

4a

m is 0, 1 or 2;

n is 1 or 2;

X is O;

R<sup>1</sup> is selected from the group consisting of hydrogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)-C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)-O-C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkylene-C<sub>1</sub>-C<sub>6</sub>cycloalkyl, and phenyl;

R<sup>2</sup> is independently selected for each occurrence from the group consisting of hydrogen, cyano, -C<sub>1</sub>-C<sub>6</sub>alkyl, and halogen;

R<sup>3</sup> is selected from the group consisting of hydrogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)-R<sup>31</sup>, -C(O)-O-R<sup>32</sup>, and phenyl;

R<sup>31</sup> is selected from the group consisting of hydrogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>haloalkyl, -C<sub>3</sub>-C<sub>6</sub>cycloalkyl, and phenyl;

R<sup>32</sup> is selected from the group consisting of hydrogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>haloalkyl, -C<sub>3</sub>-C<sub>6</sub>cycloalkyl, and phenyl;

wherein any aforementioned C<sub>1</sub>-C<sub>6</sub>alkyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from -C(O)NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, hydroxyl, -SH, phenyl, -O-CH<sub>2</sub>-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)NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -C<sub>1</sub>-C<sub>3</sub>alkoxy, hydroxyl, and halogen;

R<sup>4</sup> is independently selected for each occurrence from the group consisting of hydrogen, halogen, hydroxyl, cyano, phenyl, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>2-4</sub>alkenyl, -C<sub>1-4</sub>alkoxy, -C(O)NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -N(R<sup>a</sup>)-phenyl, -N(R<sup>a</sup>)-C<sub>1</sub>-C<sub>6</sub>alkylene-phenyl, -N(R<sup>a</sup>)-C(O)-C<sub>1</sub>-C<sub>6</sub>alkyl, -N(R<sup>a</sup>)-C(O)-C<sub>1</sub>-C<sub>6</sub>alkylene-phenyl, -N(R<sup>a</sup>)-C(O)-O-C<sub>1</sub>-C<sub>6</sub>alkyl, and -N(R<sup>a</sup>)-C(O)-O-C<sub>1</sub>-C<sub>6</sub>alkylene-phenyl; wherein C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkylene, C<sub>2-4</sub>alkenyl, C<sub>1-4</sub>alkoxy, and phenyl are optionally substituted by one or more substituents selected from R<sup>P</sup>; or

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two R<sup>4</sup> moieties, when present on adjacent carbons, form a 3-membered carbocyclic ring taken together with the adjacent carbons to which they are attached, optionally substituted by one or two substituents independently selected from the group consisting of halogen, hydroxyl, -C<sub>1</sub>-C<sub>3</sub>alkyl, -C<sub>1</sub>-C<sub>3</sub>alkoxy, -C(O)NR<sup>a</sup>R<sup>b</sup>, and -NR<sup>a</sup>R<sup>b</sup>;

R<sup>a</sup> and R<sup>b</sup> are each independently for each occurrence selected from the group consisting of hydrogen, -C<sub>1</sub>-C<sub>4</sub>alkyl, and -CH<sub>2</sub>-phenyl; or R<sup>a</sup> and R<sup>b</sup> taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring;

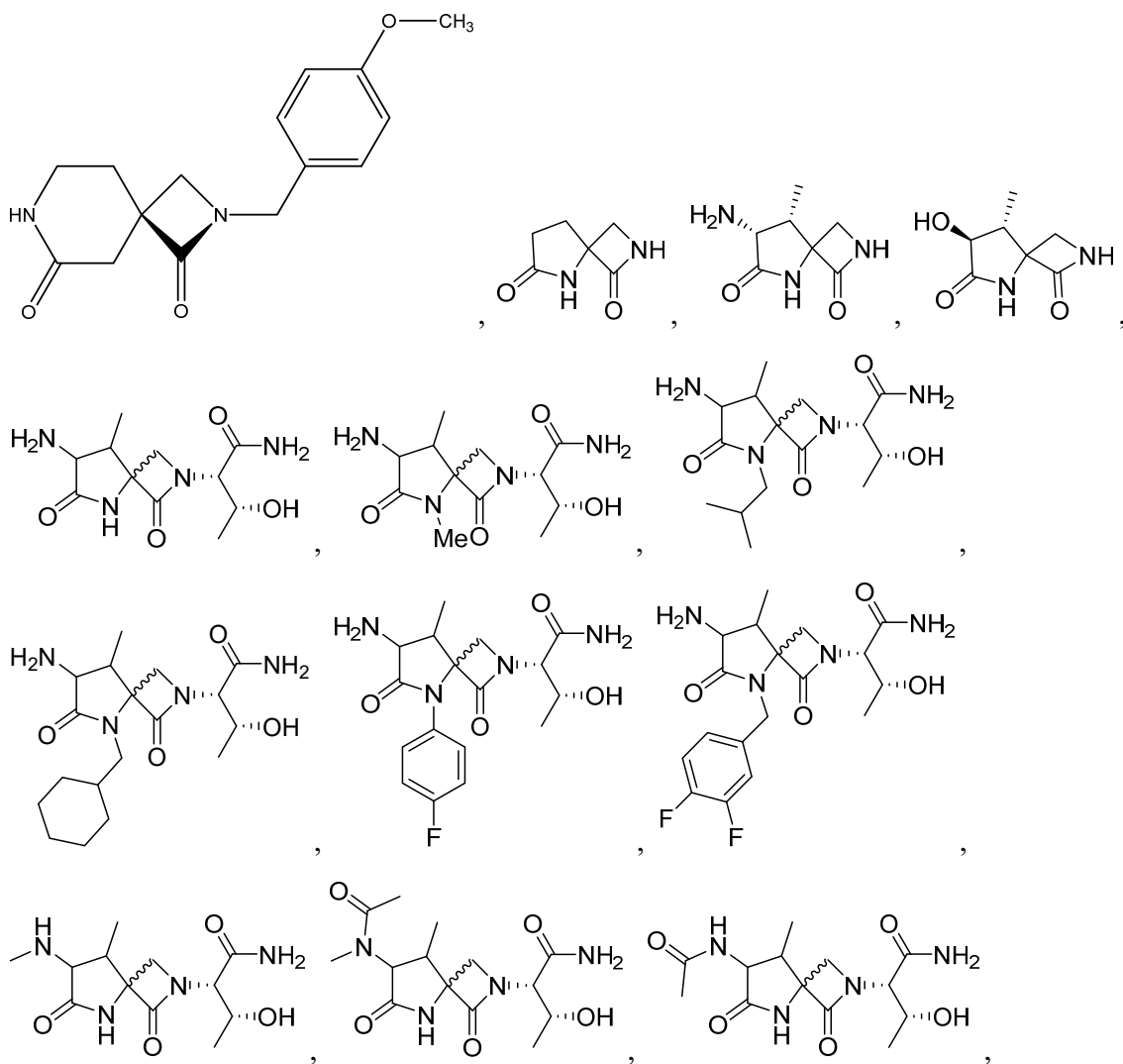
R<sup>5</sup> is hydrogen;

