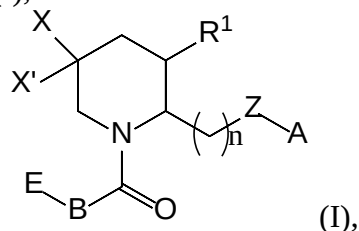


Claims

1. A compound of formula (I),



or a pharmaceutically acceptable salt thereof, wherein:

X is halogen;

X' is H or halogen;

Z is NR² or O;

A is aryl, aroyl, heteroaryl, or heteroaroyl, wherein A is optionally substituted with one or more substituents independently selected from the group consisting of alkyl, cycloalkyl, halo, -OH, alkoxy, -CHF₂, -CF₃, -CN, -NR^aR^b, -N(R^a)C(O) alkyl, -N(R^a)CO₂alkyl, -N(R^a)SO₂alkyl, -C(O)alkyl, -CO₂H, -CO₂alkyl, -CONR^aR^b, -SO₂alkyl, and -SO₂NR^aR^b; wherein R^a and R^b are independently for each occurrence H or alkyl;

B is aryl or heteroaryl, wherein B is optionally substituted with one or more substituents independently selected from the group consisting of alkyl, cycloalkyl, halo, -OH, alkoxy, CH₂CF₃, -CHF₂, -CF₃, -CN, -NR^cR^d, -N(R^c)C(O) alkyl, -N(R^c)CO₂alkyl, -N(R^c)SO₂alkyl, -C(O)alkyl, -CO₂H, -CO₂alkyl, -CONR^cR^d, -SO₂alkyl, and -SO₂NR^cR^d; wherein R^c and R^d are independently for each occurrence H or alkyl;

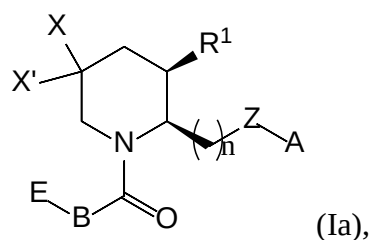
E is aryl or heteroaryl, wherein E is optionally substituted with one or more substituents independently selected from the group consisting of alkyl, cycloalkyl, halo, -OH, alkoxy, -CHF₂, -CF₃, -CN, -NR^eR^f, -N(R^e)C(O) alkyl, -N(R^e)CO₂alkyl, -N(R^e)SO₂alkyl, -C(O)alkyl, -CO₂H, -CO₂alkyl, -CONR^eR^f, -SO₂alkyl, and -SO₂NR^eR^f; wherein R^e and R^f are independently for each occurrence H or alkyl;

n = 1, 2, or 3;

R¹ is alkyl; and

R² is H or alkyl.

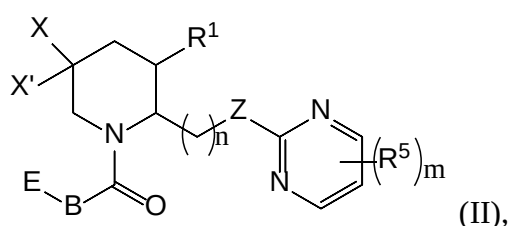
2. The compound of claim 1, wherein A is optionally substituted aryl or heteroaryl, or a pharmaceutically acceptable salt thereof.
3. The compound of claim 1, wherein the compound has the structure of formula (Ia):



or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein Z is NR^2 , or a pharmaceutically acceptable salt thereof.
5. The compound of claim 1, wherein R^2 is hydrogen, or a pharmaceutically acceptable salt thereof.
6. The compound of claim 1, wherein X is -F, or a pharmaceutically acceptable salt thereof.
7. The compound of claim 1, wherein X' is -F, or a pharmaceutically acceptable salt thereof.
8. The compound of claim 1, wherein R^1 is methyl, or a pharmaceutically acceptable salt thereof.
9. The compound of claim 1, wherein A is selected from the list consisting of optionally substituted pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, and benzoxazolyl, or a pharmaceutically acceptable salt thereof.
10. The compound of claim 1, wherein A is optionally substituted with one or more substituents independently selected from the list consisting -F, -Br, -Cl, -CHF₂, -CF₃, methyl, ethyl and methoxy, or a pharmaceutically acceptable salt thereof.
11. The compound of claim 1, wherein A is substituted with -CHF₂ or -CF₃, or a pharmaceutically acceptable salt thereof.
12. The compound of claim 1, wherein B is an optionally substituted aryl, or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1, wherein B is selected from the list consisting of optionally substituted pyridinyl, thiophenyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, and benzoimidazolyl, or a pharmaceutically acceptable salt thereof.
14. The compound of claim 1, wherein B is optionally substituted with one or more substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, methyl, ethyl, isopropyl, -CF₃, -CH₂CF₃, isopropoxy and methoxy, or a pharmaceutically acceptable salt thereof.
15. The compound of claim 14, wherein B is substituted with one or more methyl, or a pharmaceutically acceptable salt thereof.
16. The compound of claim 1, wherein E is an optionally substituted phenyl, or a pharmaceutically acceptable salt thereof.
17. The compound of claim 1, wherein E is selected from the group consisting of optionally substituted triazolyl, tetrazolyl, pyrazolyl, pyridinyl, oxadiazolyl, pyrazinyl, and pyrimidinyl, or a pharmaceutically acceptable salt thereof.
18. The compound of claim 1, wherein E is optionally substituted with one or more -F, -Cl, -Br, methoxy, methyl, ethyl, -CHF₂ or -CF₃, or a pharmaceutically acceptable salt thereof.
19. The compound of claim 1, wherein E is optionally substituted with one or more methyl or -F, or a pharmaceutically acceptable salt thereof.
20. The compound of claim 1, wherein Z is O, or a pharmaceutically acceptable salt thereof.
21. The compound of claim 1, wherein n =1, or a pharmaceutically acceptable salt thereof.
22. The compound of claim 1, wherein the compound has a structure of formula (II):



