such as Valium®) produce their therapeutically useful effects by interacting with specific regulatory sites on the GRC. Accumulated evidence has now indicated that in addition to the benzodiazepine and barbiturate binding site, the GRC contains a distinct site for neuroactive steroids. See, e.g., Lan, N. C. et al., Neurochem. Res. (1991) 16:347–356.

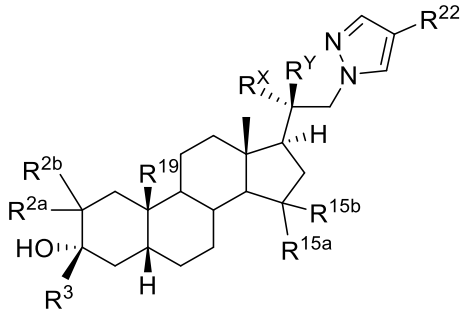
[0005] Neuroactive steroids occur endogenously. The most potent endogenous neuroactive steroids are 3α–hydroxy-5-reduced pregnan-20-one and 3α-21-dihydroxy-5-reduced pregnan-20-one, metabolites of hormonal steroids progesterone and deoxycorticosterone, respectively. The ability of these steroid metabolites to alter brain excitability was recognized in 1986 (Majewska, M. D. *et al.*, *Science* 232:1004-1007 (1986); Harrison, N. L. *et al.*, *J Pharmacol. Exp. Ther.* 241:346-353 (1987)).

[0006] New and improved compounds are needed that act as modulating agents for brain excitability, as well as agents for the prevention and treatment of CNS-related diseases. The compounds, compositions, and methods described herein are directed toward this end.

Summary

[0007] Provided herein are compounds designed, for example, to act as GABA modulators. In some examples, such compounds are envisioned to be useful as therapeutic agents for treating a CNS-related disorder.

[0007a] In a first aspect of the present disclosure, there is provided a compound of Formula (**I-e6**):



(**I-e6**),

or a pharmaceutically acceptable salt thereof;

wherein:

each of R^{2a}, R^{2b}, R^{15a}, and R^{15b} is hydrogen;

R^3 is unsubstituted $C_{1\text{-}3}$ alkyl, $–CH_2OCH_3$, or $–CH_2OCH_2CH_3$;

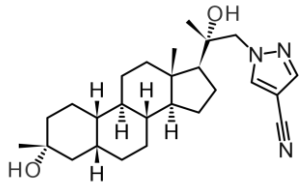
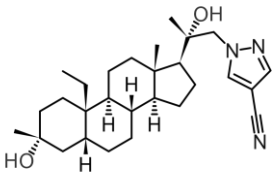
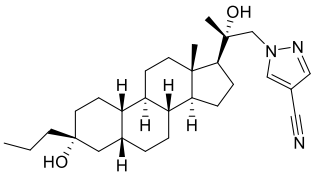
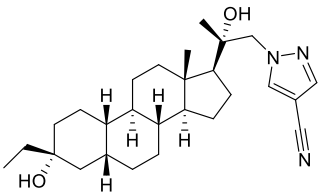
R^{19} is hydrogen, methyl, or ethyl;

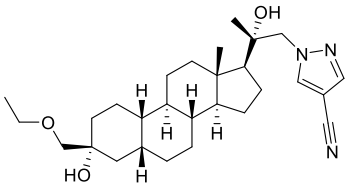
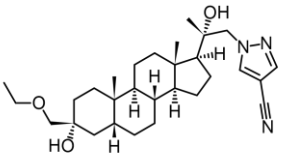
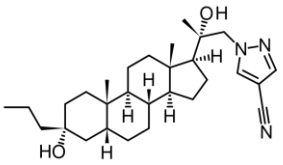
R^X is –OH;

R^Y is methyl; and

R^{22} is –CN.

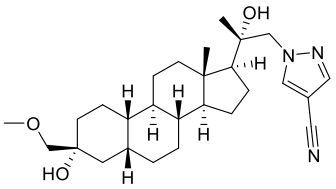
[0007b] In another aspect of the present disclosure, there is provided a compound selected from

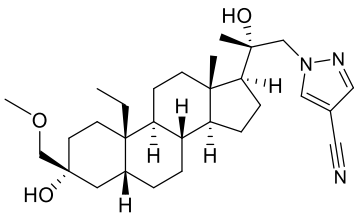
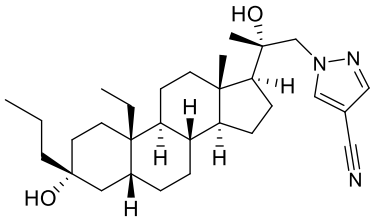
Compound No.	Structure
2	
3	
7	
11	

Compound No.	Structure
15	
24	
26	

or a pharmaceutically acceptable salt thereof.

