(12) STANDARD PATENT (11) Application No. **AU 2017305240 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Spiro-lactam NMDA receptor modulators and uses thereof

(51) International Patent Classification(s)
C07D 487/10 (2006.01) ***A61P 25/00*** (2006.01)
A61K 31/499 (2006.01) ***C07D 498/10*** (2006.01)
A61K 31/5386 (2006.01)

(21) Application No: **2017305240** (22) Date of Filing: **2017.08.01**

(87) WIPO No: **WO18/026782**

(30) Priority Data

(31) Number	(32) Date	(33) Country
62/369,456	**2016.08.01**	**US**

(43) Publication Date: **2018.02.08**
(44) Accepted Journal Date: **2021.12.09**

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(56) Related Art
US 20100160255 A1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
08 February 2018 (08.02.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/026782 A1

(51) International Patent Classification:
C07D 487/10 (2006.01) *A61K 31/499* (2006.01)
C07D 498/10 (2006.01) *A61P 25/00* (2006.01)
A61K 31/5386 (2006.01)

(21) International Application Number:
PCT/US2017/044841

(22) International Filing Date:
01 August 2017 (01.08.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/369,456 01 August 2016 (01.08.2016) US

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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

WO 2018/026782 A1

(54) Title: SPIRO-LACTAM NMDA RECEPTOR MODULATORS AND USES THEREOF

(57) Abstract: Disclosed are compounds having potency in the modulation of NMDA receptor activity. Such compounds can be used in the treatment of conditions such as depression and related disorders. Orally delivered formulations and other pharmaceutically acceptable delivery forms of the compounds, including intravenous formulations, are also disclosed.

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. 62/369,456, filed on August 1, 2016; the contents 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 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 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 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 damaged or oxygen deprived neurons. This excess glutamate binds to the NMDA receptors

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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 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 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 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 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.

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.

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive

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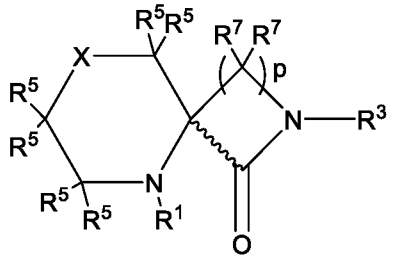
sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

SUMMARY

According to a first aspect, the present invention provides a compound represented by:



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

X is O or NR^2;

R^1 is selected from the group consisting of H, C_1-C_6alkyl, phenyl, -C(O)-C_1-C_6alkyl, and -C(O)-O-C_1-C_6 alkyl;

R^2 is selected from the group consisting of H, C_1-C_6alkyl, phenyl, -C(O)-C_1-C_6alkyl, and -C(O)-O-C_1-C_6 alkyl;

p is 1 or 2;

R^5 is independently selected for each occurrence from the group consisting of H, C_1-C_6alkyl, -$S(O)_w$-C_1-C_3alkyl, - NR^aR^b, C_1-C_3alkoxy, cyano and halogen;

w is 0, 1, or 2;

R^3 is selected from the group consisting of H, C_1-C_6 alkyl, phenyl, -C(O)R^{31} and -C(O)OR^{32};

R^{31} and R^{32} are each independently selected from the group consisting of H, C_1-C_6alkyl, -C_3-C_6cycloalkyl, and phenyl;

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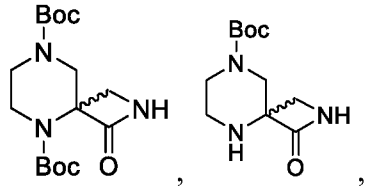
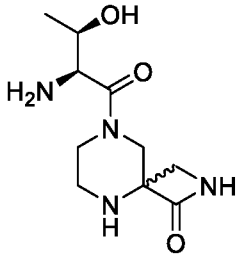
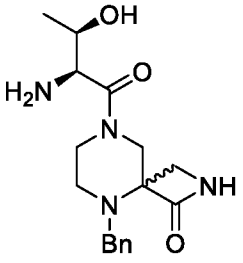
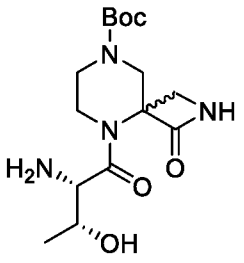
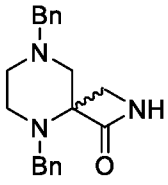
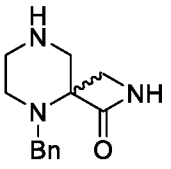
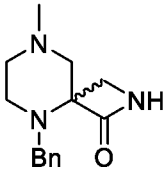
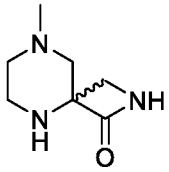
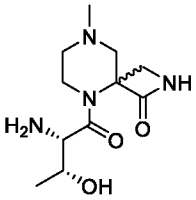
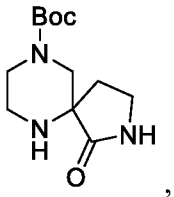
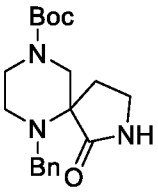
R^7 is independently selected for each occurrence from the group consisting of H, halogen, and phenyl; and

R^a and R^b are each independently for each occurrence selected from the group consisting of H, C_1-C_3alkyl, and phenyl, or R^a and R^b taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring;

wherein any aforementioned C_1-C_6 alkyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from –C(O)NR^aR^b, -NR^aR^b, hydroxyl, $S(O)_w$-C_1-C_3alkyl, SH, phenyl and halogen, and any aforementioned phenyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from hydroxyl, halogen, -C(O)-O-C_1-C_3alkyl, -C(O)-C_1-C_3alkyl, methyl, and CF_3.

According to a second aspect, the present invention provides a compound selected from the group consisting of:



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

According to a third aspect, the present invention provides a compound selected from the group consisting of:

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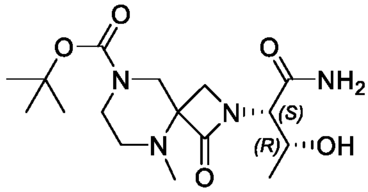
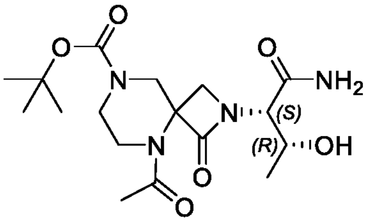
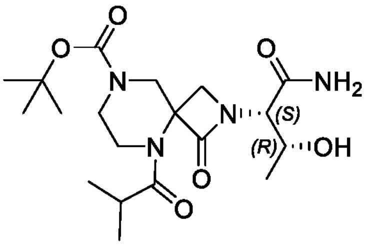
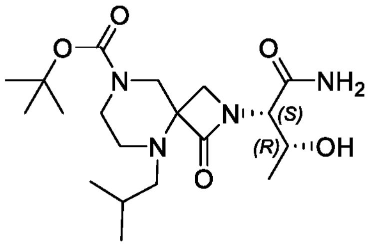
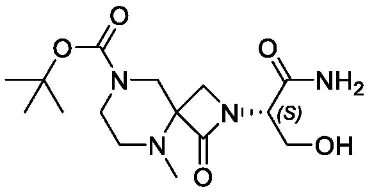
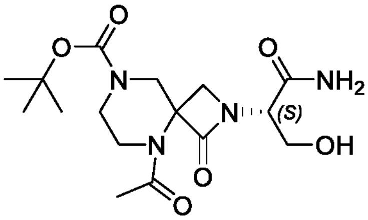
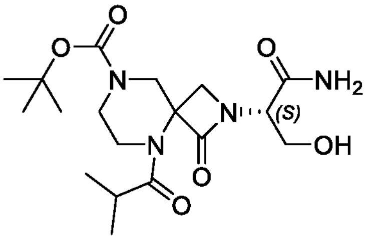
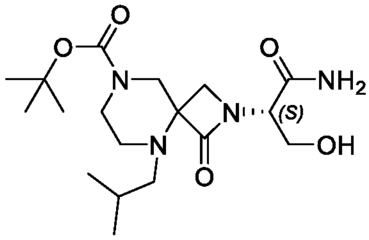
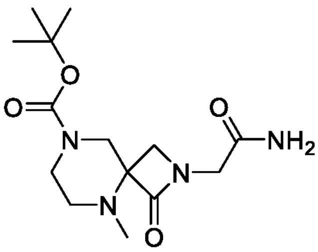
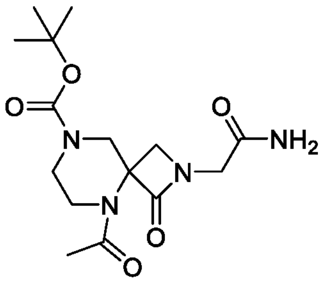
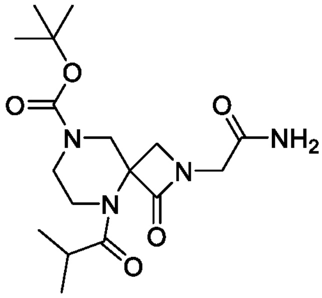
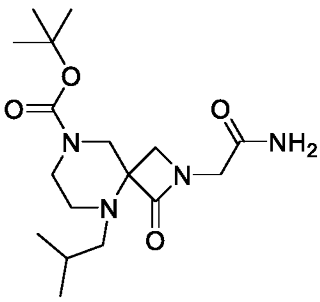
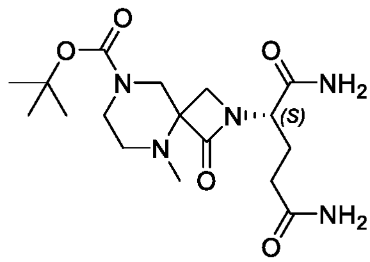
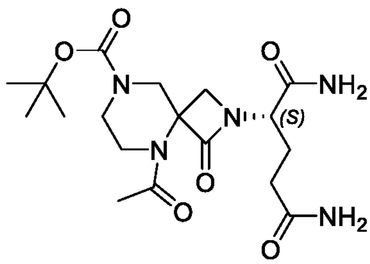
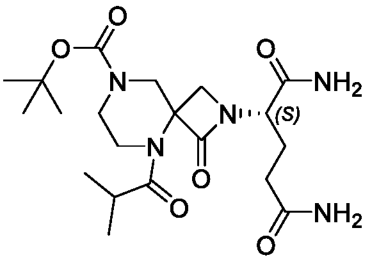
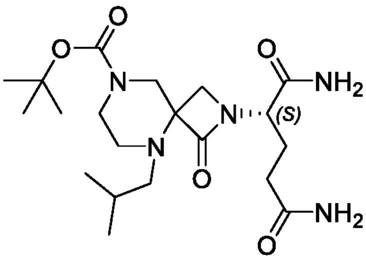
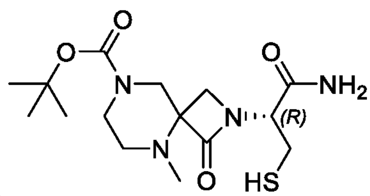
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,

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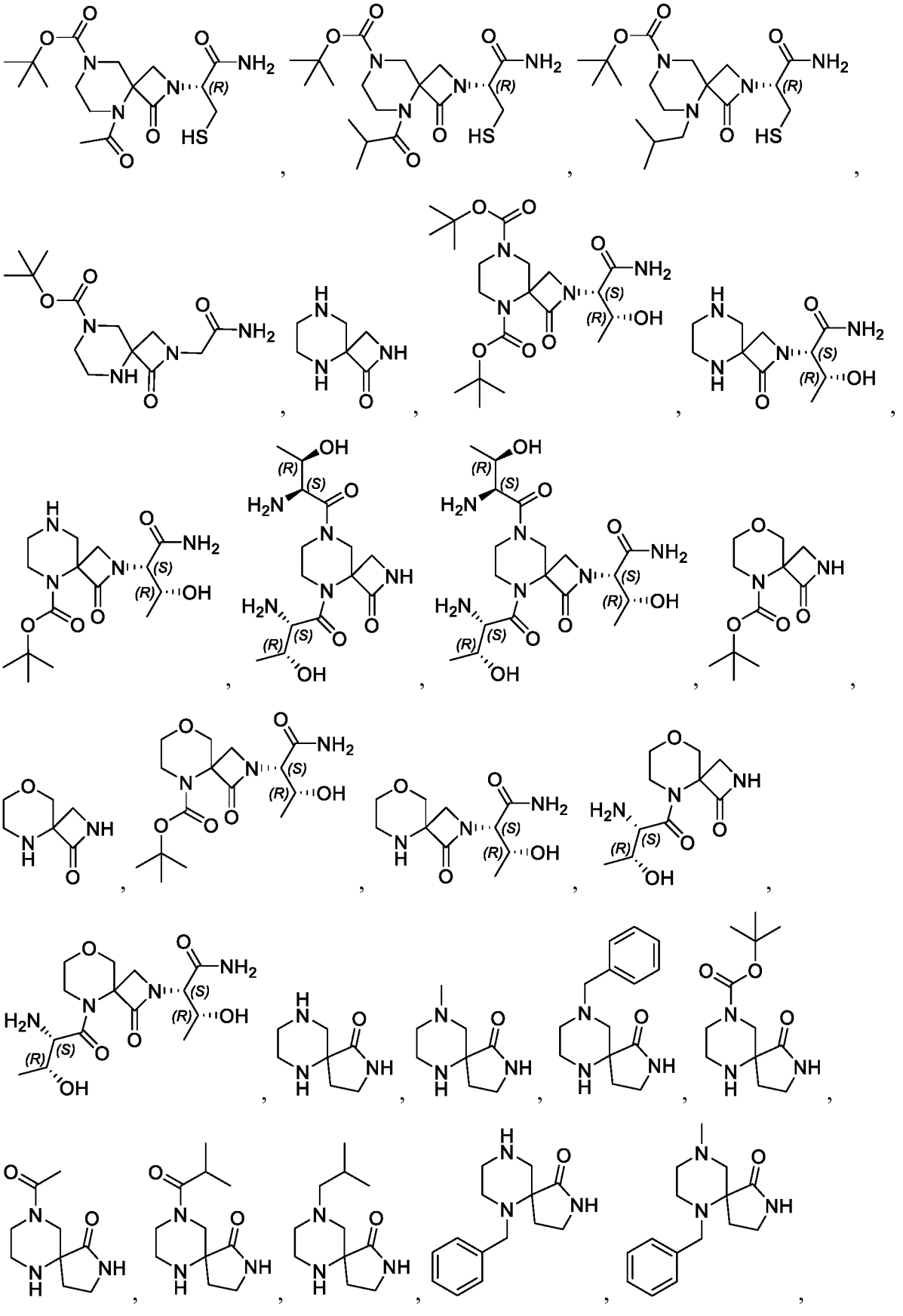

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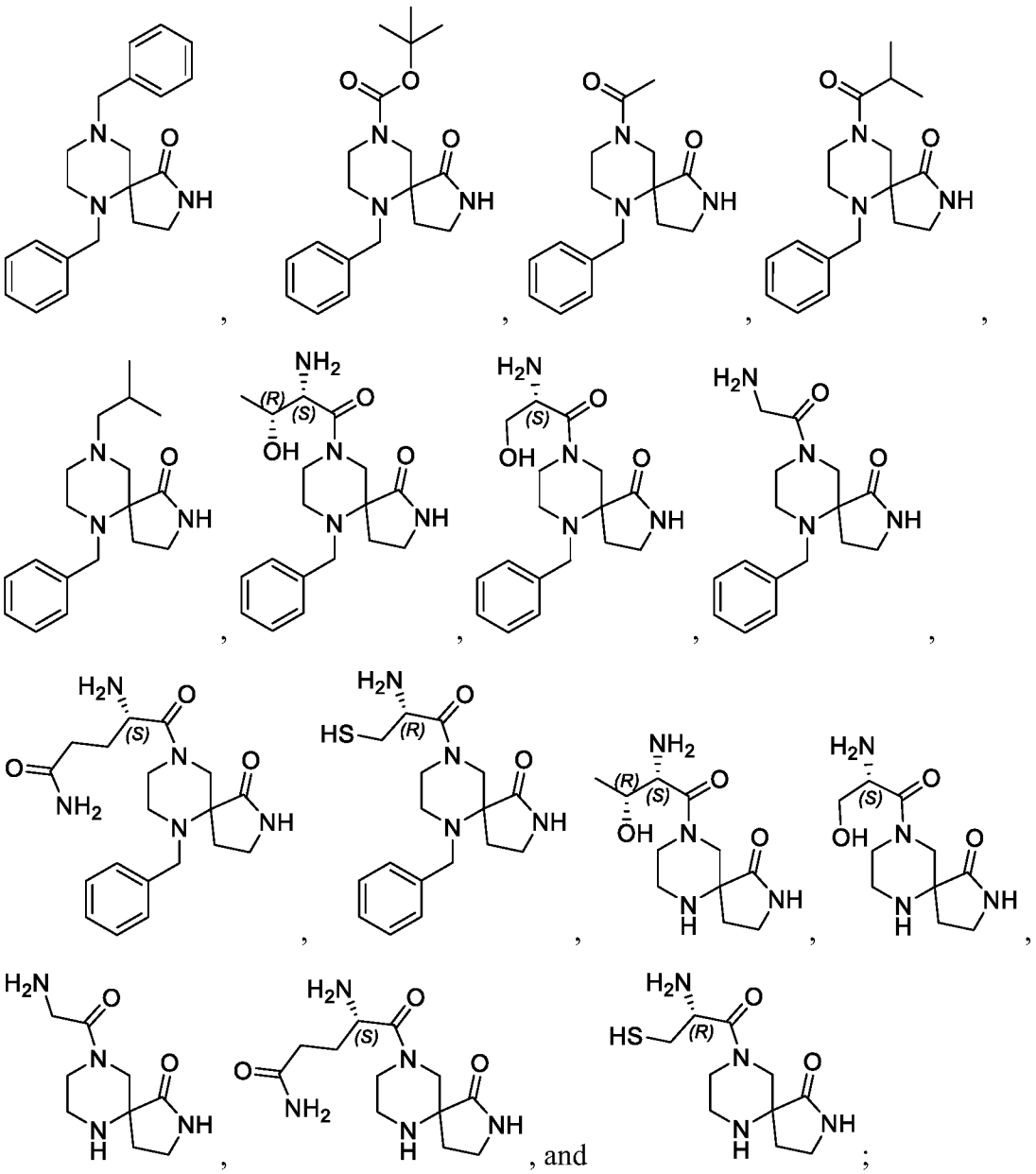

or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

According to a fourth aspect, the present invention provides a pharmaceutical composition comprising a compound of the invention, and a pharmaceutically acceptable excipient.

According to a fifth aspect, the present invention provides a method of treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety, in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of the compound of the invention or the pharmaceutical composition of the invention.

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According to a sixth aspect, the present invention provides a method of treating acute neuropathic pain or chronic neuropathic pain, in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of the compound of the invention or the pharmaceutical composition of the invention.

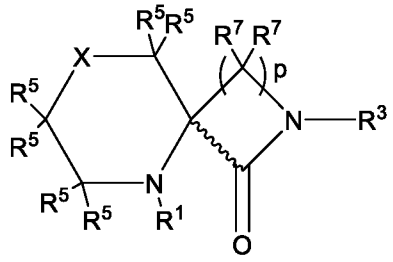
According to a seventh aspect, the present invention provides a method of treating a neurodevelopmental disorder related to synaptic dysfunction in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of the compound of the invention, or the pharmaceutical composition of the invention.

