SECONDARY STRUCTURE STABILIZED NMDA RECEPTOR MODULATORS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application 61/303,472, filed February 11, 2010, hereby incorporated by reference in its entirety.

BACKGROUND

[0002] 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 ah,* 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.

[0003] 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 ah,* 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.

[0004] 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 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

cardiac arrest to epilepsy. In addition, there are preliminary reports indicating similar involvement in the chronic neurodegeneration of Huntington's, Parkinson's, 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.

[0005] 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.

[0006] NMDA receptor compounds may exert dual (agonist/antagonist) effect on the NMDA receptor through the allosteric sites. These compounds are typically termed "partial agonists". In the presence of the principal site ligand, a partial agonist will displace some of the ligand and thus decrease Ca^{++} flow through the receptor. In the absence of or lowered level of the principal site ligand, the partial agonist acts to increase Ca^{++} flow through the receptor channel.

[0007] A need continues to exist in the art for novel and more specific/potent compounds that are capable of binding to, or modulating the glycine binding site of NMDA receptors, e.g the NMDA receptor NR1 ligand binding core, with e.g. with significant specificity and/or potency, especially in-vivo, to provide pharmaceutical benefits. In addition, a need continues to exist in the medical arts for an orally deliverable forms of such compounds.

SUMMARY

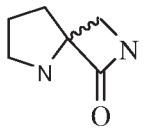
[0008] Provided herein, at least in part, are compounds that are NMDA modulators, for example, partial agonists of NMDA. For example, provided herein are compounds that can

mimic a beta-turn structure that is capable of selectively interacting with the glycine binding region of NMDA receptor NR1, e.g. SEQ ID. NO. 1. Disclosed peptide mimetics, for example, have a beta-turn motif when binding to SEQ ID NO. 1. In some embodiments, disclosed peptide mimetics substantially maintain a beta-turn motif in vivo or in an aqueous solution.

[0009] In some embodiments, a peptide mimetic capable of binding to, or associating with, the NMDA ligand binding core of SEQ ID NO. 1 is provided, wherein said peptide mimetic has at least two alpha carbons about 6 to about 14Å apart, e.g., about 6 to about 8Å apart. For example, disclosed mimetics may include a cyclic amide core, e.g. a spiro-beta-lactam.

[0010] In another embodiment, a disclosed peptide mimetic may be a peptide having two or three amino acids replaced with a moiety having a carboxyl group and an amino group. In an embodiment, a disclosed peptide mimetic of any one of claims 1-6, where said peptide mimetic is capable of forming a hydrogen bond at least one, two, three or four of the following amino acids of SEQ ID NO.l: PR0124, THR126, GLU178 and SER180, or may be capable of forming a hydrogen bond with all four amino acids.

[0011] For example, provided herein is a peptide mimetic capable of binding to the NMDA ligand binding core of SEQ ID NO. 1, wherein said peptide mimetic has two alpha carbons about 6 to about 14 Å apart, (e.g., about 6 to about 10 Å apart) and a beta-turn motif comprising a bicyclic amide core (e.g., a spiro-beta-lactam) such that, when the peptide mimetic binds to said SEQ ID NO. 1, the bicyclic amide core substantially retains configuration. Such peptide mimetic may include a core represented by:



. Exemplary peptide mimetics may substantially maintains the beta-turn motif in vivo or in an aqueous solution, and may be capable of forming a hydrogen bond with the following amino acids of SEQ ID NO.l: PR0124, THR126, GLU178 and SER180. In some embodiments, the beta-turn core may be conjugated to one or two amino acids.

[0012] Methods of treating or preventing a NMDA receptor mediated disorders in a patient are also provided, comprising administering to a patient in need thereof an acceptable NMDA ligand binding core receptor agonistic or antagonistic amount of a glycine mimicking beta-turn peptidomimetic cyclic compound having a cyclic amide moiety, for example, a beta-lactam moiety.

[0013] Also provided herein is a method of modulating the activity of SEQ ID NO. 1, wherein the modulation arises from a favorable conformation adopted by a compound, and wherein said modulation arises from a hydrogen bonding interaction between the compound and one, two, three or four of the following amino acids of SEQ ID NO.l: PR0124, THR126, GLU178 and SER180.

[0014] In another embodiment, a method of identifying a compound capable of binding to SEQ ID NO. 1 is provided, comprising: a) providing a molecular model comprising one or more target regions of SEQ ID NO. 1 derived from at least a portion of: SEQ ID NO. 1, atomic coordinates by molecular modeling of SEQ ID NO. 1, or atomic coordinates deposited in the Protein Data Bank under accession number 1PBQ; b) using the molecular model to identify a compound that can bind to the one or more target regions in the molecular model; and c) producing the compound. In some embodiments, such a method may further comprise the additional step of determining whether the compound modulates SEQ ID NO. 1.

[0015] Also provided herein are pharmaceutically acceptable compositions comprising a disclosed compound, and a pharmaceutically acceptable excipient. For example, such compositions may be suitable for oral administration to a patient.

[0016] A method for treating a cognitive disorder, such as a disorder associated with memory loss or impaired learning comprising administering to an patient in need thereof an effective amount of a disclosed compound. For example, provided herein are methods of treating or ameliorating memory loss or impaired learning in a patient in need thereof.

[0017] In an embodiment, methods for treating neuropathic pain in a patient in need thereof comprising administering an effective amount of a disclosed compound is provided.

[0018] Also disclosed herein are methods for treating depression, obsessive-compulsive disorder, or schizophrenia in a patient in need thereof comprising administering an effective amount of a disclosed compound. In another embodiment, methods for treating post traumatic stress disorder, an alcohol dependency disorder, or an addiction to an addictive drug in a patient in need thereof comprising administering an effective amount of a disclosed compounds are provided.

DESCRIPTION OF FIGURES

[0019] Figures 1A-1D indicate that a disclosed compound (AK52) biphasically alters postsynaptic NMDA receptor-mediated excitatory postsynaptic currents (e.p.s.c.s) at Shaffer collateral-CAl synapses, and selectively enhances induction of LTP. 1A: Time course of the marked reduction by AK52 (IμM ; solid bar) of the NMDA component of Schaffer collateral-evoked e.p.s.c.s in CA1 pyramidal neurons. (Each point is the mean ± SEM of e.p.s.c. peNRXe amplitude of 5 cells.) IB: Time course of the enhancement of a ten-fold lower concentration of AK52 (100 NM; grey bar) of the NMDA component of Schaffer collateral-evoked e.p.s.c.s. in CA1 pyramidal neurons. (Each point is the mean ± SEM of e.p.s.c. peNRX amplitude of 5 cells). 1C: Time course of LTD induced by a low frequency stimulus train (2Hz/10 min; Starting at arrow) at Schaffer collateral -CA1 synapses in slices pre-treated with IμM (filled circles; n=10) and 100 nM (filled diamonds; n=6) NRX- 10,052, compared to control, untreated slices (open circles; n-8). (Each point is the mean ± SEM of normalized extracellular field EPSP slope of n slices.) ID: Time course of experiments comparing LTP induced by a high frequency stimulus train (3xl00Hz/500ms; arrow) at Schaffer collateral-CAl synapses in slices pre-treated with IμM (filled circles; n=10 or 100 nM (filled diamonds; n=8) NRX- 10,052, compared to control, untreated slices (open circles; n=15). (Each point is the mean ± SEM of normalized field e.p.s.p. lsope of n slices).

[0020] Figures 2A-2E indicate a low concentration of a disclosed compound B markedly enhances pharmacologically-isolated postsynaptic NMDA receptor-mediated excitatory postsynaptic currents (e.p.s.c.s) at Shaffer collateral-CAl synapses and potentiates LTP, while a 20-fold higher concentration reduces NMDA e.p.s.c.s. 2A: Time course of the marked enhancement by Compound B (50 nM; solid bar) of single shock Schaffer collateral-evoked pharmacologically-isolated NMDA e.p.s.c.s. recorded in CA1 pyramidal neurons. 2B: Time course of the enhancement by compound B (50nM; solid bar) of burst-evoked (4 pulses/ 100 Hz) NMDA e.p.s.c.s. 2C: Time course of the marked reduction by compound B (IμM ; solid bar) of single shock Schaffer collateral-evoked NMDA e.p.s.c.s. recorded in CA1 pyramidal neurons. 2D: Time course of the reduction by compound B (IμM ; solid bar) of burst-evoked (4 pulses 100 Hz) Schaffer collateral-evoked NMDA e.p.s.c.s recorded in CA1 pyramidal neurons. 2E: Enhancement of high frequency (100 Hz/500ms x3; solid arrow) Schaffer collateral stimulus-evoked LTP at synapses on CA1 pyramidal neurons by 50 nM Compound B

(filled circles) compared to control, untreated slices (open circles). (Each point is the mean ± SEM of e.p.s.c. peNRX amplitude of n cells.).

[0021] Figures 3A-3C demonstrate 100 nM and IμM concentrations of a disclosed compound (AK51) both enhance pharmacologically-isolated postsynaptic NMDA receptor-mediated (e.p.s.c.s.) at Shaffer collateral-CAl synapse and potentiate LTP. 3A: Time course of the marked enhancement by NRX-10,051 (100 nM; solid bar) of single shock Schaffer collateral-evoked pharmacologically-isolated NMDA e.p.s.c.s recorded in CA1 pyramidal neurons (n=x). 3B: Time course of the enhancement by AK51 (IμM ; solid bar) of single shock Schaffer collateral-evoked pharmacologically-isolated NMDA e.p.s.c.s recorded in CA1 pyramidal neurons (n=y). 3C: Enhancement of high frequency (100 Hz/500ms x3; solid arrow) Schaffer collateral stimulus-evoked LTP at synapses on CA1 pyramidal neurons by 100 nM () and IμM (filled circles) AK5151, compared to control, untreated slices (open circles). 3D: Time course of LTD induced by a low frequency stimulus train (2Hz/10min; starting at arrow) at Schaffer collateral-CAl synapses in slices pre-treated with IμM (filled circles; n=10) or 100 nM (filled diamonds; n=6 NRX-10,051, compared to control, untreated slices (open circles; n=8). Each point is the mean +EM of e.p.s.c. peNRX amplitude of n cells.).

[0022] Figure 4 indicates that a disclosed compound enhances NMDA current and LTP. A: Time course of effect of 20 min bath application of IOOηM AK51 (solid bar) on normalized pharmacologically-isolated NMDA receptor-gated current in CA1 pyramidal neurons under whole-cell recording (mean ± SEM, n=5). B: Time course of effect of 20 min bath application of IμM AK51 (solid bar) on normalized pharmacologically-isolated NMDA receptor-gated current in CA1 pyramidal neurons under whole-cell recording (mean ± SEM, n=6). C: Time course of effect of bath application of IOOηM AK51 (solid bar, filled circles, n=8) compared to untreated control slices (open circles, n=6) on the magnitude of long-term potentiation (LTP) of extracellular excitatory postsynaptic potential slope (mean ± SEM, fEPSP) induced by high-frequency Schaffer collateral stimulation (arrow,2xl00Hz/500msec). D: Time course of effect of bath application of IμM AK51 (solid bar, filled circles, n=8) compared to untreated control slices (open circles, n=6) on the magnitude of LTP of fEPSP slope (mean ± SEM) induced by high-frequency Schaffer collateral stimulation (arrow,2xl00Hz/500msec). E: Time course of effect of bath application of IμM AK51 (solid bar, filled circles, n=10) compared to untreated control slices (open circles, n=8) on the magnitude of long-term depression of fEPSP slope (mean ± SEM) induced by low-frequency Schaffer collateral stimulation (arrow, 2Hz/10min)

[0023] Figure 5 depicts the results of a T-maze test in rats using a disclosed compound.

[0024] Figure 6 depicts the results of a formalin neuropathic pain assay in rats.

[0025] Figure 7 indicates that one isomer of a disclosed compound AK-55-A potently enhances NMDA current and LTP, while AK-55-B does not.

[0026] Figure 8 depicts quantification by GC/MS and shows the area under the curve for AK-51 and [2H7]proline internal standard and was analyzed with GC/MS by selective ion monitoring following TBDMS derivatization based on methods adapted from Wood et al. Journal of Chromatography B, 831, 313-9 (2005). The quantitative range of the assay for this compound was 0.312 pmol to 10 pmol column. The ions utilized for SIM were 241.2 (this compound) and 350.3 (deuterated proline). R2 = 0.9998 (Quadratic non-liner regression).

