Abstract: This invention relates to imidazopyrimidine substituted piperidine derivatives of formula (I) and their use as orexin receptor antagonists useful in the treatment of sleep disorders, mood disorders and anxiety related disorders.
PIPERIDINE DERIVATIVES USEFUL AS OREXIN RECEPTOR ANTAGONISTS

This invention relates to imidazopyrimidylmethyl substituted piperidine 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 WO 96/34877. 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 pp 1 to 3; Willie et al (2001) Ann. Rev. Neurosciences 24 pp 429 to 458; Sakurai (2007) Nature Reviews Neuroscience 8 pp 171 to 181; Ohno and Sakurai (2008) Front. Neuroendocrinology 29 pp 70 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 pp 9996 to 10015; Willie et al (2001) Ann. Rev. Neurosciences 24 pp 429 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 pp 223 1 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 maybe 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 pp 1091 l 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 pp 70 to 87; Chemelli et al (1999) Cell 98 pp 437 to 451; Lee et al (2005) J.Neuroscience 25 pp 6716 to 6720; Piper et al (2000) European J Neuroscience 12 pp 726-730 and Smart and Jerman (2002) Pharmacology and Therapeutics 94 pp 51 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 pp 256 to 258) and more recently dogs and humans (Brisbare-Roch et al (2007) Nature Medicine 13(2) pp 150 to 155) further support this.


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. WO05/18548 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 WO08/03 8251 all disclose cyclic amine derivatives.

WO03/002561 discloses N-aroyl cyclic amine derivatives as orexin antagonists. Compounds disclosed in WO03/002561 include piperidine derivatives substituted at the 2-position with bicyclic heteroaryl methyl groups. We have now found that some piperidine derivatives substituted at the 2-position with an imidazo[1,2- α]pyrimidin-2-ylmethyl group have beneficial properties including, for example, increased oral bioavailability and significantly increased solubility in physiologically relevant media compared to the prior art compounds. Such properties make these imidazo[1,2-α]pyrimidin-2-ylmethyl substituted piperidine derivatives very attractive as potential pharmaceutical agents which may be useful in the prevention or treatment of obesity, including obesity observed in Type 2 (non-insulin-dependent) diabetes patients, sleep disorders, anxiety, depression, schizophrenia, drug dependency or compulsive behaviour. Additionally these compounds may be useful in the treatment of stroke, particularly ischemic or haemorrhagic stroke, and/or blocking the emetic response, i.e. useful in the treatment of nausea and vomiting.
Accordingly the present invention provides a compound of formula (I)

Where Ar is selected from the group consisting of formula:

R₁ is (C₁₋₄)alkyl, halo, halo(C₁₋₄)alkyl, (C₁₋₄)alkoxy, halo(C₁₋₄)alkoxy, (C₁₋₄)alkyl-O-(C₁₋₄)alkyl, CN, NR₂R₆ wherein R² is H or (C₁₋₄)alkyl and R⁶ is H or (C₁₋₄)alkyl;
R₂ is (C₁₋₄)alkyl, halo, halo(C₁₋₄)alkyl, (C₁₋₄)alkoxy, halo(C₁₋₄)alkoxy, (C₁₋₄)alkyl-O-(C₁₋₄)alkyl, CN, NR²R₆ wherein R² is H or (C₁₋₄)alkyl and R⁶ is H or (C₁₋₄)alkyl;
R₃ is (C₁₋₄)alkyl, halo, halo(C₁₋₄)alkyl, (C₁₋₄)alkoxy, halo(C₁₋₄)alkoxy, (C₁₋₄)alkyl-O-(C₁₋₄)alkyl, CN, NR²R₆ wherein R² is H or (C₁₋₄)alkyl and R⁶ is H or (C₁₋₄)alkyl;

n is Oor 1;
p is 0 or 1: and
q is Oor 1;

with the proviso that p and q are not both 0;
or a pharmaceutically acceptable salt thereof.

In one embodiment Ar is a group of formula (II).
In another embodiment Ar is a group of formula (III).

In one embodiment Ar is a group of formula (II) and n is 0.
In one embodiment Ar is a group of formula (II) and n is 1.
In another embodiment Ar is a group of formula (II), n is 1 and R₁ is halogen.
In a further embodiment Ar is a group of formula (II), n is 1 and R₁ is chlorine.
In a still further embodiment Ar is a group of formula (II), n is 1, p is 1, q is 0, R₁ is chlorine and R₂ is methyl.

In one embodiment Ar is a group of formula (II), n is 0, p is 1, q is 0 and R₂ is methyl.

In one embodiment Ar is a group of formula (II), n is 0, p is 1, q is 1 and one of R₂ and R₃ is halo and the other is (C₁₋₄)alkyl.
In one embodiment A is a group of formula (II), n is 0, p is 1, q is 1, R₂ is halo and R₃ is (C₁₋₄)-alkyl.
In another embodiment A is a group of formula (II), n is 0, p is 1, q is 1, R₂ is chloro and R₃ is methyl.

