

[0009] Finally the Orexin/OX₁ pathway has been implicated in nicotine self-administration (33, 34) and re-instatement of nicotine seeking (35, 36). Such data suggest that OX₁ antagonists could find utility as smoking cessation therapies.

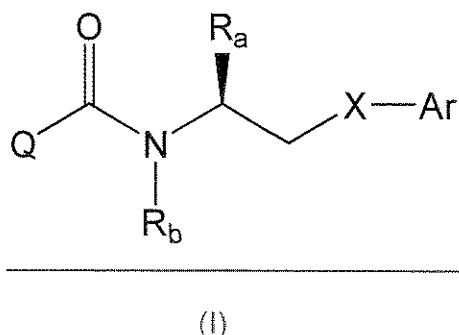
5 [0010] Taken together the orexin system, in particular the OX₁ pathway may be considered a target for the treatment of reward seeking behaviours, addiction and related disorders.

[0011] There is therefore a need for compounds capable of attenuating orexin-1 (OX₁) activity. There is a further need for compounds capable of selectively modulating orexin-1 (OX₁) function.

10

SUMMARY OF THE INVENTION

[0012] In one aspect, the present invention provides a compound of Formula I

15 wherein:

R_a is ethyl, propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, or cyclopropylmethyl, each of which is optionally substituted by one or more fluoro;

R_b is selected from:

- 20 (i) hydrogen;
 (ii) a (1-4C)alkyl which is optionally substituted by one or more fluoro;
 (iii) a (3-6C)cycloalkyl which is optionally substituted by one or more fluoro; or
 (iv) a (3-6C)cycloalkyl(1-2C)alkyl which is optionally substituted by one or more fluoro;

X is a group:

25 $-(\text{CR}^{2a}\text{R}^{3a})_m-\text{X}^0-(\text{CR}^{2b}\text{R}^{3b})_n-$

Wherein

X⁰ is selected from -O-, -N(R₁)-, -N(R₁)-C(O)-, -C(O)-N(R₁)-, -N(R₁)C(O)N(R₁)- or -S-;

m is 0;

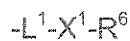
n is 0 or 1;

R1 is selected from hydrogen or a (1-2C)alkyl group which is optionally substituted by one or more (e.g. one to five) substituents selected from fluoro, hydroxyl, NR1aR1b, (1-2C)alkoxy or (1-2C)haloalkoxy;

5 R1a and R1b are each independently selected from hydrogen or (1-2C)alkyl or R1a and R1b are linked such that, together with the nitrogen atom to which they are attached, they form a 4, 5 or 6 membered heterocyclic ring;

R2a, R3a, R2b, and R3b are all hydrogen;

10 Ar is aryl or heteroaryl, each of which is optionally substituted with one or more substituents selected from the group consisting of halo, cyano, nitro or a group of the formula:



wherein

15 L¹ is absent or a linker group of the formula $-\text{[CR}^7\text{R}^8\text{]}_r\text{-}$ in which r is an integer selected from 1, 2, 3 or 4, and R⁷ and R⁸ are each independently selected from hydrogen, halo, hydroxy or a (1-4C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl group which is optionally substituted by one or more fluoro substituents; or R⁷ and R⁸ are optionally linked to such that, together with the carbon atom to which they are attached, they form a (3-6C)cycloalkyl ring which
 20 is optionally substituted by one or more fluoro substituents;

X1 is absent or selected from -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R9)-, -N(R9)-C(O)-, -C(O)-N(R9)-, -N(R9)-C(O)O-, -OC(O)-N(R9)-, -N(R9)C(O)N(R10)-, -S-, -SO-, -SO2-, -S(O)2N(R9)-, -N(R9)SO2- or -S(O)(=NR10)-, wherein R9 and R10 are selected from hydrogen, (1-4C)alkyl, (1-4C)fluoroalkyl or (3-6C)cycloalkyl; and

25 R6 is hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, aryl, aryl(1-2C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, heterocyclyl, heterocyclyl-(1-2C)alkyl, heteroaryl, or heteroaryl-(1-2C)alkyl,

30 and wherein R6 is optionally further substituted by one or more substituent groups independently selected from oxo, halo, cyano, nitro, or a group of the formula:



