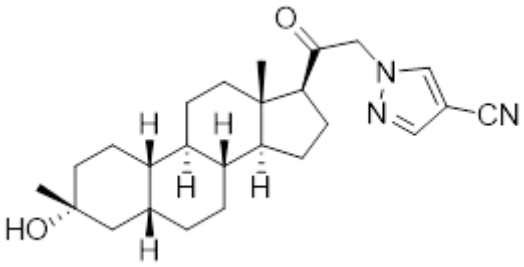
[0004] Accumulated evidence has indicated that the GRC contains a distinct site for neuroactive steroids (Lan, N. C. et al., *Neuwchem. Res*. 16:347-356 (1991)). Neuroactive steroids can occur endogenously. The most potent endogenous neuroactive steroids are 3α-hydroxy-5-reduced pregnan-20-one and 3α-21-dihydroxy-5-reduced 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)).

SUMMARY

[0004a] In a first aspect of the present disclosure, there is provided a use of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**;

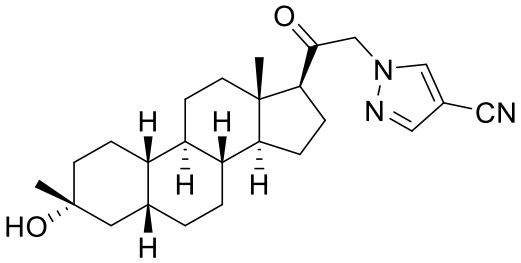
in the manufacture of a medicament for treating major depressive disorder (MDD) in a subject in need thereof, wherein:

(i) Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject as part of an initial treatment; and

(ii) 0, 1, or 2 subsequent treatment courses is to be performed on the subject, wherein for each subsequent treatment course, the Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are to be performed over a period of 12 months from the beginning of the initial treatment course.

[0004b] In another aspect of the present disclosure, there is provided a use of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**;

in the manufacture of a medicament for treating major depressive disorder (MDD) in a subject in need thereof, wherein:

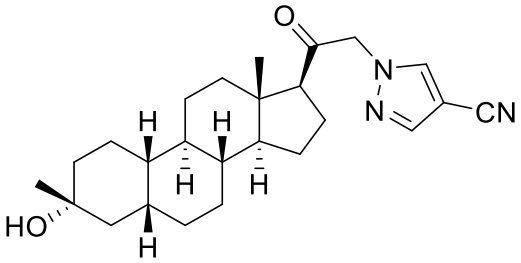
(i) Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject as part of an initial treatment; and

(ii) 0, 1, or 2 subsequent treatment courses is to be performed on the subject, wherein for each subsequent treatment course, the Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are to be performed over a period of 12 months from the beginning of the initial treatment course, and

wherein the subject is treatment naïve.

[0004c] In yet another aspect of the present disclosure, there is provided a use of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**;

in the manufacture of a medicament for treating major depressive disorder (MDD) in a subject in need thereof, wherein:

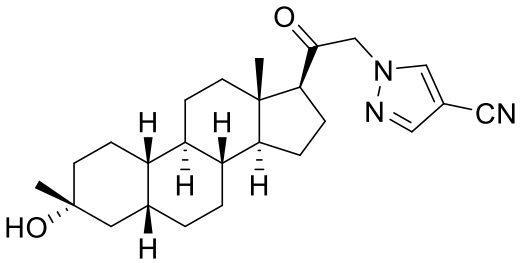
(i) about 30 mg to about 50 mg of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject as part of an initial treatment; and

(ii) 0, 1, or 2 subsequent treatment courses is to be performed on the subject, wherein for each subsequent treatment course, about 30 mg to about 50 mg of Compound **(1)**,

or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are to be performed over a period of 12 months from the beginning of the initial treatment course.

[0004d] In a further aspect of the present disclosure, there is provided a use of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**;

in the manufacture of a medicament for treating major depressive disorder (MDD) in a subject in need thereof, wherein:

(i) about 30 mg to about 50 mg of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**, is to be administered once a day for about 14 days to the subject as part of an initial treatment; and

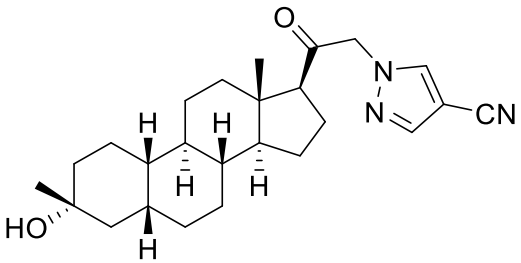
(ii) 0, 1, or 2 subsequent treatment courses is to be performed on the subject, wherein for each subsequent treatment course, about 30 mg to about 50 mg of Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered once a day for about 14 days to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are to be performed over a period of 12 months from the beginning of the initial treatment course;

optionally, wherein there is at least about a 6 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course; or

optionally, wherein the subject has been on a stable dose of an additional antidepressant for at least 60 days.

