(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 October 2009 (15.10.2009)

PCT

(10) International Publication Number
WO 2009/124956 A1

(51) International Patent Classification:
C07D 401/12 (2006.01) *A61P 25/22* (2006.01)
A61K 31/4545 (2006.01) *A61P 25/24* (2006.01)
A61P 25/00 (2006.01) *A61P 25/30* (2006.01)

(21) International Application Number:
PCT/EP2009/054189

(22) International Filing Date:
8 April 2009 (08.04.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0806536.9 10 April 2008 (10.04.2008) GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 ONN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ALVARO, Giuseppe** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **AMANTINI, David** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **STASI, Luigi, Piero** [IT/IT]; c/o GlaxoSmithKline SpA, Via Alessandro Fleming 2, I-37135 Verona (IT).

(74) Agents: **LAWRENCE, Geoffrey, Mark, Prouse** et al.; GlaxoSmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

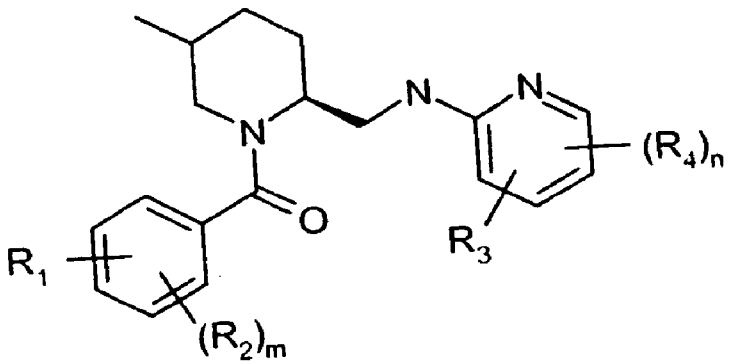
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: PYRIDINE DERIVATIVES USED TO TREAT OREXIN RELATED DISORDERS



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(57) Abstract: This invention relates to pyridinamine methyl substituted piperidinyl derivatives I and their use as pharmaceuticals.

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PYRIDINE DERIVATIVES USED TO TREAT OREXIN RELATED DISORDERS

This invention relates to pyridinamine methyl substituded piperidinyl derivatives and their use as pharmaceuticals.

Many medically significant biological processes are mediated by proteins participating in signal transduction pathways that involve G-proteins and/or second messengers.

Polypeptides and polynucleotides encoding the human 7-transmembrane G-protein coupled neuropeptide receptor, orexin-1 (HFGAN72), have been identified and are disclosed in EP875565, EP875566 and WO96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP849361.

The orexin ligand and receptor system has been well characterised since its discovery (see for example Sakurai, T. et al (1998) Cell, 92 pp 573 to 585; Smart et al (1999) British Journal of Pharmacology 128 pp1 to 3; Willie et al (2001) Ann. Rev. Neurosciences 24 pp429 to 458; Sakurai (2007) Nature Reviews Neuroscience 8 pp 171 to 181; Ohno and Sakurai (2008) Front. Neuroendocrinology 29 pp70 to 87). From these studies it has become clear that orexins and orexin receptors play a number of important physiological roles in mammals and open up the possibility of the development of new therapeutic treatments for a variety of diseases and disorders as described hereinbelow.

Experiments have shown that central administration of the ligand orexin-A stimulated food intake in freely-feeding rats during a 4 hour time period. This increase was approximately four-fold over control rats receiving vehicle. These data suggest that orexin-A may be an endogenous regulator of appetite (Sakurai, T. et al (1998) Cell, 92 pp 573 to 585; Peyron et al (1998) J. Neurosciences 18 pp9996 to 10015; Willie et al (2001) Ann. Rev. Neurosciences 24 pp429 to 458). Therefore, antagonists of the orexin-A receptor(s) may be useful in the treatment of obesity and diabetes. In support of this it has been shown that orexin receptor antagonist SB334867 potently reduced hedonic eating in rats (White et al (2005) Peptides 26 pp2231 to 2238) and also attenuated high-fat pellet self-administration in rats (Nair et al (2008) British Journal of Pharmacology, published online 28 January 2008). The search for new therapies to treat obesity and other eating disorders is an important challenge. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese in westernised societies. It has been estimated that 5.7% of all healthcare costs in the USA are a consequence of obesity. About 85% of Type 2 diabetics are obese. Diet and exercise are of value in all diabetics. The incidence of diagnosed diabetes in westernised countries is typically 5% and there are estimated to be an equal number undiagnosed. The incidence of both diseases is rising, demonstrating the inadequacy of current treatments which may be either ineffective or have toxicity risks including cardiovascular effects. Treatment of diabetes with sulfonylureas or insulin can cause hypoglycaemia, whilst metformin causes GI side-effects. No drug treatment for Type 2 diabetes has been shown

to reduce the long-term complications of the disease. Insulin sensitisers will be useful for many diabetics, however they do not have an anti-obesity effect.

As well as having a role in food intake, the orexin system is also involved in sleep and wakefulness. Rat sleep/EEG studies have shown that central administration of orexin-A, an agonist of the orexin receptors, causes a dose-related increase in arousal, largely at the expense of a reduction in paradoxical sleep and slow wave sleep 2, when administered at the onset of the normal sleep period (Hagan et al (1999) Proc.Natl.Acad.Sci. 96 pp10911 to 10916). The role of the orexin system in sleep and wakefulness is now well established (Sakurai (2007) Nature Reviews Neuroscience 8 pp 171 to 181; Ohno and Sakurai (2008) Front. Neuroendocrinology 29 pp70 to 87; Chemelli et al (1999) Cell 98 pp437 to 451; Lee et al (2005) J. Neuroscience 25 pp6716 to 6720; Piper et al (2000) European J Neuroscience 12 pp726-730 and Smart and Jerman (2002) Pharmacology and Therapeutics 94 pp51 to 61). Antagonists of the orexin receptors may therefore be useful in the treatment of sleep disorders including insomnia. Studies with orexin receptor antagonists, for example SB334867, in rats (see for example Smith et al (2003) Neuroscience Letters 341 pp256 to 258) and more recently dogs and humans (Brisbare-Roch et al (2007) Nature Medicine 13(2) pp150 to 155) further support this.

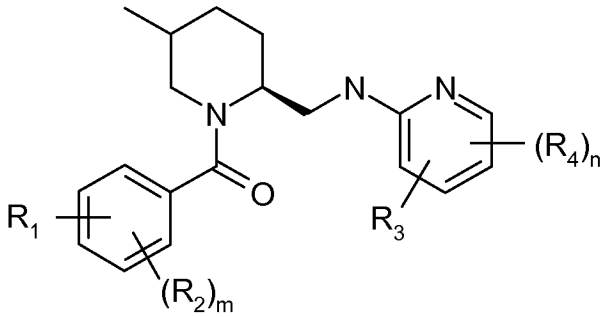
In addition, recent studies have suggested a role for orexin antagonists in the treatment of motivational disorders, such as disorders related to reward seeking behaviours for example drug addiction and substance abuse (Borgland et al (2006) Neuron 49(4) pp589-601; Boutrel et al (2005) Proc.Natl.Acad.Sci. 102(52) pp19168 to 19173; Harris et al (2005) Nature 437 pp556 to 559).

International Patent Applications WO99/09024, WO99/58533, WO00/47577 and WO00/47580 disclose phenyl urea derivatives and WO00/47576 discloses quinolinyl cinnamide derivatives as orexin receptor antagonists. WO05/118548 discloses substituted 1,2,3,4-tetrahydroisoquinoline derivatives as orexin antagonists.

WO01/96302, WO02/44172, WO02/89800, WO03/002559, WO03/002561, WO03/032991, WO03/037847, WO03/041711 and WO08/038251 all disclose cyclic amine derivatives. In addition WO02/090355 discloses unsubstituted piperidine derivatives and WO04/026866 discloses dialkyl substituted piperidine derivatives as orexin antagonists.

The present invention relates to piperidine derivatives which are monosubstituted with a methyl group at the 5 position on the piperidine ring. The compounds of the invention have been shown to have advantageous properties compared with the compounds in the prior art. These advantages include higher binding affinity to the orexin receptors and an increased bioavailability over prior art compounds when administered *in-vivo*. Such benefits make the compounds of the invention attractive candidates for use in therapies directed to the treatment of diseases and disorders associated with the orexin system.

The invention provides compounds of formula (I):



(I)

where:

R_1 is C_{1-4}alkyl, halo, C_{1-4}alkoxy, haloC_{1-4}alkyl or haloC_{1-4}alkoxy;

R_2 is C_{1-4}alkyl, halo, C_{1-4}alkoxy, haloC_{1-4}alkyl or haloC_{1-4}alkoxy;

R_3 is C_{1-4}alkyl, halo, C_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy or cyano;

R_4 is C_{1-4}alkyl, halo, C_{1-4}alkoxy, haloC_{1-4}alkyl or haloC_{1-4}alkoxy; and

m is 0 or 1;

n is 0 or 1;

provided that when m is 1 and one of R_1 and R_2 is trifuoromethyl, the other is not trifluoromethyl;

or a pharmaceutically acceptable derivative salt thereof.

In one embodiment of the present invention the compound has the methyl at the 5 position on the piperidyl ring in the 5*S* isomeric form. In another embodiment the compound has the methyl at the 5 position on the piperidyl ring in the 5*R* isomeric form. In a further embodiment the compound has a racemic mixture of both 5*S* and 5*R* isomeric forms.

In one embodiment n is 0.

In another embodiment n is 1.

In one embodiment m is 0.

In another embodiment m is 1.

In one embodiment R_1 is C_{1-4}alkyl. In another embodiment R_1 is methyl.

In one embodiment R_1 is C_{1-4}alkoxy. In another embodiment R_1 is methyloxy, ethyloxy or propyloxy.

In one embodiment R_1 is halo. In another embodiment R_1 is fluoro or chloro.

In one embodiment R_1 is haloC_{1-4}alkoxy. In another embodiment R_1 is trifluoromethyloxy.

In one embodiment m is 1, R_1 is C_{1-4}alkoxy and R_2 is C_{1-4}alkoxy. In another embodiment m is 1, R_1 is ethyloxy and R_2 is ethyloxy.

In one embodiment m is 1, R_1 is C_{1-4}alkoxy and R_2 is halo. In another embodiment m is 1, R_1 is methyloxy and R_2 is fluoro. In a further embodiment m is 1, R_1 is methyloxy and R_2 is chloro. In a still further embodiment m is 1, R_1 is ethyloxy and R_2 is chloro. In a yet further embodiment m is 1, R_1 is 2-methylpropyloxy and R_2 is

chloro. In a still further embodiment m is 1, R_1 is ethyloxy and R_2 is fluoro. In a yet further embodiment m is 1, R_1 is propyloxy and R_2 is fluoro.

