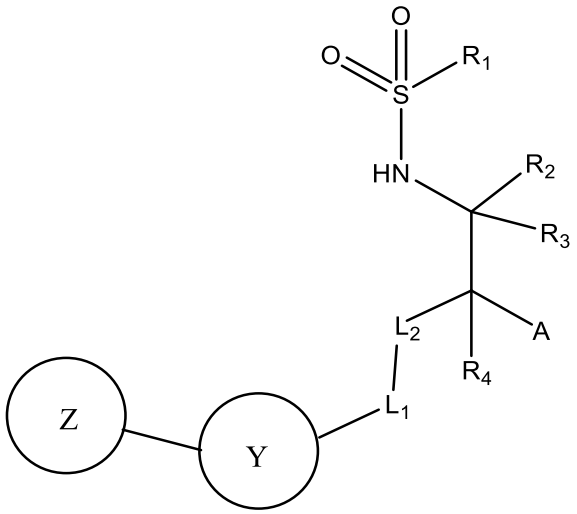
SUMMARY

[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.

[0005a] In an aspect of the present disclosure, there is provided a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

A is a heteroaryl;

L_1 is –O–, $–CR_5R_6–$ or a bond;

L_2 is $–CR_5R_6$;

R_1 is alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-NR_7R_8$, or R_1 and R_2 together with the atom to which they are attached form a heterocycle;

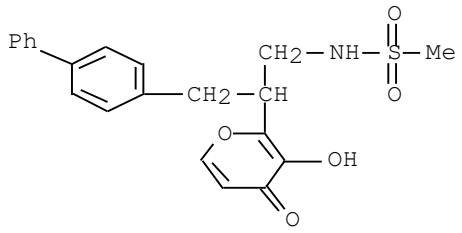
R_2, R_3, R_4 are independently hydrogen, alkyl, cycloalkyl, heterocyclyl, or halogen, or R_2 and R_3 together with the atom to which they are attached to form a carbocycle or heterocycle, or R_2 and R_4 together with the atom to which they are attached to form a carbocycle or heterocycle;

R_5 and R_6 are each independently hydrogen, alkyl, cycloalkyl, heterocyclyl, alkoxy, –O–cycloalkyl, –O–heterocyclyl, or halogen, or R_5 and R_6 together with the atom to which they are attached to form a carbocycle or heterocycle;

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

Y is cycloalkyl, heterocyclyl, heteroaryl or aryl; and

Z is absent, heteroaryl or aryl, wherein if L_1 is a bond or CR_5R_6 then Z is heteroaryl or aryl; and with the proviso that the compound is not:



.

[0005b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and pharmaceutically acceptable excipient.

[0005c] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein or the composition disclosed herein, in the manufacture of a medicament for treating a disease or disorder that is treatable by administration of an Orexin agonist.

[0005d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein or the composition disclosed herein, in the manufacture of a medicament for treating a sleep disorder in a subject in need thereof.

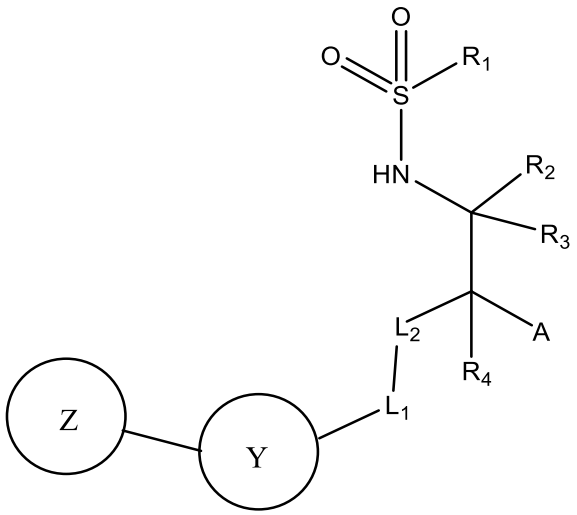
[0005e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein or the composition disclosed herein, in the manufacture of a medicament for treating narcolepsy in a subject in need thereof.

