

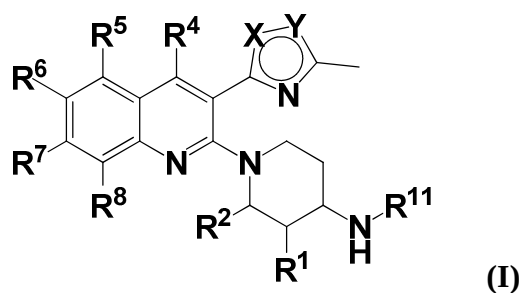
which avoid the drawbacks associated with the prototypical KOR antagonists discussed above. Other studies have shown that KOR antagonists may be particularly useful for the treatment of stress-mediated symptoms, as well as for treating social anxiety disorder and phobias. Prophylactic therapy has also been suggested to prevent adverse conditions arising from stress, and in this regard KOR antagonism has been proposed as a preventative treatment of PTSD in individuals at risk of the same. Other therapeutic applications of KOR antagonism include the treatment of impairment in reward-related function as it frequently occurs in patients with mood and anxiety spectrum disorders, and which may also occur with other types of conditions such as schizophrenia or a schizoaffective disorder.

In summary, KOR antagonism provides significant promise for the treatment of a wide variety of disorders and conditions. As a result, a number of compounds are currently in development that are highly selective and potent KOR antagonists for treating a variety of conditions, such as substance use disorders, major depression, anhedonia, and stress-related symptoms. However, and despite the advances made in this field, there remains a need for new and improved KOR antagonists, as well as for pharmaceutical products containing the same, and for methods related to their use and manufacture.

SUMMARY

The present disclosure is directed to compounds that antagonize the kappa opioid receptor (KOR), to compositions containing the same, and to methods of their preparation and use for treatment of a disease or condition wherein antagonism of a KOR is medically indicated or beneficial.

In one aspect, there is provided A compound having the structure of Formula (I) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



wherein

X is O when Y is N or X is N when Y is O;

R¹ is H or F;

5 R² is H or lower alkyl;

R⁴ and R⁸ are each independently H, lower alkyl, halo, or cyano;

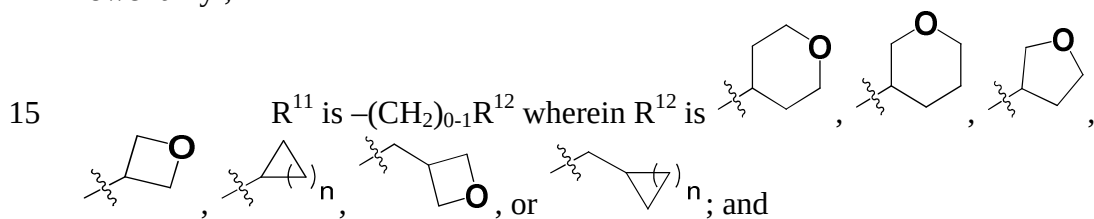
R⁵ and R⁷ are each independently H, halo, or cyano;

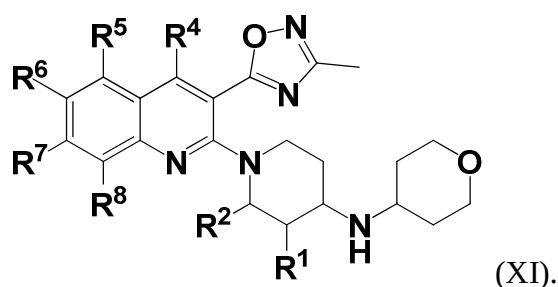
wherein

at least one of R⁵ and R⁷ is H, and

10 when R² is H, at least one of R⁴ and R⁸ is not H or when R², R⁴, and R⁸ are H, R⁷ is not H;

R⁶ is lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, lower alkynyl, cycloalkyl, halo or cyano, wherein R⁶ is not lower alkyl when R⁸ is lower alkyl;





wherein

R^1 is H, F, or lower alkyl;

R^2 is H or lower alkyl;

5 R^4 and R^8 are each independently H, lower alkyl, halo, or cyano;

R^5 and R^7 are each independently H, halo, or cyano;

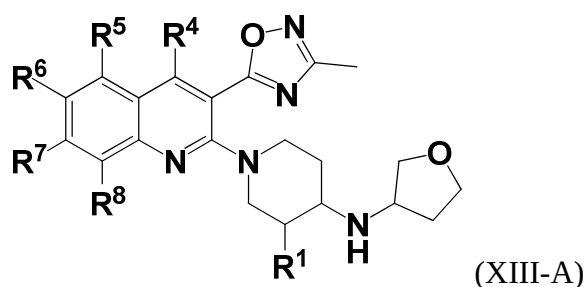
wherein

at least one of R^5 and R^7 is H, and

(i) when R^2 is H, at least one of R^4 and R^8 is lower alkyl,
 10 halo, or cyano or (ii) when R^2 , R^4 , and R^8 are H, R^7 is halo or cyano; and

R^6 is lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, cycloalkoxy, lower alkynyl, cycloalkyl, halo or cyano, wherein R^6 is not lower alkyl when R^8 is lower alkyl.