[0004e] In another aspect of the present disclosure, there is provided a use of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**;

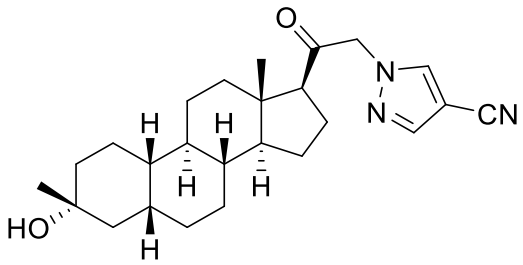
in the manufacture of a medicament for treating major depressive disorder (MDD) in a subject in need thereof, wherein:

(i) about 45 mg to about 55 mg of Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered once a day for about 14 days to the subject as part of an initial treatment; and

(ii) 0, 1, or 2 subsequent treatment courses is to be performed on the subject, wherein for each subsequent treatment course, about 45 mg to about 55 mg of Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are to be performed over a period of 12 months from the beginning of the initial treatment course.

[0004f] In yet another aspect of the present disclosure, there is provided a use of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)** once a day for about 14 days:



Compound **(1)**;

in the manufacture of a medicament for treating major depressive disorder (MDD) in a subject in need thereof, wherein:

(i) about 45 mg to about 55 mg of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**, is to be administered once a day for about 14 days to the subject as part of an initial treatment; and

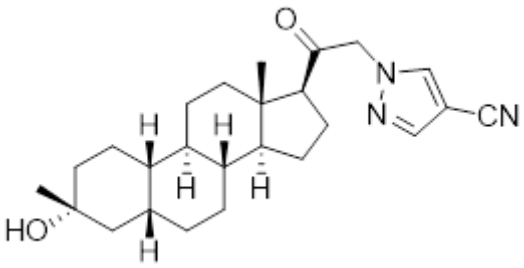
(ii) 0, 1, or 2 subsequent treatment courses is to be performed on the subject, wherein for each subsequent treatment course, about 45 mg to about 55 mg of Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered once a day for about 14 days to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are to be performed over a period of 12 months from the beginning of the initial treatment course;

optionally, wherein there is at least about a 6 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course.

[0005] In one example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering a therapeutically effective amount of Compound **(1)**:



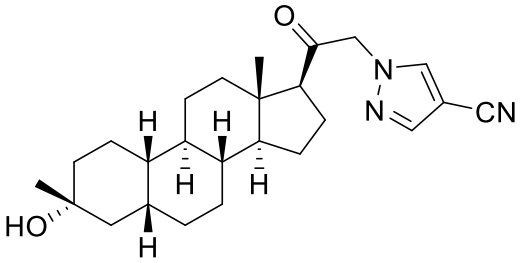
Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering a therapeutically effective amount of Compound **(1)** in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0006] In one example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)** in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0007] In some examples, 0 or 1 subsequent treatment courses are performed. In some examples, 1 subsequent treatment course is performed.

[0008] In some examples, there is at least about a 4 week, at least about a 6 week, or at least about an 8 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course. In some examples, there is about a 4 week, about a 6 week, or about an 8 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course.

[0009] In some examples, the recurrence of depression symptoms is indicated by an evaluation of the subject using the Hamilton Rating Scale for Depression (HAM-D), Montgomery – Asberg Depression Rating Scale (MADRS), the Patient Health Questionnaire (PHQ-9), or a combination thereof. In some examples, the recurrence of depression symptoms in the subject is indicated by a PHQ-9 score greater than or equal to 10 or a HAM-D score greater than or equal to 20.

[0010] In some examples, the initial treatment course has a duration of about 2 weeks or about 14 days. In some examples, each subsequent treatment course has a duration of about 2 weeks or about 14 days. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is administered once a day for about 14 days in the initial treatment course. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is administered once a day for about 14 days in each subsequent treatment course.

[0011] In some examples, Compound **(1)** is administered at a dose of about 20 mg to about 55 mg. In some examples, Compound **(1)** is administered at a dose of about 30 mg

to about 50 mg. In some examples, Compound **(1)** is administered at a dose of about 50 mg. In some examples, wherein Compound **(1)** is administered at a dose of about 40 mg. In some examples, the pharmaceutically acceptable salt of Compound **(1)** is administered at a dose equivalent to about 20 mg to about 55 mg of the free base compound. In some examples, the pharmaceutically acceptable salt of Compound **(1)** is administered at a dose equivalent to about 30 mg to about 50 mg of the free base compound. In some examples, the pharmaceutically acceptable salt of Compound **(1)** is administered at a dose equivalent to about 50 mg of the free base compound. In some examples, the pharmaceutically acceptable salt of Compound **(1)** is administered at a dose equivalent to about 40 mg of the free base compound.

[0012] In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1),** is administered orally, parenterally, intradermally, intrathecally, intramuscularly, subcutaneously, vaginally, as a buccal, sublingually, rectally, topically, as an inhalation, intranasaly, or transdermally. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is administered orally. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is administered with food. In some examples, the pharmaceutically acceptable salt of Compound **(1)**, is administered once a day at night.

