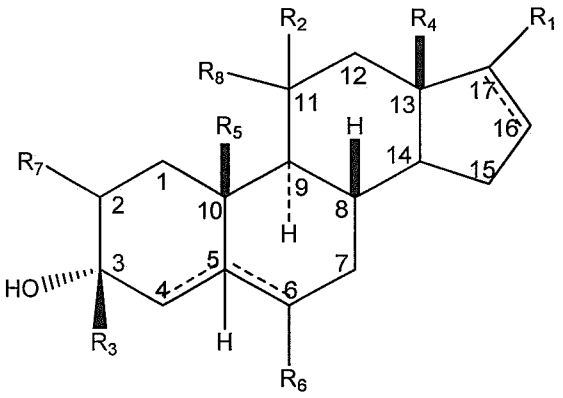
receptors and enhancement of GABAA receptors appear to play important roles in mediating the acute effects of ethanol in the nervous system, while related studies suggest that GABAergic neurosteroids may be involved in some of the pharmacological effects of ethanol and that neuroactive steroids may be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

[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 examples 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;

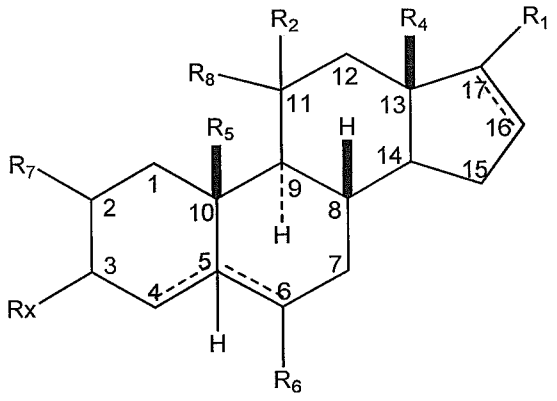
[0012] R4 is independently selected from H and unsubstituted C1-C4 alkyl;

[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

- - - 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, in the manufacture of a medicament for treating disorders related to GABA function.

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



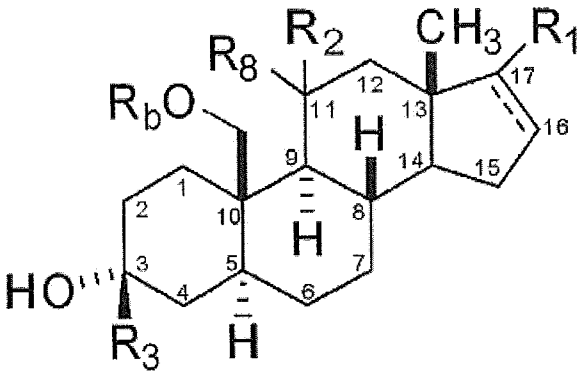
(II)

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 examples 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 the present invention provides a compound of Formula (I-g):



(I-g)

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;

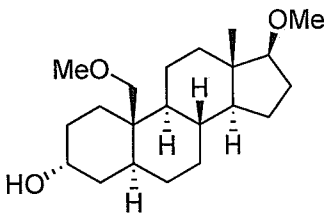
R_3 is H, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, or optionally substituted aryl;

R_b is methyl;

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

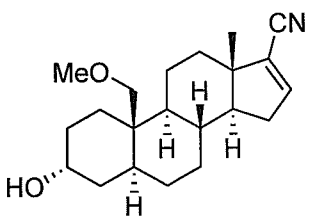
- - - denotes an optional, additional C-C bond, resulting in a C=C bond between C_{16}-C_{17}, with the proviso that when present, the R_1 is not =O or spirooxirane.

[0030b] In another aspect, the present invention provides a compound of the formula:



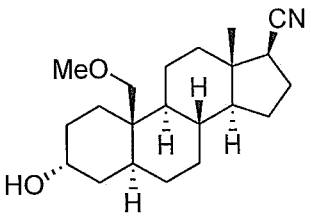
, or a pharmaceutically acceptable salt thereof.

[0030c] In yet another aspect, the present invention provides a compound of the formula:



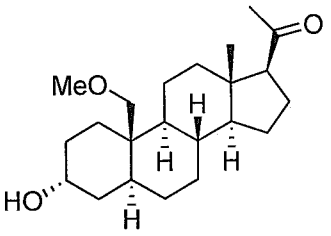
,or a pharmaceutically acceptable salt thereof.