In one embodiment A is a group of formula (III) and n is 0.
In one embodiment A is a group of formula (III) and n is 1.
In another embodiment A is a group of formula (III), n is 1 and R₁ is halogen.
In a further embodiment A is a group of formula (III), n is 1 and R₁ is chlorine.
In a still further embodiment A is a group of formula (III), n is 1, p is 1, q is 0, R₁ is chlorine and R₂ is methyl.

In one embodiment A is a group of formula (III), n is 0, p is 1, q is 0 and R₂ is methyl.
In one embodiment A is a group of formula (III), n is 0, p is 1, q is 1 and one of R₂ and R₃ is halo and the other is (C₁₋₄)-alkyl.

In one embodiment A is a group of formula (III), n is 0, p is 1, q is 1, R₂ is halo and R₃ is (C₁₋₄)-alkyl.
In another embodiment A is a group of formula (III), n is 0, p is 1, q is 1, R₂ is chloro and R₃ is methyl.

Examples of the compounds of the invention include:

7-methyl-2-(((25)-1-[[2-methyl-5-phenyl-1,3-thiazol-4-yl]carbonyl]-2-piperidinyl)methyl)imidazo[1,2-α]pyrimidine;
3-chloro-7-methyl-2-(((25)-1-[[2-methyl-5-phenyl-1,3-thiazol-4-yl]carbonyl]-2-piperidinyl)methyl)imidazo[1,2-α]pyrimidine; and
7-chloro-6-methyl-2-(((25)-1-[[2-methyl-5-phenyl-1,3-thiazol-4-yl]carbonyl]-2-piperidinyl)methyl)imidazo[1,2-α]pyrimidine.

When the compound contains a (C₁₋₄)alkyl group, whether alone or forming part of a larger group, e.g. (C₁₋₄)alkoxy, the alkyl group may be straight chain, branched or cyclic, or combinations thereof. Examples of (C₁₋₄)alkyl are methyl or ethyl. An example Of(C₁₋₄)alkoxy is methoxy.

Examples of halo(C₁₋₄)alkyl include trifluoromethyl (i.e. -CF₃).
Examples of (C₁₋₄)alkoxy include methoxy and ethoxy.
Examples of halo(C₁₋₄)alkoxy include trifluoromethoxy (i.e. -OCF₃).
Halogen or "halo" (when used, for example, in halo(C₁₋₄)alkyl) means fluoro, chloro, bromo or iodo.

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, pp 1-19. 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-toluensulfonic, 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.

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).

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.

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable 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.

The compounds of formula (I) are S enantiomers. Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible enantiomers and diastereoisomers, including mixtures thereof. 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.

The subject invention also includes isotopically-labeled compounds which are identical to those recited in formula (I) 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 of 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.

Scheme

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.
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.

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) or their pharmaceutically acceptable salts may be of use for the treatment or prophylaxis of a disease or disorder 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) or their pharmaceutically acceptable salts may be of use for the treatment or prophylaxis of a disease or disorder 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) or their pharmaceutically acceptable salts may be of use for the treatment or prophylaxis of a disease or disorder 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
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 (300.2), 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) or their pharmaceutically acceptable salts may be of use for the treatment or prophylaxis of a disease or disorder 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) or their pharmaceutically acceptable salts may be of use for the treatment or prophylaxis of a disease or disorder where an antagonist of a human orexin receptor is required such as feeding disorders such as bulimia nervosa, binge eating, obesity, including obesity observed in Type 2 (non-insulin-dependent) diabetes patients. Further, the compounds of formula (I) or their pharmaceutically acceptable salts may be of use for the treatment or prophylaxis of a disease or disorder where an antagonist of a human orexin receptor is required such as stroke, particularly ischemic or haemorrhagic and/or in blocking an emetic response i.e. nausea and vomiting.

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 a disease or disorder 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 salt thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of a disease or disorder 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 salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder 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 salt thereof, and a pharmaceutically acceptable carrier.

The compounds of formula (I) or their pharmaceutically acceptable salts 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) or their pharmaceutically acceptable salts 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.

In one embodiment 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 salt 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 contain from 0.1% to 100% by weight, for example from 10 to 60% by weight, of the active material, depending on the method of administration. The composition may contain from 0% to 99% by weight, for example 40% to 90% by weight, of the carrier, depending on the method of administration. The composition may contain from 0.05mg to 1000mg, for example from 1.0mg to 500mg, of the active material, depending on the method of administration. The composition may contain from 50 mg to 1000 mg, for example from 100mg to 400mg of the carrier, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors.

However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 500mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

Compounds of the invention may be identified and characterised using screening procedures and assays including, for example, activity assays and functional assays.

Orexin-A (Sakurai, T. et al (1998) Cell, 92 pp 573-585)) can be employed in screening procedures for compounds which inhibit the ligand's activation of the orexin-1 or orexin-2 receptors.