two R<sup>6</sup> moieties together with the carbon to which they are attached form a carbonyl or thiocarbonyl moiety; and

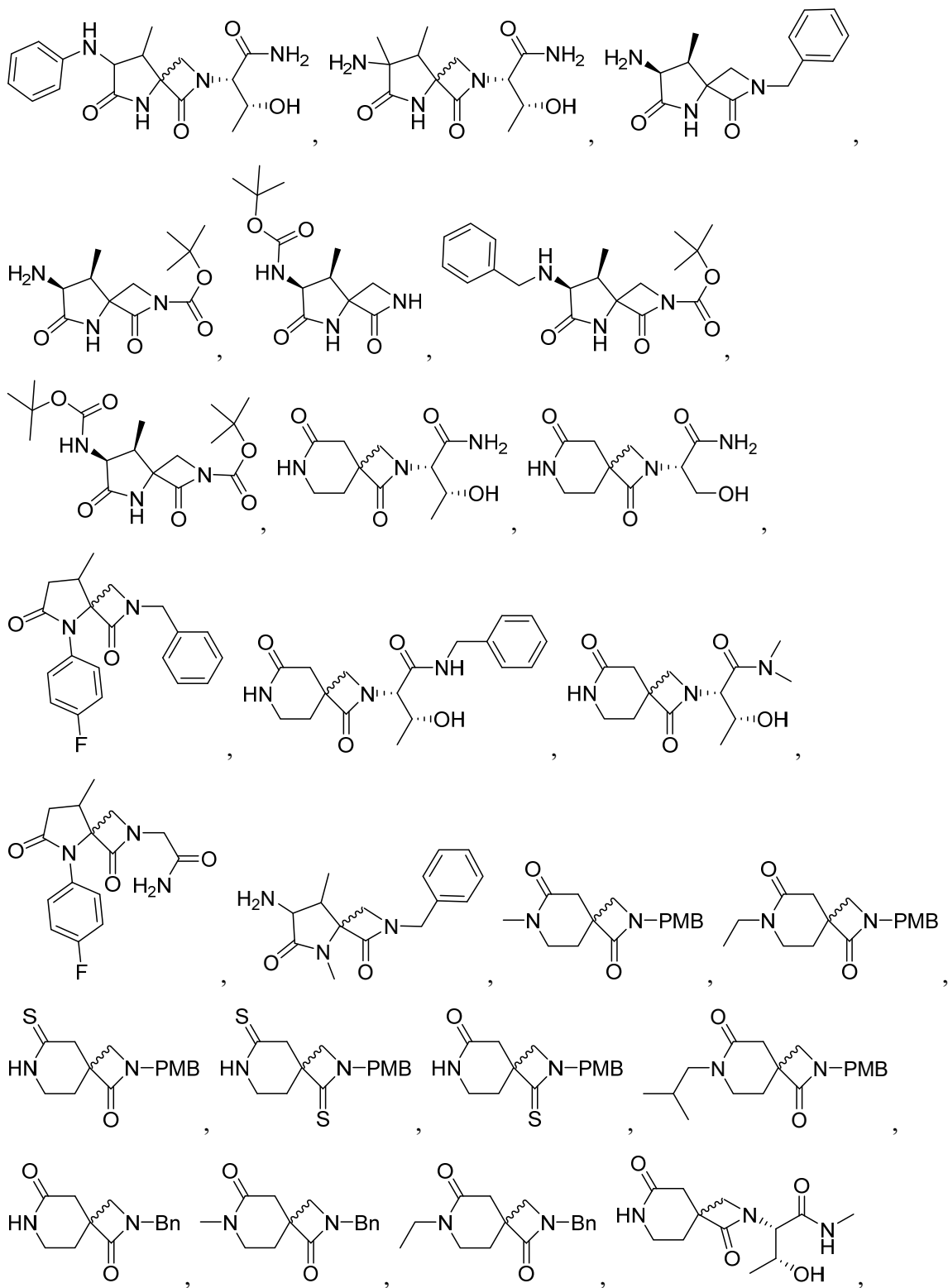
R<sup>p</sup> is independently selected for each occurrence from the group consisting of carboxy, hydroxyl, halogen, -NR<sup>a</sup>R<sup>b</sup>, phenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, and -C<sub>1</sub>-C<sub>6</sub>alkyl; wherein each phenyl, C<sub>1</sub>-C<sub>6</sub>alkoxy and C<sub>1</sub>-C<sub>6</sub>alkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen and hydroxyl.