[0005f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein or the composition disclosed herein, in the manufacture of a medicament for treating hypersomnia in a subject in need thereof.

[0005g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein or the composition disclosed herein, in the manufacture of a medicament for decreasing or treating excessive sleepiness in a subject in need thereof.

[0005h] In another aspect of the present disclosure, there is provided a compound of the compound disclosed herein or the composition disclosed herein, for use in therapy.

[0006] In one example, provided herein are compounds of Formula (I):



(I)

or a pharmaceutically acceptable salt or N-oxide thereof,

wherein

A is a heteroaryl;

L_1 is –O–, $–CR_5R_6–$ or a bond;

L_2 is $–CR_5R_6$;

R_1 is alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-NR_7R_8$, or R_1 and R_2 together with the atom to which they are attached form a heterocycle;

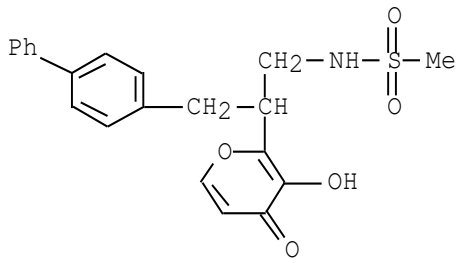
R_2, R_3, R_4 are independently hydrogen, alkyl, cycloalkyl, heterocyclyl, or halogen, or R_2 and R_3 together with the atom to which they are attached to form a carbocycle or heterocycle, or R_2 and R_4 together with the atom to which they are attached to form a carbocycle or heterocycle;

R_5 and R_6 are each independently hydrogen, alkyl, cycloalkyl, heterocyclyl, alkoxy, –O–cycloalkyl, –O–heterocyclyl, or halogen, or R_5 and R_6 together with the atom to which they are attached to form a carbocycle or heterocycle;

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

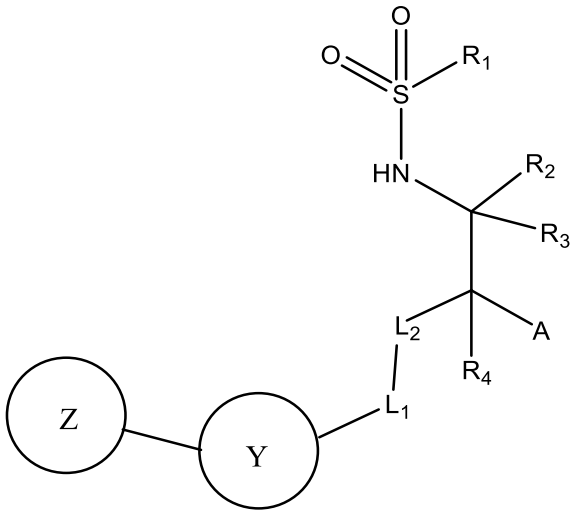
Y is cycloalkyl, heterocyclyl, heteroaryl or aryl; and

Z is absent, heteroaryl or aryl, wherein if L_1 is a bond or CR_5R_6 then Z is heteroaryl or aryl; and with the proviso that the compound is not:



.

[0007] In one example, provided herein are compounds of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

A is a heteroaryl;

L_1 is –O–, $–CR_5R_6–$ or a bond;

L_2 is $–CR_5R_6$;

R_1 is alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-NR_7R_8$, or R_1 and R_2 together with the atom to which they are attached form a heterocycle;

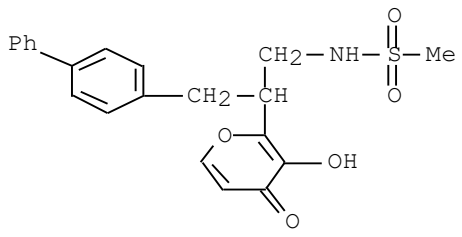
R_2, R_3, R_4 are independently hydrogen, alkyl, cycloalkyl, heterocyclyl, or halogen, or R_2 and R_3 together with the atom to which they are attached to form a carbocycle or heterocycle, or R_2 and R_4 together with the atom to which they are attached to form a carbocycle or heterocycle;