In another aspect, there is provided a compound having the structure of
 15 Formula (XIII-A) or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotove, or salt thereof:



wherein

R^1 is H, F, or lower alkyl;

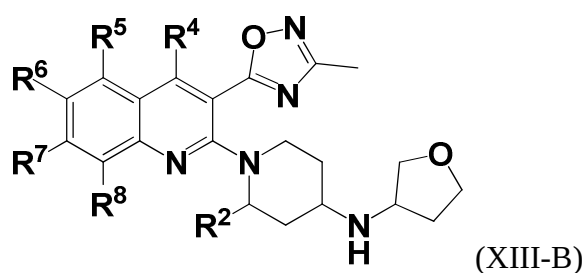
20 R^4 and R^8 are each independently H, lower alkyl, halo, or cyano;

R⁵ and R⁷ are each independently H, halo, or cyano;

wherein when R⁴ and R⁸ are H, R⁷ is halo or cyano; and

R⁶ is lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, cycloalkoxy, lower alkynyl, cycloalkyl, halo, or cyano.

- 5 In another aspect, there is provided a compound having the structure of Formula (XIII-B) or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotove, or salt thereof:



wherein

- 10 R² is lower alkyl;
R⁴ and R⁸ are each independently H, lower alkyl, halo, or cyano;
R⁵ and R⁷ are each independently H, halo, or cyano;
R⁶ is lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, cycloalkoxy, lower alkynyl, cycloalkyl, halo or cyano.

- 15 In another aspect, there is provided a composition comprising a compound of the present invention, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

- 20 In another aspect, there is provided a method for antagonizing the KOR, comprising contacting the KOR with an effective amount of a compound the present invention, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a composition comprising the same.

- 25 In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the

same, in the manufacture of a medicament for reducing serum prolactin levels, wherein the medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

In another aspect, there is provided use of an effective amount of a
5 compound of the present invention, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating a neuropsychiatric or behavioral condition, whether organic, stress-induced or iatrogenic, that is characterized by elevations in serum prolactin, wherein the medicament is to be administered to a subject
10 in need thereof at a frequency and for a duration sufficient to provide a beneficial effect to the subject.

In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the
15 same, in the manufacture of a medicament for treating disorders related to substance abuse or addiction, wherein the medicament is to be administered to a subject in need thereof at a frequency and for a duration sufficient to provide a beneficial effect to the subject.

In another aspect, there is provided use of an effective amount of a
20 compound of the present invention, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating a CNS-related disorder, wherein the medicament is to be administered to a subject in need thereof at a frequency and for a duration sufficient to provide a beneficial effect to the subject.

25 In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating an anxiety disorder, wherein the medicament is to be administered to a subject in need thereof at a frequency and for
30 duration sufficient to provide a beneficial effect to the subject.

In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating a depressive disorder, wherein
5 the medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

In another aspect, there is provided use of a compound of the present invention, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the
10 manufacture of a medicament for treating a mood disorder, wherein the medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable isomer, racemate,
15 hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating a schizophrenia or a schizoaffective disorder, wherein the medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

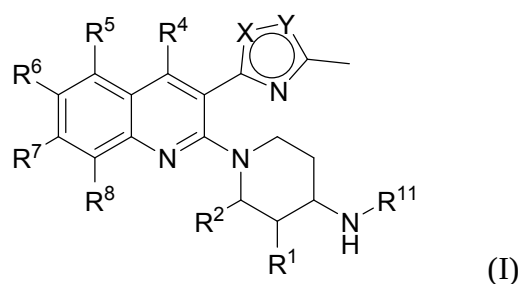
20 In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating obesity or an eating disorder, wherein the medicament is to be administered to a subject in need thereof at a
25 frequency and for duration sufficient to provide a beneficial effect to the subject.

In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating migraine, wherein the

medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating postnatal depression, wherein the medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

In an example, compounds are provided having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof:



wherein X, Y, R¹, R², R⁴, R⁵, R⁶, R⁷, R⁸ and R¹¹ are as defined below.

In an example, a pharmaceutical composition is provided comprising a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

In an example, use of a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, for the manufacture of a medicament is provided.

In an example, a method is provided for antagonizing the KOR, the method comprising contacting the receptor with an effective amount of a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same.

In an example, a method is provided for treatment of a neuropsychiatric or behavioral condition, whether organic, stress-induced or iatrogenic, that is characterized by elevations in serum prolactin and respond to KOR antagonist administration with a reduction in serum prolactin. Such method comprises administering to the subject an effective amount of a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, at a frequency and for duration sufficient to provide a beneficial effect to the subject.