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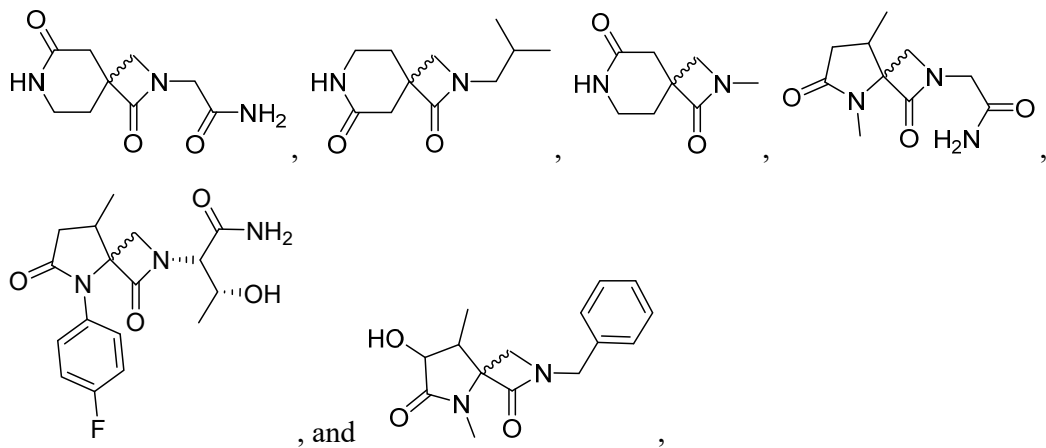
In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of



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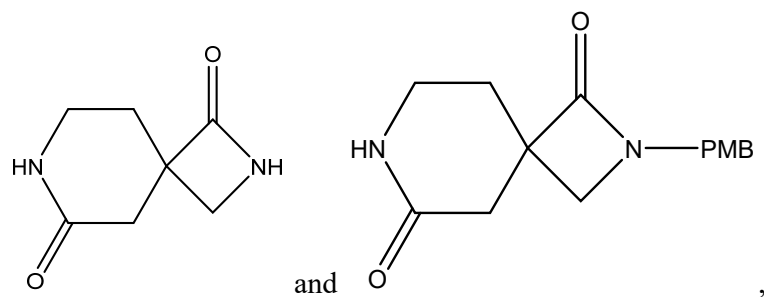


4e



or a pharmaceutically acceptable salts and/or a stereoisomer and/or an N-oxide thereof.

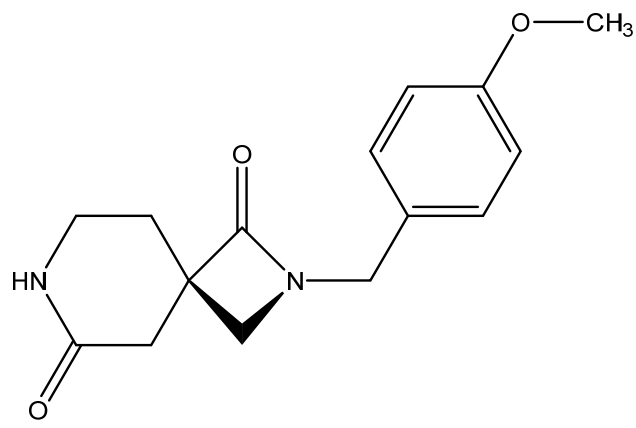
In another aspect of the present disclosure, there is provided a compound selected from:



or a pharmaceutically acceptable salt, a stereoisomer, and/or an N-oxide thereof.

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In a further aspect of the present disclosure, there is provided a compound having the formula:



or a pharmaceutically acceptable salt thereof.

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

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

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating dementia in a patient in need thereof.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a memory disorder associated with aging, schizophrenia, special learning disorders, seizures, post-stroke convulsions, brain ischemia, hypoglycemia, cardiac arrest, epilepsy, Lewy body dementia, migraine, AIDS dementia, Huntington's chorea, Parkinson's disease, early stage Alzheimer's disease, or Alzheimer's disease in a patient in need thereof.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating traumatic brain injury in a patient in need thereof.

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

In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutical composition disclosed herein, for use in treating depression, Alzheimer's disease, migraine, neuropathic pain, attention deficit disorder, schizophrenia, anxiety, dementia, memory disorder associated with aging, schizophrenia, special learning disorders, seizures, post-stroke convulsions, brain ischemia, hypoglycemia, cardiac arrest, epilepsy, Lewy body dementia, migraine, AIDS dementia, Huntington's chorea, Parkinson's disease, early stage Alzheimer's disease, Alzheimer's disease, a traumatic brain injury, or a neurodevelopmental disorder related to synaptic dysfunction.

