 24h, and 0% at 1 wk. For the study, gabapentin was confirmed effective (demonstrating at

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least 50% analgesia at 1 h post-administration). Gabapentin was not different from vehicle and resulted in no analgesia (<5%) at 24 h and 1 week post-administration.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than
5 routine experimentation, many equivalents to the specific embodiments of the invention
described herein. Such equivalents are intended to be encompassed by the following claims.

INCORPORATION BY REFERENCE

The entire contents of all patents, published patent applications, websites, and other
references cited herein are hereby expressly incorporated herein in their entireties by reference.