According to an eighth aspect, the present invention provides a use of a therapeutically effective amount of the compound of the invention or the pharmaceutical composition of the invention for the manufacture of a medicament for treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety in a patient in need thereof.

According to a ninth aspect, the present invention provides a use of a therapeutically effective amount of the compound of the invention or the pharmaceutical composition of the invention for the manufacture of a medicament for treating acute neuropathic pain or chronic neuropathic pain in a patient in need thereof.

According to a tenth aspect, the present invention provides a use of a therapeutically effective amount of the compound of the invention, or the pharmaceutical composition of the invention for the manufacture of a medicament for treating a neurodevelopmental disorder related to synaptic dysfunction in a patient in need thereof.

The present disclosure includes compounds that can be NMDA modulators. More specifically, the present disclosure provides a compound having the formula:



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

X is O or NR^2;

R^1 is selected from the group consisting of H, C_1-C_6alkyl, phenyl, -C(O)-C_1-C_6alkyl, and -C(O)-O-C_1-C_6 alkyl;

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R^2 is selected from the group consisting of H, C_1-C_6alkyl, phenyl, -C(O)-C_1-C_6alkyl, and -C(O)-O-C_1-C_6 alkyl;

p is 1 or 2;

R^5 is independently selected for each occurrence from the group consisting of H, C_1-C_6alkyl, -$S(O)_w$-C_1-C_3alkyl, - NR^aR^b, C_1-C_3alkoxy, cyano, and halogen;

w is 0, 1, or 2

R^3 is selected from the group consisting of H, C_1-C_6 alkyl, phenyl -$C(O)R^{31}$ and -$C(O)OR^{32}$;

R^{31} and R^{32} are each independently H, C_1-C_6alkyl, -C_3-C_6cycloalkyl, and phenyl;

R^7 is independently selected for each occurrence from the group consisting of H, halogen, phenyl, and C_1-C_6 alkyl;

R^a and R^b are each independently for each occurrence selected from the group consisting of H, C_1-C_3alkyl, and phenyl, or R^a and R^b taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring;

wherein any aforementioned C_1-C_6 alkyl, independently for each occurrence, can be optionally substituted by one, two or three substituents each independently selected from –C(O)NR^aR^b, -NR^aR^b, hydroxyl, $S(O)_w$-C_1-C_3alkyl, SH, phenyl and halogen, and wherein any aforementioned phenyl, independently for each occurrence, can be

optionally substituted by one, two or three substituents each independently selected from hydroxyl, halogen, -C(O)-O-C_1-C_3alkyl, -C(O)-C_1-C_3alkyl, methyl, and CF_3.

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 some aspects, compounds described herein bind to NMDA receptors expressing certain NR2 subtypes. In some aspects, the compounds described herein bind to one NR2 subtype and not another. It should be appreciated that disclosed compounds may modulate other protein targets and/or specific NMDA receptor subtype.

In another aspect, a method of treating a condition selected from the group consisting of 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 syndrome, a behavior disorder, an impulse control disorder, a substance abuse disorder, a sleep disorder, a memory disorder, 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, infantile spasms, 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 the patient a pharmaceutically effective amount of a disclosed compound or pharmaceutically acceptable salts, stereoisomers, N-oxides, and hydrates thereof.

In some embodiments, a method of this disclosure includes treating neuropathic pain, wherein the neuropathic pain is selected from the group consisting of herpes, HIV, traumatic nerve injury, stroke, post-ischemia, chronic back pain, post-herpetic neuralgia, fibromyalgia, reflex sympathetic dystrophy, complex regional pain syndrome, spinal cord injury, sciatica,

phantom limb pain, diabetic neuropathy, and cancer chemotherapeutic-induced neuropathic pain.

In some embodiments, a method of this disclosure includes treating depression. For example, depression may include one or more of major depressive disorder, dysthymic disorder, psychotic depression, postpartum depression, seasonal affective disorder, bipolar disorder, mood disorder, or depression caused by a chronic medical condition. In some embodiments, a disclosed method may treat schizophrenia. Such schizophrenia may be, for example, paranoid type schizophrenia, disorganized type schizophrenia, catatonic type schizophrenia, undifferentiated type schizophrenia, residual type schizophrenia, post-schizophrenic depression, or simple schizophrenia.

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. 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 C_1-C_6 alkyl, C_1-C_4 alkyl, and C_1-C_3 alkyl, respectively. For example, "C_1-C_6 alkyl" refers to a straight-chain or branched saturated hydrocarbon containing 1-6 carbon atoms. Examples of a C_1-C_6 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, "C_1-C_4 alkyl" refers to a straight-chain or branched saturated hydrocarbon containing 1-4 carbon atoms. Examples of a C_1-C_4 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 "alkoxy," as used herein, refers to an alkyl group attached to an oxygen atom (alkyl-O-). Alkoxy groups can have 1-6 or 2-6 carbon atoms and are referred to herein as C_1-C_6 alkoxy and C_2-C_6 alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to, methoxy, ethoxy, propyloxy, isopropoxy, and tert-butoxy.

The term "carbonyl," as used herein, refers to the radical -C(O)- or C=O.

The term "cyano," as used herein, refers to the radical -CN.

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 C_3-C_6 cycloalkyl or C_4-C_6 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 term "heteroatom," as used herein, refers to an atom of any element other than carbon or hydrogen and includes, for example, nitrogen (N), oxygen (O), silicon (Si), sulfur (S), phosphorus (P), and selenium (Se).

The term "heterocyclic ring" or "heterocycloalkyl," as used herein, is art-recognized and refer to saturated or partially unsaturated 3- to 8-membered ring structures, whose ring system include one, two or three heteroatoms, such as nitrogen, oxygen, and/or sulfur. A heterocyclic ring can be fused to one or more phenyl, partially unsaturated, or saturated rings. Examples of heterocyclic rings include, but are not limited to, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, and piperazinyl.

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

The term "oxo," as used herein, refers to the radical =O (double bonded oxygen).

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, esters 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, an ester, or an N-oxide thereof. It should be understood that a compound can refer to a pharmaceutically acceptable salt, or a hydrate, an ester or an N-oxide of a stereoisomer of the compound and/or an isotopically-labelled compound.

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 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 $\overset{\cdots\cdots}{=}$ 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 ^{2}H ("D"), ^{3}H, ^{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.

Certain isotopically-labeled compounds (*e.g.*, those labeled with ^{3}H and ^{14}C) can be useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H) 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.*, ^{2}H) can afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* 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 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.

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 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.

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, 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, 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 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.

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, 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.

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 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 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. In some embodiments, the compound is amorphous. In certain embodiments, the compound is a single polymorph. In various embodiments, the compound is a mixture of polymorphs. In particular embodiments, the compound is in a crystalline form.

The term "prodrug" refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (such as by esterase, amidase, phosphatase, oxidative and or reductive metabolism) in various locations (such as in the intestinal lumen or upon transit of the intestine, blood or liver). Prodrugs are well known in the art (for example, see Rautio, Kumpulainen, *et al,* Nature Reviews Drug Discovery 2008, 7, 255). For example, if a compound described herein or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as $(C_1$-$C_8)$alkyl, $(C_2$-$C_{12})$alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-$(C_1$-$C_2)$alkylamino$(C_2$-$C_3)$alkyl (such as β-dimethylaminoethyl), carbamoyl-$(C_1$-$C_2)$alkyl, N,N-di$(C_1$-$C_2)$alkylcarbamoyl-$(C_1$-$C_2)$alkyl and piperidino-, pyrrolidino- or morpholino$(C_2$-$C_3)$alkyl.

Similarly, if a compound described herein contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as $(C_1$-$C_6)$alkanoyloxymethyl, 1-$((C_1$-$C_6)$alkanoyloxy)ethyl, 1-methyl-1-$((C_1$-$C_6)$alkanoyloxy)ethyl $(C_1$-$C_6)$alkoxycarbonyloxymethyl, N-$(C_1$-$C_6)$alkoxycarbonylaminomethyl, succinoyl, $(C_1$-$C_6)$alkanoyl, α-amino$(C_1$-$C_4)$alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$,

-P(O)(O(C_1-C_6)alkyl)$_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

If a compound described herein incorporates an amine functional group, a prodrug can be formed, for example, by creation of an amide or carbamate, an N-acyloxyakyl derivative, an (oxodioxolenyl) methyl derivative, an N-Mannich base, imine or enamine. In addition, a secondary amine can be metabolically cleaved to generate a bioactive primary amine, or a tertiary amine can metabolically cleaved to generate a bioactive primary or secondary amine. For examples, see Simplício, *et al., Molecules* 2008, *13,* 519 and references therein.

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, 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.

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.

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 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 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.

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 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.

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 ±10% variation from the nominal value unless otherwise indicated or inferred.

Where a percentage is provided with respect to an amount of a component or material in 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.

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 subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose C_1, C_2, C_3, C_4, C_5, C_6, C_1-C_6, C_1-C_5, C_1-C_4, C_1-C_3, C_1-C_2, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6 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, 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, 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.

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.

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, Rb, 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.

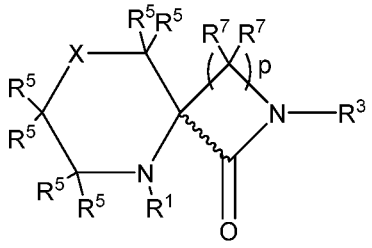
Definitions of the variables and/or substituents in formulae and/or compounds herein encompass multiple chemical groups. The present disclosure includes embodiments where, for example, i) the definition of a variable and/or substituent is a single chemical group selected from those chemical groups set 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 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 apply to any aspect, embodiment, or feature of the present disclosure.

Compounds

Disclosed compounds include a compound having the formula:



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

X is O or NR^2;

R^1 is selected from the group consisting of H, C_1-C_6alkyl, phenyl, -C(O)-C_1-C_6alkyl, and -C(O)-O-C_1-C_6 alkyl;

R^2 is selected from the group consisting of H, C_1-C_6alkyl, phenyl, -C(O)-C_1-C_6alkyl, and -C(O)-O-C_1-C_6 alkyl;

p is 1 or 2;

R^5 is independently selected for each occurrence from the group consisting of H, C_1-C_6alkyl, -$S(O)_w$-C_1-C_3alkyl, - NR^aR^b, C_1-C_3alkoxy, cyano and halogen;

w is 0, 1, or 2

R^3 is selected from the group consisting of H, phenyl, C_1-C_6 alkyl, -$C(O)R^{31}$ and -$C(O)OR^{32}$;

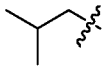
R^{31} and R^{32} are each independently H, C_1-C_6alkyl, -C_3-C_6cycloalkyl, and phenyl;

R^7 is independently selected for each occurrence from the group consisting of H, halogen, phenyl, and C_1-C_6 alkyl; and

R^a and R^b are each independently for each occurrence selected from the group consisting of H, C_1-C_3alkyl, and phenyl, or R^a and R^b taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring;

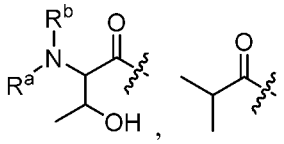
wherein any aforementioned C_1-C_6 alkyl, independently for each occurrence, may be optionally substituted by one, two or three substituents each independently selected from –C(O)NR^aR^b, -NR^aR^b, hydroxyl, $S(O)_w$-C_1-C_3alkyl, SH, phenyl and halogen, and wherein any aforementioned phenyl, independently for each occurrence, may be optionally substituted by one, two or three substituents each independently selected from hydroxyl, halogen, -C(O)-O-C_1-C_3alkyl, -C(O)-C_1-C_3alkyl, methyl, and CF_3.

In certain embodiments, R^1 can be -C(O)-O-C_1-C_6 alkyl. For example, R^1 can be tert-butyloxycarbonyl.

In certain embodiments, R^1 can be C_1-C_6alkyl, optionally substituted by benzyl or one, two or three fluorines. For example, R^1 can be methyl; while in some embodiments, R^1 can be  .

In some embodiments, R^1 can be H.

In certain embodiments, R^1 can be -C(O)-C_1-C_6alkyl, where -C(O)-C_1-C_6alkyl can be represented by:

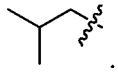
 , , or  , wherein R^a and R^b can be independently selected for each occurrence from the group consisting of hydrogen and -C_1-C_6alkyl.

In some embodiments, R^1 can be benzyl.

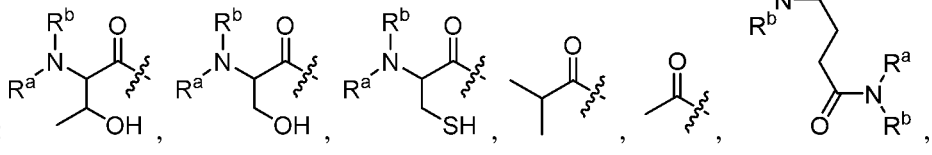
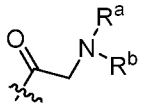
In certain embodiments, X can be O; while in certain embodiments, X can be NR^2.

In certain embodiments, R^2 can be H.

In certain embodiments, R^2 can be C_1-C_6alkyl, optionally substituted by benzyl or one, two or three fluorines, -C(O)-C_1-C_6alkyl, or -C(O)-O-C_1-C_6 alkyl. For example, R^2 can be

methyl or  .

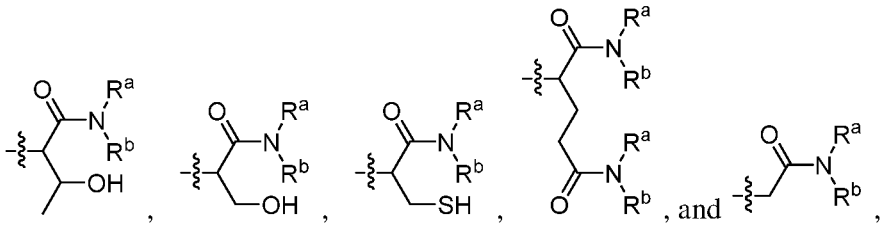
In some embodiments, R^2 can be benzyl.

In certain embodiments, R^2 can be -C(O)-C_1-C_6alkyl, where -C(O)-C_1-C_6alkyl can be represented by:  , or  , wherein R^a and R^b can be each independently selected for each occurrence from the group consisting of hydrogen and -C_1-C_6alkyl.

In some embodiments, R^2 can be -C(O)-O-C_1-C_6 alkyl, for example, tert-butyloxycarbonyl.

In certain embodiments, p is 1; while in certain embodiments, p is 2.

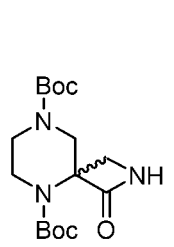
In some embodiments, R^3 can be H.

In certain embodiments, R^3 can be selected from the group consisting of:  , and , wherein R^a and R^b are each independently selected for each occurrence from the group consisting of hydrogen and -C_1-C_6alkyl.

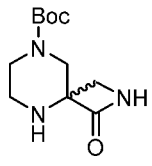
In certain embodiments, R^1, R^2, and/or R^3 independently can be an amino acid or a derivative of an amino acid, for example, an alpha "amino amide" represented by H_2N-CH(amino acid side chain)-C(O)NH_2. In certain embodiments, the nitrogen atom of the amino group of the amino acid or the amino acid 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 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/or R^3 independently can be an alpha amino acid, an alpha 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 some embodiments, the compound is selected from the compounds delineated in the Examples, and includes pharmaceutically acceptable salts and/or stereoisomers thereof. In certain embodiments, a disclosed compound includes one having the formula:



EE-1
EE-2



EB-1
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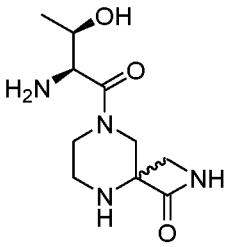

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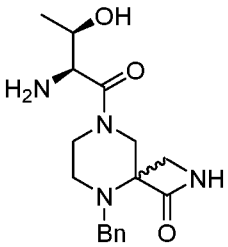
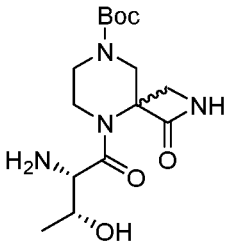
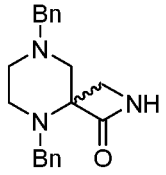


EL-1
EL-2

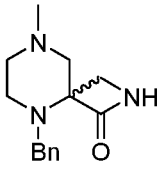


EC-1
EC-2

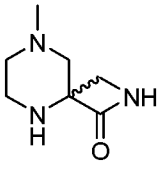


EA-1
EA-2

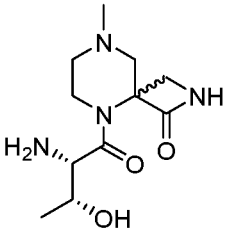
ED-1
ED-2



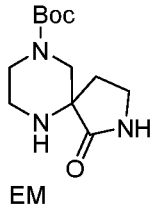
EG-1
EG-2



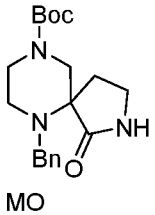
EH-1
EH-2



EJ-1
EJ-2



EM
EN



MO
MP

, and .

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 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, 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, 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 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 NMDA receptor subtypes. For example, a disclosed compound may bind to one NMDA subtype and not another. In some 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.

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 the disclosure, a pharmaceutical formulation or a pharmaceutical composition including a disclosed compound and a pharmaceutically acceptable excipient is provided. In some embodiments, a pharmaceutical composition comprises a racemic 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 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 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.

For example, pharmaceutical compositions of the disclosure can be suitable for delivery to the eye, i.e., ocularly. Related methods can include administering a pharmaceutically 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, subtenonly, intravitreally, retrobulbarly, 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 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 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.

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 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 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 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 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 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.

In some embodiments, a compound can be formulated with one or more additional compounds that enhance the solubility of the compound.

Methods of the disclosure for treating a condition in a patient in need thereof include administering a therapeutically effective amount of a compound described herein or a composition including such a compound. In some embodiments, the condition may be a mental condition. For example, a mental illness may be treated. In another aspect, 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, olivio-ponto-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, methods of treating a memory disorder associated with aging, schizophrenia, special learning disorders, seizures, post-stroke convulsions, brain ischemia, hypoglycemia, cardiac arrest, epilepsy, Lewy body dementia, migraine, AIDS dementia, Huntington's chorea, Parkinson's disease, early stage Alzheimer's disease, and Alzheimer's disease are provided.

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 disclosed 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 disclosed herein.

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

In various embodiments, methods for treating social withdrawal in conditions including, but not limited to, social anxiety disorder, avoidant personality disorder, and schizotypal personality disorder are provided.

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 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 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 neuroligin (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, 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 include a method of treating autism and/or an autism spectrum disorder in a patient need thereof, comprising administering an effective amount of a compound to the patient. In certain embodiments, a method for reducing the symptoms of autism in a patient in need thereof comprises administering an effective amount of a 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).

Also provided herein is a method of modulating an autism target gene expression in a 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.

In certain 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 modulating an Alzheimer's amyloid protein (e.g., beta amyloid peptide, e.g. the isoform $A\beta_{1-42}$), 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 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 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 pharmaceutically effective amount of a disclosed compound to a patient in need thereof.

In certain embodiments, a method of treating depression includes administering a therapeutically effective amount of a compound described herein. 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 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, 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 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.

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 disclosed herein.