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

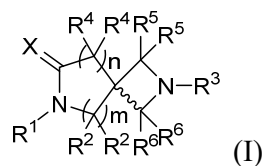
In some embodiments, compounds described herein bind to NMDA receptors expressing certain NR2 subtypes. In some embodiments, the compounds described herein bind to one NR2 subtype and not another. It is appreciated that disclosed compounds may bind to another protein target and/or another NMDA receptor type.

In another embodiment, a method of treating a condition selected from the group consisting of autism, anxiety, depression, bipolar disorder, attention deficit disorder, attention deficit

## CLAIMS

What is claimed is:

1. A compound represented by Formula I:



or a pharmaceutically acceptable salt, a stereoisomer, and/or an N-oxide thereof, wherein:

m is 0, 1 or 2;

n is 1 or 2;

X is O;

R<sup>1</sup> is selected from the group consisting of hydrogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)-C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)-O-C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkylene-C<sub>3</sub>-C<sub>6</sub>cycloalkyl, and phenyl;

R<sup>2</sup> is independently selected for each occurrence from the group consisting of hydrogen, cyano, -C<sub>1</sub>-C<sub>6</sub>alkyl, and halogen;

R<sup>3</sup> is selected from the group consisting of hydrogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)-R<sup>31</sup>, -C(O)-O-R<sup>32</sup>, and phenyl;

R<sup>31</sup> is selected from the group consisting of hydrogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>haloalkyl, -C<sub>3</sub>-C<sub>6</sub>cycloalkyl, and phenyl;

R<sup>32</sup> is selected from the group consisting of hydrogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>haloalkyl, -C<sub>3</sub>-C<sub>6</sub>cycloalkyl, and phenyl;

wherein any aforementioned C<sub>1</sub>-C<sub>6</sub>alkyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from -C(O)NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, hydroxyl, -SH, phenyl, -O-CH<sub>2</sub>-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)NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -C<sub>1</sub>-C<sub>3</sub>alkoxy, hydroxyl, and halogen;

R<sup>4</sup> is independently selected for each occurrence from the group consisting of hydrogen, halogen, hydroxyl, cyano, phenyl, -C<sub>1</sub>-C<sub>4</sub>alkyl, -C<sub>2-4</sub>alkenyl, -C<sub>1-4</sub>alkoxy, -C(O)NR<sup>a</sup>R<sup>b</sup>,

--NR<sup>a</sup>R<sup>b</sup>, -N(R<sup>a</sup>)-phenyl, -N(R<sup>a</sup>)-C<sub>1</sub>-C<sub>6</sub>alkylene-phenyl, -N(R<sup>a</sup>)-C(O)-C<sub>1</sub>-C<sub>6</sub>alkyl, -N(R<sup>a</sup>)-C(O)-C<sub>1</sub>-C<sub>6</sub>alkylene-phenyl, -N(R<sup>a</sup>)-C(O)-O-C<sub>1</sub>-C<sub>6</sub>alkyl, and -N(R<sup>a</sup>)-C(O)-O-C<sub>1</sub>-C<sub>6</sub>alkylene-phenyl; wherein C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkylene, C<sub>2</sub>-C<sub>4</sub>alkenyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, and phenyl are optionally substituted by one or more substituents selected from R<sup>P</sup>; or

two R<sup>4</sup> moieties, when present on adjacent carbons, form a 3-membered carbocyclic ring taken together with the adjacent carbons to which they are attached, optionally substituted by one or two substituents independently selected from the group consisting of halogen, hydroxyl, -C<sub>1</sub>-C<sub>3</sub>alkyl, -C<sub>1</sub>-C<sub>3</sub>alkoxy, -C(O)NR<sup>a</sup>R<sup>b</sup>, and -NR<sup>a</sup>R<sup>b</sup>;

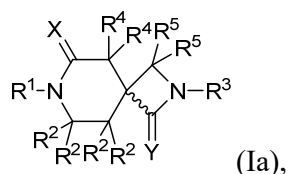
R<sup>a</sup> and R<sup>b</sup> are each independently for each occurrence selected from the group consisting of hydrogen, -C<sub>1</sub>-C<sub>4</sub>alkyl, and -CH<sub>2</sub>-phenyl; or R<sup>a</sup> and R<sup>b</sup> taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring;

R<sup>5</sup> is hydrogen;

two R<sup>6</sup> moieties together with the carbon to which they are attached form a carbonyl or thiocarbonyl moiety; and

R<sup>P</sup> is independently selected for each occurrence from the group consisting of carboxy, hydroxyl, halogen, -NR<sup>a</sup>R<sup>b</sup>, phenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, and -C<sub>1</sub>-C<sub>6</sub>alkyl; wherein each phenyl, C<sub>1</sub>-C<sub>6</sub>alkoxy and C<sub>1</sub>-C<sub>6</sub>alkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen and hydroxyl.

2. The compound of claim 1, wherein m is 2 and n is 1.
3. The compound of claim 1 or 2, wherein two R<sup>6</sup> moieties together with the carbon to which they are attached form a carbonyl moiety.
4. The compound of any one of claims 1-3, represented by Formula Ia:

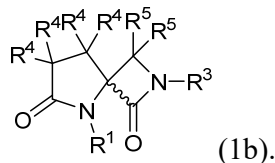


wherein Y is O or S.

