A syndrome also related to low progesterone levels is postnatal depression (PND). Immediately after birth, progesterone levels decrease dramatically leading to the onset of PND. The symptoms of PND range from mild depression to psychosis requiring hospitalization. PND is also associated with severe anxiety and irritability. PND-associated depression is not amenable to treatment by classic antidepressants, and women experiencing PND show an increased incidence of PMS (Dalton, K., *Premenstrual Syndrome and Progesterone Therapy*, 2nd edition, Chicago Yearbook, Chicago (1984)).

Collectively, these observations imply a crucial role for progesterone and deoxycorticosterone and more specifically their metabolites in the homeostatic regulation of brain excitability, which is manifested as an increase in seizure activity or symptoms associated with catamenial epilepsy, PMS, and PND. The correlation between reduced levels of progesterone and the symptoms associated with PMS, PND, and catamenial epilepsy (Backstrom, T. *et al., J Psychosom.Obstet. Gynaecol.* 2:8-20 (1983)); Dalton, K., Premenstrual Syndrome and Progesterone Therapy, 2nd edition, Chicago Yearbook, Chicago (1984)) has prompted the use of progesterone in their treatment (Mattson *et al.*, "Medroxyprogesterone therapy of catamenial epilepsy," in *Advances in Epileptology: XVth Epilepsy International Symposium*, Raven Press, New York (1984), pp. 279-282, and Dalton, K., *Premenstrual Syndrome and Progesterone Therapy*, 2nd edition, Chicago Yearbook, Chicago (1984)). However, progesterone is not consistently effective in the treatment of the aforementioned syndromes. For example, no dose-response relationship exists for progesterone in the treatment of PMS (Maddocks *et al., Obstet. Gynecol.* 154:573-581 (1986); Dennerstein *et al., Brit. Med J* 290:16-17 (1986)).

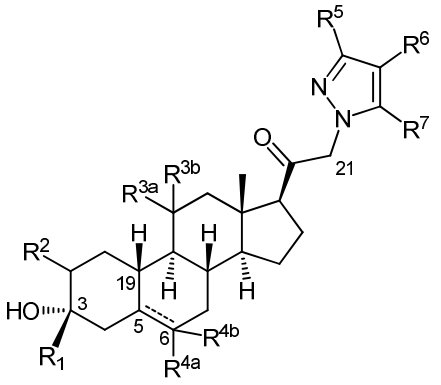
New and improved neuroactive steroids are needed that act as modulating agents for brain excitability, as well as agents for the prevention and treatment of CNS-related diseases. The compounds, compositions, and methods described herein are directed toward this end.

Summary

The present disclosure is based, in part, on the desire to provide novel 19-nor (i.e., C19 desmethyl) compounds, e.g., related to progesterone, deoxycorticosterone, and their metabolites, with good potency, pharmacokinetic (PK) properties, oral bioavailability, formulatability, stability, safety, clearance and/or metabolism. One key feature of the compounds as described herein is

disubstitution at the C3 position (e.g., with one substituent being a 3α hydroxy moiety. The inventors envision disubstitution at C-3 will eliminate the potential for oxidation of the hydroxy moiety to the ketone, prevent further metabolism, and reduce the potential for secondary elimination pathways, such as glucuronidation. The inventors further envision the overall effect of C3 disubstitution should be of improving the overall PK parameters and reducing potential toxicities and side effects, which may allow, in certain examples, administration orally and/or chronically. Another key feature of the compounds as described herein is the presence of a hydrogen at the C19 position ("19-nor") rather than a methyl group. The inventors envision 19-nor compounds, as compared to their C19-methyl counterparts, will have improved physical properties, such as improved solubility. The inventors envision futher enhancement of solubility, for example, when the AB ring system is in the *cis* configuration.

Thus, in one example, provided herein are 19-nor C3,3-disubstituted C21-pyrazolyl steroids of Formula (**I**):



(**I**)

and pharmaceutically acceptable salts thereof;

wherein:

⁼⁼⁼⁼ represents a single or double bond;

R^1 is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl;

R^2 is hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6}

carbocyclyl, or $–OR^{A2}$, wherein R^{A2} is hydrogen or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl;

R^{3a} is hydrogen or $–OR^{A3}$, wherein R^{A3} is hydrogen or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl, and R^{3b} is hydrogen; or R^{3a} and R^{3b} are joined to form an oxo (=O) group;

each instance of R^{4a} and R^{4b} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or halogen, provided if the ----- between C5 and C6 is a single bond, then the hydrogen at C5 and R^{4a} are each independently provided in the *alpha* or *beta* configuration, and R^{4b} is absent;

each instance of R^5, R^6, and R^7 is, independently, hydrogen, halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(O)R^{GA}$, *e.g.*, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, or substituted or unsubstituted 3- to 6- membered heterocylyl; and

each instance of R^{GA} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocylyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocylyl or heteroaryl ring.