Also provided herein are combination therapies comprising a compound of the disclosure in combination 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, 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 should be understood that combinations of a compound and one or more of

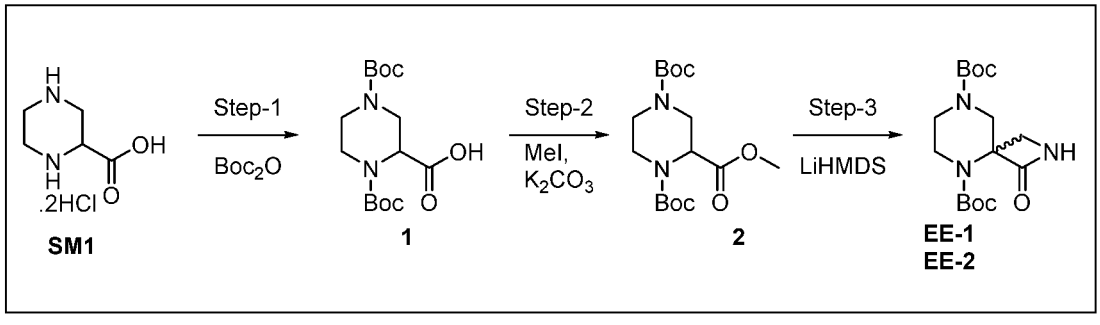
the above therapeutics may be used for treatment of any suitable condition and are not limited to use as antidepressants or antipsychotics.

EXAMPLES

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

The following abbreviations may be used herein and have the indicated definitions: Ac is acetyl (-C(O)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, DMSO is dimethyl sulfoxide, ESI is electrospray ionization, EtOAc is ethyl acetate, h is hour, HATU is 2-(7-aza-1*H*-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, LiHMDS is lithium hexamethyldisilazane, NMDAR is N-methyl-d-apartate 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), TEA is triethylamine, TLC is thin layer chromatography, TFA is trifluoroacetic acid, THF is tetrahydrofuran, and TMS is trimethylsilyl.

EXAMPLE 1: Synthesis of exemplary compounds



Synthesis of 1,4-bis(tert-butoxycarbonyl)piperazine-2-carboxylic acid (1):

To a stirring solution of piperazine-2-carboxylic acid dihydrochloride (**SM1**) (5 g, 24.6 mmol) in 1,4-dioxane (40 mL) were added 5 N NaOH solution (3.5 g, 88.6 mmol) and Boc-anhydride (12.9 mL, 56.6 mmol) at 0 °C and the reaction mixture was stirred at RT for 16 h. After

consumption of the starting material (by TLC), volatiles were evaporated under reduced pressure. Obtained crude was dissolved in water (50 mL) and extracted with Et_2O (2 x 100 mL). Organic layer was acidified with 1 N HCl solution and extracted with EtOAc (2 x 100 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford crude compound which was triturated with *n*-pentane to obtain compound **1** (6 g, 74%) as white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.91 (br s, 1H), 4.42 (d, J = 24.8 Hz, 1H), 4.35-4.27 (dd, J = 20.4, 13.6 Hz, 1H),3.82 (s, 1H), 3.66 (d, J = 13.2 Hz, 1H), 2.99-2.79 (m, 2H), 2.79 (br s, 1H), 1.37 (s, 18H).

LCMS (m/z): 329.3 [M^+-1]

Synthesis of 1,4-di-tert-butyl 2-methyl piperazine-1,2,4-tricarboxylate (2):

To a stirring solution of compound **1** (6 g, 18.2 mmol) in DMF (30 mL) were added K_2CO_3 (3 g, 21.8 mmol) and MeI (1.7 mL, 27.2 mmol) at 0 °C and the reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with citric acid (50 mL), brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting with 10% EtOAc/ hexanes to obtain compound **2** (5 g, 82%) as white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 4.56 (d, J = 28.8 Hz, 1H), 4.32-4.22 (dd, J = 24.8, 14.0 Hz, 1H), 3.82 (br s, 1H), 3.82-3.66 (m, 4H), 3.14-2.82 (m, 3H), 1.37 (s, 18H).

LCMS (ESI): *m/z* 145.0 [(M^++1)-2Boc].

Synthesis of di-tert-butyl 1-oxo-2,5,8-triazaspiro[3.5]nonane-5,8-dicarboxylate (EE-1 & EE-2):

To a stirring solution of compound **2** (1 g, 2.91 mmol) in dry THF (20 mL) were added LiHMDS (1.0 M in THF) (10.2 mL, 10.2 mmol), paraformaldehyde (69 mg, 2.32 mmol) at -78 °C under nitrogen atmosphere. The reaction mixture was brought to RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction was quenched with ice water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine solution (2 x 10 mL), dried over Na_2SO_4 and concentrated to obtain crude compound which was purified by column chromatography by eluting 30% EtOAc/ hexanes to afford

racemic **EE** (320 mg, 32%) as white solid. The racemic was separated by chiral HPLC purification to give 75mg each of **EE-1** and **EE-2**.

EE-1:

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.98 (s, 1H), 3.78 (d, *J* = 12.8 Hz, 1H), 3.67-3.60 (m, 1H), 3.51 (d, *J* = 13.6 Hz, 1H), 3.41-3.30 (m, 4H), 3.07 (br s, 1H), 1.39 (s, 18H).

LCMS (ESI): *m/z* 340.1 [M^+-1];

UPLC: 99.74%

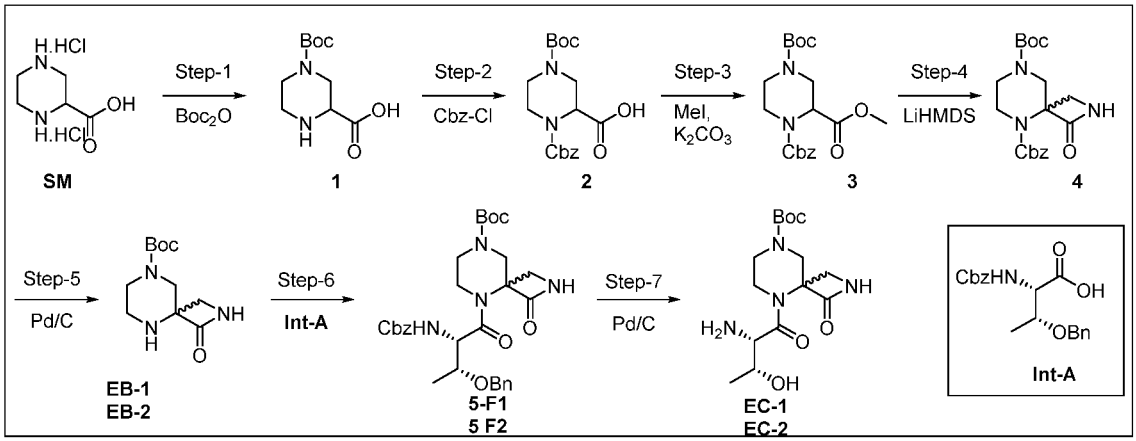
EE-2:

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.99 (s, 1H), 3.78 (d, *J* = 12.8 Hz, 1H), 3.65-3.61 (m, 1H), 3.51 (d, *J* = 13.6 Hz, 1H), 3.40-3.30 (m, 4H), 3.07 (br s, 1H), 1.39 (s, 18H).

LCMS (ESI): *m/z* 340.1 [M^+-1];

UPLC: 99.04%

EXAMPLE 2: Synthesis of exemplary compounds



Synthesis of 4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (1)

To a stirred suspension of piperazine-2-carboxylic acid (**SM**) (5 g, 24.6 mmol) in 1, 4-dioxane: water (1: 1, 100 mL) was added $NaHCO_3$ (3.1 g, 36.9 mmol) followed by Boc-anhydride (5.6 mL, 24.6 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction was diluted with water (50 mL) and extracted with Et_2O (2 x 100 mL). Aqueous layer was acidified with 2N HCl solution and extracted with *n*-BuOH. Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford compound **1** (5 g, 88%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 10.18 (br s, 1H), 4.08 (br s, 1H), 3.81-3.71 (m, 2H), 3.63 (t, J = 6.5 Hz, 1H), 3.17-3.15 (m, 2H), 2.91-2.86 (m, 1H), 1.36 (s, 9H), 1.31-1.26 (m, 0.5H), 0.87-0.84 (m, 0.5H).

LCMS (ESI): *m/z* 229.0 [(M^+-1)].

Synthesis of 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (2):

To a stirring solution of compound **1** (5 g, 21.7 mmol) in EtOAc (70 mL) were added saturated $NaHCO_3$ solution (70 mL) followed by drop wise addition of Cbz-Cl (3.7 mL, 26.1 mmol) at 0 °C. The reaction mixture was brought to RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). Aqueous layer was acidified with 2 N HCl solution and extracted with EtOAc. Combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting with 50 % EtOAc: *n*-hexane to afford compound **2** (4 g, 50 %) as thick syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 13.06 (br s, 1H), 7.37-7.30 (m, 5H), 5.12-5.05 (m, 2H), 4.57-4.53 (m, 1H), 4.38-4.32 (m, 1H), 3.86-3.76 (m, 2H), 3.18-3.08 (m, 2H), 2.83 (br s, 1H), 1.37 (s, 9H).

LCMS (ESI): *m/z* 363.1 [M^+-1]

Synthesis of 1-benzyl 4-(tert-butyl) 2-methyl piperazine-1,2,4-tricarboxylate (3):

To a stirring solution of compound 2 (4 g, 10.9 mmol) in DMF (40 mL) were added K_2CO_3 (1.82 g, 13.2 mmol) and MeI (1 mL, 16.5 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was brought to RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction was diluted with water (20 mL) and extracted with Et_2O (2 x 50 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting 10% EtOAc/ hexanes to afford compound 3 (3.2 g, 77%) as thick syrup.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 5H), 5.21-5.11 (m, 2H), 4.78 (s, 0.5H), 4.66-4.50 (m, 1.5H), 4.02-3.88 (m, 2H), 3.68 (s, 3H), 3.24 (br s, 1H), 3.08 (dd, J = 13.6, 3.2 Hz, 1H), 2.83 (br s, 1H), 1.44 (s, 9H).

LCMS (ESI): *m/z* 279.3 [(M^++1)-Boc]

Synthesis of 5-benzyl 8-(tert-butyl) 1-oxo-2,5,8-triazaspiro[3.5]nonane-5,8-dicarboxylate (4):

To a stirring solution of compound **3** (3.2 g, 8.46 mmol) in THF (30 mL) was added paraformaldehyde (203 mg, 6.77 mmol) at RT under nitrogen atmosphere. The reaction mixture was cooled to -78 °C and added LiHMDS (1M in THF) (33.8 mL, 23.2 mmol) and allowed to stir at RT for 12 h. After consumption of the starting material (by TLC), the reaction was quenched with ice water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with water (2 x 15 mL) followed by brine solution (2 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated to obtain crude material which was purified by column chromatography by eluting with 40% EtOAc / hexanes to afford compound **4** (640 mg, 20%) as thick syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 8.04 (s, 1H), 7.37-7.31 (m, 5H), 5.14-5.07 (m, 2H), 4.07-4.01 (m, 1H), 3.83-3.73 (m, 2H), 3.72-3.41 (m, 4H),3.09 (br s, 1H), 1.40 (s, 9H).

LCMS (ESI): *m/z* 376.5 [(M^++1)]

Synthesis of tert-butyl 1-oxo-2,5,8-triazaspiro[3.5]nonane-8-carboxylate (EB-1 & EB-2):

To a stirring solution of compound **4** (600 mg, 1.6 mmol) in EtOAc (10 mL) was added 10% Pd/C (180 mg) at RT under nitrogen atmosphere. The reaction mixture was stirred at RT for 4h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite. Organic layer was dried over Na_2SO_4 and concentrated to obtain crude material which was purified by column chromatography by eluting 4% MeOH/DCM to afford **EB** (320 mg, crude) as a white solid. The racemic was separated by chiral HPLC purification and obtained 80 mg each of **EB-1** and **EB-2.**

EB-1:

^{1}H-NMR: (400 MHz, DMSO-d_6):δ 7.89 (s, 1H), 3.53 (d, J = 12.8 Hz, 1H), 3.39-3.35 (m, 1H), 3.21 (s, 1H), 3.17-3.11 (m, 1H), 3.06 (d, J = 5.2 Hz, 1H), 2.98 (d, J = 5.2 Hz, 1H), 2.92-2.87 (m, 1H), 2.59-2.53 (m, 1H), 1.38 (s, 9H).

LCMS (ESI): *m/z* 240.1 [(M^+-1)]

HPLC: 98.30%

EB-2:

^{1}H-NMR: (400 MHz, DMSO-d_6):δ 7.89 (s, 1H), 3.53 (d, J = 12.8 Hz, 1H), 3.39-3.35 (m, 1H), 3.21 (s, 1H), 3.17-3.11 (m, 1H), 3.06 (d, J = 5.2 Hz, 1H), 2.98 (d, J = 5.2 Hz, 1H), 2.92-2.87 (m, 1H), 2.59-2.53 (m, 1H), 1.38 (s, 9H).

LCMS (ESI): *m/z* 240.1 [(M^+-1)]

HPLC: 99.94%

Synthesis of tert-butyl 5-(O-benzyl-N-((benzyloxy)carbonyl)-L-threonyl)-1-oxo-2,5,8-triazaspiro[3.5]nonane-8-carboxylate (5)

To a stirred solution of Int-**A** (1.7g, 4.98 mmol) in DCM (50 mL) were added N-methyl morpholine (2.51 g, 24.89 mmol), 1-Propanephosphonic anhydride solution (50 wt. % in ethyl acetate) (7.9 g, 24.89 mmol) and racemic tert-butyl 1-oxo-2,5,8-triazaspiro[3.5]nonane-8-carboxylate (**EB-racemic**) (1 g, 4.15 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was brought to RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction was diluted with water (50 mL) and extracted with DCM (3 x 50 mL). Combined organic layer was dried over Na_2SO_4 and concentrated to obtain crude material which was purified by column chromatography by eluting 10% MeOH/ DCM to afford racemic compound **5** (700 mg, 30%) as an off white solid. The racemic was separated by chiral HPLC purification and obtained 80 mg each of compound **5-F1** and compound **5-F2.**

Compound 5-F1:

^{1}H-NMR: (400 MHz, DMSO-d_6):δ 7.99 (s, 1H), 7.42-7.24 (m, 11H), 5.04 (t, J = 14.0 Hz, 2H), 4.55-4.48 (m, 3H), 3.80-3.71 (m, 4H), 3.43 (d, J = 14.0 Hz, 1H), 3.43 (d, J = 4.0 Hz, 1H), 3.32-3.30 (m, 2H), 3.00 (br s, 1H), 1.40 (s, 9H), 1.12 (d, J = 6.4 Hz, 3H).

Compound 5-F2:

^{1}H-NMR: (400 MHz, DMSO-d_6):δ 7.96 (s, 1H), 7.35-7.25 (m, 11H), 5.08-5.01 (dd, J = 16.8, 12.8 Hz, 2H), 4.69-466 (dd, J = 8.8, 5.6 Hz, 1H), 3.54 (d, J = 12.0 Hz, 1H), 3.44 (d, J = 12.0 Hz, 1H), 3.86-3.74 (m, 4H), 3.43 (m, 1H), 3.39 (d, J = 5.4 Hz, 1H), 3.29-3.27 (m, 2H), 2.94 (br s, 1H), 1.39 (s, 9H), 1.12 (d, J = 6.4 Hz, 3H).

Synthesis of tert-butyl 5-(L-threonyl)-1-oxo-2,5,8-triazaspiro[3.5]nonane-8-carboxylate (EC-1):

To a stirring solution of compound **5**-F1 (140 mg, 0.25 mmol) in methanol (10 mL) was added 10% Pd/C (45 mg) at RT under nitrogen atmosphere. The reaction mixture was stirred at RT

for 48h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite. Organic layer was dried over Na_2SO_4 and concentrated to obtain crude material which was purified by preparative HPLC to afford **EC-1** (12 mg) as a white solid.

EC-1:

^{1}H-NMR: (400 MHz, D_2O):δ 4.51 (d, *J* = 13.6 Hz, 1H), 4.40-4.28 (m, 2H), 4.18 (s, 2H), 4.42 (d, *J* = 14.0 Hz, 1H), 3.22 (d, *J* = 14.0 Hz, 2H), 3.13-3.05 (m, 1H), 2.92 (br s, 1H), 1.51 (s, 9H), 1.33 (d, *J* = 6.8 Hz, 3H).

LCMS (ESI): *m/z* 343.1 [(M^++1)]

HPLC: 95.90%

Chiral HPLC: 99.00%

Synthesis of tert-butyl 5-(L-threonyl)-1-oxo-2,5,8-triazaspiro[3.5]nonane-8-carboxylate (EC-2):

To a stirring solution of compound **5**-F2 (70 mg, 0.12 mmol) in methanol (3 mL) was added 10% Pd/C (23 mg) at RT under nitrogen atmosphere. The reaction mixture was stirred at RT for 12h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite. Organic layer was dried over Na_2SO_4 and concentrated to obtain crude material was triturated with pentane/ ether to afford **EC-2** (23 mg, 59%) as an off white solid.

EC-2:

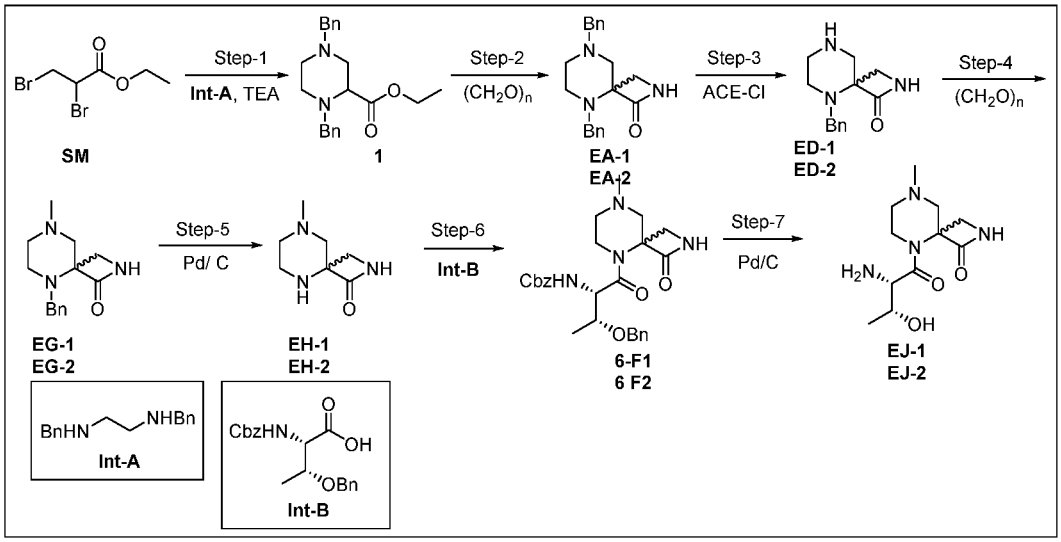
^{1}H-NMR: (400 MHz, D_2O):δ 4.52-4.49 (m, 1H), 4.38-4.30 (m, 2H), 4.22-4.16 (s, 2H), 3.22 (d, *J* = 14.4 Hz, 2H), 3.12-3.01 (m, 3H), 1.52 (s, 9H), 1.31 (d, *J* = 6.8 Hz, 3H).