R_5 and R_6 are each independently hydrogen, alkyl, cycloalkyl, heterocyclyl, alkoxy, –O–cycloalkyl, –O–heterocyclyl, or halogen, or R_5 and R_6 together with the atom to which they are attached to form a carbocycle or heterocycle;

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

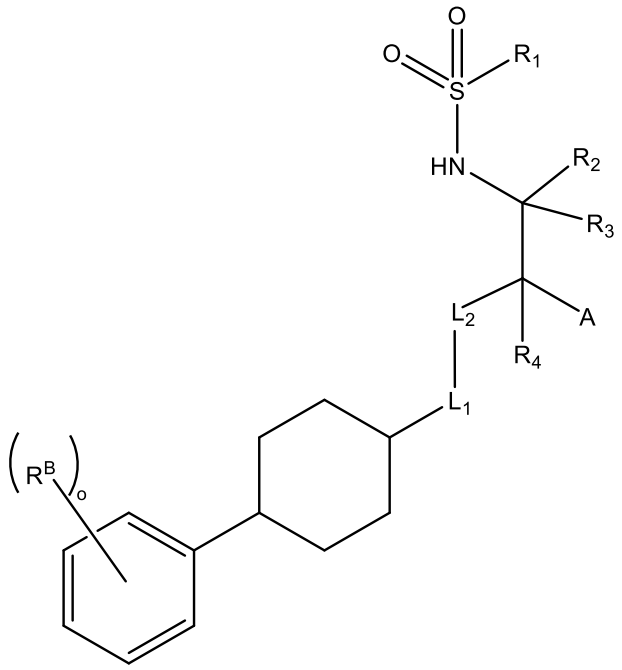
Y is cycloalkyl, heterocyclyl, heteroaryl or aryl; and

Z is absent, heteroaryl or aryl, wherein if L_1 is a bond or CR_5R_6 then Z is heteroaryl or aryl; and with the proviso that the compound is not:



.

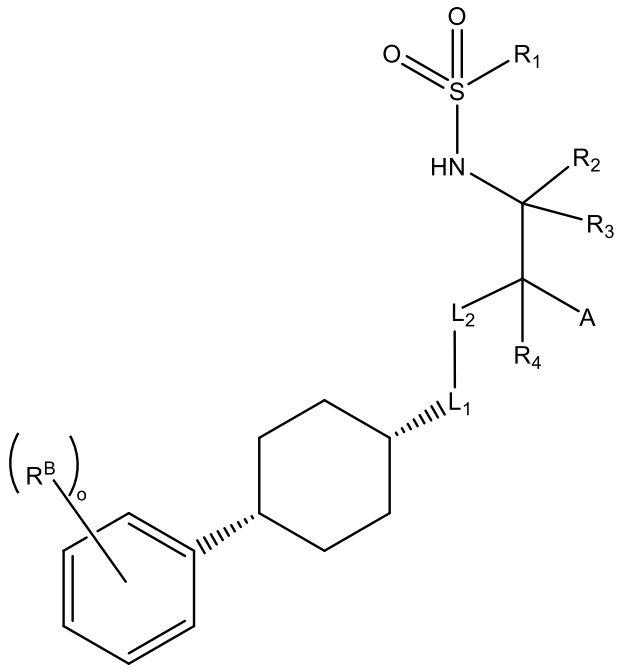
[0008] In some examples, the present disclosure provides a compound of Formula (I-A)



(I-A)

or a pharmaceutically acceptable salt thereof, wherein o, A, L_1, L_2, R_1, R_2, R_3, R_4, and R^B are defined herein.