Steroids of Formula (**I**), sub-genera thereof, and pharmaceutically acceptable salts thereof are collectively referred to herein as “compounds of the present disclosure.”

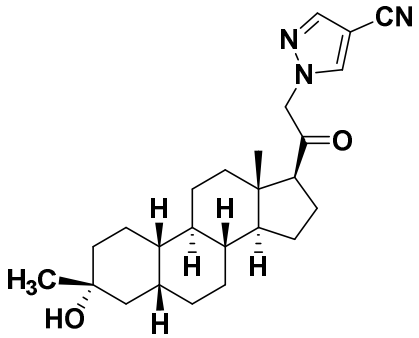
In another example, provided is a pharmaceutical composition comprising a compound of the present disclosure and a pharmaceutically acceptable excipient. In certain examples, the compound of

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. In certain examples, the compound of the present disclosure is provided in a prophylactically effective amount.

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.

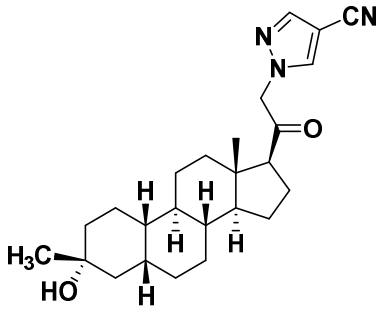
Thus, in another example, provided are methods of treating a CNS–related disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present disclosure. In certain examples, the CNS–related disorder is selected from the group consisting of a 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, and tinnitus. In certain examples, the compound is administered orally, subcutaneously, intravenously, or intramuscularly. In certain examples, the compound is administered chronically.

In one aspect, the present disclosure refers to use of a compound of the formula:



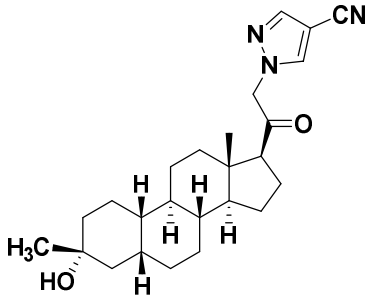
in the manufacture of a medicament for treating a mood disorder in a human subject.

In one aspect, the present disclosure refers to use of a pharmaceutically acceptable salt of a compound of the formula:



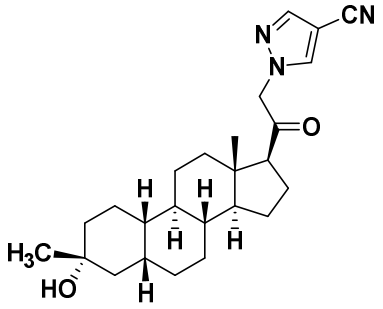
in the manufacture of a medicament for treating a mood disorder in a human subject.

In one aspect, the present disclosure refers to use of a compound of the formula:



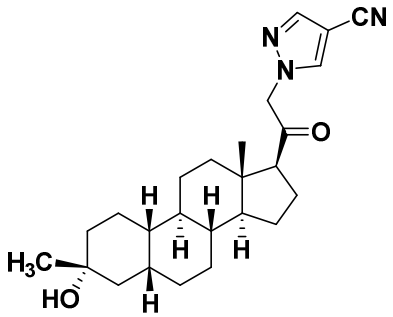
in the manufacture of a medicament for modulating a $GABA_A$ receptor in a human subject.

In one aspect, the present disclosure refers to use of a pharmaceutically acceptable salt of a compound of the formula:



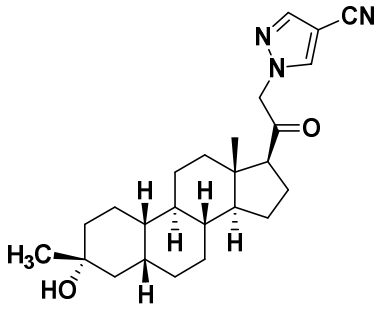
in the manufacture of a medicament for modulating a $GABA_A$ receptor in a human subject.

In one aspect, the present disclosure refers to use of a compound of the formula:



in the manufacture of a medicament for treating tremor in a human subject.

In one aspect, the present disclosure refers to use of a pharmaceutically acceptable salt of a compound of the formula:



in the manufacture of a medicament for treating tremor in a human subject.

Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing Detailed Description, Examples, and Claims.

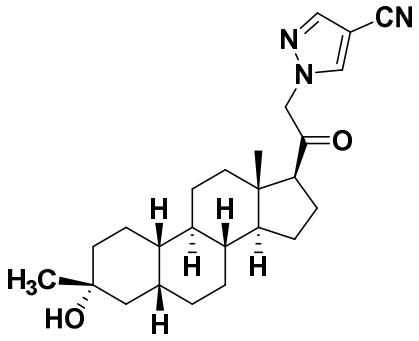
Definitions

Chemical Definitions

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,

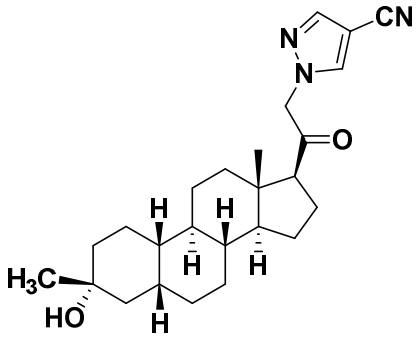
CLAIMS

1. Use of a compound of the formula:



in the manufacture of a medicament for treating a mood disorder in a human subject.