In general, such screening procedures involve providing appropriate cells which express the orexin-1 or orexin-2 receptor on their surface. Such cells include cells from mammals, yeast, Drosophila or E. coli. In particular, a polynucleotide encoding the orexin-1 or orexin-2 receptor is used to transfect cells to express the receptor. The expressed receptor is then contacted with a test compound and an orexin-1 or orexin-2 receptor ligand, as appropriate, to observe inhibition of a functional response. One such screening procedure
involves the use of melanophores which are transfected to express the orexin-1 or orexin-2 receptor, as described in WO 92/01810.

Another screening procedure involves introducing RNA encoding the orexin-1 or orexin-2 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 or orexin-2 receptor ligand to cells which have the orexin-1 or orexin-2 receptor (as appropriate) on their surface. This method involves transfecting a eukaryotic cell with DNA encoding the orexin-1 or orexin-2 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 or orexin-2 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 or orexin-2 receptor ligand with the orexin-1 or orexin-2 receptor as appropriate.

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 5 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 batch referred to.

The compounds described in the Examples described hereinafter have all been prepared as a first step from stereochemically pure methyl 5-oxo-L-prolinate or ethyl 5-oxo-D-prolinate. The stereochemistry of the compounds of the Descriptions and Examples have been assigned on the assumption that the pure configuration of 5-oxo-prolinate is maintained.

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 300, 400 or 500 MHz, or on a Bruker instrument at 300 and 400 MHz. 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 reported.

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

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 (33×4.6 mm, 3μm) (mobile phase: 100% [water +0.1% HCO₂H] for 1 min, then from 100% [water +0.1% HCO₂H] to 5% [water +0.1% HCO₂H] and 95% [CH₃CN ] in 5 min, finally under these conditions for 2 min; T=40°C; flux= 1 mL/min; LC/MS - ES (-):analysis performed on a Supelcosil ABZ +Plus (33×4.6 mm, 3μm) (mobile phase: 100% [water +0.05% NH₃] for 1 min, then from 100% [water +0.05% NH₃] to 5% [water +0.05% NH₃] and 95% [CH₃CN ] in 5 min, finally under these conditions for 2 min; T=40°C; flux= 1 mL/min].

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

Flash silica gel chromatography was carried out on silica gel 230-400 mesh (supplied by Merck AG Darmstadt, Germany) or over Varian Mega Be-Si pre-packed cartridges or over pre-packed Biotage 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.

In a number of preparations, purification was performed using either Biotage manual flash chromatography (Flash+) or automatic flash chromatography (Horizon) systems. All these instruments work with Biotage Silica cartridges.

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

The following table lists the abbreviations used in the text:

<table>
<thead>
<tr>
<th>AcCl</th>
<th>Acetyl chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>BINAP</td>
<td>2’’-Bis(diphenylphosphino)-1,1’’-binaphthyl</td>
</tr>
<tr>
<td>Boc</td>
<td>t-Butoxycarbonyl</td>
</tr>
</tbody>
</table>
Into a 250 ml round bottom flask ((2S)-l-[(l,l-dimethylethyl)oxy]carbonyl]-2-piperidinyl)acetic acid (1.00 g, 4.11 mmol), DMF (25 ml), DIPEA (2.15 ml, 12.33 mmol) and TBTU (1.98 g, 6.17 mmol) were added. The mixture was stirred at rt for 20 min and a brown colour was formed. After this time MeOH (0.25 ml, 6.17 mmol) was added and the resulting solution stirred at rt for 30 min. Then it was transferred into e separatory funnel containing brine (20 ml) and extracted with EtOAc (20 ml x 2), the combined organic layers were washed with water/ice (5 x 20 ml). The organic layer was dried (Na₂SO₄), filtered and concentrated. The crude obtained was purified by column chromatography (Biotage SPI, Cy-EtOAc from 100/0 to 85/15). Collected fractions gave the title compound (1.01 g, 3.92 mmol, 95% yield) as a colorless oil. $^1$H-NMR (500 MHz, CDCl₃) δ(ppm): 4.67 - 4.75 (m, 1
H), 3.96 - 4.05 (m, 1 H), 3.67 (s, 3 H), 2.79 (t, 1 H), 2.61 (dd, 1 H), 2.53 (dd, 1 H), 1.60 - 1.70 (m, 6 H), 1.46 (s, 9 H).

