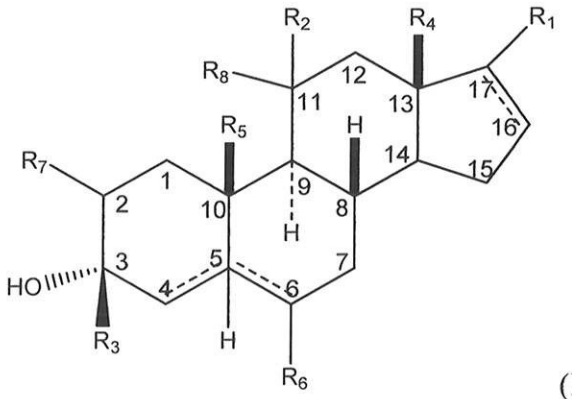
receptors and enhancement of GABAA receptors appear to play important roles in mediating the acute effects of ethanol in the nervous system, while related studies suggest that GABAergic neurosteroids may be involved in some of the pharmacological effects of ethanol and that neuroactive steroids may be useful in treating ethanol withdrawal.

[0007] In view of the foregoing, it is clear that there are a number of potentially advantageous uses for neurosteroids. As a result, there is a continuing need for the further synthesis and understanding of new neuroactive steroids, particularly those having utility as an anesthetic and/or in the treatment of a disorder relating to GABA function and activity.

Summary

[0008] Disclosed is a compound having a structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

[0009] R1 is selected from (C1-C4 alkyl)-O, spirooxirane, cyano, =O, nitro, (C1-C4 alkyl)C(O), and HO(C1-C4 alkyl)C(O), with R1 preferably being in the beta position when other than =O, and/or in one or more preferred embodiments C1-C4 alkyl being methyl, R1 therefore being is selected from methoxy, spirooxirane, cyano, =O, nitro, CH3C(O)- and OHCH2C(O)-;

[0010] R2 is =O, H, or ORa, where Ra is selected from H, optionally substituted C1-C4 alkyl, or optionally substituted aryl, with the proviso that when R2 is =O, R8 is not present;

[0011] R3 is H, optionally substituted C1-C4 alkyl, optionally substituted C2-C4 alkenyl, optionally substituted C2-C4 alkynyl, or optionally substituted aryl;

[0012] R4 is independently selected from H and unsubstituted C1-C4 alkyl;

[0013] R5 is substituted C1-C4 alkyl, optionally substituted C2-C4 alkenyl, or optionally substituted C2-C4 alkynyl (and in particular is alkoxy-substituted methyl, or even more particular is –CH2–ORb, where Rb is C1-C4 alkyl, or even still more particularly is –CH2–OCH3);

[0014] R6 is H, optionally substituted C1-C4 alkyl, or optionally substituted C1-C4 alkoxy;

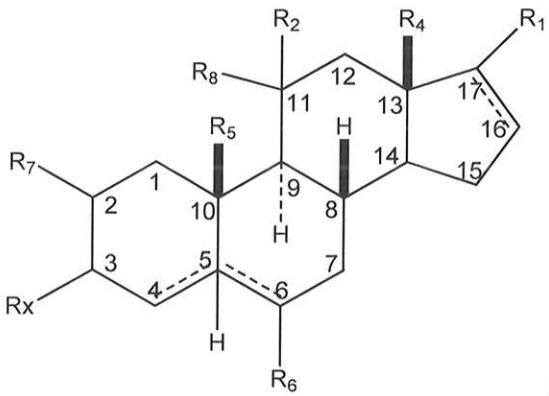
[0015] R7 is H, optionally substituted C1-C4 alkoxy, or an optionally substituted morpholinyl ring;

[0016] R8, when present, is H or optionally substituted C1-C4 alkyl;

[0017] - - - denotes an optional, additional C-C bond, resulting in either a C=C bond between C4-C5 or C5-C6, with the proviso that when present, the R5-H substituent is not present; and,

[0018] - - - denotes an optional, additional C-C bond, resulting in a C=C bond between C16-C17, with the proviso that when present, the R1 is not =O.

[0019] The present disclosure is further directed to a pharmaceutically acceptable salt of the noted compounds, or alternatively to prodrugs thereof. In one aspect, there is provided a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof;

wherein:

[0020] R_1 is selected from (C1-C4 alkyl)-O, spirooxirane, cyano, =O, nitro, (C1-C4 alkyl)C(O), and HO(C1-C4 alkyl)C(O), with R1 preferably being in the beta position when other than =O, and/or in one or more preferred embodiments C1-C4 alkyl being methyl, R1 therefore being is selected from methoxy, spirooxirane, cyano, =O, nitro, CH3C(O)- and OHCH2C(O)-;

[0030a] In one aspect, there is provided a pharmaceutically acceptable salt of any of the compound disclosed herein.

[0031] The present disclosure is still further directed to a pharmaceutical composition comprising a therapeutically effective amount of one or more of the above-noted steroids, or prodrugs, or pharmaceutically acceptable salts thereof, and optionally a pharmaceutically acceptable carrier. The present disclosure also provides kits comprising steroids, salts thereof, pro-drugs thereof, and/or pharmaceutical compositions thereof.