[0013] In some examples, Compound **(1)** is in a crystalline form having an XRPD pattern comprising peaks between and including 9.7 to 10.1 degrees in 2θ, between and including 11.6 to 12.0 degrees in 2θ, between and including 13.2 to 13.6 degrees in 2θ, between and including 14.2 to 14.6 degrees in 2θ, between and including 14.6 to 15.0 degrees in 2θ, between and including 16.8 to 17.2 degrees in 2θ, between and including 20.5 to 20.9 degrees in 2θ, between and including 21.3 to 21.7 degrees in 2θ, between and including 21.4 to 21.8 degrees in 2θ, and between and including 22.4 to 22.8 degrees in 2θ. In some examples, Compound **(1)** is in a crystalline form having an XRPD pattern comprising peaks between and including 9.3 to 9.7 degrees in 2θ, between and including 10.6 to 11.0 degrees in 2θ, between and including 13.0 to 13.4 degrees in 2θ, between and including 14.7 to 15.1 degrees in 2θ, between and including 15.8 to 16.2 degrees in 2θ, between and including 18.1 to 18.5 degrees in 2θ, between and including 18.7 to 19.1 degrees in 2θ, between and including 20.9 to 21.3 degrees in 2θ, between and including 21.4 to 21.8 degrees in 2θ, and between and including 23.3 to 23.7 degrees in 2θ. In some examples, Compound **(1)** is in a crystalline form having an XRPD pattern comprising peaks between and including 9.7 to 10.1 degrees in 2θ, between and including 14.6 to 15.0 degrees in 2θ, between and including 16.8 to 17.2 degrees in 2θ,

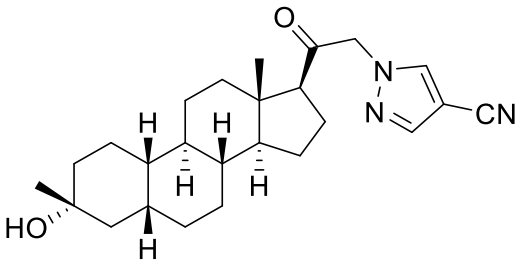
between and including 20.5 to 20.9 degrees in 2θ, and between and including 21.3 to 21.7 degrees in 2θ. In some examples, Compound **(1)** is in a crystalline form having an XRPD pattern comprising peaks between and including 9.3 to 9.7 degrees in 2θ, between and including 10.6 to 11.0 degrees in 2θ, between and including 13.0 to 13.4 degrees in 2θ, between and including 18.7 to 19.1 degrees in 2θ, and between and including 21.4 to 21.8 degrees in 2θ.

[0014] In some examples, the subject is treatment naïve.

[0015] In some examples, the subject has been on a stable dose of an additional antidepressant for at least 60 days prior to the beginning of the initial treatment course.

[0016] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering a therapeutically effective amount of Compound **(1)**:



Compound **(1)**; and

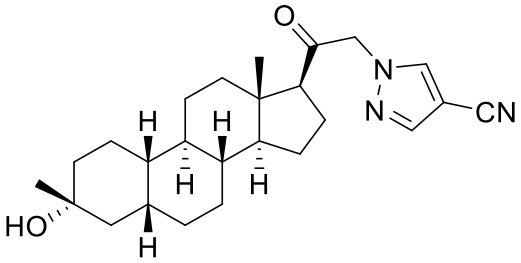
(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering a therapeutically effective amount of Compound **(1)** in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course, and

wherein the subject is treatment naïve.

[0017] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)** in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course, and

wherein the subject is treatment naïve.

[0018] In some examples, 0 or 1 subsequent treatment courses are performed. In some examples, 1 subsequent treatment course is performed.

[0019] In some examples, there is at least about a 4 week, at least about a 6 week, or at least about an 8 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course. In some examples, there is about a 4 week, about a 6 week, or about an 8 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course.

[0020] In some examples, the recurrence of depression symptoms is indicated by an evaluation of the subject using the Hamilton Rating Scale for Depression (HAM-D), Montgomery – Asberg Depression Rating Scale (MADRS), the Patient Health Questionnaire (PHQ-9), or a combination thereof. In some examples, the recurrence of depression symptoms in the subject is indicated by a PHQ-9 score greater than or equal to 10 or a HAM-D score greater than or equal to 20.

[0021] In some examples, the initial treatment course has a duration of about 2 weeks or about 14 days. In some examples, each subsequent treatment course has a duration of about 2 weeks or about 14 days. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is administered once a day for about 14 days in the initial treatment course. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is administered once a day for about 14 days in each subsequent treatment course. In some examples, Compound **(1)** is administered at a dose of about 20 mg to about 55 mg. In some examples, Compound **(1)** is administered at a dose of about

30 mg to about 50 mg. In some examples, Compound **(1)** is administered at a dose of about 50 mg. In some examples, Compound **(1)** is administered at a dose of about 40 mg. In some examples, the pharmaceutically acceptable salt of Compound **(1)** is administered at a dose equivalent to about 20 mg to about 55 mg of the free base compound. In some examples, the pharmaceutically acceptable salt of Compound **(1)** is administered at a dose equivalent to about 30 mg to about 50 mg of the free base compound. In some examples, the pharmaceutically acceptable salt of Compound **(1)** is administered at a dose equivalent to about 50 mg of the free base compound. In some examples, the pharmaceutically acceptable salt of Compound **(1)** is administered at a dose equivalent to about 40 mg of the free base compound.