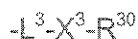
wherein

L^2 is absent or a linker group of the formula $-[CR^{12}R^{13}]_s-$ in which s is an integer selected from 1, 2, 3 or 4, and R^{12} and R^{13} are each independently selected from hydrogen or a (1-4C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl group which is optionally substituted by one or more fluoro substituents; or R^{12} and R^{13} are optionally linked to such that, together with the carbon atom to which they are attached, they form a (3-6C)cycloalkyl ring which is optionally substituted by one or more fluoro substituents;

X_2 is absent or selected from -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R14)-, -N(R14)-C(O)-, -C(O)-N(R14)-, -N(R14)-C(O)O-, -OC(O)-N(R14)-, -N(R14)C(O)N(R15)-, -S-, -SO-, -SO₂-, -S(O)₂N(R14)-, -N(R14)SO₂- or -S(O)(=NR14)-, wherein R14 and R15 are selected from hydrogen, (1-4C)alkyl, (1-4C)fluoroalkyl or (3-6C)cycloalkyl; and

R_{11} is hydrogen or a (1-6C)alkyl (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl group which is optionally substituted by one or more fluoro substituents;

Q is aryl or heteroaryl, each of which is optionally substituted with one or more R^Z substituents, wherein R^Z is selected from the group consisting of halo, cyano, nitro, or a group of the formula:



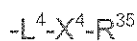
wherein

L^3 is absent or a linker group of the formula $-[CR^{31}R^{32}]_t-$ in which t is an integer selected from 1, 2, 3 or 4, and R^{31} and R^{32} are each independently selected from hydrogen or a (1-4C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl group which is optionally substituted by one or more fluoro substituents; or R^{31} and R^{32} are optionally linked to such that, together with the carbon atom to which they are attached, they form a (3-6C)cycloalkyl ring which is optionally substituted by one or more fluoro substituents;

X_3 is absent, -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R33)-, -N(R33)-C(O)-, -C(O)-N(R33)-, -N(R33)-C(O)O-, -OC(O)-N(R33)-, -N(R33)C(O)N(R34)-, -S-, -SO-, -SO₂-, -S(O)₂N(R33)-, -N(R33)SO₂- or -S(O)(=NR33)-, wherein R33 and R34 are selected from hydrogen, (1-4C)alkyl, (1-4C)fluoroalkyl or (3-6C)cycloalkyl; and

R30 is hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, aryl, aryl(1-2C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, heterocyclyl, heterocyclyl-(1-2C)alkyl, heteroaryl, or heteroaryl-(1-2C)alkyl,

and wherein R³⁰ is optionally further substituted by one or more substituent groups independently selected from oxo, halo, cyano, nitro, or a group of the formula:



Wherein

L4 is absent or a linker group of the formula $-[CR^{36}R^{37}]_u-$ in which u is an integer selected from 1, 2, 3 or 4, and R36 and R37 are each independently selected from hydrogen or a (1-4C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl group which is optionally substituted by one or more fluoro substituents; or R36 and R37 are optionally linked to such that, together with the carbon atom to which they are attached, they form a (3-6C)cycloalkyl ring which is optionally substituted by one or more fluoro substituents;

X4 is absent or selected from -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R38)-, -N(R38)-C(O)-, -C(O)-N(R38)-, -N(R38)-C(O)O-, -OC(O)-N(R38)-, -N(R38)C(O)N(R39)-, -S-, -SO-, -SO2-, -S(O)2N(R38)-, -N(R38)SO2- or -S(O)(=NR38)-, wherein R38 and R39 are selected from hydrogen, (1-4C)alkyl, (1-4C)fluoroalkyl or (3-6C)cycloalkyl; and

R35 is hydrogen or a (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl group which is optionally substituted by one or more fluoro substituents;

or a pharmaceutically acceptable salt or solvate thereof. Also disclosed is a compound, or a pharmaceutically acceptable salt or solvate thereof as defined herein.