LCMS (ESI): *m/z* 343.1 [(M^++1)]

HPLC: 91.00%

Chiral HPLC: 98.20%

EXAMPLE 3: Synthesis of exemplary compounds



Synthesis of ethyl 1,4-dibenzylpiperazine-2-carboxylate (1):

To a solution of Int-A (20 g, 83.2 mmol) and triethylamine (23.0 mL, 166.4 mmol) in toluene (300 mL) was added ethyl 2,3-dibromopropanoate (SM) (12.1 mL, 83.2 mmol) slowly at 40 °C. The reaction mixture was heated to 80 °C and stirred for 4 h. After consumption of the starting material (by TLC), the reaction mixture was brought to RT and volatiles were evaporated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting 5%-30% EtOAc/ hexanes to afford compound 1 (21.2 g, 75%) as light green syrup.

^{1}H-NMR: (500 MHz,CDCl3): δ 7.33-7.7.22 (m, 10H), 4.17-4.15 (q, *J* = 7.0 Hz, 2H), 3.90 (d, *J* = 13.5 Hz, 1H), 3.59-3.54 (m, 2H), 3.42 (d, *J* = 13.5 Hz, 1H), 3.31-3.29 (m, 1H), 2.76-2.62 (m, 2H), 2.48-2.38 (m, 4H), 1.25 (t, *J* = 7.0 Hz, 3H).

LCMS (m/z): 339 [M^++1]

Synthesis of 5,8-dibenzyl-2,5,8-triazaspiro[3.5]nonan-1-one (EA-1 & EA-2):

To a solution of compound **1** (1.5 g, 4.43 mmol) in THF (15 mL) was added paraformaladehyde (133 mg, 4.43 mmol) and LiHMDS (1M in THF) (13.3 mL, 13.3 mmol) at -10 °C. The reaction mixture was brought to RT and stirred for 16h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 100 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain racemic compound **2** (800 mg, 56%) as white solid. The

racemic was separated by chiral HPLC purification and obtained 350 mg of **EA-1** and 350 mg of **EA-2** .

EA-1:

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.01 (s, 1H), 7.34-7.20 (m, 10H), 3.74 (d, J = 13.6 Hz, 1H), 3.55-3.52 (m, 2H), 3.45 (d, J = 13.2 Hz, 1H), 3.39 (d, J = 13.2 Hz, 1H), 2.96 (d, J = 6.0 Hz, 1H), 2.74-2.72 (m, 1H), 2.59 (d, J = 10.8 Hz, 1H), 2.49 (s, 1H), 2.35 (d, J = 10.8 Hz, 1H), 2.26-2.20 (td, J = 14.8, 2.8 Hz, 1H), 2.11-2.05 (td, J = 14.8, 2.8 Hz, 1H).

LCMS (ESI): *m/z* 321 [(M^+]

HPLC: 98.68%

EA-2:

^{1}H-NMR: (400 MHz, DMSO-d_6):δ 8.01 (s, 1H), 7.34-7.21 (m, 10H), 3.74 (d, J = 13.6 Hz, 1H), 3.55-3.52 (m, 2H), 3.45 (d, J = 13.2 Hz, 1H), 3.39 (d, J = 13.2 Hz, 1H), 2.96 (d, J = 6.0 Hz, 1H), 2.74-2.72 (m, 1H), 2.59 (d, J = 10.8 Hz, 1H), 2.49 (s, 1H), 2.35 (d, J = 10.8 Hz, 1H), 2.26-2.20 (td, J = 14.8, 2.8 Hz, 1H), 2.11-2.05 (td, J = 14.8, 2.8 Hz, 1H).

LCMS (ESI): *m/z* 321 [(M^+]

HPLC: 99.03%

Synthesis of 5-benzyl-2,5,8-triazaspiro[3.5]nonan-1-one (ED-1):

To a solution of **EA-1** (270 mg, 0.84 mmol) in 1,2-dichloroethane (3 mL) was added 1-chloro ethylchloroformate (132 mg, 0.92 mmol) in 1,2-dichloroethane (2 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was heated to reflux and stirred for 1h. The reaction mixture was brought to RT and volatiles were evaporated under reduced pressure. Crude material was dissolved in methanol (5 mL) and heated to reflux again for 1h. The reaction mixture was brought to RT and diluted with ice water (5 mL) and extracted with DCM (2x50 mL). Aqueous layer was basified with $NaHCO_3$ solution extracted with 10% MeOH/ DCM. Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Obtained crude material was triturated with ether and pentane to afford **ED-1** (140 mg, 72%) as an off white solid.

ED-1:

^{1}H-NMR: (400 MHz, DMSO-d_6):δ 7.98 (s, 1H), 7.31-7.20 (m, 5H), 3.71 (d, J = 13.6 Hz, 1H), 3.49 (d, J = 6.0 Hz, 1H), 3.36 (d, J = 13.6 Hz, 1H), 3.07 (d, J = 5.6 Hz, 1H), 2.96 (d, J = 6.0 Hz, 1H), 2.91-2.84 (m, 2H), 2.69-2.66 (m, 1H), 2.57-2.53 (m, 1H), 2.40-2.36 (td, J = 11.2, 3.2 Hz, 1H), 2.09-2.03 (td, J = 11.2, 3.2 Hz, 1H).

LCMS (ESI): *m/z* 231 [(M^+]

HPLC: 99.18%

Chiral HPLC: 99.41%

Synthesis of 5-benzyl-2,5,8-triazaspiro[3.5]nonan-1-one (ED-2):

To a solution of **EA-2** (270 mg, 0.84 mmol) in 1,2-dichloroethane (4 mL) was added 1-chloro ethylchloroformate (132 mg, 0.92 mmol) in 1,2-dichloroethane (2 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was heated to reflux and stirred for 1h. The reaction mixture was brought to RT and volatiles were evaporated under reduced pressure. Crude material was dissolved in methanol (5 mL) and heated to reflux again for 1h. The reaction mixture was brought to RT and diluted with ice water (5 mL) and extracted with DCM (2x50 mL). Aqueous layer was basified with $NaHCO_3$ solution extracted with 10% MeOH/ DCM. Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Obtained crude material was triturated with ether and pentane to afford **ED-2** (110 mg, 56%) as an off white solid.

ED-2:

^{1}H-NMR: (400 MHz, DMSO-d_6):δ 7.99 (s, 1H), 7.31-7.20 (m, 5H), 3.71 (d, *J* = 13.6 Hz, 1H), 3.49 (d, *J* = 6.0 Hz, 1H), 3.36 (d, *J* = 13.6 Hz, 1H), 3.07 (d, *J* = 6.0 Hz, 1H), 2.96 (d, *J* = 6.0 Hz, 1H), 2.91-2.84 (m, 2H), 2.69-2.66 (m, 1H), 2.57-2.53 (m, 1H), 2.40-2.36 (td, *J* = 11.2, 3.2 Hz, 1H), 2.09-2.03 (td, *J* = 11.2, 3.2 Hz, 1H).

LCMS (ESI): *m/z* 231 [(M^+]

HPLC: 99.50%

Chiral HPLC: 99.18%

Synthesis of 5-benzyl-8-methyl-2,5,8-triazaspiro[3.5]nonan-1-one (EG-1):

To a stirred solution of racemic ED (1.6 g, 6.92 mmol, racemic) in 1,2-dichloroethane (20 mL) was added paraformaladehyde (415 mg, 13.8 mmol), sodium cyanoborohydride (872 mg, 13.8 mmol) and acetic acid (0.8 mL, 13.8 mmol) at 0 °C. The reaction mixture was stirred at RT for 16h. After consumption of the starting material (by TLC), the reaction mixture was dissolved in 10% MeOH/ DCM and washed with $NaHCO_3$ solution. Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford racemic EG (550 mg, 33%) as an off white solid. The racemic was separated by chiral HPLC purification and obtained 170 mg each of EG-1 and EG-2.

EG-1:

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.04 (s, 1H), 7.31-7.22 (m, 5H), 3.74 (d, *J* = 13.2 Hz, 1H), 3.52 (d, *J* = 6.0 Hz, 1H), 3.38 (d, *J* = 13.6 Hz, 1H), 3.03 (d, *J* = 6.0 Hz, 1H), 2.76 (d, *J* = 10.8 Hz, 1H), 2.47-2.42 (m, 1H), 2.30 (d, *J* = 10.8 Hz, 1H), 2.23 (d, *J* = 2.8 Hz, 1H), 2.22- (d, *J* = 3.2 Hz, 1H), 2.17 (s, 3H), 1.98-1.92 (td, *J* = 10.8, 2.8 Hz, 1H).

LCMS (ESI): *m/z* 246.0 [(M^++1]

HPLC: 99.12%

EG-2:

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.04 (s, 1H), 7.31-7.22 (m, 5H), 3.74 (d, *J* = 13.2 Hz, 1H), 3.52 (d, *J* = 6.0 Hz, 1H), 3.38 (d, *J* = 13.6 Hz, 1H), 3.03 (d, *J* = 6.0 Hz, 1H), 2.76 (d, *J* = 10.8 Hz, 1H), 2.47-2.43 (m, 1H), 2.30 (d, *J* = 10.8 Hz, 1H), 2.23 (d, *J* = 2.8 Hz, 1H), 2.22- (d, *J* = 3.2 Hz, 1H), 2.17 (s, 3H), 1.98-1.92 (td, *J* = 10.8, 2.8 Hz, 1H).

LCMS (ESI): *m/z* 246.0 [(M^++1]

HPLC: 98.20%

Synthesis of 8-methyl-2,5,8-triazaspiro[3.5]nonan-1-one (EH-1):

To a stirring solution of **EG-1** (70 mg, 0.28 mmol) in methanol (3 mL) was added 10% Pd/C (23 mg) at RT under nitrogen atmosphere. The reaction mixture was stirred at RT for 4h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. Obtain crude material was triturated with pentane to afford **EH-1** (35 mg, 79%) as a white solid.

EH-1:

^{1}H-NMR: (400 MHz, DMSO-d_6):δ 7.81 (s, 1H), 3.10 (d, *J* = 5.2 Hz, 1H), 2.99 (d, *J* = 5.2 Hz, 1H), 2.82-2.79 (m, 2H), 2.66-2.60 (m, 1H), 2.56-2.50 (m, 1H), 2.41-2.39 (m, 1H), 2.18 (d, *J* = 10.4 Hz, 1H), 2.14 (s, 3H), 2.02-1.97 (m, 1H).

LCMS (ESI): *m/z* 156.1 [(M^++1)]

HPLC: 93.30%

Chiral HPLC: 99.00%

Synthesis of 8-methyl-2,5,8-triazaspiro[3.5]nonan-1-one (EH-2):

To a stirring solution of **EG-2** (70 mg, 0.28 mmol) in methanol (3 mL) was added 10% Pd/C (23 mg) at RT under nitrogen atmosphere. The reaction mixture was stirred at RT for 4h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was

filtered through a pad of celite and concentrated under reduced pressure. Obtain crude material was triturated with pentane to afford **EH-2** (30 mg, 68%) as a white solid.

EH-2:

^{1}H-NMR: (400 MHz, DMSO-d_6):δ 7.81 (s, 1H), 3.10 (d, J = 5.2 Hz, 1H), 2.99 (d, J = 5.2 Hz, 1H), 2.82-2.79 (m, 2H), 2.66-2.60 (m, 1H), 2.56-2.50 (m, 1H), 2.41-2.39 (m, 1H), 2.18 (d, J = 10.4 Hz, 1H), 2.14 (s, 3H), 2.02-1.97 (m, 1H).

LCMS (ESI): *m/z* 156.1 [(M^++1)]

HPLC: 95.20%

Chiral HPLC: 92.30%

Synthesis of benzyl ((2S,3R)-3-(benzyloxy)-1-(8-methyl-1-oxo-2,5,8-triazaspiro[3.5] nonan-5-yl)-1-oxobutan-2-yl)carbamate (6)

To a stirred solution of Int-**B** (2.21g, 6.44 mmol) in DCM (30 mL) were added N-methyl morpholine (2.6 g, 25.81 mmol), 1-Propanephosphonic anhydride solution (50 wt. % in ethyl acetate) (8.2 g, 25.81 mmol) and racemic tert-butyl 1-oxo-2,5,8-triazaspiro[3.5]nonane-8-carboxylate (**EH**) (1 g, 6.45 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was brought to RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction was diluted with water (50 mL) and extracted with 10% MeOH/ DCM (3 x 50 mL). Combined organic layer was dried over Na_2SO_4 and concentrated to obtain crude material which was purified by column chromatography by eluting 10% MeOH/DCM to afford racemic compound **6** (350 mg, 12%) as an off white solid. The racemic was separated by chiral HPLC purification and obtained 130 mg of compound **6-F1** and 60 mg of compound **6-F2.**

Compound 6-F1:

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.87 (s, 1H), 7.35-7.24 (m, 11H), 5.08-5.00 (m, 2H), 4.56-4.46 (m, 3H), 3.91 (d, J = 12.4 Hz, 1H), 3.73-3.71 (m, 1H), 3.22 (d, J = 5.2 Hz, 1H), 3.17 (d, J = 4.8 Hz, 1H), 3.04-2.99 (m ,1H), 2.77 (d, J = 11.6 Hz, 1H), 2.64 (d, J = 12.0 Hz, 1H), 2.18-2.13 (m, 4H), 1.88-1.83 (m, 1H), 1.11 (d, J = 6.4 Hz, 3H).

Compound 6-F2:

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.88 (s, 1H), 7.42 (d, J = 9.2 Hz, 1H), 7.35-7.25 (m, 10H), 5.08-5.01 (m, 2H), 4.63-4.44 (m, 3H), 3.97 (d, J = 12.8 Hz, 1H), 3.85-3.82 (m, 1H), 3.23 (d, J = 5.2 Hz, 1H), 3.07 (d, J = 4.4 Hz, 1H), 3.05-3.02 (m ,1H), 2.77 (d, J = 12.0 Hz, 1H), 2.69 (d, J = 11.6 Hz, 1H), 2.120-2.13 (m, 4H), 1.98 -1.91 (m, 1H), 1.12 (d, J = 6.4 Hz, 3H).

Synthesis of 5-(L-threonyl)-8-methyl-2,5,8-triazaspiro[3.5]nonan-1-one (EJ-1):

To a stirring solution of compound **6**-F1 (130 mg, 0.27 mmol) in methanol (5 mL) was added 10% Pd/C (43 mg) at RT under nitrogen atmosphere. The reaction mixture was stirred at RT for 48 h under H_2 atmosphere (balloon pressure). After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite. Obtain crude material was triturated with ether and pentane to afford **EJ-1** (35 mg, 51%) as an off white solid.

EJ-1:

^{1}H-NMR: (400 MHz, D_2O):δ 4.51-4.47 (m, 1H), 4.40-4.34 (m, 1H), 4.16 (s, 1H), 3.55 (d, *J* = 14.0 Hz, 1H), 3.15 (d, *J* = 12.0 Hz, 1H), 3.12-3.05 (m, 2H), 2.93 (d, *J* = 12.0 Hz, 1H), 2.32 (d, *J* = 12.0 Hz, 1H), 2.27 (s, 3H), 2.12-2.05 (td, *J* = 12.0, 3.6 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 3H).

LCMS (ESI): *m/z* 257.1 [(M^++1)]

HPLC: 97.70%

Chiral HPLC: 83.80%

Synthesis of 5-(L-threonyl)-8-methyl-2,5,8-triazaspiro[3.5]nonan-1-one (EJ-2):

To a stirring solution of compound 6-F2 (60 mg, 0.12 mmol) in methanol (5 mL) was added 10% Pd/C (20 mg) at RT under nitrogen atmosphere (balloon pressure). The reaction mixture was stirred at RT for 48 h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite. Obtain crude material was triturated with ether and pentane to afford **EJ-2** (20 mg, 62%) as an off white solid.

EJ-2:

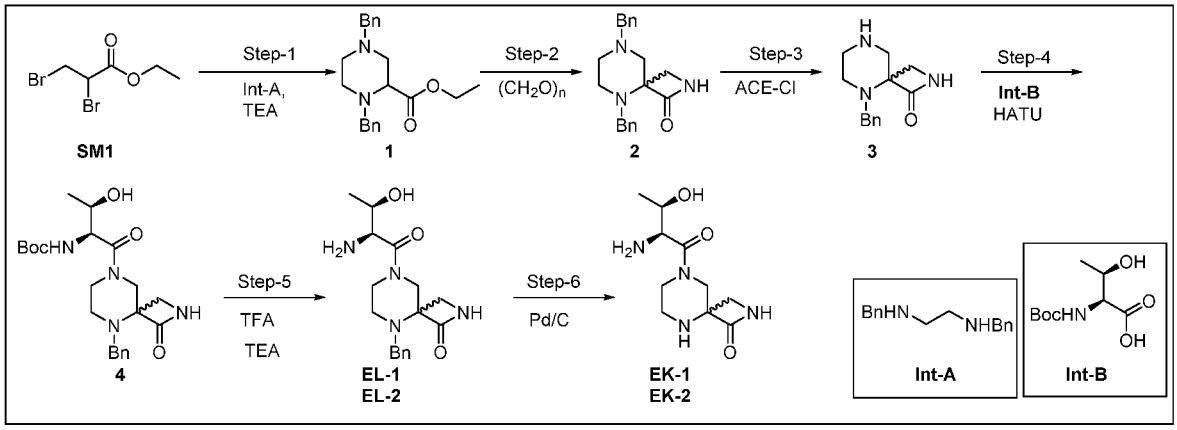
^{1}H-NMR: (400 MHz, D_2O):δ 4.56-4.52 (m, 1H), 4.38-4.33 (m, 1H), 4.18 (s, 1H), 3.44 (d, *J* = 14.4 Hz, 1H), 3.22 (d, *J* = 10.8 Hz, 1H), 3.13 (d, *J* = 14.0 Hz, 1H), 3.10-3.02 (m, 1H), 2.96-2.93 (m, 1H), 2.36 (d, *J* = 13.2 Hz, 1H), 2.32 (s, 3H), 2.19-2.12 (td, *J* = 12.0, 3.6 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 3H).

LCMS (ESI): *m/z* 257.1 [(M^++1)]

HPLC: 92.09%

Chiral HPLC: 79.20%

EXAMPLE 4: Synthesis of exemplary compounds



Synthesis of ethyl 1,4-dibenzylpiperazine-2-carboxylate (1):

To a solution of Int-A (20 g, 83.2 mmol) and triethylamine (23.0 mL, 166.4 mmol) in toluene (300 mL) was added ethyl 2,3-dibromopropanoate (SM) (12.1 mL, 83.2 mmol) slowly at 40 °C. The reaction mixture was heated to 80 °C and stirred for 4h. After consumption of the starting material (by TLC), the reaction mixture was brought to RT and volatiles were evaporated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting with 5-30% EtOAc/hexane to afford compound 1 (21.2 g, 75%) as light green syrup.

^{1}H-NMR: (500 MHz,$CDCl_3$): δ 7.33-7.7.22 (m, 10H), 4.17-4.15 (q, *J* = 7.0 Hz, 2H), 3.90 (d, *J* = 13.5 Hz, 1H), 3.59-3.54 (m, 2H), 3.42 (d, *J* = 13.5 Hz, 1H), 3.31-3.29 (m, 1H), 2.76-2.62 (m, 2H), 2.48-2.38 (m, 4H), 1.25 (t, *J* = 7.0 Hz, 3H).

