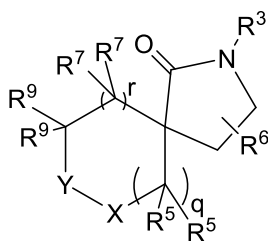


SUMMARY

In an aspect of the present disclosure, there is provided a compound represented by:



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

X is NR¹ or CR²R²;

Y is NR¹ or CR²R², wherein one of X or Y is NR¹;

R¹ is selected from the group consisting of H, C₁-C₆alkyl, phenyl, -C(O)-C₁-C₆alkyl, and -C(O)-O-C₁-C₆ alkyl;

10 q is 0 or 1;

r is 1 or 2;

R⁷ is independently selected from the group consisting of H, -C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, and halogen;

15 R⁹ is independently selected from the group consisting of H, -C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, and halogen, or one R⁷ and one R⁹ taken together with the adjacent carbons to which they are attached form a 3-membered carbocyclic ring which can be optionally substituted by one or two substituents independently selected from the group consisting of halogen, hydroxyl, -C₁-C₃alkyl, -C₁-C₃alkoxy, -C(O)NR^aR^b, and -NR^aR^b;

20 R² is independently selected for each occurrence from the group consisting of H, C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, -NR^aR^b and halogen;

R⁵ is independently selected for each occurrence from the group consisting of H, C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, -NR^aR^b and halogen;

R⁶ represents one or two optional substitutions each on one or more available ring carbons, and is independently selected for each occurrence from the group consisting of C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, -NR^aR^b and halogen;

w is 0, 1, or 2;

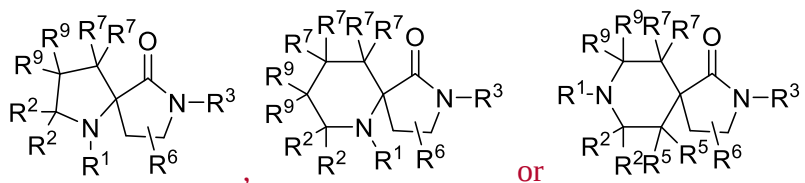
R³ is selected from the group consisting of H, phenyl, C₁-C₆ alkyl, -C(O)R³¹ and -C(O)OR³²;

R³¹ and R³² are each independently selected from the group consisting of H, C₁-C₆alkyl, -C₃-C₆cycloalkyl, and phenyl; and

R^a and R^b are each independently for each occurrence selected from the group consisting of H, phenyl, and C₁-C₃alkyl, or R^a and R^b taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring;

wherein any aforementioned C₁-C₆ alkyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from -C(O)NR^aR^b, -NR^aR^b, hydroxyl, S(O)_w-C₁-C₃alkyl, SH, phenyl and halogen, and any aforementioned phenyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from -C(O)-C₁-C₃alkyl, hydroxyl, -C(O)-C₁-C₃alkyl, methyl, CF₃ and halogen.

In another aspect of the present disclosure, there is provided a compound represented by:



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

R¹ is selected from the group consisting of H, C₁-C₆alkyl, phenyl, -C(O)-C₁-C₆alkyl, and -C(O)-O-C₁-C₆ alkyl;

R⁷ is independently selected from the group consisting of H, -C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, and halogen;

3b

R⁹ is independently selected from the group consisting of H, -C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, and halogen, or one R⁷ and one R⁹ taken together with the adjacent carbons to which they are attached form a 3-membered carbocyclic ring which can be optionally substituted by one or two substituents independently selected from the group consisting of halogen, hydroxyl, -C₁-C₃alkyl, -C₁-C₃alkoxy, -C(O)NR^aR^b, and -NR^aR^b;

R² is independently selected for each occurrence from the group consisting of H, C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, -NR^aR^b and halogen;

R⁵ is independently selected for each occurrence from the group consisting of H, C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, -NR^aR^b and halogen;

R⁶ represents one or two optional substitutions each on one or more available ring carbons, and is independently selected for each occurrence from the group consisting of C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, -NR^aR^b and halogen;

w is 0, 1, or 2;

R³ is selected from the group consisting of H, phenyl, C₁-C₆ alkyl, -C(O)R³¹ and -C(O)OR³²;

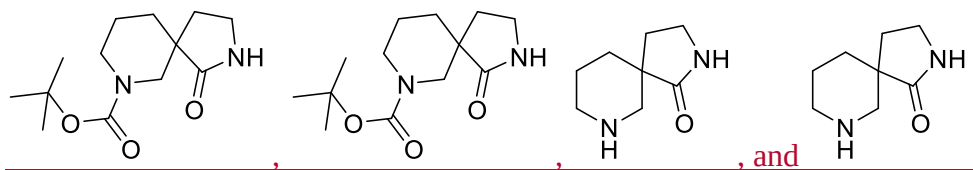
R³¹ and R³² are each independently selected from the group consisting of H, C₁-C₆alkyl, -C₃-C₆cycloalkyl, and phenyl; and