[0012a] In another aspect, the present invention provides a compound which is selected from any one of the following:

(S)-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide;

(S)-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide;

(S)-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-N-methyl-[1,1'-biphenyl]-2-carboxamide;

(S)-N-(1-((5-chloropyridin-2-yl)amino)-3-methylbutan-2-yl)-[1,1'-biphenyl]-2-carboxamide;

- (S)-N-(1-((5-chloropyridin-2-yl)amino)-4-methylpentan-2-yl)-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)-3-methylbutan-2-yl)-2-methyl-4-phenylthiazole-5-carboxamide;
- 5 (S)-N-(1-((5-chloropyridin-2-yl)amino)-4-methylpentan-2-yl)-2-methyl-4-phenylthiazole-5-carboxamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)-4-methylpentan-2-yl)-N-methyl-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)-4-methylpentan-2-yl)-N,2-dimethyl-4-phenylthiazole-5-carboxamide;
- 10 (S)-N-(1-((5-chloropyridin-2-yl)amino)-3-methylbutan-2-yl)-N-methyl-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)-3-methylbutan-2-yl)-N,2-dimethyl-4-phenylthiazole-5-carboxamide;
- 15 (S)-N-(1-((5-chloropyridin-2-yl)amino)-3,3-dimethylbutan-2-yl)-N-methyl-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-(2-((5-chloropyridin-2-yl)amino)-1-cyclopropylethyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)propan-2-yl)-N-methyl-[1,1'-biphenyl]-2-carboxamide;
- 20 (S)-N-(1-((5-chloropyridin-2-yl)amino)-3-methylbutan-2-yl)-N-cyclopropyl-[1,1'-biphenyl]-2-carboxamide;
- (S)-5-chloro-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide;
- 25 (S)-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-N-methyl-2-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)benzamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-5-fluoro-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide;
- (S)-5-bromo-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide;
- 30 (S)-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-N-methyl-2-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethoxy)benzamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- 35 (S)-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-N,5-dimethyl-2-morpholinobenzamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-5-(dimethylamino)-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide;

- (S)-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-N-methyl-2-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)nicotinamide;
- (S)-5-chloro-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide;
- 5 (S)-N-(1-((5-chloropyridin-2-yl)amino)-3-methylbutan-2-yl)-N,2-dimethyl-5-phenylthiazole-4-carboxamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)-3-methylbutan-2-yl)-N-methyl-2-phenyl-1H-indole-3-carboxamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)-3-methylbutan-2-yl)-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide;
- 10 (S)-N-(1-((4-fluorobenzyl)oxy)-3-methylbutan-2-yl)-N-methyl-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-(1-((4,6-dimethylpyrimidin-2-yl)oxy)-3-methylbutan-2-yl)-N-methyl-[1,1'-biphenyl]-2-carboxamide;
- 15 (S)-N-methyl-N-(3-methyl-1-(quinazolin-2-yloxy)butan-2-yl)-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-methyl-N-(3-methyl-1-((4-phenylpyrimidin-2-yl)oxy)butan-2-yl)-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-methyl-N-(3-methyl-1-((1-methyl-1H-benzof[d]imidazol-2-yl)oxy)butan-2-yl)-[1,1'-biphenyl]-2-carboxamide;
- 20 (S)-N-(1-((5-chloropyridin-2-yl)oxy)-3-methylbutan-2-yl)-N-methyl-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-methyl-N-(3-methyl-1-((4-phenylpyrimidin-2-yl)amino)butan-2-yl)-[1,1'-biphenyl]-2-carboxamide;
- 25 (S)-N-methyl-N-(3-methyl-1-(quinazolin-2-ylamino)butan-2-yl)-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-(1-((4,6-dimethylpyrimidin-2-yl)amino)-3-methylbutan-2-yl)-N-methyl-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-methyl-N-(3-methyl-1-((1-methyl-1H-benzof[d]imidazol-2-yl)amino)butan-2-yl)-[1,1'-biphenyl]-2-carboxamide;
- 30 (S)-5-chloro-N-methyl-2-(2H-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)benzamide;
- (S)-5-chloro-N-methyl-2-(2H-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyrazin-2-yl)amino)butan-2-yl)benzamide;
- 35 (S)-5-chloro-N-methyl-2-(2H-1,2,3-triazol-2-yl)-N-(1-((6-(trifluoromethyl)pyridazin-3-yl)amino)butan-2-yl)benzamide;