[0030d] In yet another aspect, the present invention provides a compound of the formula:



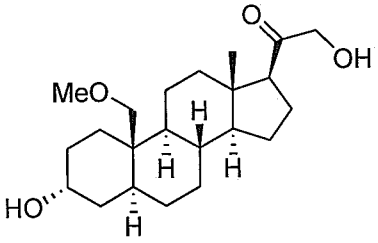
,or a pharmaceutically acceptable salt thereof.

[0030e] In yet another aspect, the present invention provides a compound of the formula:



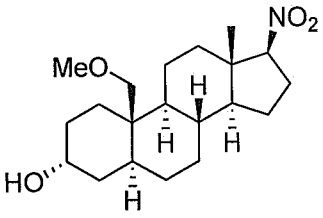
, or a pharmaceutically acceptable salt thereof.

[0030f] In yet another aspect, the present invention provides a compound of the formula:



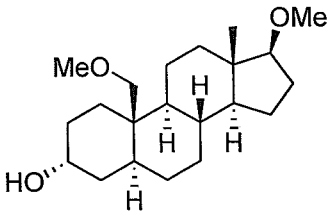
, or a pharmaceutically acceptable salt thereof.

[0030g] In yet another aspect, the present invention provides a compound of the formula:



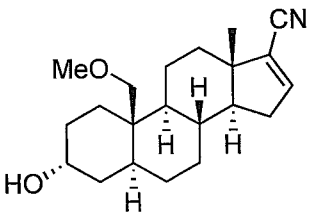
, or a pharmaceutically acceptable salt thereof.

[0030h] In yet another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula:



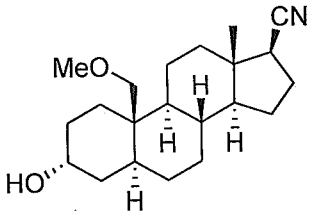
, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0030i] In yet another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula:

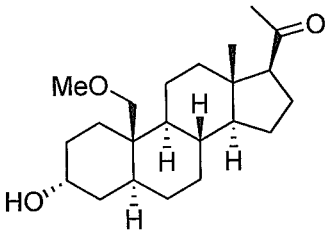


, or a

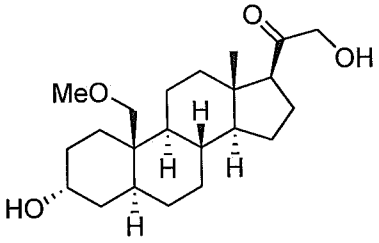
pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0030j] In yet another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula: 

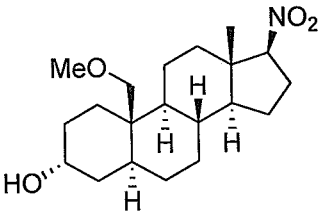
, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0030k] In yet another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula: 

, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

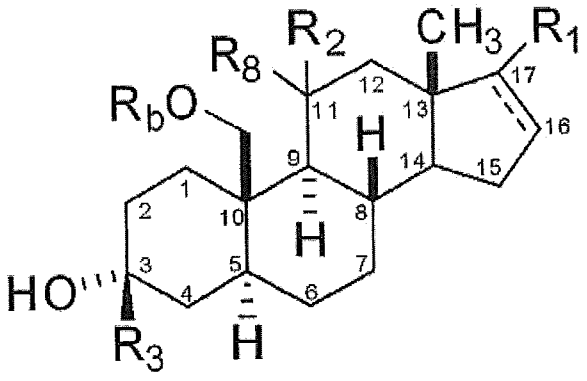
[0030l] In yet another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula: 

, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0030m] In yet another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula: 

, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0030n] In yet another aspect, the present invention provides use of a therapeutically effective amount of a compound of Formula (I-g):



(I-g)

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_3 is H, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, or optionally substituted aryl;

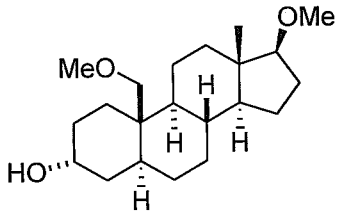
R_b is methyl;