R^a and R^b are each independently for each occurrence selected from the group consisting of H, phenyl, and C₁-C₃alkyl, or R^a and R^b taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring;

wherein any aforementioned C₁-C₆ alkyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from -C(O)NR^aR^b, -NR^aR^b, hydroxyl, S(O)_w-C₁-C₃alkyl, SH, phenyl and halogen, and any aforementioned phenyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from -C(O)-C₁-C₃alkyl, hydroxyl, -C(O)-C₁-C₃alkyl, methyl, CF₃ and halogen.

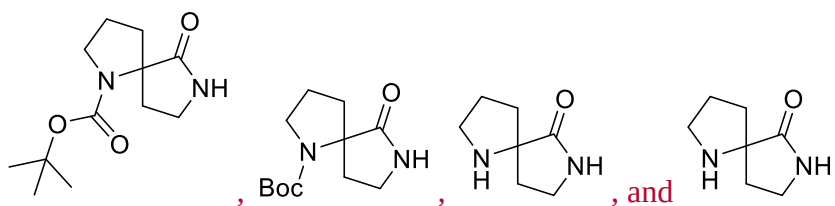
In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of:

3c



or a pharmaceutically acceptable salt or a stereoisomer thereof.

In another aspect of the present disclosure, there is provided a compound selected from the group consisting of:



or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a further aspect of the present disclosure, there is provided a compound selected from the compounds delineated in the table of Example 2 and the table of Example 4, or a pharmaceutically acceptable salt or a stereoisomer thereof.

10 In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, and a pharmaceutically acceptable excipient.

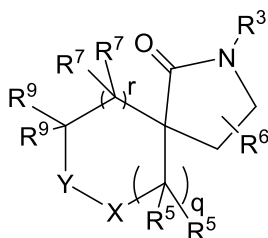
15 In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety.

In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating acute neuropathic pain or chronic neuropathic pain.

20 In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a neurodevelopmental disorder related to synaptic dysfunction.

In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in therapy.

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



5

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

X is NR^1 or CR^2R^2 ;

Y is NR^1 or CR^2R^2 , wherein one of X or Y is NR^1 ;

10

R^1 is selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, phenyl, $\text{-C(O)-C}_1\text{-C}_6$ alkyl, and $\text{-C(O)-O-C}_1\text{-C}_6$ alkyl;

q is 0 or 1;

r is 1 or 2;

R^7 is independently selected from the group consisting of H, $\text{-C}_1\text{-C}_6$ alkyl, $\text{-S(O)}_w\text{-C}_1\text{-C}_3$ alkyl, and halogen;

15

R^9 is independently selected from the group consisting of H, $\text{-C}_1\text{-C}_6$ alkyl, $\text{-S(O)}_w\text{-C}_1\text{-C}_3$ alkyl, and halogen, or R^7 and R^9 taken together with the adjacent carbons to which they are attached form a 3-membered carbocyclic ring which can be optionally substituted by one or two substituents independently selected from the group consisting of halogen, hydroxyl, $\text{-C}_1\text{-C}_3$ alkyl, $\text{-C}_1\text{-C}_3$ alkoxy, $\text{-C(O)NR}^a\text{R}^b$, and $\text{-NR}^a\text{R}^b$;

20

R^2 is independently selected for each occurrence from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{-S(O)}_w\text{-C}_1\text{-C}_3$ alkyl, $\text{-NR}^a\text{R}^b$ and halogen;

R^5 is independently selected for each occurrence from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{-S(O)}_w\text{-C}_1\text{-C}_3$ alkyl, $\text{-NR}^a\text{R}^b$ and halogen;

R^6 represents one or two optional substitutions each on one or more available ring carbons, and is independently selected for each occurrence from the group consisting of C_1 - C_6 alkyl, $-S(O)_w$ - C_1 - C_3 alkyl, $-NR^aR^b$ and halogen;

w is 0, 1, or 2;

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

R^{31} and R^{32} are each independently H, C_1 - C_6 alkyl, $-C_3$ - C_6 cycloalkyl, and phenyl; and

R^a and R^b are each independently for each occurrence selected from the group consisting of H, phenyl, and C_1 - C_3 alkyl, or R^a and R^b taken together with the nitrogen
10 to which they are attached form a 4-6 membered heterocyclic ring;

wherein any aforementioned C_1 - C_6 alkyl, independently for each occurrence, can be optionally substituted by one, two or three substituents each independently selected from $-C(O)NR^aR^b$, $-NR^aR^b$, hydroxyl, $S(O)_w$ - C_1 - C_3 alkyl, SH, phenyl and halogen, and any aforementioned phenyl, independently for each occurrence, can be
15 optionally substituted by one, two or three substituents each independently selected from $-C(O)$ - C_1 - C_3 alkyl, hydroxyl, $-C(O)$ - C_1 - C_3 alkyl, methyl, CF_3 and halogen.