[0027] Figure 9 depicts the sequence of the NMDA receptor NR1 and various compounds that associate via hydrogen bonding to specific amino acids.

[0028] Figure 10 depicts the crystal structure of compound X (GLYX-13) with the NMDA receptor NR1.

[0029] Figure 11 depicts a model peptide (GLYX-13) that has a distance of 12.171 Å between alpha carbons.

[0030] Figure 12 depicts a ^{1}H NMR spectra of a compound disclosed herein.

[0031] Figure 13 depicts a ^{1}H NMR spectra of a compound disclosed herein.

DETAILED DESCRIPTION

[0032] This disclosure is generally directed to compounds that are capable of modulating NMDA, e.g. NMDA antagonists or partial agonists, and compositions and/or methods of using the disclosed compounds.

[0033] The following definitions are used throughout the description of the present disclosure:

[0034] The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2-12, 2-10, or 2-6 carbon atoms, referred to herein as C_2-C_{12}alkenyl, C_2-C_{10}alkenyl, and C_2-C_6alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl, etc.

[0035] The term "alkoxy" as used herein refers to an alkyl group attached to an oxygen (-0-alkyl). Exemplary alkoxy groups include, but are not limited to, groups with an alkyl group of 1-12, 1-8, or 1-6 carbon atoms, referred to herein as **Ci**-C^alkoxy, Q-Cgalkoxy, and C_1-C_6alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, etc. Similarly, exemplary "alkenoxy" groups include, but are not limited to vinyloxy, allyloxy, butenoxy, etc.

[0036] The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-l-butyl, 3-methyl-l-butyl, 2-methyl-3-butyl, 2,2-dimethyl- 1-propyl, 2-methyl-l-pentyl, 3-methyl-l-pentyl, 4-methyl-l-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl- 1-butyl, 3,3-dimethyl-l-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

[0037] Alkyl, alkenyl and alkynyl groups can optionally be substituted, if not indicated otherwise, with one or more groups selected from alkoxy, alkyl, cycloalkyl, amino, halogen, and -C(0)alkyl. In certain embodiments, the alkyl, alkenyl and alkynyl groups are not substituted, i.e., they are unsubstituted.

[0038] The term "alkynyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, and butynyl.

[0039] The term "amide" or "amido" as used herein refers to a radical of the form **-R_aC(0)N(Rb)-, -RaC(0)N(R_b)Rc-,** or **-C(0)N$R_b$$R_c$,** wherein R_a, R_b and R_c are each independently selected from alkoxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, and nitro. The amide can be attached to another group through the carbon, the nitrogen, **R_b, R_c,** or **R_a.** The amide also may be cyclic, for example R_b and **R_c, R_a** and **R_b,** or **R_a** and **R_c** may be joined to form a 3- to 12-membered ring, such as a 3- to 10-membered ring or a 5- to 6-membered ring. The term "carboxamido" refers to the structure **-C(0)N$R_b$$R_c$.**

[0040] The term "amine" or "amino" as used herein refers to a radical of the form **-N$R_d$$R_e$,** where R_d and **R_e** are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, haloalkyl, heteroaryl, and heterocyclyl. The amino also may be cyclic,

for example, R_d and R_e are joined together with the N to form a 3- to 12-membered ring, e.g., morpholino or piperidinyl. The term amino also includes the corresponding quaternary ammonium salt of any amino group, e.g., -[N(Rd)(Re)(Rf)]+. Exemplary amino groups include aminoalkyl groups, wherein at least one of R_d, R_e, or R_f is an alkyl group. In certain embodiment, R_d and R_e are hydrogen or alkyl.

[0041] The terms "halo" or "halogen" or "Hal" as used herein refer to F, CI, Br, or I. The term "haloalkyl" as used herein refers to an alkyl group substituted with one or more halogen atoms.

[0042] The terms "heterocyclyl" or "heterocyclic group" are art-recognized and refer to saturated or partially unsaturated 3- to 10-membered ring structures, alternatively 3- to 7-membered rings, whose ring structures include one to four heteroatoms, such as nitrogen, oxygen, and sulfur. Heterocycles may also be mono-, bi-, or other multi-cyclic ring systems. A heterocycle may be fused to one or more aryl, partially unsaturated, or saturated rings. Heterocyclyl groups include, for example, biotinyl, chromenyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, homopiperidinyl, imidazolidinyl, isoquinolyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, oxolanyl, oxazolidinyl, phenoxanthenyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazolinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidin-2-onyl, pyrrolinyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydropyranyl, tetrahydroquinolyl, thiazolidinyl, thiolanyl, thiomorpholinyl, thiopyranyl, xanthenyl, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring may be substituted at one or more positions with substituents such as alkanoyl, alkoxy, alkyl, alkenyl, alkynyl, amido, amidino, amino, aryl, arylalkyl, azido, carbamate, carbonate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, imino, ketone, nitro, phosphate, phosphonato, phosphinato, sulfate, sulfide, sulfonamido, sulfonyl and thiocarbonyl. In certain embodiments, the heterocyclic group is not substituted, i.e., the heterocyclic group is unsubstituted.

[0043] The term "heterocycloalkyl" is art-recognized and refers to a saturated heterocyclyl group as defined above. The term "heterocyclylalkoxy" as used herein refers to a heterocyclyl attached to an alkoxy group. The term "heterocyclyloxyalkyl" refers to a heterocyclyl attached to an oxygen (-0-), which is attached to an alkyl group.

[0044] The terms "hydroxy" and "hydroxyl" as used herein refers to the radical -OH.

[0045] "Pharmaceutically or pharmacologically acceptable" include molecular entities and compositions 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 Biologies standards

[0046] As used in the present disclosure, the term "partial NMDA receptor agonist" is defined as a compound that is capable of binding to a glycine binding site of an NMDA receptor; at low concentrations a NMDA receptor agonist acts substantially as agonist and at high concentrations it acts substantially as an antagonist. These concentrations are experimentally determined for each and every "partial agonist.

[0047] As used herein "pharmaceutically acceptable carrier" or "exipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, sublingual or oral administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0048] The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in compounds used in the present compositions. 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 may 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., l,l'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the

acids mentioned above. 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.

[0049] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[0050] Individual stereoisomers of compounds of the present invention 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, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Stereoisomeric mixtures can also be resolved into their component stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Stereoisomers can also be obtained from stereomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

[0051] Geometric isomers can also exist in the compounds of the present invention. The symbol $\overline{\cdots\cdots}$ denotes a bond that may be a single, double or triple bond as described herein. The present invention encompasses the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are

designated as being in the "Z" or *"E"* configuration wherein 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.

[0052] 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 are 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."

[0053] The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. In one embodiment, the compound is amorphous. In one embodiment, the compound is a polymorph. In another embodiment, the compound is in a crystalline form.

[0054] The invention also embraces isotopically labeled compounds of the invention which are identical to those 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 of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, $^{18}0$, $^{17}0$, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and $^{36}C1$, respectively.

[0055] Certain isotopically-labeled disclosed compounds *(e.g.,* those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated *(i.e.,* ^{3}H) and carbon-14 *(i.e.,* ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium *(i.e.,* ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability *(e.g.,* increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the e.g., Examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0056] As used in the present disclosure, "NMDA" is defined as N-methyl-d-aspartate.

[0057] In the present specification, the term "therapeutically effective amount" means the amount of the subject 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 of the invention are administered in therapeutically effective amounts to treat a disease. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in defined as that amount needed to give maximal enhancement of a behavior (for example, learning), physiological response (for example, LTP induction), or inhibition of neuropathic pain.

[0058] As used herein, "beta-turn motif or beta-turn refers to a chemical structure having C^{α} (alpha carbon) atoms (a carbon atom next to a carbonyl carbon) substantially close, e.g. having a hydrogen bond between a donor and acceptor residue, where the donor and acceptor residue are separated by a distance that corresponds to the distance of two or three peptide bonds. A disclosed chemical structure has, for example, a beta-turn motif when the structure includes bicyclic rings (e.g., bicyclic spiro-lactam) that have restricted rotation, e.g., which may be evidenced by weak nOe (nuclear overhauser effect) spectra e.g., between H3 and H5 atoms.

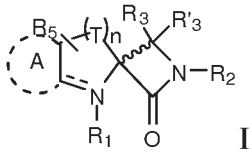
Compounds

[0059] Compounds, e.g. peptide mimetics disclosed herein, in some embodiments are capable of binding to the NDMA ligand binding core of SEQ ID No. 1. For example, a disclosed peptide mimetic may have e.g. two alpha carbons that may be about 6 to about 14 Å, or about 9 to about 14 Å, or about 10 to about 13 Å apart. In some embodiments, a contemplated peptide mimetic may be internally constrained or conformally constrained so that it may, for example, mimic a biologically active conformation of a peptide. For example, a disclosed peptide mimetic may include a cyclic amide core, e.g. a bicyclic beta-lactam. For example, a disclosed peptide mimetic may be a disclosed compound having a two modular units (e.g., a bicyclic beta-lactam core), wherein each unit can be substituted with a naturally occurring amino acid.

[0060] For example, a disclosed compound may have a beta-turn motif that is stable upon administration to a patient, e.g. is substantially stable in-vivo or in an aqueous solution. In some embodiments, a disclosed compound may be capable of forming a hydrogen bond, or

may be capable of binding to at least one, two, three or four amino acids of SEQ ID NO. 1, e.g. selected from the group consisting of PR0124, THR126, GLU178 and SER180.

[0061] A disclosed peptide mimetic may include a small synthetic (i.e. non-peptidyl) conformationally restricted component (e.g. a spirolactam moiety), which may for example, contribute to partial glycine site agonist activity of the compounds. For example, disclosed compounds include those represented by Formula I:



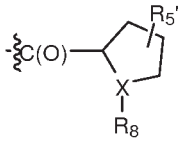
I

and pharmaceutically acceptable salts, stereoisomers, and N-oxides thereof; wherein

T is, independently for each occurrence, CR_4R_4', and n is 0, 1, 2 or 3;

A is optionally present and is selected from phenyl or pyridine, wherein A is optionally substituted by one or more substituents selected from R_a;

Ri is selected from the group consisting of H, hydroxyl, $-S(0)_2$-Ci-$_4$alkyl; $-S0_2$, C_1-$_4$alkyl, C_2-C_4alkenyl, phenyl, R_7, or



, wherein Ci-$_4$alkyl, C_2-$_4$alkenyl, or phenyl is optionally substituted by one or more substituents selected from R_a;

X is CH or N;

R_3 and R_3' are independently selected from the group consisting of H, halogen, hydroxyl, phenyl, Ci-$_4$alkyl, amido, amine, or C_2-$_4$alkenyl, wherein Ci-$_4$alkyl, C_2-$_4$alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_4 and R_4' are independently selected from the group consisting of H, halogen, hydroxyl, phenyl, Ci-$_4$alkyl, amido, amine, Ci-$_4$alkoxy or C_2-$_4$alkenyl, wherein C_1-$_4$alkyl, C_2-$_4$alkenyl, Ci-$_4$alkoxy, and phenyl are optionally substituted by one or more substituents selected from R_a;

R_2 is selected from the group consisting of H, R_7, -S(0) $_2$, S(0) $_2$-C_1-C_4alkyl, C_{1-4}alkyl, hydroxyl, or phenyl wherein Ci-$_4$alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_5 and $R_{5'}$ are each independently selected from group consisting of H, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, cyano, amino, phenyl, and hydroxyl, wherein C_{1-4}alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_7 is selected from group consisting of -C(0)-Rg, -C(0)-0-Rg, or -C(0)-NR $_d$-R9,

R_9 is selected from the group consisting of H, C_{1-4}alkyl, phenyl, or heterocyclic, wherein C_{1-4}alkyl, phenyl or heterocyclic is optionally substituted by 1, 2 or 3 substituents selected from R_b

R_8 is selected from group consisting of H, -C(O)- Ci-$_4$alkyl or C(0)-0- C_{1-4} alkyl, wherein C_{1-4}alkyl is optionally substituted by 1, 2 or 3 substituents selected from R_a;

R_a is selected, independently for each occurrence, from carboxy, hydroxyl, halogen, amino, phenyl, Ci-$_4$alkyl, and C_{1-4}alkoxy;

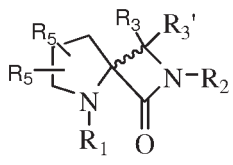
R_b is selected, independently for each occurrence, from the group consisting of carboxy, hydroxyl, halogen, amino, phenyl, Ci-$_4$alkyl, C_{1-4}alkoxy, and -NH-R_C;

R_c is selected, independently for each occurrence from the group consisting of: -C(O)-0-Ci- $_4$alkyl; and -C(0)-Ci- $_4$alkyl; and

R_d is selected, independently for each occurrence, H and Ci-$_4$alkyl;

and pharmaceutically acceptable salts, N-oxides or stereoisomers thereof.

