OREXIN RECEPTOR AGONISTS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/183,321, filed on May 3, 2021, the contents of which is hereby incorporated by reference in its entirety for all purposes.

BACKGROUND

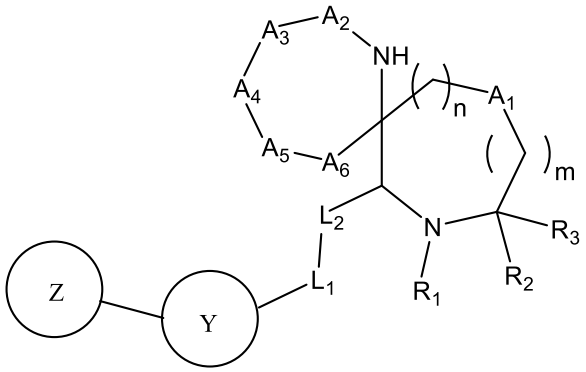
[0002] Orexin is a neuropeptide specifically produced in particular neurons located sparsely in the lateral hypothalamus and its surrounding area. Orexin consists of two subtypes, orexin A and orexin B. Both orexin A (OX-A) and orexin B (OX-B) are endogenous ligands of the orexin receptors, which are mainly present in the brain. Two orexin receptors have been cloned and characterized in mammals. They belong to the super family of G-protein coupled receptors: the orexin-1 receptor (OX or OX1R) is partially selective for OX-A and the orexin-2 receptor (OX2 or OX2R) is capable of binding OX-A as well as OX-B with similar affinity. The physiological actions in which orexins are presumed to participate are thought to be expressed via one or both of OX1 receptor and OX2 receptor as the two subtypes of orexin receptors.

[0003] Orexins regulate states of sleep and wakefulness making the orexin system a target for potential therapeutic approaches to treat sleep disorders. Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behavior. Orexins have also been indicated as playing a role in arousal, emotion, energy homeostasis, reward, learning and memory.

[0004] There is a need for compounds that modulate orexin receptors, as well as compositions and methods for treating a disease or disorder that is treatable by administration of an Orexin agonist.

SUMMARY

[0004a] In a first aspect of the present disclosure, there is provided a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

n and m are independently 0 or 1;

A_1 is –O–, $–CR_4R_5–$, $–NR_6–$, –S– or a bond;

A_2 is $–C(O)–$ or $–S(O)_2–$;

A_3 and A_4, are independently –O–, $–CR_4R_5–$, $–NR_6$, –S–, a bond; or A_3 and A_4 together are $–C(R_4)=C(R_5)–$;

A_5 and A_6 are independently –O–, $–CR_4R_5–$, $–NR_6$, –S– or a bond; with the proviso that ring that includes A_2, A_3, A_4, A_5 and A_6 does not contain –O–O–, $–NR_6–$ $NR_6–$ or $–O– NR_6–$;

L_1 is –O–, $–CR_4R_5–$ or a bond;

L_2 is $-CR_4R_5$;

R_1 is a alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, –(C=O)alkyl, –(C=O)cycloalkyl, –(C=O)heterocyclyl, –(C=O)aryl, –(C=O)heteroaryl, –(C=O)–O–alkyl, –(C=O)–O–cycloalkyl, –(C=O)–O–heterocyclyl, –(C=O)–O–aryl, –(C=O)–O–heteroaryl,$–S(O)_2–$alkyl, $–S(O)_2–$cycloalkyl, $–S(O)_2–$heterocyclyl, $–S(O)_2–$aryl, $–S(O)_2–$heteroaryl, $–(C=O)NR_7R_8$, or R_1 and R_2 together with the atom to which they are attached form a heterocycle or heteroaryl;

R_2 and R_3 are independently hydrogen, halogen, alkyl, cycloalkyl, heterocyclyl, or R_2 and R_3 together with the atom to which they are attached form a carbocycle or heterocycle;

R_4 and R_5 are independently hydrogen, alkyl, cycloalkyl, heterocyclyl, alkoxy, —O–cycloalkyl, –O–heterocyclyl, halogen, or R_4 and R_5 together with the atom to which they are attached to form a carbocycle or heterocycle;

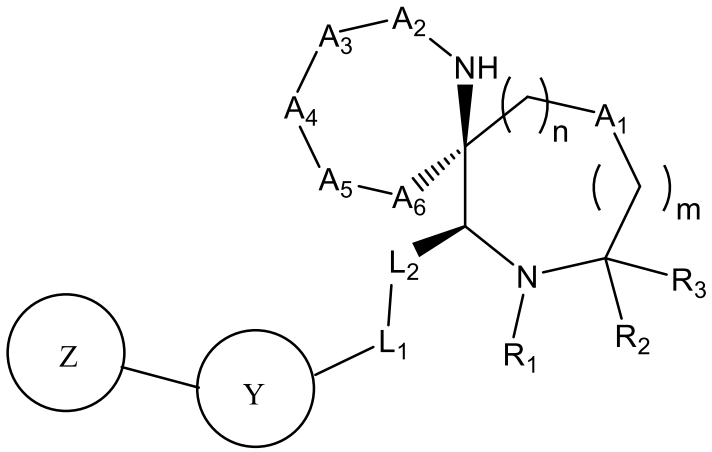
R_6 is hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, –(C=O)alkyl, –(C=O) cycloalkyl, –(C=O)heterocyclyl, –(C=O)aryl, –(C=O)heteroaryl, –(C=O)–O–alkyl, –(C=O)–O–cycloalkyl,–(C=O)–O–heterocyclyl, –(C=O)–O–aryl, –(C=O)–O–heteroaryl, –$S(O)_2$–alkyl, –$S(O)_2$–cycloalkyl, –$S(O)_2$–heterocyclyl, –$S(O)_2$–aryl, –$S(O)_2$–heteroaryl –$(C=O)NR_7R_8$,

R_7 and R_8 are independently hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, or R_7 and R_8 together with the atom to which they are attached to form a heterocycle;

Y is cycloalkyl, heterocyclyl, heteroaryl or aryl; and

Z is absent, heteroaryl or aryl.