In one embodiment m is 1, R_1 is methyloxy which is attached at the 2 position on the phenyl ring and R_2 is fluoro which is attached at the 3 position on the phenyl ring.

In one embodiment R_3 is halo. In another embodiment R_3 is bromo, chloro or fluoro. In a still further embodiment R_3 is bromo.

In one embodiment R_3 is C_{1-4}alkyl. In another embodiment R_3 is methyl.

In one embodiment R_3 is cyano.

In one embodiment R_3 is haloC_{1-4}alkyl. In another embodiment R_3 is trifluoromethyl.

In a further embodiment R_3 is attached at the 5 position of the pyridyl ring.

In one embodiment n is 1 and R_4 is C_{1-4}alkyl. In another embodiment n is 1 and R_4 is methyl.

In one embodiment n is 1 and R_4 is halo. In another embodiment n is 1 and R_4 is fluoro.

In one embodiment n is 1, R_3 is halo and R_4 is C_{1-4}alkyl. In another embodiment n is 1, R_3 is fluoro and R_4 is methyl.

In one embodiment n is 1, R_3 is halo and R_4 is halo. In another embodiment n is 1, R_3 is fluoro and R_4 is fluoro.

In one embodiment m is 1, n is 0, R_1 is C_{1-4}alkoxy, R_2 is halo and R_3 is halo. In another embodiment m is 1, n is 0, R_1 is methyloxy, R_2 is fluoro and R_3 is bromo or chloro. In one embodiment m is 1, n is 0, R_1 is C_{1-4}alkoxy, R_2 is halo and R_3 is haloC_{1-4}alkyl. In another embodiment m is 1, n is 0, R_1 is methyloxy, R_2 is fluoro and R_3 is trifluoromethyl.

In a another embodiment m is 1, n is 0, R_1 is methyloxy which is attached at the 2 position on the phenyl ring, R_2 is fluoro which is attached at the 3 position on the phenyl ring and R_3 is bromo which is attached at the 5 position of the pyridyl ring.

In a further embodiment m is 1, n is 0, R_1 is methyloxy which is attached at the 2 position on the phenyl ring, R_2 is fluoro which is attached at the 3 position on the phenyl ring and R_3 is trifluoromethyl which is attached at the 5 position of the pyridyl ring.

In a still further embodiment m is 1, n is 0, R_1 is methyloxy which is attached at the 2 position on the phenyl ring, R_2 is fluoro which is attached at the 3 position on the phenyl ring and R_3 is chloro which is attached at the 5 position of the pyridyl ring.

Examples of compounds of the invention include:

N-[((2S,5S)-1-{[2,6-bis(ethyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-5-bromo-2-pyridinamine;

5-bromo-N-[((2S,5S)-5-methyl-1-{[2-(methyloxy)phenyl]carbonyl}-2-piperidinyl)methyl]-2-pyridinamine;

5-bromo-N-[((2S,5S)-1-{[2-(ethyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;

5-bromo-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;

5-bromo-N-[((2S,5S)-1-{[4-chloro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
5-bromo-N-{[(2S,5S)-5-methyl-1-({2-[(trifluoromethyl)oxy]phenyl}carbonyl)-2-piperidinyl]methyl}-2-pyridinamine;
5-bromo-N-({(2S,5S)-5-methyl-1-[(2-methylphenyl)carbonyl]-2-piperidinyl}methyl)-2-pyridinamine;
N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-6-methyl-2-pyridinamine hydrochloride;
6-methyl-N-{[(2S,5S)-5-methyl-1-({2-[(trifluoromethyl)oxy]phenyl}carbonyl)-2-piperidinyl]methyl}-2-pyridinamine;
5-bromo-N-[((2S,5S)-1-{[5-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
5-bromo-N-[((2S,5S)-1-{[4-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
5-bromo-N-[((2S,5S)-1-{[2-fluoro-6-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
N-{[(2S,5S)-1-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}carbonyl)-5-methyl-2-piperidinyl]methyl}-6-methyl-2-pyridinamine hydrochloride;
N-[((2S,5S)-1-{[5-chloro-2-(ethyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-6-methyl-2-pyridinamine hydrochloride;
6-{[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]amino}-3-pyridinecarbonitrile;
N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-5-(trifluoromethyl)-2-pyridinamine;
N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-6-(trifluoromethyl)-2-pyridinamine;
N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-3-(trifluoromethyl)-2-pyridinamine;
3,5-difluoro-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-4-(trifluoromethyl)-2-pyridinamine;
N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-5-methyl-2-pyridinamine;
5-chloro-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
5-fluoro-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-4-methyl-2-pyridinamine;
5-ethyl-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
5-chloro-N-[((2S,5S)-1-{[2-(ethyloxy)-3-fluorophenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine; and

N-[((2S,5S)-1-{[3-fluoro-2-(propyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-5-methyl-2-pyridinamine.

The compounds of the invention are (2*S*) diastereoisomers. The stereochemistry of the methyl at the 5 position on the piperidine may be either (5*R*) or (5*S*), although the racemic form of the compounds (ie. having both (5*R*) or (5*S*) configurations) are included within the scope of the invention. If required the different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses. The invention also extends to any tautomeric forms or mixtures thereof.

It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable derivatives.

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art. Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse J.Pharm.Sci (1977) 66, pp1-19. Such pharmaceutically acceptable salts include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates or formates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

The subject invention also includes isotopically-labeled compounds which are identical to those recited in formula (I) and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples if isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, iodine and chlorine such as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I or

^{125}I.

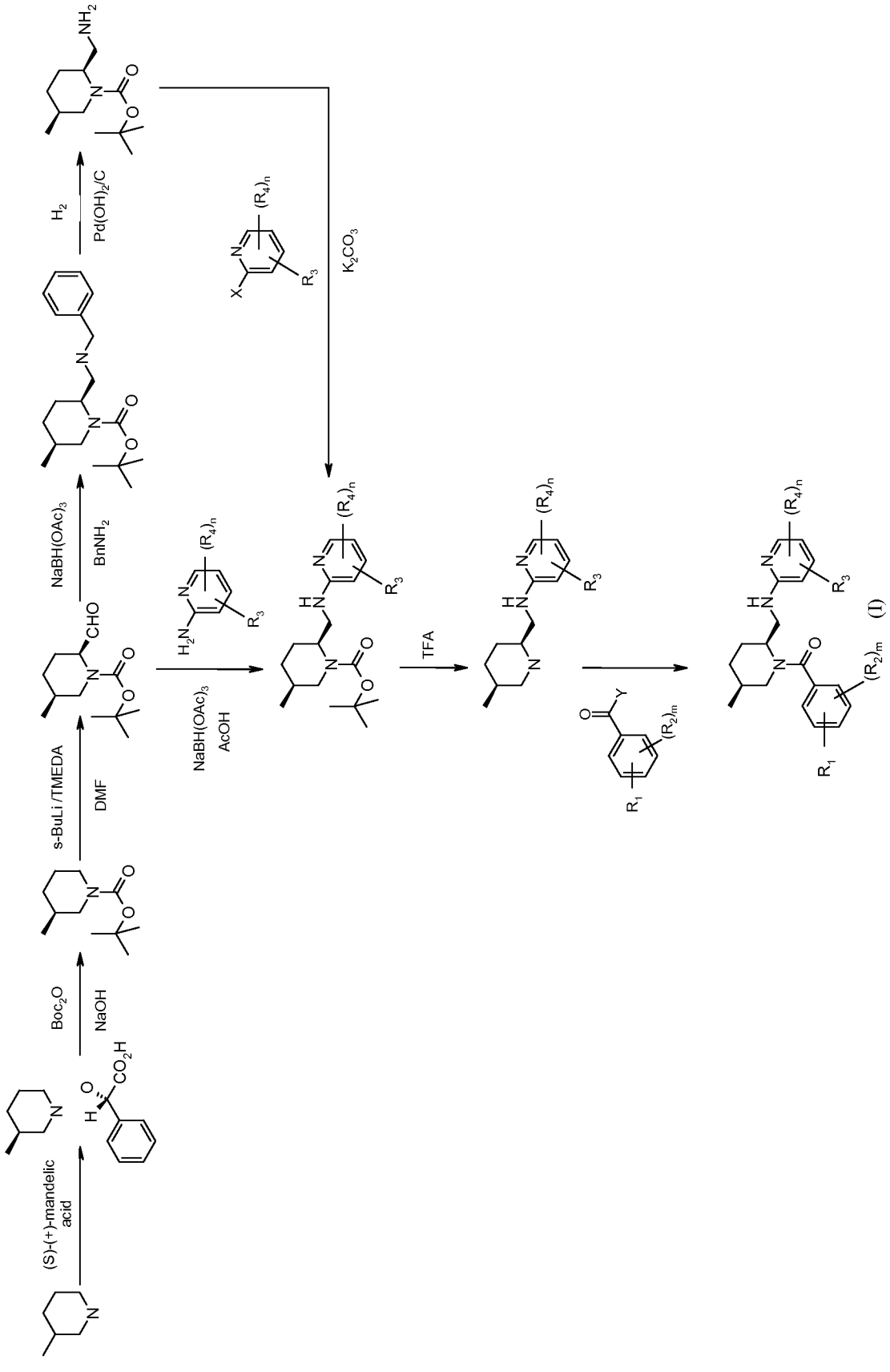
Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H or ^{14}C have been incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, ie. ^{3}H, and carbon-14, ie. ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography).

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

According to a further aspect of the present invention there is provided a process for the preparation of compounds of formula (I) and derivatives thereof. The following schemes detail some synthetic routes to compounds of the invention. In the following schemes reactive groups can be protected with protecting groups and deprotected according to well established techniques.

Schemes

According to a further feature of the invention there is provided a process for the preparation of compounds of formula (I) and derivatives thereof. The following is an example of a synthetic scheme that may be used to synthesise the compounds of the invention.


(S)-(+)-mandelic acid
Boc2O
NaOH
s-BuLi /TMEDA
DMF
NaBH(OAc)3
BnNH2
H2
Pd(OH)2/C
NaBH(OAc)3
AcOH
K2CO3
TFA
(I)

It will be understood by those skilled in the art that certain compounds of the invention can be converted into other compounds of the invention according to standard chemical methods.

The starting materials for use in the scheme are commercially available, known in the literature or can be prepared by known methods.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, e.g. 5 to 1000, preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I), or pharmaceutically acceptable derivatives thereof.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The present invention provides compounds of formula (I) and their pharmaceutically acceptable derivatives for use in human or veterinary medicine.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be of use for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as sleep disorders selected from the group consisting of Dyssomnias such as Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47); primary sleep disorders such as Parasomnias such as Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition, in particular sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases; and Substance-Induced Sleep Disorder including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type; Sleep Apnea and Jet-Lag Syndrome.