[0062] For example, disclosed compounds may include those represented by:

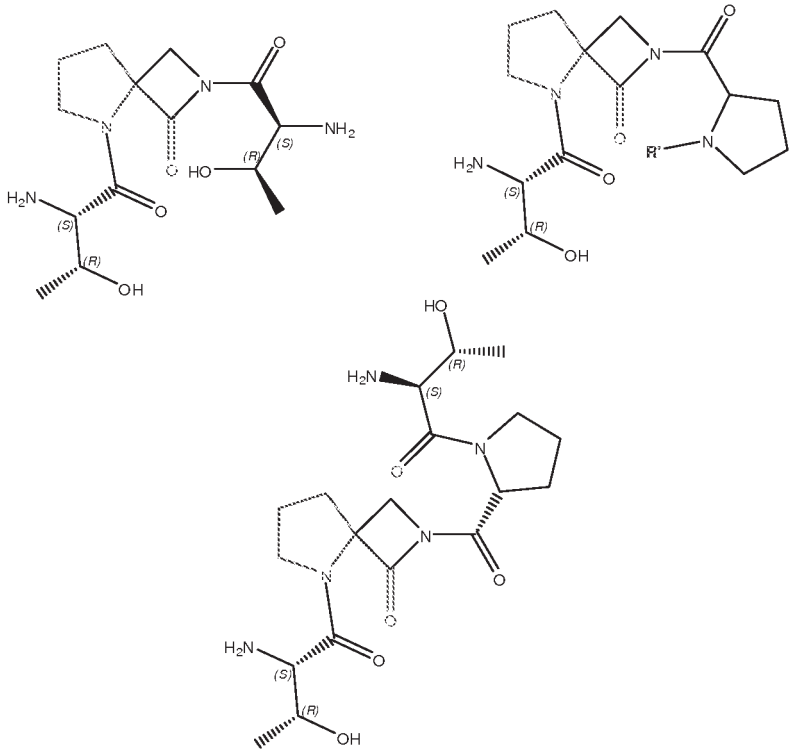


Ia

wherein Ri is C(0)-C $_{2-4}$alkyl, wherein C_{2-4}alkyl is substituted at one carbon with NH_2 or -N-carbobenzyloxy and at a different carbon by hydroxyl. For example, Ri may be C(0)-0-Ci_

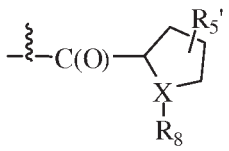
$_4$alkyl (e.g., methyl, ethyl, propyl, wherein Ci-$_4$alkyl is substituted by phenyl, and R_3, R_3', R_5 and R_2 are provided above.

[0063] In another embodiment, Ri and R_2 of formula la may each independently be selected from an amino acid, e.g. a L- or D- isomer of an amino acid, e.g., alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and/or valine. For example, Ri and R_2 may each be independently L-Thr or L-Ser, e.g. compounds such as:



[0064] , wherein R' is selected from the group consisting of H, or Ci-$_4$alkyl.

[0065] In an embodiment, Ri may be carbobenzyloxy, or may be represented by:

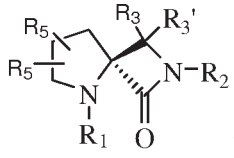


; wherein X may be N; R_5' may be H; and R_8 may be -C(0)-C $_{2-4}$alkyl (e.g. ethyl, propyl, n-butyl, or t-butyl), wherein C_2-$_4$alkyl is substituted at one carbon with NH_2 or -N-carbobenzyloxy and at a different carbon by hydroxyl.

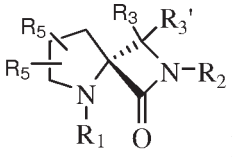
[0066] In certain embodiments, R_3 may be phenyl (optionally substituted as above), or may be H. R_2 may be, in some embodiments, a -C(0)-C_{2-4}alkyl, (e.g. ethyl, propyl, n-butyl, or t-butyl), optionally substituted at one carbon with NH_2 and another carbon with hydroxyl.

[0067] For any contemplated R-group that includes C_{1-4}alkyl (e.g. R_1, R_3, R5), the alkyl may be selected from the group consisting of methyl, ethyl, propyl, n-butyl or t-butyl, and wherein said C_{1-4}alkyl is optionally substituted by one, two, or three substituents selected from the group consisting of F, CI, or Br.

[0068] Such compounds may have differing isomerizations, and in some embodiments, may be represented by:

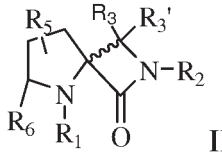


Ia or



lb, and wherein R_1, R_2, R_3, R'_3, and R_5 may be as described above.

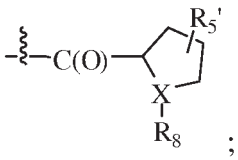
[0069] In another embodiment, compounds represented by formula II are contemplated:



II

and pharmaceutically acceptable salts, stereoisomers and N-oxides thereof; wherein

Ri is selected from the group consisting of H, hydroxyl, -S(0)$_2$-Ci-$_4$alkyl; -S0$_2$, C_1-$_4$alkyl; R_7, or



;

X is CH or N;

R_3 and R_3' are each independently selected from the group consisting of H, halogen, hydroxyl, phenyl, Ci-$_4$alkyl, amido, amine, or C_2-$_4$alkenyl, wherein Ci-$_4$alkyl, C_2-$_4$alkenyl and phenyl are optionally substituted by one or more substituents selected from Ra;

R_2 is selected from the group consisting of H, R_7, -S(0) $_2$, S(0)$_2$-Ci$_4$alkyl, C^alkyl, hydroxyl, or phenyl wherein C^alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

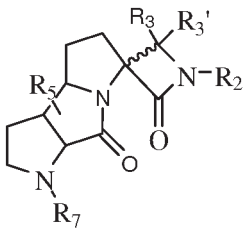
R 5 is selected from group consisting of H, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4} alkenyl, cyano, amino, phenyl, and hydroxyl, wherein C_{1-4}alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_6 is selected from group consisting of H, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, cyano, amino, phenyl, and hydroxyl wherein C_{1-4} alkyl, C_{2-4}alenyl and phenyl are optionally substituted by 1, 2 or 3 substituents selected from R_a;

R_7 is selected from group consisting of - C(0)-R_9, -C(0)-0 -R9, or -C(0)-NRd-R9,

R_9 is selected from the group consisting of H, C_{1-4}alkyl, phenyl, or heterocyclic, wherein C_{1-4}alkyl, phenyl or heterocyclic is optionally substituted by 1, 2 or 3 substituents selected from R_b; or

or Ri and R_6, taken together with formula II form:



;

R_8 is selected from group consisting of H, - C(O)- C^alkyl or C(0)-0 -C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted by 1, 2 or 3 substituents selected from R_a;

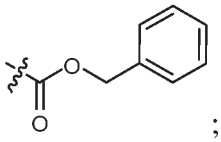
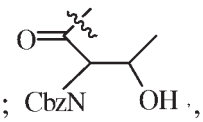
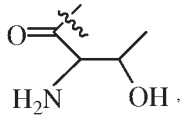
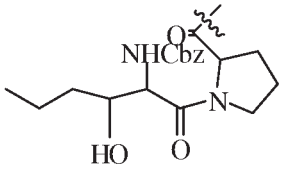
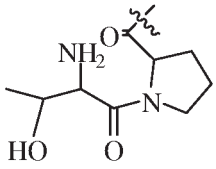
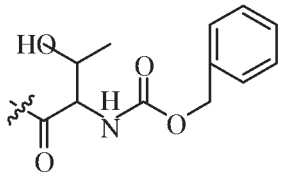
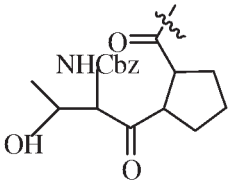
R_a is selected, independently for each occurrence, from carboxy, hydroxyl, halogen, amino, phenyl, C^alkyl, and C_{1-4}alkoxy;

R_b is selected, independently for each occurrence, from the group consisting of carboxy, hydroxyl, halogen, amino, phenyl, C^alkyl, C_{1-4}alkoxy, and -NH-R_c;

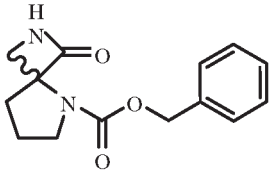
R_c is selected, independently for each occurrence, -C(0)-0 -C_{1-4}alkyl; and - C(0)-Cr $_4$alkyl; and

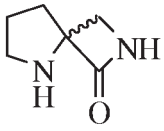
R_d is H or C_{1-4}alkyl.

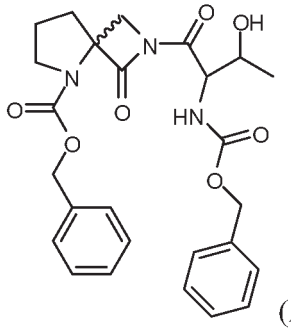
[0070] In an exemplary embodiment, the R_1 moiety of Formula I, II, Ia or Ib may be selected from the group consisting of:

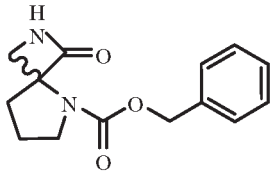
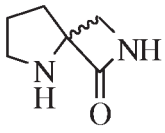
[0071] Exemplary compounds include


(compound B),


(AK-51); and


(AK-52).

[0072] Disclosed herein are compounds selected from the group consisting of: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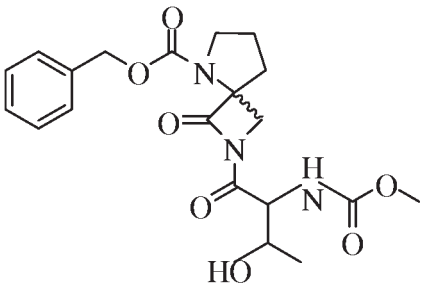
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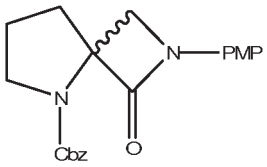
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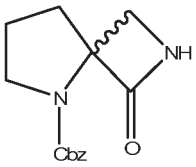
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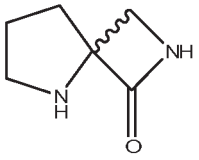
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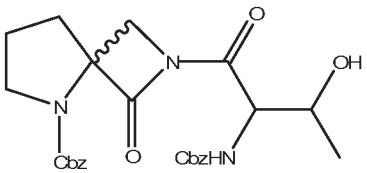
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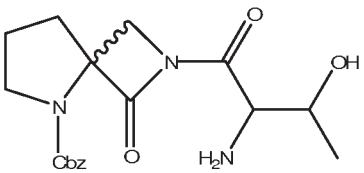
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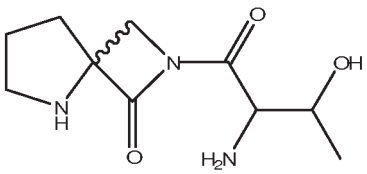
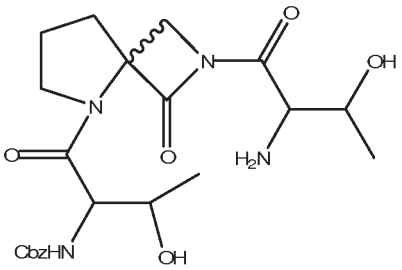