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

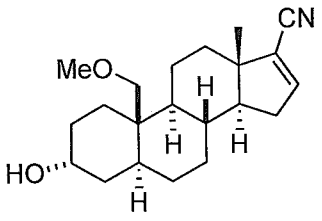
- - - denotes an optional, additional C-C bond, resulting in a C=C bond between C_{16}-C_{17}, with the proviso that when present, the R_1 is not =O or spirooxirane;

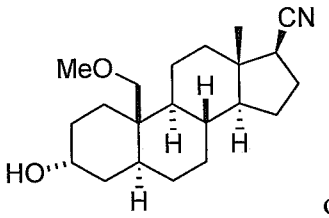
in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

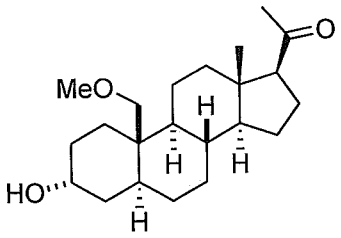
[0030o] In yet another aspect, the present invention provides use of a therapeutically effective amount of a compound of the formula:

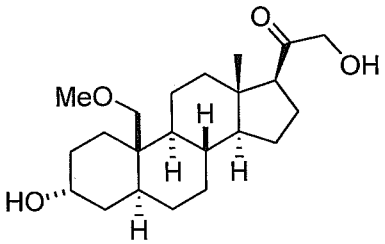


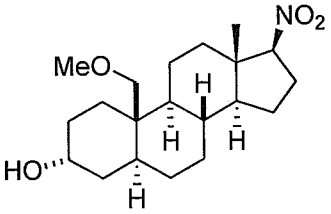
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

[0030p] In yet another aspect, the present invention provides use of a therapeutically effective amount of a compound of the formula:  or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

[0030q] In yet another aspect, the present invention provides use of a therapeutically effective amount of a compound of the formula:  or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

[0030r] In yet another aspect, the present invention provides use of a therapeutically effective amount of a compound of the formula:  or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

[0030s] In yet another aspect, the present invention provides use of a therapeutically effective amount of a compound of the formula:  or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

[0030t] In yet another aspect, the present invention provides use of a therapeutically effective amount of a compound of the formula:  or a

pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

[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.

[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.

[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 examples, the disorder is selected from the group consisting of insomnia, mood disorders, convulsive disorders, anxiety, or symptoms of ethanol withdrawal.

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.

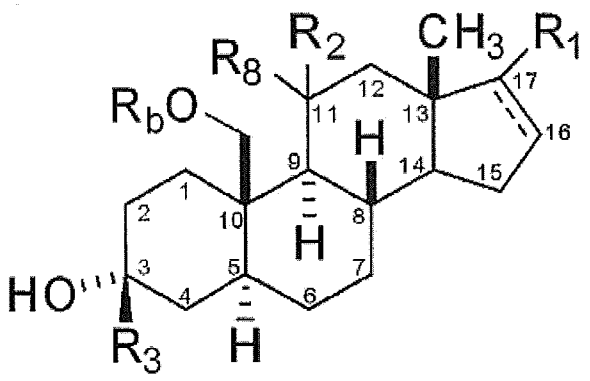
1. Steroid Structure

[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 (I-g):



(I-g)

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_3 is H, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, or optionally substituted aryl;

R_b is methyl;

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

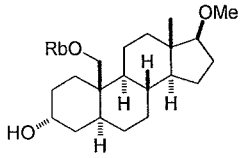
- - - denotes an optional, additional C-C bond, resulting in a C=C bond between C_{16}-C_{17}, with the proviso that when present, the R_1 is not =O or spirooxirane.

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

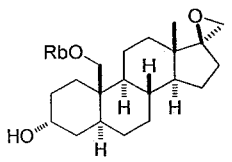
3. The compound of claim 1, wherein R_2 is =O, methoxy or H.