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

In some [aspectexamples](#), compounds described herein bind to NMDA receptors expressing certain NR2 subtypes. In some [aspectexamples](#), the compounds described herein bind to one NR2 subtype and not another.

In another [aspectexample](#), a method of treating a condition selected from the group
25 consisting of autism, anxiety, depression, bipolar disorder, attention deficit disorder, attention deficit hyperactivity disorder (ADHD), schizophrenia, a psychotic disorder, a psychotic symptom, social withdrawal, obsessive-compulsive disorder, phobia, post-traumatic stress syndrome, a behavior disorder, an impulse control disorder, a substance abuse disorder, a sleep disorder, a

memory disorder, a learning disorder, urinary incontinence, multiple system atrophy, progressive supra-nuclear palsy, Friedrich's ataxia, Down's syndrome, fragile X syndrome, tuberous sclerosis, olivio-ponto-cerebellar atrophy, Rett syndrome, cerebral palsy, drug-induced optic neuritis, ischemic retinopathy, diabetic retinopathy, glaucoma, dementia, AIDS
5 dementia, Alzheimer's disease, Huntington's chorea, spasticity, myoclonus, muscle spasm, Tourette's syndrome, epilepsy, cerebral ischemia, stroke, a brain tumor, traumatic brain injury, cardiac arrest, myelopathy, spinal cord injury, peripheral neuropathy, fibromyalgia, acute neuropathic pain, and chronic neuropathic pain, in a patient in need thereof is provided. Such methods may comprise administering to the patient a pharmaceutically effective amount of a
10 disclosed compound or pharmaceutically acceptable salts, stereoisomers, N-oxides, and hydrates thereof.

In some embodimentexamples, a method of the disclosure includes treating neuropathic pain, wherein the neuropathic pain is selected from the group consisting of herpes, HIV, traumatic nerve injury, stroke, post-ischemia, chronic back pain, post-herpetic neuralgia,
15 fibromyalgia, reflex sympathetic dystrophy, complex regional pain syndrome, spinal cord injury, sciatica, phantom limb pain, diabetic neuropathy, and cancer chemotherapeutic-induced neuropathic pain.

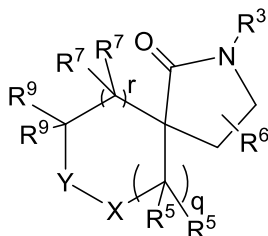
In some embodimentexamples, a method of the disclosure includes treating depression. For example, depression may include one or more of major depressive disorder, dysthymic
20 disorder, psychotic depression, postpartum depression, seasonal affective disorder, bipolar disorder, mood disorder, or depression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

DETAILED DESCRIPTION

This disclosure is generally directed to compounds that are capable of modulating NMDA receptors, for example, NMDA receptor antagonists, agonists, or partial agonists, and compositions and/or methods of using the disclosed compounds. It should be appreciated that

What is claimed is:

1. A compound represented by:



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

X is NR^1 or CR^2R^2 ;

Y is NR¹ or CR²R², wherein one of X or Y is NR¹;

R¹ is selected from the group consisting of H, C₁-C₆alkyl, phenyl, -C(O)-C₁-C₆alkyl, and -C(O)-O-C₁-C₆ alkyl;

10 q is 0 or 1;

r is 1 or 2;

R⁷ is independently selected from the group consisting of H, -C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, and halogen;

15 R⁹ is independently selected from the group consisting of H, -C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, and halogen, or one R⁷ and one R⁹ taken together with the adjacent carbons to which they are attached form a 3-membered carbocyclic ring which can be optionally substituted by one or two substituents independently selected from the group consisting of halogen, hydroxyl, -C₁-C₃alkyl, -C₁-C₃alkoxy, -C(O)NR^aR^b, and -NR^aR^b;

20 R² is independently selected for each occurrence from the group consisting of H, C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, -NR^aR^b and halogen;

R⁵ is independently selected for each occurrence from the group consisting of H, C₁-C₆alkyl, -S(O)_w-C₁-C₃alkyl, -NR^aR^b and halogen;

