

Señores

DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Santafé de Bogotá, D.C.

02-01-08
Re.: Expediente No. 00 - 9.233

Solicitud de Patente

En relación con la última providencia recaída en este expediente, me permito manifestarle lo siguiente:

- 1.- Acompaño el arte final por triplicado.
- 2.- Debidamente traducidas, acompaño las copias oficiales de las siguientes solicitudes básicas de patente británicas

GB 9903266.6
GB 9903241.9
GB 9926430.1
GB 9926441.8
- 3.- Mi cliente estima que la observación del Señor Examinador sobre mencionar las ventajas que tienen los compuestos reivindicados sobre los conocidos, carece de estructura ya que no identifica qué arte anterior relacionado con antagonistas del receptor orexina-1, es sobre el que se basa al expresar su comentario.

Si se determina tal circunstancia con precisión, mi cliente
estaría listo a dar una respuesta.

Espero su comentario.

Pero si no lo hay, renuncio al término faltante de traslado y
le solicito ordenar la publicación del extracto.

De Ustedes atentamente,

GERMAN CASTILLO GRAU

T.P. No. 2978 del C.S.J.

Se retiró del folio 85, Arte final
tamaño 12x12cm y 6x6cm.

202041

18 feb /02

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

80

Expediente No		No de Folio
Item	No de unidades	
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6	DISQUETES	
7	SOBRE DE MANILA	
8	SOBRE BLANCO TAMAÑO CARTA	1
9	SOBRE BLANCO TAMAÑO OFICIO	
10	OTROS:	

Observaciones:

Arte Final.



Castillo Grau & Asociados

ABOGADOS

APARTADO AEREO 251473

BOGOTÁ, COLOMBIA

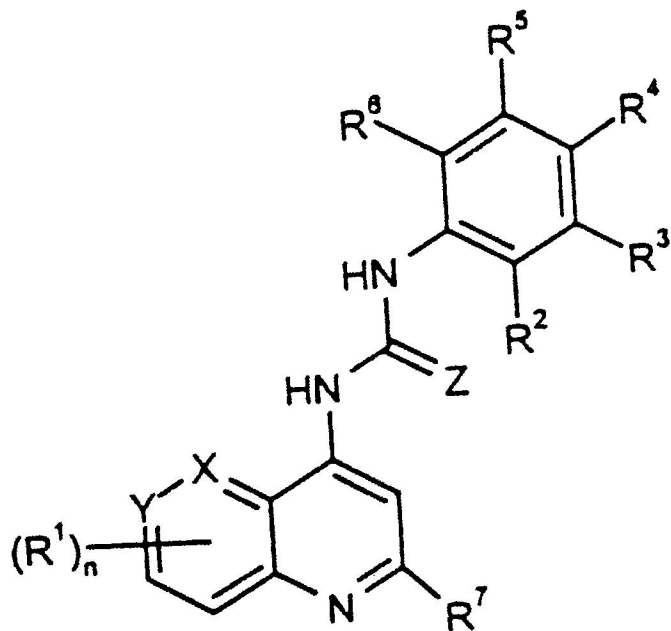
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Solicitud de Patente

Contiene arte final por triplicado

22





(I)



The
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INVESTOR IN PEOPLE

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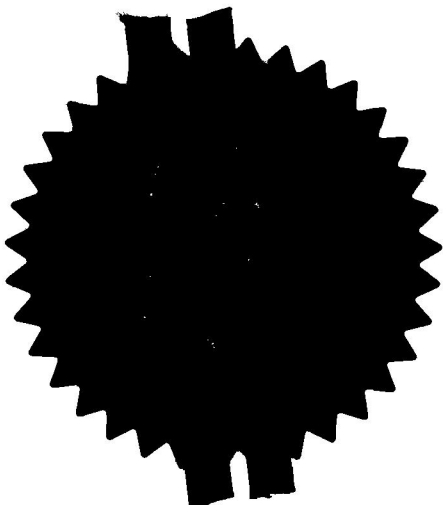
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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

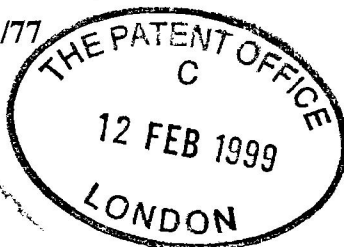
In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed *Andrew George*

Dated 30 November 1999



The
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12 FEB 1999

1/77 82

15FEB99 E425229-2 D02029
P01/7700 0.00 - 9903266.6

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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The Patent Office
Cardiff Road
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Gwent NP9 1RH

1. Your reference	AJB/PS/P32240		
2. Patent application number (The Patent Office will fill in his part)			
3. Full name, address and postcode of the or of each applicant (underline all surnames) Patents ADP number (if you know it) If the applicant is a corporate body, give the country/state of its incorporation	SmithKline Beecham plc New Horizons Court, Brentford, Middx TW8 9EP. Great Britain 5776299 002		
4. Title of the invention	Compounds		
5. Name of your agent (if you have one) "Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode) Patents ADP number (if you know it)	CORPORATE INTELLECTUAL PROPERTY SMITHKLINE BEECHAM PLC TWO NEW HORIZONS COURT BRENTFORD MIDDLESEX TW8 9EP 5800974 003		
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day / month / year)
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)	
8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer yes if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is named as an applicant, or c) any named applicant is a corporate body See note (d)			

Patents Form 1/77

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Description	15
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10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 1/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11.

We request the grant of a patent on the basis of this application

Signature A J Blakey Date 12-Feb-99
A J Blakey

12. Name and daytime telephone number of person to contact in the United Kingdom

A J Blakey 01279 644355

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After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

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85COMPOUNDS

This invention relates to phenyl urea and phenyl thiourea derivatives and their use as pharmaceuticals.

- 5 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 EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP-A-893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.

- 15 Orexin receptors are found in the mammalian host and may be responsible for many biological functions, including pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual
20 dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourett's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's
25 disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism;
30 Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; and sleep disturbances
35 associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure;
40 renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection,

e.g. HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; 5 tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders, which includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

10 Experiments have shown that central administration of the ligand orexin-A (described in more detail below) 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. Therefore, antagonists of its receptor may be useful in the treatment of 15 obesity and diabetes, see *Cell*, 1998, **92**, 573-585.

There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. 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, and 20 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 25 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.

Rat sleep/EEG studies have also shown that central administration of orexin- 30 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. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

The present invention provides phenyl urea and phenyl thiourea derivatives 35 which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity including obesity observed in Type 2 (non-insulin-dependent) diabetes patients and/or sleep disorders.

Several phenyl urea derivatives are known in the literature, viz: 40 WO 93/18028, WO 94/14801 and WO 94/18170 disclose indolylurea, benzo[b]thienylurea and N-phenyl-N'-heteroarylurea derivatives respectively [compounds a)-i) below] as 5HT_{2C} receptor antagonists;

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JP 04178362 discloses the compound N-(2-methyl-4-quinolinyl)-N'-(5,6,7,8-tetrahydro-1-naphthalenyl)urea [compound j) below] as an agrochemical pesiticide;

EP 123146 discloses the compound N-(2-methyl-4-quinolinyl)-N'-(3,4,5-trimethoxyphenyl)urea [compound k) below] as an anti-inflammatory agent;

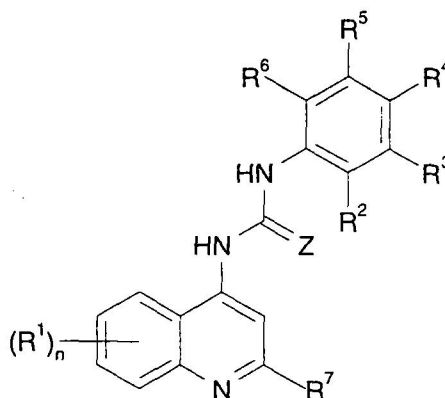
5 GB 2009155 and *J. Am. Chem. Soc.*, 1956, **78**, 3703, disclose various N-phenyl-N'-(2-methyl-4-quinolinyl)urea derivatives [compounds m)-r) and compounds s)-w) below respectively];

J. Serb. Chem. Soc., 1993, **58**(10), 737-43, discloses the synthesis of the compound N-(1,2-dihydro-6-methyl-2-oxo-4-quinolinyl)-N'-phenylthiourea
10 [compound x) below];

none of these documents suggest the use of phenyl urea derivatives as orexin receptor antagonists.

International Patent Application PCT/GB98/02437 (published after the priority date of the present application) discloses various phenyl urea derivatives as orexin
15 receptor antagonists.