Description 2: 1,1-dimethylethyl (2S)-2-(3-bromo-2-oxopropyl)-l-piperidinecarboxylate (D2)

In a 500 ml round-bottomed flask under nitrogen at rt, D1 (11.1 g, 43.1 mmol) was dissolved in THF (100 ml) to give a pale yellow solution. This solution was cooled to -78 °C and the Tebbe reagent (104 ml of a 0.5 M solution in toluene, 51.8 mmol) was added dropwise. The thick mixture was diluted with further 70 ml of dry toluene. The resulting brown-orange mixture was stirred at this temperature for 30 min and then slowly warmed up to rt and left under stirring for 2 h. The reaction mixture was charged into a dropping funnel and then added dropwise to a 2 L round-bottomed flask containing -400 ml of NaOH 1 M aqueous solution cooled at 0 °C. At the end of the quench, the resulting grey suspension was diluted with EtOAc (250 ml) and allowed to stir overnight (mechanical stirring). The resulting yellow suspension was then filtered over a Gooch funnel (using Sterimat): salts were washed with EtOAc (-500 ml). Phases were then separated and the organic layer was washed with brine (2 x 500 ml). The combined organic phases were dried (Na₂SO₄), filtered and concentrated to give a deep orange oil. This material was diluted with -500 ml OfEt₂O: some salts precipitated, so the resulting suspension was filtered over a Gooch funnel (using Sterimat). The filtrate was concentrated under vacuum to give 12.4 g of crude 1,1-dimethylethyl (2S)-2-[2-(methyloxy)-2-propen-l-yl]-l-piperidinecarboxylate as an orange-brown oil. The material contained some residual salts (as the overall recovered amount was higher than the theoretical amount). The material was used without further purification in the next reaction and supposed to be pure at 89 wt%. In a 1 L round-bottomed flask under nitrogen at rt 1,1-dimethylethyl (2S)-2-[2-(methyloxy)-2-propen-l-yl]-l-piperidinecarboxylate (12.4 g, 43.1 mmol) was dissolved in THF (125 ml) and water (35 ml) to give a pale yellow solution. NBS (7.67 g, 43.1 mmol) was then added dissolved in -100 ml of THF. The resulting grey mixture was stirred at rt for 1h. Then additional NBS (0.2 eq, 1.5 g) dissolved in 50 ml of THF was added and the reaction mixture stirred at rt for 1h. The mixture was concentrated under vacuum to remove THF, then was diluted with EtOAc (-500 ml) and water (200 ml). Phases were separated and the aqueous layer was back-extracted with EtOAc (250 ml). The combined organic layers were dried (Na₂SO₄) filtered and concentrated to give: 17.8 g of a brown oil. This material was purified by flash-chromatography (Biotage 75L, Cy-EtOAc from 100-0 to 90-10) to give the title compound (6.0 g, 18.7 mmol, 43% yield from D1, two steps) as a slightly yellow oil that solidified upon standing. UPLC: rt = 0.79, peaks observed: 344 [M+Na, 100%], 342 [M+Na, 100%],
266 [M-fBu,100%] and 264 [M-fBu,100%]. 1H NMR (500 MHz, CDCl₃) δ (ppm): 4.72 - 4.79 (m, 1 H), 3.91 - 4.10 (m, 3 H), 2.77 - 2.97 (m, 3 H), 1.49 - 1.75 (m, 6 H), 1.46 (s, 9 H).

**Description 3**: 1,1-dimethylethyl (2S)-2-[(7-methylimidazo[1,2-a]pyrimidin-2-yl)methyl]-1-piperidinecarboxylate (D3):

To a solution of 1,1-dimethylethyl (2S)-2-(3-bromo-2-oxopropyl)-1-piperidinecarboxylate D2 (0.300 g, 0.94 mmol) in DMF (2 ml) was added 4-methyl-2-pyrimidinamine (0.153 g, 1.41 mmol) and the mixture was stirred at 80 °C for 1.5 h. To the reaction mixture was added brine and a saturated NaHCO₃ aqueous solution and extracted with EtOAc. The organic layer was dried (Na₂SO₄), filtered and evaporated and the residue was purified by flash chromatography on silica gel (Biotage 25+M, DCM/MeOH from 100/0 to 90/10). Collected fractions gave the title compound (0.350 g slightly contaminated with residual 4-methyl-2-pyrimidinamine). UPLC: rt = 0.53, peak observed: 331 (M+l). C₁₈H₂₆N₄O₂ requires 330.

**Description 4**: 1,1-dimethylethyl (2S)-2-[(3-chloro-7-methylimidazo[1,2-a]pyrimidin-2-yl)methyl]-1-piperidinecarboxylate (D4):

To a solution of 1,1-dimethylethyl (2S)-2-(7-methylimidazo[1,2-a]pyrimidin-2-yl)methyl]-1-piperidinecarboxylate (0.350 g, 0.53 mmol) in DCM (5 ml) was added NCS (0.071 g, 0.53 mmol) and the reaction mixture was stirred for 1.5 h at rt. The solvent was evaporated and the residue purified by chromatography on silica gel (Biotage, NH phase 25+M, Cy/EtOAc from 100/0 to 50/50). Collected fractions gave the title compound (0.085 g, 0.23 mmol, 44% yield) as a colourless solid. UPLC: rt = 0.70, peak observed: 365 (M+l, 100%) and 367 (M+l, 33%). C₁₈H₂₅ClN₄O₂ requires 365.