5. The compound of claim 4, wherein Y is O.
6. The compound of claim 4, wherein R<sup>2</sup> for each occurrence is hydrogen.
7. The compound of claim 1, wherein m is 0 and n is 2.

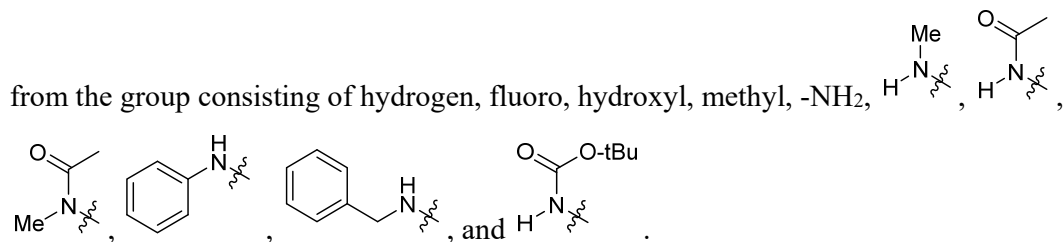
8. The compound of claim 7, wherein two R<sup>6</sup> moieties together with the carbon to which they are attached form a carbonyl moiety.

9. The compound of claim 7 or 8, represented by Formula 1b:



10. The compound of any one of claims 1-9, wherein R<sup>4</sup> is independently selected for each occurrence from the group consisting of hydrogen, halogen, hydroxyl, -C<sub>1</sub>-C<sub>4</sub>alkyl, -NR<sup>a</sup>R<sup>b</sup>, -N(R<sup>a</sup>)-phenyl, -N(R<sup>a</sup>)-C<sub>1</sub>-C<sub>6</sub>alkylene-phenyl, -N(R<sup>a</sup>)-C(O)-C<sub>1</sub>-C<sub>6</sub>alkyl, and -N(R<sup>a</sup>)-C(O)-O-C<sub>1</sub>-C<sub>6</sub>alkyl; wherein R<sup>a</sup> and R<sup>b</sup> are each independently for each occurrence selected from the group consisting of hydrogen and -C<sub>1</sub>-C<sub>3</sub>alkyl.

11. The compound of claim 10, wherein R<sup>4</sup> is independently selected for each occurrence

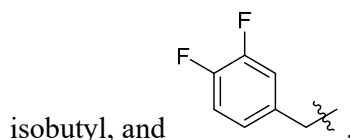


12. The compound of any one of claims 1-11, wherein R<sup>5</sup> is independently selected for each occurrence from the group consisting of hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, and phenyl.

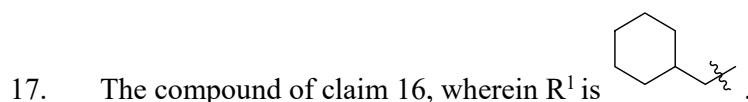
13. The compound of any one of claims 1-12, wherein R<sup>1</sup> is hydrogen.

14. The compound of any one of claims 1-12, wherein R<sup>1</sup> is -C<sub>1</sub>-C<sub>6</sub>alkyl optionally substituted by phenyl, wherein phenyl is optionally substituted by one, two or three substituents each independently selected from -C<sub>1</sub>-C<sub>3</sub>alkoxy and fluoro.

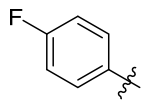
15. The compound of claim 14, wherein R<sup>1</sup> is selected from the group consisting of methyl,

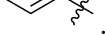


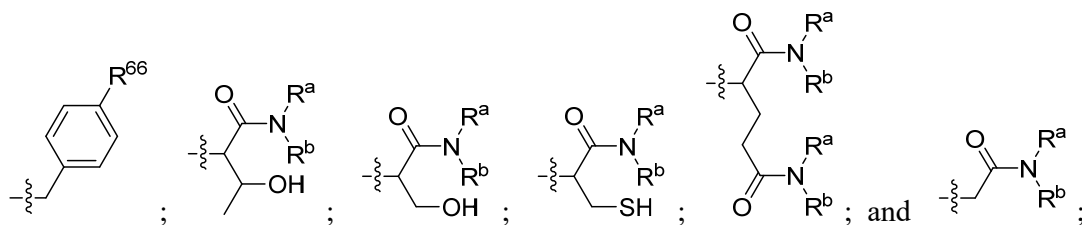
16. The compound of any one of claims 1-12, wherein R<sup>1</sup> is -C<sub>1</sub>-C<sub>6</sub>alkyl-C<sub>1</sub>-C<sub>6</sub>cycloalkyl.



18. The compound of any one of claims 1-12, wherein R<sup>1</sup> is phenyl, wherein phenyl is optionally substituted by one, two or three substituents each independently selected from -C<sub>1</sub>-C<sub>3</sub>alkoxy and fluoro.