The present invention relates to N-phenyl-N'-(2-substituted-quinolinyl)urea derivatives. Thus according to the invention there is provided a compound of formula (I):



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(I)

in which :

Z represents oxygen or sulphur;

R^1 represents (C₁₋₆)alkyl, (C₂₋₆)alkenyl or (C₁₋₆)alkoxy, any of which may
25 be optionally substituted; halogen, R⁸CO- or NR⁹R¹⁰CO-;

R², R³, R⁴, R⁵ and R⁶ independently represent (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxy or (C₁₋₆)alkylthio, any of which may be optionally substituted; hydrogen, halogen, nitro, cyano, aryloxy, aryl(C₁₋₆)alkyloxy, aryl(C₁₋₆)alkyl, R⁸CO-, R⁸SO₂NH-, R⁸CON(R¹¹)-, NR⁹R¹⁰-, NR⁹R¹⁰CO-, -COOR⁹, heterocyclyl or
30 heterocyclyl(C₁₋₆)alkyl;

or an adjacent pair of R², R³, R⁴, R⁵ and R⁶ together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

R^7 is (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy or (C_{1-6}) alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano, NR^9R^{10} -, $NR^9R^{10}CO$ -, N_3 -, $-OCOR^9$ or $R^8CON(R^{11})$ -;

R^8 is (C_{1-6}) alkyl or aryl;

5 R^9 and R^{10} independently represent hydrogen, (C_{1-6}) alkyl, aryl or aryl(C_{1-6})alkyl;

R^{11} is hydrogen or (C_{1-6}) alkyl; and

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

or a pharmaceutically acceptable salt thereof;

10 provided that the compound is not:

- a) N-(2-methyl-4-quinolinyl)-N'-[3-(trifluoromethyl)phenyl]urea;
- b) N-(4-methoxy)-N'-(2-methyl-4-quinolinyl)urea;
- c) N-[3-(dimethylamino)phenyl]-N'-(2-methyl-4-quinolinyl)urea;
- d) N-(3-methoxyphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- 15 e) Ethyl 3-[[[(2-methyl-4-quinolinyl)amino]carbonyl]amino]benzoate;
- f) N-[3-hydroxyphenyl]-N'-(2-methyl-4-quinolinyl)urea;
- g) N-[2,3-dichlorophenyl]-N'-(2-methyl-4-quinolinyl)urea;
- h) N-benzo[b]thien-5-yl-N'-(2-methyl-4-quinolinyl)urea;
- i) N-(1-methyl-1H-indol-5-yl)-N'-(2-methyl-4-quinolinyl)urea;
- 20 j) N-(2-methyl-4-quinolinyl)-N'-(5,6,7,8-tetrahydro-1-naphthalenyl)urea;
- k) N-(2-methyl-4-quinolinyl)-N'-(3,4,5-trimethoxyphenyl)urea;
- l) N-(2-methylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- m) N-(4-methylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- n) N-(3,5-dimethylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- 25 o) N-(4-chlorophenyl)-N'-(2-methyl-4-quinolinyl)urea;
- p) N-(2-methyl-4-quinolinyl)-N'-[3-(trifluoromethyl)phenyl]urea;
- q) N-(2-methoxyphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- r) N-(2-methyl-4-quinolinyl)-N'-phenylurea;
- s) N-(3,4-dimethylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- 30 t) N-(4-methyl-2-nitrophenyl)-N'-(2-methyl-4-quinolinyl)urea;
- u) N-(3-chloro-4-methylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- v) N-(5-chloro-2-methoxyphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- w) 1-(6-amino-2-methyl-4-quinolinyl)-3-(o-nitrophenyl)urea; or
- 35 x) N-(1,2-dihydro-6-methyl-2-oxo-4-quinolinyl)-N'-phenylthiourea.

In formula (I) Z preferably represents oxygen.

When a halogen atom is present in the compound of formula (I) this may be fluorine, chlorine, bromine or iodine.

n is preferably 0 or 1.

40 When Y is nitrogen and n is 1, the group R^1 is preferably in the 6- or 8-position, particularly the 6-position.

A 90
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R^1 is preferably halogen e.g. fluoro, or (C_{1-6}) alkoxy e.g. methoxy. R^1 is most preferably fluoro.

When any one of R^1 to R^7 comprise a (C_{1-6}) alkyl group, whether alone or forming part of a larger group, e.g. alkoxy or alkylthio, the alkyl group may be straight chain or branched, it preferably contains 1 to 4 carbon atoms and is most preferably methyl or ethyl.

When any one of R^1 to R^7 comprise a (C_{2-6}) alkenyl group, whether alone or forming part of a larger group, the alkenyl group may be straight chain or branched, it preferably contains 2 to 4 carbon atoms and is most preferably allyl.

Suitable optional substituents for (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy and (C_{1-6}) alkylthio groups include one or more substituents selected from halogen e.g. fluoro, (C_{1-4}) alkoxy e.g. methoxy, hydroxy, carboxy and (C_{1-6}) alkyl esters thereof, amino, mono- or di- (C_{1-6}) alkylamino and cyano.

When used herein the term "aryl", whether alone or forming part of a larger group, includes optionally substituted aryl groups such as phenyl and naphthyl, preferably phenyl. The aryl group may contain up to 5, more preferably 1, 2 or 3 optional substituents. Examples of suitable substituents for aryl groups include halogen, (C_{1-4}) alkyl e.g. methyl, (C_{1-4}) haloalkyl e.g. trifluoromethyl, (C_{1-4}) alkoxy e.g. methoxy, (C_{1-4}) alkoxy (C_{1-4}) alkyl e.g. methoxymethyl, hydroxy, carboxy and (C_{1-6}) alkyl esters thereof, amino, nitro, arylsulphonyl e.g. p-toluenesulphonyl, and (C_{1-4}) alkylsulphonyl e.g. methanesulphonyl.

When any one of R^2 to R^6 represent heterocyclyl or heterocyclyl (C_{1-6}) alkyl the heterocyclyl group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may be saturated or unsaturated, for example containing 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur; for example pyrrolidine, oxazole, morpholine, pyrimidine or phthalimide. A ring containing one or two nitrogen atoms is especially preferred. The heterocyclyl group may contain up to 5, more preferably 1, 2 or 3 optional substituents. Examples of suitable substituents for heterocyclyl groups include halogen, (C_{1-4}) alkyl e.g. methyl, (C_{1-4}) haloalkyl e.g. trifluoromethyl, (C_{1-4}) alkoxy e.g. methoxy, (C_{1-4}) alkoxy (C_{1-4}) alkyl e.g. methoxymethyl, hydroxy, carboxy, amino, nitro, arylsulphonyl e.g. p-toluenesulphonyl, and (C_{1-4}) alkylsulphonyl e.g. methanesulphonyl.

When an adjacent pair of R^2 to R^6 together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring it is preferably a 5- to 7-membered ring, which may be aromatic or non-aromatic. Heterocyclic rings preferably contain 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur; for example oxazole, imidazole, thiophene, pyran, dioxan, pyrrole or pyrrolidine. A ring containing one nitrogen atom and one oxygen atom is preferred. It is particularly preferred for the nitrogen to be attached directly to the R^4 position. A carbocyclic or heterocyclic ring formed by an adjacent pair of R^2 to R^6 together with the carbon

atoms to which they are attached may be optionally substituted on carbon or nitrogen by one or more substituents, e.g. up to 3 substituents. Examples of suitable substituents for the carbocyclic or heterocyclic ring include =O, (C₁₋₄)alkyl e.g. methyl, aryl(C₁₋₄)alkyl e.g. benzyl or 3-phenylpropyl, aryl e.g. phenyl, (C₁₋₄)alkoxy, (C₁₋₄)alkoxy(C₁₋₄)alkyl e.g. methoxymethyl, hydroxy, hydroxy(C₁₋₄)alkyl e.g. hydroxyethyl, R^aCO₂-, R^aCO₂(C₁₋₄)alkyl e.g. carboethoxypropyl, cyano, cyano(C₁₋₄)alkyl e.g. 3-cyanopropyl, R^aR^bN and R^aR^bN(C₁₋₄)alkyl; in which R^a and R^b are independently selected from hydrogen and (C₁₋₄)alkyl.

A preferred group of compounds are those in which R² to R⁶ independently represent hydrogen, halogen, (C₁₋₆)alkoxy e.g. methoxy, (C₁₋₆)alkylthio e.g. methylthio, or NR⁹R¹⁰ wherein R⁹ and R¹⁰ preferably represent (C₁₋₆)alkyl e.g. dimethylamino, and at least one of R² to R⁶ is other than hydrogen; or an adjacent pair of R² to R⁶ together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring, e.g. a 6- or 7-membered non-aromatic heterocyclic ring or a 5- or 6-membered aromatic heterocyclic ring.

A further preferred group of compounds are those in which R², R⁵ and R⁶ represent hydrogen.

A further preferred group of compounds are those in which R², R⁴ and R⁶ represent hydrogen.

A preferred group of compounds are those in which either R³ and R⁴, or R³ and R⁵ are other than hydrogen.

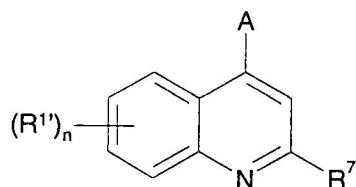
Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable salts.

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 and include for example 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-toluenesulphonic, methanesulphonic or naphthalenesulphonic acid. Other salts e.g. oxalates, 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).

The invention extends to all isomeric forms including stereoisomers and geometric isomers of the compounds of formula (I) including enantiomers and mixtures thereof e.g. racemates. 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.

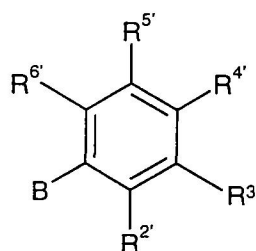
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According to a further feature of the invention we provide a process for the preparation of the compounds of formula (I) and salts thereof which comprises coupling a compound of formula (II);



(II)

with a compound of formula (III);



(III)

wherein A and B are appropriate functional groups to form the -NHCONH- or -NHCSNH- moiety when coupled; n is as defined in formula (I); and R¹' to R⁷' are R¹ to R⁷ as defined in formula (I) or groups convertible thereto; and thereafter optionally and as necessary and in any appropriate order, converting any R¹' to R⁷' when other than R¹ to R⁷ respectively to R¹ to R⁷, and/or forming a pharmaceutically acceptable salt thereof.