[0007c] In yet another aspect of the present disclosure, there is provided a compound selected from

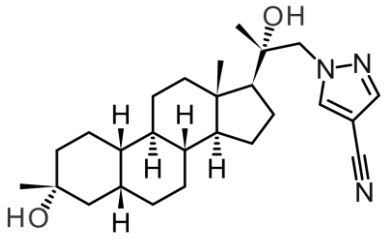
Compound No.	Structure
29	

Compound No.	Structure
42	
44	

or a pharmaceutically acceptable salt thereof.

[0007d] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt as disclosed herein and a pharmaceutically acceptable excipient.

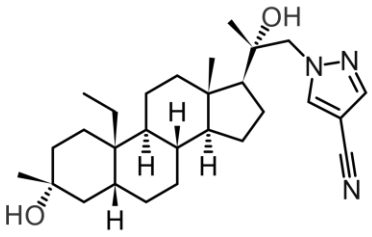
[0007e] In another aspect of the present disclosure, there is provided a compound of the formula



,

or a pharmaceutically acceptable salt thereof.

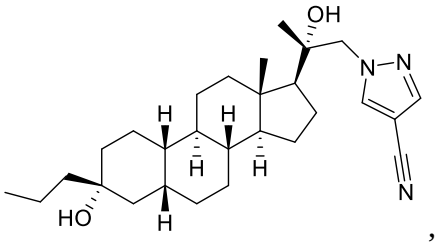
[0007f] In yet another aspect of the present disclosure, there is provided a compound of the formula



,

or a pharmaceutically acceptable salt thereof.

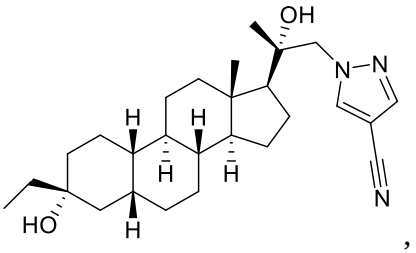
[0007g] In a further aspect of the present disclosure, there is provided a compound of the formula



,

or a pharmaceutically acceptable salt thereof.

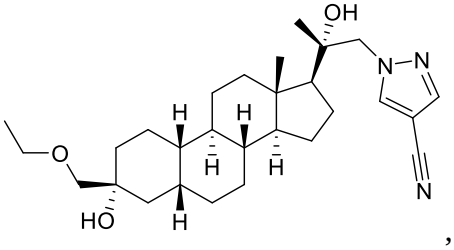
[0007h] In another aspect of the present disclosure, there is provided a compound of the formula



,

or a pharmaceutically acceptable salt thereof.

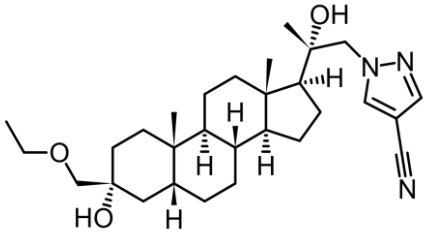
[0007i] In yet another aspect of the present disclosure, there is provided a compound of the formula



,

or a pharmaceutically acceptable salt thereof.

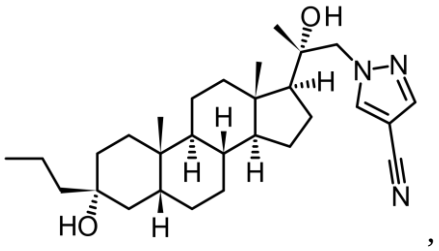
[0007j] In a further aspect of the present disclosure, there is provided a compound of the formula



,

or a pharmaceutically acceptable salt thereof.

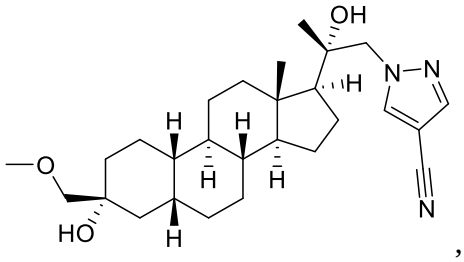
[0007k] In another aspect of the present disclosure, there is provided a compound of the formula



,

or a pharmaceutically acceptable salt thereof.

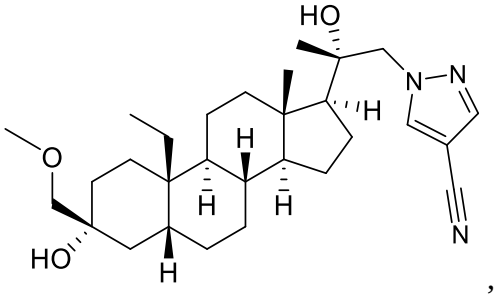
[0007l] In yet another aspect of the present disclosure, there is provided a compound of the formula



,

or a pharmaceutically acceptable salt thereof.