19. The compound of claim 18, wherein R<sup>1</sup> is .
20. The compound of any one of claims 1-12, wherein R<sup>1</sup> is -C(O)-O-C<sub>1</sub>-C<sub>6</sub>alkyl, wherein C<sub>1</sub>-C<sub>6</sub>alkyl is optionally substituted by one, two or three substituents each independently selected from -C(O)NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, hydroxyl, -SH, phenyl, -O-CH<sub>2</sub>-phenyl, and halogen; and wherein each phenyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from -C(O)NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -C<sub>1</sub>-C<sub>3</sub>alkoxy, hydroxyl, and halogen.
21. The compound of claim 20, wherein R<sup>1</sup> is -C(O)-O-CH<sub>2</sub>-phenyl.
22. The compound of any one of claims 1-21, wherein R<sup>3</sup> is hydrogen.
23. The compound of any one of claims 1-21, wherein R<sup>3</sup> is -C(O)-O-C<sub>1</sub>-C<sub>6</sub>alkyl.
24. The compound of claim 23, wherein R<sup>3</sup> is -C(O)-O-*tert*-butyl.
25. The compound of any one of claims 1-21, wherein R<sup>3</sup> is -C<sub>1</sub>-C<sub>6</sub>alkyl, wherein C<sub>1</sub>-C<sub>6</sub>alkyl is optionally substituted by one, two or three substituents each independently selected from -C(O)NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, hydroxyl, -SH, phenyl, -O-CH<sub>2</sub>-phenyl, and halogen; and wherein phenyl, independently for each occurrence, is optionally substituted by one, two or three substituents each independently selected from -C(O)NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -C<sub>1</sub>-C<sub>3</sub>alkoxy, hydroxyl, and halogen.
26. The compound of claim 25, wherein R<sup>3</sup> is selected from the group consisting of:



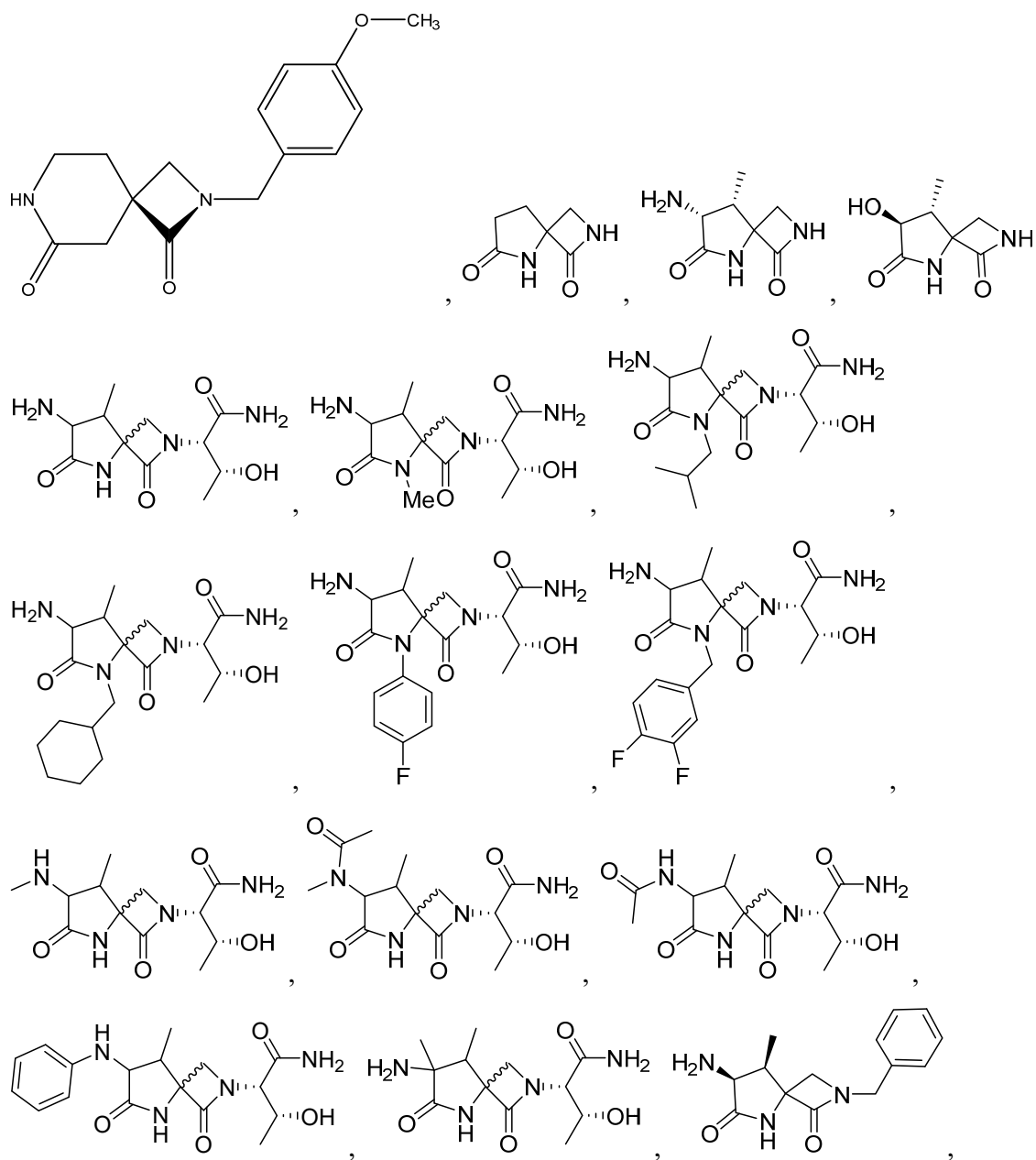
wherein:

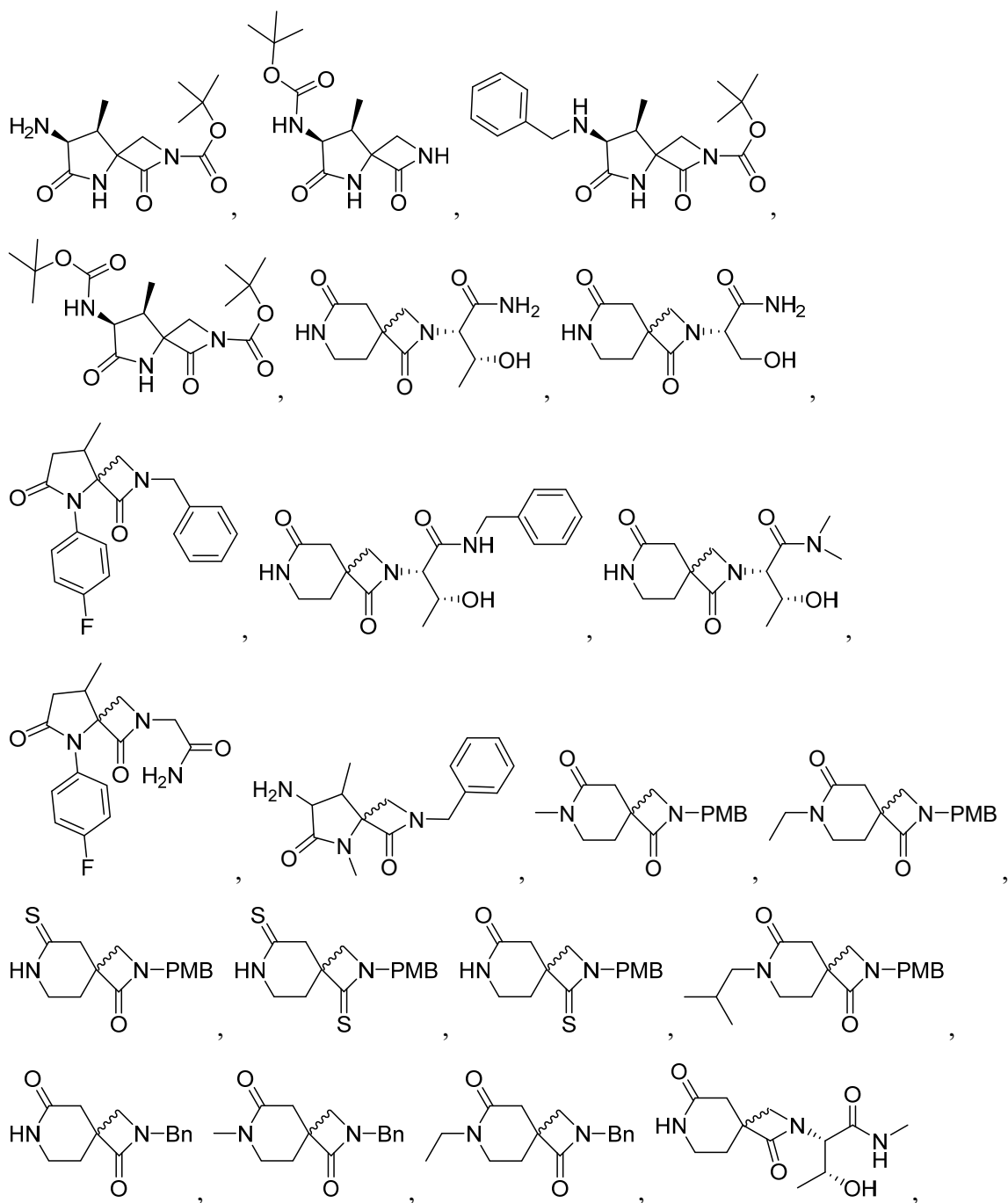
$R^{66}$  is selected from the group consisting of hydrogen and  $-C_1-C_3$ alkoxy; and  $R^a$  and  $R^b$  are each independently selected for each occurrence from the group consisting of hydrogen and  $-C_1-C_6$ alkyl.

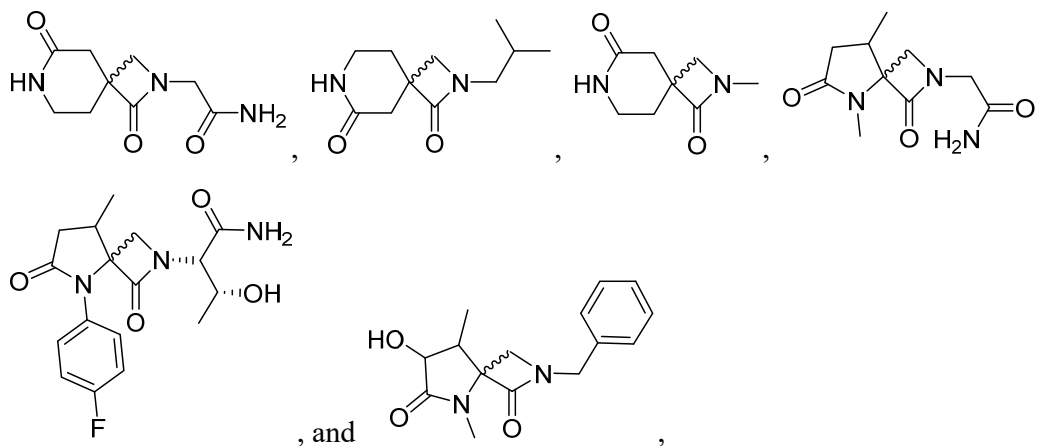
27. The compound of claim 26, wherein  $R^{66}$  is hydrogen or methoxy.