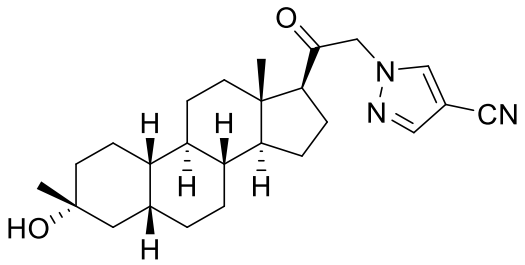
[0022] In some examples, Compound **(1),** or the pharmaceutically acceptable salt of Compound **(1),** is administered orally, parenterally, intradermally, intrathecally, intramuscularly, subcutaneously, vaginally, as a buccal, sublingually, rectally, topically, as an inhalation, intranasaly, or transdermally. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is administered orally. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is administered with food. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is administered once a day at night.

[0023] In some examples, Compound **(1)** is in a crystalline form having an XRPD pattern comprising peaks between and including 9.7 to 10.1 degrees in 2θ, between and including 11.6 to 12.0 degrees in 2θ, between and including 13.2 to 13.6 degrees in 2θ, between and including 14.2 to 14.6 degrees in 2θ, between and including 14.6 to 15.0 degrees in 2θ, between and including 16.8 to 17.2 degrees in 2θ, between and including 20.5 to 20.9 degrees in 2θ, between and including 21.3 to 21.7 degrees in 2θ, between and including 21.4 to 21.8 degrees in 2θ, and between and including 22.4 to 22.8 degrees in 2θ. In some examples, Compound **(1)** is in a crystalline form having an XRPD pattern comprising peaks between and including 9.3 to 9.7 degrees in 2θ, between and including 10.6 to 11.0 degrees in 2θ, between and including 13.0 to 13.4 degrees in 2θ, between and including 14.7 to 15.1 degrees in 2θ, between and including 15.8 to 16.2 degrees in 2θ, between and including 18.1 to 18.5 degrees in 2θ, between and including 18.7 to 19.1 degrees in 2θ, between and including 20.9 to 21.3 degrees in 2θ, between and including 21.4 to 21.8 degrees in 2θ, and between and including 23.3 to 23.7 degrees in 2θ. In some examples, Compound **(1)** is in a crystalline form having an XRPD pattern comprising peaks between and including 9.7 to 10.1 degrees in 2θ, between and including 14.6 to 15.0 degrees in 2θ, between and including 16.8 to 17.2 degrees in 2θ,

between and including 20.5 to 20.9 degrees in 2θ, and between and including 21.3 to 21.7 degrees in 2θ. In some examples, Compound **(1)** is in a crystalline form having an XRPD pattern comprising peaks between and including 9.3 to 9.7 degrees in 2θ, between and including 10.6 to 11.0 degrees in 2θ, between and including 13.0 to 13.4 degrees in 2θ, between and including 18.7 to 19.1 degrees in 2θ, and between and including 21.4 to 21.8 degrees in 2θ.

[0024] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering about 30 mg to about 50 mg of Compound **(1)**:



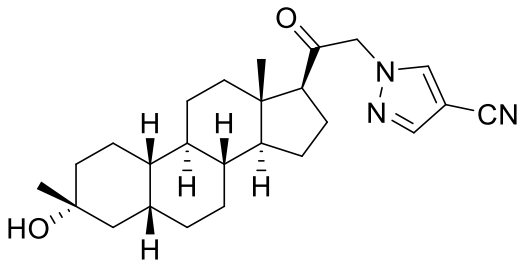
Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering about 30 mg to about 50 mg of Compound **(1)** to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0025] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 30 mg to about 50 mg of the free base compound:



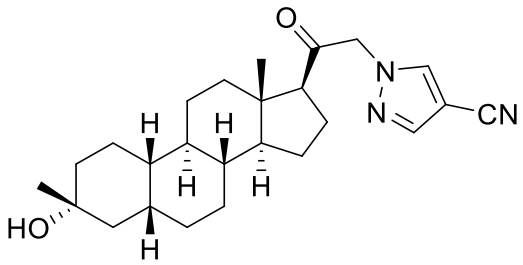
Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 30 mg to about 50 mg of the free base compound to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0026] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering about 30 mg to about 50 mg of Compound **(1)** once a day for about 14 days:



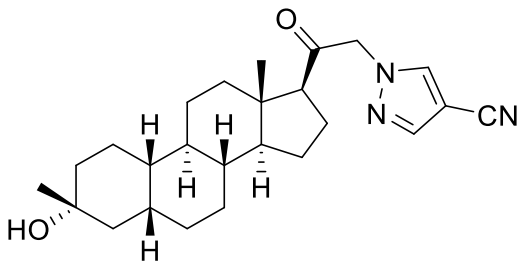
Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering about 30 mg to about 50 mg of Compound **(1)** once a day for about 14 days to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0027] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 30 mg to about 50 mg of the free base compound once a day for about 14 days:



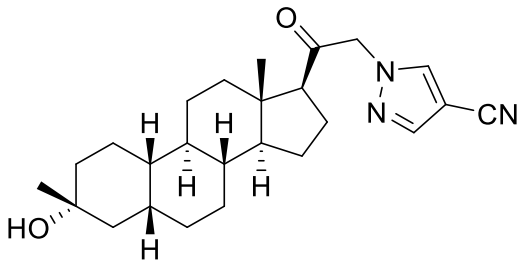
Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 30 mg to about 50 mg of the free base compound once a day for about 14 days to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0028] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering about 30 mg to about 50 mg of Compound **(1)** once a day for about 14 days:



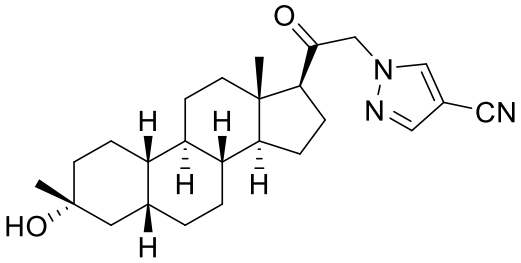
Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering about 30 mg to about 50 mg of Compound **(1)** once a day for about 14 days to the subject in response to a recurrence of depression symptoms, provided there is at least about a 6 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0029] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 30 mg to about 50 mg of the free base compound once a day for about 14 days:



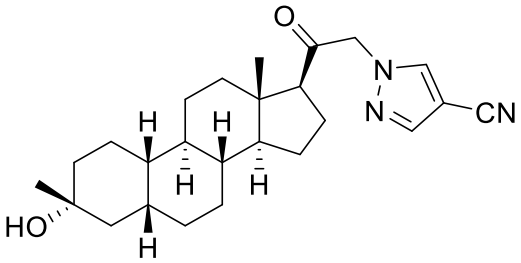
Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 30 mg to about 50 mg of the free base compound once a day for about 14 days to the subject in response to a recurrence of depression symptoms, provided there is at least about a 6 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0030] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering about 30 mg to about 50 mg of Compound **(1)** once a day for about 14 days:



Compound **(1)**; and

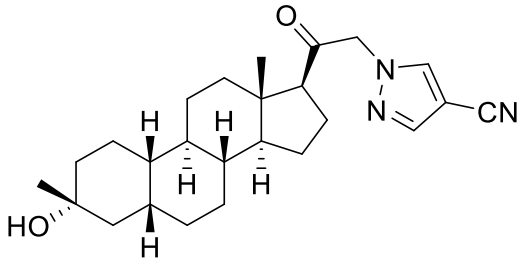
(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering about 30 mg to about 50 mg of Compound **(1)** once a day for about 14 days to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course, and

wherein the subject has been on a stable dose of an additional antidepressant for at least 60 days.

[0031] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 30 mg to about 50 mg of the free base compound once a day for about 14 days:



Compound **(1)**; and

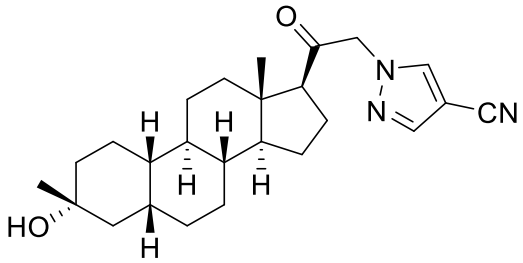
(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 30 mg to about 50 mg of the free base compound once a day for about 14 days to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course, and

wherein the subject has been on a stable dose of an additional antidepressant for at least 60 days.

[0032] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering about 45 mg to about 55 mg of Compound **(1)**:



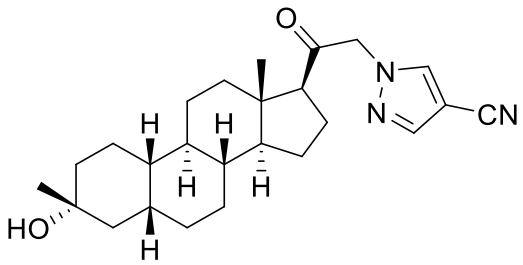
Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering about 45 mg to about 55 mg of Compound **(1)** to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0033] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 45 mg to about 55 mg of the free base compound:



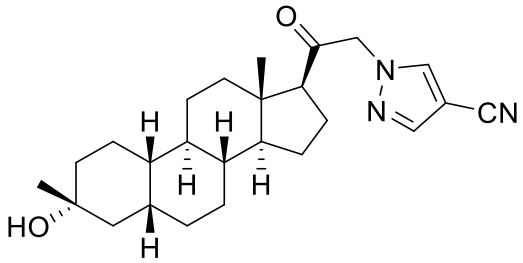
Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 45 mg to about 55 mg of the free base compound to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0034] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering about 45 mg to about 55 mg of Compound **(1)** once a day for about 14 days:



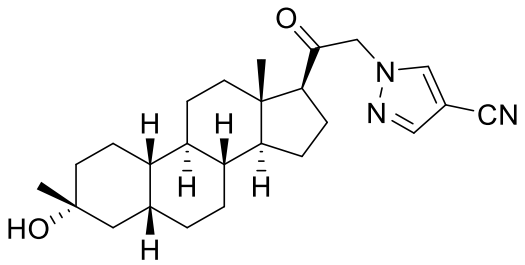
Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering about 45 mg to about 55 mg of Compound **(1)** once a day for about 14 days to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0035] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 45 mg to about 55 mg of the free base compound once a day for about 14 days:



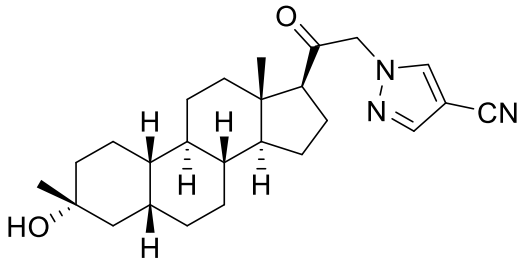
Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 45 mg to about 55 mg of the free base compound once a day for about 14 days to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0036] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering about 45 mg to about 55 mg of Compound **(1)** once a day for about 14 days:



Compound **(1)**; and

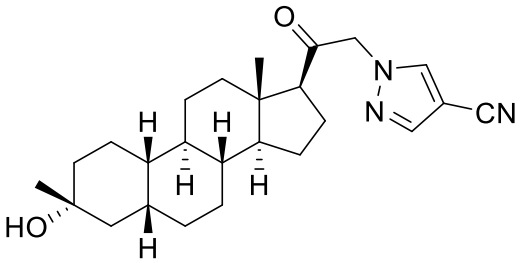
(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering about 45 mg to about 55 mg of Compound **(1)** once a day for about 14 days to the subject in response to a recurrence of

depression symptoms, provided there is at least about a 6 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0037] In another example, the disclosure includes a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) performing an initial treatment course on the subject comprising administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 45 mg to about 55 mg of the free base compound once a day for about 14 days:



Compound **(1)**; and

(ii) performing 0, 1, or 2 subsequent treatment courses on the subject, wherein each subsequent treatment course comprises administering a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 45 mg to about 55 mg of the free base compound once a day for about 14 days to the subject in response to a recurrence of depression symptoms, provided there is at least about a 6 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course,

wherein the 0, 1, or 2 subsequent treatment courses are performed over a period of 12 months from the beginning of the initial treatment course.

[0038] In some examples, 0 or 1 subsequent treatment courses are performed.

[0039] In some examples, the recurrence of depression symptoms is indicated by an evaluation of the subject using the Hamilton Rating Scale for Depression (HAM-D), Montgomery–Asberg Depression Rating Scale (MADRS), the Patient Health Questionnaire (PHQ-9), or a combination thereof. In some examples, the recurrence of depression symptoms in the subject is indicated by a PHQ-9 score greater than or equal to 10 or a HAM-D score greater than or equal to 20.

[0040] In some examples, Compound **(1)** is administered at a dose of about 50 mg or the pharmaceutically acceptable salt of Compound **(1)** is administered at a dose equivalent to about 50 mg of the free base compound. In some examples, Compound **(1)** is administered

at a dose of about 40 mg or the pharmaceutically acceptable salt of Compound **(1)** is administered at a dose equivalent to about 40 mg of the free base compound.

[0041] In some examples, Compound **(1),** or the pharmaceutically acceptable salt of Compound **(1),** is administered orally, parenterally, intradermally, intrathecally, intramuscularly, subcutaneously, vaginally, as a buccal, sublingually, rectally, topically, as an inhalation, intranasaly, or transdermally. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is administered orally. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is administered with food. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is administered once a day at night.

[0042] In some examples, the subject is treatment naïve.

BRIEF DESCRIPTION OF THE DRAWINGS

[0043] **FIG. 1** is an overview of the clinical study of Example 1.

[0044] **FIG. 2** is a depiction of the eligibility criteria for clinical study of Example 1.

[0045] **FIG. 3** is a flow chart of the dosing cohorts.

[0046] **FIG. 4A** is an overview of the flow of subjects (30 mg Cohort).

[0047] **FIG. 4B** is an overview of the flow of subjects (50 mg Cohort).

[0048] **FIG. 5** shows HAM-D total score LS mean change from baseline over time for 30 mg and 50 mg Cohorts. .

[0049] **FIG. 6A** is a bar graph of the HAMD-17 response at specific time points for 30 mg and 50 mg Cohorts.

[0050] **FIG. 6B** is a bar graph of the HAMD-17 remission at specific time points for 30 mg and 50 mg Cohorts.

[0051] **FIG. 7** is a bar graph of the change in HAM-D total score over time – Study Period 1 (safety set).

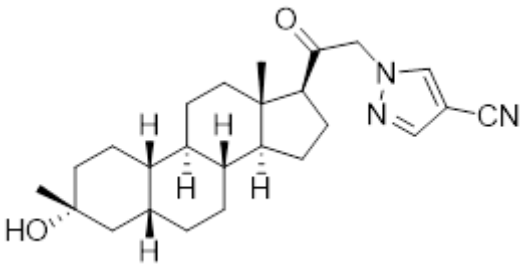
[0052] **FIG. 8** is a box plot of change from period-specific baseline in HAM-D total score at Day 15 for in each treatment cycle, by antidepressant use (yes/no) at period-specific baseline – Low Dose Cohort (safety set for cycle 1, full analysis set for C2-5).

[0053] **FIG. 9** shows box plots of change from baseline HAM-D total score at Day 15 in each treatment cycle (safety set for Treatment Cycle 1, FAS for C2-C5).