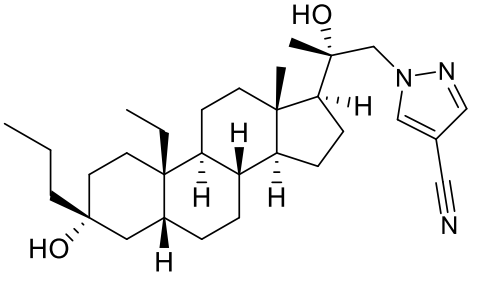
[0007m] In a further aspect of the present disclosure, there is provided a compound of the formula



,

or a pharmaceutically acceptable salt thereof.

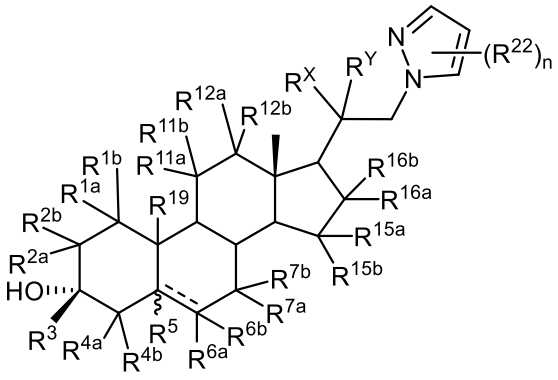
[0007n] In another aspect of the present disclosure, there is provided a compound of the formula



,

or a pharmaceutically acceptable salt thereof.

[0008] In an example, provided herein is a compound of Formula (**I**):



(**I**)

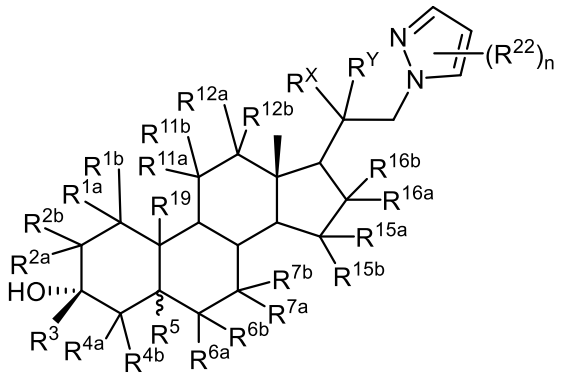
or a pharmaceutically acceptable salt thereof;

wherein:

$\overline{\overline{\text{------}}}$ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -CN, -OH, -OR^{Q1}, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

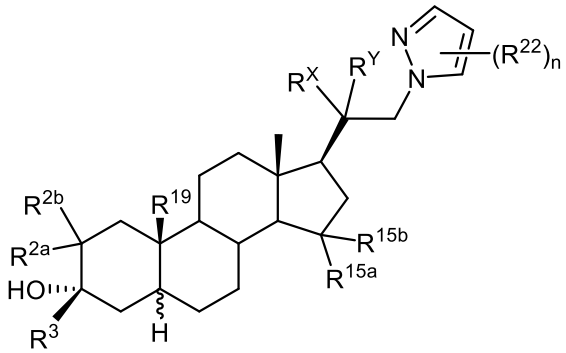
[0009] In some examples, the compound is a compound of Formula **I-a**:



(**I-a**)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined above.

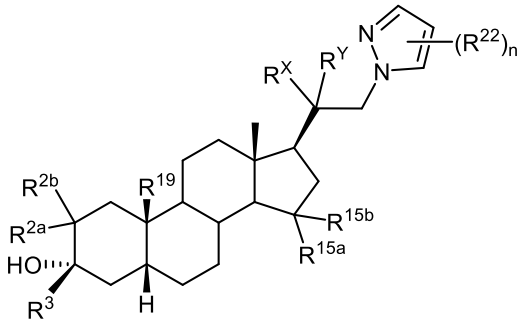
[0010] In some examples, the compound is a compound of Formula **I-b1**:



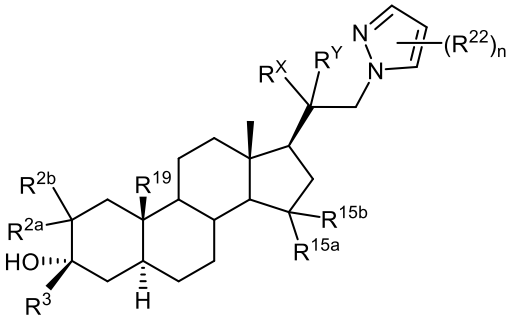
(**I-b1**)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined above.