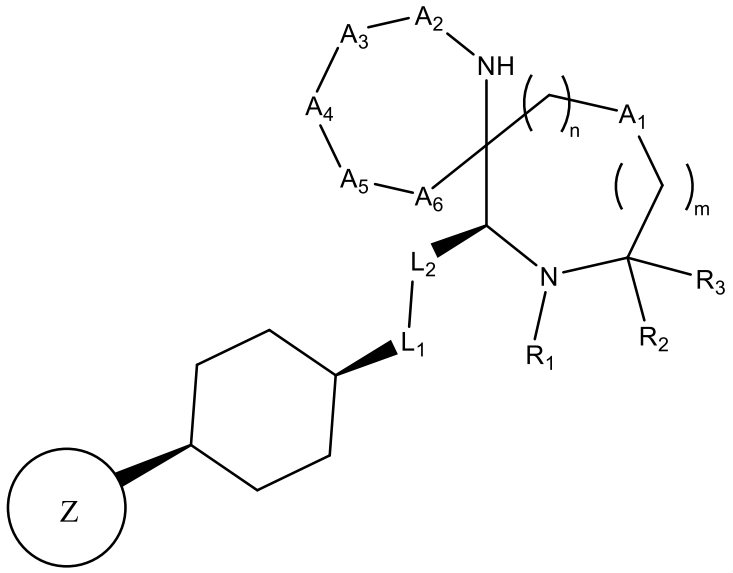
[0004b] In another aspect of the present disclosure, there is provided a compound of Formula (II),



, or a pharmaceutically acceptable salt thereof,

wherein n, m, A_1, A_2, A_3, A_4, A_5, A_6, L_1, L_2, R_1, R_2, R_3 , Y and Z have the definitions as disclosed herein.

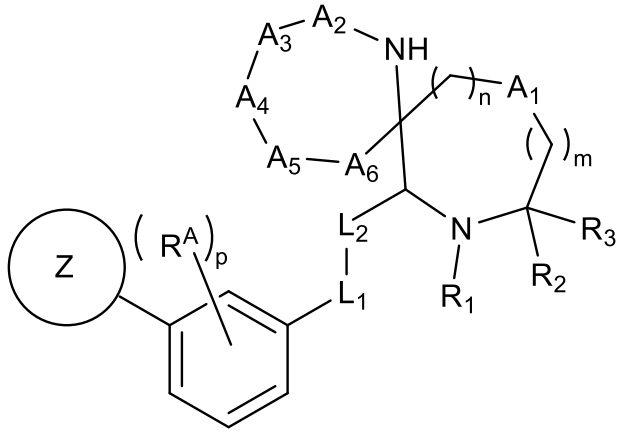
[0004c] In yet another aspect of the present disclosure, there is provided a compound of Formula (III),



, or a pharmaceutically acceptable salt thereof,

wherein n, m, A_1, A_2, A_3, A_4, A_5, A_6, L_1, L_2, R_1, R_2, R_3, and Z have the definitions as disclosed herein.

[0004d] In a further aspect of the present disclosure, there is provided a compound of Formula (IV),



(IV)

or a pharmaceutically acceptable salt thereof,

wherein R^A is independently, for each occurrence, selected from the group consisting of hydroxy, halo, $-NO_2$, -CN, $-NR_7R_8$, $-CO_2R_9$, $-OC(O)R_9$, $-COR_9$, $-C(O)NR_7R_8$, $-NR_7C(O)R_8$, $-OC(O)NR_7R_8$, $-NR_7C(O)OR_9$, $-S(O)_wR_9$ (wherein w is 0, 1, or 2), $-OSO_2R_9$, $-SO_3R_9$, $-S(O)_2NR_7R_8$, $-NR_7S(O)_2R_9$, $-NR_7C(O)NR_7R_8$, $-C_{1-6}$ alkyl-NR_7R_8, $-C_{1-6}$ alkyl-O-C_{1-6} alkyl, $-C_{1-6}$ alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R_7 and R_8 are independently hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, or R_7 and R_8 together with the atom to which they are attached to form a heterocycle;

R_9 is independently for each occurrence, selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl; and

p is 0, 1, 2, 3, or 4;

wherein n, m, A_1, A_2, A_3, A_4, A_5, A_6, L_1, L_2, R_1, R_2, R_3, and Z, have the definitions as disclosed herein.

[0004e] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein and pharmaceutically acceptable excipient.

[0004f] In yet another aspect of the present disclosure, there is provided a use of the compound as disclosed herein or the composition as disclosed herein, in the manufacture of a medicament for treating a disease or disorder that is treatable by administration of an Orexin agonist.

[0004g] In a further aspect of the present disclosure, there is provided a use of the compound as disclosed herein or the composition as disclosed herein, in the manufacture of a medicament for treating a sleep disorder in a subject in need thereof.

[0004h] In another aspect of the present disclosure, there is provided a use of the compound as disclosed herein or the composition as disclosed herein, in the manufacture of a medicament for treating narcolepsy in a subject in need thereof.