- (S)-5-chloro-N-methyl-2-(2H-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyridin-2-yl)amino)butan-2-yl)benzamide;
- (S)-N-(1-(benzo[d]oxazol-2-ylamino)butan-2-yl)-5-chloro-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide;
- 5 (S)-N-(1-(benzo[d]thiazol-2-ylamino)butan-2-yl)-5-chloro-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide;
- (S)-5-chloro-N-(1-((5-chloro-3-nitropyridin-2-yl)amino)butan-2-yl)-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide;
- (S)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)picolinamide;
- 10 (S)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyrazin-2-yl)amino)butan-2-yl)picolinamide;
- (S)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyridin-2-yl)amino)butan-2-yl)picolinamide;
- 15 (S)-N-(1-((5-chloropyridin-2-yl)amino)-3-methylbutan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)-3-methylbutan-2-yl)-N,1-dimethyl-1H-indole-3-carboxamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)-3-methylbutan-2-yl)-N,2-dimethylquinoline-4-
- 20 carboxamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)-3-methylbutan-2-yl)-N-methyl-2-(trifluoromethoxy)benzamide;
- (S)-5-chloro-N-methyl-N-(1-((6-methylpyridin-2-yl)amino)butan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide;
- 25 (S)-5-chloro-N-methyl-2-(2H-1,2,3-triazol-2-yl)-N-(1-((6-(trifluoromethyl)pyridin-3-yl)amino)butan-2-yl)benzamide;
- (S)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)-N-(1-((6-(trifluoromethyl)pyridin-3-yl)amino)butan-2-yl)picolinamide;
- (S)-N-(1-(4-fluorobenzamido)-3-methylbutan-2-yl)-N-methyl-[1,1'-biphenyl]-2-
- 30 carboxamide;
- (S)-N-(1-((4-fluorobenzyl)amino)-3-methylbutan-2-yl)-N-methyl-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-methyl-N-(3-methyl-1-(3-phenylureido)butan-2-yl)-[1,1'-biphenyl]-2-carboxamide;
- (S)-N-(1-((4-chlorophenyl)amino)-3-methylbutan-2-yl)-N-methyl-[1,1'-biphenyl]-2-
- 35 carboxamide;
- (S)-N-(1-((3-amino-5-chloropyridin-2-yl)amino)butan-2-yl)-5-chloro-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide;

- (S)-N,6-dimethyl-N-(1-(quinazolin-2-ylamino)butan-2-yl)-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- (S)-N-(1-(benzo[d]oxazol-2-ylamino)butan-2-yl)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- 5 (S)-N-(1-(benzo[d]thiazol-2-ylamino)butan-2-yl)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- (S)-N-(1-((5-chlorobenzo[d]oxazol-2-yl)amino)butan-2-yl)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- (S)-N,6-dimethyl-N-(1-(quinoxalin-2-ylamino)butan-2-yl)-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- 10 (S)-N,6-dimethyl-N-(3-methyl-1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- (S)-N,6-dimethyl-N-(3-methyl-1-((5-(trifluoromethyl)pyrazin-2-yl)amino)butan-2-yl)-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- 15 (S)-N,6-dimethyl-N-(3-methyl-1-(quinazolin-2-ylamino)butan-2-yl)-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- (S)-N,6-dimethyl-N-(3-methyl-1-((5-(trifluoromethyl)pyridin-2-yl)amino)butan-2-yl)-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- (S)-N-ethyl-6-methyl-3-(2H-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyrazin-2-yl)amino)butan-2-yl)picolinamide;
- 20 (S)-N-ethyl-6-methyl-3-(2H-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyridin-2-yl)amino)butan-2-yl)picolinamide;
- (S)-N-ethyl-6-methyl-N-(1-(quinazolin-2-ylamino)butan-2-yl)-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- 25 (S)-N-ethyl-6-methyl-3-(2H-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)picolinamide;
- (S)-N-(1-cyclopropyl-2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)ethyl)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- (S)-N,6-dimethyl-N-(1-(quinolin-2-ylamino)butan-2-yl)-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- 30 (S)-N-(1-((1,5-naphthyridin-2-yl)amino)butan-2-yl)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- (S)-5-chloro-N-methyl-N-(1-(quinolin-2-ylamino)butan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide;
- 35 (S)-N,3-dimethyl-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)isoquinoline-1-carboxamide;