[0011] In some examples, the compound is a compound of Formula **I-c3** or Formula **I-c4**:



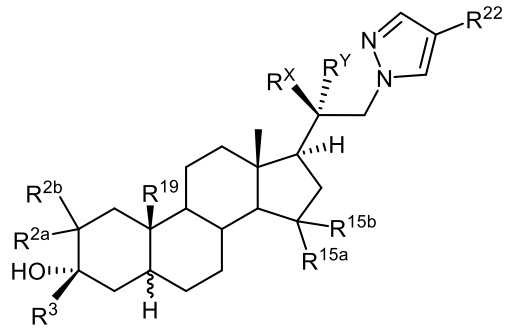
(**I-c3**),



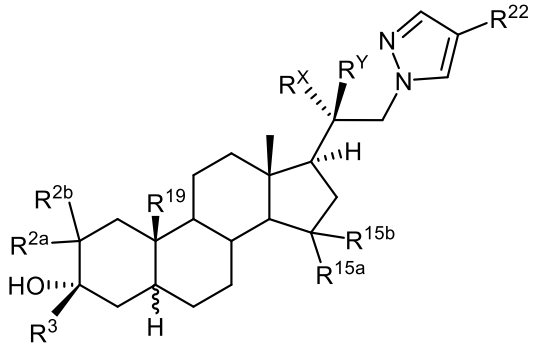
(**I-c4**),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined above.

[0012] In some examples, the compound is a compound of Formula **I-d3** or Formula **I-d4**:



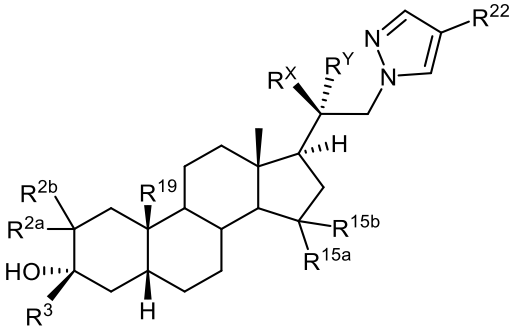
(**I-d3**),



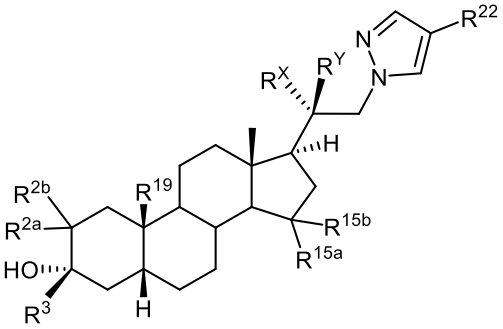
(**I-d4**),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined above.

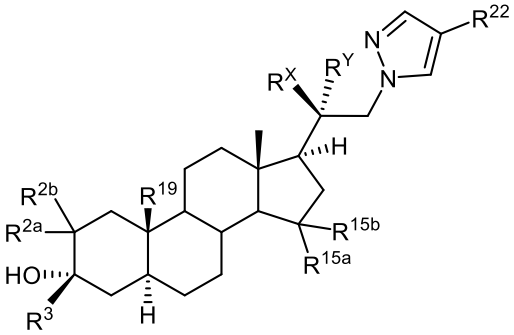
[0013] In some examples, the compound is a compound of Formula **I-e5**, Formula **I-e6**, Formula **I-e7**, or Formula **I-e8**:



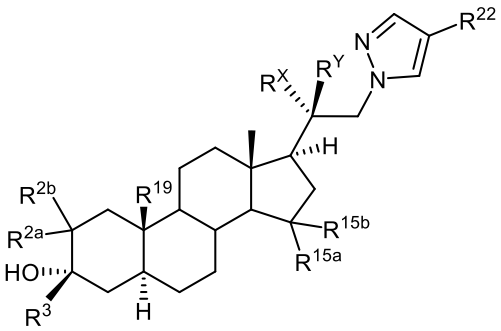
(**I-e5**),



(**I-e6**),



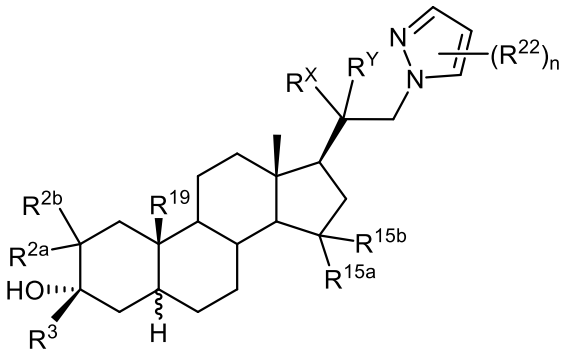
(**I-e7**), or



(**I-e8**),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined above.