4. The compound of claim 1, wherein R_1 is beta-cyano.

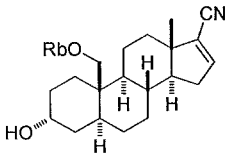
5. The compound of claim 1 selected from the group consisting of:



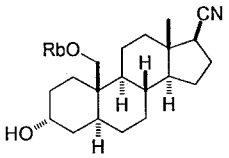
MQ-89
Drug



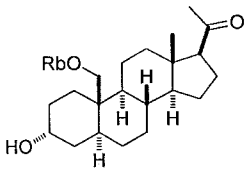
MQ-90
Drug



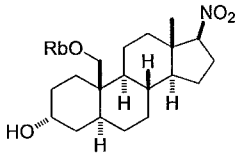
MQ-91
Drug



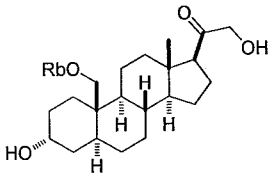
MQ-92
Drug



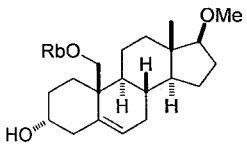
MQ-93
Drug



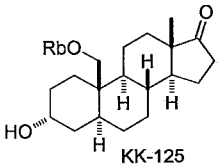
MQ-97
Drug



MQ-98
Drug



MQ-101
Drug



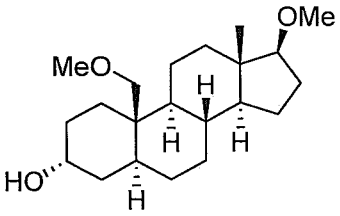
KK-125
Drug

and pharmaceutically acceptable salts thereof.

6. The compound of claim 1, wherein

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

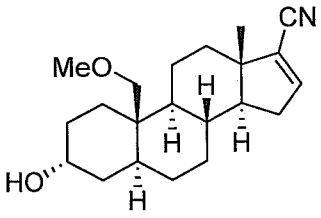
7. A compound of the formula:



,

or a pharmaceutically acceptable salt thereof.

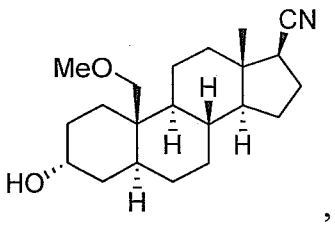
8. A compound of the formula:



,

or a pharmaceutically acceptable salt thereof.

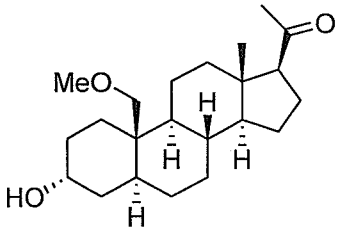
9. A compound of the formula:



,

or a pharmaceutically acceptable salt thereof.

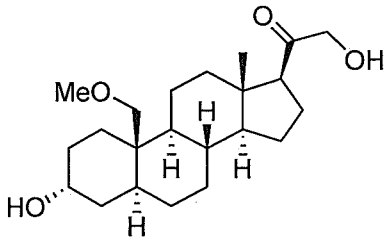
10. A compound of the formula:



,

or a pharmaceutically acceptable salt thereof.

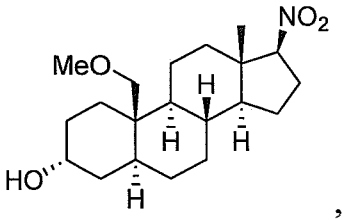
11. A compound of the formula:



,

or a pharmaceutically acceptable salt thereof.

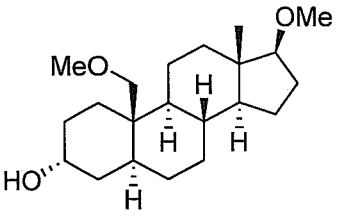
12. A compound of the formula:



,

or a pharmaceutically acceptable salt thereof.