- (S)-N-methyl-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)quinoline-8-carboxamide;
- (S)-6-chloro-N-methyl-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)quinoline-8-carboxamide;
- 5 (S)-3-(dimethylamino)-N-methyl-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)isoquinoline-1-carboxamide;
- (S)-N,6-dimethyl-N-(1-(methyl(5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- (S)-N-(1-((2-methoxyethyl)(5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)-N,6-
- 10 dimethyl-3-(2H-1,2,3-triazol-2-yl)picolinamide;
- (S)-N,6-dimethyl-3-(pyrimidin-2-yl)-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)picolinamide formic acid salt;
- (S)-N-methyl-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)isoquinoline-1-carboxamide;
- 15 (S)-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-N,4,5-trimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide;
- (S)-N-(1-((5-chloropyridin-2-yl)amino)butan-2-yl)-5-methoxy-N,4-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide;
- (S)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)-N-(4,4,4-trifluoro-1-((5-
- 20 (trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)picolinamide;
- (S)-N,6-dimethyl-3-(1H-1,2,4-triazol-1-yl)-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)picolinamide formic acid salt;
- (S)-N,6-dimethyl-3-(1H-pyrazol-1-yl)-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)picolinamide formic acid salt;
- 25 (S)-2-fluoro-N-methyl-6-(2H-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)benzamide;
- (S)-6-methoxy-N-methyl-3-(2H-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)picolinamide; or a pharmaceutically acceptable salt or solvate thereof.
- 30 **[0013]** In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the invention as defined herein, or a pharmaceutically acceptable salt or solvate thereof, and one or more pharmaceutically acceptable excipients.
- [0014]** In another aspect, the present invention relates to a compound of the invention as defined herein, or a pharmaceutically acceptable salt or solvate thereof, or a
- 35 pharmaceutical composition as defined herein, for use in therapy.

[0015] In another aspect, the present invention relates to a compound as described herein, for use in the treatment of schizophrenia and other psychotic disorders (e.g., psychotic disorder, psychosis or schizoaffective disorder); dementia and other cognitive disorders; anxiety disorders (e.g., generalized anxiety disorder, post-traumatic stress disorder, panic disorders, acute stress disorder, social anxiety disorder, phobias including agoraphobia, obsessive compulsive disorder, trichlofillomania or body dismorphic disorder); mood disorders (e.g., depressive disorders, major depressive disorders, bipolar disorders including bipolar I and II, bipolar mania, bipolar depression); addiction including substance dependence (e.g. cocaine, opiates, cannabis or prescription drug dependence), alcohol dependence, nicotine dependence or gambling disorder; eating disorders (e.g. binge eating, bulimia nervosa, anorexia nervosa or obesity); sleep disorders (e.g. rapid eye movement sleep disorder); disorders usually first diagnosed in infancy, childhood, or adolescence (e.g., attention-deficit disorder, autistic spectrum disorders, Rett syndrome, Fragile X syndrome, Asperger syndrome and disruptive behaviour disorders); restless leg syndrome; pain (e.g. neuropathic pain including chemotherapy induced pain or migraine); osteoporosis and neurodegenerative disorders (e.g. Parkinson's or Alzheimer's disease). Also disclosed is a compound of the invention as defined herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of diseases or conditions in which orexin-1 (OX₁) activity is implicated.

~~**[0016]** In another aspect, the present invention relates to~~ Also disclosed is the use of a compound of the invention as defined herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for use in the treatment of diseases or conditions in which orexin-1 (OX₁) activity is implicated.