In an example, a method is provided for treatment of a malcondition in a subject for which antagonism of the KOR is medically indicated. Such method comprises administering to the subject an effective amount of a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate,

solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, at a frequency and for duration sufficient to provide a beneficial effect to the subject.

In an example, a method is provided for treatment of an addictive disorder, including disorders related to substance abuse or addiction, comprising
5 administering to a subject in need thereof an effective amount of a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, at a frequency and for a duration sufficient to provide a beneficial effect to the subject.

10 In an example, a method is provided for treatment of central nervous system (CNS)-related disorder, comprising administering to a subject in need thereof an effective amount of a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, at a frequency and for a duration
15 sufficient to provide a beneficial effect to the subject.

In an example, a method is provided for treatment of an anxiety disorder, comprising administering to a subject in need thereof an effective amount of a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition
20 comprising the same, at a frequency and for a duration sufficient to provide a beneficial effect to the subject. In one example, the anxiety disorder is a social anxiety disorder. In one example, the anxiety disorder is a generalized anxiety disorder (GAD). In one embodiment, the anxiety disorder is phobia. In one example, the anxiety disorder is a stress-related disorder.

25 In an example, a method is provided for treatment of a depressive disorder, depression, or depressive illness, comprising administering to a subject in need thereof an effective amount of a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, at a frequency and for

duration sufficient to provide a beneficial effect to the subject. In one example, the depressive disorder is major depression.

In an example, a method is provided for treatment of a mood disorder, comprising administering to a subject in need thereof an effective amount of a
5 compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, at a frequency and for duration sufficient to provide a beneficial effect to the subject. In one example, the mood disorder is anhedonia. In one example, the mood disorder is major depression.

10 In an example, a method is provided for treatment of a schizophrenia or a schizoaffective disorder, comprising administering to a subject in need thereof an effective amount of a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, at a frequency and for duration
15 sufficient to provide a beneficial effect to the subject.

In an example, a method is provided for treatment of obesity or an eating disorder, comprising administering to a subject in need thereof an effective amount of a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition
20 comprising the same, at a frequency and for duration sufficient to provide a beneficial effect to the subject.

In an example, a method is provided for treatment of migraine, comprising administering to a subject in need thereof an effective amount of a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer,
25 racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, at a frequency and for duration sufficient to provide a beneficial effect to the subject.

In an example, a method is provided for treatment of postnatal depression, comprising administering to a subject in need thereof an effective amount
30 of a compound having the structure of Formula (I), or a pharmaceutically acceptable

isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, at a frequency and for a duration sufficient to provide a beneficial effect to the subject.

In an example, a method is provided for treatment of disorders of mood
5 and behavior associated with neurodegenerative diseases, comprising administering to a subject in need thereof an effective amount of a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, at a frequency and for a duration sufficient to provide a beneficial effect to the subject.

10 In an example, a method of synthesis is provided for a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof.

In an example, a pharmaceutical composition is provided comprising a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer,
15 racemate, hydrate, solvate, isotope or salt thereof, in combination with at least one pharmaceutically acceptable carrier, diluent or excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the activity of a representative compound, Compound 142, to serve as an antagonist in an OPRK1 agonist-induced prolactin challenge to 8-10
20 week old male C57BL/6J mice following IP dosing (Figure 1A) and PO dosing (Figure 1B).

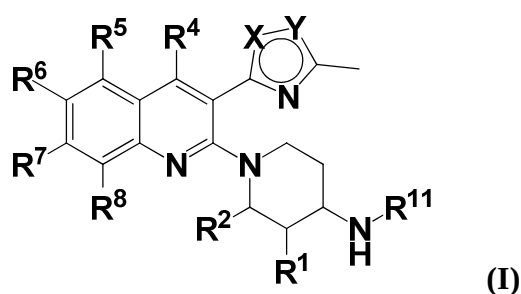
Figure 2 illustrates the activity of a representative compound, Compound 141, to serve as an antagonist in an OPRK1 agonist-induced prolactin challenge to 8-10-week-old male C57BL/6J mice following IP dosing (Figure 2A) and PO dosing
25 (Figure 2B).

Figure 3 illustrates the activity of a representative compound, Compound 145, to serve as an antagonist in an OPRK1 agonist-induced prolactin challenge to 8-

CLAIMS

We claim:

1. A compound having the structure of Formula (I) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



wherein

X is O when Y is N or X is N when Y is O;

R¹ is H or F;

R² is H or lower alkyl;

R⁴ and R⁸ are each independently H, lower alkyl, halo, or cyano;