(AK55),

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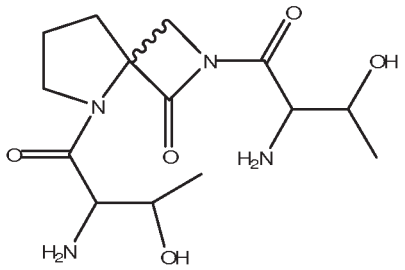
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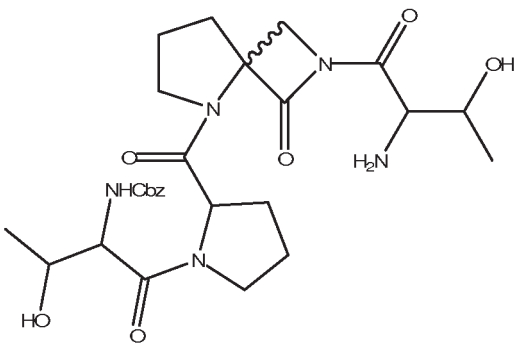
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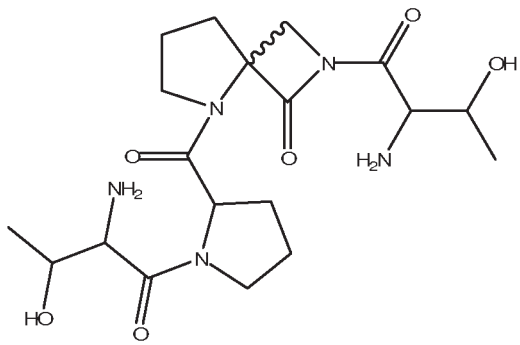
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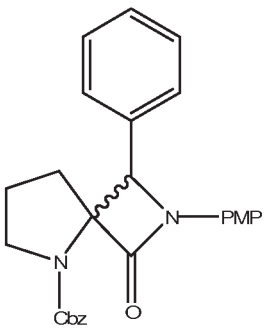
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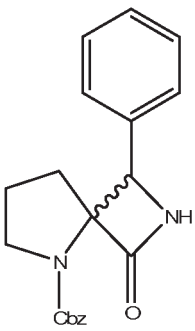
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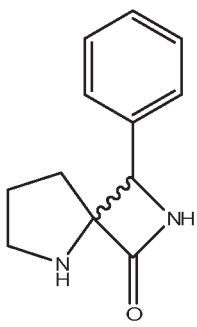
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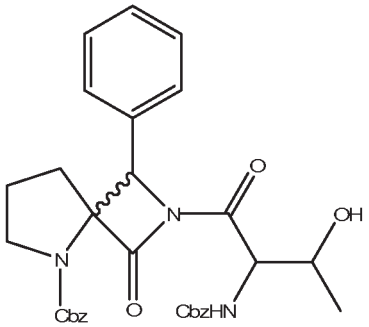
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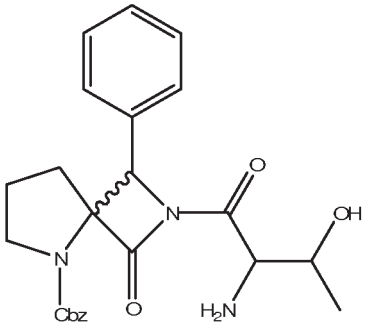
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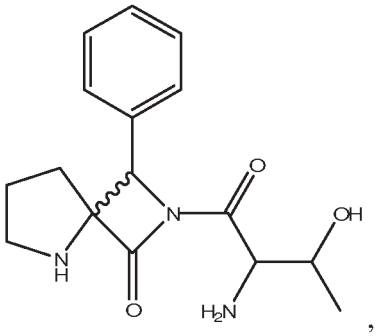
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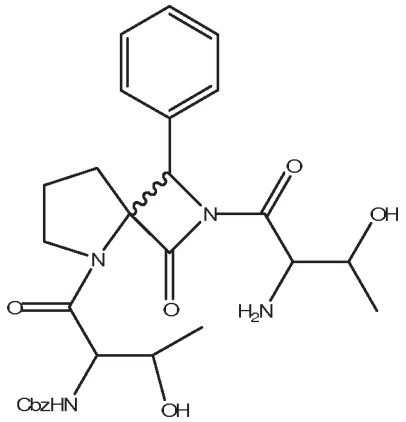
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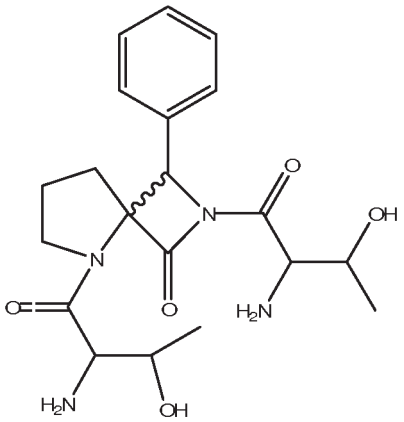
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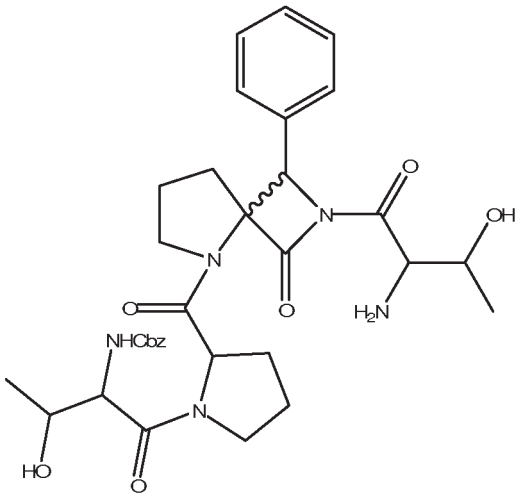
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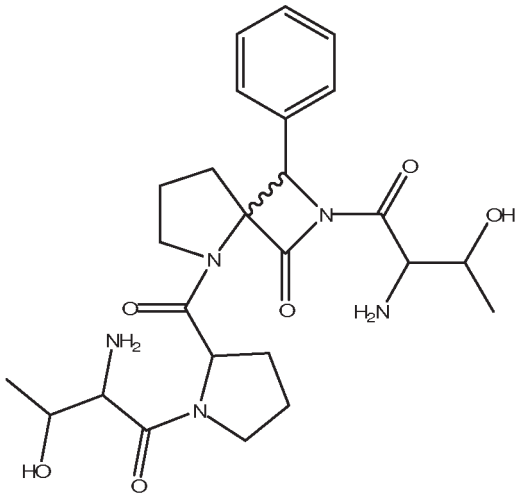
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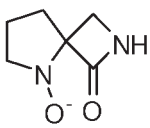
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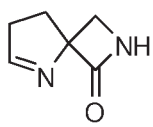
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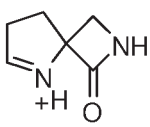
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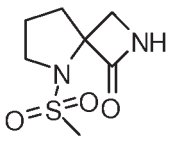
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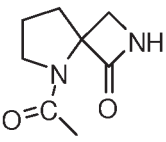
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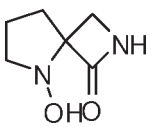
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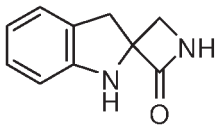
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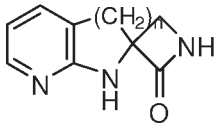
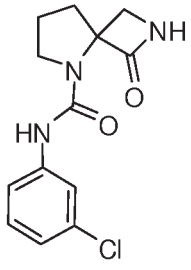
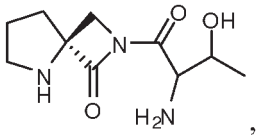

(where n is 0, 1, 2 or 3), and

; or pharmaceutically acceptable salts thereof.

and pharmaceutically acceptable salts, stereoisomers, or N-oxides thereof.

[0073] The compounds of the present disclosure and formulations thereof are intended to include both a D-isomeric form, an L-isomeric form, or a racemic mixture (both D- and L-isomeric forms) of any one or more of the compounds. In addition, the formulations of the compounds are intended to include any combination or ratio of L-isomeric forms to D-isomeric forms of one or more of the analogs described herein. These and other formulations of the disclosed compounds comprising a greater ratio of the D- and/or L-isomeric analog form may posses enhanced therapeutic characteristic relative to racemic formulations of a disclosed compounds or mixture of compounds. For example, disclosed compounds may be enantiomers, e.g.: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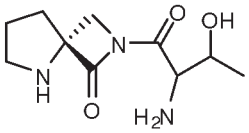
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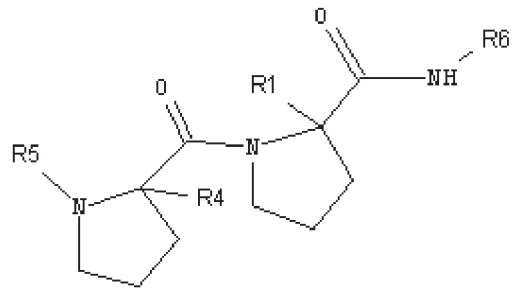
[0074] Disclosed compounds may provide for efficient cation channel opening at the NMDA receptor, e.g. may bind or associate with the glutamate site of the NMDA receptor to assist in opening the cation channel. The disclosed compounds may be used to regulate (turn on or turn off) the NMDA receptor through action as an agonist.

[0075] Other compounds contemplated herein include those having a cyclic amide core. Other exemplary compounds may be, in an embodiment, peptides, or in another embodiment, peptide mimetics. Contemplated compounds include those represented by:

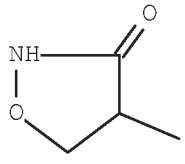
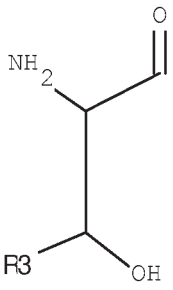
[0076]

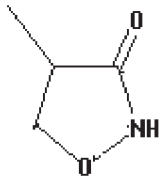
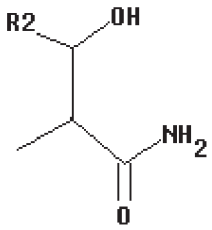


wherein,

R_1 is H or benzyl group;

R_4 is H or benzyl group;

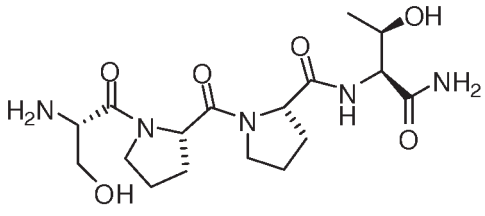
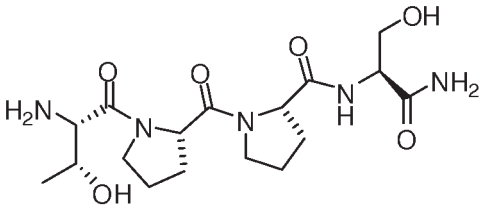
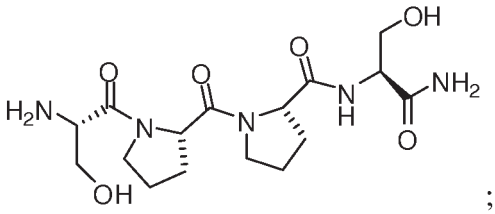
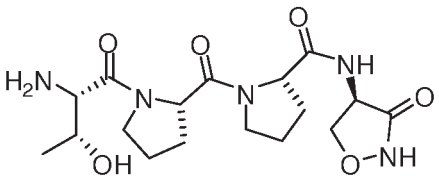
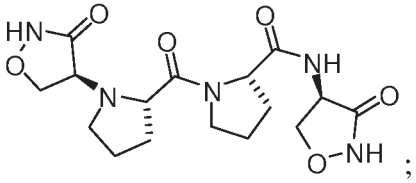
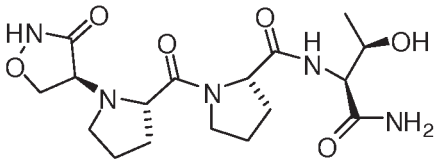
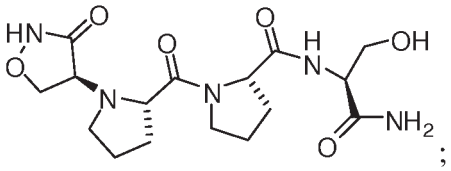
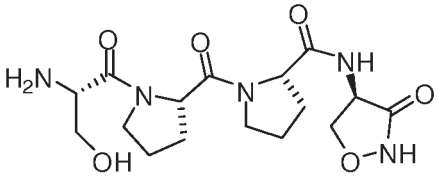
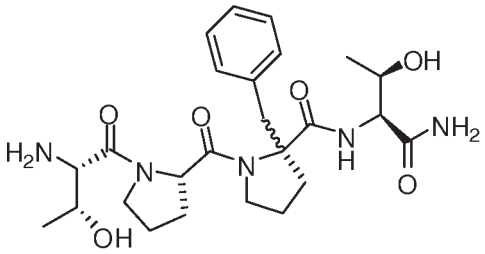
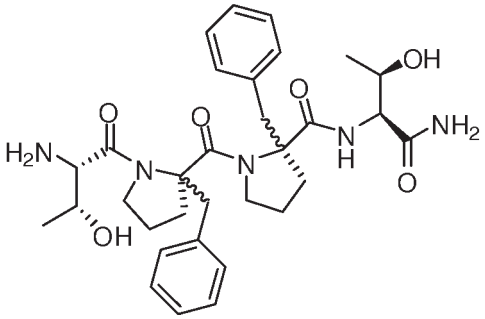
R_5 is  or 

R_6 is  or 

R_2 is H or CH_3;

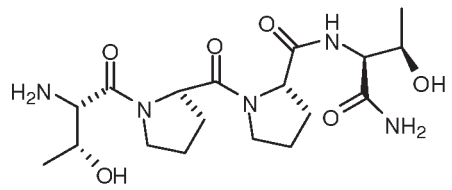
R_3 is H or CH_3; and stereoisomers, or pharmaceutically acceptable salts or N-oxides thereof.