**Description 5**: 3-chloro-7-methyl-2-[(2S)-2-piperidinylmethyl]imidazo[1,2-fl]pyrimidine (D5):
To a solution of 1,1-dimethylethyl (25)-2-[(3-chloro-7-methylimidazo[1,2-α]pyrimidin-2-yl)methyl]-1-piperidinecarboxylate (D4) (0.085 g, 0.23 mmol) in DCM (2 ml), TFA (0.5 ml) was added dropwise at 0 °C and the solution was stirred for 1 h. The solvent was removed and the residue charged into a SCX column and eluted with methanol and ammonia 2 M in methanol. Collected fractions gave the title compound (0.060 g, 0.23 mmol, 97% yield) as a colorless oil. UPLC: rt = 0.39, peak observed: 265 (M+1, 100%) and 267 (M+1, 33%).

**EXAMPLES**

**Example 1: 7-methyl-2-((2S)-1-[(2-methyl-5-phenyl-1,3-thiazol-4-yl)carbonyl]-2-piperidinyl)methyl)imidazo[1,2-a]pyrimidine (HCl salt) (EI):**

![Chemical Structure](image)

To a solution of 1,1-dimethylethyl (25)-2-(3-bromo-2-oxopropyl)-1-piperidinecarboxylate (D2) (0.215 g, 0.54 mmol) in DMF (2 ml) was added 4-methyl-2-pyrimidinamine (0.059 g, 0.54 mmol) and the mixture was stirred at 80 °C for 2.5 h. The reaction mixture was charged into a SCX column and was eluted with methanol and ammonia 2 M in methanol. Collected fractions gave 0.087 g of an oil containing a mixture of N-Boc protected 7-methyl-2-((2S)-2-piperidinylmethyl)imidazo[1,2-a]pyrimidine and free amine contaminated with residual 4-methyl-2-pyrimidinamine. LC-MS: rt = 1.43 min, m/z = 331 (M+1), C_{18}H_{26}N_{4}O_{2} requires 330. To a solution of this material (0.087 g) in DCM (2.5 ml), TFA (0.5 ml) was added dropwise at 0 °C and the solution was stirred for 1 h. The solvent was removed and the residue charged into a SCX column and eluted with methanol and ammonia 2 M in methanol. Collected fractions gave a crude (0.068 g) containing the free amine 7-methyl-2-((2S)-2-piperidinylmethyl)imidazo[1,2-a]pyrimidine contaminated with
residual 4-methyl-2-pyrimidinamine. MS: (ES+)/m/z: 231 [M+1]. CoH₁₈N₄ requires 230.
Into a 7 ml screw capped vial 2-methyl-5-phenyl-1,3-thiazole-4-carboxylic acid (0.036 g, 0.16 mmol) was dissolved in DCM (1 ml), Oxalyl chloride (0.031 ml, 0.36 mmol) then DMF (0.01 1 ml, 0.15 mmol) were added and the resulting mixture was stirred for 30 min at rt. The solvent was removed under reduced pressure and the resulting yellow solid dissolved in DCM (1 ml) and added dropwise to a solution containing 7-methyl-2-[(2S)-2-piperidinylmethyl]imidazo[1,2-a]pyrimidine (0.034 g of the crude prepared previously), and TEA (0.062 ml, 0.44 mmol) in DCM (1 ml) cooled at 0 °C. The ice-bath was removed and the reaction mixture left under stirring at rt for 1 h. DCM (1 ml) was added and the mixture washed with NaHCO₃ (2 ml); the organic phase was separated, dried (Na₂SO₄), filtered and concentrated. The residue was purified by column chromatography on silica gel (Biotage 12 M, DCM/MeOH 98/2). The free base of the title compound (0.018 g, 0.04 mmol, 7% yield from D2, three steps) was obtained as a brown solid. UPLC: rt = 0.55, peak observed: 432 (M+1). C₂₄H₂₅NsOS requires 431. 1H NMR [the product is present as a mixture of conformers (ratio c.ca 60/40) and the assignment refers to the single conformer] (500 MHz, CDCl₃) δ (ppm): 8.69 (d, 1 H) 7.65 (s, 1 H) 7.27 - 7.41 (m, 5 H) 6.84 (d, 1 H) 4.48 (dd, 1 H) 3.85 - 3.93 (m, 1 H) 3.01 (dt, 1 H) 2.90 (dd, 1 H) 2.78 (dd, 1 H) 2.69 (s, 3 H) 2.47 (s, 3 H) 1.21 - 1.74 (m, 5 H) 0.81 - 0.90 (m, 1 H). The free base (0.018 g, 0.04 mmol) was transferred into a 7 ml screw capped vial with anhydrous DCM (1 ml) and the solution cooled to 0 °C. HCl (0.063 ml of a 1 M solution in Et₂O, 0.06 mmol) was added dropwise and the mixture stirred for 15 min. The solvent was removed under reduced pressure and the resulting solid triturated with anhydrous Et₂O. The title compound was obtained as a light brown solid (0.019 g, 0.04 mmol, 99% yield). HPLC (walk-up): rt = 3.47 min. MS: (ES+)/m/z: 432 [M+1-HCl]. C₂₄H₂₆ClN₄SO requires 468.