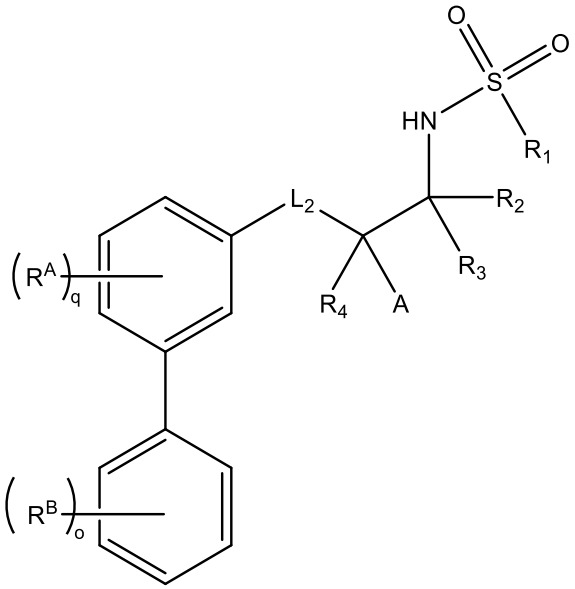
[0009] In some examples, the present disclosure provides a compound of Formula (I-A-I)



(I-A-I)

or a pharmaceutically acceptable salt thereof, wherein o, A, L_1, L_2, R_1, R_2, R_3, R_4, and R^B are defined herein.

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



(I-B)

or a pharmaceutically acceptable salt thereof, wherein o, q, A, L_2, R_1, R_2, R_3, R_4, R^A, R^B are defined herein.

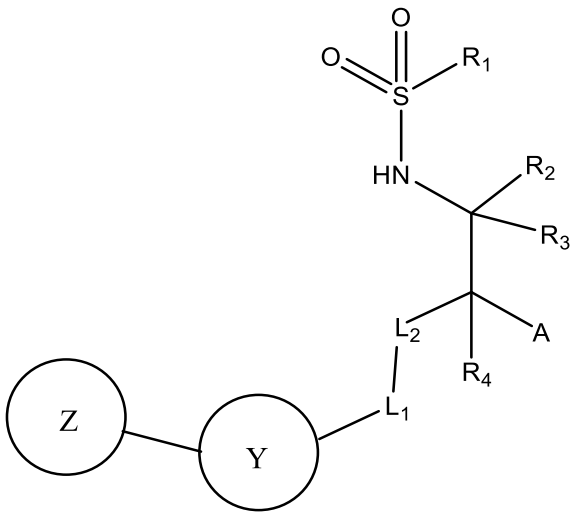
[0011] In some examples, the present disclosure provides a pharmaceutical composition comprising one or more compounds of the present disclosure or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0012] In some examples, the present disclosure provides a pharmaceutical composition comprising one or more compounds of the present disclosure or a pharmaceutically acceptable salt or N-oxide thereof and a pharmaceutically acceptable carrier.

[0013] In some examples, the present disclosure provides a method of treating a disease or disorder that is treatable by administration of an orexin agonist comprising administering a therapeutically effective amount of one or more compounds of the present disclosure or a pharmaceutically acceptable salt thereof.

CLAIMS

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

A is a heteroaryl;

L_1 is –O–, $–CR_5R_6–$ or a bond;

L_2 is $–CR_5R_6$;

R_1 is alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-NR_7R_8$, or R_1 and R_2 together with the atom to which they are attached form a heterocycle;

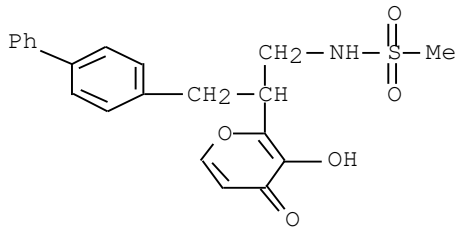
R_2, R_3, R_4 are independently hydrogen, alkyl, cycloalkyl, heterocyclyl, or halogen, or R_2 and R_3 together with the atom to which they are attached to form a carbocycle or heterocycle, or R_2 and R_4 together with the atom to which they are attached to form a carbocycle or heterocycle;

R_5 and R_6 are each independently hydrogen, alkyl, cycloalkyl, heterocyclyl, alkoxy, –O–cycloalkyl, –O–heterocyclyl, or halogen, or R_5 and R_6 together with the atom to which they are attached to form a carbocycle or heterocycle;

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

Y is cycloalkyl, heterocyclyl, heteroaryl or aryl; and

Z is absent, heteroaryl or aryl, wherein if L_1 is a bond or CR_5R_6 then Z is heteroaryl or aryl; and with the proviso that the compound is not:



.