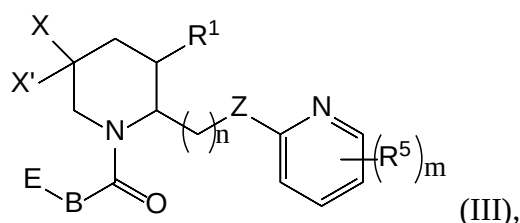
or a pharmaceutically acceptable salt thereof; wherein:

m is 1, 2, or 3;

R⁵ represents alkyl, cycloalkyl, halo, -OH, alkoxy, -CN, -NR^jR^k, -N(R^j)C(O) alkyl, -N(R^j)CO₂alkyl, -N(R^j)SO₂alkyl, -C(O)alkyl, -CO₂H, -CO₂alkyl, -CONR^jR^k, -SO₂alkyl, or -SO₂NR^jR^k; wherein R^j and R^k are independently for each occurrence H or alkyl; and

X, X', Z, B, E, n, R¹ and R² are as defined in claim 1.

23. The compound of claim 1, wherein the compound has a structure of formula (III):



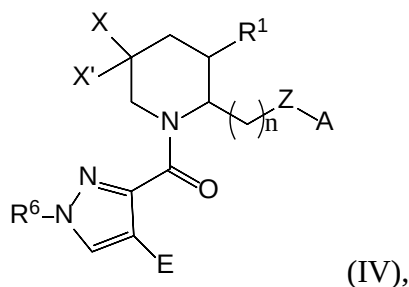
or a pharmaceutically acceptable salt thereof; wherein:

m is 1, 2, 3 or 4;

R⁵ represents alkyl, cycloalkyl, halo, -OH, alkoxy, -CN, -NR^jR^k, -N(R^j)C(O) alkyl, -N(R^j)CO₂alkyl, -N(R^j)SO₂alkyl, -C(O)alkyl, -CO₂H, -CO₂alkyl, -CONR^jR^k, -SO₂alkyl, or -SO₂NR^jR^k; wherein R^j and R^k are independently for each occurrence H or alkyl; and

X, X', Z, B, E, n, R¹ and R² are as defined in claim 1.

24. The compound of claim 1, wherein the compound has a structure of formula (IV):



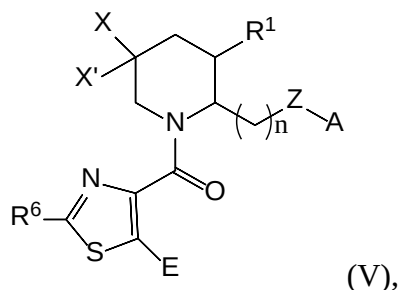
or a pharmaceutically acceptable salt thereof; wherein:

R⁶ represents alkyl, cycloalkyl, halo, -OH, alkoxy, -CN, -NR^oR^p, -N(R^o)C(O) alkyl, -N(R^p)CO₂alkyl, -N(R^o)SO₂alkyl, -C(O)alkyl, -CO₂H, -CO₂alkyl, -CONR^oR^p, -

SO₂alkyl, or -SO₂NR^oR^p; wherein R^o and R^p are independently for each occurrence H or alkyl; and

X, X', Z, A, E, n, R¹ and R² are as defined in claim 1.