Suitable examples of groups A and B are:

- (i) A is -CON₃ and B is -NH₂
- (ii) A is -NH₂ and B is -NH₂
- (iii) A is -CO₂H and B is -NH₂
- (iv) A is -N=C=O and B is -NH₂
- (v) A is -NH₂ and B is -N=C=O
- (vi) A is -N=C=S and B is -NH₂
- (vii) A is -NH₂ and B is -N=C=S
- (viii) A is -NHCOL and B is -NH₂
- (ix) A is -NH₂ and B is -NHCOL
- (x) A is halogen and B is -NHCONH₂.

Wherein L is a leaving group such as chloro or bromo, imidazole or phenoxy or phenylthio optionally substituted for example with halogen, for example chlorine.

When A and B are both -NH₂, the reaction is generally effected in the presence of a urea coupling agent such as carbonyldiimidazole.

When A is $-\text{CO}_2\text{H}$ and B is $-\text{NH}_2$ the reaction is generally effected in the presence of an agent such as diphenylphosphoryl azide and in the presence of a base such as triethylamine.

When A is $-\text{N}=\text{C}=\text{O}$ or $-\text{N}=\text{C}=\text{S}$ and B is $-\text{NH}_2$, or when A is $-\text{NH}_2$ and B is $-\text{N}=\text{C}=\text{O}$ or $-\text{N}=\text{C}=\text{S}$ the reaction is suitably carried out in an inert solvent for example dimethylformamide or dichloromethane and/or toluene at ambient or elevated temperature, preferably ambient.

When A is $-\text{CON}_3$ or $-\text{CO}_2\text{H}$ and B is $-\text{NH}_2$ the reaction is suitably carried out in an inert solvent for example toluene or dimethylformamide at elevated temperature.

Where A is $-\text{NHCOL}$ and B is $-\text{NH}_2$ or when A is $-\text{NH}_2$ and B is $-\text{NHCOL}$, the reaction is suitably carried out in an inert solvent such as dichloromethane at ambient temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature.

When A is halogen and B is $-\text{NHCONH}_2$ the reaction is suitably carried out in an inert solvent such as toluene at elevated temperature, optionally in the presence of base.

Suitable examples of compounds having groups $\text{R}^{1'}$ to $\text{R}^{7'}$ which are convertible to R^1 to R^7 respectively include compounds where an adjacent pair of $\text{R}^{2'}$ to $\text{R}^{6'}$ together with the carbon atoms to which they are attached represent a fused pyrrole ring which is unsubstituted on nitrogen, where treatment with a base, e.g. sodium hydride, and reaction with an electrophile, e.g. methyl iodide, benzyl chloride or benzenesulfonyl chloride, affords the corresponding substituent on the pyrrole nitrogen.

Compounds of formula (II) where A is $-\text{NH}_2$ are known compounds or can be prepared analogously to known compounds.

Compounds of formula (II) where A is $-\text{N}=\text{C}=\text{O}$ may be prepared by treating a compound of formula (II) in which:

- (i) A is amino, with phosgene or a phosgene equivalent, in the presence of excess base or an inert solvent.
- (ii) A is acylazide (i.e. $-\text{CON}_3$), via the nitrene, by thermal rearrangement using conventional conditions (ref. L.S. Trifonov *et al*, *Helv. Chim. Acta*, 1987, **70**, 262).
- (iii) A is $-\text{CONH}_2$, via the nitrene intermediate using conventional conditions.

Compounds of formula (II) where A is $-\text{N}=\text{C}=\text{S}$ are known compounds or can be prepared analogously to known compounds.

Compounds of formula (II) where A is $-\text{NHCOL}$ may be prepared by reacting a compound of formula (II) in which A is $-\text{NH}_2$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of a base such as triethylamine.

Compounds of formula (II) in which A is halogen are known compounds or can be prepared analogously to known compounds.

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Compounds of formula (III) where B is $-NH_2$ are known compounds or can be prepared analogously to known compounds.

Compounds of formula (III) where B is $-N=C=O$ may be prepared by treating a compound of formula (III) in which:

- 5 (i) B is amino, with phosgene or a phosgene equivalent, in the presence of excess base or an inert solvent.
- (ii) B is acylazide (i.e. $-CON_3$), via the nitrene, by thermal rearrangement using conventional conditions (ref. L.S. Trifonov *et al*, *Helv. Chim. Acta*, 1987, **70**, 262).
- (iii) B is $-CONH_2$, via the nitrene intermediate using conventional conditions.

10 Compounds of formula (III) where B is $-N=C=S$ are known compounds or can be prepared analogously to known compounds.

Compounds of formula (III) where B is $-NHCOL$ may be prepared by reacting a compound of formula (III) in which B is $-NH_2$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of a base such as triethylamine. Examples of phosgene equivalents include triphosgene, carbonyldiimidazole, phenyl chloroformate and phenyl chlorothioformate.

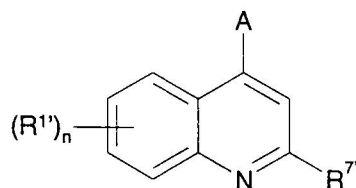
15 Compounds of formula (III) where B is $-NHCONH_2$ can be prepared from the corresponding precursor where B is $-NH_2$ by reaction with an isocyanate under conventional conditions.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) 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 salts thereof.

30 Novel intermediates of formulae (II) and (III) are also part of this invention.

According to a further feature of the invention we provide a compound of formula (II):



(II)

35 wherein A is $-CON_3$, $-NH_2$, $-CO_2H$, $-N=C=O$, $-N=C=S$, $-NHCOL$ or halogen, L is a leaving group, n is as defined in formula (I) and $R^{1'}$ and $R^{7'}$ are R^1 and R^7 as defined in formula (I) or groups convertible thereto.

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

As indicated above the compounds of formula (I) and their pharmaceutically acceptable salts, without provisos a)-x), are useful for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required especially feeding disorders, such as obesity and diabetes; prolactinoma; hypoprolactinemia, hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; Cushing's syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases, mental illness such as depression or schizophrenia, and addictions; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; bulimia; and hypopituitarism.

The compounds of formula (I) and their pharmaceutically acceptable salts, without provisos a)-x), are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, and sleep disorders.

Other diseases or disorders which may be treated in accordance with the invention include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and tolerance to narcotics or withdrawal from narcotics.

The present invention also provides a method of treating or preventing diseases or disorders 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 of formula (I), or a pharmaceutically acceptable salt thereof, without provisos a)-x).

The present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, without provisos a)-x), for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, without provisos a)-x), 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 use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition. The present invention also provides

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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) and their pharmaceutically acceptable salts, without provisos a)-x), may be administered by any convenient method, for example 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 salts, without provisos a)-x), which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example 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. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, 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), for example 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 compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example 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 substance in a physiologically 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 unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein 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 salt thereof, without provisos a)-x), 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 500.0 mg; such 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; and such therapy may extend for a number of weeks or months. In the case of physiologically acceptable salts the above figures are calculated as the parent compound of formula (I), without provisos a)-x).

No toxicological effects are indicated/expected when a compound of formula (I), without provisos a)-x), is administered in the above mentioned dosage range.

Human orexin-A referred to above has the amino acid sequence:

pyroGlu	Pro	Leu	Pro	Asp	Cys	Cys	Arg	Gln	Lys	Thr	Cys	Ser	Cys	Arg	Leu
1			5				10					15			
Tyr	Glu	Leu	Leu	His	Gly	Ala	Gly	Asn	His	Ala	Ala	Gly	Ile	Leu	Thr
			20				25					30			
Leu-NH ₂															

Orexin-A can be employed in a process for screening for compounds (antagonists) which inhibit the ligand's activation of the orexin-1 receptor.

In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on the surface thereof. Such cells include cells from mammals, yeast, *Drosophila* or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is employed to transfect cells to thereby 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 procedure involves the use of melanophores which are transfected to express the orexin-1 receptor. Such a screening technique is described in WO 92/01810.

Another such screening technique involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes may then be contacted with a receptor ligand and a compound to be screened, 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.

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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 the surface thereof. Such a 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 can be labelled, e.g. by radioactivity. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity of the receptors. If the compound binds to the receptor as determined by a reduction of labelled ligand which binds to the receptors, the binding of labelled ligand to the receptor is inhibited.

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. The ligand used in the screening method described below to determine the antagonist activity of compounds according to the invention is orexin-A which has the amino acid sequence shown above.

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. In the Examples ¹H NMR's were measured at 250MHz in d₆-DMSO unless otherwise stated. All hydrochloride salts unless otherwise stated were prepared by dissolving/suspending the free-base in methanol and treating with an excess of ethereal HCl (1M).

Example 1

1-(2-Methylbenzoxazol-6-yl)-3-(2-methylquinolin-4-yl)urea

A slurry of 4-amino-2-methylquinoline (0.158 g) in dichloromethane (10 ml) was added to solution of carbonyl diimidazole (0.162 g) in dichloromethane (5 ml). The mixture was stirred for 2.5h, solvent removed at reduced pressure and the residue dissolved in dimethylformamide (15 ml). 6-Amino-2-methylbenzoxazole (0.148 g) was added and the mixture warmed to 100°C for 1h. Solvent was removed at reduced pressure and triturated with diethyl ether and methanol to give the title compound (0.035 g) as a colourless solid.