[0031a] In one aspect, there is provided a pharmaceutical composition comprising any of the compound disclosed herein, a pharmaceutically acceptable salt thereof, or a combination of two or more thereof, and a pharmaceutically acceptable carrier.

[0032] The present disclosure further provides methods of inducing anesthesia in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of one or more of the above-noted steroids, or prodrugs, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

[0032a] In one aspect, there is provided use of a therapeutically effective amount of any compound disclosed herein, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

[0033] The present disclosure further provides methods of treating disorders related to GABA function in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of one or more of the above-noted steroids, or prodrugs, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In certain embodiments, the disorder is selected from the group consisting of insomnia, mood disorders, convulsive disorders, anxiety, or symptoms of ethanol withdrawal.

[0033a] In one aspect, there is provided use of a therapeutically effective amount of any compound disclosed herein, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating disorders related to GABA function in a subject in need thereof.

Detailed Description of Certain Embodiments

[0034] In accordance with the present disclosure, it has been discovered that compounds having certain 17-substituted steroid structures, more specifically certain 19-alkoxy-17-substituted steroid structures, and even more specifically certain 19-methoxy-17-substituted steroid structures, are neuroactive and are also suitable for use as anesthetics and in the treatment of disorders associated with GABA function, as well as pharmaceutically acceptable salts and

prodrugs thereof. The compounds may be used, for example, as an effective continuous infusion sedative for non-surgical procedures (*e.g.*, colonoscopy). The compounds also offer advantages over anesthetics known in the art, such as a lower likelihood for bacterial contamination, as well as an improved relationship with solubilizing agents.

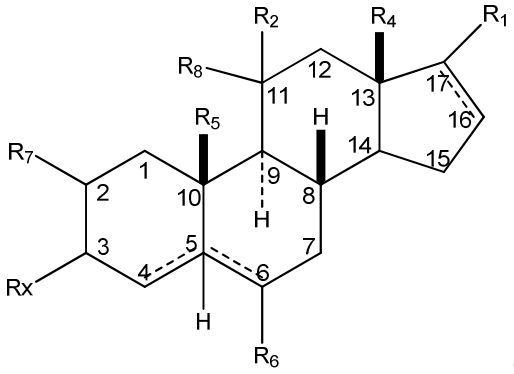
1. Steroid Structure

[0035] Generally speaking, the steroid of the present disclosure has a tetracyclic, fused ring structure, such as a cyclopenta[*a*]phenanthrene ring system (an embodiment of which is illustrated and discussed in greater detail below), wherein the C_3-position of the A ring has a hydroxyl substituent in the α-position, and the C_{17}-position of the D ring has a substituent attached thereto selected from the group consisting of methoxy, spirooxirane, cyano, =O, nitro,

Claims

What is claimed is:

1. A compound of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof;

wherein:

R_1 is selected from (C_1-C_4 alkyl)-O, spirooxirane, cyano, =O, nitro, (C_1-C_4 alkyl)C(O), and HO(C_1-C_4 alkyl)C(O);

R_2 is =O, H, or OR_a, where R_a is selected from H, optionally substituted C_1-C_4 alkyl, or optionally substituted aryl, with the proviso that when R_2 is =O, R_8 is not present;

R_x is =O or OR_d, where R_d is H or $C(O)R_e$, where R_e is optionally substituted C_1-C_{22} alkyl or optionally substituted C_2-C_{22} alkenyl, with the proviso that when R_x is OH, it is in the beta configuration (and when R_x is R_d, with R_d being $C(O)R_e$, then it is preferably in the beta configuration);

R_4 is independently selected from H and unsubstituted C_1-C_4 alkyl;

R_5 is substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, or optionally substituted C_2-C_4 alkynyl;

R_6 is H, optionally substituted C_1-C_4 alkyl, or optionally substituted C_1-C_4 alkoxy;

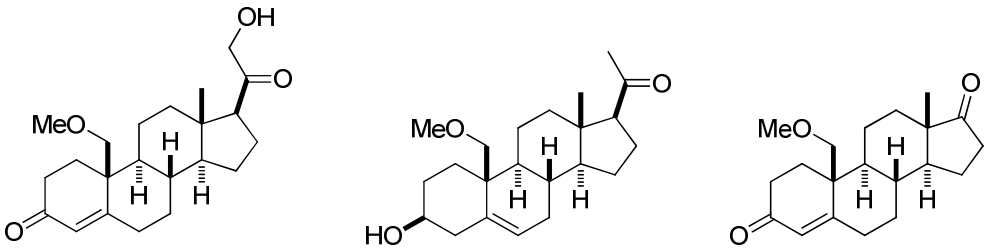
R_7 is H, optionally substituted C_1-C_4 alkoxy, or an optionally substituted morpholinyl ring;

R_8, when present, is H or optionally substituted C_1-C_4 alkyl;

- - - denotes an optional, additional C-C bond, resulting in either a C=C bond between C_4-C_5 or C_5-C_6, with the proviso that when present, the C_5-H substituent is not present; and,

- - - denotes an optional, additional C-C bond, resulting in a C=C bond between C_{16}-C_{17}, with the proviso that when present, the R_1 is not =O,

provided that the compound does not have one of the following structures:



or alternatively provided that: (i) when R_x is =O, a C=C bond is present between C_4-C_5, and R_5 is CH_2OCH_3, then R_1 is selected from methoxy, spirooxirane, cyano, nitro, and $CH_3C(O)$-; and/or (ii) when R_x is beta-OH, a C=C bond is present between C_5-C_6, and R_5 is CH_2OCH_3, then R_1 is selected from methoxy, spirooxirane, cyano, nitro, and $HOCH_2C(O)$-.