In addition the compounds of formula (I) and their pharmaceutically acceptable derivatives may be of use for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as depression and mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311); Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder (Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80); Other Mood Disorders including Mood Disorder Due to a General Medical Condition (293.83) which includes the subtypes With Depressive Features, With Major Depressive-like

Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90).

Further, the compounds of formula (I) and their pharmaceutically acceptable derivatives may be of use for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as anxiety disorders including Panic Attack; Panic Disorder including Panic Disorder without Agoraphobia (300.01) and Panic Disorder with Agoraphobia (300.21); Agoraphobia; Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia (300.29, formerly Simple Phobia) including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (Social Anxiety Disorder, 300.23), Obsessive-Compulsive Disorder (300.3), Posttraumatic Stress Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.02), Anxiety Disorder Due to a General Medical Condition (293.84), Substance-Induced Anxiety Disorder, Separation Anxiety Disorder (309.21), Adjustment Disorders with Anxiety (309.24) and Anxiety Disorder Not Otherwise Specified (300.00).

In addition the compounds of formula (I) and their pharmaceutically acceptable derivatives may be of use for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as substance-related disorders including Substance Use Disorders such as Substance Dependence, Substance Craving and Substance Abuse; Substance-Induced Disorders such as Substance Intoxication, Substance Withdrawal, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnestic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnestic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9); Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not Otherwise Specified (292.9); Caffeine Related Disorders such as Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20),

Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89), Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9); Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9); Phencyclidine (or Phencyclidine-Like)-Related Disorders such as Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication (292.89), Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic, or Anxiolytic Dependence (304.10), Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic- Persisting Amnestic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide.

In addition the compounds of formula (I) and their pharmaceutically acceptable derivatives may be of use for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as feeding disorders such as Eating disorders include Anorexia Nervosa (307.1) including the subtypes Restricting Type and Binge-Eating/Purging Type; Bulimia Nervosa (307.51) including the subtypes Purging Type and Nonpurging Type; Obesity; Compulsive Eating Disorder; Binge Eating Disorder; and Eating Disorder Not Otherwise Specified (307.50).

The numbers in brackets after the listed diseases refer to the classification code in DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association. The various subtypes of the disorders mentioned herein are contemplated as part of the present invention.

The invention also provides a method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, for example those diseases and disorders mentioned hereinabove, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required, for example those diseases and disorders mentioned hereinabove.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required, for example those diseases and disorders mentioned hereinabove.

For use in therapy the compounds of the invention are usually administered as a pharmaceutical composition. The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

A liquid formulation will generally consist of a suspension or solution of the active ingredient in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. Aerosol dosage forms can also take the form of pump-atomisers.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

The dose of the compound of formula (I), or a pharmaceutically acceptable derivative thereof, used in the treatment or prophylaxis of the abovementioned disorders or diseases will vary in the usual way with the particular disorder or disease being treated, the weight of the subject and other similar factors. However, as a general rule, suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 500 mg. Unit doses may be administered more than once a day for example two or three times a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg. Such therapy may extend for a number of weeks or months. In the case of pharmaceutically acceptable derivatives the above figures are calculated as the parent compound of formula (I).

No toxicological effects are indicated/expected when a compound of formula (I) is administered in the above mentioned dosage range.

Orexin-A (Sakurai, T. et al (1998) Cell, 92 pp 573-585) can be employed in

screening or assay procedures for compounds which inhibit the ligand's activation of the orexin-1 receptor.

In general, such screening or assay procedures involve providing appropriate cells which express the orexin-1 receptor on their surface. Such cells include cells from mammals, yeast, Drosophila or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is used to transfect cells to express the receptor. The expressed receptor is then contacted with a test compound and an orexin-1 receptor ligand to observe inhibition of a functional response. One such screening or assay procedure involves the use of melanophores which are transfected to express the orexin-1 receptor, as described in WO 92/01810.

Another screening or assay procedure involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes are then contacted with a receptor ligand and a test compound, followed by detection of inhibition of a signal in the case of screening for compounds which are thought to inhibit activation of the receptor by the ligand.

Another method involves screening for compounds which inhibit activation of the receptor by determining inhibition of binding of a labelled orexin-1 receptor ligand to cells which have the receptor on their surface. This method involves transfecting a eukaryotic cell with DNA encoding the orexin-1 receptor such that the cell expresses the receptor on its surface and contacting the cell or cell membrane preparation with a compound in the presence of a labelled form of an orexin-1 receptor ligand. The ligand may contain a radioactive label. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity.

Yet another screening technique involves the use of FLIPR equipment for high throughput screening of test compounds that inhibit mobilisation of intracellular calcium ions, or other ions, by affecting the interaction of an orexin-1 receptor ligand with the orexin-1 receptor.

Throughout the specification and claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising' will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The Descriptions 1 to 11 illustrate the preparation of intermediates to compounds of the invention.

In the procedures that follow, after each starting material, reference to a description is typically provided. This is provided merely for assistance to the skilled chemist. The starting material may not necessarily have been prepared from the Description referred to.

The yields were calculated assuming that products were 100 % pure if not

stated otherwise.

The compounds described in the Examples have all been prepared from stereochemically pure (minimum enantiomeric purity 94 %) 1,1-dimethylethyl (3*S*)-3-methyl-1-piperidinecarboxylate (**D2**). The stereochemistry of the compounds of the Descriptions and Examples have been assigned on the assumption that the pure configuration of this centre is retained.

Compounds are named using ACD/Name PRO 6.02 chemical naming software (Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada).

Proton Magnetic Resonance (NMR) spectra were recorded either on Varian instruments at 400, 500 or 600 MHz, or on Bruker instruments at 400 MHz. Mono-(1H and 1H with homonuclear decoupling) and two-dimensional techniques (1H–1H COSY, 1H–1H ROESY, 1H-13C HSQC) were used for stereochemistry investigation. Chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designed as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. The NMR spectra were recorded at a temperature ranging from 25 to 90 °C. When more than one conformer was detected the chemical shifts for the most abundant one is usually reported.

HPLC analysis indicated by R_t(HPLC): x min, was performed on an Agilent 1100 series instrument using a Luna 3u C18(2) 100A (50x2.0mm) column (mobile phase: 100% [water + 0.05% TFA] to 95% [acetonitrile + 0.05% TFA] in 8min, flux = 1ml/min, detection wavelength 220 nm.

Mass spectra (MS) were taken on a 4 II triple quadrupole Mass Spectrometer (Micromass UK) or on a Agilent MSD 1100 Mass Spectrometer, operating in ES (+) and ES (-) ionization mode or on an Agilent LC/MSD 1100 Mass Spectrometer, operating in ES (+) and ES (-) ionization mode coupled with HPLC instrument Agilent 1100 Series [LC/MS - ES (+): analysis performed on a Supelcosil ABZ +Plus (33x4.6 mm, 3μm) (mobile phase: 100% [water +0.1% HCO_2H] for 1 min, then from 100% [water +0.1% HCO_2H] to 5% [water +0.1% HCO_2H] and 95% [CH_3CN] in 5 min, finally under these conditions for 2 min; T=40^{O}C; flux= 1 mL/min; LC/MS - ES (-): analysis performed on a Supelcosil ABZ +Plus (33x4.6 mm, 3μm) (mobile phase: 100% [water +0.05% NH_3] for 1 min, then from 100% [water +0.05% NH_3 to 5% [water +0.05% NH_3] and 95% [CH_3CN] in 5 min, finally under these conditions for 2 min; T = 40 ^{O}C; flux= 1 mL/min]. In the mass spectra only one peak in the molecular ion cluster is reported.

Total ion current (TIC) and DAD UV chromatographic traces together with MS and UV spectra associated with the peaks were taken also on a UPLC/MS AcquityTM system equipped with 2996 PDA detector and coupled to a Waters Micromass ZQTM mass spectrometer operating in positive or negative electrospray ionisation mode. [LC/MS - ES (+/-): analyses performed using an AcquityTM UPLC BEH C18 column (50 x 21 mm, 1.7 μm particle size), column temperature 40 °C (mobile phase: A-water + 0.1% HCOOH / B - CH_3CN + 0.075% HCOOH, Flow rate: 1.0 mL/min, Gradient: t=0 min 3% B, t=0.05 min 6% B, t= 0.57 min 70% B, t=1.4

min 99% B, t=1.45 min 3% B)]. The usage of this methodology is indicated by "UPLC" in the analytic characterization of the described compounds.

Preparative LC-MS purifications were performed on a MDAP (Mass Detector Auto Purification) Waters instrument. The usage of this methodology is indicated by "Fraction Lynx" in the analytic characterization of the described compounds. [LC3_100 mg method. Column: Waters XTerra Prep MS C18 OBD, 30 x 150 mm, 10 µm particle size. Mobile phase: A: H_2O + 0.1% formic acid; B: CH_3CN + 0.1% formic acid. Flow rate 40 ml/min. Gradient: 30% to 55% (B) in 10 min, 55% to 99% (B) in 4 min, 95% to 100% (B) in 1 min. UV range: 210-400 nm. Ionization: ES+/ES- . Mass range: 150-900 amu].

For reactions involving microwave irradiation, a Personal Chemistry EmrysTM Optimizer was used.

In a number of preparations, purification was performed using Biotage manual flash chromatography (Flash+), Biotage automatic flash chromatography (Horizon, SP1 and SP4), Companion CombiFlash (ISCO) automatic flash chromatography, Flash Master Personal or Vac Master systems.

Flash chromatography was carried out on silica gel 230-400 mesh (supplied by Merck AG Darmstadt, Germany), Varian Mega Be-Si pre-packed cartridges, pre-packed Biotage silica cartridges (e.g. Biotage SNAP cartridge), KP-NH prepacked flash cartridges or ISCO RediSep Silica cartridges.

SPE-SCX cartridges are ion exchange solid phase extraction columns supplied by Varian. The eluent used with SPE-SCX cartridges is methanol followed by 2N ammonia solution in methanol.

SPE-Si cartridges are silica solid phase extraction columns supplied by Varian.