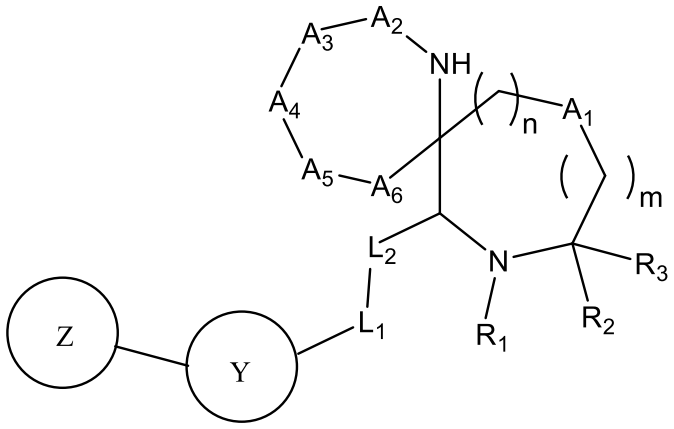
[0004i] In yet another aspect of the present disclosure, there is provided a use of the compound as disclosed herein or the composition as disclosed herein, in the manufacture of a medicament for treating hypersomnia in a subject in need thereof.

[0004j] In a further aspect of the present disclosure, there is provided a use of the compound as disclosed herein or the composition as disclosed herein, in the manufacture of a medicament for decreasing or treating excessive sleepiness in a subject in need thereof.

[0004k] In another aspect of the present disclosure, there is provided the compound as disclosed herein or the composition as disclosed herein, for use in therapy.

[0005] The present disclosure is directed to compounds that are agonists of the orexin-2 receptor as well as pharmaceutical compositions thereof and uses thereof in treating a disease or disorder that is treatable by administration of an Orexin agonist.

[0006] In one example, the present disclosure provides a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

n and m are independently 0 or 1;

A_1 is –O–, $–CR_4R_5–$, $–NR_6–$, –S– or a bond;

A_2 is $–C(O)–$ or $–S(O)_2–$;

A_3 and A_4, are independently –O–, $–CR_4R_5–$, $–NR_6$, –S–, a bond; or A_3 and A_4 together are $–C(R_4)=C(R_5)–$;

A_5 and A_6 are independently –O–, $–CR_4R_5–$, $–NR_6$, –S– or a bond; with the proviso that ring that includes A_2, A_3, A_4, A_5 and A_6 does not contain –O–O–, $–NR_6–NR_6–$ or $–O–NR_6–$;

L_1 is –O–, $–CR_4R_5–$ or a bond;

L_2 is $-CR_4R_5$;

R_1 is a alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, –(C=O)alkyl, –(C=O)cycloalkyl, –(C=O)heterocyclyl, –(C=O)aryl, –(C=O)heteroaryl, –(C=O)–O–alkyl, –(C=O)–O–cycloalkyl, –(C=O)–O–heterocyclyl, –(C=O)–O–aryl, –(C=O)–O–heteroaryl,$–S(O)_2–$alkyl, $–S(O)_2–$cycloalkyl, $–S(O)_2–$heterocyclyl, $–S(O)_2–$aryl, $–S(O)_2–$heteroaryl, $–(C=O)NR_7R_8$, or R_1 and R_2 together with the atom to which they are attached form a heterocycle or heteroaryl;

R_2 and R_3 are independently hydrogen, halogen, alkyl, cycloalkyl, heterocyclyl, or R_2 and R_3 together with the atom to which they are attached form a carbocycle or heterocycle;

R_4 and R_5 are independently hydrogen, alkyl, cycloalkyl, heterocyclyl, alkoxy, —O–cycloalkyl, –O–heterocyclyl, halogen, or R_4 and R_5 together with the atom to which they are attached to form a carbocycle or heterocycle;

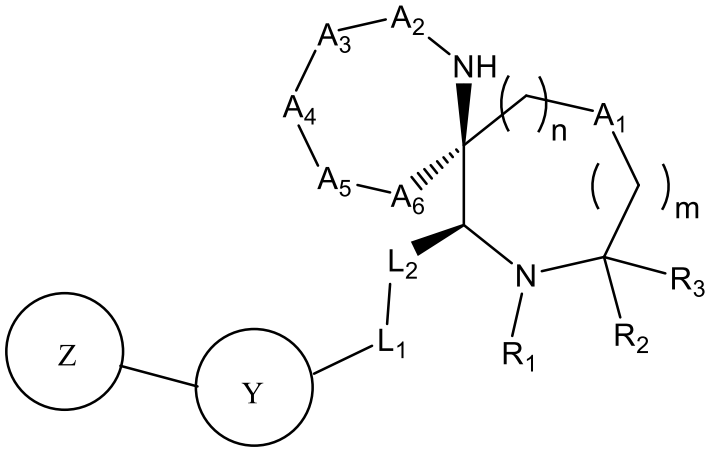
R_6 is hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, –(C=O)alkyl, –(C=O) cycloalkyl, –(C=O)heterocyclyl, –(C=O)aryl, –(C=O)heteroaryl, –(C=O)–O–alkyl, –(C=O)–O–cycloalkyl,–(C=O)–O–heterocyclyl, –(C=O)–O–aryl, –(C=O)–O–heteroaryl, –$S(O)_2$–alkyl, –$S(O)_2$–cycloalkyl, –$S(O)_2$–heterocyclyl, –$S(O)_2$–aryl, –$S(O)_2$–heteroaryl, or –(C=O)NR_7R_8,

R_7 and R_8 are independently hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, or R_7 and R_8 together with the atom to which they are attached to form a heterocycle;

Y is cycloalkyl, heterocyclyl, heteroaryl or aryl; and

Z is absent, heteroaryl or aryl.