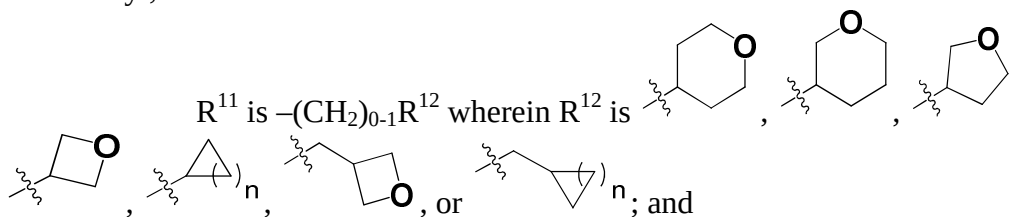
R⁵ and R⁷ are each independently H, halo, or cyano;

wherein

at least one of R⁵ and R⁷ is H, and

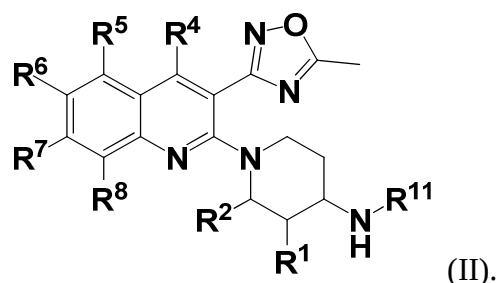
when R² is H, at least one of R⁴ and R⁸ is not H or when R², R⁴, and R⁸ are H, R⁷ is not H;

R⁶ is lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, lower alkynyl, cycloalkyl, halo or cyano, wherein R⁶ is not lower alkyl when R⁸ is lower alkyl;

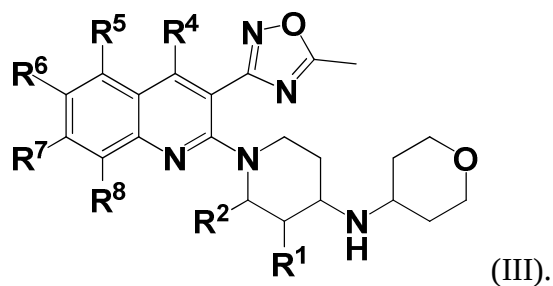


n is an integer from 1-5.

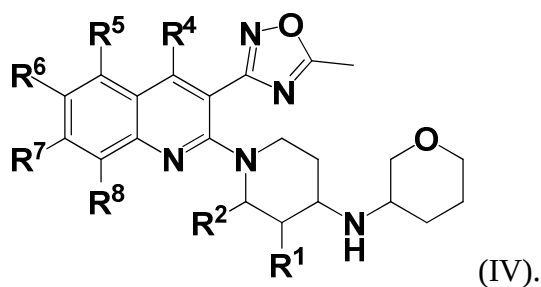
2. The compound of claim 1 having the structure of Formula (II) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



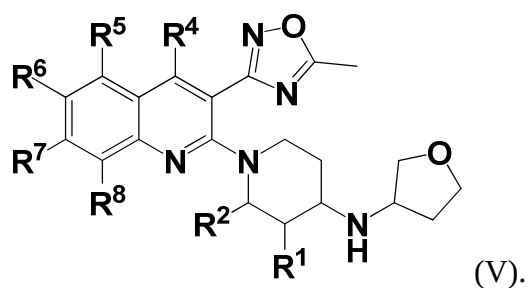
3. The compound of claim 1 having the structure of Formula (III) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



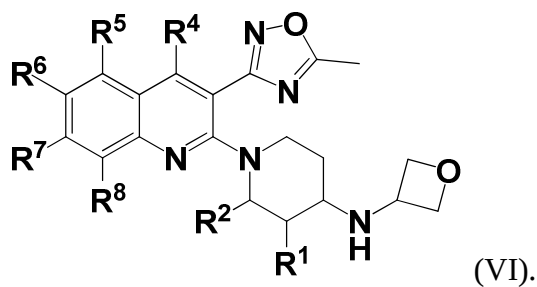
4. The compound of claim 1 having the structure of Formula (IV) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



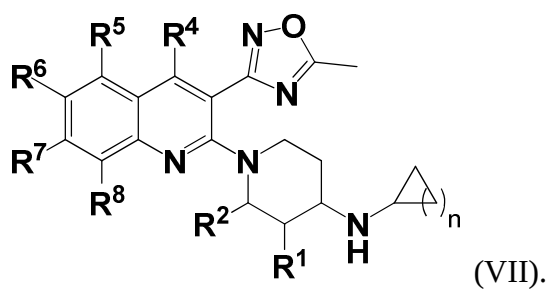
5. The compound of claim 1 having the structure of Formula (V) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



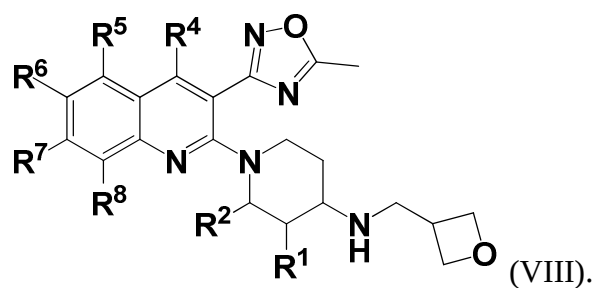
6. The compound of claim 1 having the structure of Formula (VI) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