¹H NMR δ: 2.59 (3H, s), 2.60 (3H, s), 7.24 (1H, dd, J = 1.9, 8.5Hz), 7.58-7.63 (2H, m), 7.73 (1H, t, J = 7.2Hz), 7.89 (1H, d, J = 7.7Hz), 8.06 (1H, d, J = 1.8Hz), 8.13-8.15 (2H, m), 9.22 (1H, bs), 9.55 (1H, bs).

m/z (API⁺): 333 (MH⁺).

Example 2

1-(4-Dimethylaminophenyl)-3-(2-methylquinolin-4-yl)urea

4-N,N-Dimethylaminophenyl isocyanate (0.162 g) was added to a stirred solution of 4-amino-2-methylquinoline (0.158 g) in dichloromethane (20 ml) containing 4-N,N-dimethylaminopyridine (2 mg). The mixture was stirred for 16h under argon, diluted with diethyl ether (20 ml), the precipitated solid collected by filtration and washed with diethyl ether to give the title compound (0.146 g) as a colourless solid.

¹H NMR δ: 2.61 (3H, s), 2.86 (6H, s), 6.74 (2H, d, J = 9.0Hz), 7.33 (2H, d, J = 9.0Hz), 7.58 (1H, t, J = 7.0Hz), 7.71 (1H, t, J = 7.6Hz), 7.87 (1H, d, J = 8.3Hz), 8.13 (1H, d, J = 8.5Hz), 8.15 (1H, s), 8.98 (1H, s), 9.04 (1H, s).

Example 31-(2-Methylbenzoxazol-6-yl)-3-(2-chloroquinolin-4-yl)urea

2-Chloro-4-chlorocarbonylquinoline (0.5 g) was added to sodium azide in aqueous dioxan (2.1 ml, 1:3) at 0°C. Acetone was added and the mixture stirred for 16h.

Water (10 ml) was added, the precipitated solid collected by filtration and air dried to give 2-chloroquinoline-4-carbonyl azide (0.455 g). The azide (0.232 g) in toluene (10 ml) was warmed from room temperature to 75°C then heating continued for 1h.

After cooling to room temperature, 6-amino-2-methylbenzoxazole (0.148 g) in dichloromethane (15 ml) containing 4-N,N-dimethylaminopyridine (20 mg) was

added and the mixture stirred for 16h. The precipitated solid was separated by filtration to give a solid (0.25g). Column chromatography (silica gel, dichloromethane:methanol:ammonia mixtures) gave the title compound (0.072 g).

¹H NMR δ: 2.60 (3H, s), 7.25 (1H, d, J = 8.5Hz), 7.61 (1H, d, J = 8.5Hz), 7.73 (1H, t, J = 7.0Hz), 7.84 (1H, t, J = 6.7Hz), 7.91 (1H, d, J = 8.0Hz), 8.05 (1H, s), 8.20 (1H, d, J = 8.25Hz), 8.28 (1H, s), 9.49 (1H, s), 9.61 (1H, s).

m/z (API⁺): 353, 355 (MH⁺).

Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

HEK293 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37°C in 5% CO₂.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC₅₀ values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5

mM CaCl₂, 1.2 mM MgCl₂ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC₅₀ values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 3.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 90 min at 37°C in 5% CO₂. The loading solution containing dye was then aspirated and cells were washed with 4x 150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37°C in 5% CO₂ for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument and maintained at 37°C in humidified air. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, 1995, *TiPS*, 16, 413-417) to generate a concentration effect value. Antagonist K_b values were calculated using the equation:

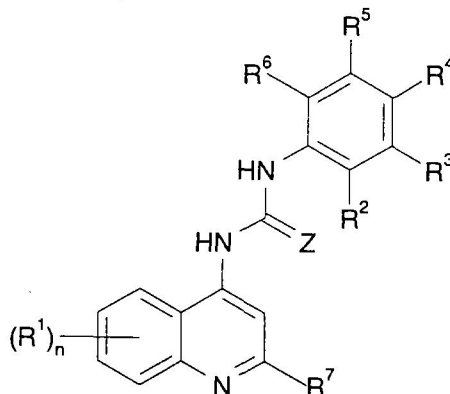
$$K_b = IC_{50} / (1 + ([3/EC_{50}]))$$

where EC₅₀ was the potency of human orexin-A determined in the assay (in nM terms) and IC₅₀ is expressed in molar terms.

As an illustration of the activity of the compounds of formula (I), the compounds of Examples 1 and 2 each had a pK_b > 6.0 in this assay.

CLAIMS

1. A compound of formula (I):



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(I)

in which :

Z represents oxygen or sulphur;

R^1 represents (C_{1-6}) alkyl, (C_{2-6}) alkenyl or (C_{1-6}) alkoxy, any of which may be optionally substituted; halogen, R^8CO- or $NR^9R^{10}CO-$;

- 10 R^2, R^3, R^4, R^5 and R^6 independently represent (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy or (C_{1-6}) alkylthio, any of which may be optionally substituted; hydrogen, halogen, nitro, cyano, aryloxy, aryl (C_{1-6}) alkyloxy, aryl (C_{1-6}) alkyl, R^8CO- , R^8SO_2NH- , $R^8CON(R^{11})-$, $NR^9R^{10}-$, $NR^9R^{10}CO-$, $-COOR^9$, heterocyclyl or heterocyclyl (C_{1-6}) alkyl;

- 15 or an adjacent pair of R^2, R^3, R^4, R^5 and R^6 together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

R^7 is (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy or (C_{1-6}) alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano, $NR^9R^{10}-$ or $NR^9R^{10}CO-$, N_3 , $-OCOR^9$ or $R^8CON(R^{11})-$;

- 20 R^8 is (C_{1-6}) alkyl or aryl;

R^9 and R^{10} independently represent hydrogen, (C_{1-6}) alkyl, aryl or aryl (C_{1-6}) alkyl;

R^{11} is hydrogen or (C_{1-6}) alkyl; and

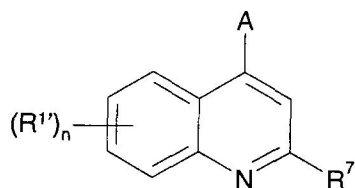
n is 0, 1, 2, 3 or 4;

- 25 or a pharmaceutically acceptable salt thereof;
provided that the compound is not:

- a) N-(2-methyl-4-quinoliny)-N'-[3-(trifluoromethyl)phenyl]urea;
b) N-(4-methoxy)-N'-(2-methyl-4-quinoliny)urea;
c) N-[3-(dimethylamino)phenyl]-N'-(2-methyl-4-quinoliny)urea;
30 d) N-(3-methoxyphenyl)-N'-(2-methyl-4-quinoliny)urea;
e) Ethyl 3-[[[(2-methyl-4-quinoliny)amino]carbonyl]amino]benzoate;

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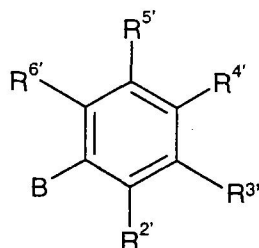
- f) N-[3-hydroxyphenyl]-N'-(2-methyl-4-quinoliny)urea;
g) N-[2,3-dichlorophenyl]-N'-(2-methyl-4-quinoliny)urea;
h) N-benzo[b]thien-5-yl-N'-(2-methyl-4-quinoliny)urea;
i) N-(1-methyl-1H-indol-5-yl)-N'-(2-methyl-4-quinoliny)urea;
5 j) N-(2-methyl-4-quinoliny)-N'-(5,6,7,8-tetrahydro-1-naphthalenyl)urea;
k) N-(2-methyl-4-quinoliny)-N'-(3,4,5-trimethoxyphenyl)urea;
l) N-(2-methylphenyl)-N'-(2-methyl-4-quinoliny)urea;
m) N-(4-methylphenyl)-N'-(2-methyl-4-quinoliny)urea;
n) N-(3,5-dimethylphenyl)-N'-(2-methyl-4-quinoliny)urea;
10 o) N-(4-chlorophenyl)-N'-(2-methyl-4-quinoliny)urea;
p) N-(2-methyl-4-quinoliny)-N'-[3-(trifluoromethyl)phenyl]urea;
q) N-(2-methoxyphenyl)-N'-(2-methyl-4-quinoliny)urea;
r) N-(2-methyl-4-quinoliny)-N'-phenylurea;
s) N-(3,4-dimethylphenyl)-N'-(2-methyl-4-quinoliny)urea;
15 t) N-(4-methyl-2-nitrophenyl)-N'-(2-methyl-4-quinoliny)urea;
u) N-(3-chloro-4-methylphenyl)-N'-(2-methyl-4-quinoliny)urea;
v) N-(5-chloro-2-methoxyphenyl)-N'-(2-methyl-4-quinoliny)urea;
w) 1-(6-amino-2-methyl-4-quinoliny)-3-(o-nitrophenyl)urea; or
x) N-(1,2-dihydro-6-methyl-2-oxo-4-quinoliny)-N'-phenylthiourea.
20
2. A compound according to claim 1 in which Z represents oxygen.
3. A compound according to claim 1 or 2 in which n is 0 or 1.
- 25 4. A compound according to any one of the preceding claims in which R² to R⁶ independently represent hydrogen, halogen, (C₁₋₆)alkoxy, (C₁₋₆)alkylthio or NR⁹R¹⁰, and at least one of R² to R⁶ is other than hydrogen; or an adjacent pair of R² to R⁶ together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring.
- 30 5. A compound according to any one of the preceding claims in which R², R⁵ and R⁶ represent hydrogen.
6. A compound according to any one of claims 1 to 5 in which R², R⁴ and R⁶
35 represent hydrogen.
7. A process for the preparation of a compound of formula (I) as defined in any one of the preceding claims or a salt thereof which comprises coupling a compound of formula (II):
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(II)

with a compound of formula (III):

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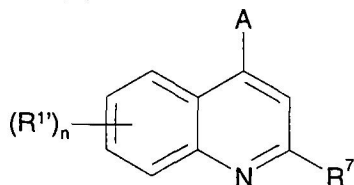


(III)

where A and B are appropriate functional groups to form the -NHCONH- or -NHCSNH- moiety when coupled; n is as defined in formula (I); and R¹' to R⁷' are R¹ to R⁷ as defined in formula (I) or groups convertible thereto; and thereafter optionally and as necessary and in any appropriate order, converting any R¹' to R⁷' when other than R¹ to R⁷ respectively to R¹ to R⁷, and/or forming a pharmaceutically acceptable salt thereof.