LCMS (m/z): 337 [M^+-1]

Synthesis of 5,8-dibenzyl-2,5,8-triazaspiro[3.5]nonan-1-one (2):

To a solution of compound **1** (25 g, 73.9 mmol) in THF (200 mL) was added paraformaladehyde (2.21 g, 73.9 mmol) and LiHMDS (1M in THF) (295 mL, 295.8 mmol) at -10 °C. The reaction mixture was brought to RT and stirred for 16h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3x100 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain racemic compound **2** (19 g, 80%) as white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6):δ 8.01 (s, 1H), 7.34-7.20 (m, 10H), 3.74 (d, *J* = 13.6 Hz, 1H), 3.55-3.52 (m, 2H), 3.45 (d, *J* = 13.2 Hz, 1H), 3.39 (d, *J* = 13.2 Hz, 1H), 2.96 (d, *J* = 6.0 Hz,

1H), 2.74-2.72 (m, 1H), 2.59 (d, *J* = 10.8 Hz, 1H), 2.49 (s, 1H), 2.35 (d, *J* = 10.8 Hz, 1H), 2.26-2.20 (td, *J* = 14.8, 2.8 Hz, 1H), 2.11-2.05 (td, *J* = 14.8, 2.8 Hz, 1H).

LCMS (ESI): *m/z* 321 [(M^+]

HPLC: 98.68%

Synthesis of 5-benzyl-2,5,8-triazaspiro[3.5]nonan-1-one (3):

To a solution of compound 2 (19 g, 59.19 mmol) in 1,2-dichloroethane (100 mL) was added 1-chloro ethylchloroformate (9.31 g, 65.11 mmol) in 1,2-dichloroethane (100 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was heated to reflux and stirred for 1h. The reaction mixture was brought to RT and volatiles were evaporated under reduced pressure. Crude material was dissolved in methanol (100 mL) and heated to reflux again for 1h. The reaction mixture was brought to RT and diluted with ice water (100 mL) and extracted with DCM (2x50 mL). Aqueous layer was basified with $NaHCO_3$ solution extracted with 10% MeOH/ DCM. Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Obtained crude material was triturated with ether and *n*-pentane to afford racemic 3 (7.5 g, 55%) as light brick red solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.99 (s, 1H), 7.31-7.20 (m, 5H), 3.71 (d, *J* = 13.6 Hz, 1H), 3.49 (d, *J* = 6.0 Hz, 1H), 3.36 (d, *J* = 13.6 Hz, 1H), 3.07 (d, *J* = 6.0 Hz, 1H), 2.96 (d, *J* = 6.0 Hz, 1H), 2.91-2.84 (m, 2H), 2.69-2.66 (m, 1H), 2.57-2.53 (m, 1H), 2.40-2.36 (td, *J* = 11.2, 3.2 Hz, 1H), 2.09-2.03 (td, *J* = 11.2, 3.2 Hz, 1H).

LCMS (ESI): *m/z* 231 [(M^+]

HPLC: 99.50%

Synthesis of tert-butyl ((2S,3R)-1-(5-benzyl-1-oxo-2,5,8-triazaspiro[3.5]nonan-8-yl)-3-hydroxy-1-oxobutan-2-yl)carbamate (4):

To a stirring solution of racemic 3 (1.5 g, 6.5 mmol) in DMF (20 mL) were added Int-**B** (1.42 g, 6.5 mmol) and HATU (2.96 g, 7.8 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 10 min, DIPEA (2.26 mL, 13 mmol) was added drop wise at 0 °C. The reaction mixture was brought to RT and stirred for 3 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (3x100 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by

eluting with 3% MeOH/ DCM to obtain racemic compound **4** (1.8 g, 64%) as an off white solid.

Synthesis of 8-(L-threonyl)-5-benzyl-2,5,8-triazaspiro[3.5]nonan-1-one (EL-1 & EL-2):

To a stirring solution of racemic compound **4** (1.8 g, 4.17 mmol) in DCM (30 mL) was added TFA (3.3 mL, 41.7 mmol) at 0 °C. The reaction mixture was brought to RT and stirred for 2 h. After consumption of the starting material (by TLC), volatiles were concentrated under reduced pressure. Crude material was washed with Et_2O (2x50 mL) and obtained as TFA salt. This salt was suspended in DCM (30 mL) followed by neutralization with TEA (1 eq.). Reaction mixture was concentrated under reduced pressure to obtain **EL** (1 g, racemic crude) as yellow syrup. The racemic was separated by chiral HPLC purification and obtained 300 mg of **EL-1** and 3000 mg of **EL-2**.

EL-1:

^{1}H-NMR: (400 MHz, DMSO-d_6):δ 8.19 (s, 1H), 7.34-7.24 (m, 5H), 4.63-4.58 (m, 1H), 4.41-3.90 (td, 2H), 3.75 (d, J = 13.6 Hz, 1H), 3.57-3.42 (m, 4H), 3.13-3.00 (m, 2H), 2.86-2.84 (m, 1H), 2.51-2.48 (m, 1H), 2.21-2.08 (m, 1H), 1.92-1.81 (m, 2H), 0.97 (d, J = 6.0 Hz, 3H).

LCMS (ESI): *m/z* 333.3 [M^++1]

HPLC: 97.22%

Chiral HPLC: 99.60%

EL-2:

^{1}H-NMR: (400 MHz, DMSO-d_6):δ 8.17 (s, 1H), 7.34-7.24 (m, 5H), 4.64-4.52 (m, 1H), 4.27-4.08 (m, 1H), 3.81 (d, J = 12.8 Hz, 1H), 3.70 (d, J = 12.8 Hz, 2H), 3.52-3.44 (m, 4H), 3.19 (d, J = 12.8 Hz, 2H), 2.93 (d, J = 5.6 Hz, 1H), 2.32-2.20 (m, 1H), 1.86-1.81 (m, 2H), 0.99 (d, J = 6.4 Hz, 3H).

LCMS (ESI): *m/z* 333.3 [M^++1]

HPLC: 98.70%

Chiral HPLC: 99.60%

Synthesis of 8-(L-threonyl)-2,5,8-triazaspiro[3.5]nonan-1-one (EK-1):

To a stirring solution of EL-1 (300 mg, 0.91 mmol) in methanol (10 mL) was added 50% wet 10% Pd/C (120 mg) at RT under nitrogen atmosphere. The reaction mixture was stirred RT for 48 h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction

mixture was filtered through a pad of celite and the pad was washed with MeOH (150 mL). Obtained filtrate was concentrated under reduced pressure to afford 300 mg crude, which was by preparative HPLC to afford EK-1 (108 mg, 49%) as white hygroscopic solid.

EK-1:

^{1}H-NMR: (400 MHz, D_2O):δ 4.03-3.97 (m, 3H), 3.93-3.86 (m, 1H), 3.80-3.60 (m, 2H), 3.49-3.33 (m, 2H), 3.27-3.15 (m, 1H), 3.01-2.95 (m, 1H), 1.26-1.23 (m, 3H).

LCMS (ESI): *m/z* 243.2 [M^++1]

HPLC: 95.62%

Synthesis of 8-(L-threonyl)-2,5,8-triazaspiro[3.5]nonan-1-one (EK-2):

To a stirring solution of EL-2 (300 mg, 0.91 mmol) in methanol (10 mL) was added 50% wet 10% Pd/C (120 mg) at RT under nitrogen atmosphere. The reaction mixture was stirred RT for 48 h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and the pad was washed with MeOH (150 mL). Obtained filtrate was concentrated under reduced pressure to afford 300 mg crude, which was purified via preparative HPLC to afford EK-2 (106 mg, 49%) as white hygroscopic solid.

EK-2:

^{1}H-NMR: (400 MHz, D_2O):δ 4.06-4.03 (m, 3H), 3.90-3.81 (m, 2H), 3.73-3.67 (m, 1H), 3.49-3.46 (m, 1H), 3.36-3.32 (m, 1H), 3.27-3.25 (m, 1H), 3.05-3.00 (m, 1H), 1.31-1.27 (m, 3H).

LCMS (ESI): *m/z* 243.2 [M^++1]

HPLC: 97.39%

EXAMPLE 5: Following the above procedures, the following compounds were or are prepared. It should be appreciated that the compound in the first column is a different stereoisomer, for example, a different enantiomer and/or different diastereomer, from the compound in the second column.

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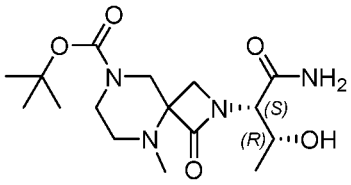
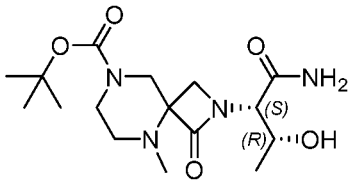
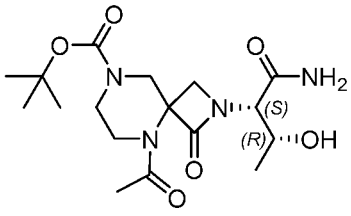
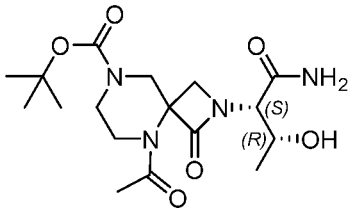
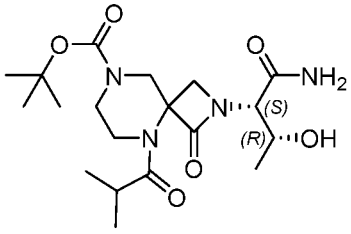
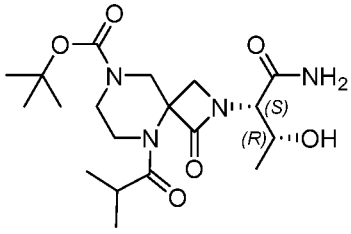
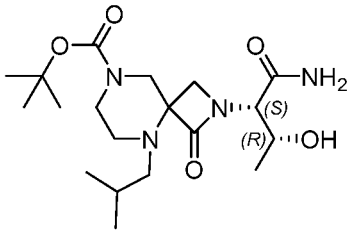
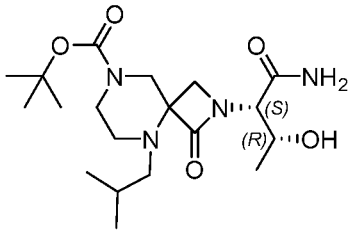
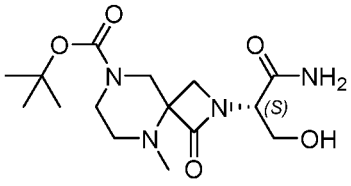
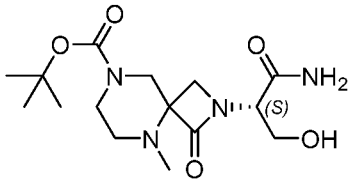
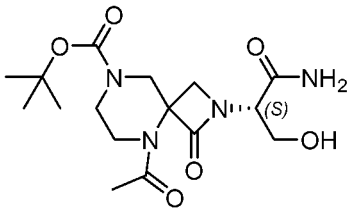
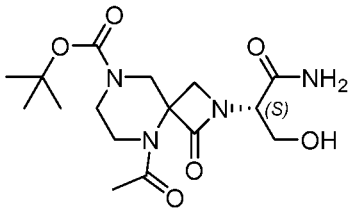
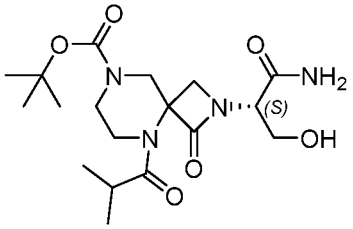
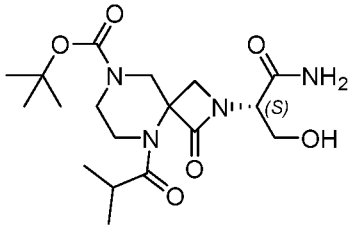
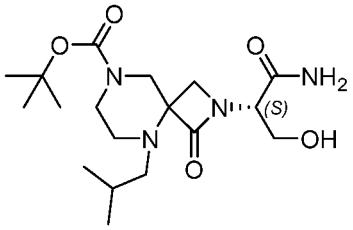
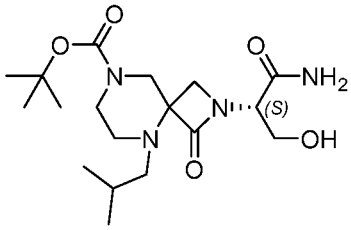
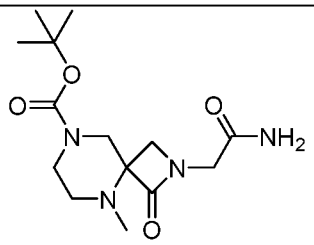
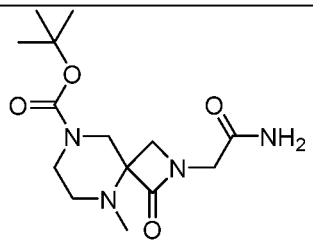
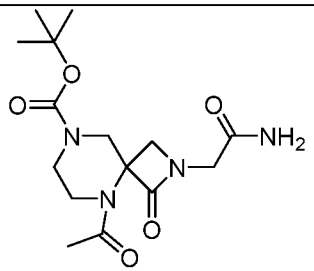
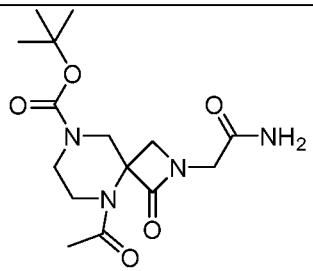
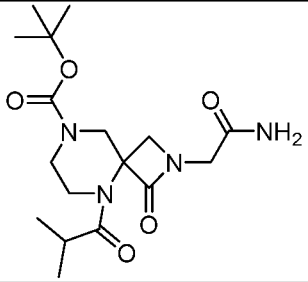
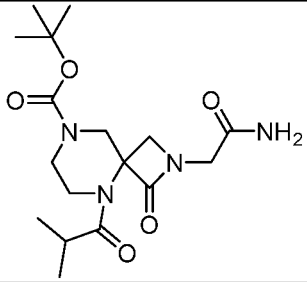
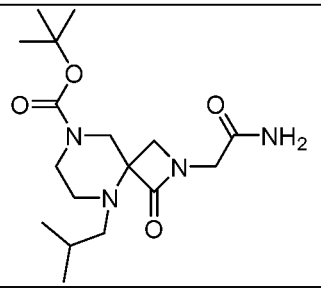
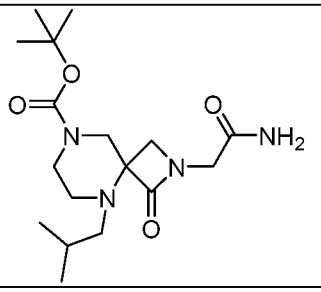
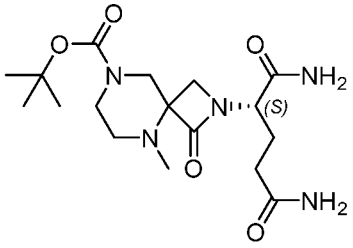
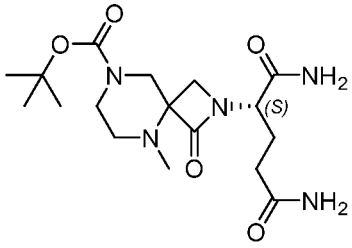
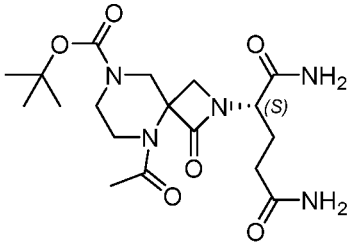
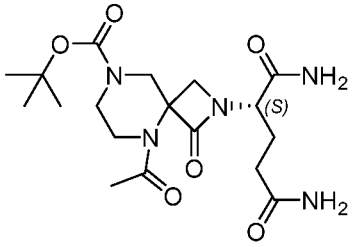
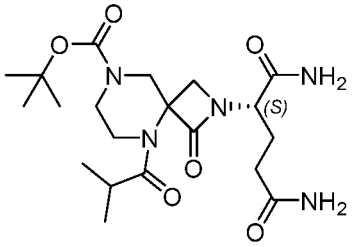
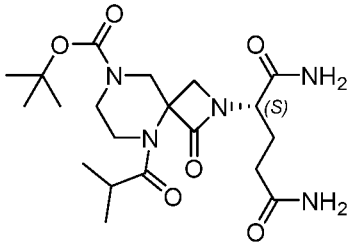
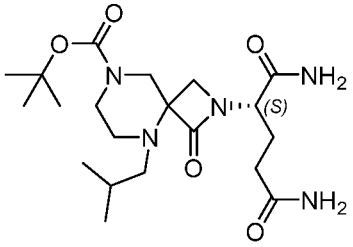
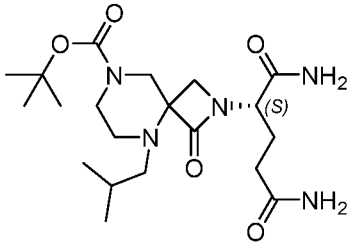
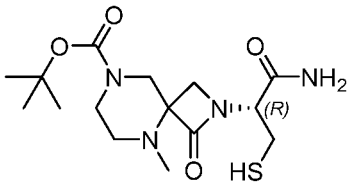
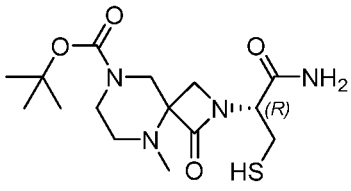
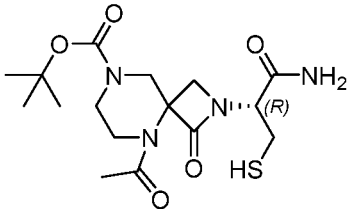
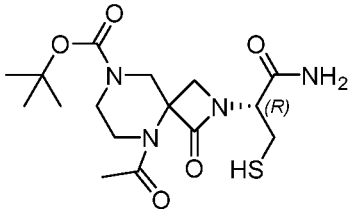
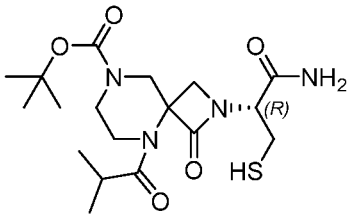
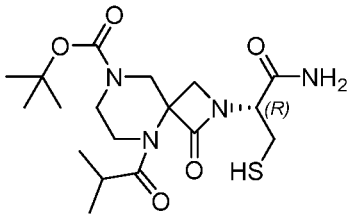
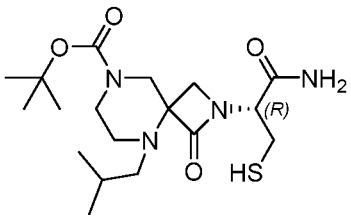
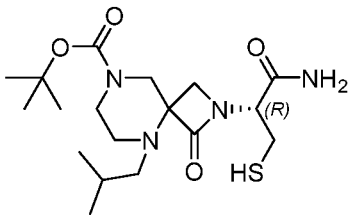
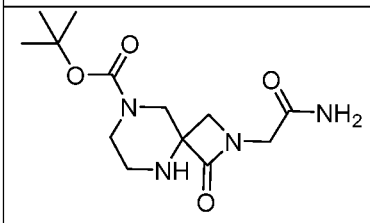
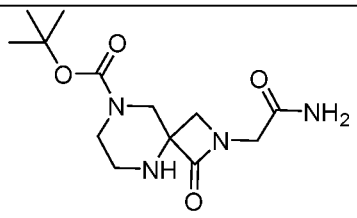
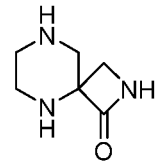
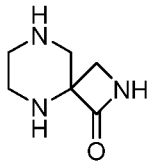
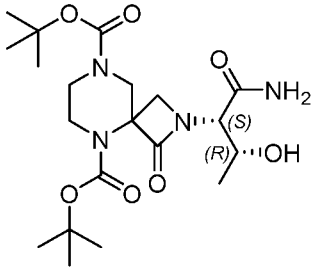
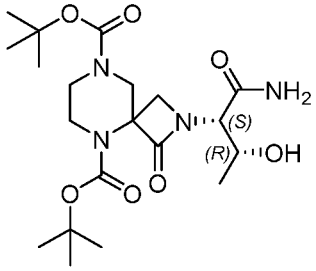
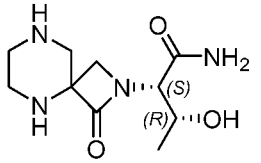
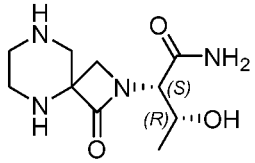
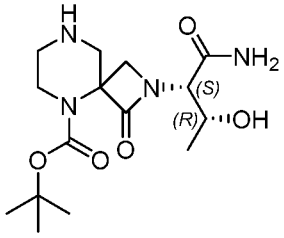
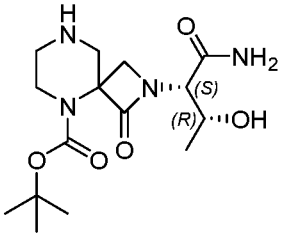
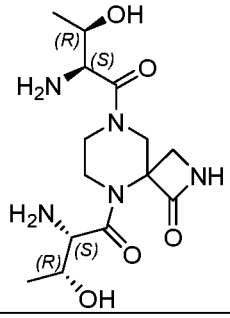
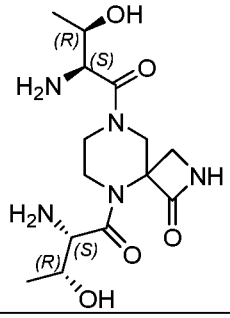
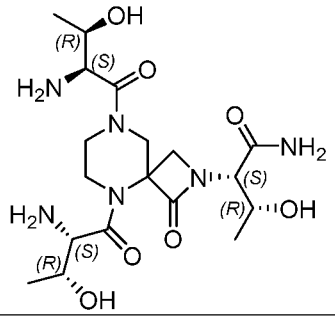
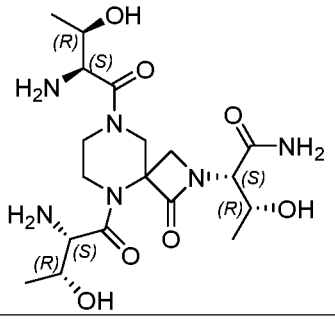
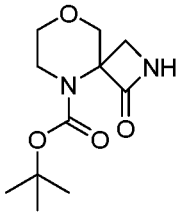
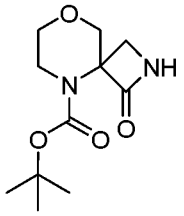
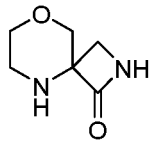
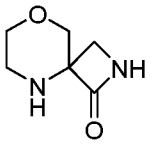
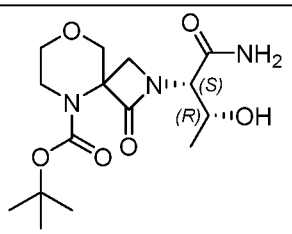
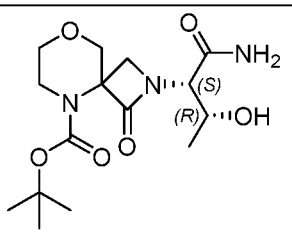
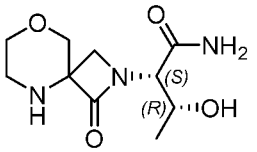
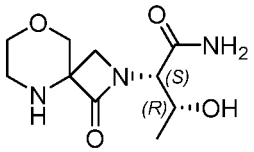
	ER-101		ER-102
	ER-103		ER-104
	ER-105		ER-106
	ER-107		ER-108
	ER-109		ER-110

