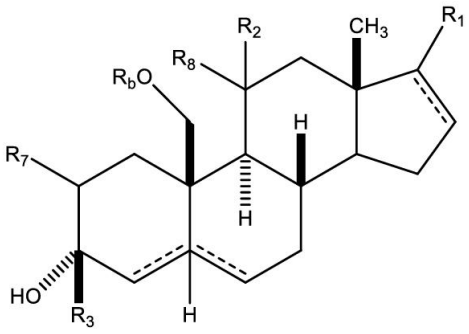
receptors and enhancement of GABAA receptors appear to play important roles in mediating the acute effects of ethanol in the nervous system, while related studies suggest that GABAergic neurosteroids may be involved in some of the pharmacological effects of ethanol and that neuroactive steroids may be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

[0007a] In one aspect, the present disclosure refers to a compound of Formula (I-a):



(Ia)

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, C_1-C_4 alkyl, or aryl, with the proviso that when R_2 is =O, R_8 is not present;

R_3 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or aryl;

R_b is C_1-C_4 alkyl;

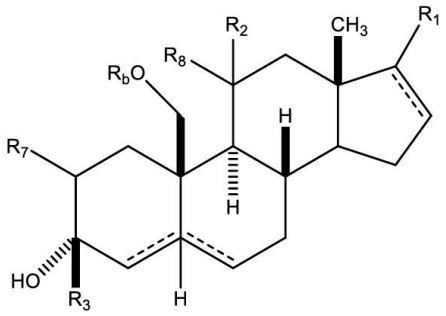
R_7 is H, C_1-C_4 alkoxy, or a morpholinyl ring;

R_8, when present, is H or 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 ~~or spirooxirane~~.

[0007b] In another aspect, the present disclosure refers to use of a therapeutically effective amount of a compound of Formula (I-a):



(Ia)

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need 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, C_1-C_4 alkyl, or aryl, with the proviso that when R_2 is =O, R_8 is not present;

R_3 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or aryl;

R_b is C_1-C_4 alkyl;

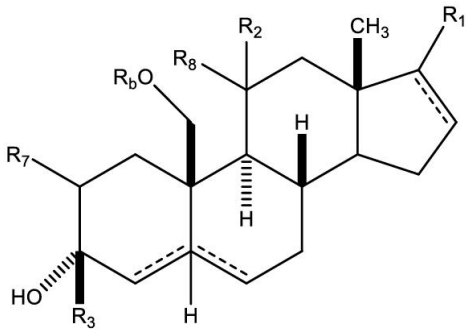
R_7 is H, C_1-C_4 alkoxy, or a morpholinyl ring;

R_8, when present, is H or 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 ~~or spirooxirane~~.

[0007c] In yet another aspect, the present disclosure refers to use of a compound of Formula (I-a):



(Ia)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder related to GABA function in a subject in need 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, C_1-C_4 alkyl, or aryl, with the proviso that when R_2 is =O, R_8 is not present;

R_3 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or aryl;

R_b is C_1-C_4 alkyl;

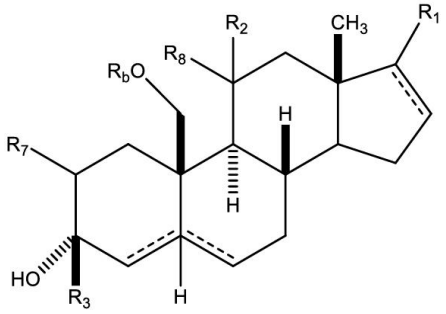
R_7 is H, C_1-C_4 alkoxy, or a morpholinyl ring;

R_8, when present, is H or 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 ~~or spirooxirane~~.