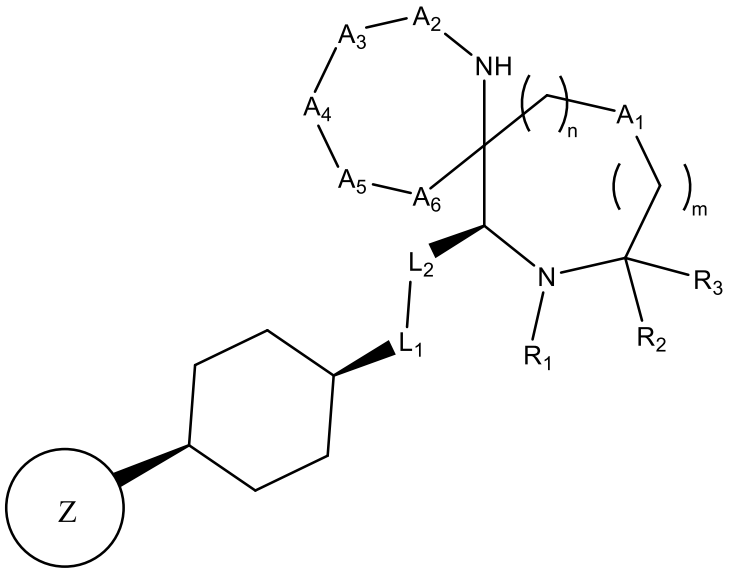
[0007] In some examples, the present disclosure provides a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein n, m, A_1, A_2, A_3, A_4, A_5, A_6, L_1, L_2, R_1, R_2, R_3, Y and Z are defined herein.

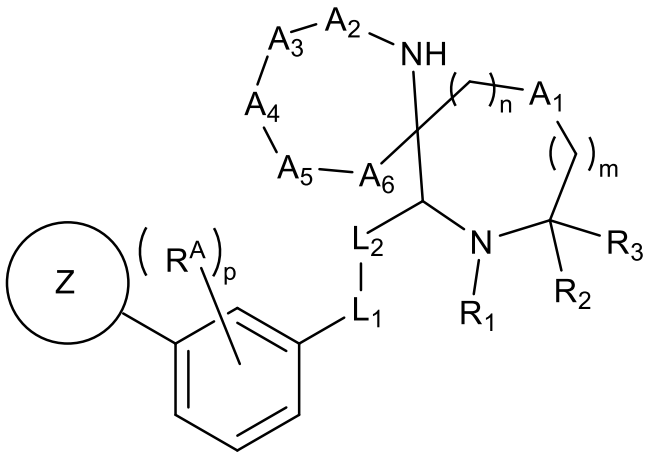
[0008] In some examples, the present disclosure provides a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein n, m, A_1, A_2, A_3, A_4, A_5, A_6, L_1, L_2, R_1, R_2, R_3, and Z are defined herein.

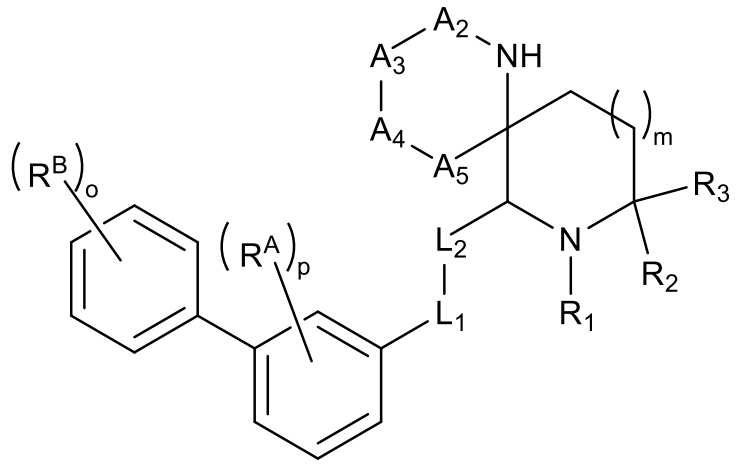
[0009] In some examples, the present disclosure provides a compound of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein n, m, p, A_1, A_2, A_3, A_4, A_5, A_6, L_1, L_2, R_1, R_2, R_3, R^A, and Z are defined herein.

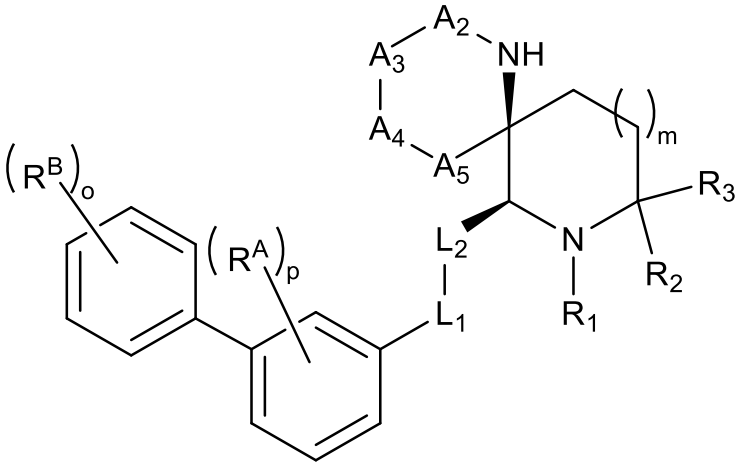
[0010] In some examples, the present disclosure provides a compound of Formula (V-A):



(V-A)

or a pharmaceutically acceptable salt thereof, wherein p, o, m, A_2, A_3, A_4, A_5, L_1, L_2, R_1, R_2, R_3, R^A, and R^B are defined herein.