[0054] **FIG. 10** is a box plot of change from period-specific baseline in HAM-D total score at Day 15 for in each treatment cycle, by antidepressant use (yes/no) at period-specific baseline – Low Dose Cohort (safety set for Treatment Cycle 1, FAS for C2-C5).

WE CLAIM:

1. Use of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**;

in the manufacture of a medicament for treating major depressive disorder (MDD) in a subject in need thereof, wherein:

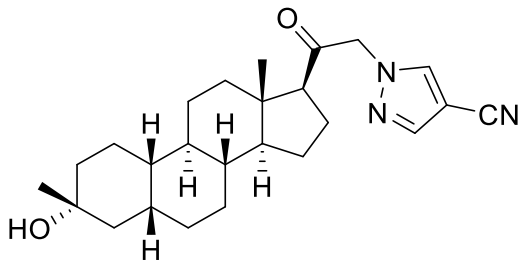
(i) Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject as part of an initial treatment; and

(ii) 0, 1, or 2 subsequent treatment courses is to be performed on the subject, wherein for each subsequent treatment course, the Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are to be performed over a period of 12 months from the beginning of the initial treatment course.

2. The use of claim 1, wherein the subject has been on a stable dose of an additional antidepressant for at least 60 days prior to the beginning of the initial treatment course.

3. Use of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**;

in the manufacture of a medicament for treating major depressive disorder (MDD) in a subject in need thereof, wherein:

(i) Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject as part of an initial treatment; and

(ii) 0, 1, or 2 subsequent treatment courses is to be performed on the subject, wherein for each subsequent treatment course, the Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are to be performed over a period of 12 months from the beginning of the initial treatment course, and

wherein the subject is treatment naïve.

4. The use of any one of claims 1-3, wherein

(A) there is at least about a 4 week, at least about a 6 week, or at least about an 8 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course; or

(B) there is about a 4 week, about a 6 week, or about an 8 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course.

5. The use of any one of claims 1-4, wherein

(A) the initial treatment course has a duration of about 2 weeks or about 14 days; and/or

(B) each subsequent treatment course has a duration of about 2 weeks or about 14 days.

6. The use of any one of claims 1-5, wherein

(A) Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered once a day for about 14 days in the initial treatment course; and/or

(B) Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered once a day for about 14 days in each subsequent treatment course.

7. The use of any one of claims 1-6, wherein Compound **(1)** is to be administered at a dose of about 20 mg to about 55 mg, or the pharmaceutically acceptable salt of Compound **(1)** is to be administered at a dose equivalent to about 20 mg to about 55 mg of the free base compound.

8. The use of any one of claims 1-7, wherein Compound **(1)** is in a crystalline form having

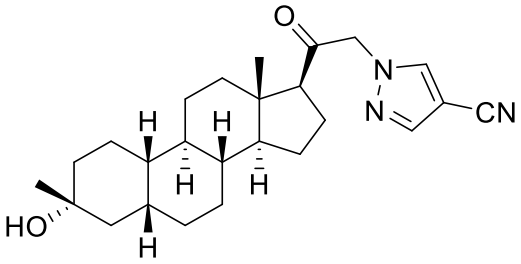
(A) an XRPD pattern comprising peaks between and including 9.7 to 10.1 degrees in 2θ, between and including 11.6 to 12.0 degrees in 2θ, between and including 13.2 to 13.6 degrees in 2θ, between and including 14.2 to 14.6 degrees in 2θ, between and including 14.6 to 15.0 degrees in 2θ, between and including 16.8 to 17.2 degrees in 2θ, between and including 20.5 to 20.9 degrees in 2θ, between and including 21.3 to 21.7 degrees in 2θ, between and including 21.4 to 21.8 degrees in 2θ, and between and including 22.4 to 22.8 degrees in 2θ;

(B) an XRPD pattern comprising peaks between and including 9.3 to 9.7 degrees in 2θ, between and including 10.6 to 11.0 degrees in 2θ, between and including 13.0 to 13.4 degrees in 2θ, between and including 14.7 to 15.1 degrees in 2θ, between and including 15.8 to 16.2 degrees in 2θ, between and including 18.1 to 18.5 degrees in 2θ, between and including 18.7 to 19.1 degrees in 2θ, between and including 20.9 to 21.3 degrees in 2θ, between and including 21.4 to 21.8 degrees in 2θ, and between and including 23.3 to 23.7 degrees in 2θ;

(C) an XRPD pattern comprising peaks between and including 9.7 to 10.1 degrees in 2θ, between and including 14.6 to 15.0 degrees in 2θ, between and including 16.8 to 17.2 degrees in 2θ, between and including 20.5 to 20.9 degrees in 2θ, and between and including 21.3 to 21.7 degrees in 2θ; or

(D) an XRPD pattern comprising peaks between and including 9.3 to 9.7 degrees in 2θ, between and including 10.6 to 11.0 degrees in 2θ, between and including 13.0 to 13.4 degrees in 2θ, between and including 18.7 to 19.1 degrees in 2θ, and between and including 21.4 to 21.8 degrees in 2θ.