![Chemical structure of Example 2](image-url)
Into a 7 ml screw capped vial 2-methyl-5-phenyl-1,3-thiazole-4-carboxylic acid (0.026 g, 0.12 mmol) was dissolved in DCM (1 ml). Oxalyl chloride (0.011 ml, 0.13 mmol) then DMF (0.020 ml) were added and the resulting mixture was stirred for 1 h at rt. The solvent was removed under reduced pressure and the resulting yellow solid dissolved in DCM (1 ml) and added dropwise to a solution of 3-chloro-7-methyl-2-[(25)-2-piperidinylmethy^imidazofl^-αpyrimidine (D5) (0.030 g, 0.11 mmol), and TEA (0.032 ml, 0.23 mmol) in DCM (1 ml) cooled at 0°C. The ice-bath was removed and the reaction mixture left under stirring at rt for 1 h. To the reaction mixture a saturated NaHCO3 aqueous solution and water were added and extracted with DCM. The organic layer was separated from the aqueous layer by separator tube and then collected and evaporated. The residue was purified by flash chromatography (Biotage NH phase 12+M, DCM/MeOH from 100/0 to 98/2). Collected fractions gave the free base of the title compound (0.027 g, 0.06 mmol, 51% yield) as a white solid. HPLC (walk-up): rt = 3.95 min. UPLC: rt = 0.67, peak observed: 466 (M+1, 100%) and 468 (M+1, 33%).

C24H24CIN5OS requires 466. 1H NMR [the product is present as a mixture of conformers (ratio c.ca 70/30)] (500 MHz, DMSO-d6). The free base (0.027 g, 0.06 mmol) was dissolved in Et2O/DCM (1/1) (2 ml) and HCl 1 M in Et2O (1.1 eq.) was added. The resulting suspension was triturated with Et2O and the solvents were evaporated affording the title compounds (0.027 g, 0.05 mmol, 47% yield) as a white solid. HPLC (walk-up): rt = 3.68 min. UPLC: rt = 0.67, peak observed: 466 (M+1-HCl, 100%) and 468 (M+1-HCl, 33%). C24H25Cl2N5O5S requires 502.

**Example 3:** 7-chloro-6-methyl-2-((25)-1-[(2-methyl-5-phenyl-1,3-thiazol-4-yl)carbonyl]-2-piperidinyl)methylimidazo[1,2-α]pyrimidine (HCl salt) (E3):

To a solution of 1,1-dimethylethyl (25)-2-(3-bromo-2-oxopropyl)-1-piperidinecarboxylate D2 (0.100 g, 0.31 mmol) in DMF (1 ml) was added 4-chloro-5-methyl-2-pyrimidinamine...
(0.067 g, 0.47 mmol) and the mixture was stirred at 80 °C for 3.5 h. The reaction mixture was charged into a SCX column and was eluted with methanol and ammonia 2 M in methanol. Collected fractions gave 0.086 g of a crude containing the desired product iV-Boc protected. MS: (ES+)/ m/z: 366 [M+1]. C_{18}H_{25}ClN_{4}O_{2} requires 365. To a solution of this material (0.086 g) in DCM (4 ml), TFA (1 ml) was added dropwise at 0 °C and the solution was stirred for 1 h at rt. The solvent was removed and the residue charged into a SCX column and eluted with methanol and ammonia 2 M in methanol. Collected fractions gave a crude (0.072 g) containing the free amine 7-chloro-6-methyl-2-[(25)-2-
piperidinylmethyl]imidazo[1,2- α]pyrimidine. UPLC: rt = 0.41, peak observed: 265 (M+1, 100%) and 267 (M+1, 33%). C_{13}H_{17}ClN_{4} requires 265. Into a 7 ml screw capped vial 2-
methyl-5-phenyl-1,3-thiazole-4-carboxylic acid (0.071 g, 0.33 mmol) was dissolved in DCM (1 ml), Oxalyl chloride (0.057 ml, 0.65 mmol) then DMF (one drop) were added and the resulting mixture was stirred for 30 min at rt. The solvent was removed under reduced pressure and the resulting yellow solid dissolved in DCM (1 ml) and added dropwise to the solution containing the crude (0.072 g) 7-chloro-6-methyl-2-[(25)-2-
piperidinylmethyl]imidazo[1,2- α]pyrimidine and TEA (0.13 ml, 0.81 mmol) in DCM (1 ml) cooled at 0 °C. The ice-bath was removed and the reaction mixture left under stirring at rt for 2 h. DCM (1 ml) was added and the mixture washed with NaHCO$_3$ (2 ml); the organic phase was separated, dried (Na$_2$SO$_4$), filtered and concentrated. The residue was purified by Fraction Lynx (two runs) and the free base of the title compound was obtained (0.004 g, 0.001 mmol, 3% yield from D2, three steps). UPLC: rt = 0.64, peak observed: 466 (M+1, 100%) and 468 (M+1, 33%). C_{24}H_{24}ClN_{5}OS requires 466. $^1$H NMR [the product is present as a mixture of conformers (ratio c.ca 60/40)] (500 MHz, DMSO-d$_6$). The free base (0.003 g, 0.0006 mmol) was transferred into a 7 ml screw capped vial with anhydrous Et$_2$O (0.2 ml) and the solution cooled to 0 °C. HCl (0.14 ml of a 1 M solution in Et$_2$O, 0.14 mmol) was added dropwise and the mixture stirred for 15 min. The solvent was removed under reduced pressure and the resulting solid triturated with anhydrous Et$_2$O. The title compound was obtained (0.003 g, 0.006 mmol, 93% yield).

