

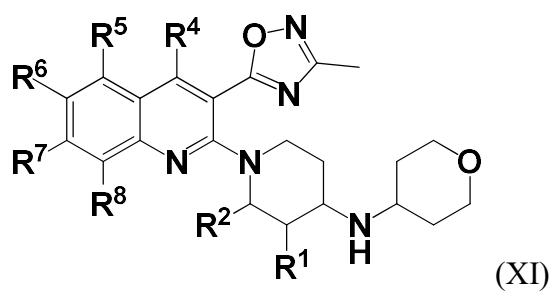
which avoid the drawbacks associated with the prototypical KOR antagonists discussed above. Other studies have shown that KOR antagonists may be particularly useful for the treatment of stress-mediated symptoms, as well as for treating social anxiety disorder and phobias. Prophylactic therapy has also 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 (XI) or a pharmaceutically acceptable stereoisomer, racemate, hydrate or solvate, isotope or salt thereof:

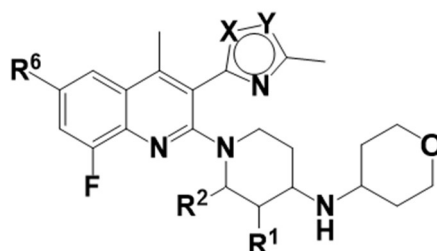


wherein

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R^1 is H, F, or lower alkyl;
 R^2 is H or lower alkyl;
 R^4 is lower alkyl;
 R^5 and R^7 are both H;
 R^6 is lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, cycloalkoxy, lower alkynyl, cycloalkyl, halo or cyano; and
 R^8 is halo or cyano.

In another aspect, there is provided a compound having the following structure, or a pharmaceutically acceptable stereoisomer, racemate, hydrate, solvate, isotope, or salt thereof:



5 wherein

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

R¹ is H, F, or lower alkyl;

R² is H or lower alkyl; and

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

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

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

In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable stereoisomer, racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating a
5 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.

In another aspect, there is provided use of an effective amount of a
10 compound of the present invention, or a pharmaceutically acceptable stereoisomer, 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
15 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 stereoisomer, 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
20 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.

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

In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable stereoisomer, 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.

In another aspect, there is provided use of a compound of the present invention, or a pharmaceutically acceptable stereoisomer, 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.

In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable stereoisomer, 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.

In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable stereoisomer, 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.

In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable stereoisomer, 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.

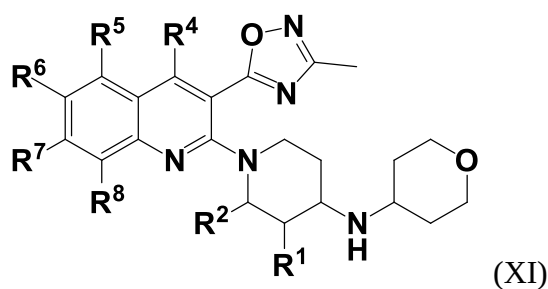
In another aspect, there is provided use of an effective amount of a compound of the present invention, or a pharmaceutically acceptable stereoisomer, 5 racemate, hydrate, solvate, isotope or salt thereof, or a pharmaceutical composition comprising the same, in the manufacture of a medicament for treating 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 10 (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof:

CLAIMS

We claim:

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



wherein

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

R^2 is H or lower alkyl;

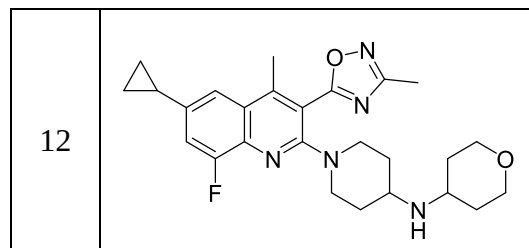
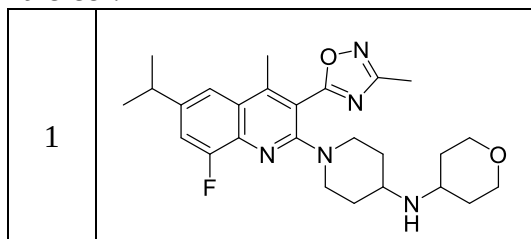
R^4 is lower alkyl;

R^5 and R^7 are both H;

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

R^8 is halo or cyano.