2. Use of a pharmaceutically acceptable salt of a compound of the formula:



in the manufacture of a medicament for treating a mood disorder in a human subject.

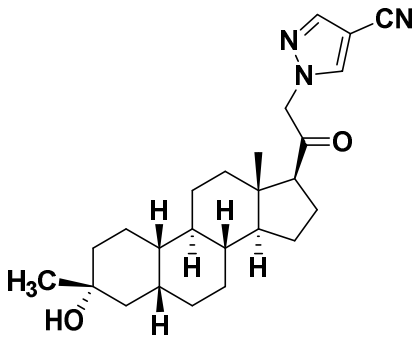
3. The use of claim 1 or claim 2, wherein the mood disorder is depression.

4. The use of any one of claims 1 to 3, wherein the medicament is formulated for oral, subcutaneous, intravenous, or intramuscular administration.

5. The use of claim 4, wherein the medicament is formulated for oral administration.

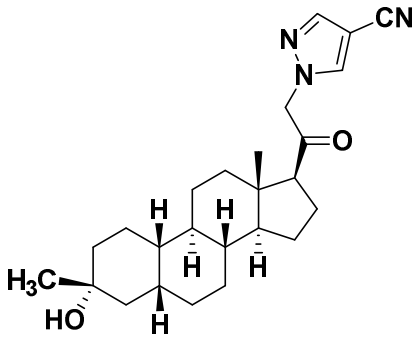
6. The use according to any one of claims 1-5, wherein the mood disorder is postnatal depression.

7. Use of a compound of the formula:



in the manufacture of a medicament for modulating a $GABA_A$ receptor in a human subject.

8. Use of a pharmaceutically acceptable salt of a compound of the formula:



in the manufacture of a medicament for modulating a $GABA_A$ receptor in a human subject.

9. The use of claim 7 or claim 8, wherein the compound affects the $GABA_A$ receptor in a positive manner.

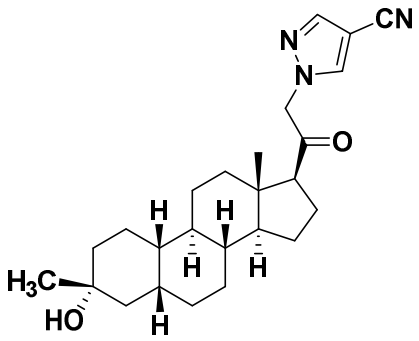
10. The use of any one of claims 7 to 9, wherein the subject has a mood disorder.

11. The use of claim 10, wherein the mood disorder is depression.

12. The use of any of claims 7 to 11, wherein the medicament is formulated for oral, subcutaneous, intravenous, or intramuscular administration.

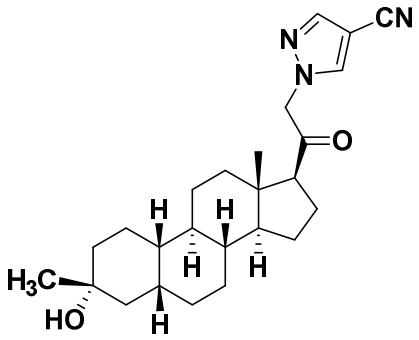
13. The use of claim 12, wherein the medicament is formulated for oral administration.

14. Use of a compound of the formula:



in the manufacture of a medicament for treating tremor in a human subject.

15. Use of a pharmaceutically acceptable salt of a compound of the formula:



in the manufacture of a medicament for treating tremor in a human subject.

16. The use of claim 14 or claim 15, wherein the medicament is formulated for oral, subcutaneous, intravenous, or intramuscular administration.

17. The use of claim 16, wherein the medicament is formulated for oral administration.

18. The use according to claim 1 or claim 2, wherein the mood disorder is generalized anxiety disorder.

19. The use of claim 18, wherein the medicament is formulated for oral, subcutaneous, intravenous, or intramuscular administration.

20. The use of claim 19, wherein the medicament is formulated for oral administration.

21. The use according to claim 1 or claim 2, wherein the mood disorder is bipolar disorder.

22. The use of claim 21, wherein the bipolar disorder is bipolar I.

23. The use of claim 21, wherein the bipolar disorder is bipolar II.

24. The use of any one of claims 21-23, wherein the medicament is formulated for oral, subcutaneous, intravenous, or intramuscular administration.

25. The use of claim 24, wherein the medicament is formulated for oral administration.