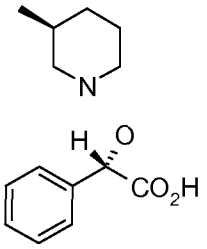
The following table lists the used abbreviations:

AcCl	Acetyl chloride
ACN	Acetonitrile
AcOH	Acetic acid
atm	atmosphere
bs	broad signal
Boc	*t*-Butoxycarbonyl
$BnNH_2$	Benzylamine
n-BuLi	*n*-Butyl Lithium
s-BuLi	*s*-Butyl Lithium
Cy	Cyclohexanes
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIPEA	*N,N*-diisopropyl-*N*-ethylamine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide

Et_2O	Diethylether
EtOAc	Ethylacetate
HATU	(2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate)
MeOH	Methanol
rt	room temperature
TBTU	*O*-(benzotriazol-1-yl)-*N,N,N'N'*-tetramethyluronium tetrafluoroborate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	*N,N,N`,N`*-Tetramethylethylendiamine

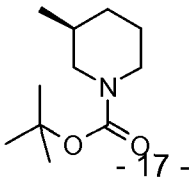
DESCRIPTIONS

Description 1: (2*S*)-hydroxy(phenyl)ethanoic acid - (3*S*)-3-methylpiperidine (1:1) (**D1**)



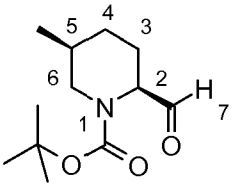
In a 10 L reactor, under nitrogen atmosphere, a solution of racemic 3-methylpiperidine (270 g, 2.72 mol) and (S)-(+)-mandelic acid (394 g, 2.59 mol) in MeOH (1 L) was cooled to 0 °C. Without stirring, Et_2O (6.21 L) was added in several portions: (10 x 540 ml) every 20 minutes and 810 ml after 30 minutes from the last addition. After each addition of Et_2O, a short and slow stirring was applied in order to obtain an homogeneous phase. The final slurry was left standing overnight at 0 °C. The precipitated solid was recovered by filtration, washed with cold Et_2O (2 x 540 ml) and dried under vacuum to afford the title compound **D1** (150 g, 0.60 mol, 23 % yield) [optical purity (94 %) was determined by preparation of the Mosher amide derivative. The diastereomeric excess of the Mosher amide, determined via NMR spectroscopy, is representative of the enantiomeric excess of the precursor].
^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 7.43 - 7.50 (m, 2 H), 7.20 – 7.34 (m, 3 H), 4.89 (s, 1 H), 2.89 – 3.05 (m, 2H), 2.17 (dt, 1 H), 2.06 (t, 1 H), 1.39 – 1.73 (m, 4 H), 0.83 – 0.98 (m, 1H), 0.80 (d, 3 H).

Description 2: 1,1-dimethylethyl (3*S*)-3-methyl-1-piperidinecarboxylate (**D2**)



To a mixture of (2*S*)-hydroxy(phenyl)ethanoic acid - (3*S*)-3-methylpiperidine (1:1) (**D1**) (150 g, 0.60 mol) in a 2.5 M NaOH aqueous solution (600 ml, 1.50 mol) cooled at 0 °C, a solution of Boc_2O (130 g, 0.60 mol) in THF (1.2 L) was added dropwise over 1 hour (internal temperature kept below 9 °C) under vigorous stirring. Once the addition was completed, the mixture was allowed to reach rt and left under stirring overnight. Volatiles were evaporated and the aqueous phase extracted with Et_2O (3 x 500 ml). The collected organic phases were dried (Na_2SO_4), filtered and concentrated to dryness. The resulting crude material was eluted (Cy/EtOAc 90/10) through a silica gel pad to give the title compound **D2** (103 g, 0.52 mol, 87% yield). UPLC: rt = 0.85 min, peak observed: 200 (M+1). $C_{11}H_{21}NO_2$ requires 199.
^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 3.95 (bd, 2H), 2.70 (dt, 1 H), 2.21 – 2.55 (m, 1 H), 1.73 – 1.86 (m, 1 H), 1.51 – 1.68 (m, 3 H), 1.47 (s, 9 H), 0.96 – 1.12 (m, 1 H), 0.88 (d, 3 H).

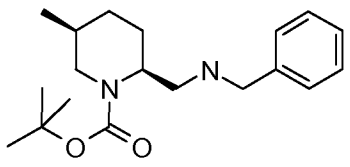
Description 3: 1,1-dimethylethyl (2*S*,5*S*)-2-formyl-5-methyl-1-piperidinecarboxylate (**D3**):



To a solution of 1,1-dimethylethyl (3*S*)-3-methyl-1-piperidinecarboxylate (**D2**) (25 g, 0.13 mol) in anhydrous Et_2O (250 ml) cooled at -78 °C under nitrogen atmosphere, TMEDA (22.6 ml, 0.15 mol) was added followed by dropwise addition of *s*-BuLi (108 ml of a 1.4 M solution in Cy, 0.15 mol) over 40 min (exothermic addition: internal temperature kept below -70 °C). The pale yellow reaction mixture was left under stirring at -78 °C for 30 min then it was gradually warmed to -50 °C and stirred at this temperature for 30 min. The reaction was cooled again to -78 °C, then TMEDA (further 0.3 eq) was added followed by dropwise addition of of *s*-BuLi (further 0.3 eq). The mixture was stirred for 30 min at -78 °C, gradually warmed up to -50 °C, stirred at this temperature for 30 min, then cooled to -78 °C. Dry DMF (29.1 ml, 0.38 mol) was added dropwise (internal temperature kept below -70 °C). The resulting mixture was stirred for 30 minutes at -78 °C and then allowed to warm up to 0 °C. The reaction mixture was quenched with a saturated NH_4Cl aqueous solution (200 ml) and water (100 ml). The layers were separated and the aqueous one back extracted with Et_2O (3 x 200 ml). The organic phases were collected, dried (Na_2SO_4), filtered and concentrated under vacuum to give a crude yellow oil. The material was purified by

flash chromatography on silica gel (Biotage 75L, Cy/EtOAc 90/10). Collected fractions gave the title compound **D3** (15 g, 0.066 mol, 53% yield).
^{1}H NMR [the relative stereochemistry of the compound was measured via NMR spectroscopy. The 1H spectrum shows that the compound gives rise to a mixture of two slowly exchanging conformers due to hindered rotation of the C=O group. 1H,1H scalar couplings [^{3}J(H3,H2)~5Hz and ^{3}J(H6ax,H5ax)~12Hz] and 1H,1H dipole dipole correlation between H7 and H4ax determine that the six member ring bears a chair conformation with H2 in equatorial position and H5 in axial position. The relative stereochemistry is therefore SYN. The ANTI stereoisomer is present at ca. 25%. The ratio between the two diastereoisomers was determined on the ratio between integrals of proton signals H7 of each diastereoisomer. The absolute configuration is 2S,5S on the assumption that the absolute configuration of **D2** is retained. The assignment refers to the SYN isomer] (400 MHz, DMSO-d_6) δ(ppm): 9.53 (d, 1 H), 4.53 - 4.72 (m, 1 H), 3.73 - 3.91 (m, 1 H), 2.39 (t, 1 H), 2.16 - 2.27 (m, 1 H), 1.52 - 1.72 (m, 3 H), 1.40 (s, 9 H), 0.80 (d, 3 H), 0.68 - 0.77 (m, 1 H).

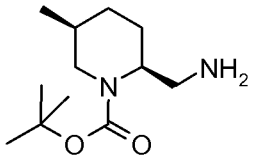
Description 4: 1,1-dimethylethyl (2*S*,5*S*)-5-methyl-2-{[(phenylmethyl)amino]methyl}-1-piperidinecarboxylate (**D4**):



A solution of 1,1-dimethylethyl (2S,5S)-2-formyl-5-methyl-1-piperidinecarboxylate (**D3**) (0.45 g, 1.98 mmol) and benzylamine (0.24 ml, 2.18 mmol) in DCM (5 ml) was left under stirring at rt under nitrogen for 2 h. Sodium triacetoxyborohydride (0.84 g, 3.96 mmol) was added and the resulting solution left under stirring at rt overnight. The mixture was diluted with water and DCM. The two layers were separated and the aqueous one extracted several times with DCM. The combined organic layers were filtered through a phase separator tube and the solvent removed under vacuum. The crude was purified by flash chromatography on silica gel (Biotage SP4 40M, from Cy/EtOAc from 80/20 to 20/80). Collected fractions gave the title compound **D4** (0.37 g, 1.16 mmol, 59% yield). HPLC (walk-up): rt = 3.86 min.
^{1}H NMR [the SYN relative stereochemistry is derived from 1H,1H scalar coupling network. A mixture of conformers due to hindered rotation of the C=O group slowly exchange in solution. Only one rotamer is assigned] (400 MHz, $CDCl_3$) δ(ppm): 7.31 – 7.36 (m, 4 H), 7.23 – 7.27 (m, 1 H), 4.23 - 4.49 (m, 1 H), 3.70 - 4.09 (m, 1 H), 3.87 (d, 1 H), 3.79 (d, 1 H), 2.89 (dd, 1 H), 2.62 (dd, 1 H), 2.21 – 2.39 (m, 1 H), 1.53 – 1.75 (m, 4 H), 1.47 (s, 9 H), 1.06 – 1.18 (m, 1 H), 0.87 (d, 3 H).

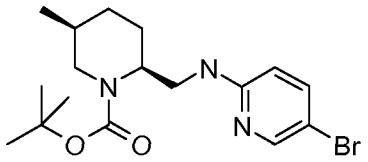
Description 5: 1,1-dimethylethyl (2*S*,5*S*)-2-(aminomethyl)-5-methyl-1-

piperidinecarboxylate (**D5**):



A mixture of 1,1-dimethylethyl (2S,5S)-5-methyl-2-{[(phenylmethyl)amino]methyl}-1-piperidinecarboxylate (**D4**) (0.37 g, 1.16 mmol) and $Pd(OH)_2$ on carbon (0.011 g) in MeOH (5 ml) was stirred under hydrogen atmosphere (1 atm) for 27 h. Further $Pd(OH)_2$ on carbon (0.011 g) was added and the resulting mixture left under stirring under hydrogen atmosphere (1 atm) for 7 h. The mixture was filtered through a celite pad and the solvent evaporated under vacuum to afford the title compound **D5** (0.24 g, 1.05 mmol, 91% yield) as a yellow oil. UPLC: rt = 0.50 min, peak observed: 229 (M+1). $C_{12}H_{24}N_2O_2$ requires 228. ^{1}H NMR [the SYN relative stereochemistry is derived from 1H,1H scalar coupling network. A mixture of conformers due to hindered rotation of the C=O group slowly exchange in solution. Only one rotamer is assigned] (400 MHz, $CDCl_3$) δ(ppm): 3.75-4.31 (m, 2 H), 2.84 – 2.99 (m, 1 H), 2.61 – 2.71 (m, 1 H), 2.24 – 2.42 (m, 1 H), 1.50 – 1.72 (m, 4 H), 1.48 (s, 9 H), 1.07 – 1.22 (m, 1 H), 0.89 (d, 3 H).