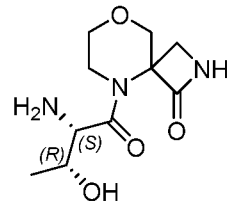
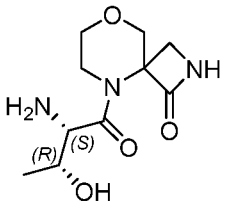
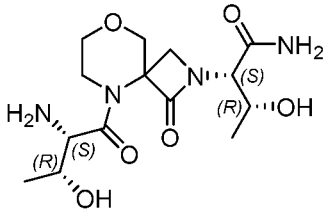
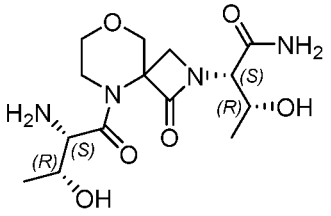
	ER-111		ER-112
	ER-113		ER-114
	ER-115		ER-116
	ER-117		ER-118
	ER-119		ER-120
	ER-121		ER-122

	ER-123		ER-124
	ER-125		ER-126
	ER-127		ER-128
	ER-129		ER-130
	ER-131		ER-132

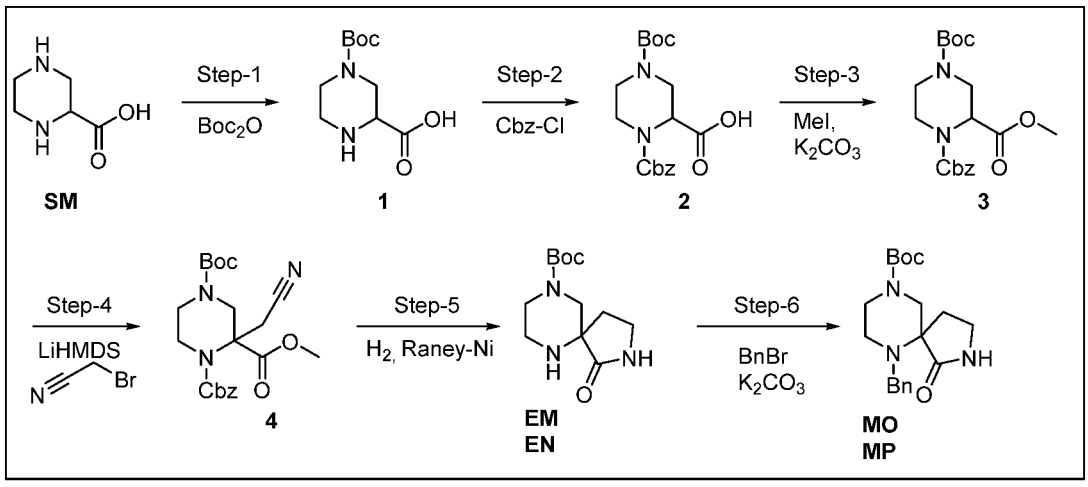
	ER-133		ER-134
	ER-135		ER-136
	ER-137		ER-138
	ER-139		ER-140
	ER-141		ER-142

	ER-143		ER-144
	ER-145		ER-146
	ER-147		ER-148
	ER-149		ER-150
	ER-151		ER-152

	ER-153		ER-154
	ER-155		ER-156
	ER-157		ER-158
	ER-159		ER-160
	ER-161		ER-162

	ER-163		ER-164
	ER-165		ER-166

EXAMPLE 6: Synthesis of exemplary compounds



Synthesis of 4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (1):

To a stirred suspension of piperazine-2-carboxylic acid (**SM**) (20 g, 153.7 mmol) in 1,4-dioxane:water (1:1, 400 mL) was added $NaHCO_3$ (19.37 g, 230.5 mmol) followed by Boc-anhydride (42.3 mL, 184.47 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was brought to RT and stirred for 16 h. After consumption of the starting material (by TLC), volatiles were reduced (200 mL) under vacuum. Obtained crude material of compound **1** (200 mL, ~35g) was taken to next step without any further purification.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 10.18 (br s, 1H), 4.08 (br s, 1H), 3.81-3.71 (m, 2H), 3.63 (t, J = 6.5 Hz, 1H), 3.17-3.15 (m, 2H), 2.91-2.86 (m, 1H), 1.36 (s, 9H), 1.31-1.26 (m, 0.5H), 0.87-0.84 (m, 0.5H).

LCMS (ESI): *m/z* 229.0 [(M^+-1)]

Synthesis of 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (2):

To a stirring solution of compound **1** (35 g, 0.152 mol) in 1,4-dioxane:water (1:1, 500 mL) was added $NaHCO_3$ (25.56g, 0.304 mol) followed by drop wise addition of Cbz-Cl (50% in toluene) (62 mL, 0.182 mol) at 0 °C. The reaction mixture was brought to RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction was diluted with water (100 mL) and washed with EtOAc (100 mL). Aqueous layer was acidified with 1N HCl solution and extracted with EtOAc (3 x 100 mL). Organic extracts washed with brine solution (100 mL) and dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford compound **2** (46 g, 83 %) as thick syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 13.06 (br s, 1H), 7.37-7.30 (m, 5H), 5.12-5.05 (m, 2H), 4.57-4.53 (m, 1H), 4.38-4.32 (m, 1H), 3.86-3.76 (m, 2H), 3.18-3.08 (m, 2H), 2.83 (br s, 1H), 1.37 (s, 9H).

LCMS (ESI): *m/z* 363.1 [M^+-1]

Synthesis of 1-benzyl 4-(tert-butyl) 2-methyl piperazine-1,2,4-tricarboxylate (3):

To a stirring solution of compound 2 (46 g, 0.126 mol) in DMF (460 mL) were added K_2CO_3 (21 g, 0.151 mol) and MeI (12 mL, 0.189 mol) at 0 °C under nitrogen atmosphere. The reaction mixture was brought to RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction was diluted with water (1 L) and extracted with Et_2O (2 x 300 mL). Combined organic layer was washed with water (100 mL) and brine solution (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting 10% EtOAc/hexane to afford compound 3 (25 g, 52%) as white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 5H), 5.21-5.11 (m, 2H), 4.78 (s, 0.5H), 4.66-4.50 (m, 1.5H), 4.02-3.88 (m, 2H), 3.68 (s, 3H), 3.24 (br s, 1H), 3.08 (dd, J = 13.6, 3.2 Hz, 1H), 2.83 (br s, 1H), 1.44 (s, 9H).

LCMS (ESI): *m/z* 279.3 [(M^++1)-Boc]

Synthesis of 1-benzyl 4-(tert-butyl) 2-methyl 2-(cyanomethyl)piperazine-1,2,4-tricarboxylate (4):

To a stirring solution of compound **3** (5 g, 13.22 mmol) in THF (50 mL) was added LiHMDS (1M in THF) (20 mL, 19.84 mmol) at -78 °C under nitrogen atmosphere. The reaction mixture was allowed to warm to -20 °C and stirred for 1h. Again the reaction mixture was cooled to -78°C, bromo acetonitrile (1.4 mL, 19.84 mmol) was added and allowed to warm to RT and stirred for 16 h. Reaction mixture was quenched with NH_4Cl solution (200 mL) and extracted with EtOAc (2 x 200 mL). Combined organic layers were washed with brine solution (100 mL), dried over Na_2SO_4 and concentrated to obtain crude material which was purified by combi-flash chromatography by eluting 20% EtOAc/*n*-hexane to afford compound **4** (1.5 g, 27%) as thick syrup.

^{1}H NMR (400MHz, DMSO-d_6): δ 7.42-7.28 (m, 5H), 5.13 (br s, 2H), 4.00 (br d, J = 14.3 Hz, 2H), 3.85 (br s, 1H), 3.73-3.53 (m, 3H), 3.40 (br s, 3H), 3.22 (s, 1H), 3.17 (d, J = 5.3 Hz, 1H), 1.39 (s, 9H).

LCMS (ESI): *m/z* 418.5 [(M^++1)]

Synthesis of tert-butyl 1-oxo-2,6,9-triazaspiro[4.5]decane-9-carboxylate (EM, EN):

To a stirring solution of compound **4** (1.5 g, 3.59 mmol) in MeOH (20 mL) was added Ra-Ni at RT under nitrogen atmosphere. The reaction mixture was stirred at RT for 16 h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and the filtrate was concentrated under vacuum. Obtained crude material was purified by column chromatography by eluting 5% MeOH/DCM to afford racemic **EM & EN** (600 mg) as a white solid. The racemic mixture was separated by chiral HPLC purification to afford 210 mg of **EM** and 220 mg of **EN.**

EM:

^{1}H NMR (400MHz, DMSO-d_6): δ 7.77 (br s, 1H), 3.68-3.49 (m, 2H), 3.26-3.16 (m, 1H), 3.14-3.04 (m, 1H), 2.87 (br d, J = 13.0 Hz, 3H), 2.57-2.52 (m, 1H), 2.14 (br s, 1H), 2.07-1.97 (m, 1H), 1.89-1.78 (m, 1H), 1.39 (s, 9H).

LCMS (ESI): *m/z* 254.3 [(M^+-1)]

EN:

^{1}H NMR (400MHz, DMSO-d_6): δ 7.77 (br s, 1H), 3.68-3.49 (m, 2H), 3.26-3.16 (m, 1H), 3.14-3.04 (m, 1H), 2.87 (br d, *J* = 13.0 Hz, 3H), 2.57-2.52 (m, 1H), 2.14 (br s, 1H), 2.07-1.97 (m, 1H), 1.89-1.78 (m, 1H), 1.39 (s, 9H).

LCMS (ESI): *m/z* 254.3 [(M^+-1)]

Synthesis of tert-butyl 6-benzyl-1-oxo-2,6,9-triazaspiro[4.5]decane-9-carboxylate (MO, MP):

To a stirring solution of racemic EM & EN (200 mg, 0.784 mmol) in CH_3CN (2 mL) were added K_2CO_3 (162 mg, 2.35 mmol) and BnBr (0.1 mL, 0.86 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (20 mL) and filtered through a pad of celite. Obtained filtrate was concentrated under reduced pressure and crude material was purified by silica gel column chromatography eluting 40% EtOAc/hexane to afford 100 mg of MO and MP as a mixture. The racemic compound was separated by chiral HPLC purification and obtained MO and MP.

MO:

^{1}H NMR (500MHz, DMSO-d_6): δ 7.90 (s, 1H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.23-7.18 (m, 1H), 3.69 (br d, *J* = 8.1 Hz, 2H), 3.44 (d, *J* = 13.3 Hz, 1H), 3.26 (br d, *J* = 4.6 Hz, 1H), 3.19-3.13 (m, 2H), 3.00-2.72 (m, 2H), 2.44 (br d, *J* = 11.6 Hz, 1H), 2.16-2.05 (m, 2H), 1.87 (dd, *J* = 7.2, 12.5 Hz, 1H), 1.39 (s, 9H).

LCMS (ESI): *m/z* 346.3 [(M^++1)]

MP:

^{1}H NMR (500MHz, DMSO-d_6): δ 7.90 (s, 1H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.23-7.18 (m, 1H), 3.69 (br d, *J* = 8.1 Hz, 2H), 3.44 (d, *J* = 13.3 Hz, 1H), 3.26 (br d, *J* = 4.6 Hz, 1H), 3.19-3.13 (m, 2H), 3.00-2.72 (m, 2H), 2.44 (br d, *J* = 11.6 Hz, 1H), 2.16-2.05 (m, 2H), 1.87 (dd, *J* = 7.2, 12.5 Hz, 1H), 1.39 (s, 9H).

LCMS (ESI): *m/z* 346.3 [(M^++1)]

EXAMPLE 7: Following the above procedures, the following compounds were or are prepared. It should be appreciated that the compound in the first column is a different stereoisomer, for example, a different enantiomer and/or different diastereomer, from the compound in the second column.