[0014] In a certain example, the compound is a compound of Formula **I-Ib1**:



(**I-Ib1**)

or a pharmaceutically acceptable salt thereof,

wherein R^{22} is CN;

n is 1;

R^{19} is selected from the group consisting of hydrogen, ethyl, and methyl;

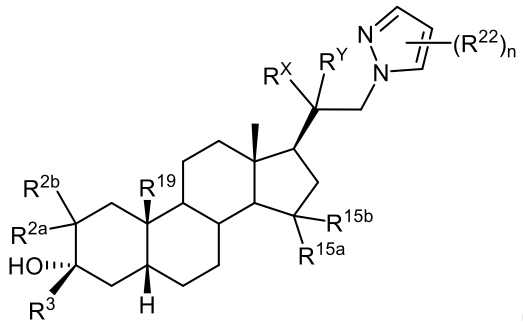
R^{15a} and R^{15b} is independently selected from the group consisting of hydrogen, methyl, and cyclopropyl;

R^{2a} and R^{2b} is each independently selected from the group consisting of hydrogen, methyl, ethyl, methoxymethyl, and methoxy;

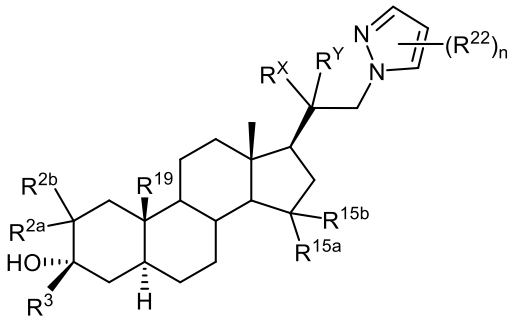
R^3 is selected from the group consisting of unsubstituted $C_{1\text{-}3}$ alkyl, $-CH_2OCH_3$, and $-CH_2OCH_2CH_3$;

and R^X and R^Y are as defined herein.

[0015] In one example, the compound is a compound of Formula **I-Ic1** or Formula **I-Ic2**:



(**I-Ic1**),



(**I-Ic2**),

or a pharmaceutically acceptable salt thereof,

wherein R^{22} is CN;

n is 1;

R^{19} is selected from the group consisting of hydrogen, ethyl, and methyl;

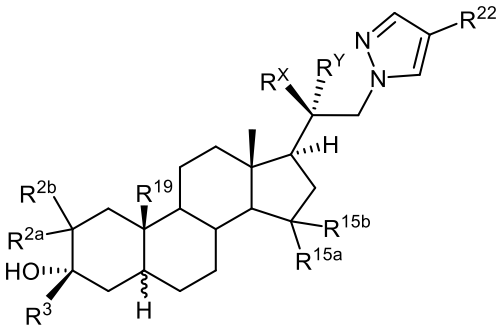
R^{15a} and R^{15b} is independently selected from the group consisting of hydrogen, methyl, and cyclopropyl;

R^{2a} and R^{2b} is each independently selected from the group consisting of hydrogen, methyl, ethyl, methoxymethyl, and methoxy;

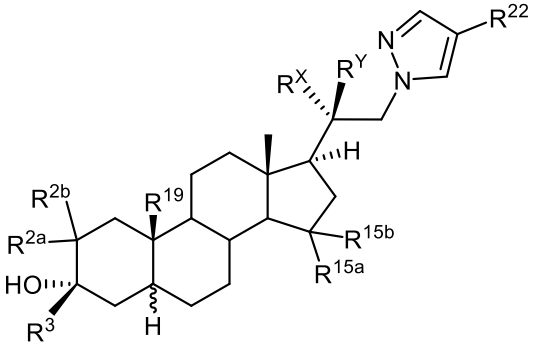
R^3 is selected from the group consisting of unsubstituted C_{1-3} alkyl, $-CH_2OCH_3$, and $-CH_2OCH_2CH_3$; and

R^X and R^Y are as defined herein.

[0016] In one example, the compound is a compound of Formula **I-Id1** or Formula **I-Id2**:



(**I-Id1**),



(**I-Id2**),

or a pharmaceutically acceptable salt thereof,

wherein R^{22} is CN;

R^{19} is selected from the group consisting of hydrogen, ethyl, and methyl;

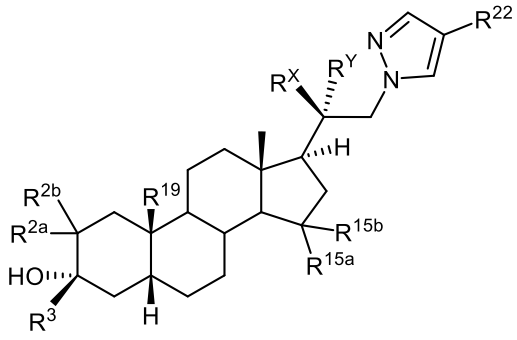
R^{15a} and R^{15b} is independently selected from the group consisting of hydrogen, methyl, and cyclopropyl;

R^{2a} and R^{2b} is each independently selected from the group consisting of hydrogen, methyl, ethyl, methoxymethyl, and methoxy;

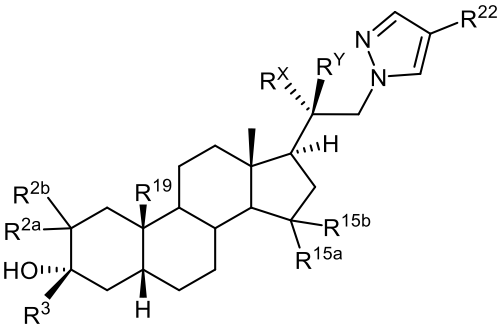
R^3 is selected from the group consisting of unsubstituted C_{1-3} alkyl, $-CH_2OCH_3$, and $-CH_2OCH_2CH_3$; and

R^X and R^Y are as defined herein.