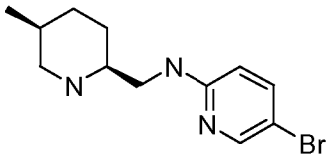
Description 6: 1,1-dimethylethyl (2*S*,5*S*)-2-{[(5-bromo-2-pyridinyl)amino]methyl}-5-methyl-1-piperidinecarboxylate (**D6**):



In a 1 L round-bottomed flask 1,1-dimethylethyl (2S,5S)-2-formyl-5-methyl-1-piperidinecarboxylate (13.0 g, 57.2 mmol) (**D3**) and 5-bromo-2-pyridinamine (11.9 g, 68.6 mmol) were dissolved in DCE (390 ml) at rt under nitrogen atmosphere. AcOH (16.4 ml, 286 mmol) was added, followed by sodium triacetoxyborohydride (14.6 g, 68.6 mmol) after 1 h. The reaction mixture was stirred for 64 h at rt. A saturated $NaHCO_3$ aqueous solution (400 ml) and DCM (400 ml) were added and the phases separated. The aqueous phase was back extracted with DCM (2 x 400 ml) and the combined organic layers were dried (Na_2SO_4). The solution was then concentrated to dryness under vacuum to get a yellow oil. This material was combined with 2.3 g of a crude coming from an identical reaction carried out on 1 g (4.4 mmol) of **D3** and purified by flash chromatography on silica gel (Biotage 75L, Cy/EtOAc 90/10). Collected fractions gave the title compound **D6** (10.6 g, 27.6 mmol, 45% yield) as

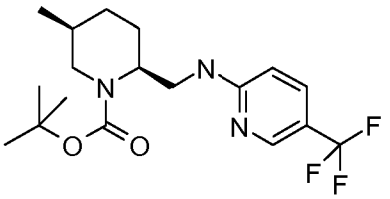
pale yellow foam. MS: (ES/+) m/z: 384 (M+1, 100%) and 386 (M+1, 100%). $C_{17}H_{26}BrN_3O_2$ requires 383.

Description 7: 5-bromo-*N*-{[(2*S*,5*S*)-5-methyl-2-piperidinyl]methyl}-2-pyridinamine (**D7**):



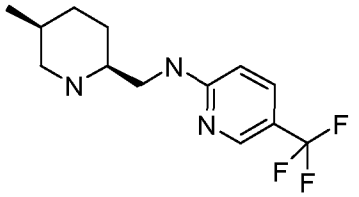
To a solution of 1,1-dimethylethyl (2S,5S)-2-{[(5-bromo-2-pyridinyl)amino]methyl}-5-methyl-1-piperidinecarboxylate (**D6**) (10.6 g, 27.6 mmol) in DCM (85 ml), TFA (21.3 ml, 276 mmol) was added dropwise at 0 °C under nitrogen atmosphere. After the addition, the reaction mixture was allowed to warm up to room temperature and left under stirring for 2.5 h at this temperature. Solvent was evaporated under vacuum at rt and the crude slurry was diluted with DCM (200 ml) and a saturated K_2CO_3 aqueous solution (80 ml). Phases were separated and the aqueous layer back-extracted with DCM (2 x 150 ml). The combined organic layers were washed with brine (1 x 50 ml). The organic phase was dried (Na_2SO_4), filtered and concentrated to get the title compound **D7** (7.82 g, 27.5 mmol, quantitative yield) as a yellow oil.
^{1}H-NMR [the SYN relative stereochemistry is derived from 1H,1H scalar coupling network] (400 MHz, $CDCl_3$) δ(ppm): 8.06 - 8.09 (m, 1 H), 7.41 (dd, 1 H), 6.32 (d, 1 H), 4.98 - 5.20 (bs, 1 H), 3.10 - 3.39 (m, 2 H), 2.85 - 2.97 (m, 1 H), 2.80 (dd, 1 H), 2.65 (dd, 1 H), 1.40 - 1.78 (m, 5 H), 0.97 (d, 3 H).

Description 8: 1,1-dimethylethyl (2*S*,5*S*)-5-methyl-2-({[5-(trifluoromethyl)-2-pyridinyl]amino}methyl)-1-piperidinecarboxylate (**D8**):



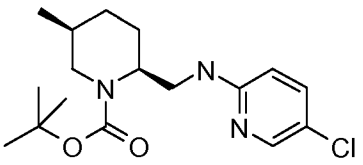
A mixture of 1,1-dimethylethyl (2*S*,5*S*)-2-(aminomethyl)-5-methyl-1-piperidinecarboxylate (**D5**) (0.13 g, 0.57 mmol), 2-chloro-5-(trifluoromethyl)pyridine (0.10 g, 0.57 mmol) and potassium carbonate (0.16 g, 1.14 mmol) in DMF (2 ml) was stirred at 80 °C for 5 h. DMF was removed under reduced pressure.The residue was taken-up in DCM (5 ml) and washed with H_2O (2 x 3 ml). The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash chromatography on silica gel (Biotage SP 25M, Cy/EtOAc from 80/20 to 60/40) to afford the title compound **D8** (0.11 g, 0.29 mmol, 52% yield).
UPLC: rt = 0.92 min, peak observed: 374 (M+1). $C_{18}H_{26}F_3N_3O_2$ requires 373.

Description 9: *N*-{[(2*S*,5*S*)-5-methyl-2-piperidinyl]methyl}-5-(trifluoromethyl)-2-pyridinamine (**D9**):



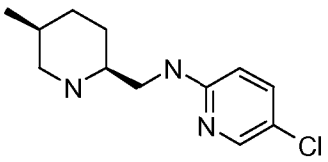
To a solution of 1,1-dimethylethyl (2*S*,5*S*)-5-methyl-2-({[5-(trifluoromethyl)-2-pyridinyl]amino}methyl)-1-piperidinecarboxylate (**D8**) (0.11 g, 0.29 mmol) in DCM (2 ml), TFA (1 ml) was added and the reaction mixture left under stirring for 2 h at room temperature. Volatiles were removed under reduced pressure and the residue eluted through a SCX column. Collected fractions gave the title compound **D9** (0.068 g, 0.25 mmol, 86 % yield). UPLC: rt = 0.52 min, peak observed: 274 (M+1). $C_{13}H_{18}F_3N_3$ requires 273. ^{1}H-NMR [the SYN relative stereochemistry is derived from the stereochemistry of the previous intermediates] (400 MHz, $CDCl_3$) δ(ppm): 8.33 (s, 1 H), 7.55 (dd, 1 H), 6.44 (d, 1 H), 5.35 - 5.55 (bs, 1 H), 3.24 - 3.50 (m, 2 H), 2.85 – 3.00 (m, 1 H), 2.83 (dd, 1 H), 2.65 (dd, 1 H), 1.40 - 1.78 (m, 5 H), 0.99 (d, 3 H).

Description 10: 1,1-dimethylethyl (2*S*,5*S*)-2-{[(5-chloro-2-pyridinyl)amino]methyl}-5-methyl-1-piperidinecarboxylate (**D10**):



A solution of 1,1-dimethylethyl (2S,5S)-2-formyl-5-methyl-1-piperidinecarboxylate (**D3**) (1.40 g, 6.16 mmol) and 5-chloro-2-pyridinamine (0.95 g, 7.39 mmol) in DCE (25 ml) was stirred for 1 h at rt. Sodium triacetoxyborohydride (1.82 g, 8.62 mmol) was then added and the resulting reaction mixture left under stirring overnight at rt. A saturated Na_2CO_3 aqueous solution was added and the aqueous phase extracted with DCM (3 x 20 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude oil was purified by flash chromatography on silica gel (Biotage SP 25M, from Cy/EtOAc 80/20 to 50/50) to afford the title compound **D10** (0.86 g, 2.53 mmol, 41% yield).
UPLC: rt = 0.82 min, peak observed: 340 (M+1). $C_{17}H_{26}ClN_3O_2$ requires 339.

Description 11: 5-chloro-N-{[(2S,5S)-5-methyl-2-piperidinyl]methyl}-2-pyridinamine (**D11**):



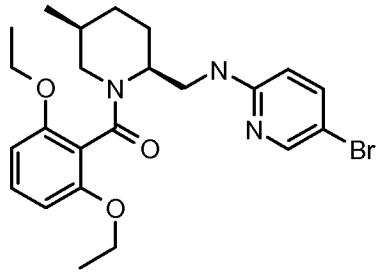
To a solution of 1,1-dimethylethyl (2*S*,5*S*)-2-{[(5-chloro-2-pyridinyl)amino]methyl}-5-methyl-1-piperidinecarboxylate (**D10**) (0.86 g, 2.53 mmol) in DCM (10 ml), TFA (3 ml, 38.90 mmol) was added and the resulting mixture stirred for 2 h. Volatiles were removed under reduced pressure and the residue eluted through a SCX column. Collected fractions gave the title compound **D11** (0.60 g, 2.51 mmol, quantitative yield).

UPLC: rt = 0.44 min, peak observed: 240 (M+1). $C_{12}H_{18}ClN_3$ requires 239.

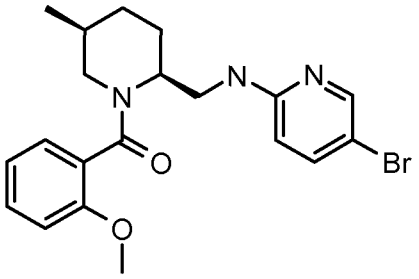
1H NMR [the SYN relative stereochemistry is derived from 1H,1H scalar coupling network. The ANTI stereoisomer is present at ca. 15 %. Quantification of the ANTI isomer versus SYN is performed by integrating signals of methyl group of both stereoisomer] (400 MHz, $CDCl_3$) δ(ppm): 7.95 – 7.98 (m, 1 H), 7.33 (dd, 1 H), 6.42 (d, 1 H), 5.93 – 6.05 (bs, 1 H), 3.60- 3.79 (m, 2 H), 2.94-3.13 (m, 3 H), 1.44 – 2.16 (m, 5 H), 1.09 (d, 3 H).