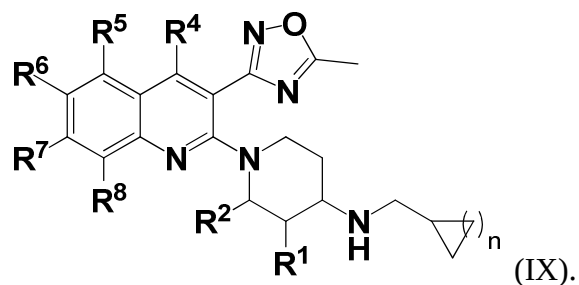
7. The compound of claim 1 having the structure of Formula (VII) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



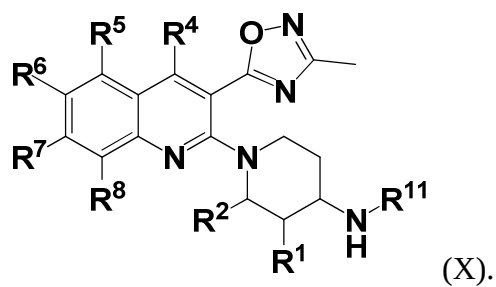
8. The compound of claim 1 having the structure of Formula (VIII) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



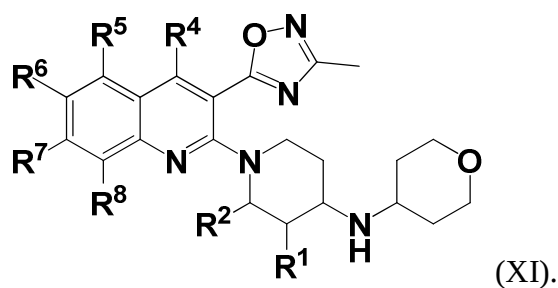
9. The compound of claim 1 having the structure of Formula (IX) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



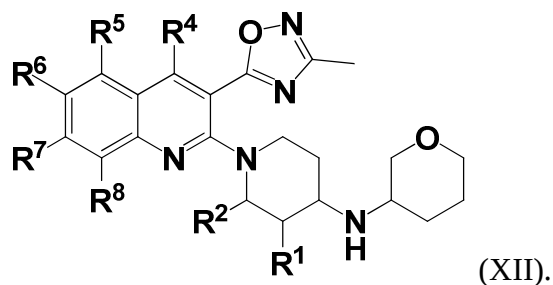
10. The compound of claim 1 having the structure of Formula (X) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



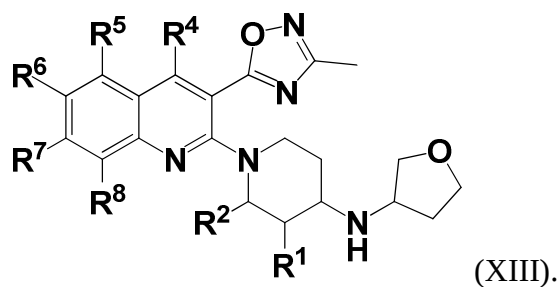
11. The compound of claim 1 having the structure of Formula (XI) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



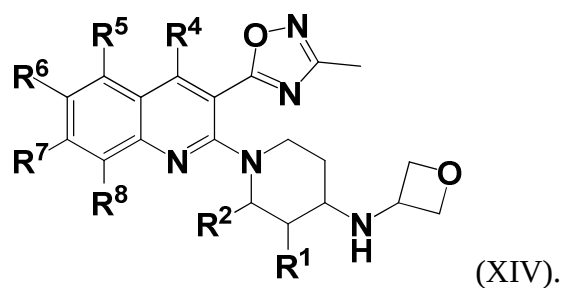
12. The compound of claim 1 having the structure of Formula (XII) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



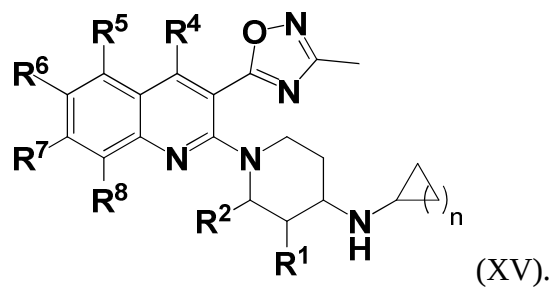
13. The compound of claim 1 having the structure of Formula (XIII) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



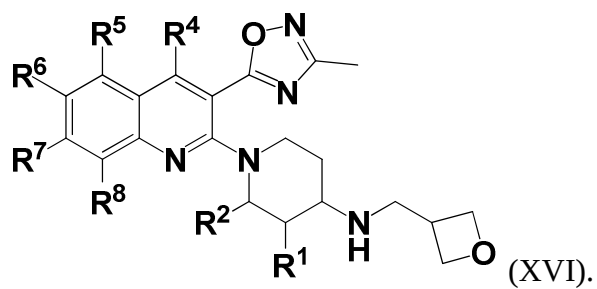
14. The compound of claim 1 having the structure of Formula (XIV) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