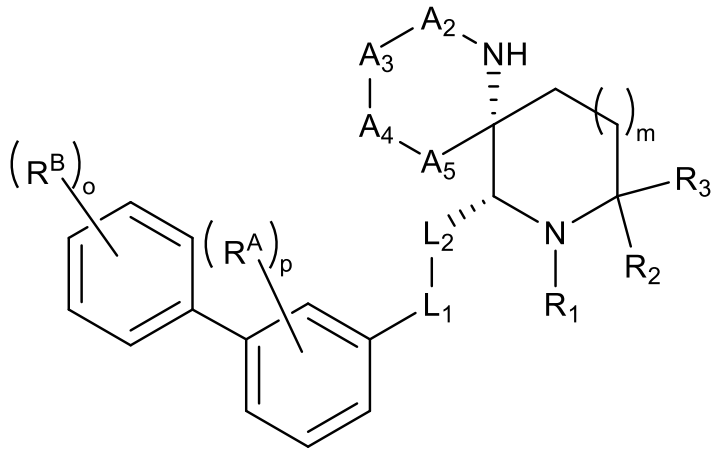
[0011] In some examples, the present disclosure provides a compound of Formula (V-B):



(V-B)

or a pharmaceutically acceptable salt thereof, wherein p, o, m, A_2, A_3, A_4, A_5, L_1, L_2, R_1, R_2, R_3, R^A, and R^B are defined herein.

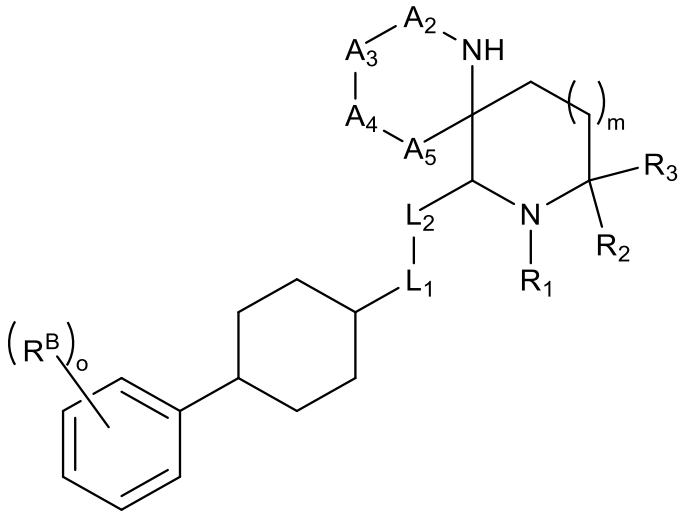
[0012] In some examples, the present disclosure provides a compound of Formula (V-C):



(V-C)

or a pharmaceutically acceptable salt thereof, wherein p, o, m, A_2, A_3, A_4, A_5, L_1, L_2, R_1, R_2, R_3, R^A, and R^B are defined herein.

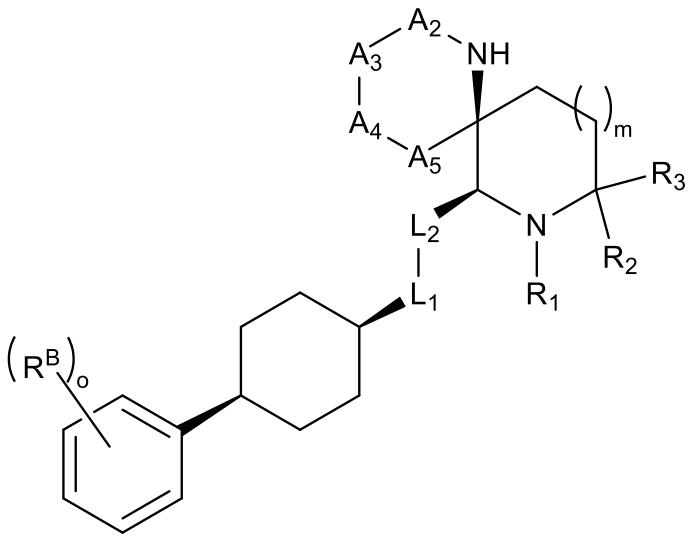
[0013] In some examples, the present disclosure provides a compound of Formula (VI-A):



(VI-A)

or a pharmaceutically acceptable salt thereof, wherein o, m, A_2, A_3, A_4, A_5, L_1, L_2, R_1, R_2, R_3, and R^B are defined herein.

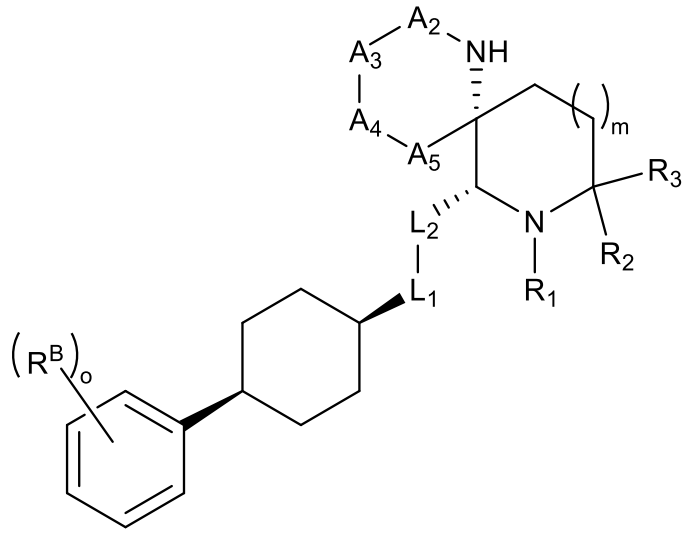
[0014] In some examples, the present disclosure provides a compound of Formula (VI-B):



(VI-B)

or a pharmaceutically acceptable salt thereof, wherein o, m, A_2, A_3, A_4, A_5, L_1, L_2, R_1, R_2, R_3, and R^B are defined herein.