EXAMPLES

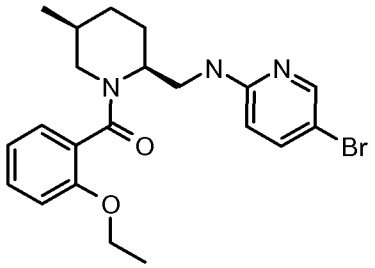
Example 1: N-[((2S,5S)-1-{[2,6-bis(ethyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-5-bromo-2-pyridinamine (E1)



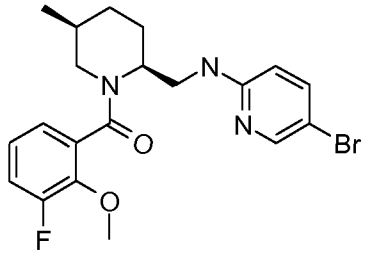
Example 2: 5-bromo-N-[((2S,5S)-5-methyl-1-{[2-(methyloxy)phenyl]carbonyl}-2-piperidinyl)methyl]-2-pyridinamine (E2)



Example 3: 5-bromo-N-[((2S,5S)-1-{[2-(ethyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine (E3)



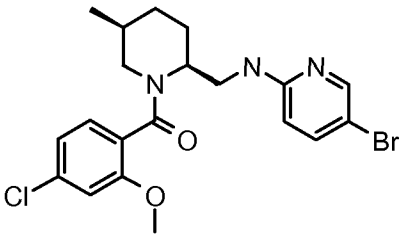
Example 4: 5-bromo-*N*-[((2*S*,5*S*)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine (E4):



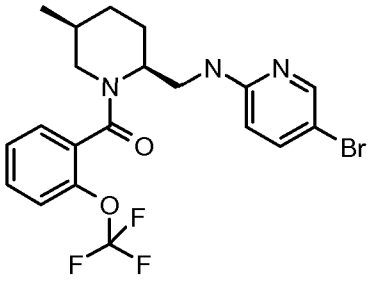
To a solution of 3-fluoro-2-(methyloxy)benzoic acid (4.7 g, 27.5 mmol) in dry DCM (78 ml), DIPEA (9.6 ml, 55 mmol) was added followed by TBTU (9.7 g, 30.3 mmol) at rt under nitrogen atmosphere. The mixture dissolved completely in about 10 minutes. After 30 minutes stirring, a solution of 5-bromo-*N*-{[(2*S*,5*S*)-5-methyl-2-piperidinyl]methyl}-2-pyridinamine (**D7**) (7.8 g, 27.5 mmol) in dry DCM (78 ml) was added dropwise. The reaction mixture was left under stirring for 16 h and then diluted with DCM (200 ml) and a saturated $NaHCO_3$ aqueous solution (150 ml). The aqueous layer was back extracted with DCM (2 x 200 ml). The combined organic phases were washed with brine (1 x 100 ml), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a crude yellow oil. The material was purified by flash chromatography on silica gel (Biotage 75M, DCM/MeOH 98/2) and then the collected fraction purified again (Biotage 75M, Cy/EtOAc from 70/30 to 60/40) to afford the title compound **E4** (8.9 g, 20.4 mmol, 74 % yield) as a pale yellow gummy solid. MS: (ES/+) m/z: 436 (M+1, 100%) and 438 (M+1, 100%). UPLC: rt = 3.41 min, peaks observed: 436 (M+1, 100%) and 438 (M+1, 100%). $C_{20}H_{23}BrFN_3O_2$ requires 435.

1H NMR [the SYN relative stereochemistry is derived from the stereochemistry of the previous intermediates. Four conformers due to hindered rotation of the C=O group slowly exchange in solution (ratio ca. 50/20/15/15). Assignment is provided for one rotamer] (500 MHz, DMSO-d_6) δ(ppm): 8.01 (dd, 1 H), 7.68 (d, 1 H), 7.40 (dd, 1 H), 7.07 - 7.14 (m, 1 H), 6.89 (t, 1 H), 6.62 - 6.68 (m, 1 H), 6.36 (d, 1 H), 4.79 - 4.99 (m, 1 H), 4.38 (dd, 1 H), 3.73 (s, 3 H), 3.22 - 3.44 (m, 2 H), 2.42 - 2.58 (m, 1 H), 1.22 - 1.81 (m, 5 H), 0.92 (d, 3 H).

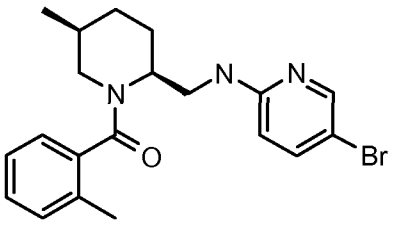
Example 5: 5-bromo-N-[((2S,5S)-1-{[4-chloro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine (E5)



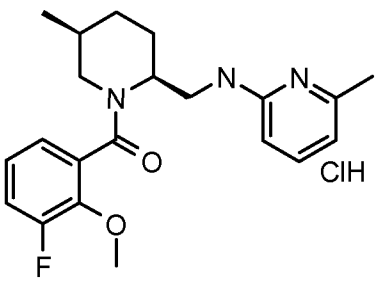
Example 6: 5-bromo-N-{[(2S,5S)-5-methyl-1-({2-[(trifluoromethyl)oxy]phenyl}carbonyl)-2-piperidinyl]methyl}-2-pyridinamine (E6)



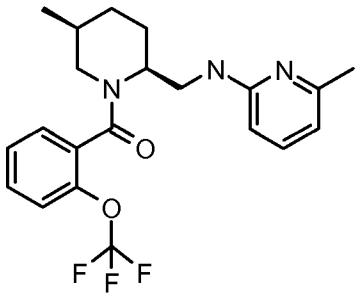
Example 7: 5-bromo-N-({(2S,5S)-5-methyl-1-[(2-methylphenyl)carbonyl]-2-piperidinyl}methyl)-2-pyridinamine (E7)



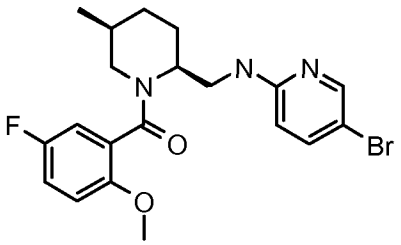
Example 8: N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-6-methyl-2-pyridinamine hydrochloride (E8)



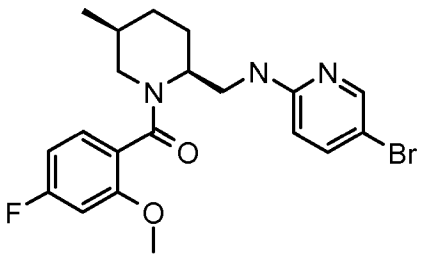
Example 9: 6-methyl-N-{[(2S,5S)-5-methyl-1-({2-[(trifluoromethyl)oxy]phenyl}carbonyl)-2-piperidinyl]methyl}-2-pyridinamine (E9)



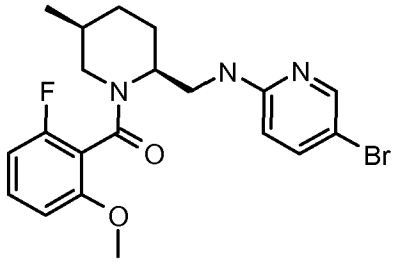
Example 10: 5-bromo-N-[((2S,5S)-1-{[5-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine (E10)



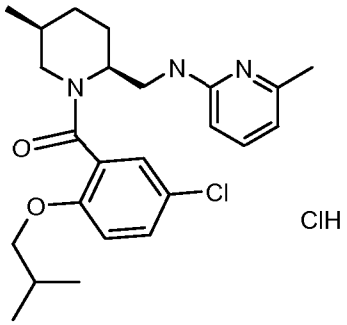
Example 11: 5-bromo-N-[((2S,5S)-1-{[4-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine (E11)



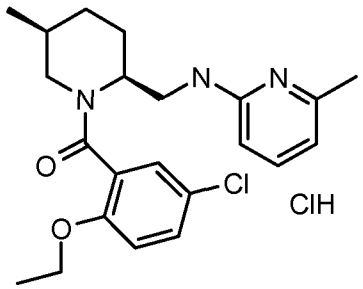
Example 12: 5-bromo-N-[((2S,5S)-1-{[2-fluoro-6-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine (E12)



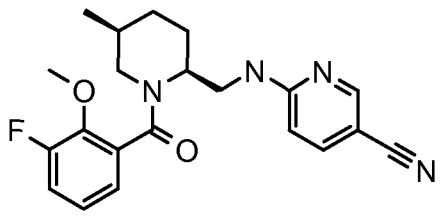
Example 13: N-{[(2S,5S)-1-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}carbonyl)-5-methyl-2-piperidinyl]methyl}-6-methyl-2-pyridinamine hydrochloride (E13)



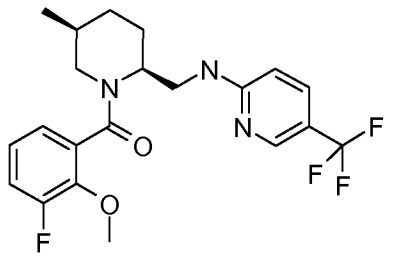
Example 14: N-[((2S,5S)-1-{[5-chloro-2-(ethyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-6-methyl-2-pyridinamine hydrochloride (E14)



Example 15: 6-{[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]amino}-3-pyridinecarbonitrile (E15)

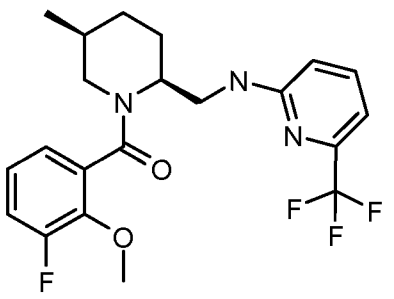


Example 16: *N*-[((2*S*,5*S*)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-5-(trifluoromethyl)-2-pyridinamine (E16)

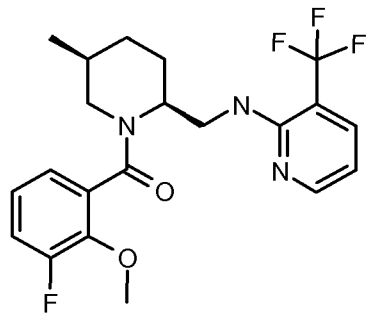


To a solution of 3-fluoro-2-(methyloxy)benzoic acid (14.9 mg, 0.088 mmol) in DMF (1 ml), DIPEA (0.077 ml, 0.44 mmol) and TBTU (32.9 mg, 0.10 mmol) were added and the reaction mixture left under stirring at rt for 1 h. A solution of *N*-{[(2*S*,5*S*)-5-methyl-2-piperidinyl]methyl}-5-(trifluoromethyl)-2-pyridinamine (**D9**) (20 mg, 0.073 mmol) in DMF (1 ml) was added at 0 °C. The reaction mixture was left under stirring overnight at room temperature and then diluted with DCM and a saturated $NaHCO_3$ aqueous solution. The organic phase was washed with brine/ice, separated through a phase separator tube and the solvent removed under reduced pressure. The material was purified by flash chromatography on NH (Biotage SP4 12M, DCM/MeOH 98/2) and then the collected fraction purified again (Biotage 75M, from Cy 100 to Cy/EtOAc 40/60) to afford the title compound **E16** (28.6 mg, 0.064 mmol, 88 % yield). UPLC: rt = 0.82 min, peak observed: 426 (M+1). $C_{21}H_{23}F_4N_3O_2$ requires 425. 1H NMR [the SYN relative stereochemistry is derived from the stereochemistry of the previous intermediates. The ANTI stereoisomer is also present at ca. 5 %. Quantification of the ANTI isomer versus SYN is performed by integrating signals of methyl group of both stereoisomer. For the SYN isomer, four conformers due to hindered rotation of the C=O group slowly exchange in solution (ratio ca. 44/26/18/12). Assignment is provided for one rotamer] (500 MHz, DMSO-d_6) δ(ppm): 8.27 (d, 1 H), 7.83 - 8.00 (m, 1 H), 6.79 - 7.67 (m, 3 H), 6.36 - 6.66 (m, 2 H), 4.91 (d, 1 H), 4.42 (d, 1 H), 3.58 - 3.94 (m, 5 H), 3.00 (d, 1 H), 1.08 - 1.84 (m, 5 H), 0.94 (d, 3 H).