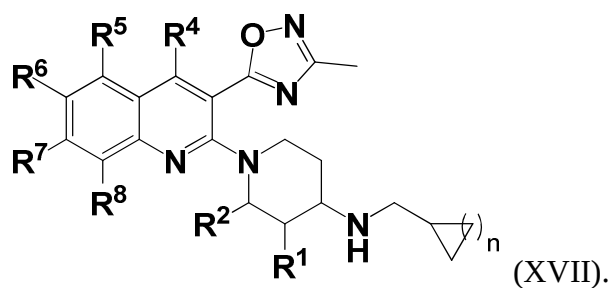
15. The compound of claim 1 having the structure of Formula (XV) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



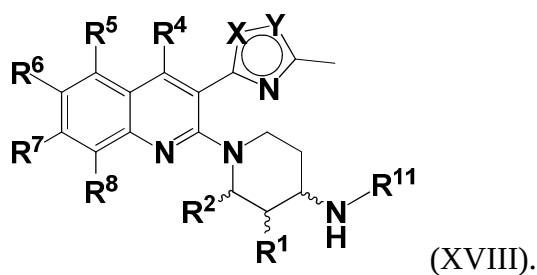
16. The compound of claim 1 having the structure of Formula (XVI) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



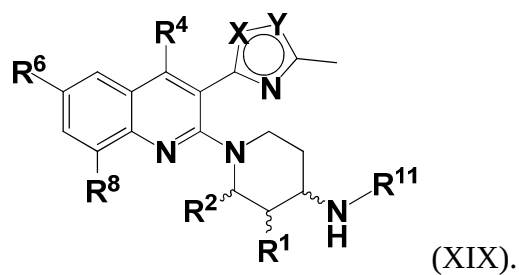
17. The compound of claim 1 having the structure of Formula (XVII) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



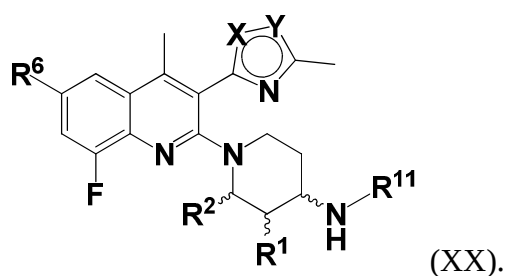
18. The compound of claim 1 having the structure of Formula (XVIII) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



19. The compound of claim 1 having the structure of Formula (XIX) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:

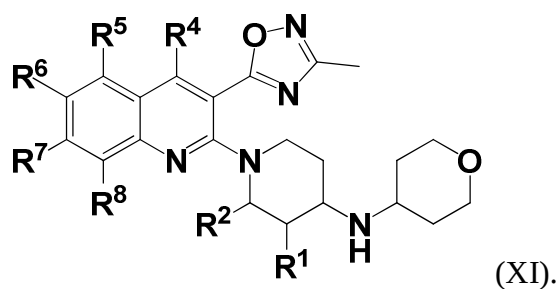


20. The compound of claim 1 having the structure of Formula (XX) or a pharmaceutically acceptable isomer, racemate, hydrate or solvate, isotope or salt thereof:



21. A compound having the structure of a compound of Table 1, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof.

22. A compound having the structure of Formula (XI) or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof:



wherein

R^1 is H, F, or lower alkyl;

R^2 is H or lower alkyl;

R^4 and R^8 are each independently H, lower alkyl, halo, or cyano;

R^5 and R^7 are each independently H, halo, or cyano;

wherein

at least one of R^5 and R^7 is H, and

(i) when R^2 is H, at least one of R^4 and R^8 is lower alkyl, halo, or cyano or (ii) when R^2 , R^4 , and R^8 are H, R^7 is halo or cyano; and

R^6 is lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, cycloalkoxy, lower alkynyl, cycloalkyl, halo or cyano, wherein R^6 is not lower alkyl when R^8 is lower alkyl.

23. The compound of claim 22 having the structure:

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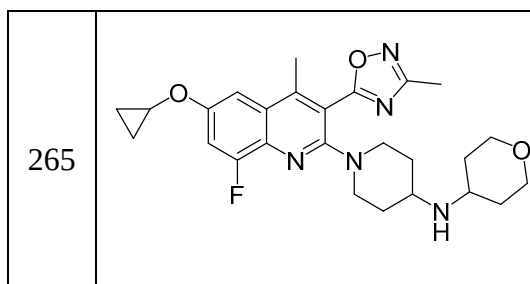
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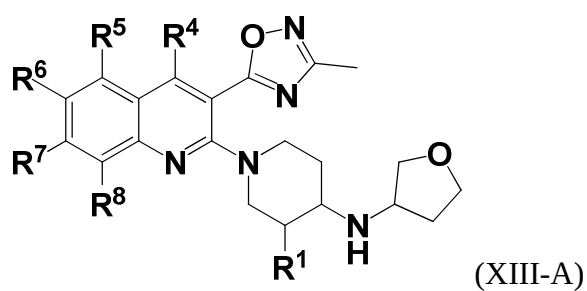
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24. A compound having the structure of Formula (XIII-A) or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotove, or salt thereof:



wherein

R^1 is H, F, or lower alkyl;