[0015] In some examples, the present disclosure provides a compound of Formula (VI-C):

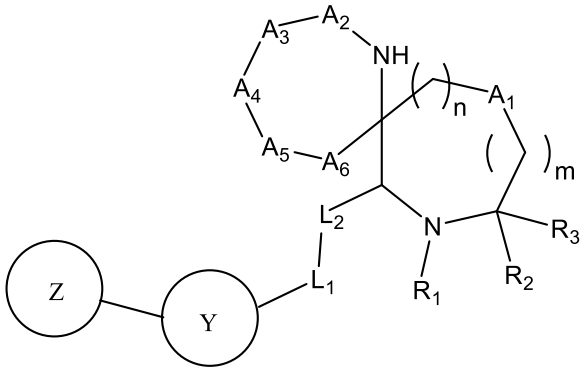


(VI-C)

or a pharmaceutically acceptable salt thereof, wherein o, m, A_2, A_3, A_4, A_5, L_1, L_2, R_1, R_2, R_3, and R^B are defined herein.

CLAIMS

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

n and m are independently 0 or 1;

A_1 is –O–, $–CR_4R_5–$, $–NR_6–$, –S– or a bond;

A_2 is $–C(O)–$ or $–S(O)_2–$;

A_3 and A_4, are independently –O–, $–CR_4R_5–$, $–NR_6$, –S–, a bond; or A_3 and A_4 together are $–C(R_4)=C(R_5)–$;

A_5 and A_6 are independently –O–, $–CR_4R_5–$, $–NR_6$, –S– or a bond; with the proviso that ring that includes A_2, A_3, A_4, A_5 and A_6 does not contain –O–O–, $–NR_6–$ $NR_6–$ or $–O– NR_6–$;

L_1 is –O–, $–CR_4R_5–$ or a bond;

L_2 is $-CR_4R_5$;

R_1 is a alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, –(C=O)alkyl, –(C=O)cycloalkyl, –(C=O)heterocyclyl, –(C=O)aryl, –(C=O)heteroaryl, –(C=O)–O–alkyl, –(C=O)–O–cycloalkyl, –(C=O)–O–heterocyclyl, –(C=O)–O–aryl, –(C=O)–O–heteroaryl,$–S(O)_2–$alkyl, $–S(O)_2–$cycloalkyl, $–S(O)_2–$heterocyclyl, $–S(O)_2–$aryl, $–S(O)_2–$heteroaryl, $–(C=O)NR_7R_8$, or R_1 and R_2 together with the atom to which they are attached form a heterocycle or heteroaryl;

R_2 and R_3 are independently hydrogen, halogen, alkyl, cycloalkyl, heterocyclyl, or R_2 and R_3 together with the atom to which they are attached form a carbocycle or heterocycle;

R_4 and R_5 are independently hydrogen, alkyl, cycloalkyl, heterocyclyl, alkoxy, —O–cycloalkyl, –O–heterocyclyl, halogen, or R_4 and R_5 together with the atom to which they are attached to form a carbocycle or heterocycle;

R_6 is hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, –(C=O)alkyl, –(C=O) cycloalkyl, –(C=O)heterocyclyl, –(C=O)aryl, –(C=O)heteroaryl, –(C=O)–O–alkyl, –(C=O)–O–cycloalkyl,–(C=O)–O–heterocyclyl, –(C=O)–O–aryl, –(C=O)–O–heteroaryl, –$S(O)_2$–alkyl, –$S(O)_2$–cycloalkyl, –$S(O)_2$–heterocyclyl, –$S(O)_2$–aryl, –$S(O)_2$–heteroaryl –$(C=O)NR_7R_8$,

R_7 and R_8 are independently hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, or R_7 and R_8 together with the atom to which they are attached to form a heterocycle;

Y is cycloalkyl, heterocyclyl, heteroaryl or aryl; and

Z is absent, heteroaryl or aryl.

2. The compound of claim 1, wherein R_1 is aryl, heteroaryl, –(C=O) C_{1-6} alkyl, –(C=O) C_{3-6} cycloalkyl, –(C=O) C_{4-6} saturated heterocyclyl, –(C=O)–O–C_{1-6} alkyl, –(C=O)–O–C_{3-6} cycloalkyl, –(C=O)–O–C_{4-6} saturated heterocyclyl, –$S(O)_2$–C_{1-6} alkyl, –$S(O)_2$–C_{3-6} cycloalkyl, –$S(O)_2$–C_{4-6} heterocyclyl, –$(C=O)NR_7R_8$, or R_1 and R_2 together with the atom to which they are attached form a 4-7 membered heterocycle or a 5-6-membered heteroaryl.

3. The compound of claim 1, wherein R_1 is C_{1-6} alkyl, 5 or 6-membered heteroaryl, –$(C=O)NR_7R_8$, –(C=O)–O–C_{1-6} alkyl, –(C=O) C_{3-6} cycloalkyl, –(C=O) C_{1-6} alkyl, –(C=O) C_{4-6} saturated heterocyclyl or –$S(O)_2$–C_{1-6} alkyl;

wherein each C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-6} saturated heterocyclyl and heteroaryl is independently optionally substituted with one or more hydroxy, –C_{1-6} alkyl, –O–C_{1-6} alkyl, or fluoro.