8. A compound library comprising at least 2 compounds of formula (I) as defined in any one of claims 1 to 6, or pharmaceutically acceptable salts thereof.

9. A compound of formula (II):



(II)

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wherein A is -CON₃, -NH₂, -CO₂H, -N=C=O, -N=C=S, -NHCOL or halogen, L is a leaving group, n is as defined in formula (I) and R¹' and R⁷' are R¹ and R⁷ as defined in formula (I) or groups convertible thereto.

10. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

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11. A method of treating or preventing diseases or disorders 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 of formula (I) as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, without provisos a)-x).
- 5
12. A compound of formula (I) as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, without provisos a)-x), for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.
- 10
13. The use of a compound of formula (I) as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, without provisos a)-x), 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.
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LEGALIZACIONES

OFICINA DE PATENTES

Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

El suscrito, un funcionario debidamente autorizado conforme a los Artículos 74(1) y (4) de la Ley de Desreglamentación y Contratación de 1994 para firmar y expedir certificados en nombre del Contralor General, certifico que la copia adjunta es una copia correcta de los documentos archivados originalmente con respecto a la solicitud de patente que allí se identifica.

De acuerdo con las Reglamentaciones de Patentes de 1982 (Re-registro de Compañías), si una compañía nombrada en este certificado y en los documentos adjuntos se ha vuelto a registrar según la Ley de Compañías de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del re-registro, salvo la sustitución o inclusión como la última parte del nombre de las palabras "sociedad anónima" o su equivalente en galés, las referencias al nombre de la compañía y sus documentos adjuntos serán tratadas como referencias al nombre con el cual fue re-registrada.

De acuerdo con las reglas, las palabras "sociedad anónima" (o en inglés *public limited company*) pueden ser reemplazadas por las letras p.l.c, plc. P.L.C ó PLC.

El re-registro bajo la Ley de Compañías no constituye una nueva entidad legal sino simplemente somete a la compañía a ciertas normas de ley adicionales.

(FIRMA) ANDREW CRESSEY

FECHA: 30 de noviembre de 1999

(SELLO DE LACRE)

27-99
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OFICINA DE PATENTES

SOLICITUD DE PATENTE

1. Su referencia: **AJB/PS/P32243**

2. Solicitud No. **9903241.9** 12 de febrero de 1999

3. Nombre completo y código postal de cada solicitante:

Dirección: SMITHKLINE BEECHAM
New Horizons Court
Brentford,
Middlesex TW8 9EP

Si el solicitante es una entidad, indique el país/estado de constitución:

GRAN BRETAÑA

ADP No.: 5776299002

4. TITULO DEL INVENTO:

COMPUESTOS

5. NOMBRE DE SU AGENTE:

Nombre del Agente: **CORPORATE INTELLECTUAL PROPERTY**

Dirección para notificaciones: **SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP**

NO. ADP Patentes 05800974003

6. N/A

7. N/A

8. SI

9. Número de hojas radicadas (En inglés). Descripción: 13 Reivindicaciones: 3

Resumen : - Dibujos: -

10. Solicitud de examen preliminar y búsqueda

11. Solicitamos se nos adjudique una patente con base en esta solicitud.

A. J. BLAKEY

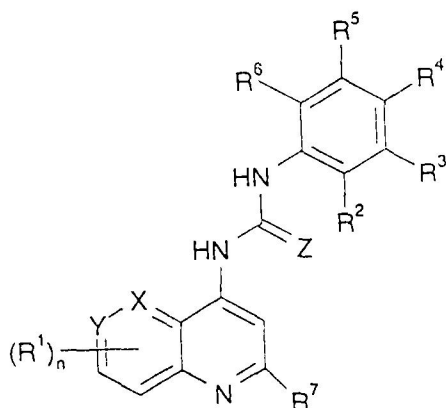
12 de febrero de 1998

12. Nombre y teléfono del contacto en el Reino Unido Nombre y teléfono del contacto en el
Reino Unido (FIRMA) A. J. BLAKEY 01279 644355

COMPUESTOS

REIVINDICACIONES:

1. Un compuesto de la fórmula (I):



en la cual:

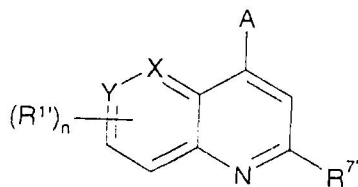
Z representa oxígeno o azufre;

R¹ representa alquil(C₁₋₆), alquenil(C₂₋₆) o alcoxi(C₁₋₆), cualquiera de los cuales puede ser sustituido opcionalmente; halógeno, R⁸CO- o NR⁹R¹⁰CO-;

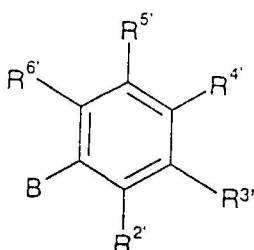
R², R³, R⁴, R⁵ y R⁶ representan independientemente alquil(C₁₋₆), alquenil(C₂₋₆), alcoxi(C₁₋₆) o alquiltio(C₁₋₆), cualquiera de los cuales puede ser sustituido opcionalmente; hidrógeno, halógeno, nitro, ciano, ariloxi, aril-alquilo(C₁₋₆), aril-alquil(C₁₋₆), R⁸CO-, R⁸SO₂NH-, R⁸CON(R¹¹)-, NR⁹R¹⁰-, NR⁹R¹⁰CO-, -COOR⁹, heterociclil o heterociclil-alquil(C₁₋₆);

o un par adyacente de R², R³, R⁴, R⁵ y R⁶ junto con los átomos de carbono a los que están fijos forman un anillo carbocíclico o heterocíclico sustituido opcionalmente;

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con un compuesto de la fórmula (III):



donde A y B son grupos funcionales adecuados para formar el medio -NHCONH- o -NHCSHN- cuando están acoplados; n es según se define en la fórmula (I); y R^{1'} a R^{7'} son R¹ a R⁷ según se define en la fórmula (I) o grupos convertibles a ello; y en seguida, opcionalmente y según sea necesario y en cualquier orden apropiado, convertir cualquiera de R^{1'} a R^{7'} cuando otro diferente de R¹ a R⁷ respectivamente a R¹ a R⁷, y/o formar una sal farmacéuticamente aceptable de lo mismo.

9. Una librería de compuestos que comprende al menos de 2 compuestos de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 7, o sales farmacéuticamente aceptables de lo mismo.

10. Un compuesto de la fórmula (II):

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R^7 es alquil(C_{1-6}), alquenal(C_{2-6}), alcoxi(C_{1-6}) o alquiltio(C_{1-6}), cualquiera de los cuales puede ser sustituido opcionalmente; halógeno, hidroxilo, nitro, ciano, NR^9R^{10} - o $NR^9R^{10}CO$ -, N_3 -, $-OCOR^9$ o $R^8CON(R^{11})$ -;

R^8 es alquil(C_{1-6}) o aril;

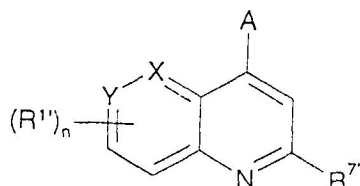
R^9 y R^{10} representan independientemente hidrógeno, alquil(C_{1-6}), aril o arilalquil(C_{1-6});

R^{11} es hidrógeno o alquil(C_{1-6}); y

n es 0, 1, 2, 3 ó 4;

o una sal farmacéuticamente aceptable de lo mismo.

2. Un compuesto según la reivindicación 1, en donde X es N y Y es CH .
3. Un compuesto según la reivindicación 1, donde Z representa oxígeno.
4. Un compuesto según la reivindicación 1 ó 2, en donde n es 0 o 1.
5. Un compuesto según cualquiera de las reivindicaciones anteriores donde R^2 a R^6 representan independientemente hidrógeno, halógeno, alcoxi(C_{1-6}), alquiltio(C_{1-6}) o NR^9R^{10} , y al menos uno de R^2 a R^6 es diferente de hidrógeno; o un par adyacente de R^2 a R^6 junto con los átomos de carbono a los que están fijados forman un anillo heterocíclico sustituido opcionalmente de 5 a 7 miembros.
6. Un compuesto según cualquiera de las reivindicaciones anteriores en donde R^2 , R^5 y R^6 representan hidrógeno.
7. Un compuesto según cualquiera de las reivindicaciones 1 a 5 en donde R^2 , R^4 y R^6 representan hidrógeno.
8. Un proceso para la preparación de un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones anteriores o sales de lo mismo, que comprende acoplar un compuesto de la fórmula (II):



donde A es $-\text{CON}_3$, $-\text{NH}_2$, $-\text{CO}_2\text{H}$, $-\text{N}=\text{C}=\text{O}$, $-\text{N}=\text{C}=\text{S}$, $-\text{NHCOL}$ o halógeno, L es un grupo saliente, n es según se define en la fórmula (I), y $\text{R}^{1'}$ y $\text{R}^{7'}$ son R^1 y R^7 según se define en la fórmula (I) o grupos convertibles a ello.