30 Example 4: 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.

The sequences of the human orexin 1 and human orexin 2 receptors used in this example were as published in Sakurai, T. et al (1998) Cell, 92 pp 573 to 585, with the exception that the human orexin 1 receptor sequence used had the amino acid residue alanine at position 280 and not glycine as reported in Sakurai et al.
Measurement of \([\text{Ca}^{2+}]\), 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 Probencid 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 (\(λ_{ex} = 488\text{ nm}, \lambda_{em} = 540\text{ nm}\)) (Sulivan E, Tucker EM, Dale IL. Measurement of \([\text{Ca}^{2+}]\) using the flourometric 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\(_r\) 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).
\[
fpKi = -\log \frac{(IC_{50})}{\left(2 + \left(\frac{[\text{agonist}]}{(EC_{50})}\right)^n\right)^{1/n} - 1}
\]

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 8.1 to 9.6 at the human cloned orexin-1 receptor (having the amino acid residue alanine at position 280 and not glycine) and from 6.3 to 7.9 at the human cloned orexin-2 receptor.
Claims

1. A compound of formula (I)

\[
\begin{align*}
\text{Ar} & \quad (R_1)_n \\
(\text{R}_2)^p & \\
(\text{R}_3)^q
\end{align*}
\]

Where Ar is selected from the group consisting of formula:

\[ \text{(II) and (III)} \]

R₁ is \((\text{C}_{1-4})\)alkyl, halo, \((\text{C}_{1-4})\)alkyl, \((\text{C}_{1-4})\)alkoxy, \((\text{C}_{1-4})\)alkyl-O-(C)\)alkyl, CN, NR^5R^6 wherein R^5 is H or \((\text{C}_{1-4})\)alkyl and R^6 is H or \((\text{C}_{1-4})\)alkyl;

R₂ is \((\text{C}_{1-4})\)alkyl, halo, \((\text{C}_{1-4})\)alkyl, \((\text{C}_{1-4})\)alkoxy, \((\text{C}_{1-4})\)alkyl-O-(C\)alkyl, CN, NR^7R^8 wherein R^7 is H or \((\text{C}_{1-4})\)-alkyl and R^8 is H or \((\text{C}_{1-4})\)-alkyl;

R₃ is \((\text{C}_{1-4})\)alkyl, halo, \((\text{C}_{1-4})\)alkyl, \((\text{C}_{1-4})\)alkoxy, \((\text{C}_{1-4})\)alkyl-O-(C\)alkyl, CN, NR^9R^10 wherein R^9 is H or \((\text{C}_{1-4})\)-alkyl and R^10 is H or \((\text{C}_{1-4})\)-alkyl;

n is 0 or 1;

p is 0 or 1; and

q is 0 or 1;

with the proviso that p and q are not both 0;

or a pharmaceutically acceptable salt thereof.

2. A compound, or a pharmaceutically acceptable salt thereof, according to claim 1 where Ar is a group of formula (II).

3. A compound, or a pharmaceutically acceptable salt thereof, according to claim 1 where Ar is a group of formula (III).

4. A compound, or a pharmaceutically acceptable salt thereof, according to claim 1 or 2 where Ar is a group of formula (II) and n is 0.

5. A compound, or a pharmaceutically acceptable salt thereof, according to claim 1 or 2 where Ar is a group of formula (II) and n is 1.
6. A compound, or a pharmaceutically acceptable salt thereof, according to claim 5 where Ar is a group of formula (II), n is 1 and R₁ is halogen.

7. A compound, or a pharmaceutically acceptable salt thereof, according to claim 6 where Ar is a group of formula (II), n is 1 and R₁ is chlorine.

8. A compound, or a pharmaceutically acceptable salt thereof, according to claims 1, 2, 5, 6, or 7 where Ar is a group of formula (II), n is 1, p is 1, q is 0, R₁ is chlorine and R₂ is methyl.

9. A compound, or a pharmaceutically acceptable salt thereof, according to claims 1, 2, or 4 where Ar is a group of formula (II), n is 0, p is 1, q is 0 and R₂ is methyl.

10. A compound, or a pharmaceutically acceptable salt thereof, according to claims 1, 2, or 4 where Ar is a group of formula (II), n is 0, p is 1, q is 1 and one of R₂ and R₃ is halo and the other is (C^alkyl).