[0017] In another aspect, the present invention relates to use of a compound as described herein, or a pharmaceutically acceptable salt or solvate therefore in the manufacture of a medicament for treating a disease or condition selected from schizophrenia and other psychotic disorders (e.g., psychotic disorder, psychosis or schizoaffective disorder); dementia and other cognitive disorders; anxiety disorders (e.g., generalized anxiety disorder, post-traumatic stress disorder, panic disorders, acute stress disorder, social anxiety disorder, phobias including agoraphobia, obsessive compulsive disorder, trichlofillomania or body dismorphic disorder); mood disorders (e.g., depressive disorders, major depressive disorders, bipolar disorders including bipolar I and II, bipolar mania, bipolar depression); addiction including substance dependence (e.g. cocaine, opiates, cannabis or prescription drug dependence), alcohol dependence, nicotine dependence or gambling disorder; eating disorders (e.g. binge eating, bulimia

5 nervosa, anorexia nervosa or obesity); sleep disorders (e.g. rapid eye movement sleep
disorder); disorders usually first diagnosed in infancy, childhood, or adolescence (e.g.,
attention-deficit disorder, autistic spectrum disorders, Rett syndrome, Fragile X
syndrome, Asperger syndrome and disruptive behaviour disorders); restless leg
syndrome; pain (e.g. neuropathic pain including chemotherapy induced pain or
migraine); osteoporosis and neurodegenerative disorders (e.g. Parkinson's or
Alzheimer's disease). Also disclosed is a method of treating a disease or condition in
which orexin-1 (OX₁) activity is implicated, said method comprising administering to a
subject in need of such treatment a therapeutically effective amount of a compound of
10 the invention as defined herein, or a pharmaceutically acceptable salt or solvate thereof,
or a pharmaceutical composition as defined herein.

[0018] Examples of conditions in which orexin-1 (OX₁) activity is implicated include
behavioural arousal, eating disorders (e.g. binge eating, obesity), psychiatric conditions

(e.g. schizophrenia, anxiety, mood disorders, reward seeking behaviours, alcohol or drug (e.g. nicotine) addiction, panic disorders (such as panic attacks) and/or anxiety).

[0019] ~~In another aspect, the present invention provides~~ Also disclosed is a compound, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of behavioural arousal, eating disorders (e.g. binge eating, obesity), psychiatric conditions (e.g. schizophrenia, anxiety, mood disorders, reward seeking behaviours, alcohol or drug (e.g. nicotine) addiction, panic disorders (such as panic attacks) and/or anxiety).

[0020] ~~In another aspect, the present invention provides~~ Also disclosed is the use of a compound, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for use in the treatment of behavioural arousal, eating disorders (e.g. binge eating, obesity), psychiatric conditions (e.g. schizophrenia, anxiety, mood disorders, reward seeking behaviours, alcohol or drug (e.g. nicotine) addiction, panic disorders (such as panic attacks) and/or anxiety).

[0021] ~~In another aspect, the present invention provides~~ Also disclosed is a method of treating behavioural arousal, eating disorders (e.g. binge eating, obesity), psychiatric conditions (e.g. schizophrenia, anxiety, mood disorders, reward seeking behaviours, alcohol or drug (e.g. nicotine) addiction, panic disorders (such as panic attacks) and/or anxiety), said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as defined herein.

[0022] ~~In another aspect, the present invention provides~~ Also disclosed is a compound, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as defined herein, for use in the production of an orexin-1 inhibitory effect.

[0023] ~~In another aspect, the present invention provides~~ Also disclosed is the use of a compound, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for use in the production of an orexin-1 inhibitory effect.

[0024] ~~In another aspect, the present invention provides~~ Also disclosed is a method of producing an orexin-1 inhibitory effect *in vitro*, said method comprising administering an effective amount of a compound, or a pharmaceutically acceptable salt or solvate thereof.

[0025] ~~In another aspect, the present invention provides~~ Also disclosed is a method of producing an orexin-1 inhibitory effect *in vivo*, said method comprising administering an effective amount of a compound, or a pharmaceutically acceptable salt or solvate thereof.

~~[0026] In another aspect, the present invention provides~~Also disclosed is a method of inhibiting orexin-1 (OX₁) *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound as defined herein, or a pharmaceutically acceptable salt or solvate thereof.

5 ~~[0027] The present invention-disclosure~~ further provides a method of synthesising a compound, or a pharmaceutically acceptable salt or solvate thereof, as defined herein.