11. Una composición farmacéutica que comprende un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 7, o una sal farmacéuticamente aceptable de lo mismo, y un vehículo farmacéuticamente aceptable.
12. Un método para el tratamiento o prevención de enfermedades o trastornos donde se requiere un antagonista de un receptor de orexina humana, que consiste en administrar a un sujeto que lo requiera, una cantidad efectiva de un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 7, o una sal farmacéuticamente aceptable de lo mismo, sin las salvedades anteriores.
13. Un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 7, o una sal farmacéuticamente aceptable de lo mismo, para uso en el tratamiento o profilaxis de enfermedades o trastornos donde se requiere un antagonista de un receptor de orexina humana.
14. El uso de un compuesto de la fórmula (I) según se define en las reivindicaciones 1 a 7, o una sal farmacéuticamente aceptable de lo mismo, para la fabricación de un medicamento para el tratamiento o profilaxis de enfermedades o trastornos donde se requiere un antagonista de un receptor de orexina humana.



The
Patent
Office



INVESTOR IN PEOPLE

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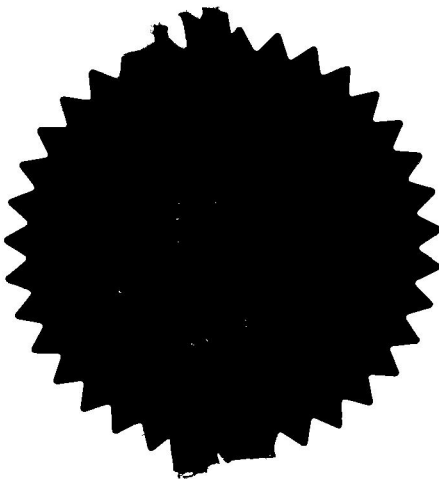
The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

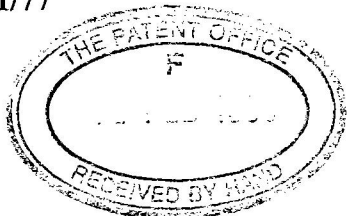
In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed *Andrew Genge*

Dated 30 November 1999



The Patent Office

24-106
1/77 (10)

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

AJB/PS/P32243

2. Patent application number

(The Patent Office will fill in this part)

112 FEB 1999

9903241.9

3. Full name, address and postcode of the or of each applicant (underline all surnames)

SmithKline Beecham plc
New Horizons Court, Brentford, Middx TW8 9EP,
Great Britain

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

57762 99002

4. Title of the invention

Compounds

5. Name of your agent (if you have one)

CORPORATE INTELLECTUAL PROPERTY

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

Patents ADP number (if you know it)

5 800 974003.

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (if you know it) the or each application number

Country	Priority application number (if you know it)	Date of filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer yes if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is named as an applicant, or
 - c) any named applicant is a corporate body
- See note (d)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form.
Do not count copies of the same document

Continuation sheets of this form	0
Description	13
Claim(s)	3
Abstract	0
Drawings	0

10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 1/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11.

We request the grant of a patent on the basis of this application

Signature Alison Blakey Date 12-Feb-99
A J Blakey

12. Name and daytime telephone number of person to contact in the United Kingdom

A J Blakey 01279 644355

Warning

After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

- If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
- Write your answers in capital letters using black ink or you may type them.
- If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- If you have answered 'Yes' Patents Form 7/77 will need to be filed.
- For details of the fee and ways to pay please contact the Patent Office.

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102COMPOUNDS

This invention relates to phenyl urea and phenyl thiourea derivatives and their use as pharmaceuticals.

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

10 Polypeptides and polynucleotides encoding the human 7-transmembrane G-protein coupled neuropeptide receptor, orexin-1 (HFGAN72), have been identified and are disclosed in EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP-A-893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.

- 15 Orexin receptors are found in the mammalian host and may be responsible for many biological functions, including pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual
20 dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourett's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's
25 disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism;
30 Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; and sleep disturbances
35 associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure;
40 renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection,

e.g. HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; 5 tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders, which includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

10 Experiments have shown that central administration of the ligand orexin-A (described in more detail below) 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. Therefore, antagonists of its receptor may be useful in the treatment of 15 obesity and diabetes, see *Cell*, 1998, **92**, 573-585.

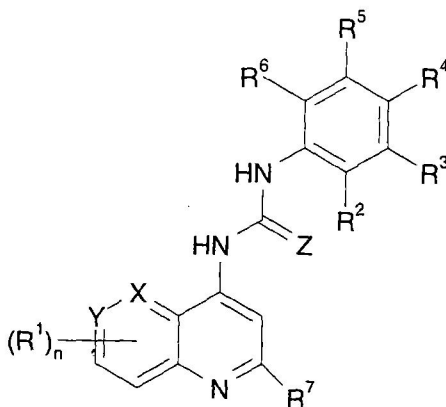
There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. It has been estimated that 5.7% of all healthcare costs in the USA are a consequence of obesity. About 85% of Type 2 diabetics are obese, and 20 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 25 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.

Rat sleep/EEG studies have also shown that central administration of orexin- 30 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. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

The present invention provides phenyl urea and phenyl thiourea derivatives 35 which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity including obesity observed in Type 2 (non-insulin-dependent) diabetes patients and/or sleep disorders.

According to the invention there is provided a compound of formula (I):

40



(I)

in which :

one of X and Y is N and the other is CH;

5 Z represents oxygen or sulphur;

R¹ represents (C₁₋₆)alkyl, (C₂₋₆)alkenyl or (C₁₋₆)alkoxy, any of which may be optionally substituted; halogen, R⁸CO- or NR⁹R¹⁰CO-;

R², R³, R⁴, R⁵ and R⁶ independently represent (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxy or (C₁₋₆)alkylthio, any of which may be optionally substituted;

10 hydrogen, halogen, nitro, cyano, aryloxy, aryl(C₁₋₆)alkyloxy, aryl(C₁₋₆)alkyl, R⁸CO-, R⁸SO₂NH-, R⁸CON(R¹¹)-, NR⁹R¹⁰-, NR⁹R¹⁰CO-, -COOR⁹, heterocyclyl or heterocyclyl(C₁₋₆)alkyl;

or an adjacent pair of R², R³, R⁴, R⁵ and R⁶ together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

15 R⁷ is (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxy or (C₁₋₆)alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano, NR⁹R¹⁰-, NR⁹R¹⁰CO-, N₃, -OCOR⁹ or R⁸CON(R¹¹)-;

R⁸ is (C₁₋₆)alkyl or aryl;

20 R⁹ and R¹⁰ independently represent hydrogen, (C₁₋₆)alkyl, aryl or aryl(C₁₋₆)alkyl;

R¹¹ is hydrogen or (C₁₋₆)alkyl; and

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

25 In formula (I) Z is preferably oxygen.

When a halogen atom is present in the compound of formula (I) this may be fluorine, chlorine, bromine or iodine.

n is preferably 0 or 1.

X is preferably N and Y is CH.

When n is 1, the group R¹ is preferably in the 6- or 8-position, particularly the 8-position.

R¹ is preferably halogen e.g. fluoro, or (C₁₋₆)alkoxy e.g. methoxy. R¹ is most preferably fluoro.

- 5 When any one of R¹ to R⁷ comprise a (C₁₋₆)alkyl group, whether alone or forming part of a larger group, e.g. alkoxy or alkylthio, the alkyl group may be straight chain or branched, it preferably contains 1 to 4 carbon atoms and is most preferably methyl or ethyl.

- 10 When any one of R¹ to R⁷ comprise a (C₂₋₆)alkenyl group, whether alone or forming part of a larger group, the alkenyl group may be straight chain or branched, it preferably contains 2 to 4 carbon atoms and is most preferably allyl.

- Suitable optional substituents for (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxy and (C₁₋₆)alkylthio groups include one or more substituents selected from halogen e.g. fluoro, (C₁₋₄)alkoxy e.g. methoxy, hydroxy, carboxy and (C₁₋₆)alkyl esters thereof, amino, mono- or di-(C₁₋₆)alkylamino and cyano.

- 15 When used herein the term "aryl", whether alone or forming part of a larger group, includes optionally substituted aryl groups such as phenyl and naphthyl, preferably phenyl. The aryl group may contain up to 5, more preferably 1, 2 or 3 optional substituents. Examples of suitable substituents for aryl groups include halogen, (C₁₋₄)alkyl e.g. methyl, (C₁₋₄)haloalkyl e.g. trifluoromethyl, (C₁₋₄)alkoxy e.g. methoxy, (C₁₋₄)alkoxy(C₁₋₄)alkyl e.g. methoxymethyl, hydroxy, carboxy and (C₁₋₆)alkyl esters thereof, amino, nitro, arylsulphonyl e.g. p-toluenesulphonyl, and C₁₋₄ alkylsulphonyl e.g. methanesulphonyl.