25. The compound of claim 1, wherein the compound has a structure of formula (V):

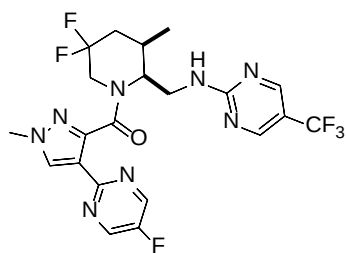


or a pharmaceutically acceptable salt thereof, wherein:

R⁶ represents alkyl, cycloalkyl, halo, -OH, alkoxy, -CN, -NR^oR^p, -N(R^o)C(O) alkyl, -N(R^p)CO₂alkyl, -N(R^o)SO₂alkyl, -C(O)alkyl, -CO₂H, -CO₂alkyl, -CONR^oR^p, -SO₂alkyl, or -SO₂NR^oR^p; wherein R^o and R^p are independently for each occurrence H or alkyl; and

X, X', Z, A, E, n, R¹ and R² are as defined in claim 1.

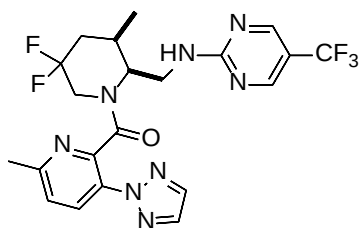
26. The compound of claim 1, wherein the compound is compound 217,



, or a pharmaceutically acceptable salt thereof.

27. A pharmaceutical composition comprising (a) a compound of claim 1; and (b) a pharmaceutically acceptable excipient.

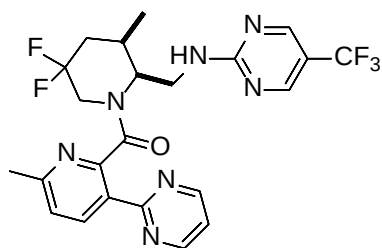
28. The compound of claim 1, wherein the compound is



Compound 12

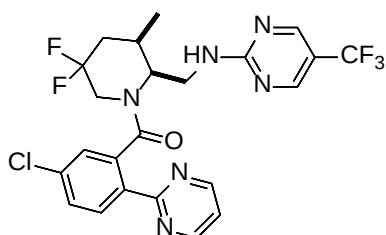
, or a pharmaceutically acceptable salt thereof.
186

29. The compound of claim 1, wherein the compound is



Compound 17, or a pharmaceutically acceptable salt thereof.

30. The compound of claim 1, wherein the compound is



Compound 56, or a pharmaceutically acceptable salt thereof.

31. A pharmaceutical composition comprising (a) a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable excipient.

32. Use of a compound of any of claims 1-30 or a pharmaceutical composition of claim 31, in the preparation of a medicament for the treatment of diseases or disorders regulated by orexin receptor activity, wherein the disease or disorder is selected from the group consisting of drug abuse or addiction, a sleep disorder, a cognitive dysfunction in a psychiatric or neurologic disorder, depression, anxiety, panic disorder, post-traumatic stress disorder, seasonal affective disorder, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's chorea, pain, epilepsy, behavior disorder, mood disorder, manic depression, dementia, sex disorder, and psychosexual disorder.

33. The use of claim 32, wherein the drug abuse or addiction is selected from abuse of or addiction to cocaine, opiates, amphetamines, ethanol, cannabis/marijuana, or nicotine.

34. Use of a compound of any of claims 1-30 or a pharmaceutical composition of claim 31, in the preparation of a medicament for the treatment of diseases or disorders regulated by orexin receptor activity, wherein the disease or disorder is selected from the group consisting of an eating disorder, obesity, alcoholism or an alcohol-related disorder, headache, migraine, gastrointestinal diseases, inflammations, immune-related diseases, ulcers, irritable bowel syndrome, diarrhea, gastroesophageal reflux, endocrine-related diseases, cancer, hypertension, and renal disease.
35. Use of a compound of any one of claims 1-30 or a pharmaceutical composition of claim 31, in the preparation of a medicament for treating a disease or disorder in a patient in need thereof, wherein the disease or disorder is selected from the group consisting of drug abuse or addiction, a sleep disorder, a cognitive dysfunction in a psychiatric or neurologic disorder, depression, anxiety, panic disorder, post-traumatic stress disorder, seasonal affective disorder, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's chorea, pain, epilepsy, behavior disorder, mood disorder, manic depression, dementia, sex disorder, and psychosexual disorder.
36. The use of claim 35, wherein the drug abuse or addiction is selected from abuse of or addiction to cocaine, opiates, amphetamines, ethanol, cannabis/marijuana, or nicotine.
37. Use of a compound of any one of claims 1-30 or a pharmaceutical composition of claim 31, in the preparation of a medicament for treating a disease or disorder in a patient in need thereof, wherein the disease or disorder is selected from the group consisting of an eating disorder, obesity, alcoholism or an alcohol-related disorder, headache, migraine, gastrointestinal diseases, inflammations, immune-related diseases, ulcers, irritable bowel syndrome, diarrhea, gastroesophageal reflux, endocrine-related diseases, cancer, hypertension, and renal disease.