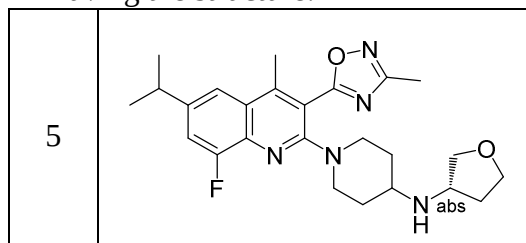
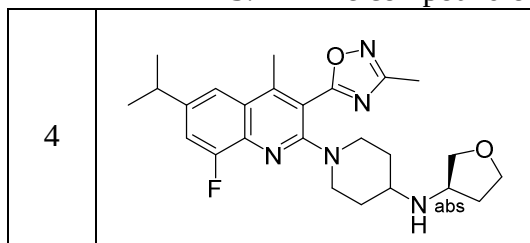
R^4 and R^8 are each independently H, lower alkyl, halo, or cyano;

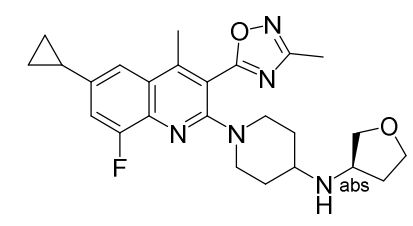
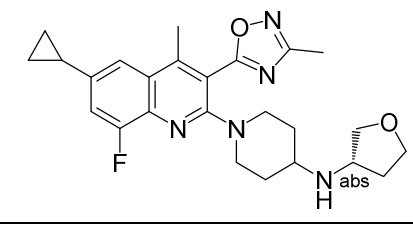
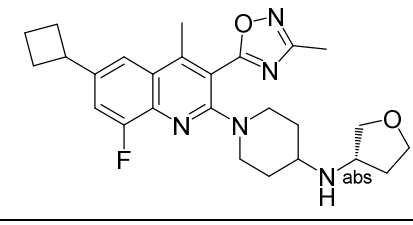
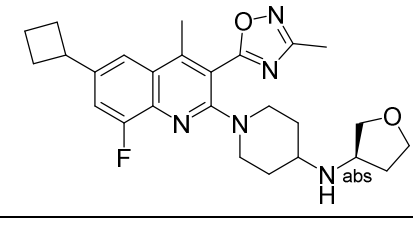
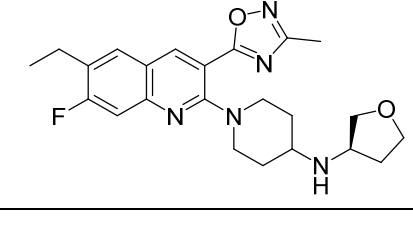
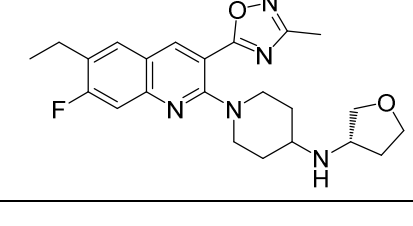
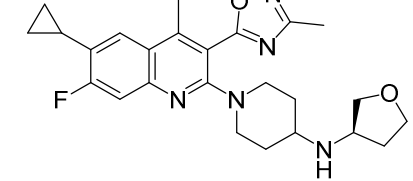
R^5 and R^7 are each independently H, halo, or cyano;