Exemplary compounds include:

[0077]  ;  ;  ;  ;  ;  ;  ;  ;  ; or  .

[0078] The compounds as described herein may be glycine site NMDA receptor partial agonists. A partial agonist as used in this context will be understood to mean that at a low concentration, the analog acts as an agonist and at a high concentration, the analog acts as an antagonist. Glycine binding is not inhibited by glutamate or by competitive inhibitors of glutamate, and also does not bind at the same site as glutamate on the NMDA receptor. A second and separate binding site for glycine exists at the NMDA receptor. The ligand-gated ion channel of the NMDA receptor is, thus, under the control of at least these two distinct allosteric sites. Disclosed compounds may be capable of binding or associating with the glycine binding site of the NMDA receptor. In some embodiments, disclosed compounds may possess a potency that is 10-fold or greater than the activity of existing NMDA receptor glycine site

partial agonists. For example, disclosed compounds may possess a 10-fold to 20-fold enhanced potency compared to GLYX-13. GLYX-13 is represented by:

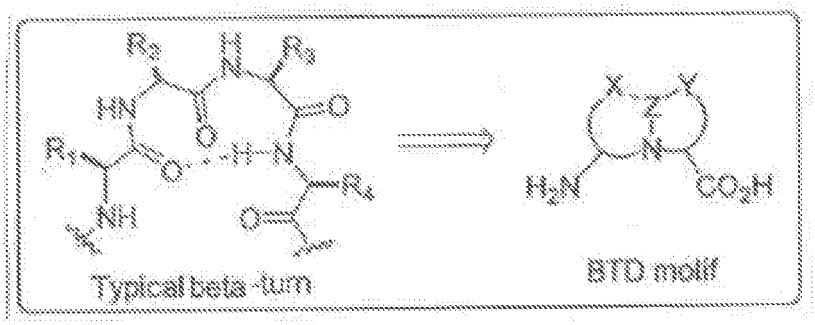


[0079] For example, provided herein are compounds that may be at least about 20-fold more potent as compared to GLYX-13, as measured by burst activated NMDA receptor-gated single neuron conductance ($\mathbf{I_{NMDA}}$) in a culture of hippocampal CA1 pyramidal neurons at a concentration of 50 nM. In another embodiment, a provided compound may be capable of generating an enhanced single shock evoked NMDA receptor-gated single neuron conductance ($\mathbf{I_{NMDA}}$) in hippocampal CA1 pyramidal neurons at concentrations of 100 nM to 1 μM. Disclosed compounds may have enhanced potency as compared to GLYX-13 as measured by magnitude of long term potentiation (LTP) at Schaffer collateral-CA-1 synapses in *in vitro* hippocampal slices.

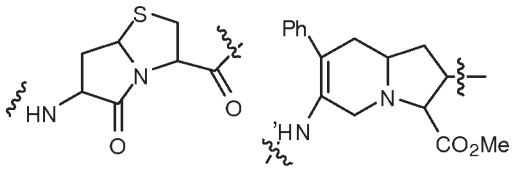
Preparation of Compounds

[0080] In some embodiments, a disclosed compound, e.g. a peptide mimetic having a beta-turn motif capable of binding to the NMDA ligand binding core of SEQ ID NO 1, may be formed by incorporating one or more dehydro amino acids within a peptide. For example, peptides containing dehydrophenylalanine and/or dehydroleucine and/or alpha-aminobisobutyric acid may be incorporated to make a peptide mimetic having a beta-turn motif.

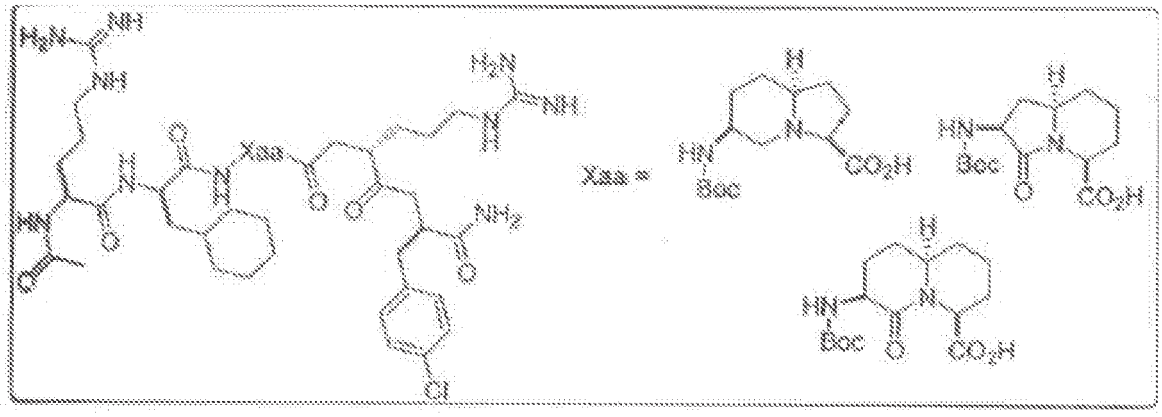
[0081] In another embodiment, a disclosed compound may be formed using a constrained bicyclic beta-turn dipeptide (BTD) motifs. This approach is based on the replacement of dipeptide component by incorporation of a carboxyl and an amino group in geometrically suitable positions for peptide coupling (see figure below) for inducing turns.



[0082] For example, a dipeptide component such as one or more azabicyclononanes may be incorporated to produce a structure having a beta-turn motif. In another example, a disclosed peptide mimetic may include a core structure as exemplified below, e.g. in place of two, three, or four amino acids:

[0083] 

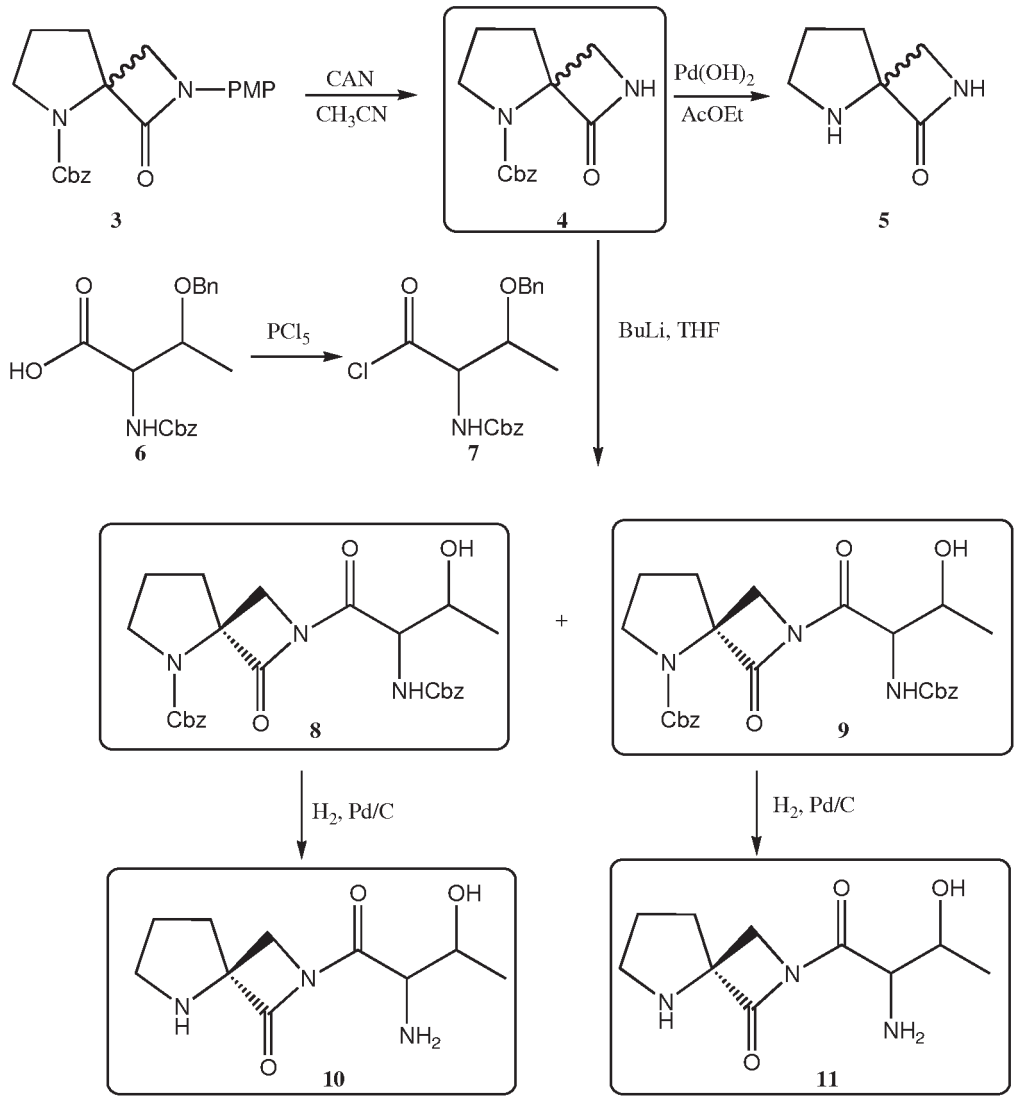
[0084] In some embodiments, an azacycloalkeane may mimic a beta turn mimetic, e.g.:



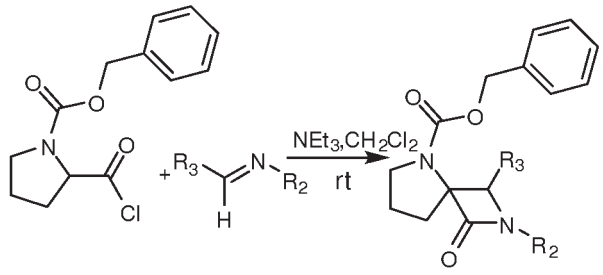
.

[0085] The following schemes are representative synthetic routes that may be used to prepare disclosed compounds and intermediates thereof.

[0086] Scheme 1: Synthetic Routes

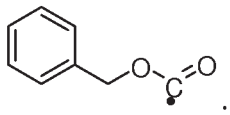


Scheme 2



5

[0087] Ceric ammonium nitrate, or "CAN", is the chemical compound with the formula $(NH_4)_2Ce(N0_3)_6$. This orange-red, water-soluble salt is widely used as an oxidizing agent in organic synthesis. This compound is used as a standard oxidant in quantitative analysis.

[0088] PMP refers to p-methoxybenzylidene; Cbz refers to a carbobenzyloxy radical that can be depicted as:  .

Compositions

[0089] In other aspects, formulations and compositions comprising the disclosed compounds and optionally a pharmaceutically acceptable excipient are provided. In some embodiments, a contemplated formulation comprises a racemic mixture of one or more of the disclosed compounds.

[0090] Contemplated formulations may be prepared in any of a variety of forms for use. By way of example, and not limitation, the compounds may be prepared in a formulation suitable for oral administration, subcutaneous injection, or other methods for administering an active agent to an animal known in the pharmaceutical arts.