[0007d] In yet another aspect, the present disclosure refers to a compound of Formula (I-a):



(Ia)

or a pharmaceutically acceptable salt thereof for use in therapy;

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, C_1-C_4 alkyl, or aryl, with the proviso that when R_2 is =O, R_8 is not present;

R_3 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or aryl;

R_b is C_1-C_4 alkyl;

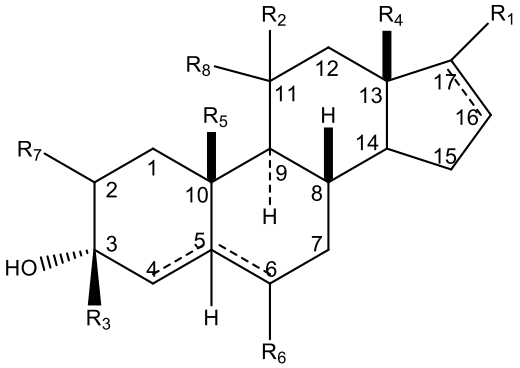
R_7 is H, C_1-C_4 alkoxy, or a morpholinyl ring;

R_8, when present, is H or 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 ~~or spirooxirane~~.

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



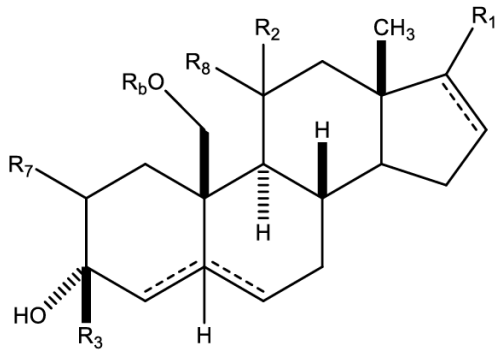
(I)

or a pharmaceutically acceptable salt thereof;

Claims

What is claimed is:

1. A compound of Formula (I-a):



(Ia)

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, C_1-C_4 alkyl, or aryl, with the proviso that when R_2 is =O, R_8 is not present;

R_3 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or aryl;

R_b is C_1-C_4 alkyl;

R_7 is H, C_1-C_4 alkoxy, or a morpholinyl ring;

R_8, when present, is H or 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 ~~or spirooxirane~~.

2. The compound of claim 1, wherein the R_3 group is selected from the group consisting of H, methyl, and trifluoromethyl.

3. The compound of claim 1 or 2, wherein R_7 is selected from the group consisting of H, methoxy, ethoxy, and a morpholinyl ring.

4. The compound of any one of claims 1 to 3, wherein R_7 is H.

5. The compound of any one of claims 1 to 4, wherein each instance of - - - between C_{54}-C_{65} and C_{65}-C_{76} is absent and C_5-H is in the alpha position.

6. The compound of any one of claims 1 to 4, wherein each instance of - - - between C_{54}-C_{65} and C_{65}-C_{76} is absent and C_5-H is in the beta position.

7. The compound of any one of claims 1 to 6, wherein each instance of - - - between C_{16}-C_{17} is absent and R_1 is in the beta position.

8. The compound of any one of claims 1 to 7, wherein R_2 is =O, methoxy or H.

9. The compound of any one of claims 1 to 8, wherein R_b is methyl.

10. The compound of any one of claims 1 to 9, wherein R_1 is beta-methoxy.

11. The compound of any one of claims 1 to 9, wherein R_1 is beta-spirooxirane.

12. The compound of any one of claims 1 to 9, wherein R_1 is beta-cyano.

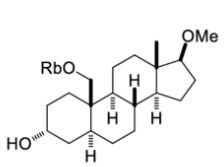
13. The compound of any one of claims 1 to 9, wherein R_1 is =O.

14. The compound of any one of claims 1 to 9, wherein R_1 is beta-nitro.

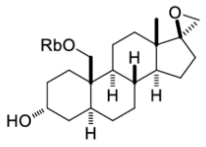
15. The compound of any one of claims 1 to 9, wherein R_1 is beta-$CH_3C(O)$-.