R^6 represents one or two optional substitutions each on one or more available ring carbons, and is independently selected for each occurrence from the group consisting of C_1 - C_6 alkyl, $-S(O)_w$ - C_1 - C_3 alkyl, $-NR^aR^b$ and halogen;

w is 0, 1, or 2;

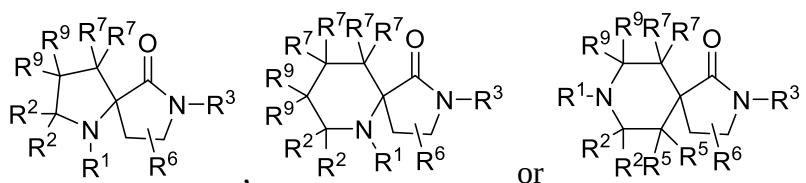
- 5 R^3 is selected from the group consisting of H, phenyl, C_1 - C_6 alkyl, $-C(O)R^{31}$ and $-C(O)OR^{32}$;

R^{31} and R^{32} are each independently selected from the group consisting of H, C_1 - C_6 alkyl, $-C_3$ - C_6 cycloalkyl, and phenyl; and

- 10 R^a and R^b are each independently for each occurrence selected from the group consisting of H, phenyl, and C_1 - C_3 alkyl, or R^a and R^b taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring;

- 15 wherein any aforementioned C_1 - C_6 alkyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from $-C(O)NR^aR^b$, $-NR^aR^b$, hydroxyl, $S(O)_w$ - C_1 - C_3 alkyl, SH, phenyl and halogen, and any aforementioned phenyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from $-C(O)$ - C_1 - C_3 alkyl, hydroxyl, $-C(O)$ - C_1 - C_3 alkyl, methyl, CF_3 and halogen.

2. The compound of claim 1, wherein q is 1.
3. The compound of claim 1, wherein q is 0.
- 20 4. The compound of claim 1 or 3, wherein q is 0 and r is 2.
5. The compound of any one of claims 1-4, wherein X is NR^1 and Y is CR^2R^2 .
6. A compound represented by:



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

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

R^7 is independently selected from the group consisting of H, $-C_1-C_6$ alkyl, $-S(O)_w-C_1-C_3$ alkyl, and halogen;

5 R^9 is independently selected from the group consisting of H, $-C_1-C_6$ alkyl, $-S(O)_w-C_1-C_3$ alkyl, and halogen, or one R^7 and one R^9 taken together with the adjacent carbons to which they are attached form a 3-membered carbocyclic ring which can be optionally substituted by one or two substituents independently selected from the group consisting of halogen, hydroxyl, $-C_1-C_3$ alkyl, $-C_1-C_3$ alkoxy, $-C(O)NR^aR^b$, and $-NR^aR^b$;

10 R^2 is independently selected for each occurrence from the group consisting of H, C_1-C_6 alkyl, $-S(O)_w-C_1-C_3$ alkyl, $-NR^aR^b$ and halogen;

R^5 is independently selected for each occurrence from the group consisting of H, C_1-C_6 alkyl, $-S(O)_w-C_1-C_3$ alkyl, $-NR^aR^b$ and halogen;

15 R^6 represents one or two optional substitutions each on one or more available ring carbons, and is independently selected for each occurrence from the group consisting of C_1-C_6 alkyl, $-S(O)_w-C_1-C_3$ alkyl, $-NR^aR^b$ and halogen;

w is 0, 1, or 2;

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

20 R^{31} and R^{32} are each independently selected from the group consisting of H, C_1-C_6 alkyl, $-C_3-C_6$ cycloalkyl, and phenyl; and

R^a and R^b are each independently for each occurrence selected from the group consisting of H, phenyl, and C_1-C_3 alkyl, or R^a and R^b taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring;

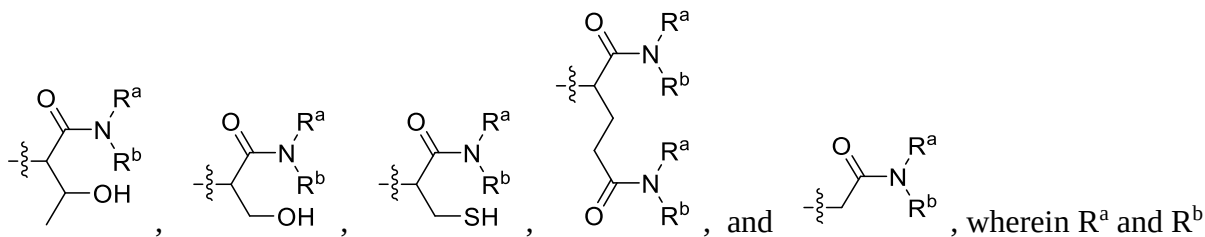
25 wherein any aforementioned C_1-C_6 alkyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from $-C(O)NR^aR^b$, $-NR^aR^b$, hydroxyl, $S(O)_w-C_1-C_3$ alkyl, SH, phenyl and halogen, and any aforementioned phenyl, independently for each occurrence, is optionally substituted by one, two or three substituents