- 25 When any one of R² to R⁶ represent heterocyclyl or heterocyclyl(C₁₋₆)alkyl the heterocyclyl group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may be saturated or unsaturated, for example containing 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur; for example pyrrolidine, oxazole, morpholine, pyrimidine or phthalimide. A ring containing one or two nitrogen atoms is especially preferred. The heterocyclyl group may contain up to 5, more preferably 1, 2 or 3 optional substituents. Examples of suitable substituents for heterocyclyl groups include halogen, (C₁₋₄)alkyl e.g. methyl, (C₁₋₄)haloalkyl e.g. trifluoromethyl, (C₁₋₄)alkoxy e.g. methoxy, (C₁₋₄)alkoxy(C₁₋₄)alkyl e.g. methoxymethyl, hydroxy, carboxy, amino, nitro, arylsulphonyl e.g. p-toluenesulphonyl, and (C₁₋₄)alkylsulphonyl e.g. methanesulphonyl.

- 35 When an adjacent pair of R² to R⁶ together with the carbon atoms to which they are attached preferably form a 5- to 7-membered ring, which may be aromatic or non-aromatic. Heterocyclic rings preferably contain 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur; for example oxazole, imidazole, thiophene, pyran, dioxan, pyrrole or pyrrolidine. A ring containing one nitrogen atom and one oxygen atom is preferred. It is particularly preferred for the nitrogen to be attached directly to

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the R⁴ position. A carbocyclic or heterocyclic ring formed by an adjacent pair of R² to R⁶ together with the carbon atoms to which they are attached may be optionally substituted on carbon or nitrogen by one or more substituents, e.g. up to 3 substituents. Examples of suitable substituents for the carbocyclic or heterocyclic ring include =O, (C₁₋₄)alkyl e.g. methyl, aryl(C₁₋₄)alkyl e.g. benzyl or 3-phenylpropyl, aryl e.g. phenyl, (C₁₋₄)alkoxy, (C₁₋₄)alkoxy(C₁₋₄)alkyl e.g. methoxymethyl, hydroxy, hydroxy(C₁₋₄)alkyl e.g. hydroxyethyl, R^aCO₂-, R^aCO₂(C₁₋₄)alkyl e.g. carboethoxypropyl, cyano, cyano(C₁₋₄)alkyl e.g. 3-cyanopropyl, R^aR^bN and R^aR^bN(C₁₋₄)alkyl; in which R^a and R^b are independently selected from hydrogen and (C₁₋₄)alkyl.

10 A preferred group of compounds are those in which R² to R⁶ independently represent hydrogen, halogen, (C₁₋₆)alkoxy e.g. methoxy, (C₁₋₆)alkylthio e.g. methylthio, or NR⁹R¹⁰ wherein R⁹ and R¹⁰ preferably represent (C₁₋₆)alkyl e.g. dimethylamino, and at least one of R² to R⁶ is other than hydrogen; or an adjacent pair of R² to R⁶ together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring, e.g. a 6- or 7-membered non-aromatic heterocyclic ring or a 5- or 6-membered aromatic heterocyclic ring.

15 A further preferred group of compounds are those in which R², R⁵ and R⁶ represent hydrogen.

20 A further preferred group of compounds are those in which R², R⁴ and R⁶ represent hydrogen.

A preferred group of compounds are those in which either R³ and R⁴, or R³ and R⁵ are other than hydrogen.

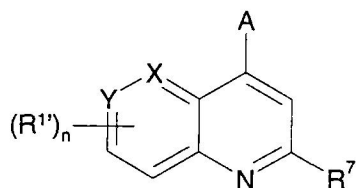
Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable salts.

25 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 and include for example 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-toluenesulphonic, methanesulphonic or naphthalenesulphonic acid. Other salts e.g. oxalates, 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).

35 The invention extends to all isomeric forms including stereoisomers and geometric isomers of the compounds of formula (I) including enantiomers and mixtures thereof e.g. racemates. 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.

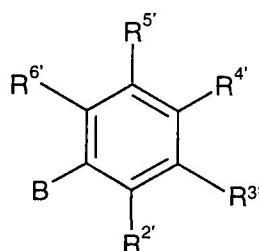
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According to a further feature of the invention we provide a process for the preparation of the compounds of formula (I) and salts thereof which comprises coupling a compound of formula (II);



(II)

with a compound of formula (III);



(III)

wherein A and B are appropriate functional groups to form the -NHCONH- or -NHCSNH- moiety when coupled; n, X and Y are as defined in formula (I); and R^{1'} to R^{7'} are R¹ to R⁷ as defined in formula (I) or groups convertible thereto; and thereafter optionally and as necessary and in any appropriate order, converting any R^{1'} to R^{7'} when other than R¹ to R⁷ respectively to R¹ to R⁷, and/or forming a pharmaceutically acceptable salt thereof.

Suitable examples of groups A and B are:

- (i) A is -CON₃ and B is -NH₂
- (ii) A is -NH₂ and B is -NH₂
- (iii) A is -CO₂H and B is -NH₂
- (iv) A is -N=C=O and B is -NH₂
- (v) A is -NH₂ and B is -N=C=O
- (vi) A is -N=C=S and B is -NH₂
- (vii) A is -NH₂ and B is -N=C=S
- (viii) A is -NHCOL and B is -NH₂
- (ix) A is -NH₂ and B is -NHCOL
- (x) A is halogen and B is -NHCONH₂.

Wherein L is a leaving group such as chloro or bromo, imidazole or phenoxy or phenylthio optionally substituted for example with halogen, for example chlorine.

When A and B are both -NH₂, the reaction is generally effected in the presence of a urea coupling agent such as carbonyldiimidazole.

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When A is $-\text{CO}_2\text{H}$ and B is $-\text{NH}_2$ the reaction is generally effected in the presence of an agent such as diphenylphosphoryl azide and in the presence of a base such as triethylamine.

When A is $-\text{N}=\text{C}=\text{O}$ or $-\text{N}=\text{C}=\text{S}$ and B is $-\text{NH}_2$, or when A is $-\text{NH}_2$ and B is $-\text{N}=\text{C}=\text{O}$ or $-\text{N}=\text{C}=\text{S}$ the reaction is suitably carried out in an inert solvent for example dimethylformamide or dichloromethane and/or toluene at ambient or elevated temperature, preferably ambient.

When A is $-\text{CON}_3$ or $-\text{CO}_2\text{H}$ and B is $-\text{NH}_2$ the reaction is suitably carried out in an inert solvent for example toluene or dimethylformamide at elevated temperature.

Where A is $-\text{NHCOL}$ and B is $-\text{NH}_2$ or when A is $-\text{NH}_2$ and B is $-\text{NHCOL}$, the reaction is suitably carried out in an inert solvent such as dichloromethane at ambient temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature.

When A is halogen and B is $-\text{NHCONH}_2$ the reaction is suitably carried out in an inert solvent such as toluene at elevated temperature, optionally in the presence of base.

Suitable examples of compounds having groups R^1 to R^7 which are convertible to R^1 to R^7 respectively include compounds where one or more of $\text{R}^{2'}$ to $\text{R}^{7'}$ are OH or NH_2 ; and compounds where an adjacent pair of $\text{R}^{2'}$ to $\text{R}^{6'}$ together with the carbon atoms to which they are attached represent a fused pyrrole ring which is unsubstituted on nitrogen, where treatment with a base, e.g. sodium hydride, and reaction with an electrophile, e.g. methyl iodide, benzyl chloride or benzenesulfonyl chloride, affords the corresponding substituent on the pyrrole nitrogen.

Compounds of formula (II) where A is $-\text{NH}_2$ are known compounds or can be prepared analogously to known compounds.

Compounds of formula (II) where A is $-\text{N}=\text{C}=\text{O}$ may be prepared by treating a compound of formula (II) in which:

- (i) A is amino, with phosgene or a phosgene equivalent, in the presence of excess base or an inert solvent.
- (ii) A is acylazide (i.e. $-\text{CON}_3$), via the nitrene, by thermal rearrangement using conventional conditions (ref. L.S. Trifonov *et al*, *Helv. Chim. Acta*, 1987, **70**, 262).
- (iii) A is $-\text{CONH}_2$, via the nitrene intermediate using conventional conditions.

Compounds of formula (II) where A is $-\text{N}=\text{C}=\text{S}$ are known compounds or can be prepared analogously to known compounds.

Compounds of formula (II) where A is $-\text{NHCOL}$ may be prepared by reacting a compound of formula (II) in which A is $-\text{NH}_2$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of a base such as triethylamine.

Compounds of formula (II) in which A is halogen are known compounds or can be prepared analogously to known compounds.

Compounds of formula (III) where B is $-NH_2$ are known compounds or can be prepared analogously to known compounds.

Compounds of formula (III) where B is $-N=C=O$ may be prepared by treating a compound of formula (III) in which:

- 5 (i) B is amino, with phosgene or a phosgene equivalent, in the presence of excess base or an inert solvent.
- (ii) B is acylazide (i.e. $-CON_3$), via the nitrene, by thermal rearrangement using conventional conditions (ref. L.S. Trifonov *et al*, *Helv. Chim. Acta*, 1987, **70**, 262).
- 10 (iii) B is $-CONH_2$, via the nitrene intermediate using conventional conditions.

- 10 Compounds of formula (III) where B is $-N=C=S$ are known compounds or can be prepared analogously to known compounds.

- 15 Compounds of formula (III) where B is $-NHCOL$ may be prepared by reacting a compound of formula (III) in which B is $-NH_2$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of a base such as triethylamine. Examples of phosgene equivalents include triphosgene, carbonyldiimidazole, phenyl chloroformate and phenyl chlorothioformate.

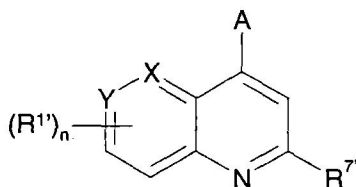
- 20 Compounds of formula (III) where B is $-NHCONH_2$ can be prepared from the corresponding precursor where B is $-NH_2$ by reaction with an isocyanate under conventional conditions.