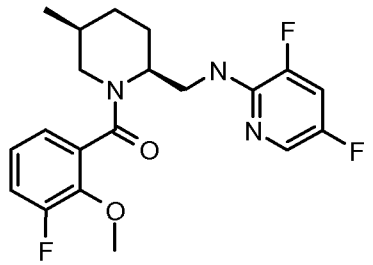
Example 17: N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-6-(trifluoromethyl)-2-pyridinamine (E17)



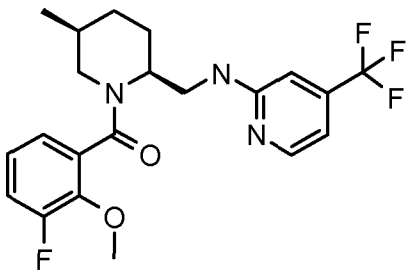
Example 18: N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-3-(trifluoromethyl)-2-pyridinamine (E18)



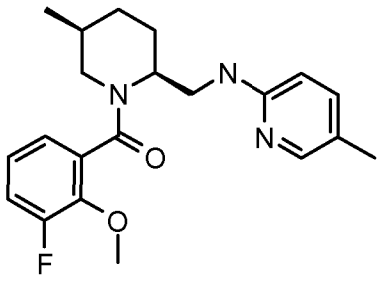
Example 19: 3,5-difluoro-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine (E19)



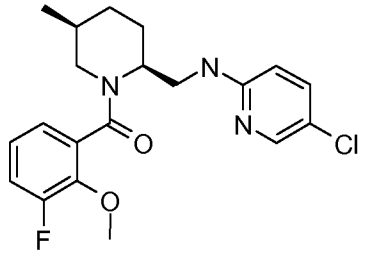
Example 20: N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-4-(trifluoromethyl)-2-pyridinamine (E20)



Example 21: N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-5-methyl-2-pyridinamine (E21)



Example 22: 5-chloro-*N*-[((2*S*,5*S*)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine (E22):

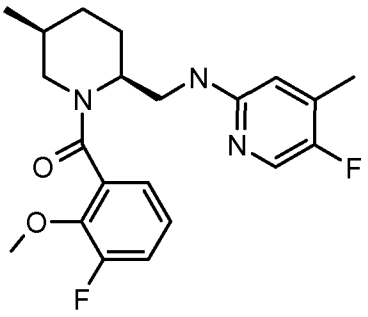


To a solution of 3-fluoro-2-(methyloxy)benzoic acid (0.47 g, 2.75 mmol) in DMF (2 ml), DIPEA (2.62 ml, 15.02 mmol) and TBTU (1.12 g, 3.50 mmol) were added and the reaction mixture left under stirring for 45 min. A solution of 5-chloro-*N*-{[(2*S*,5*S*)-5-methyl-2-piperidinyl]methyl}-2-pyridinamine (**D11**) (0.60 g, 2.50 mmol) in DMF (1 ml) was added and the reaction mixture stirred for 2 h at rt. DMF was evaporated under vacuum and the residue was taken-up in DCM (10 ml) and washed with a saturated $NaHCO_3$ aqueous solution (10 ml). The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The material was purified by flash chromatography on silica gel (Biotage SP 350g SNAP column, from Cy to Cy/EtOAc 60/40). Collected fractions gave the title compound **E22** (0.33 g, 0.84 mmol, 34 % yield).

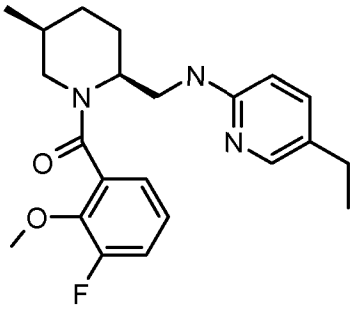
UPLC: rt = 0.75 min, peak observed: 392 (M+1). $C_{20}H_{23}ClFN_3O_2$ requires 391.

1H NMR [the SYN relative stereochemistry is derived from the stereochemistry of the previous intermediates. Conformers due to hindered rotation of the C=O group slowly exchange in solution. Assignment is provided for one rotamer] (400 MHz, DMSO-d_6) δ(ppm): 7.96 (dd, 1 H), 7.62 (d, 1 H), 7.35 (dd, 1 H), 7.07 - 7.14 (m, 1 H), 6.88 (t, 1 H), 6.62 - 6.68 (m, 1 H), 6.41 (d, 1 H), 4.83 - 4.97 (m, 1 H), 4.43 (dd, 1 H), 3.75 (s, 3 H), 3.22 - 3.44 (m, 2 H), 2.42 - 2.58 (m, 1 H), 1.22 - 1.81 (m, 5 H), 0.92 (d, 3 H).

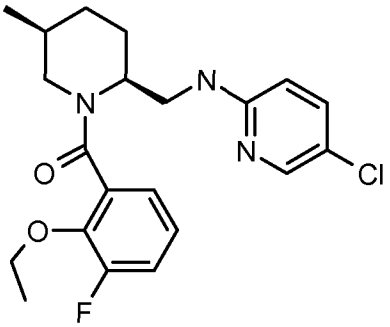
Example 23: 5-fluoro-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-4-methyl-2-pyridinamine (E23)



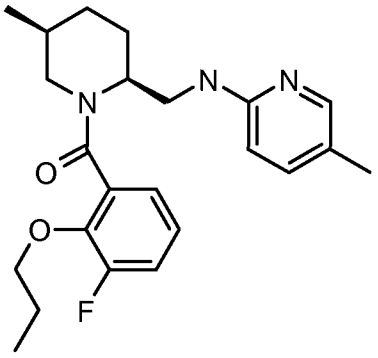
Example 24: 5-ethyl-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine (E24)



Example 25: 5-chloro-N-[((2S,5S)-1-{[2-(ethyloxy)-3-fluorophenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine (E25)



Example 26: N-[((2S,5S)-1-{[3-fluoro-2-(propyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-5-methyl-2-pyridinamine (E26)



Example 27: Determination of antagonist affinity at human Orexin-1 and 2 receptors using FLIPR

Cell Culture

Adherent Chinese Hamster Ovary (CHO) cells, stably expressing the recombinant human Orexin-1 (hOX1) or human Orexin-2 receptors (hOX2), were maintained in culture in Alpha Minimum Essential Medium (Gibco/Invitrogen, cat. no.; 22571-020), supplemented with 10% decomplemented foetal bovine serum (Life Technologies, cat. no. 10106-078) and 400ug/mL Geneticin G418 (Calbiochem, cat. no.345810). Cells were grown as monolayers under 95%:5% air:CO_2 at 37°C and passaged every 3-4 days. The highest passage used was 25.

Measurement of $[Ca^{2+}]_i$ using the FLIPR™

CHO-hOX1 or CHO-hOX2 cells were seeded into black clear-bottom 384-well plates at a density of 20,000 cells per well in culture medium as described above and maintained overnight (95%:5% air:CO_2 at 37°C).

On the day of the experiment, culture medium were discarded and the cells washed three times with standard buffer (NaCl, 145mM; KCl, 5mM; HEPES, 20mM; Glucose, 5.5mM; $MgCl_2$, 1mM; $CaCl_2$, 2mM) added with Probenecid 2.5mM.

The plates were then incubated at room temperature for 60 minutes in the dark with 1 µM FLUO-4AM dye to allow cell uptake of the FLUO-4AM, which is then converted by intracellular esterases to FLUO-4, which is unable to leave the cells.

After incubation, cells were washed three times with standard buffer to remove extracellular dye and 30 µL of buffer were left in each well after washing.

Compounds of the invention were tested in a final assay concentration range from 1.66E-05M to 1.58E-11M.

Compounds of the invention were dissolved in dimethylsulfoxide (DMSO) at a stock concentration of 10 mM. These solutions are serially diluted with DMSO in a 384 compound plate and 1 µL of each dilution is transferred to the test compound plate. Just prior compounds addition to the cells, buffer (50µl/well) was added to the 1µL compound copy plate.

An agonist stimulus 384-well plate containing 50µL/well of human orexin A (hOrexinA) was prepared just before using by diluting with buffer a stock plate: final concentration is equivalent to the calculated EC80 for hOrexinA. This value was

obtained by testing hOrexinA in concentration response curve (at least 16 replicates) the same day of the experiment.

The loaded cells were then incubated for 10min at 37°C with test compound. The plates were then placed into a FLIPR™ (Molecular Devices, UK) to monitor cell fluorescence (λ_{ex} = 488nm, λ_{EM} = 540nm) (Sullivan E, Tucker EM, Dale IL. Measurement of $[Ca^{2+}]_i$ using the fluometric imaging plate reader (FLIPR). In: Lambert DG (ed.), *Calcium Signaling Protocols*. New Jersey: Humana Press, 1999, 125-136). A baseline fluorescence reading was taken over a 5 to 10 second period, and then 10 µL of EC80 hOrexinA solution was added. The fluorescence was then read over a 4-5 minute period.

Data Analysis

Functional responses using FLIPR were measured as peak fluorescence intensity minus basal fluorescence and expressed as a percentage of a non-inhibited Orexin-A-induced response on the same plate. Iterative curve-fitting and parameter estimations were carried out using a four parameter logistic model and Microsoft Excel (Bowen WP, Jerman JC. Nonlinear regression using spreadsheets. *Trends Pharmacol. Sci.* 1995; **16**: 413-417). Antagonist affinity values (IC_{50}) were converted to functional pK_i values using a modified Cheng-Prusoff correction (Cheng YC, Prusoff WH. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50 percent inhibition (IC_{50}) of an enzymatic reaction. *Biochem. Pharmacol.* 1973, **22**: 3099-3108).

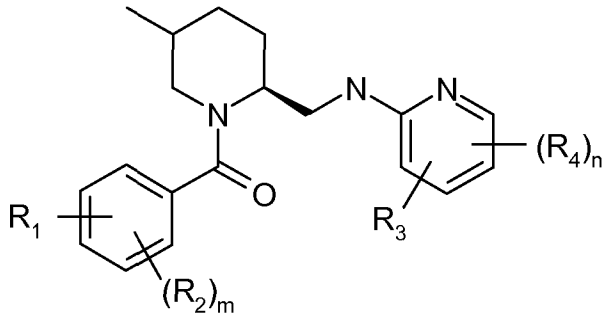
$$\text{fpKi} = -\log \frac{(IC_{50})}{\left(2+\left(\frac{[agonist]}{(EC_{50})}\right)^{n}\right)^{1/n}-1}$$

Where [agonist] is the agonist concentration, EC_{50} is the concentration of agonist giving 50% activity derived from the agonist dose response curve and n=slope of the dose response curve. When n=1 the equation collapses to the more familiar Cheng-Prusoff equation.