4. The compound of any one of claims 1-3, wherein R_2 and R_3 are independently hydrogen, fluorine, C_{1-5} alkyl, C_{3-6} cycloalkyl, C_{4-6} saturated heterocyclyl, or R_2 and R_3 together with the atom to which they are attached form a 3-6 membered carbocycle or 5-6 membered saturated heterocycle.

5. The compound of claim 4, wherein R_2 and R_3 are independently hydrogen or C_{1-5} alkyl; wherein C_{1-5} alkyl is optionally substituted with one or more fluoro.

6. The compound of any one of claims 1-5, wherein R_4 and R_5 are independently hydrogen, C_{1-5} alkyl, C_{3-6} cycloalkyl, C_{4-6} saturated heterocyclyl, C_{1-6} alkoxy, —O– (C=O) C_{3-6} cycloalkyl, –O–C_{4-6} saturated heterocyclyl, fluorine, or R_4 and R_5 together with the atom to which they are attached to form a 3-6 membered carbocycle or 4-6 membered saturated heterocycle.

7. The compound of any one of claims 1-5, wherein R_4 and R_5 are independently hydrogen, halo, or C_{1-5} alkyl.

8. The compound of any one of claims 1-7, wherein R_6 is hydrogen, C_{1-5} alkyl, C_{3-6} cycloalkyl, C_{4-6} saturated heterocyclyl, –(C=O) C_{1-6} alkyl, –(C=O) C_{3-6} cycloalkyl, –(C=O) C_{4-6} saturated heterocyclyl, –(C=O)–O–C_{1-6} alkyl, –(C=O)–O–C_{3-6} cycloalkyl,–(C=O)–O–C_{4-6} saturated heterocyclyl, –$S(O)_2$–C_{1-6} alkyl, –$S(O)_2$–C_{3-6} cycloalkyl, –$S(O)_2$–C_{4-6} heterocyclyl, or –(C=O)NR_7R_8.

9. The compound of claim 8, wherein R_6 is hydrogen or C_{1-5} alkyl.

10. The compound of any one of claims 1-9, wherein R_7 and R_8 are independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-6} heterocyclyl, 5-6-membered heteroaryl, or R_7 and R_8 together with the atom to which they are attached to form a heterocycle.

11. The compound of claim 10, wherein R_7 and R_8 are independently hydrogen or C_{1-6} alkyl or R_7 and R_8 together with the atom to which they are attached to form a saturated heterocycle, wherein the C_{1-6} alkyl, and saturated heterocycle are independently optionally substituted with one or more fluoro or –O–C_{1-6} alkyl.

12. The compound of any one of claims 1-11, wherein Y is 3-7 membered monocycloalkyl, 5-8 membered bicycloalkyl, 4-7 membered saturated heterocyclyl, 5-8 membered biheterocyclyl, 5-6-membered heteroaryl or phenyl.

13. The compound of claim 12, wherein Y is a 3-7 membered monocycloalkyl, 4-7 membered saturated heterocyclyl, or phenyl; wherein the phenyl is optionally substituted with one or more fluoro.

14. The compound of any one of claims 1-13, wherein Z is absent, 5-10 membered heteroaromatic or phenyl.

15. The compound of claim 14, wherein Z is a 6 membered heteroaromatic or phenyl; wherein the 6 membered heteroaromatic and phenyl are independently optionally substituted with one or more fluoro.

16. The compound of any one of claims 1-15, wherein Y and Z are phenyl.

17. The compound of any one of claims 1-15, wherein Y is cyclohexyl and Z is phenyl.

18. The compound of any one of claims 1-17, wherein m and n are 0.

19. The compound of any one of claims 1-17, wherein m is 1 and n is 0.

20. The compound of any one of claims 1-17, wherein m is 0 and n is 1

21. The compound of any one of claims 1-17, wherein m is 1 and n is 1.

22. The compound of any one of claims 1-21, wherein A_1 is $–CR_4R_5–$.

23. The compound of any one of claims 1-22, wherein A_2 is $–C(O)–$.

24. The compound of any one of claims 1-22, wherein A_2 is $–S(O)_2–$.

25. The compound of any one of claims 1-24, wherein A_2, A_3, A_4, A_5, and A_6 together with the atoms to which they are attached to form a 5-membered heterocycle.

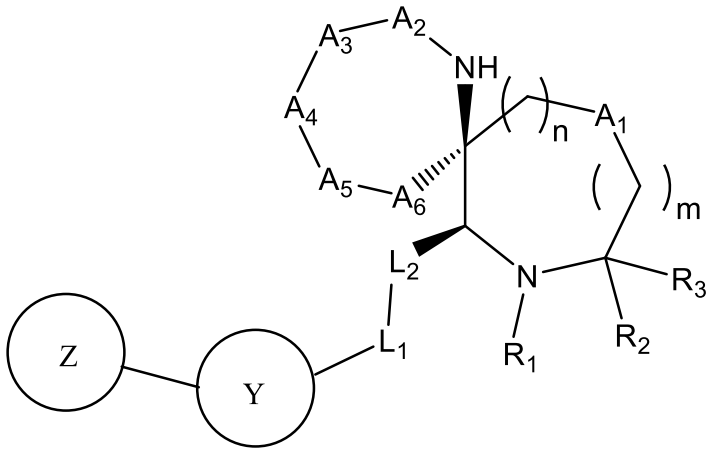
26. The compound of any one of claims 1-24, wherein A_2, A_3, A_4, A_5, and A_6 together with the atoms to which they are attached to form a 6-membered heterocycle.

27. The compound of any one of claims 1-24, wherein A_2, A_3, A_4, A_5, and A_6 together with the atoms to which they are attached to form a 7-membered heterocycle.