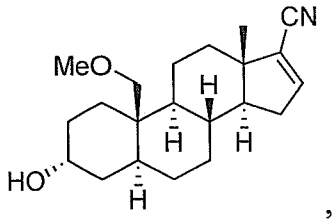
13. A pharmaceutical composition comprising a compound of formula:



,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

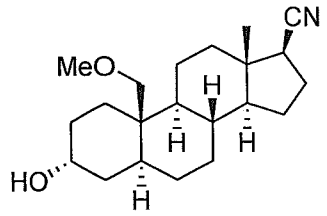
14. A pharmaceutical composition comprising a compound of formula:



,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

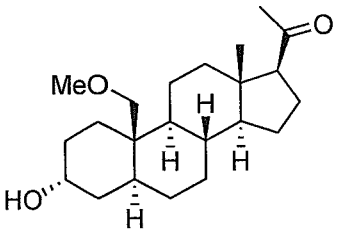
15. A pharmaceutical composition comprising a compound of formula:



,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

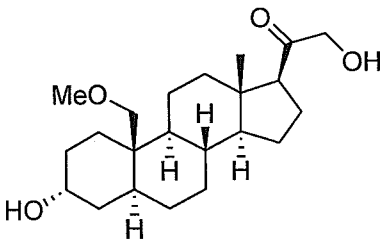
16. A pharmaceutical composition comprising a compound of formula:



,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

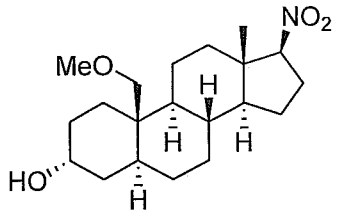
17. A pharmaceutical composition comprising a compound of formula:



,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

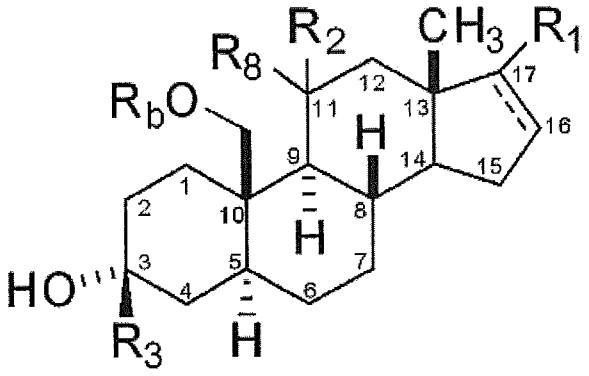
18. A pharmaceutical composition comprising a compound of formula:



,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

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



(I-g)

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_3 is H, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, or optionally substituted aryl;

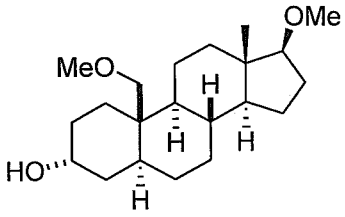
R_b is methyl;

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

- - - 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;

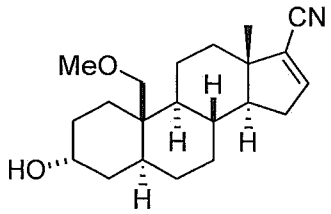
in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

20. Use of a therapeutically effective amount of a compound of the formula:



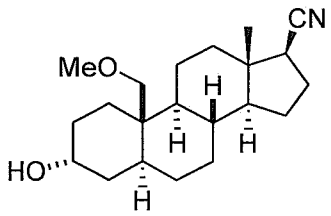
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

21. Use of a therapeutically effective amount of a compound of the formula:



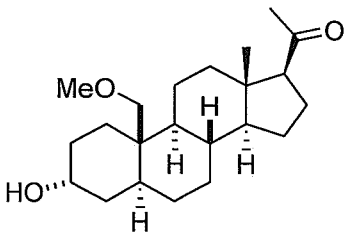
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

22. Use of a therapeutically effective amount of a compound of the formula:



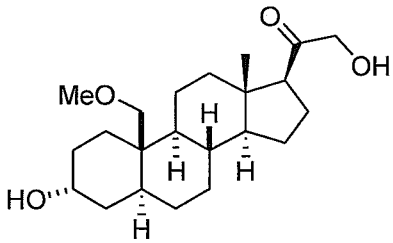
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

23. Use of a therapeutically effective amount of a compound of the formula:



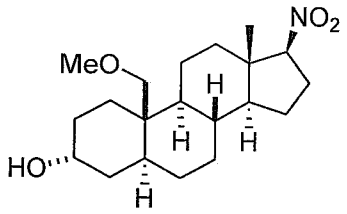
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

24. Use of a therapeutically effective amount of a compound of the formula:



or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.

25. Use of a therapeutically effective amount of a compound of the formula:



or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing anesthesia in a subject in need thereof.