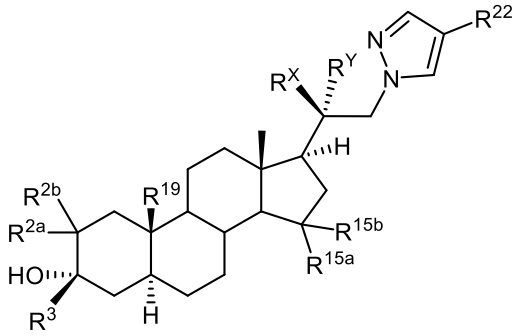
[0017] In one example, the compound is a compound of Formula **I-Ie1**, Formula **I-Ie2**, Formula **I-Ie3**, or Formula **I-Ie4**:



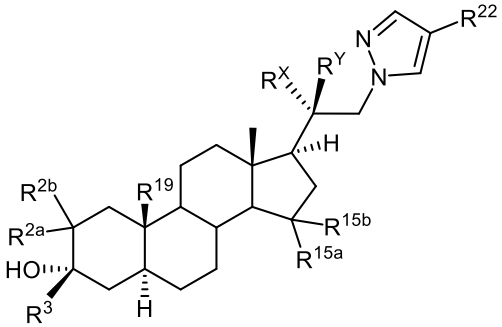
(**I-Ie1**),



(**I-Ie2**),



(**I-Ie3**), or



(**I-Ie4**)

or a pharmaceutically acceptable salt thereof,

wherein R^{22} is CN;

R^{19} is selected from the group consisting of hydrogen, ethyl, and methyl;

R^{15a} and R^{15b} is independently selected from the group consisting of hydrogen, methyl, and cyclopropyl;

R^{2a} and R^{2b} is each independently selected from the group consisting of hydrogen, methyl, ethyl, methoxymethyl, and methoxy;

R^3 is selected from the group consisting of unsubstituted $C_{1\text{-}3}$ alkyl, $-CH_2OCH_3$, and $-CH_2OCH_2CH_3$; and

R^X and R^Y are as defined herein.

[0018] In one example, provided herein is a pharmaceutically acceptable salt of a compound described herein (*e.g.*, a compound of Formula (I)).

[0019] In one example, provided herein is a pharmaceutical composition comprising a compound described herein (*e.g.*, a compound of Formula (I)) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In certain examples, the compound of the present disclosure is provided in an effective amount in the pharmaceutical composition. In certain examples, the compound of the present disclosure is provided in a therapeutically effective amount.

[0020] In some examples, a method of treating a CNS-related disorder in a subject in need thereof, comprises administering to the subject an effective amount of a compound described herein (*e.g.*, a compound of Formula (I)) or a pharmaceutically acceptable salt thereof. In some examples, the CNS–related disorder is a sleep disorder, a mood disorder, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, tinnitus, or status epilepticus. In some examples, the CNS-related disorder is depression. In some examples, the CNS-related disorder is postpartum depression. In some examples, the CNS-related disorder is major depressive disorder. In some examples, the major depressive disorder is moderate major depressive disorder. In some examples, the major depressive disorder is severe major depressive disorder.

[0021] In some examples, the compound is selected from the group consisting of the compounds identified in **Table 1** herein.

[0022] Compounds of the present disclosure as described herein, act, in certain examples, as GABA modulators, *e.g.*, effecting the $GABA_A$ receptor in either a positive or negative manner. As modulators of the excitability of the central nervous system (CNS), as mediated by their ability to modulate $GABA_A$ receptor, such compounds are expected to have CNS-activity.

[0023] Thus, in another example, provided are methods of treating a CNS–related disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present disclosure. In certain examples, CNS–related disorder is a sleep disorder, a mood disorder, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, tinnitus, or status epilepticus. In certain examples, the CNS-related disorder is depression. In certain examples, the CNS-related disorder is postpartum depression. In certain examples, the CNS-related disorder is major depressive disorder. In certain examples, the major depressive disorder is moderate major depressive disorder. In certain examples, the major depressive disorder is severe major depressive disorder. In certain examples, the compound is administered orally, subcutaneously, intravenously, or intramuscularly. In certain examples, the compound is administered orally. In certain examples, the compound is administered chronically. In certain

examples, the compound is administered continuously, *e.g.*, by continuous intravenous infusion.