2. The compound of claim 1, wherein R_x is OH in the beta configuration.

3. The compound of claim 1, wherein R_x is =O.

4. The compound of one of preceding claims 1-3, wherein R_7 is selected from the group consisting of H, methoxy, ethoxy, and an optionally substituted morpholinyl ring.

5. The compound of one of preceding claims 1-4, wherein R_7 is in the beta position.

6. The compound of one of preceding claims 1-5, wherein R_5 is substituted methyl.

7. The compound of one of preceding claims 1-6, wherein the C_5-H is in the alpha configuration and R_5 is in the beta configuration.

8. The compound of one of preceding claims 1-6, wherein the C_5-H is in the beta configuration and R_5 is in the beta configuration.

9. The compound of one of preceding claims 1-8, wherein R_6 is H.

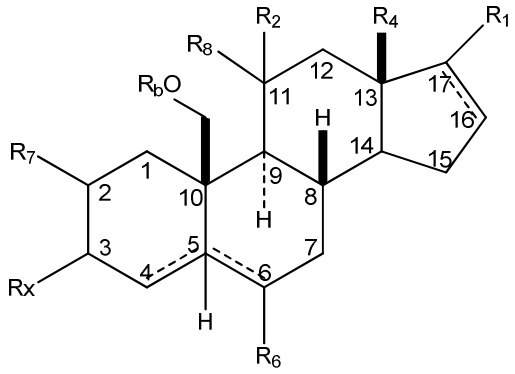
10. The compound of one of preceding claims 1-9, wherein R_2 is =O, methoxy or H.

11. The compound of one of preceding claims 1-10, wherein R_4 is methyl.

12. The compound of claim 1, wherein a carbon-carbon double bond is present between the C_4 and C_5 carbon atoms.

13. The compound of claim 1, wherein a carbon-carbon double bond is present between the C_5 and C_6 carbon atoms.

14. The compound of claim 1 having the structure:



or a pharmaceutically acceptable salt thereof, wherein R_b is optionally substituted C_1-C_4 alkyl.

15. The compound of claim 14 wherein R_b is methyl.

16. The compound of claim 14 or 15, wherein R_1 is beta-methoxy.

17. The compound of claim 14 or 15, wherein R_1 is beta-spirooxirane.

18. The compound of claim 14 or 15, wherein R_1 is beta-cyano.

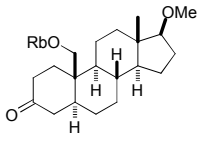
19. The compound of claim 14 or 15, wherein R_1 is =O.

20. The compound of claim 14 or 15, wherein R_1 is beta-nitro.

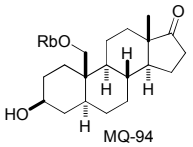
21. The compound of claim 14 or 15, wherein R_1 is beta-$CH_3C(O)$-.

22. The compound of claim 14 or 15, wherein R_1 is beta-$HOCH_2C(O)$-.

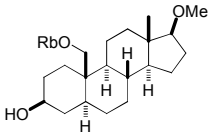
23. The compound of claim 1, selected from the group consisting of:



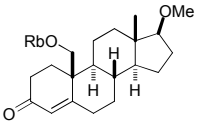
MQ-88
Prodrug



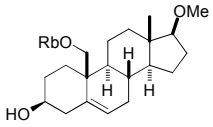
MQ-94
Prodrug



MQ-96
Prodrug



MQ-99
Prodrug



MQ-100
Prodrug

and pharmaceutically acceptable salts thereof, wherein R_b is optionally substituted C_1-C_4 alkyl.

24. The compound of claim 23, wherein R_b is methyl.

25. A pharmaceutically acceptable salt of a compound of one of preceding claims 1-24.

26. A pharmaceutical composition comprising a compound of one of claims 1-24, a pharmaceutically acceptable salt thereof, or a combination of two or more thereof, and a pharmaceutically acceptable carrier.

27. Use of a therapeutically effective amount of a compound of one of claims 1-24, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 26 in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

28. Use of a therapeutically effective amount of a compound of one of claims 1-24, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 26 in the manufacture of a medicament for treating disorders related to GABA function in a subject in need thereof.

29. The use of claim 28, wherein the disorder is selected from the group consisting of insomnia, mood disorders, convulsive disorders, anxiety, or symptoms of ethanol withdrawal.