16. The compound of any one of claims 1 to 9, wherein R_1 is beta-$HOCH_2C(O)$-.

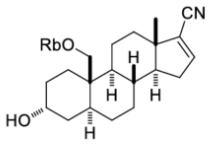
17. The compound of claim 1 selected from the group consisting of:



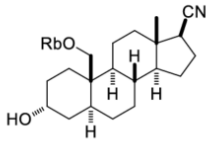
MQ-89 Drug



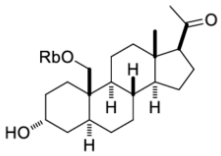
MQ-90 Drug



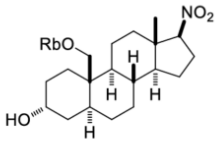
MQ-91 Drug



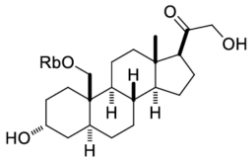
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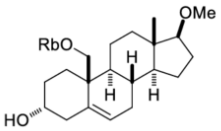
MQ-93 Drug



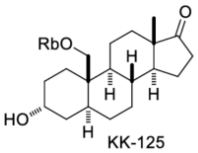
MQ-97 Drug



MQ-98 Drug



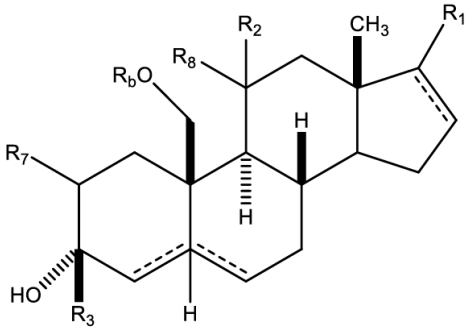
MQ-101 Drug



KK-125 Drug

and pharmaceutically acceptable salts thereof.

18. Use of a therapeutically effective amount of a compound of Formula (I-a):



(Ia)

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need 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, C_1-C_4 alkyl, or aryl, with the proviso that when R_2 is =O, R_8 is not present;

R_3 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or aryl;

R_b is C_1-C_4 alkyl;

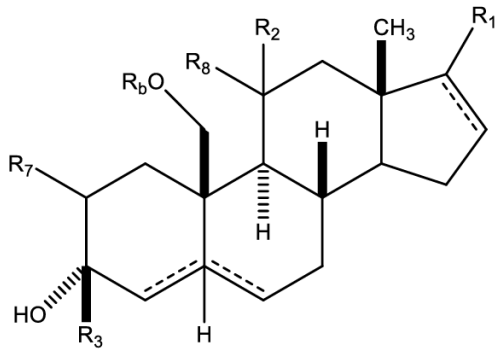
R_7 is H, C_1-C_4 alkoxy, or a morpholinyl ring;

R_8, when present, is H or 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 ~~or spirooxirane~~.

19. Use of a compound of Formula (I-a):



(Ia)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder related to GABA function in a subject in need 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, C_1-C_4 alkyl, or aryl, with the proviso that when R_2 is =O, R_8 is not present;

R_3 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or aryl;

R_b is C_1-C_4 alkyl;

R_7 is H, C_1-C_4 alkoxy, or a morpholinyl ring;

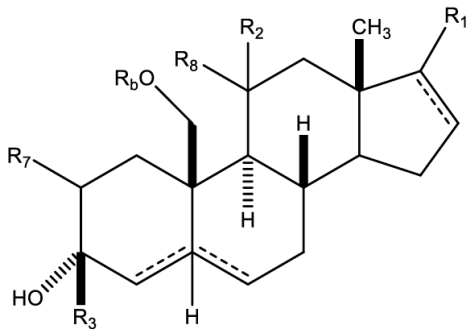
R_8, when present, is H or C_1-C_4 alkyl;

- - - 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 ~~or spirooxirane~~.

20. The use of claim 19, wherein the disorder is selected from the group consisting of insomnia, mood disorders, convulsive disorders, anxiety, and symptoms of ethanol withdrawal.

21. A compound of Formula (I-a):



(Ia)

or a pharmaceutically acceptable salt thereof for use in therapy;

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, C_1-C_4 alkyl, or aryl, with the proviso that when R_2 is =O, R_8 is not present;

R_3 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or aryl;

R_b is C_1-C_4 alkyl;

R_7 is H, C_1-C_4 alkoxy, or a morpholinyl ring;

R_8, when present, is H or 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 ~~or spirooxirane~~.