Detailed Description of Certain Embodiments of the Invention

[0024] As generally described herein, the present invention provides compounds designed, for example, to act as GABAA receptor modulators. In certain embodiments, such compounds are envisioned to be useful as therapeutic agents for treating a CNS-related disorder (e.g., a disorder as described herein, for example depression, such as post-partum depression or major depressive disorder).

Definitions

Chemical definitions

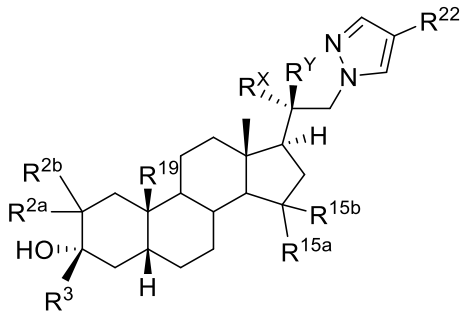
[0025] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics,* 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0026] Isomers, *e.g.*, stereoisomers, can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds

CLAIMS

What is claimed:

1. A compound of Formula (**I-e6**):



(**I-e6**),

or a pharmaceutically acceptable salt thereof;

wherein:

each of R^{2a}, R^{2b}, R^{15a}, and R^{15b} is hydrogen;

R^3 is unsubstituted $C_{1\text{-}3}$ alkyl, $–CH_2OCH_3$, or $–CH_2OCH_2CH_3$;

R^{19} is hydrogen, methyl, or ethyl;

R^X is –OH;

R^Y is methyl; and

R^{22} is –CN.

2. The compound or pharmaceutically acceptable salt of claim 1, wherein R^3 is methyl, ethyl, or propyl.

3. The compound or pharmaceutically acceptable salt of claim 2, wherein R^3 is methyl.

4. The compound or pharmaceutically acceptable salt of claim 2, wherein R^3 is ethyl.

5. The compound or pharmaceutically acceptable salt of claim 2, wherein R^3 is propyl.

6. The compound or pharmaceutically acceptable salt of claim 1, wherein R^3 is $–CH_2OCH_3$.

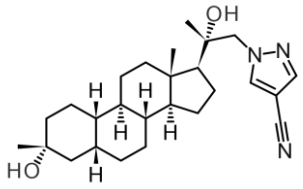
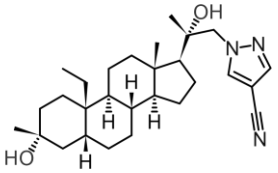
7. The compound or pharmaceutically acceptable salt of claim 1, wherein R^3 is $–CH_2OCH_2CH_3$.

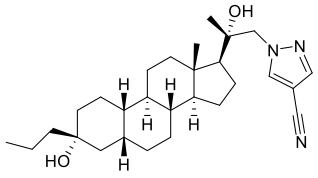
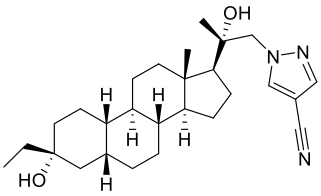
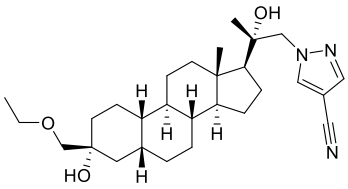
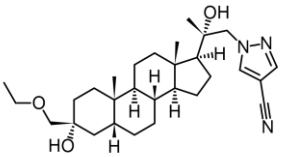
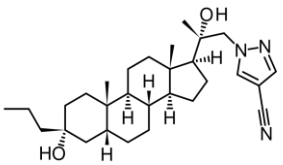
8. The compound or pharmaceutically acceptable salt of any one of claims 1-7, wherein R^{19} is hydrogen.

9. The compound or pharmaceutically acceptable salt of any one of claims 1-7, wherein R^{19} is methyl.

10. The compound or pharmaceutically acceptable salt of any one of claims 1-7, wherein R^{19} is ethyl.

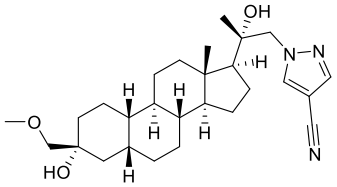
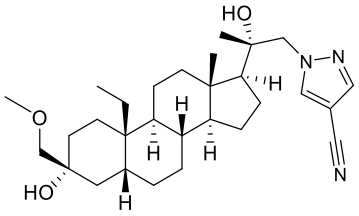
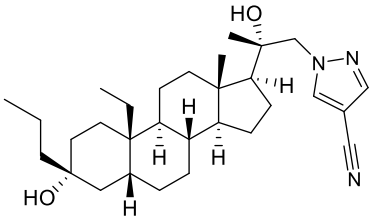
11. A compound selected from

Compound No.	**Structure**
2	
3	

Compound No.	Structure
7	
11	
15	
24	
26	

or a pharmaceutically acceptable salt thereof.