[0091] 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.

[0092] The specification for the dosage unit forms of the invention 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.

[0093] As used herein "pharmaceutically acceptable carrier" or "excipient" includes any and all

[0094] 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.

[0095] 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.

[0096] Sterile injectable solutions can be prepared by incorporating the comound 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.

[0097] In accordance with an alternative aspect of the invention, a compound may be formulated with one or more additional compounds that enhance the solubility of the compound. .

Methods

[0098] Methods for treating cognitive disorders and for enhancing learning is provided. Such methods include administering a pharmaceutically acceptable formulation of one or more of the disclosed compounds to a patient in need thereof. Also contemplated are methods of treating

patients suffering from, memory deficits associated with aging, schizophrenia, special learning disorders, seizures, post-stroke convulsions, brain ischemia, hypoglycemia, cardiac arrest, epilepsy, migraine, as well as Huntington's, Parkinson's and Alzheimer's disease.

[0099] Other methods contemplated include the treatment of cerebral ischemia, stroke, brain trauma, brain tumors, acute neuropathic pain, chronic neuropathic pain, sleep disorders, drug addiction, depression, certain vision disorders, ethanol withdrawal, anxiety, and memory and learning disabilities. In yet another aspect, a method for enhancing pain relief and for providing analgesia to an animal is provided

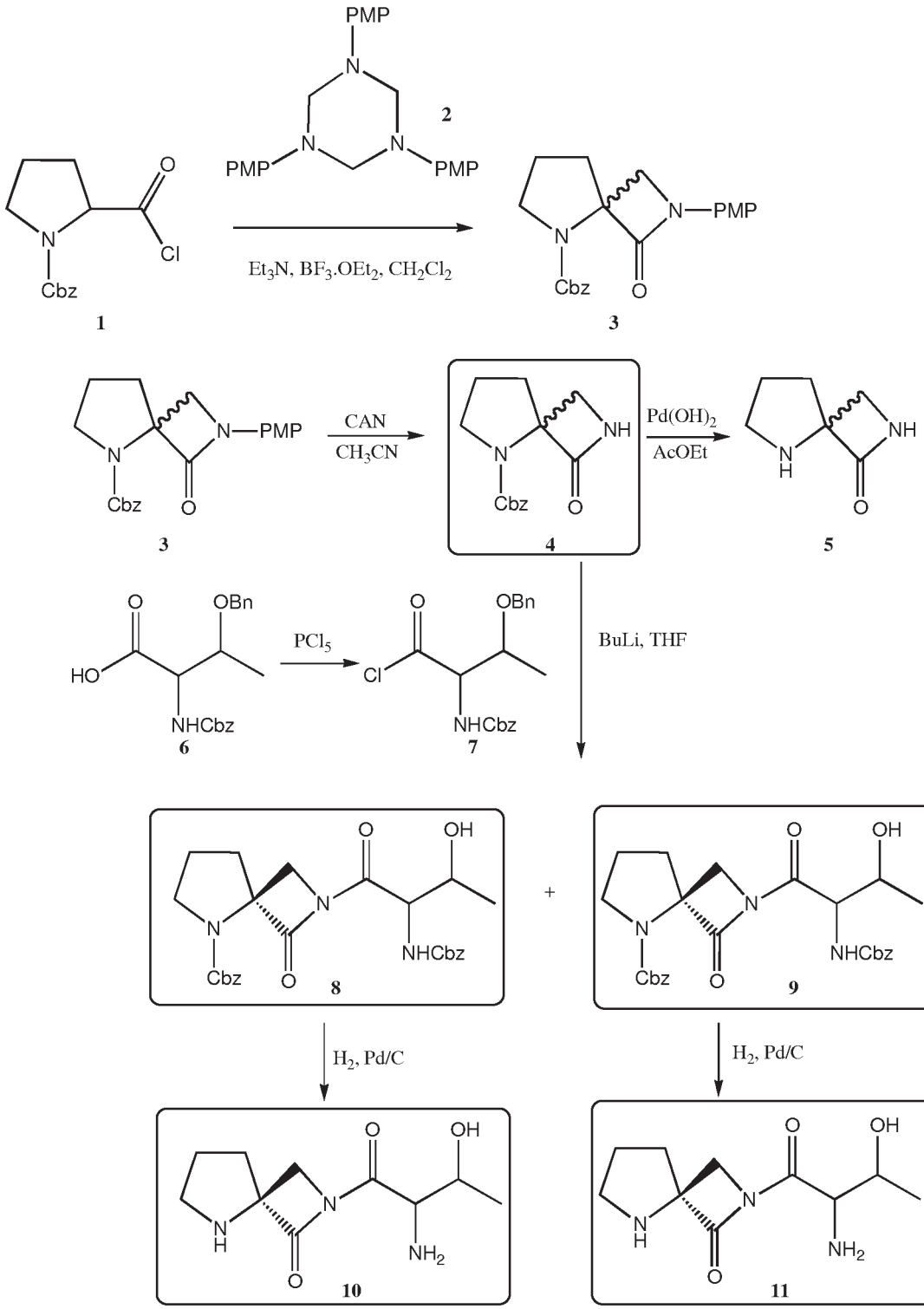
EXAMPLES

[0100] The following examples are provided for illustrative purposes only, and are not intended to limit the scope of the disclosure.

Example 1—Synthesis of Pyrrolidine-derived Spiro β-Lactam Derivatives

[0101] The following reaction sequence was used (Scheme A) to synthesize Spiro Lactams. Hexahydrol,3,5-triazines, Cbz-L-proline acid chloride and N-(Cbz) O-(benzylether)-L-threonine acid chloride as starting materials.

Scheme A :


PMP
N
N
N
PMP
PMP
2
O
N
Cl
Cbz
1
Et3N, BF3.OEt2, CH2Cl2
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N
Cbz
O
3
CAN
CH3CN
NH
Pd(OH)2
AcOEt
4
5
HO
OBn
NHCbz
6
PCl5
Cl
7
BuLi, THF
OH
8
9
+
H2, Pd/C
NH2
10
11

Table 1.

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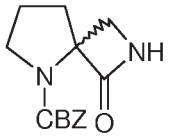
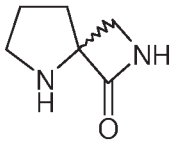
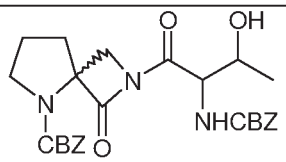
4		20 mg	93	261	YES
5(AK-51)		150 mg	-	127	YES (>95% purity)
8		17 mg	73	496	-

Example 2 - Synthesis of Compounds and Intermediates

[0102] Spiro Lactam 3. The synthesis of C4 unsubstituted spiro lactam 3 was conducted via Staudinger reaction of methyleneimine derived from triazine 2. The [2 + 2]-cycle addition reaction between the ketene derived from Cbz-L-proline acid chloride and the methyleneimine was carried out in the following way: ketene was generated by dehydrochlorination of the acid chloride with triethylamine at -40°C for 45 min, and then a dichloromethane solution of triazine 2 and boron trifluoride etherate (which depolymerize the triazine) was added. After 12 hours, the corresponding spiro lactam 3 was obtained as a mixture of enantiomers, with 30 to 50% yield. The oxidative removal of the PMP group from spiro lactam 3 in the presence of CAN gave the N-unsubstituted derivative spiro lactam 4, which upon treatment with $Pd(OH)_2/C$ gave the corresponding spiro lactam intermediates 5.

[0103] Spiro lactam 4 was obtained in 93% purity (HPLC) after purification by chromatography on silica gel. Spiro lactam 5 were obtained with purities >90% purity (by NMR) after chromatography on silica gel using gradient elution 20% to 70% Ethyl Acetate Cyclohexane, in 50% yield.

Example 3 - Synthetic Routes to Intermediate Compounds

[0104] Triazine **2.** To a solution of p-anisidine (24.6 g, 200 mmol.) in a mixture (500 mL) of ethyl acetate / water (1:1), cooled at 0°C, an aqueous solution (17 mL) of formaldehyde (37%) was added. The reaction mixture was stirred for 3 hours at 0°C then 1 hour at room temperature, and the organic layer was separated, washed with water (50 mL), and dried over Na_2S0_4. The solvent was removed under vacuum, and a white solid was obtained. This solid was washed once with diethyl ether to provide 26.3 g (solid was dried at 40°C overnight) of pure triazine **2** in 97% yield.

[0105] Spiro lactam Intermediates 3. To a stirred solution of the N-benzyloxycarbonyl L-proline acid chloride (5g, 18.7 mmol.) in dry dichloromethane (65 mL) cooled to -40°C, was added dropwise dry triethylamine (10.4 mL, 74.7 mmol.). The solution became yellow to confirm that the ketene was formed.

[0106] After 45 min at -40°C, a purple solution of triazine **2** (2.52g, 6.16 mmol.) and BF_3 OEt_2 (2.37 mL, 18.7 mmol.), previously mixed in CH_2Cl_2 (35 mL), was added dropwise. The mixture was allowed to warm slowly to room temperature overnight and then quenched with saturated aqueous $NaHC0_3$. The aqueous layer was extracted twice with CH_2Cl_2 (20 mL); the combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2S0_4. The solution was then concentrated and purified by column chromatography over silica gel using gradient elution 100% / cyclohexane to 20% ethyl acetate / cyclohexane to give 7.01g of pure product with 37% yield.

[0107] Spiro lactam Intermediates 4. To a stirred solution of spiro lactam 3 (2.4g, 6.55 mmol.) in acetonitrile (49 mL) at -10°C, was added dropwise over 1 hour CAN (10.8g, 19.6 mmol.), previously dissolved in H_20 (30 mL). After the addition was complete, the mixture was stirred for 45 min (TLC showed no remaining starting material). The reaction mixture was diluted with ethyl acetate (100 mL) and saturated $NaHCO_3$(50 mL). To the organic layer was added water (100 mL) and solid sodium bisulfite (20eq). The organic layer was washed with brine and dried over anhydrous Na_2S0_4. The solution was then concentrated and purified by column chromatography over silica gel using gradient elution 100% / cyclohexane to 50% ethyl acetate / cyclohexane to give 0.87 g of pure product in 50% yield.

[0108] Spiro lactam Intermediates **5 (AK-51).** 0.5g of 4 were dissolved in 20 mL of ethyl acetate and transferred via cannula to a flask under H2 (1 atm) containing 50 mg of 10%

$Pd(OH)_2$-C catalyst. The mixture was stirred for overnight under ¾ at 50 PSi and then the catalyst was filtered off through celite. The organic layer was concentrated and purified by chromatography on silica gel to afford 120 mg of product in 50% yield.

[0109] N-(Cbz)-0-(benzyl ether)-L-threonine acid chloride **7.** To a stirred solution of N-(Cbz)-0-(benzyl ether)-L-threonine (0.95 g, 2.7 mmol.) in dry ether (27 mL) was added PC15 (0.61 g, 2.9 mmol.) and the mixture was stirred for 3 hours at room temperature. Then the solvent was removed with high vacuum at room temperature. Toluene was added and removed as above. The crude white solid was used without any purification for the coupling reaction.

[0110] Spiro lactams Intermediates **8 and 9.** To a stirred solution of spiro lactam 4 (200 mg, 0.76 mmol.) in dry THF (4 mL) at -78°C was added BuLi (0.32 mL, 0.80 mmol. in hexane) dropwise. After addition was complete, the mixture was stirred at -78°C for 1 hour. N-(Cbz)-O-(benzyl ether)-L-threonine acid chloride 7 in THF (4 mL) was added at -78°C. The mixture was stirred for overnight from -78°C to room temperature.

[0111] The reaction mixture was quenched with saturated NH_4CI (10 mL) and ethyl acetate (10 mL) was added. The water layer was extracted twice with ethyl acetate. The combined organic layers were dried with MgSC^ and concentrated to give 0.44 g of crude product. The crude product was eluted through silica gel with a gradient from 100% CH_2CI_2 to 2% MeOH / CH_2CI_2 giving fractions that ranged in purity from 44% to 73%. This reaction was repeated on 0.28g of spiro lactam **4** and gave after chromatography fractions with purities that ranged from 50% to 73%.