9. Use of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**;

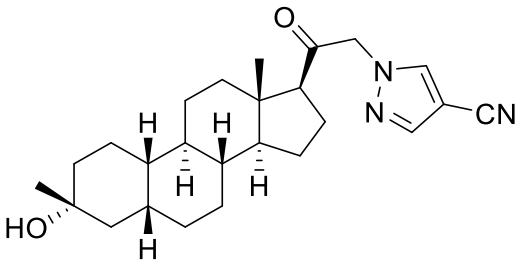
in the manufacture of a medicament for treating major depressive disorder (MDD) in a subject in need thereof, wherein:

(i) about 30 mg to about 50 mg of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject as part of an initial treatment; and

(ii) 0, 1, or 2 subsequent treatment courses is to be performed on the subject, wherein for each subsequent treatment course, about 30 mg to about 50 mg of Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are to be performed over a period of 12 months from the beginning of the initial treatment course.

10. Use of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**;

in the manufacture of a medicament for treating major depressive disorder (MDD) in a subject in need thereof, wherein:

(i) about 30 mg to about 50 mg of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**, is to be administered once a day for about 14 days to the subject as part of an initial treatment; and

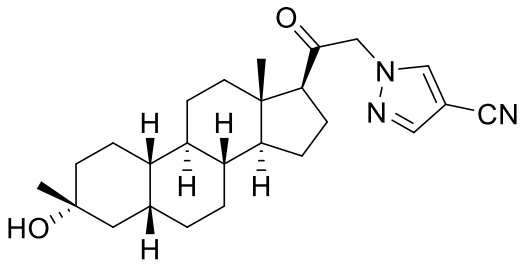
(ii) 0, 1, or 2 subsequent treatment courses is to be performed on the subject, wherein for each subsequent treatment course, about 30 mg to about 50 mg of Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered once a day for about 14 days to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are to be performed over a period of 12 months from the beginning of the initial treatment course;

optionally, wherein there is at least about a 6 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course; or

optionally, wherein the subject has been on a stable dose of an additional antidepressant for at least 60 days.

11. Use of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**;

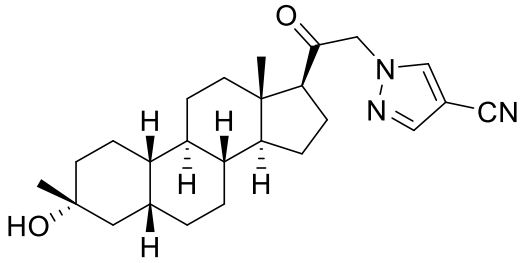
in the manufacture of a medicament for treating major depressive disorder (MDD) in a subject in need thereof, wherein:

(i) about 45 mg to about 55 mg of Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered once a day for about 14 days to the subject as part of an initial treatment; and

(ii) 0, 1, or 2 subsequent treatment courses is to be performed on the subject, wherein for each subsequent treatment course, about 45 mg to about 55 mg of Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are to be performed over a period of 12 months from the beginning of the initial treatment course.

12. Use of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)** once a day for about 14 days:



Compound **(1)**;

in the manufacture of a medicament for treating major depressive disorder (MDD) in a subject in need thereof, wherein:

(i) about 45 mg to about 55 mg of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)**, is to be administered once a day for about 14 days to the subject as part of an initial treatment; and

(ii) 0, 1, or 2 subsequent treatment courses is to be performed on the subject, wherein for each subsequent treatment course, about 45 mg to about 55 mg of Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered once a day for about 14 days to the subject in response to a recurrence of depression symptoms,

wherein the 0, 1, or 2 subsequent treatment courses are to be performed over a period of 12 months from the beginning of the initial treatment course;

optionally, wherein there is at least about a 6 week interval between the end of the initial treatment course and the beginning of the subsequent treatment course.

13. The use of any one of claims 1-12, wherein 0 or 1 subsequent treatment courses are to be performed; or wherein 1 subsequent treatment course is to be performed.

14. The use of any one of claims 1-13, wherein the recurrence of depression symptoms is indicated by an evaluation of the subject using the Hamilton Rating Scale for Depression (HAM-D), Montgomery – Asberg Depression Rating Scale (MADRS), the Patient Health Questionnaire (PHQ-9), or a combination thereof;

optionally, wherein the recurrence of depression symptoms in the subject is indicated by a PHQ-9 score greater than or equal to 10 or a HAM-D score greater than or equal to 20.

15. The use of any one of claims 1-14, wherein Compound **(1)** is to be administered at a dose of about 50 mg or the pharmaceutically acceptable salt of Compound **(1)** is to be administered at a dose equivalent to about 50 mg of the free base compound.

16. The use of any one of claims 1-14, wherein Compound **(1)** is to be administered at a dose of about 40 mg or the pharmaceutically acceptable salt of Compound **(1)** is to be administered at a dose equivalent to about 40 mg of the free base compound.

17. The use of any one of claims 1-16, wherein Compound **(1),** or the pharmaceutically acceptable salt of Compound **(1)**, is to be administered

(A) orally, parenterally, intradermally, intrathecally, intramuscularly, subcutaneously, vaginally, as a buccal, sublingually, rectally, topically, as an inhalation, intranasaly, or transdermally; optionally, wherein the administration is orally;

(B) with food; and/or

(C) once a day at night.

18. The use of any one of claims 1-2 or 4-17, wherein the subject is treatment naïve.