Compounds of the Examples tested according to this method had fpKi values in the range from 7.2 to 10 at the human cloned orexin-1 receptor and from 5.9 to 8.6 at the human cloned orexin-2 receptor.

Claims

1. A compound of formula (I):



(I)

where:
R_1 is C_{1-4}alkyl, halo, C_{1-4}alkoxy, haloC_{1-4}alkyl or haloC_{1-4}alkoxy;
R_2 is C_{1-4}alkyl, halo, C_{1-4}alkoxy, haloC_{1-4}alkyl or haloC_{1-4}alkoxy;
R_3 is C_{1-4}alkyl, halo, C_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy or cyano;
R_4 is C_{1-4}alkyl, halo, C_{1-4}alkoxy, haloC_{1-4}alkyl or haloC_{1-4}alkoxy; and
m is 0 or 1;
n is 0 or 1;
provided that when m is 1 and one of R_1 and R_2 is trifuoromethyl, the other is not trifluoromethyl;
or a pharmaceutically acceptable derivative salt thereof.

2. A compound according to claim 1 wherein the compound has the methyl at the 5 position on the piperidyl ring in the 5*S* isomeric form, or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2 where n is 0, or a pharmaceutically acceptable salt thereof.

4. A compound according to any one of claims 1 to 3 where m is 1, or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 4 where R_3 is halo, or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 4 where R_3 is C_{1-4}alkyl, or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 6 where R_1 is C_{1-4}alkyl, or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 6 where R_1 is C_{1-4}alkoxy, or a pharmaceutically acceptable salt thereof.

9. A compound selected from the list consisting of:
N-[((2S,5S)-1-{[2,6-bis(ethyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-5-bromo-2-pyridinamine;
5-bromo-N-[((2S,5S)-5-methyl-1-{[2-(methyloxy)phenyl]carbonyl}-2-piperidinyl)methyl]-2-pyridinamine;
5-bromo-N-[((2S,5S)-1-{[2-(ethyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
5-bromo-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
5-bromo-N-[((2S,5S)-1-{[4-chloro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
5-bromo-N-{[(2S,5S)-5-methyl-1-({2-[(trifluoromethyl)oxy]phenyl}carbonyl)-2-piperidinyl]methyl}-2-pyridinamine;
5-bromo-N-({(2S,5S)-5-methyl-1-[(2-methylphenyl)carbonyl]-2-piperidinyl}methyl)-2-pyridinamine;
N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-6-methyl-2-pyridinamine hydrochloride;
6-methyl-N-{[(2S,5S)-5-methyl-1-({2-[(trifluoromethyl)oxy]phenyl}carbonyl)-2-piperidinyl]methyl}-2-pyridinamine;
5-bromo-N-[((2S,5S)-1-{[5-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
5-bromo-N-[((2S,5S)-1-{[4-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
5-bromo-N-[((2S,5S)-1-{[2-fluoro-6-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
N-{[(2S,5S)-1-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}carbonyl)-5-methyl-2-piperidinyl]methyl}-6-methyl-2-pyridinamine hydrochloride;
N-[((2S,5S)-1-{[5-chloro-2-(ethyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-6-methyl-2-pyridinamine hydrochloride;
6-{[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]amino}-3-pyridinecarbonitrile;
N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-5-(trifluoromethyl)-2-pyridinamine;
N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-6-(trifluoromethyl)-2-pyridinamine;
N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-3-(trifluoromethyl)-2-pyridinamine;
3,5-difluoro-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;

N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-4-(trifluoromethyl)-2-pyridinamine;
N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-5-methyl-2-pyridinamine;
5-chloro-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
5-fluoro-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-4-methyl-2-pyridinamine;
5-ethyl-N-[((2S,5S)-1-{[3-fluoro-2-(methyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine;
5-chloro-N-[((2S,5S)-1-{[2-(ethyloxy)-3-fluorophenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-2-pyridinamine; and
N-[((2S,5S)-1-{[3-fluoro-2-(propyloxy)phenyl]carbonyl}-5-methyl-2-piperidinyl)methyl]-5-methyl-2-pyridinamine,
or a pharmaceutically acceptable salt thereof.

10. The compound as defined in any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in therapy.

11. The compound as defined in any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or disorder where an antagonist of a human orexin receptor is required.

12. The compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder is a sleep disorder, a depression or mood disorder, an anxiety disorder, a substance-related disorder or a feeding disorder.

13. The compound according to claim 12, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder is a sleep disorder.

14. The compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein the sleep disorder is selected from the group consisting of Dyssomnias such as Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47); primary sleep disorders such as Parasomnias such as Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition, in particular sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases; and Substance-Induced Sleep Disorder including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type; Sleep Apnea and Jet-Lag Syndrome.

15. Use of a compound as defined in any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a disease or disorder where an antagonist of a human orexin receptor is required.

16. Use according to claim 15 where the disease or disorder is a sleep disorder, a depression or mood disorder, an anxiety disorder, a substance-related disorder or a feeding disorder.

17. Use according to claim 16 wherein the disease or disorder is a sleep disorder.

18. Use according to claim 17 where the sleep disorder is selected from the group consisting of Dyssomnias such as Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47); primary sleep disorders such as Parasomnias such as Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition, in particular sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases; and Substance-Induced Sleep Disorder including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type; Sleep Apnea and Jet-Lag Syndrome.

19. A method for the treatment of a disease or disorder where an antagonist of a human orexin receptor is required, in a subject in need thereof, comprising administering to said subject an effective amount of a compound as defined in any one claims 1 to 9, or a pharmaceutically acceptable salt thereof.

20. A method according to claim 19 where the disease or disorder is a sleep disorder, a depression or mood disorder, an anxiety disorder, a substance-related disorder or a feeding disorder.

21. A method according to claim 20 where the disease or disorder is a sleep disorder.

22. A method according to claim 21 where the sleep disorder is selected from the group consisting of Dyssomnias such as Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47); primary sleep disorders such as Parasomnias such as Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and

Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition, in particular sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases; and Substance-Induced Sleep Disorder including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type; Sleep Apnea and Jet-Lag Syndrome.

23. A pharmaceutical composition comprising a) the compound as defined in any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, and b) one or more pharmaceutically acceptable carriers.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/054189

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 A61K31/4545 A61P25/00 A61P25/22 A61P25/24
A61P25/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/090355 A (SMITHKLINE BEECHAM PLC [GB]; BRANCH CLIVE LESLIE [GB]; COULTON STEVEN) 14 November 2002 (2002-11-14) cited in the application claims 2,9	1-23
X	WO 2004/026866 A (GLAXO GROUP LTD [GB]; BRANCH CLIVE LESLIE [GB]; COULTON STEVEN [GB]; J) 1 April 2004 (2004-04-01) cited in the application claims 1,2,4,9	1-23
P,A	WO 2008/147518 A (MERCK & CO INC [US]; BRESLIN MICHAEL J [US]; COLEMAN PAUL J [US]; COX) 4 December 2008 (2008-12-04) page 2, line 30 - line 35; claim 1	1-23

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 2009	22/06/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gettins, Marc

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/054189

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/089800 A (SMITHKLINE BEECHAM PLC [GB]; GAILLARD PASCALE [GB]; JOHNSON CHRISTOPHE) 14 November 2002 (2002-11-14) cited in the application page 2, line 22 - line 23; claims 1,5	1-23
A	WO 03/002559 A (SMITHKLINE BEECHAM PLC [GB]; CHAN WAI NGOR [GB]; JOHNS AMANDA [GB]; JO) 9 January 2003 (2003-01-09) cited in the application page 2, line 24 - line 25; claim 1	1-23
A	WO 03/002561 A (SMITHKLINE BEECHAM PLC [GB]; BRANCH CLIVE LESLIE [GB]; CHAN WAI NGOR [) 9 January 2003 (2003-01-09) cited in the application claims 1,10	1-23
A	CAI J ET AL: "Antagonists of the orexin receptors" EXPERT OPINION ON THERAPEUTIC PATENTS, INFORMA HEALTHCARE, GB, vol. 16, no. 5, 1 May 2006 (2006-05-01), pages 631-646, XP002458093 ISSN: 1354-3776 page 635; example 16	1-23

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/054189

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02090355 A	14-11-2002	AR 033306 A1	10-12-2003
		AT 383359 T	15-01-2008
		AU 2002253361 B2	17-08-2006
		BR 0209334 A	15-06-2004
		CA 2446396 A1	14-11-2002
		CN 1633433 A	29-06-2005
		CZ 20032990 A3	14-04-2004
		DE 60224521 T2	08-01-2009
		EP 1385845 A1	04-02-2004
		EP 1956020 A2	13-08-2008
		HU 0400048 A2	28-04-2004
		JP 2004533440 T	04-11-2004
		MX PA03010129 A	10-03-2004
		NO 20034925 A	09-12-2003
		NZ 528851 A	31-03-2006
		PL 366853 A1	07-02-2005
		US 2004143115 A1	22-07-2004
		US 2009093478 A1	09-04-2009
		US 2009012073 A1	08-01-2009
		US 2009029986 A1	29-01-2009
WO 2004026866 A	01-04-2004	AT 344261 T	15-11-2006
		AU 2003262516 A1	08-04-2004
		DE 60309481 T2	21-06-2007
		EP 1539747 A1	15-06-2005
		ES 2273083 T3	01-05-2007
		JP 2006504695 T	09-02-2006
		US 2006040937 A1	23-02-2006
WO 2008147518 A	04-12-2008	NONE	
WO 02089800 A	14-11-2002	AU 2002341123 A1	18-11-2002
		EP 1435955 A2	14-07-2004
		JP 2004534026 T	11-11-2004
		US 2004192673 A1	30-09-2004
WO 03002559 A	09-01-2003	AT 356818 T	15-04-2007
		DE 60218852 T2	13-12-2007
		EP 1406897 A2	14-04-2004
		ES 2283609 T3	01-11-2007
		JP 2005501026 T	13-01-2005
		US 2009082390 A1	26-03-2009
		US 2004215014 A1	28-10-2004
WO 03002561 A	09-01-2003	AT 332300 T	15-07-2006
		BR 0210609 A	20-07-2004
		CA 2451464 A1	09-01-2003
		CN 1549816 A	24-11-2004
		CZ 20033437 A3	15-09-2004
		DE 60212968 T2	01-02-2007
		EP 1399441 A1	24-03-2004
		ES 2266549 T3	01-03-2007
		HU 0400326 A2	28-09-2004
		JP 2005501027 T	13-01-2005
		MX PA03011706 A	19-03-2004
		US 2004180887 A1	16-09-2004
		US 2009036442 A1	05-02-2009
		US 2009012083 A1	08-01-2009

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/054189

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03002561 A		US 2008318944 A1	25-12-2008
		US 2009012122 A1	08-01-2009