11. A compound, or a pharmaceutically acceptable salt thereof, according to claim 10 where Ar is a group of formula (II), n is 0, p is 1, q is 1, R₂ is halo and R₃ is (C^alkyl).

12. A compound, or a pharmaceutically acceptable salt thereof, according to claims 10 or 11 where Ar is a group of formula (II), n is 0, p is 1, q is 1, R₂ is chloro and R₃ is methyl.

13. A compound, or a pharmaceutically acceptable salt thereof, according to claim 1 or 3, where Ar is a group of formula (III) and n is 0.

14. A compound, or a pharmaceutically acceptable salt thereof, according to claim 1 or 3 where Ar is a group of formula (III) and n is 1.

15. A compound, or a pharmaceutically acceptable salt thereof, according to claim 14 where Ar is a group of formula (III), n is 1 and R₁ is halogen.

16. A compound, or a pharmaceutically acceptable salt thereof, according to claims 1, 3, 14, or 15 Ar is a group of formula (III), n is 1 and R₁ is chlorine.

17. A compound, or a pharmaceutically acceptable salt thereof, according to claims 1, 3, 14, 15, or 16 where Ar is a group of formula (III), n is 1, p is 1, q is 0, R₁ is chlorine and R₂ is methyl.

18. A compound, or a pharmaceutically acceptable salt thereof, according to claims 1, 3, or 13 where Ar is a group of formula (III), n is 0, p is 1, q is 0 and R₂ is methyl.
19. A compound, or a pharmaceutically acceptable salt thereof, according to claims 1, 3, or 13 where Ar is a group of formula (III), n is 0, p is 1, q is 1 and one of $R_2$ and $R_3$ is halo and the other is (C$_{1-4}$)-alkyl.

20. A compound, or a pharmaceutically acceptable salt thereof, according to claim 19 where Ar is a group of formula (III), n is 0, p is 1, q is 1, $R_2$ is halo and $R_3$ is (C$_{1-4}$)-alkyl.

21. A compound, or a pharmaceutically acceptable salt thereof, according to claims 19 or 20 where Ar is a group of formula (III), n is 0, p is 1, q is 1, $R_2$ is chloro and $R_3$ is methyl.

22. A compound, or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of:

- 7-methyl-2-((25)-1-[(2-methyl-5-phenyl-1,3-thiazol-4-yl)carbonyl]-2-piperidinyl)methyl)imidazo[1,2-α]pyrimidine;
- 3-chloro-7-methyl-2-((25)-1-[(2-methyl-5-phenyl-1,3-thiazol-4-yl)carbonyl]-2-piperidinyl)methyl)imidazo[1,2-α]pyrimidine; and
- 7-chloro-6-methyl-2-((25)-1-[(2-methyl-5-phenyl-1,3-thiazol-4-yl)carbonyl]-2-piperidinyl)methyl)imidazo[1,2-α]pyrimidine.

23. The compound as defined in any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use in therapy.

24. The compound as defined in any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, for the treatment of a disease or disorder where an antagonist of a human orexin receptor is required.

25. The compound according to claim 24, 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.

26. The compound according to claim 25, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder is a sleep disorder.

27. The compound according to claim 26, 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,
Hypersonnia Type, Parasomnia Type and Mixed Type; Sleep Apnea and Jet-Lag
Syndrome.

28. Use of a compound as defined in any one of claims 1 to 22, or a pharmaceutically
acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease or
disorder where an antagonist of a human orexin receptor is required.

29. Use according to claim 28 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.

30. Use according to claim 29 wherein the disease or disorder is a sleep disorder.

31. Use according to claim 30 where the sleep disorder is selected from the group
consisting of Dyssomnias such as Primary Insomnia (307.42), Primary Hypersonnia
(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 Hypersonnia 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, Hypersonnia Type, Parasomnia Type and Mixed
Type; Sleep Apnea and Jet-Lag Syndrome.

32. A method of treating or preventing a disease or disorder where an antagonist of a
human orexin receptor is required, which comprises administering to a subject in need
thereof an effective amount of a compound as defined in any one claims 1 to 22, or a
pharmaceutically acceptable salt thereof.

33. A method according to claim 32 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.

34. A method according to claim 33 where the disease or disorder is a sleep disorder.

35. A method according to claim 34 where the sleep disorder is selected from the group
consisting of Dyssomnias such as Primary Insomnia (307.42), Primary Hypersonnia
(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.

36. A pharmaceutical composition comprising a) the compound as defined in any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, and b) a pharmaceutically acceptable carrier.
**INTERNATIONAL SEARCH REPORT**

**PCT/EP2008/066216**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D487/04 A61K31/519 A61P3/00 A61P25/00

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 A61K A61P

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, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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* Further documents are listed in the continuation of Box C.

**D**

See patent family annex.

**E**

Date of the actual completion of the international search

23 April 2009

Date of mailing of the international search report

07/05/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk

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Marzi, Elena

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