- [illegible]

12. The compound of claim 9, wherein R¹ is .

14. The compound of any one of claims 1-6, wherein R¹ is  or .

16. The compound of ~~any one of claims 1-14~~, wherein R³ is selected from the group consisting of:



are each independently selected for each occurrence from the group consisting of hydrogen and -C₁-C₃alkyl.

17. The compound of any one of claims 1-16, wherein R^2 is H at each occurrence

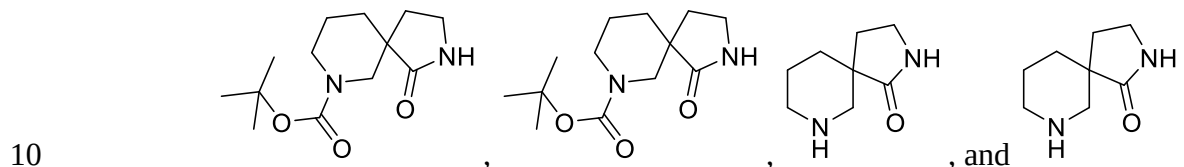
5 18. The compound of any one of claims 1-17, wherein R^5 is H at each occurrence.

19. The compound of any one of claims 1-18, wherein R^6 is H.

20. The compound of any one of claims 1-19, wherein R^7 is H at each occurrence.

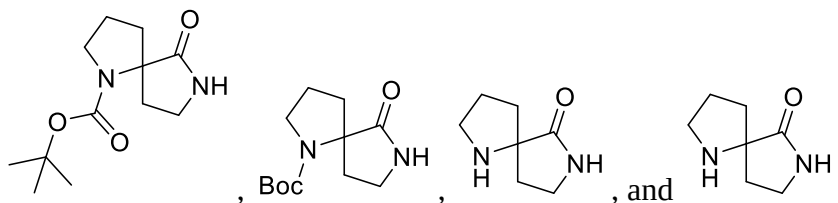
21. The compound of any one of claims 1-20, wherein R^9 is H at each occurrence.

22. A compound selected from the group consisting of:



or a pharmaceutically acceptable salt or a stereoisomer thereof.

23. A compound selected from the group consisting of:



or a pharmaceutically acceptable salt or a stereoisomer thereof.

15 24. A compound selected from the compounds delineated in the table of Example 2 and the table of Example 4, or a pharmaceutically acceptable salt or a stereoisomer thereof.

25. A- pharmaceutical composition comprising a compound of anyone of claims 1-24, and a pharmaceutically acceptable excipient.

26. The pharmaceutical composition of claim 25, suitable for oral administration, parenteral administration, topical administration, intravaginal administration, intrarectal administration, sublingual administration, ocular administration, transdermal administration, or nasal administration.

27. ~~A method of~~ Use of a compound of any one of claims 1-24, or a pharmaceutical composition of claim 25 or 26, in the manufacture of a medicament for treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety, ~~in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-24, or the pharmaceutical composition of claim 25 or~~

28. ~~A method of~~ Use of a compound of any one of claims 1-24, or a pharmaceutical composition of claim 25 or 26, in the manufacture of a medicament for treating acute neuropathic pain or chronic neuropathic pain, ~~in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-24, or the pharmaceutical composition of claim 25 or 26.~~

29. The ~~method~~ use of claim 28, wherein the neuropathic pain is chronic or acute.

30. The ~~method~~ use of claim 29, wherein the neuropathic pain is selected from the group consisting of herpes, HIV, traumatic nerve injury, stroke, post-ischemia, chronic back pain, post-herpetic neuralgia, fibromyalgia, reflex sympathetic dystrophy, complex regional pain syndrome, spinal cord injury, sciatica, phantom limb pain, diabetic neuropathy, and cancer chemotherapeutic-induced neuropathic pain.

31. ~~A method of~~ Use of a compound of any one of claims 1-24, or a pharmaceutical composition of claim 25 or 26, in the manufacture of a medicament for treating a neurodevelopmental disorder related to synaptic dysfunction ~~in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-24, or the pharmaceutical composition of claim 25 or 26.~~

32. A compound of any one of claims 1-24, or a pharmaceutical composition of claim 25 or 26, for use in therapy.