Example 4 - NMDA Receptor Binding Assay

Tissue preparation:

[0112] Crude synaptic membranes were prepared from rat hippocampi or from rat forebrains (male Sprague-Dawley rats) and washed extensively to remove endogenous amino acids, as previously described by Ransom and Stec (1988). Briefly, the crude synaptic membranes were resuspended in 20 volumes of 5m*M* Tris-HCI buffer, pH 7.4 (for use in [^{3}H]TCP-binding experiments), or in 20 volumes of 5 m*M* Tris-acetate buffer, pH 7.4 (for use in [^{3}H]glycine-binding studies) and homogenized using a Polytron (Virtis shear; Virtis, NY, U.S.A.). Membranes were then pelleted by centrifugation at 48,000 *g* for 20 min. This step was repeated twice and the homogenate was stored at -70° C in the same buffer. Before each

use, homogenates were thawed at room temperature, pelleted, and washed four additional times. For the [^{3}H]glycine experiment, the pellet was first incubated for 30 min at 25°C in 5 mM Tris-acetate buffer containing 0.04% Triton X-100 and then washed four times by homogenization and centrifugation. The final washed membranes were resuspended at concentrations of 2-3 mg/ml in either 5 mM Tris-HCI buffer or 5 mM Tris-acetate buffer.

[0113] TCP binding assays: Measurements of specific [^{3}H]TCP binding were performed as described previously (Haring *et ah,* 1986, 1987; Kloog *et ah,* 1988a). Final reaction mixtures consisted of 50-100 μg of membrane protein in 200 μï of 5 mM Tris-HCI buffer and contained either [^{3}H]TCP, or [^{3}H]TCP and the appropriate concentration of NMDA-receptor ligands or mAbs. Reactions were initiated by the addition of the membranes to the reaction mixtures. Unless otherwise indicated, binding assays were performed under nonequilibrium conditions at 25°C for 1 h. Nonspecific binding was determined in parallel samples containing 100 μM unlabeled PCP. Binding reactions were determined by filtration on Whatman GF/B glass filters that had been pretreated with 0.1% polyethyleneimine for 1 h.

[0114] The dissociation of [^{3}H]TCP from its membrane-binding site was measured after equilibrating the receptors with 20 nM [^{3}H]TCP for 120 min. The dissociation reaction was initiated by the addition of 100 μM unlabeled PCP in the presence and absence of NMDA-receptor ligands or mAb. Reactions were terminated immediately (zero time) and after incubation for the additional periods of time indicated.

[0115] The effects of the three compounds were examined on 1) NMDA receptor - gated single neuron conductance (I_{NMDA}) in hippocampal CAI pyramidal neurons and 2) the magnitude of long -term potentiation (LTP) and long term depression(LTD) at Schaffer collateral CAl synapses, in *in vitro* hippocampal slices. GLYX-13 has been reported to exibit a low concentration (1-10 μM) enhancement of burst-activated I_{NMDA} and LTP, while simultaneously reducing LTD and single pulse evoked I_{NMDA}- A hundred fold higher GLYX-13 concentration of 100 μM converted to reducing LTP and burst I_{NMDA}, and no longer affected LTD.

[0116] Compound B showed a 20-fold enhancement in potency compared to GLYX-13. 50 nM of this compound markedly enhanced both single shock (1A) and burst evoked (IB) I_{NMDA} , as well as doubling the magnitude of LTP (IE). In contrast, 1 μM NRX-10,050

significantly reduced both single shock (1C) and burst evoked ((ID) I_{NMDA}, reminiscent of 100 μM GLYX-13. (See Figure 2).

[0117] AK-51 exhibited less potency than compound B, but a wider concentration range in its stimulatory actions (Figure 3). Both 100 nM (2A) and 1 μM NRX-10,051 enhanced single-shock evoked I_{NMDA}, while 1 uM NRX-10,051 doubled the magnitude of LTP (2D), while not altering LTD (2E).

[0118] AK-52 produced only a mild enhancement of single-shock evoked I_{NMDA} at a low concentration (100 nM; 3A), which converted to significant reduction in I_{NMDA} at a 1 uM concentration (3B). 100 nM AK-52 produced an enhancement of LTP similar in magnitude to compound B and AK-51, but this converted to a slight, but significant, reduction in LTP at the 1 μM concentration, without altering LTD.

[0119] These three compound showed about a 20-fold enhancement in potency compared to GLYX-13. Compound B is the most potent enhancer of I_{NMDA} at low concentrations (50 nM). While AK-51 enhancement of I_{NMDA} was smaller in magnitude, this effect remained when the AK-51 was increased 10-fold (100 nM to 1 μM). The AK-52 was the weakest enhancer of I_{NMDA}, and this effect reversed more quickly to a frank reduction in I_{NMDA}.

[0120] These compounds enhanced the magnitude of LTP to similar extents, approximately to a doubling. GLYX-13 was the only compound that could simultaneously increase LTP and reduce LTD: AK-52 did not affect LTD, even at a concentration that reduced I_{NMDA}. GLYX-13 can selectively enhance I_{NMDA} mediated by NMDA receptors containing NR2A/B subunits, and these receptors are localized to extrasynaptic loci and are more strongly activated by neuronal bursts that induce LTP. While all of the tested compounds have potent effects on LTP and I_{NMDA}, the lesser effects on LTD suggest that they have increased selectivity for NR2A/B containing NMDA receptor glycine sites than the GLYX-13.

Example 5 - *T-Maze* Learning Model

[0121] Male 3 month old Fisher 344 X Brown Norway F1 cross rats (FBNF1) were used for this study. The t-maze was constructed with arms (45 cm long x 10 cm wide x 10 cm high)made of black Plexiglas enclosing the maze. Two plastic bottle caps, lined with wire mesh, were secured to the end of each goal arm in which the food reward (Cheerios, 100 mg/piece) was placed. Before the start of training, animals were gradually deprived of food to approximately 85% of their free feeding weight. On three successive days before the start of training, animals were habituated to the t-maze with food located throughout the maze. On the first day of training, animals were rewarded for right arm choices and were trained to a criterion of 9 out of 10 consecutive correct choices. On the second day of training, animals were rewarded for left arm choices, and were trained to a criterion of 9 out of 10 consecutive correct choices. On the subsequent testing day, animals were given injections of AK51(0.3,1,3,10,30 mg/kg p.o.), or DMSO vehicle (1 mg/ml; Sigma, Saint Louis MO) in a blind manner via gastric gavage (4", 16-ga; Braintree Scientific, Braintree MA) 60 min prior to the start of testing (n = 8-9 per group. On the first trial of testing, both arms were baited with food and for the subsequent 20 trials only alternating choices (opposite of the animal's previous choice) were rewarded (-30 sec inter-trial interval). The number of trials to criterion (5 consecutive correct choices) was calculated for each animal. Data was analyzed by ANOVA followed by Fisher PLSD post hoc tests comparing individual drug doses to vehicle (a = .05).

[0122] Figure 5 depicts mean (± SEM) trials to criterion in the alternating T-maze task (20 trials) in food deprived 3 month old rats. Animals were injected p.o. with 0, 0.3, 1, 3, 10, or 30 mg/kg AK051 in DMSO vehicle (n= 8-9 per group) 60 min before the start of testing. *** P < .001, ** P < .01, Fisher PLSD post hoc vs. vehicle

Example 6 Formalin Test of Neuropathic Pain

[0123] Experiments were conducted as previously described (Abbott et al. *Pain,* 60, 91-102, 1995; Wood et al., *Neuroreport,* 19, 1059-1061 2008). Male 3 month old Fisher 344 X Brown Norway F1 cross rats (FBNF1) were used for this study. Before the start of testing, animals were habituated to the testing chamber (30 x 30 x 60 cm opaque plexiglass) for 10 min each day over 2 consecutive days. On the testing day, animals were given injections of AK51 (0.3,1,3,10,30 mg/kg p.o.), or DMSO vehicle (1 mg/ml; Sigma, Saint Louis MO) in a blind

manner via gastric gavage (4", 16-ga; Braintree Scientific, Braintree MA) 60 min prior to formalin injections (n = 8-9 per group). Animals were placed into the testing chamber 10 min prior to formalin injection. For the formalin injection, rats were manually restrained and given a subcutaneous injection of 1.5% formalin (50 µï¿½ with a 26-ga needle; Sigma, Saint Louis MO) into the lateral footpad on the plantar surface of the left hind paw. After formalin injections rats were placed back into the testing chambers. Animals were videotaped from below with the aid of an angled mirror for 50 min post formalin injection. Total time spent licking the injected paw and total number of injected paw flinches during the late phase (30-50 min post formalin injection) were quantified off-line in a blind manner by a trained experimenter with high (r > 0.9) inter- and intra-rater reliability for both measures. All animals were euthanized by $C0_2$ immediately after testing. Data was analyzed by ANOVA followed by Fisher PLSD post hoc tests comparing individual drug doses to vehicle (a = .05). Figure 6 depicts mean (± SEM) % Analgesia defined as % reduction in flinches in the late phase response (30-50 min) after intraplantar formalin injection (50 µï¿½ of 1.5% formalin).

Example 7- Oral Formulations Enhancing Learning and Memory

[0124] An oral preparation of AK-51, was prepared in dimethylsulfoxide (DMSO). All doses were administered in a volume of 300 µï. The animals were then fed p.o. by gavage (force fed by mouth with an inserted feeding needle) a volume calculated to deliver to the animal a defined dose based on body weight as follows 0.0 mg/kg 300 µï¿½ DMSO (vehicle); 0.3 mg/kg, 300 µL in DMSO; 1.0 mg/kg, 300 µL in DMSO; 3.0 mg/kg, 300 µL in DMSO; 10.0 mg/kg, 300 µï¿½ in DMSO; 30.0 mg/kg, 300 µï¿½ in DMSO.

[0125] Animals were injected 60 minutes before the start of testing with one of the dose amounts recited above. Then, an alternating T-maze task (20 trials) was used to asses learning behavior in the animals. This protocol is described at Example 5. Briefly, the T-maze is a choice task. The subject rat was placed in the base of the "T". Following a short delay, it was allowed to explore the maze and choose to enter either the right or left arms. The choice is scored according to variety of criterion, including spontaneous alternation, cued reward, or to indicate a preference. Based on the criterion used in this study, the T-maze was used to test learning and memory. Food placed at one end of the maze was used as the positive reinforcer for each animal test.

[0126] Animals given a 1.0 mg/kg dose by mouth of AK-51 demonstrated a statistically significant enhancement of learning behavior in the T-maze test ($P < 0.001$). Animals given a 3.0 mg/kg dose by mouth of the non-peptide analog NRX-10,051 also demonstrated a statistically significant enhancement of learning behavior in the T-maze test ($P < 0.01$).

Example 8 Isomers

[0127] The two different isomers of AK-55 was used in a NDMA binding assay as in Example 4. One isomer of AK-55 potently enhances NMDA while the other does not. Figure 7A indicates the time course of effect of 15 min bath application of IμM AK55 (solid bar) on normalized pharmacologically-isolated NMDA receptor-gated current in CA1 pyramidal neurons under whole-cell recording (mean ± SEM, n=6). B: Time course of effect of 15 min bath application of IμM AK55 (solid bar) on normalized pharmacologically-isolated NMDA receptor-gated current in CA1 pyramidal neurons under whole-cell recording (mean ± SEM, n=7). C: Time course of effect of bath application of IμM AK6 (solid bar, filled circles, n=8) compared to untreated control slices (open circles, n=8) on the magnitude of long-term potentiation (LTP) of extracellular excitatory postsynaptic potential slope (mean ± SEM fEPSP) induced by high-frequency Schaffer collateral stimulation (2xl00Hz/500msec).