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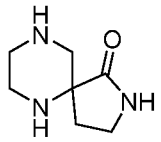
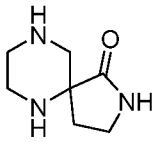
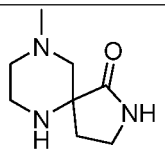
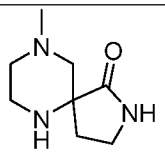
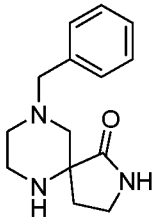
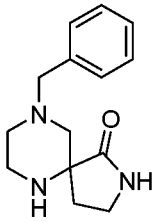
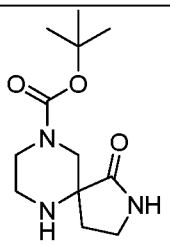
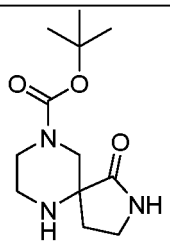
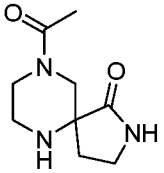
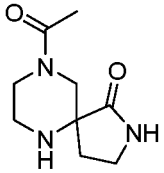
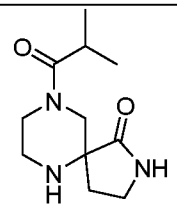
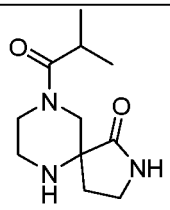
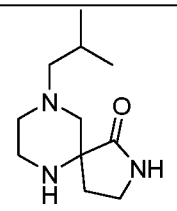
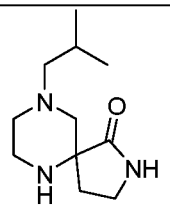
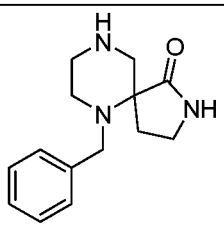
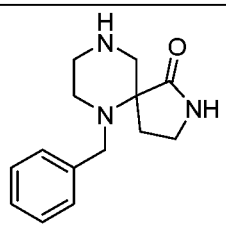
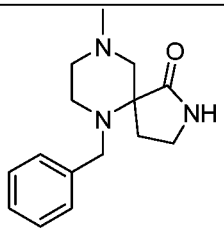
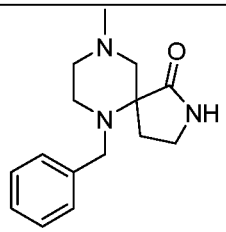
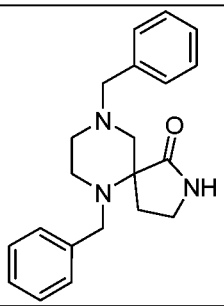
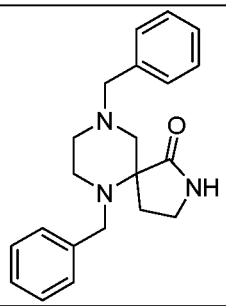
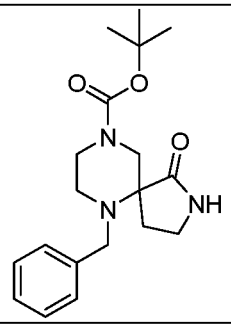
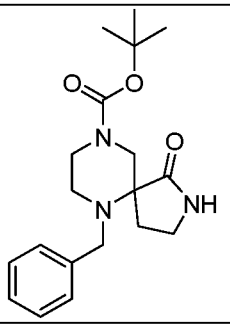
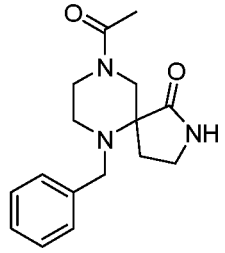
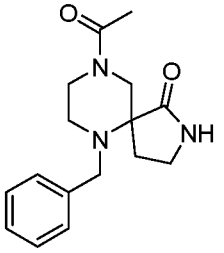
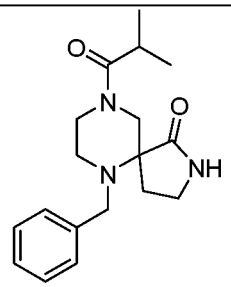
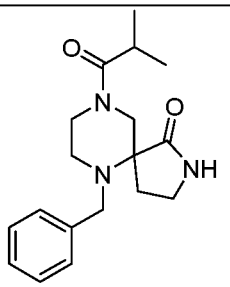
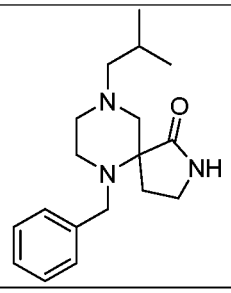
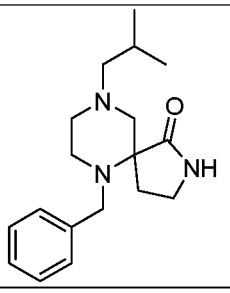
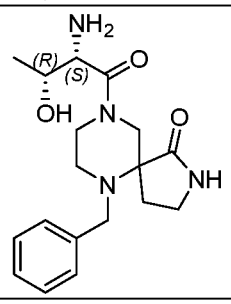
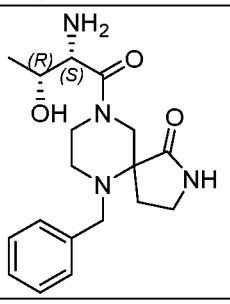
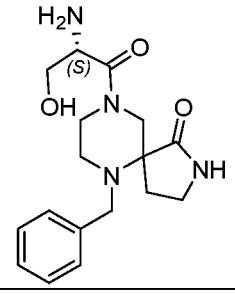
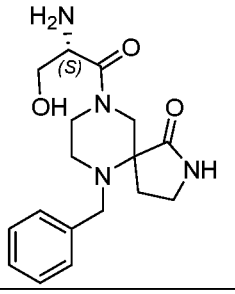
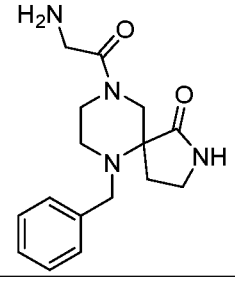
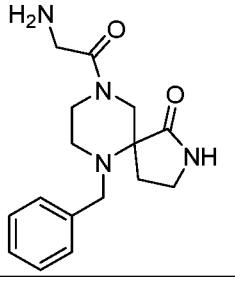
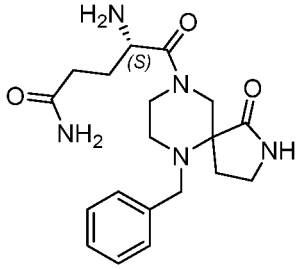
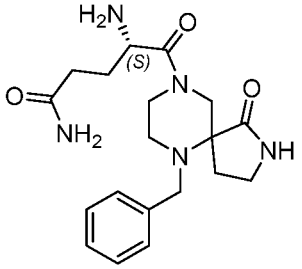
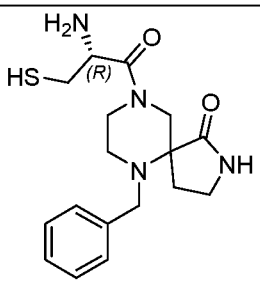
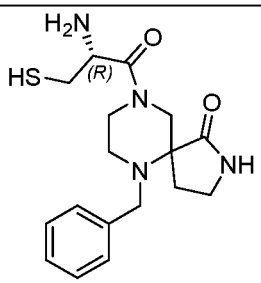
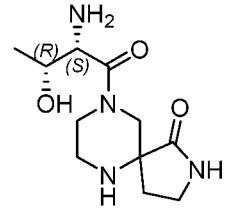
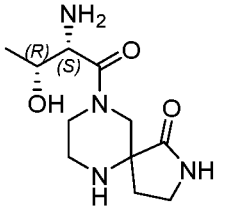
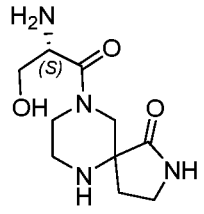
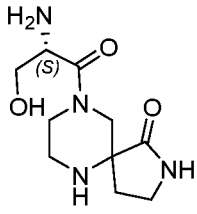
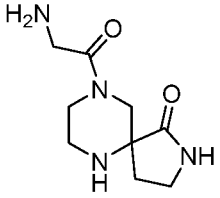
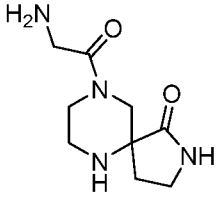
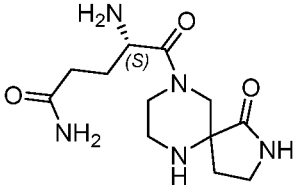
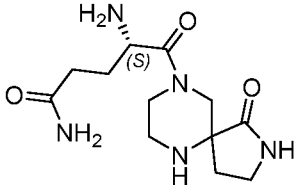
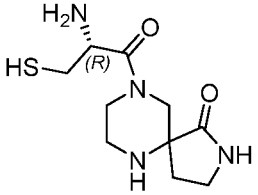
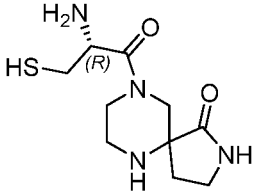
	ES-301		ES-302
	ES-303		ES-304
	ES-305		ES-306
	EM		EN
	ES-307		ES-308

	ES-309		ES-310
	ES-311		ES-312
	ES-313		ES-314
	ES-315		ES-316
	ES-317		ES-318

	MO		MP
	ES-319		ES-320
	ES-321		ES-322
	ES-323		ES-324
	ES-325		ES-326

	ES-327		ES-328
	ES-329		ES-330
	ES-331		ES-332
	ES-333		ES-334
	ES-335		ES-336

	ES-337		ES-338
	ES-339		ES-340
	ES-341		ES-342
	ES-343		ES-344

EXAMPLE 8

This example demonstrates the positive emotional learning (PEL) test. Experiments were conducted as described in Burgdorf et al., "The effect of selective breeding for differential rates of 50-kHz ultrasonic vocalizations on emotional behavior in rats," Devel. Psychobiol., 51:34-46 (2009). Rat 50-kHz ultrasonic vocalization (hedonic USVs) is a validated model for the study of positive affective state and is best elicited by rough-and-tumble play. 50-kHz ultrasonic vocalizations have previously been shown to be positively correlated with reward and appetitive social behavior in rats, and to reflect a positive affective state.

The PEL assay measures the acquisition of positive (hedonic) 50-kHz ultrasonic vocalizations (USVs) to a social stimulus, heterospecific rough and tumble play stimulation. Heterospecific rough-and-tumble play stimulation was administered by the experimenter's right hand. One hour after administration of test compound or vehicle negative control (0.5% sodium carboxymethyl cellulose in 0.9% sterile saline vehicle), animals received 3 min of heterospecific rough-and-tumble play that consisted of alternating 15 sec blocks of heterospecific play and 15 sec of no-stimulation. High frequency ultrasonic vocalizations (USVs) were recorded and analyzed by sonogram with Avasoft SASlab Pro (Germany) as previously described by Burgdorf et al., "Positive emotional learning is regulated in the medial prefrontal cortex by GluN2B-containing NMDA receptors," Neuroscience, 192:515-523 (2011). Frequency modulated 50-kHz USVs that occurred during each of the no-stimulation periods were quantified to measure PEL. Animals were not habituated to play stimulation before testing. Positive emotional learning was measured during the conditioned stimulus (CS) trials preceding the tickle unconditioned stimulus (UCS) trials. Animals received 15 second trials consisting of 6 CS and 6 UCS trials each (3 min total).

The table below summarizes the findings. As each experiment includes its own vehicle group, an example (typical) vehicle score is shown. Max effect (mean number of 50 kHz USVs per 15 seconds) is reported as ^: <6.0; *: 6.0-7.6; **: 7.7-10; ***: 10.1-20.

Compound	Route	Dose (mg/kg)	Max Effect
Vehicle	PO	NA	^
EC-2	PO	.1	**
ED-2	PO	.001-1	***
EL-1	PO	.1	***
EG-1	PO	.001-1	***
EK-2	PO	.1	*

EXAMPLE 9

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 [^{3}H]MK-801 binding.

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 ($1x10^{-15}$M – $1x10^{-7}$M), or 1 mM glycine. Following the addition of 0.3 µCi of [^{3}H]MK-801 (22.5 Ci/mmol), reactions were again incubated for 15 minutes at 25 ° C (nonequilibrium conditions). Bound and free [^{3}H]MK-801 were separated via rapid filtration using a Brandel apparatus.

In analyzing the data, the DPM (disintegrations per minute) of [^{3}H]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 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 [^{3}H]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 EC_{50} and % maximal activity were then obtained from the best fit curve of the % maximal [^{3}H]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 % maximal [^{3}H]MK-801 binding relative to 1 mM glycine (- = 0; < 100% = +; and > 100% = ++); and column B is based on log EC_{50} values (0 = -; ≥ $1x10^{-9}$ M (e.g., -8) = +; and < $1x10^{-9}$ M (e.g., -10) = ++).

Compound	NMDAR2A		NMDAR2B	
	A	B	A	B
EE-1	-	-	+	++
EE-2	-	-	+	++
EB-1	+	++	-	-

Compound	NMDAR2A		NMDAR2B	
	A	B	A	B
EB-2	+	++	+	+
EC-1	+	++	-	-
EC-2	+	+	++	++
EA-1	+	++	+	++
EA-2	-	-	-	-
ED-1	-	-	-	-
ED-2	-	-	+	++
EL-1	-	-	+	++
EL-2	-	-	+	++
EG-1	+	++	+	++
EK-2	+	+	+	++
EG-2	-	-	-	-
EH-1	+	++	+	++
EH-2	+	++	+	++
EK-1	+	++	-	-
ER-117	-	-	+	++
ER-118	-	-	+	++
ER-141	-	-	+	++
ER-142	+	++	-	-
ES-335	+	++	+	++
ES-336	+	++	+	++
ES-301	-	-	+	++
ES-302	-	-	++	++
EM	+	++	++	+
EN	-	-	-	-
ES-315	+	++	+	++
ES-316	+	++	+	++
ES-319	+	++	+	++
ES-320	-	-	-	-

Compound	NMDAR2A		NMDAR2B	
	A	B	A	B
ES-321	+	+	++	++
ES-322	-	-	-	-

Compound	NMDAR2C		NMDAR2D	
	A	B	A	B
EE-1	-	-	-	-
EE-2	+	++	-	-
EB-1	+	+	+	++
EB-2	+	++	+	++
EA-1	NR	NR	-	-
ED-1	NR	NR	+	++
ED-2	+	++	+	++
EG-1	++	+	-	-
EC-1	NR	NR	+	++
EL-2	+	++	-	-
EG-2	+	++	+	++
EH-1	-	-	+	++
EH-2	-	-	-	-
EK-1	NR	NR	+	++
ER-117	-	-	+	++
ER-118	-	-	++	++

EXAMPLE 10

Sprague Dawley rats were dosed intravenously using a normal saline formulation containing 2 mg/kg of the compounds identified in the below table (except for the compounds marked with an asterisk that were delivered in 1% NMP and 99% normal saline formulation). The table below summarizes the results of the IV pharmacokinetics.

Compound	C_0 (ng/mL)	AUC_{last} (hr*ng/mL)	$T_{1/2}$ (hr)	Cl (mL/min/kg)	V_{ss} (L/kg)
EJ-1	4029.19	3160.28	1.3	10.51	0.62
EJ-2	3415.56	1737	1.59	18.95	1.35
ED-1	1183.98	1022.78	0.79	32.07	1.88
ED-2*	1793.2	806.5	0.54	40.6	1.45
EL-1*	3248.4	4324.9	6.77	7.35	2.12
EG-1	2010.43	622.05	0.43	53.51	0.96
EG-2	1103.29	399.89	0.48	83.3	1.87
EK-1	6459	2260	0.8	15	0.4
ER-117	1673	593	0.52	57.16	1.44
ER-141	4275	1674	0.55	19.88	0.7
ES-336	13682	4772	13.67	6.84	0.73
ES-302	6089	1716	2.36	18.89	1.33
ES-316	2088	1109	2.3	30.6	1.75
ES-319	2769	1792	4.65	18.2	1.74
ES-321	2570	577	0.17	58.6	0.71

In another experiment, Sprague Dawley rats were dosed per os using a normal saline formulation containing 10 mg/kg of the compounds identified in the table below (except for the compounds marked with an asterisk that were delivered in 1% NMP and 99% normal saline formulation). Plasma, brain, and CSF samples were analyzed at various time points over a 24 hour period. The table below summarizes the results of the oral pharmacokinetics.

Compound	T_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)	CSF C_{max} (ng/mL)	Brain C_{max} (ng/mL)	%F
EJ-1	0.75	186.14	568.18	NR	NR	4
EJ-2	1.33	201.12	811.97	NR	NR	9
ED-1	0.67	2801.95	7053.49	NR	NR	138
ED-2*	0.25	1563.1	2178.53	178.3	478.5	54
EL-1*	0.5	4977	19441.3	56.9	143	90
EG-1	0.25	700.4	428.79	367.18	334.3	14
EG-2	0.25	3526.63	3082.39	NR	NR	100
EK-1	1.67	1625	5739	7	0	51
EK-2	1	1910.5	NR	81.6	NR	
ER-117	0.5	1540	2054	232	121	69
ER-141	0.83	962	2623	42	NR	31
ES-336	1	2687	9819	143	32	44
ES-302	0.83	339.7	1039	NR	NR	12
ES-316	0.25	2770.2	3025.5	430.2	1583	55
ES-319	0.33	4764	6468	520	758	72
ES-321	0.25	795	466	NR	NR	16

EXAMPLE 11

A non-clinical *in vivo* pharmacology study (Porsolt assay) was performed to measure antidepressant-like effects. A negative control (0.5% sodium carboxymethyl cellulose in 0.9% sterile saline vehicle) and a positive control (fluoxetine) are shown for comparison against test compound. 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. Positive control fluoxetine was dosed 3 times (24 h, 5 h and 1 h) prior to testing. Animals were tested 1 h post-dosing with the test compounds or vehicle. Animals received a 15 min habituation session 1 day before the 5 min test. A subset of compounds tested at 1 h post-dosing were retested at 1 wk post-dosing in the same sets of animals. 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).

The results for test compounds are shown in the table below. Each compound tested at dose level shown. Significance vs. vehicle group for each experiment is marked. A compound marked "Yes" was found to be statistically significant ($p <= 0.05$) from vehicle at dose level shown. A compound marked "No" was not statistically significant from vehicle. Data was averaged for test compound and vehicle groups (N approximately 8 per group) and the percent reduction in floating for group treated with test compound relative to group treated with vehicle is shown.

Compound	1 h post-dose			1 wk post-dose		
	Dose (mg/kg)	Significance vs. vehicle	% reduction in float time	Dose (0.1 mg/kg)	Significance vs. vehicle	% reduction in float time
Fluoxetine	20	Yes	54%	NA	NA	NA
ER-117	0.1	Yes	55.0%	NR	NR	NR
ES-335	0.1	Yes	58.5%	0.1	Yes	72.9%
ES-336	0.1	Yes	81.6%	0.1	Yes	86.5%
ES-315	0.1	Yes	44.1%	0.1	No	25.0%
ES-316	0.1	Yes	49.4%	0.1	Yes	42.4%
ES-319	0.1	Yes	76.3%	0.1	Yes	60.5%

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure 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.

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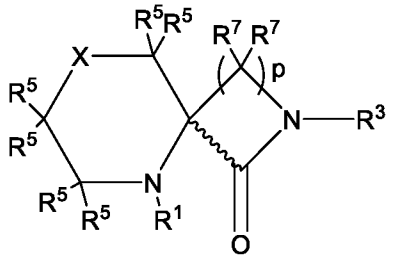
What is claimed is:

1. A compound represented by:



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

X is O or NR^2;

R^1 is selected from the group consisting of H, C_1-C_6alkyl, phenyl, -C(O)-C_1-C_6alkyl, and -C(O)-O-C_1-C_6 alkyl;

R^2 is selected from the group consisting of H, C_1-C_6alkyl, phenyl, -C(O)-C_1-C_6alkyl, and -C(O)-O-C_1-C_6 alkyl;

p is 1 or 2;

R^5 is independently selected for each occurrence from the group consisting of H, C_1-C_6alkyl, -$S(O)_w$-C_1-C_3alkyl, - NR^aR^b, C_1-C_3alkoxy, cyano and halogen;

w is 0, 1, or 2;

R^3 is selected from the group consisting of H, C_1-C_6 alkyl, phenyl, -C(O)R^{31} and -C(O)OR^{32};

R^{31} and R^{32} are each independently selected from the group consisting of H, C_1-C_6alkyl, -C_3-C_6cycloalkyl, and phenyl;

R^7 is independently selected for each occurrence from the group consisting of H, halogen, and phenyl; and

R^a and R^b are each independently for each occurrence selected from the group consisting of H, C_1-C_3alkyl, and phenyl, or R^a and R^b taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring;

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wherein any aforementioned C_1-C_6 alkyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from –C(O)NR^aR^b, -NR^aR^b, hydroxyl, $S(O)_w$-C_1-C_3alkyl, SH, phenyl and halogen, and any aforementioned phenyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from hydroxyl, halogen, -C(O)-O-C_1-C_3alkyl, -C(O)-C_1-C_3alkyl, methyl, and CF_3.

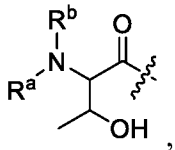
2. The compound of claim 1, wherein R^1 is -C(O)-O-C_1-C_6 alkyl.

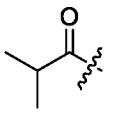
3. The compound of claim 1, wherein R^1 is -C(O)-C_1-C_6alkyl.

4. The compound of claim 1, wherein R^1 is C_1-C_6alkyl, optionally substituted by phenyl or one, two or three fluorines.

5. The compound of claim 1, wherein R^1 is H.

6. The compound of claim 3, wherein R^1 is a substituent selected from the group consisting of:



, 

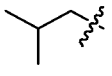
, and 

, wherein R^a and R^b are each independently selected from the group consisting of hydrogen and -C_1-C_3alkyl.