28. The compound of any one of 1-27, wherein L_1 is a bond or $–O–$.

29. The compound of claim 28, wherein L_1 is a bond.

30. A compound of Formula (II),



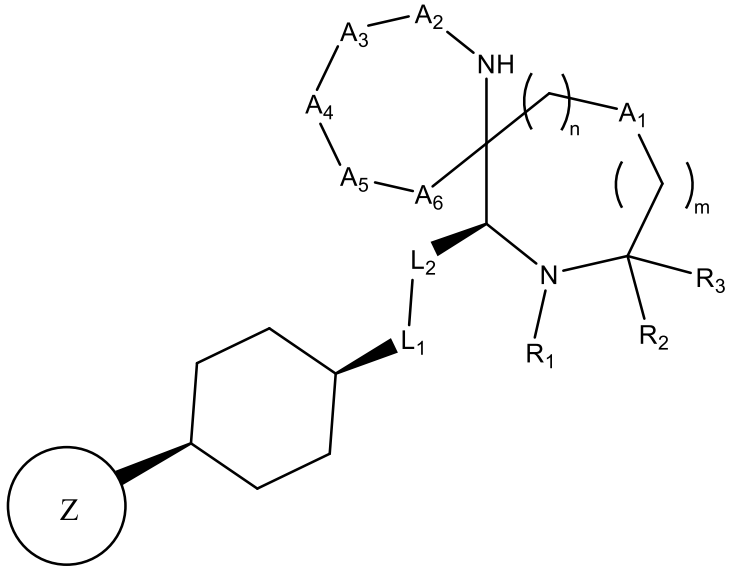
, or a pharmaceutically acceptable salt thereof,

wherein n, m, A_1, A_2, A_3, A_4, A_5, A_6, L_1, L_2, R_1, R_2, R_3 , Y and Z have the definitions provided in any one of claims 1-29.

31. The compound of claim 30, wherein Y is cyclohexyl and Z is aryl.

32. The compound of claim 30, wherein Y is aryl and Z is aryl.

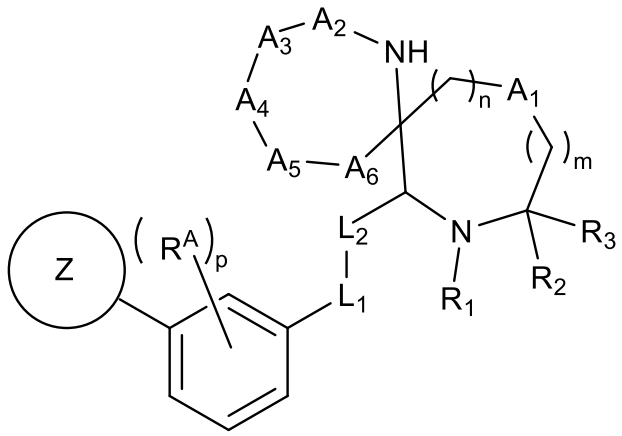
33. A compound of Formula (III),



, or a pharmaceutically acceptable salt thereof,

wherein n, m, A_1, A_2, A_3, A_4, A_5, A_6, L_1, L_2, R_1, R_2, R_3, and Z have the definitions provided in any one of claims 1-29.

34. A compound of Formula (IV),



(IV)

or a pharmaceutically acceptable salt thereof,

wherein R^A is independently, for each occurrence, selected from the group consisting of hydroxy, halo, $-NO_2$, -CN, $-NR_7R_8$, $-CO_2R_9$, $-OC(O)R_9$, $-COR_9$, $-C(O)NR_7R_8$, $-NR_7C(O)R_8$, $-OC(O)NR_7R_8$, $-NR_7C(O)OR_9$, $-S(O)_wR_9$ (wherein w is 0, 1, or 2), $-OSO_2R_9$, $-SO_3R_9$, $-S(O)_2NR_7R_8$, $-NR_7S(O)_2R_9$, $-NR_7C(O)NR_7R_8$, $-C_{1-6}$ alkyl-NR_7R_8, $-C_{1-6}$ alkyl-O-C_{1-6} alkyl, $-C_{1-6}$ alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R_7 and R_8 are independently hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, or R_7 and R_8 together with the atom to which they are attached to form a heterocycle;

R_9 is independently for each occurrence, selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl; and

p is 0, 1, 2, 3, or 4;

wherein n, m, A_1, A_2, A_3, A_4, A_5, A_6, L_1, L_2, R_1, R_2, R_3, and Z, have the definitions provided in any one of claims 1-29.

35. The compound of claim 33 or 34, wherein Z is aryl.

36. The compound of claim 1, wherein the compound of Formula (I) is selected from the group consisting of compounds in Table 1.

37. A pharmaceutical composition comprising a compound of any one of claims 1-36 and pharmaceutically acceptable excipient.

38. Use of the compound of any one of claims 1-36 or the composition of claim 37, in the manufacture of a medicament for treating a disease or disorder that is treatable by administration of an Orexin agonist.

39. Use of the compound of any one of claims 1-36 or the composition of claim 37, in the manufacture of a medicament for treating a sleep disorder in a subject in need thereof.

40. Use of the compound of any one of claims 1-36 or the composition of claim 37, in the manufacture of a medicament for treating narcolepsy in a subject in need thereof.

41. Use of the compound of any one of claims 1-36 or the composition of claim 37, in the manufacture of a medicament for treating hypersomnia in a subject in need thereof.

42. Use of the compound of any one of claims 1-36 or the composition of claim 37, in the manufacture of a medicament for decreasing or treating excessive sleepiness in a subject in need thereof.

43. The compound of any one of claims 1-36 or the composition of claim 37, for use in therapy.