2. The compound of claim 1, wherein the compound having the structure of Formula (XI) is a compound having one of the following structures, or a pharmaceutically acceptable stereoisomer, racemate, hydrate, solvate, isotope, or salt thereof:



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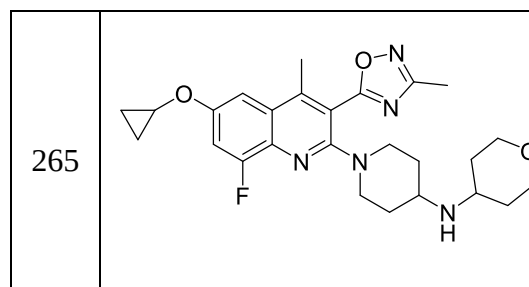
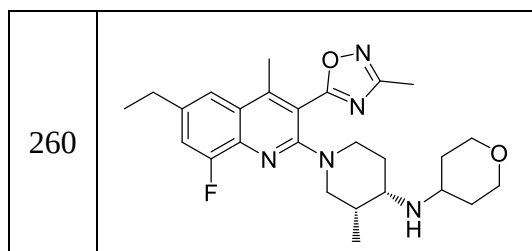
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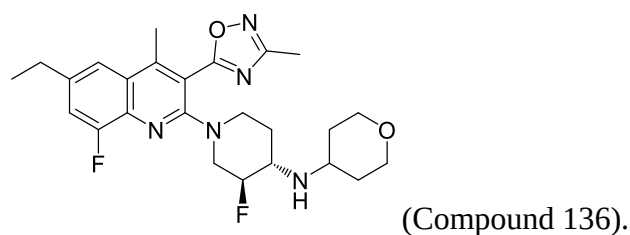
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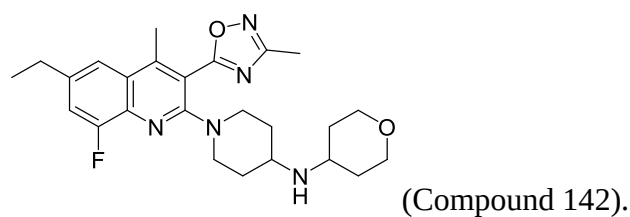
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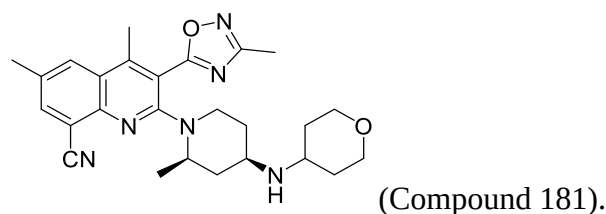
3. The compound of claim 2, wherein the compound having the structure of Formula (XI) is Compound 136, or a pharmaceutically acceptable stereoisomer, racemate, hydrate, solvate, isotope, or salt thereof:



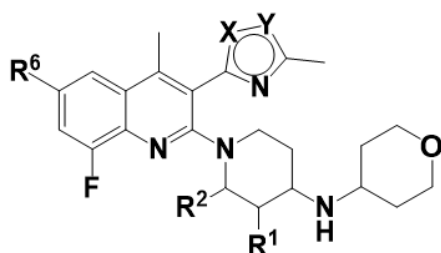
4. The compound of claim 2, wherein the compound having the structure of Formula (XI) is Compound 142, or a pharmaceutically acceptable stereoisomer, racemate, hydrate, solvate, isotope, or salt thereof:



5. The compound of claim 2, wherein the compound having the structure of Formula (XI) is Compound 181, or a pharmaceutically acceptable stereoisomer, racemate, hydrate, solvate, isotope, or salt thereof:



6. A compound having the following structure, or a pharmaceutically acceptable stereoisomer, racemate, hydrate, solvate, isotope, or salt thereof:



wherein

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

R¹ is H, F, or lower alkyl;

R² is H or lower alkyl; and

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

7. A composition comprising a compound of any one of claims 1-6, or a pharmaceutically acceptable stereoisomer, racemate, hydrate, solvate, isotope or salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

8. An *in vitro* method for antagonizing the KOR, comprising contacting the KOR with an effective amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable stereoisomer, racemate, hydrate, solvate, isotope or salt thereof, or a composition comprising the same.

9. Use of an effective amount of a compound of any one of claims 1- 6, or a pharmaceutically acceptable stereoisomer, 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.

10. Use of an effective amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable stereoisomer, 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.

11. Use of an effective amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable stereoisomer, 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.

12. Use of an effective amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable stereoisomer, 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.

13. Use of an effective amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable stereoisomer, 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.

14. Use of a compound of any one of claims 1-6, or a pharmaceutically acceptable stereoisomer, 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.

15. Use of an effective amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable stereoisomer, 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.

16. Use of an effective amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable stereoisomer, 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.

17. Use of an effective amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable stereoisomer, 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.

18. Use of an effective amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable stereoisomer, 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.