28. The compound of claim 26, wherein  $R^a$  and  $R^b$  are hydrogen.

29. A compound selected from the group consisting of

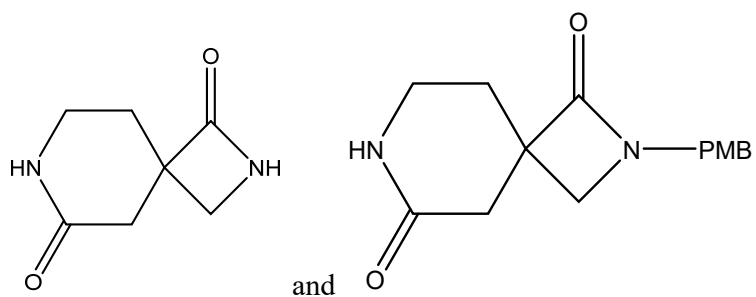






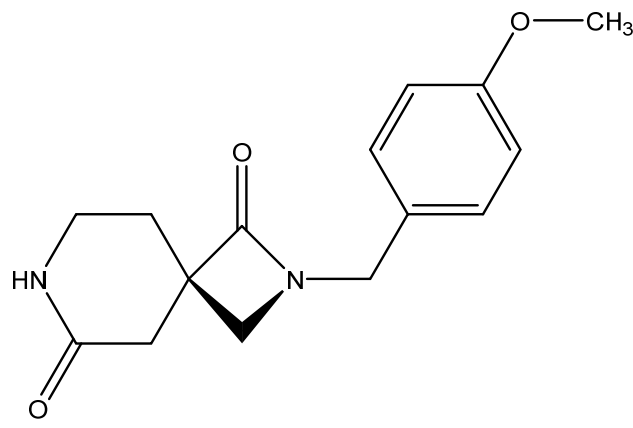
or a pharmaceutically acceptable salts and/or a stereoisomer and/or an N-oxide thereof.

30. A compound selected from:



or a pharmaceutically acceptable salt, a stereoisomer, and/or an N-oxide thereof.

31. A compound having the formula:



or a pharmaceutically acceptable salt thereof.

32. The compound of claim 31, wherein the compound is in a crystalline Form A and said crystalline Form A is characterized by unit cell parameters approximately equal to the following:

cell dimensions

$$a = 6.348(3) \text{ \AA}, \quad \alpha = 90^\circ$$

$$b = 9.402(4) \text{ \AA}, \quad \beta = 90^\circ$$

$$c = 47.10(2) \text{ \AA}, \quad \gamma = 90^\circ;$$

space group =  $P2_12_12_1$ ;

Volume =  $2811(2) \text{ \AA}^3$ ;

crystal system = orthorhombic; and

molecules per unit cell = 8.

33. A pharmaceutical composition comprising the compound of any one of claims 1-32; and a pharmaceutically acceptable excipient.

34. The pharmaceutical composition of claim 33, suitable for oral administration, parenteral administration, topical administration, intravaginal administration, intrarectal administration, sublingual administration, ocular administration, transdermal administration, or nasal administration.

35. Use of a compound of any one of claims 1-32, or a pharmaceutical composition of claim 33 or 34, in the manufacture of a medicament for treating depression, Alzheimer's disease, a migraine, neuropathic pain, attention deficit disorder, schizophrenia, or anxiety, in a patient in need thereof.

36. Use of a compound of any one of claims 1-32, or a pharmaceutical composition of claim 33 or 34, in the manufacture of a medicament for treating dementia in a patient in need thereof.

37. Use of a compound of any one of claims 1-32, or a pharmaceutical composition of claim 33 or 34, in the manufacture of a medicament for treating a memory disorder associated with aging, schizophrenia, special learning disorders, seizures, post-stroke convulsions, brain ischemia, hypoglycemia, cardiac arrest, epilepsy, Lewy body dementia, migraine, AIDS

dementia, Huntington's chorea, Parkinson's disease, early stage Alzheimer's disease, or Alzheimer's disease in a patient in need thereof.

38. Use of a compound of any one of claims 1-32, or a pharmaceutical composition of claim 33 or 34, in the manufacture of a medicament for treating traumatic brain injury in a patient in need thereof.

39. Use of a compound of any one of claims 1-32, or a pharmaceutical composition of claim 33 or 34, in the manufacture of a medicament for treating a neurodevelopmental disorder related to synaptic dysfunction in a patient in need thereof.

40. A compound of any one of claims 1-32, or a pharmaceutical composition of claim 33 or 34, for use in treating depression, Alzheimer's disease, migraine, neuropathic pain, attention deficit disorder, schizophrenia, anxiety, dementia, memory disorder associated with aging, schizophrenia, special learning disorders, seizures, post-stroke convulsions, brain ischemia, hypoglycemia, cardiac arrest, epilepsy, Lewy body dementia, migraine, AIDS dementia, Huntington's chorea, Parkinson's disease, early stage Alzheimer's disease, Alzheimer's disease, a traumatic brain injury, or a neurodevelopmental disorder related to synaptic dysfunction.