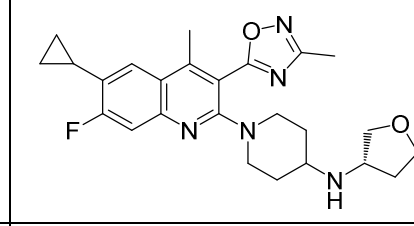
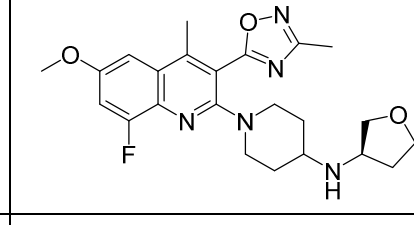
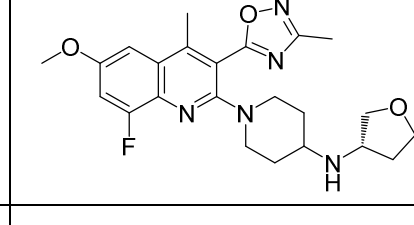
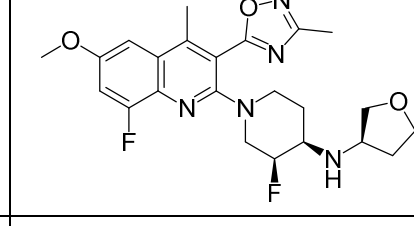
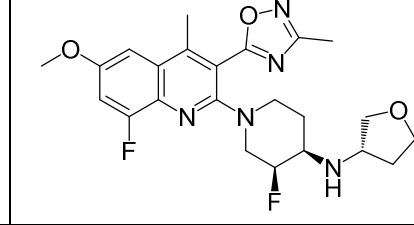
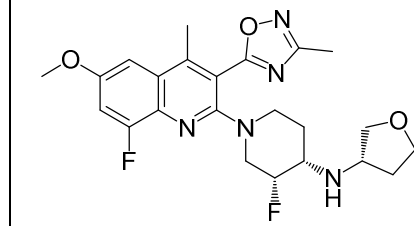
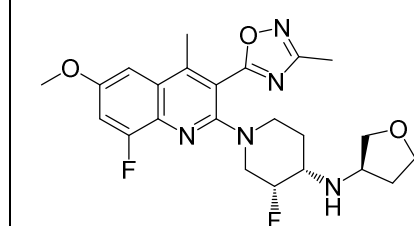
wherein when R^4 and R^8 are H, R^7 is halo or cyano; and

R^6 is lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, cycloalkoxy, lower alkynyl, cycloalkyl, halo, or cyano.

25. The compound of claim 24 having the structure:



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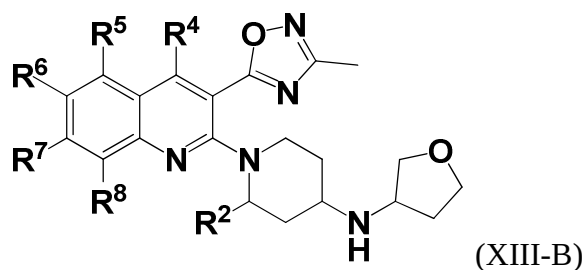
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26. A compound having the structure of Formula (XIII-B) or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotove, or salt thereof:



wherein

R^2 is lower alkyl;

R^4 and R^8 are each independently H, lower alkyl, halo, or cyano;

R^5 and R^7 are each independently H, halo, or cyano;

R^6 is lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, cycloalkoxy, lower alkynyl, cycloalkyl, halo or cyano.

27. The compound of claim 26 having the structure:

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219 a	
219 b	
220 a	
220 b	
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236 a	
236 b	
237 a	
237 b	
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28. A composition comprising a compound of any one of claims 1, 21, 22, 24 and 26, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

29. A method for antagonizing the KOR, comprising contacting the KOR with an effective amount of a compound of any one of claims 1, 21, 22, 24 and 26, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a composition comprising the same.

30. Use of an effective amount of a compound of any one of claims 1, 21, 22, 24 and 26, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for reducing serum prolactin levels, wherein the medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

31. Use of an effective amount of a compound of any one of claims 1, 21, 22, 24 and 26, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating a neuropsychiatric or behavioral condition, whether organic, stress-induced or iatrogenic, that is characterized by elevations in serum prolactin, wherein the medicament is to be administered to a subject in need thereof at a frequency and for a duration sufficient to provide a beneficial effect to the subject.

32. Use of an effective amount of a compound of any one of claims 1, 21, 22, 24 and 26, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating disorders related to substance abuse or addiction, wherein the medicament is to be administered to a subject in need thereof at a frequency and for a duration sufficient to provide a beneficial effect to the subject.

33. Use of an effective amount of a compound of any one of claims 1, 21, 22, 24 and 26, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating a CNS-related disorder, wherein the medicament is to be administered to a subject in need thereof at a frequency and for a duration sufficient to provide a beneficial effect to the subject.

34. Use of an effective amount of a compound of any one of claims 1, 21, 22, 24 and 26, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same,

in the manufacture of a medicament for treating an anxiety disorder, wherein the medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

35. Use of an effective amount of a compound of any one of claims 1, 21, 22, 24 and 25, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating a depressive disorder, wherein the medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

36. Use of a compound of any one of claims 1, 21, 22, 24 and 26, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating a mood disorder, wherein the medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

37. Use of an effective amount of a compound of any one of claims 1, 21, 22, 24 and 26, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating a schizophrenia or a schizoaffective disorder, wherein the medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

38. Use of an effective amount of a compound of any one of claims 1, 21, 22, 24 and 26, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating obesity or an eating disorder, wherein the medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

39. Use of an effective amount of a compound of any one of claims 1, 21, 22, 24 and 26, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating migraine, wherein the medicament is to

be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.

40. Use of an effective amount of a compound of any one of claims 1, 21, 22, 24 and 26, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating postnatal depression, wherein the medicament is to be administered to a subject in need thereof at a frequency and for duration sufficient to provide a beneficial effect to the subject.