Example 9 Biochemical Assays

[0128] Table B depicts the results of binding assays against various targets with AK51:

[0129] Table B

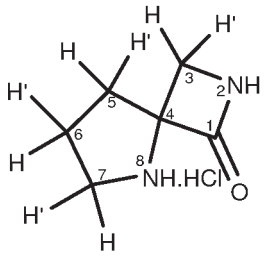
Target	Species	Concentration	%Inhibition
Glutamate, AMPA	rat	10 μM	-8
Glutamate, Kainate	rat	10 μM	-13
Glutamate, Metabotropic,$mGlu_s$	human	10 μM	-7
Glutamate, NMDA, Agonism	rat	10 μM	27
Glutamate, NMDA, Glycine	rat	10 μM	-6
Glutamate, NMDA, Phencyclidine	rat	10 μM	-5
Glutamate, NMDA, Polyamine	rat	10 μM	-14
Glutamate, Non-Selective	rat	10 μM	-10

Target	Species	Concentration	%Inhibition
Glycine, Strychnine-Sensitive	rat	10 μM	4
Potassium Channel hERG	human	10 μM	3

Example 10 Identification of β turn in spiro compounds

[0130] Proton 1-D experiments ^{1}H, ^{13}C, DEPT, homo nuclear 2-D experiments (DQF-COSY, TOCSY, NOESY) and Hetero nuclear experiments HSQC and HMBC in DMSO-D_6 at 30 degree Celsius are conducted to confirm the exact carbon chemical shifts and protons chemical shifts of the spiro compound:

[0131]



[0132] Chemical shifts are observed as follows: 1H, DMSO-d_6, 600MHz, δ in ppm, TMS at O.OOppm: 8.72 (bs, 1H), 3.47dd, 2H), 3.37(t, 2H), 2.21(m,2H), 2.02(m,lH), 1.89(m,lH) (see Figure 12);

[0133] ^{13}C, DMSO-d_6, 150MHz, δ in ppm, reference DMSO at 39.5ppm: 169.6, 68.7, 45.6, 40.7, 32.9, 22.4.

[0134] The chemical shift of the amide proton was located at 8.72 ppm as a broad singlet, and cross peaks were observed between 8.72 and 3.37. This finding established the chemical shift of H-3 at 3.47ppm. Weak nOe between 3.37 and 2.21 ppm indicates the populations of H-5 at 2.21ppm. Total correlation was found from 3.37 to 2.21ppm through2.02 lnd 1.89ppm; nOe correlation was observed between 2.21, 2.02, 1.89 and 3.37 ppm. This finding was understandable as the resonances H-6 and H-7 are: H-6 (2.02 and 1.89ppm), H-7 (3.37ppm). The heteronuclear 2-D experiments (HSQC and HMBC) also confirmed the chemical shifts of protons and carbon.

[0135] The chemical shift of individual protons and carbon were observed as follows:

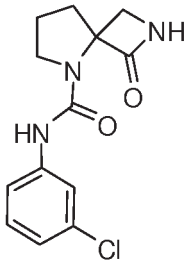
[0136] 8.72 (bs, H-2, 1H), 3.47(dd, H-3, 2H), 3.37(t, H-7, 2H), 2.21(m, H-5, 2H), 2.02(m, H-6,1H), 1.89(m, H-6' H)

[0137] 169.6(C-1), 68.7(C-4), 45.6(C-7), 40.7(C-3), 32.9(C-5), 22.4(C-6)

[0138] A weak nOe between H-3 and H-5 is suggestive of restricted rotation of the rings with respect to each other. The absence of hydrogen bonds in which the donor and acceptor residues i (i ± 3) and also absence of long range nOe (C^{α} atoms <7A°) between two rings indicates there is no significant secondary fold.

Example 11

[0139] Proton 1-D experiments ^{1}H, ^{13}C, DEPT, homo nuclear 2-D experiments (DQF-COSY, TOCSY, NOESY) and Hetero nuclear experiments HSQC and HMBC in DMSO-D_6 at 30 degree Celsius are conducted to confirm the exact carbon chemical shifts and protons chemical shifts of the spiro compound



. The ^{1}H NMR in DMSO is shown in Figure 13. A N15-HSQC experiment at 600MHz can be performed to confirm amide chemical shifts.

EQUIVALENTS

[0140] 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 invention described herein. Such equivalents are intended to be encompassed by the following claims.

INCORPORATION BY REFERENCE

[0141] 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, including the following incorporated by reference:

[0142] Abbott FV, Franklin KB, Westbrook RF, The formalin test: scoring properties of the first and second phases of the pain response in rats. Pain, 60 (1995) 91-102; Bennett GJ, Xie YK., A peripheral mononeuropathy in rat that produces disorders of pain sensation like

those seen in man. Pain, 33 (1988) 87-107; U.S. Patent No. 7,273,889; U.S. Patent No. 6,821,985; U.S. Patent No. 6,667,317; U.S. Patent No. 6,635,270; U.S. Patent No. 6,521,414; U. S. Patent No. 6,197,820; U. S. Patent No. 6,147,230; U. S. Patent No. 6,007,841; U.S. Patent No. 5,952,389; U.S. Patent No. 5,902,815; U.S. Patent No. 5,741,778; U.S. Patent No. 5,605,911; U.S. Patent No. 5,523,323; U.S. Patent No. 4,959,493; Moskal, et al. (2005), Neuropharmacology, 49(7): 1077-87; Narahshi, Toshio et al. (2004) Biol. Pharm. Bull., 27(1):1701-1706; Lynch, Gary et al. (2006), Aging Research Reviews, 5:255-280; Rajashankar et al. J. Am. Chem. Soc. (1992), 114, 9225;; Rajashankar et al. J. Am. Chem. Soc. (1995), 117, 10129; A. Karle et al, Biochemistry (1990), 29, 6747; Regan et al, Science (1998), 241, 976; Kaumaya et al, Biochemistry (1990), 29, 13; Hanessian et al, Tetrahedron (1997), 53, 12789; Zhang et al, Org. Lett. (2003), 53115; Xuyuan et al, Org. Lett. (2004), 6, 3285; Halab et al, J. Med. Chem. (2002), 45, 5353

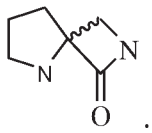
What is claimed is:

CLAIMS

1. A peptide mimetic capable of binding to the NMDA ligand binding core of SEQ ID NO. 1, wherein said peptide mimetic has two alpha carbons about 6 to about 14 Å apart, and a beta-turn motif comprising a bicyclic amide core such that, when the peptide mimetic binds to said SEQ ID NO. 1, the bicyclic amide core substantially retains configuration.

2. The peptide mimetic of claim 2, wherein the bicyclic core is a spiro-beta-lactam.

3. The peptide mimetic of claim 1 or 2, wherein peptide mimetic has a core represented by:



.

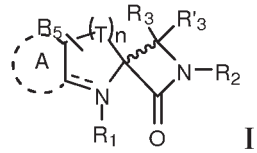
4. The peptide mimetic of any one of claims 1-3, wherein the peptide mimetic substantially maintains the beta-turn motif in vivo or in an aqueous solution.

5. The peptide mimetic of any one of claims 1-4, where said peptide mimetic is capable of forming a hydrogen bond with the following amino acids of SEQ ID NO.l: PR0124, THR126, GLU178 and SER180.

6. The peptide mimetic of any one of claims 1-5, where the core is conjugated to one or two amino acids.

7. The peptide mimetic of any one of claims 1-6, where the peptide mimetic comprises a bicyclic amide core with two alpha carbons about 6 to about 10 Å apart.

8. The peptide mimetic of any one of claims 1-7, represented by Formula I:



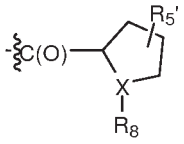
I

and pharmaceutically acceptable salts, stereoisomers, and N-oxides thereof; wherein

T is, independently for each occurrence, CR_4R_4', and n is 0, 1, 2 or 3;

A is optionally present and is selected from phenyl or pyridine, wherein A is optionally substituted by one or more substituents selected from R_a;

Ri is selected from the group consisting of H, hydroxyl, -S(0)$_2$-Ci-$_4$alkyl; -S0$_2$, C_1-$_4$alkyl, C_2-C_4alkenyl, phenyl, R_7, or



, wherein C_{1-4}alkyl, C_{2-4}alkenyl, or phenyl is optionally substituted by one or more substituents selected from R_a;

X is CH or N;

R_3 and R_3' are independently selected from the group consisting of H, halogen, hydroxyl, phenyl, Q^alkyl, amido, amine, or C_{2-4}alkenyl, wherein C_{1-4}alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_4 and R_4' are independently selected from the group consisting of H, halogen, hydroxyl, phenyl, C_{1-4}alkyl, amido, amine, C_{1-4}alkoxy or C_{2-4}alkenyl, wherein C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, and phenyl are optionally substituted by one or more substituents selected from R_a;

R_2 is selected from the group consisting of H, R_7, -S(0)$_2$, S(0)$_2$-C_1-C_4alkyl, C^alkyl, hydroxyl, or phenyl wherein C_{1-4}alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_5 and R5' are each independently selected from group consisting of H, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, cyano, amino, phenyl, and hydroxyl, wherein C_{1-4}alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_7 is selected from group consisting of -C(0)-R$_9$, -C(0)-0-R$_9$, or -C(0)-NR$_d$-R_9,

R9 is selected from the group consisting of H, C_{1-4}alkyl, phenyl, or heterocyclic, wherein C_{1-4}alkyl, phenyl or heterocyclic is optionally substituted by 1, 2 or 3 substituents selected from R_b;

R_8 is selected from group consisting of H, -C(O)- C^alkyl or C(0)-0- C_{1-4} alkyl, wherein C_{1-4}alkyl is optionally substituted by 1, 2 or 3 substituents selected from R_a;

R_a is selected, independently for each occurrence, from carboxy, hydroxyl, halogen, amino, phenyl, C^alkyl, and C_{1-4}alkoxy;

R_b is selected, independently for each occurrence, from the group consisting of carboxy, hydroxyl, halogen, amino, phenyl, Q^alkyl, C_1-$_4$alkoxy, and -NH-R_c;

R_c is selected, independently for each occurrence from the group consisting of: -C(O)-0-Ci-$_4$alkyl; and -C(0)-Ci-$_4$alkyl; and

R_d is selected, independently for each occurrence, H and Ci^alkyl.

9. A method for treating a cognitive disorder comprising administering to an patient in need thereof an effective amount of a compound of any one of claims 1-8.

10. The method of claim 9, wherein the cognitive disorder is associated with memory loss or impaired learning..

11. A pharmaceutically acceptable composition comprising a compound of any one of claims 1-8, and a pharmaceutically acceptable excipient.

12. A method for treating neuropathic pain in a patient in need thereof comprising administering an effective amount of a compound of any one of claims 1-8.

13. A method for treating depression, obsessive-compulsive disorder, or schizophrenia in a patient in need thereof comprising administering an effective amount of a compound of any one of claims 1-8.

14. A method for treating post traumatic stress disorder, an alcohol dependency disorder, or an addiction to an addictive drug in a patient in need thereof comprising administering an effective amount of a compound of any one of claims 1-8.

15. A method of treating or preventing a NMDA receptor mediated disorder in a patient comprising administering to a patient in need thereof an acceptable NMDA ligand binding core receptor agonistic or antagonistic amount of a glycine mimicking beta-turn peptidomimetic cyclic compound having a cyclic amide moiety.

16. The method of claim 15, wherein the cyclic amide is a beta-lactam moiety.

17. A method of modulating the activity of SEQ ID NO. 1, wherein the modulation arises from a favorable conformation adopted by a compound, and wherein said modulation arises from a hydrogen bonding interaction between the compound and one, two, three or four of the following amino acids of SEQ ID NO.l: PR0124, THR126, GLU178 and SER180.

18. A method of identifying a compound capable of binding to SEQ ID NO. 1, comprising:

providing a molecular model comprising one or more target regions of SEQ ID NO. 1 derived from at least a portion of: SEQ ID NO. 1, atomic coordinates by molecular modeling

of SEQ ID NO. 1, or atomic coordinates deposited in the Protein Data Bank under accession number 1PBQ;

using the molecular model to identify a compound that is capable of binding to PR0124, THR126, GLU178 and SER180 of the target regions in the molecular model;

contacting the compound with the target regions of SEQ ID NO. 1;

measuring the activity of the target regions of SEQ ID NO 1 after said contacting.

19. A method of identifying a compound which modulates binding of a sequence comprising SEQ ID NO. 1, comprising: (A) designing or screening for a compound which binds to or associates with PR0124, THR126, GLU178 and SER180 of SEQ ID NO 1, and (B) testing the compound designed or screened for in (A) for its ability to modulate binding to SEQ ID NO 1 in vivo or in vitro, thereby identifying a compound that is a partial agonist of NDMA.

20. A compound identified by the method of claim 19.

21. A method of treating depression in a patient in need thereof comprising administering an effective amount of the compound of claim 20.