12. A compound selected from

Compound No.	Structure
29	
42	
44	

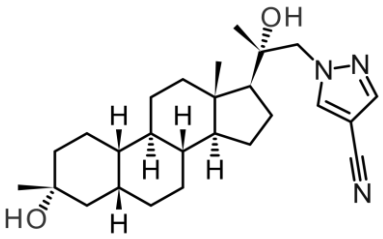
or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt of claim 1 and a pharmaceutically acceptable excipient.

14. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt of claim 11 and a pharmaceutically acceptable excipient.

15. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt of claim 12 and a pharmaceutically acceptable excipient.

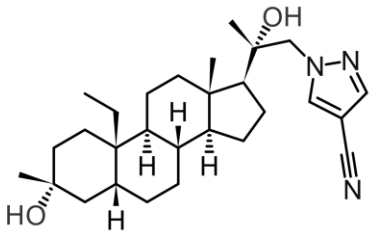
16. A compound of the formula



,

or a pharmaceutically acceptable salt thereof.

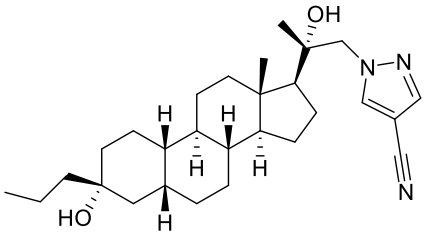
17. A compound of the formula



,

or a pharmaceutically acceptable salt thereof.

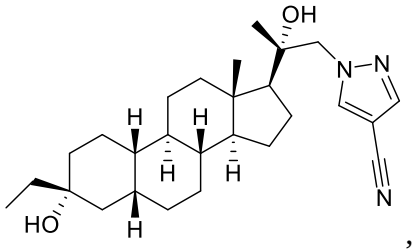
18. A compound of the formula



,

or a pharmaceutically acceptable salt thereof.

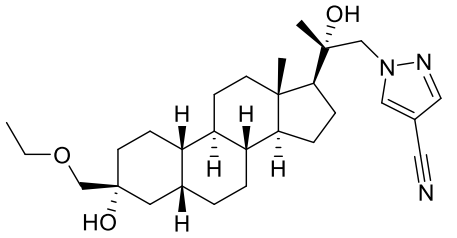
19. A compound of the formula



,

or a pharmaceutically acceptable salt thereof.

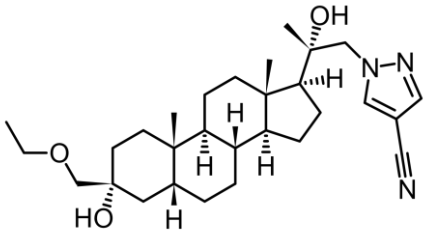
20. A compound of the formula



,

or a pharmaceutically acceptable salt thereof.

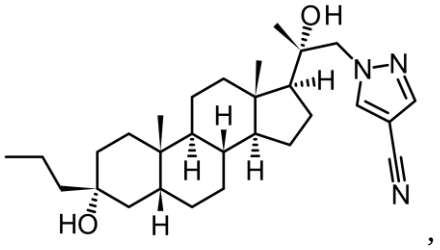
21. A compound of the formula



,

or a pharmaceutically acceptable salt thereof.

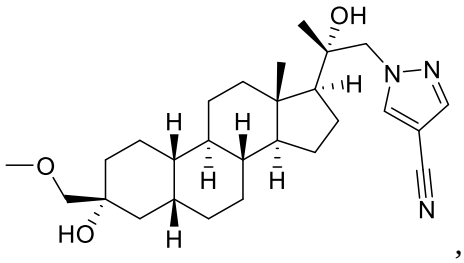
22. A compound of the formula



,

or a pharmaceutically acceptable salt thereof.

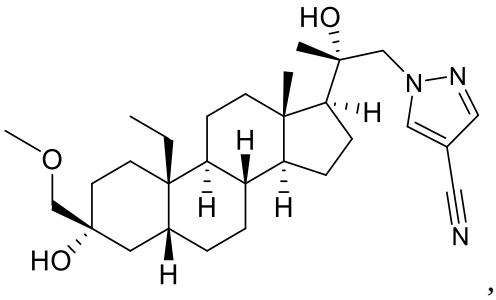
23. A compound of the formula



,

or a pharmaceutically acceptable salt thereof.

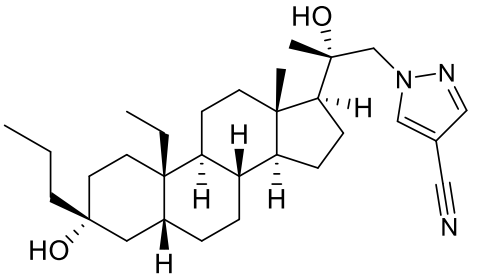
24. A compound of the formula



,

or a pharmaceutically acceptable salt thereof.

25. A compound of the formula



,

or a pharmaceutically acceptable salt thereof.