7. The compound of claim 2, wherein R^1 is tert-butyloxycarbonyl.

8. The compound of claim 4, wherein R^1 is benzyl.

9. The compound of claim 4, wherein R^1 is methyl.

10. The compound of claim 4, wherein R^1 is  .

11. The compound of any one of claims 1-10, wherein X is O.

12. The compound of any one of claims 1-10, wherein X is NR^2.

13. The compound of claim 12, wherein R^2 is H.

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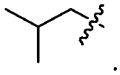
14. The compound of claim 12, wherein R^2 is C_1-C_6alkyl, optionally substituted by phenyl or one, two or three fluorines.

15. The compound of claim 12, wherein R^2 is -C(O)-C_1-C_6alkyl.

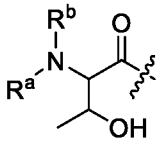
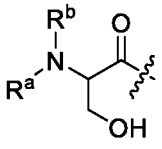
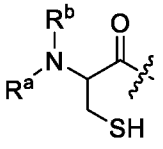
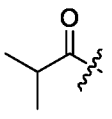
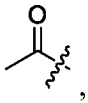
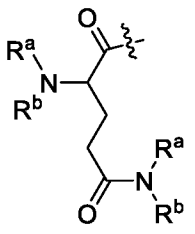
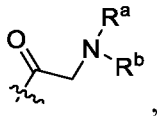
16. The compound of claim 12, wherein R^2 is -C(O)-O-C_1-C_6 alkyl.

17. The compound of claim 14, wherein R^2 is methyl.

18. The compound of claim 14, wherein R^2 is benzyl.

19. The compound of claim 14, wherein R^2 is  .

20. The compound of claim 15, wherein R^2 is a substituent selected from the group consisting of:

 ,  ,  ,  ,  ,  , or  , wherein R^a and R^b are each independently selected for each occurrence from the group consisting of hydrogen and -C_1-C_3alkyl.

21. The compound of claim 16, wherein R^2 is tert-butyloxycarbonyl.

22. The compound of any one of claims 1-21, wherein p is 1.

23. The compound of any one of claims 1-21, wherein p is 2.

24. The compound of any one of claims 1-23, wherein R^3 is H.

25. The compound of any one of claims 1-23, wherein R^3 is selected from the group consisting of:

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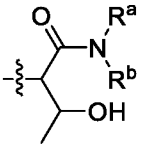
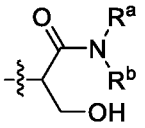
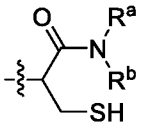
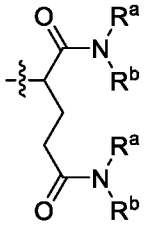
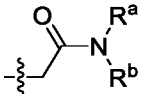
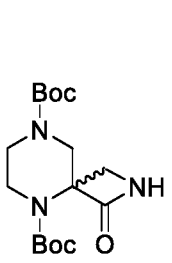
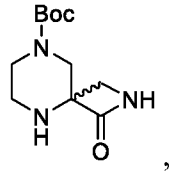
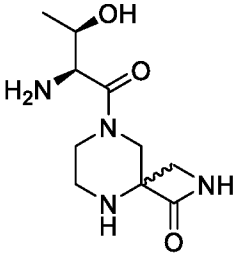
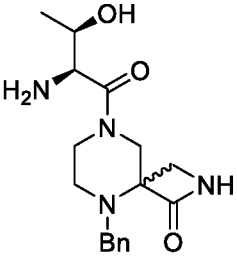
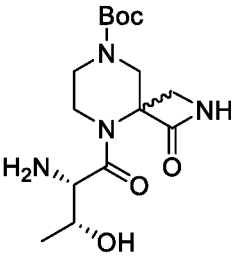
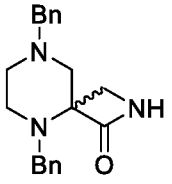
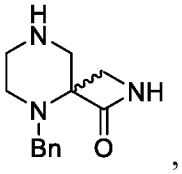
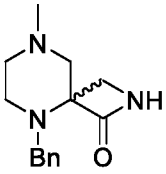
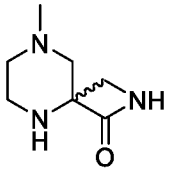
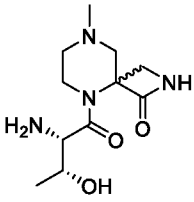
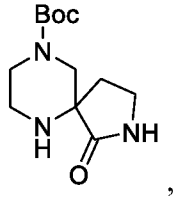
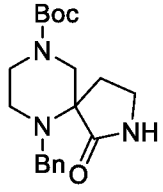
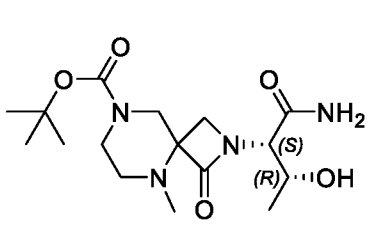
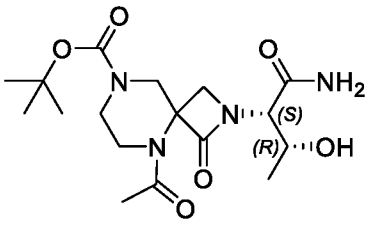
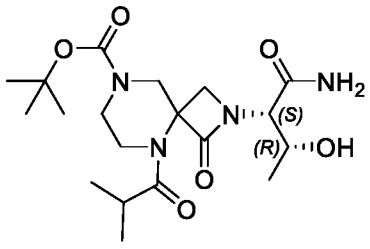
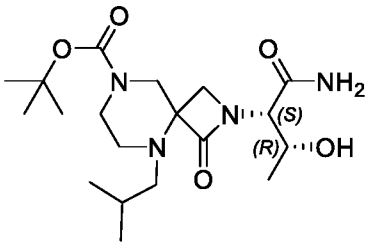




, and  , wherein

R^a and R^b are each independently selected for each occurrence from the group consisting of hydrogen and -C_1-C_6alkyl.

26. A compound selected from the group consisting of:












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

27. A compound selected from the group consisting of:

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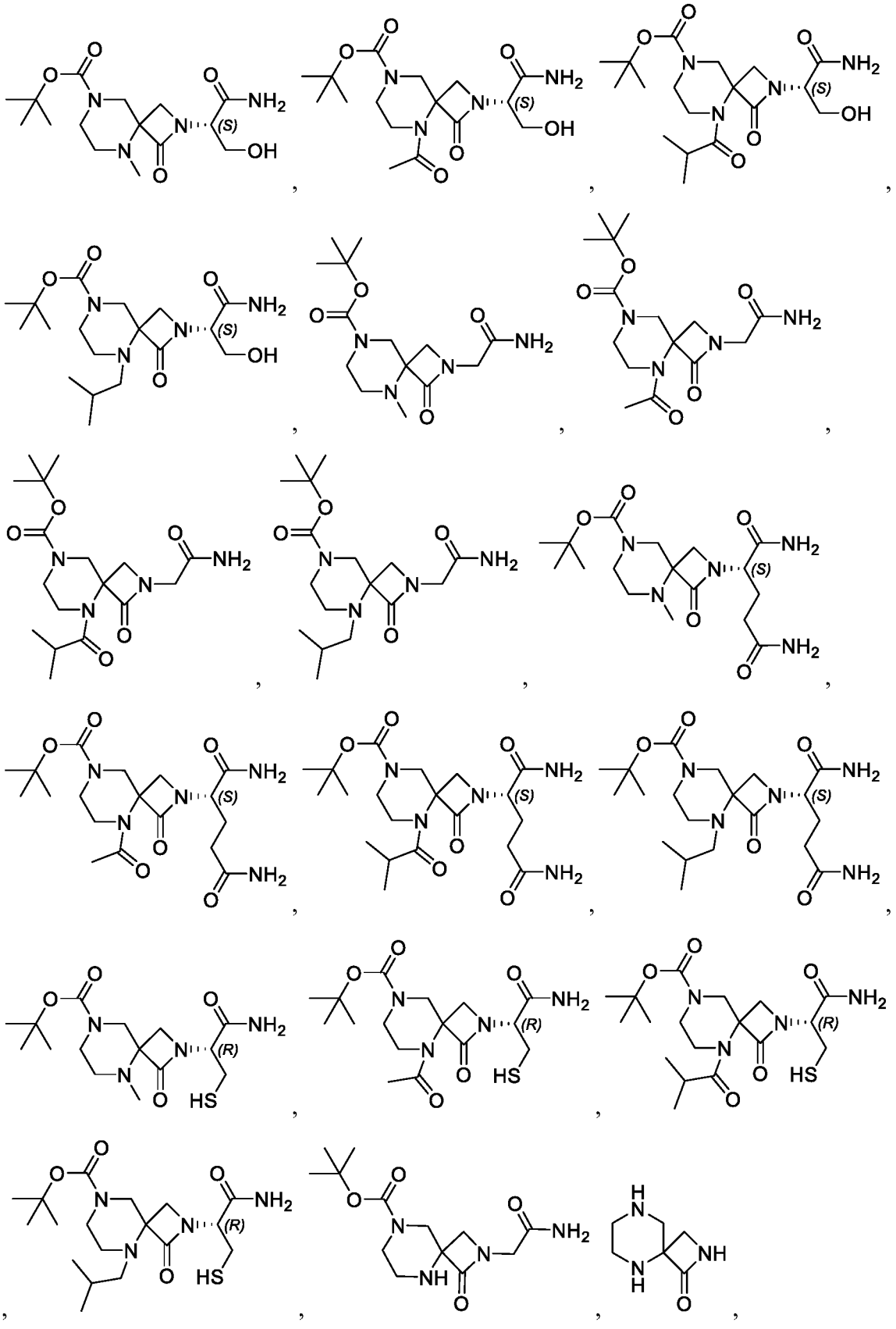
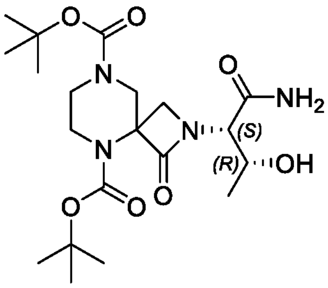
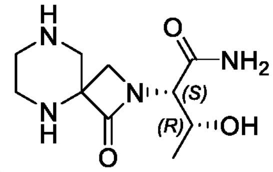
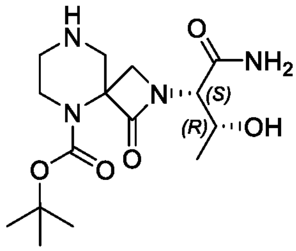
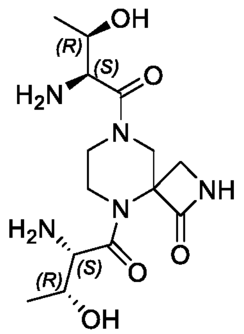
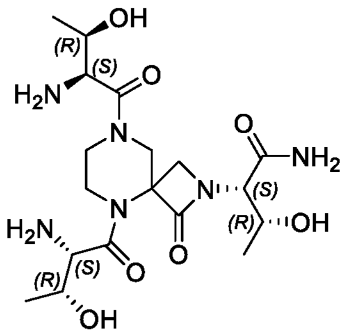
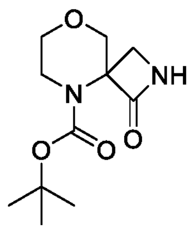
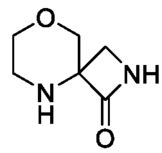
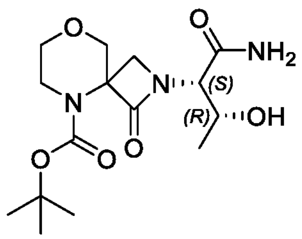
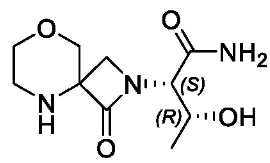
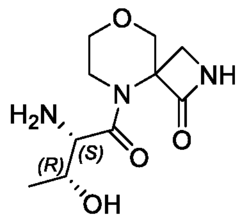
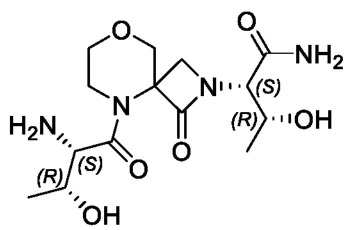
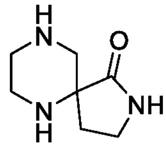
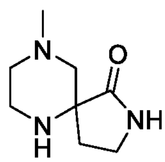
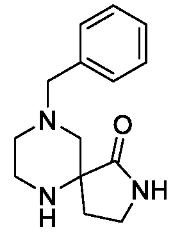
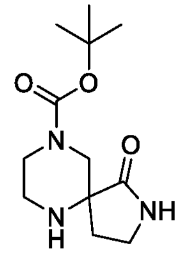
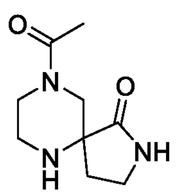
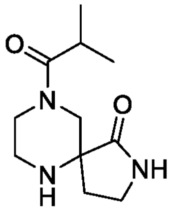
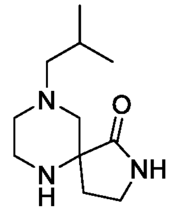
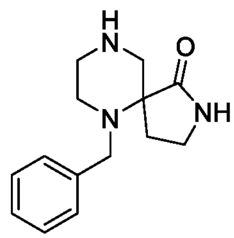
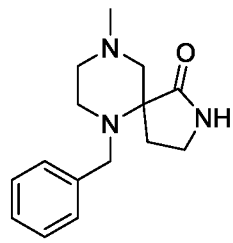


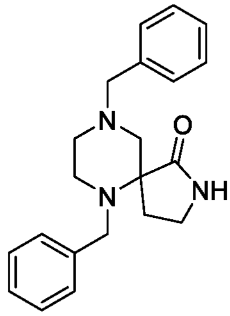
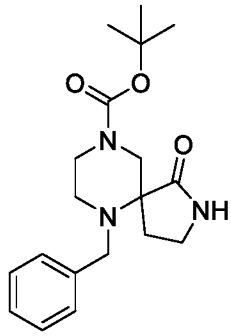
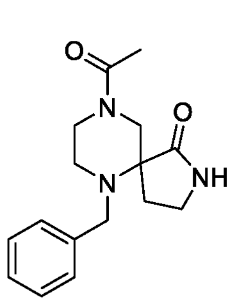
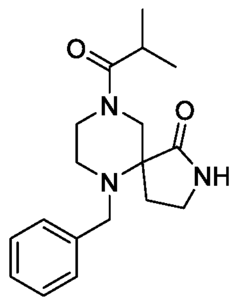
 ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,

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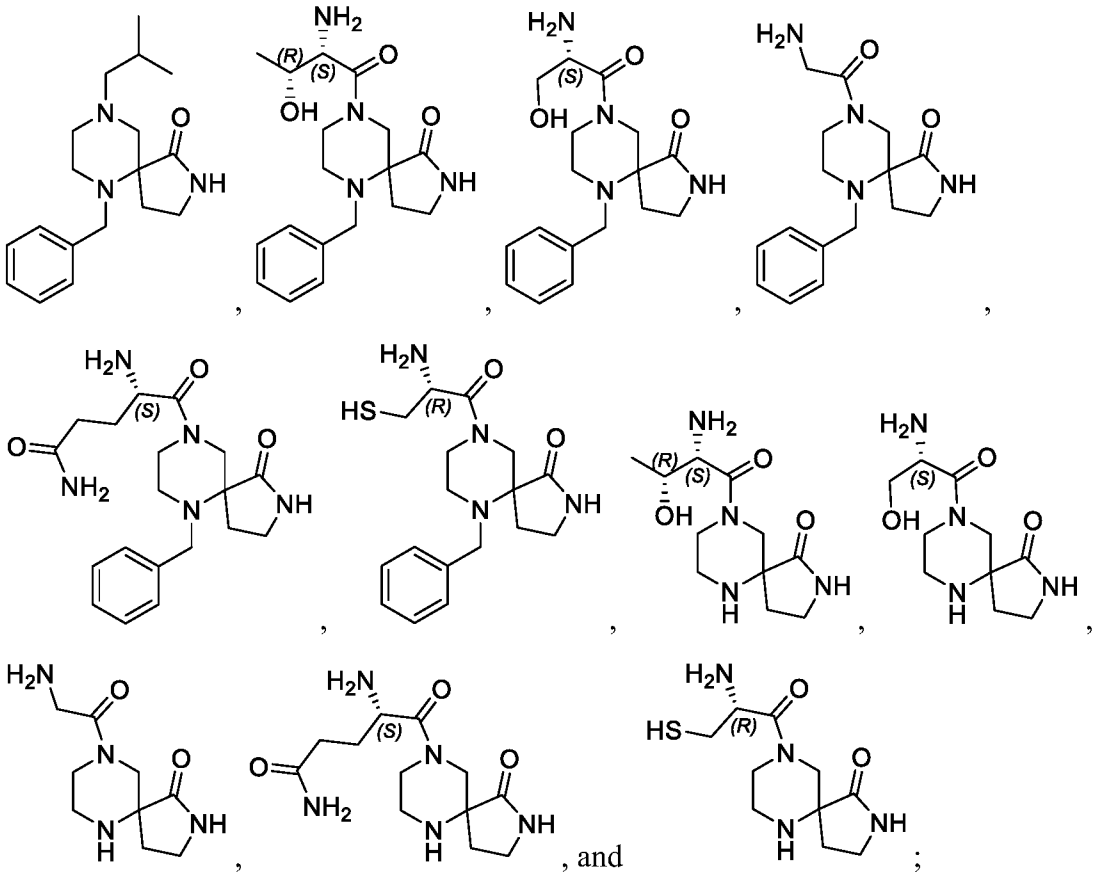

or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

28. A pharmaceutical composition comprising a compound of any one of claims 1-27, and a pharmaceutically acceptable excipient.

29. The pharmaceutical composition of claim 28, suitable for oral administration, parenteral administration, topical administration, intravaginal administration, intrarectal administration, sublingual administration, ocular administration, transdermal administration, or nasal administration.

30. A method of treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety, in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-27 or the pharmaceutical composition of claim 28 or 29.

31. A method of treating acute neuropathic pain or chronic neuropathic pain, in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-27 or the pharmaceutical composition of claim 28 or 29.

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32. The method of claim 31, wherein the neuropathic pain is chronic or acute.

33. The method of claim 31, wherein the neuropathic pain is selected from the group consisting of herpes, HIV, traumatic nerve injury, stroke, post-ischemia, chronic back pain, post-herpetic neuralgia, fibromyalgia, reflex sympathetic dystrophy, complex regional pain syndrome, spinal cord injury, sciatica, phantom limb pain, diabetic neuropathy, and cancer chemotherapeutic-induced neuropathic pain.

34. A method of treating a neurodevelopmental disorder related to synaptic dysfunction in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-27, or the pharmaceutical composition of claim 28 or 29.

35. Use of a therapeutically effective amount of the compound of any one of claims 1-27 or the pharmaceutical composition of claim 28 or 29 for the manufacture of a medicament for treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety in a patient in need thereof.

36. Use of a therapeutically effective amount of the compound of any one of claims 1-27 or the pharmaceutical composition of claim 28 or 29 for the manufacture of a medicament for treating acute neuropathic pain or chronic neuropathic pain in a patient in need thereof.

37. Use of a therapeutically effective amount of the compound of any one of claims 1-27, or the pharmaceutical composition of claim 28 or 29 for the manufacture of a medicament for treating a neurodevelopmental disorder related to synaptic dysfunction in a patient in need thereof.