~~[0028] In another aspect, the present invention provides~~Also disclosed is a compound, or a pharmaceutically acceptable salt or solvate thereof, obtainable by, or obtained by, or directly obtained by a method of synthesis as defined herein.

10 ~~[0029] In another aspect, the present invention provides~~Also disclosed is novel intermediates as defined herein which are suitable for use in any one of the synthetic methods set out herein.

~~[0030] Preferred, suitable, and optional features of any one particular aspect of the present invention are also preferred, suitable, and optional features of any other aspect.~~

15

DETAILED DESCRIPTION OF THE INVENTION

Definitions

~~[0031] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.~~

20 ~~[0032] It is to be appreciated that references to "treating" or "treatment" include prophylaxis as well as the alleviation of established symptoms of a condition. "Treating" or "treatment" of a state, disorder or condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human that may be afflicted with or predisposed to the state, disorder or~~
 25 ~~condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, *i.e.*, arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, *i.e.*, causing regression of the state, disorder or~~
 30 ~~condition or at least one of its clinical or subclinical symptoms.~~

~~[0033] A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.~~

(S)-2-fluoro-N-methyl-6-(2*H*-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)benzamide;
 (S)-6-methoxy-N-methyl-3-(2*H*-1,2,3-triazol-2-yl)-N-(1-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butan-2-yl)picolinamide; or a pharmaceutically acceptable salt or solvate thereof.

26. A pharmaceutical composition comprising a compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt or solvate thereof, and one or more pharmaceutically acceptable excipients.

27. A compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as defined herein, for use in therapy.

28. A compound according to any one of claims 1 to 25, for use in the treatment of schizophrenia and other psychotic disorders (e.g., psychotic disorder, psychosis or schizoaffective disorder); dementia and other cognitive disorders; anxiety disorders (e.g., generalized anxiety disorder, post-traumatic stress disorder, panic disorders, acute stress disorder, social anxiety disorder, phobias including agoraphobia, obsessive compulsive disorder, trichotillomania or body dysmorphic disorder); mood disorders (e.g., depressive disorders, major depressive disorders, bipolar disorders including bipolar I and II, bipolar mania, bipolar depression); addiction including substance dependence (e.g. cocaine, opiates, cannabis or prescription drug dependence), alcohol dependence, nicotine dependence or gambling disorder; eating disorders (e.g. binge eating, bulimia nervosa, anorexia nervosa or obesity); sleep disorders (e.g. rapid eye movement sleep disorder); disorders usually first diagnosed in infancy, childhood, or adolescence (e.g., attention-deficit disorder, autistic spectrum disorders, Rett syndrome, Fragile X syndrome, Asperger syndrome and disruptive behaviour disorders); restless leg syndrome; pain (e.g. neuropathic pain including chemotherapy induced pain or migraine); osteoporosis and neurodegenerative disorders (e.g. Parkinson's or Alzheimer's disease).

~~A method of~~ Use of a compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating a disease or condition selected from schizophrenia and other psychotic disorders (e.g., psychotic disorder, psychosis or schizoaffective disorder); dementia and other cognitive disorders; anxiety disorders (e.g., generalized anxiety disorder, post-traumatic stress disorder, panic disorders, acute stress disorder, social anxiety disorder, phobias including agoraphobia, obsessive compulsive disorder, trichotillomania or body dysmorphic disorder); mood disorders (e.g., depressive

disorders, major depressive disorders, bipolar disorders including bipolar I and II, bipolar mania, bipolar depression); addiction including substance dependence (e.g. cocaine, opiates, cannabis or prescription drug dependence), alcohol dependence, nicotine dependence or gambling disorder; eating disorders (e.g. binge eating, bulimia nervosa, anorexia nervosa or obesity); sleep disorders (e.g. rapid eye movement sleep disorder); disorders usually first diagnosed in infancy, childhood, or adolescence (e.g., attention-deficit disorder, autistic spectrum disorders, Rett syndrome, Fragile X syndrome, Asperger syndrome and disruptive behaviour disorders); restless leg syndrome; pain (e.g. neuropathic pain including chemotherapy induced pain or migraine); osteoporosis and neurodegenerative disorders (e.g. Parkinson's or Alzheimer's disease), said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt or solvate thereof.