2. The compound of claim 1, wherein L_1 is –O–.

3. The compound of claim 1, wherein L_1 is a bond.

4. The compound of any one of claims 1-3, wherein R_1 is an alkyl, haloalkyl, cycloalkyl, alkylene-alkoxy, $-NR_7R_8$.

5. The compound of claim 4, wherein R_1 is an alkyl, haloalkyl, or $-NR_7R_8$.

6. The compound of claim 4, wherein R_1 is methyl.

7. The compound of any one of claims 1-5, wherein R_1 is $-NR_7R_8$.

8. The compound of claim 7, wherein R_7 and R_8 are alkyl.

9. The compound of any one of claims 1-8, wherein R_2 and R_3 are independently hydrogen or alkyl and R_4 is hydrogen.

10. The compound of any one of claims 1-9, wherein R_2, R_3, R_4 are hydrogen.

11. The compound of any one of claims 1-10, wherein Y is 3-7 membered monocyclic cycloalkyl, 5-8 membered bicyclic cycloalkyl, 4-7 membered saturated heterocyclyl, 5-8 membered bicyclic heterocyclyl, 5-6-membered heteroaryl or phenyl.

12. The compound of any one of claims 1-11, wherein Z is 5-10 membered heteroaryl or phenyl.

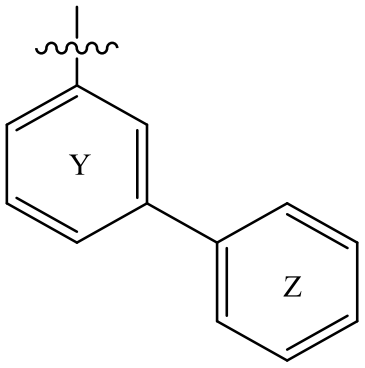
13. The compound of claim 12, wherein Z is phenyl substituted with one or two halogens.

14. The compound of any one of claims 1-12, wherein Y and Z are phenyl.

15. The compound of any one of claims 1-12, wherein Y is cyclohexyl and Z is phenyl.

16. The compound of claim 11, wherein Y is a 2-oxaspiro[4.5]decane or cyclohexyl optionally substituted one or more alkyl or cycloalkyl.

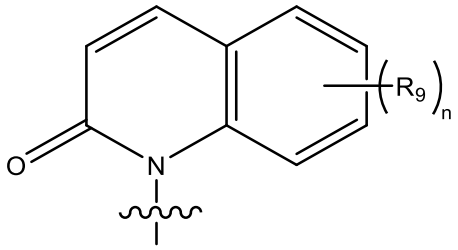
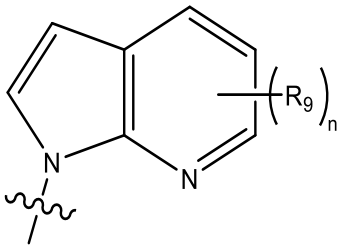
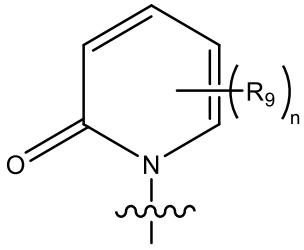
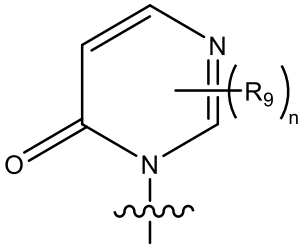
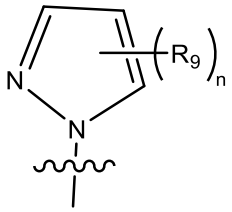
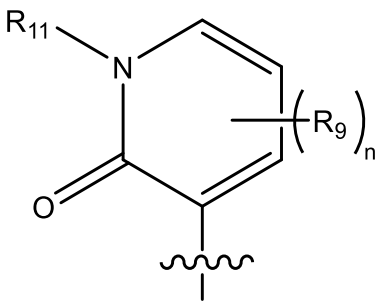
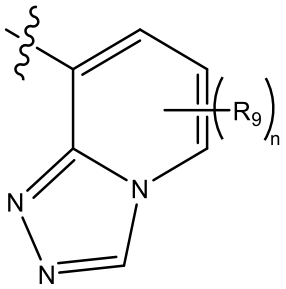
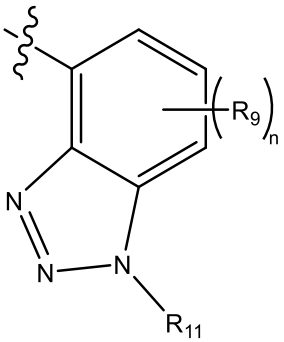
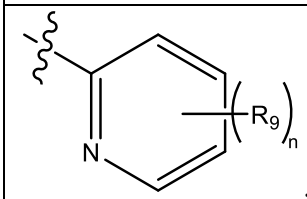
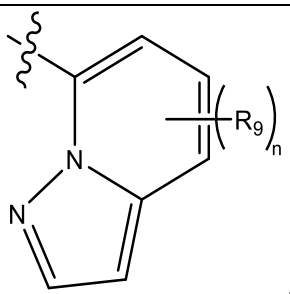
17. The compound of claim 14, wherein Y and Z together are:

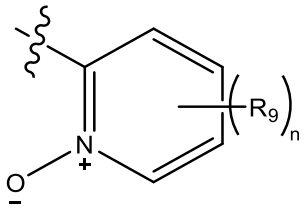


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18. The compound of any one of claims 1-17, wherein A is a substituted or unsubstituted monocyclic or bicyclic nitrogen-containing heteroaryl.

19. The compound of claim 18, wherein A is selected from the group consisting of:

	
	
	
	
 ,	 , or

wherein n is an integer from 0-6;

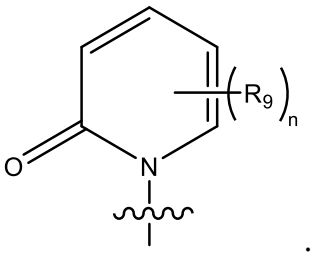
R_9 is hydrogen, alkyl, haloalkyl, haloalkoxy, halogen, cyano, alkoxy, cycloalkyl, heterocyclyl, or heteroaryl; and

R_{11} is alkyl optionally substituted with cyano, haloalkyl, cycloalkyl or heterocyclyl.

20. The compound of claim 19, wherein n is 1.

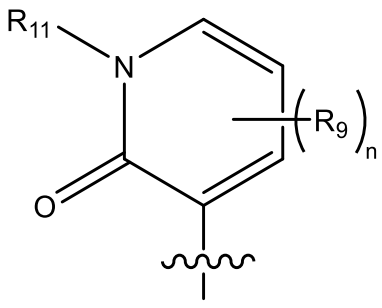
21. The compound of claim 19, wherein n is 2.

22. The compound of claim 19, wherein A is



.

23. The compound of claim 19, wherein A is



.

24. The compound of any one of claims 19-23, wherein R_9 is alkyl or halogen.

25. The compound of any one of claims 19-24, wherein R_{11} is alkyl or haloalkyl.

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

27. A pharmaceutical composition comprising a compound of any one of claims 1-26 and pharmaceutically acceptable excipient.

28. Use of a compound of any one of claims 1-26 or the composition of claim 27, in the manufacture of a medicament for treating a disease or disorder that is treatable by administration of an Orexin agonist.

29. Use of a compound of any one of claims 1-26 or the composition of claim 27, in the manufacture of a medicament for treating a sleep disorder in a subject in need thereof.

30. Use of a compound of any one of claims 1-26 or the composition of claim 27, in the manufacture of a medicament for treating narcolepsy in a subject in need thereof.

31. Use of a compound of any one of claims 1-26 or the composition of claim 27, in the manufacture of a medicament for treating hypersomnia in a subject in need thereof.

32. Use of a compound of any one of claims 1-26 or the composition of claim 27, in the manufacture of a medicament for decreasing or treating excessive sleepiness in a subject in need thereof.

33. A compound of the compound of any one of claims 1-26 or the composition of claim 27, for use in therapy.