- 25 The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) 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 salts thereof.

- 30 Novel intermediates of formulae (II) and (III) are also part of this invention.

According to a further feature of the invention we provide a compound of formula (II):



(II)

- 35 wherein A is $-CON_3$, $-NH_2$, $-CO_2H$, $-N=C=O$, $-N=C=S$, $-NHCOL$ or halogen and L is a leaving group, n, X and Y are as defined in formula (I), and $R^{1'}$ and $R^{7'}$ are R^1 and R^7 as defined in formula (I) or groups convertible thereto.

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

As indicated above the compounds of formula (I) and their pharmaceutically acceptable salts are useful for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required especially feeding disorders, such as obesity and diabetes; prolactinoma; hypoprolactinemia, hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; Cushing's syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases; depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delirium; dementia; bulimia; and hypopituitarism.

The compounds of formula (I) and their pharmaceutically acceptable salts are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, and sleep disorders.

Other diseases or disorders which may be treated in accordance with the invention include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and tolerance to narcotics or withdrawal from narcotics.

The present invention also provides a method of treating or preventing diseases or disorders 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 of formula (I), or a pharmaceutically acceptable salt thereof.

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

The present 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 diseases or disorders where an antagonist of a human orexin receptor is required.

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition. The present 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) and their pharmaceutically acceptable salts may be administered by any convenient method, for example 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 salts which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example 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. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, 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), for example 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 compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example 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 substance in a physiologically 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 unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

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

- 5 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.

- 10 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 be 0.05 to 1000 mg, more suitably 0.05 to 500 mg; such
15 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; and such therapy may extend for a number of weeks or months. In the case of physiologically acceptable salts the above figures are calculated as the parent compound of formula (I).

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

Human orexin-A, referred to above, has the amino acid sequence:
pyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu

- 1 5 10 15
25 Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr
20 25 30
Leu-NH₂

Orexin-A can be employed in a process for screening for compounds (antagonists) which inhibit the ligand's activation of the orexin-1 receptor.

- 30 In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on the surface thereof. Such cells include cells from mammals, yeast, *Drosophila* or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is employed to transfect cells to thereby express the receptor. The expressed receptor is then contacted with a test compound and an orexin-1
35 receptor ligand to observe inhibition of a functional response.

One such screening procedure involves the use of melanophores which are transfected to express the orexin-1 receptor. Such a screening technique is described in WO 92/01810.

- 40 Another such screening technique involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes may then be contacted with a receptor ligand and a compound to be screened, 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 the surface thereof. Such a 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 can be labelled, e.g. by radioactivity. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity of the receptors. If the compound binds to the receptor as determined by a reduction of labelled ligand which binds to the receptors, the binding of labelled ligand to the receptor is inhibited.

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. The ligand used in the screening method described below to determine the antagonist activity of compounds according to the invention is orexin-A which has the amino acid sequence shown above.

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 invention.

Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

HEK293 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 μ l/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 μ g/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37°C in 5% CO₂.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC₅₀ values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM CaCl₂, 1.2 mM MgCl₂ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC₅₀ values (the concentration of compound needed to inhibit 50% of the agonist response) were

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determined against 3.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

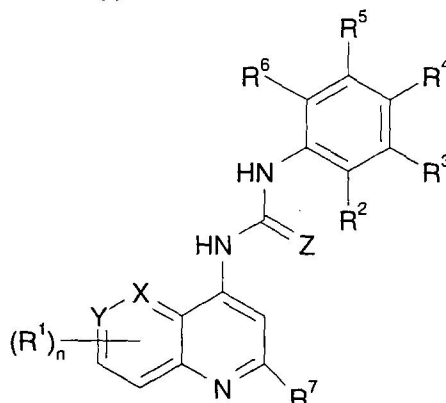
On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 90 min at 37°C in 5% CO₂. The loading solution containing dye was then aspirated and cells were washed with 4x 150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37°C in 5% CO₂ for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument and maintained at 37°C in humidified air. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, 1995, *TiPS*, 16, 413-417) to generate a concentration effect value. Antagonist K_b values were calculated using the equation:

$$K_b = IC_{50} / (1 + ([3/EC_{50}])$$

where EC₅₀ was the potency of human orexin-A determined in the assay (in nM terms) and IC₅₀ is expressed in molar terms.

CLAIMS

1. A compound of formula (I):



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(I)

in which :

one of X and Y is N and the other is CH;

Z represents oxygen or sulphur;

- 10 R^1 represents (C_{1-6}) alkyl, (C_{2-6}) alkenyl or (C_{1-6}) alkoxy, any of which may be optionally substituted; halogen, R^8CO- or $NR^9R^{10}CO-$;

R^2 , R^3 , R^4 , R^5 and R^6 independently represent (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy or (C_{1-6}) alkylthio, any of which may be optionally substituted; hydrogen, halogen, nitro, cyano, aryloxy, aryl (C_{1-6}) alkyloxy, aryl (C_{1-6}) alkyl, R^8CO- , R^8SO_2NH- , $R^8CON(R^{11})-$, $NR^9R^{10}-$, $NR^9R^{10}CO-$, $-COOR^9$, heterocyclyl or

15 heterocyclyl (C_{1-6}) alkyl;

or an adjacent pair of R^2 , R^3 , R^4 , R^5 and R^6 together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

- R^7 is (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy or (C_{1-6}) alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano, $NR^9R^{10}-$ or
- 20 $NR^9R^{10}CO-$, N_3 , $-OCOR^9$ or $R^8CON(R^{11})-$;

R^8 is (C_{1-6}) alkyl or aryl;

R^9 and R^{10} independently represent hydrogen, (C_{1-6}) alkyl, aryl or aryl (C_{1-6}) alkyl;

R^{11} is hydrogen or (C_{1-6}) alkyl; and

- 25 n is 0, 1, 2 or 3;

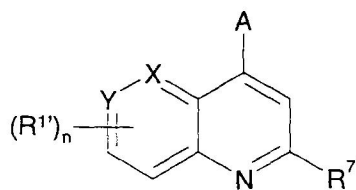
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which X is N and Y is CH.

- 30 3. A compound according to claim 1 or 2 in which Z represents oxygen.

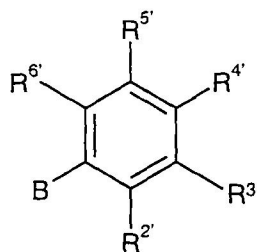
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4. A compound according to any one of the preceding claims in which n is 0 or 1.
5. A compound according to any one of the preceding claims in which R^2 to R^6 independently represent hydrogen, halogen, (C_{1-6}) alkoxy, (C_{1-6}) alkylthio or NR^9R^{10} , and at least one of R^2 to R^6 is other than hydrogen; or an adjacent pair of R^2 to R^6 together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring.
6. A compound according to any one of the preceding claims in which R^2 , R^5 and R^6 represent hydrogen.
7. A compound according to any one of claims 1 to 5 in which R^2 , R^4 and R^6 represent hydrogen.
8. A process for the preparation of a compound of formula (I) as defined in any one of the preceding claims or a salt thereof which comprises coupling a compound of formula (II):



(II)

with a compound of formula (III):

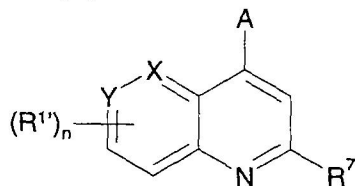


(III)

where A and B are appropriate functional groups to form the $-NHCONH-$ or $-NHCSNH-$ moiety when coupled; n , X and Y are as defined in formula (I); and $R^{1'}$ to $R^{7'}$ are R^1 to R^7 as defined in formula (I) or groups convertible thereto; and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$ to $R^{7'}$ when other than R^1 to R^7 respectively to R^1 to R^7 , and/or forming a pharmaceutically acceptable salt thereof.

9. A compound library comprising at least 2 compounds of formula (I) as defined in any one of claims 1 to 7, or pharmaceutically acceptable salts thereof.

10. A compound of formula (II):



(II)

wherein A is $-\text{CON}_3$, $-\text{NH}_2$, $-\text{CO}_2\text{H}$, $-\text{N}=\text{C}=\text{O}$, $-\text{N}=\text{C}=\text{S}$, $-\text{NHCOL}$ or halogen and L is a leaving group, n, X and Y are as defined in formula (I), and $\text{R}^{1'}$ and $\text{R}^{7'}$ are R^1 and R^7 as defined in formula (I) or groups convertible thereto.

11. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

12. A method of treating or preventing diseases or disorders 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 of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof.

13. A compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

14. The use of a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt 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.

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LEGALIZACIONES

OFICINA DE PATENTES

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NP10 8QQ

El suscrito, un funcionario debidamente autorizado conforme a los Artículos 74(1) y (4) de la Ley de Desreglamentación y Contratación de 1994 para firmar y expedir certificados en nombre del Contralor General, certifico que la copia adjunta es una copia correcta de los documentos archivados originalmente con respecto a la solicitud de patente que allí se identifica.

De acuerdo con las Reglamentaciones de Patentes de 1982 (Re-registro de Compañías), si una compañía nombrada en este certificado y en los documentos adjuntos se ha vuelto a registrar según la Ley de Compañías de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del re-registro, salvo la sustitución o inclusión como la última parte del nombre de las palabras "sociedad anónima" o su equivalente en galés, las referencias al nombre de la compañía y sus documentos adjuntos serán tratadas como referencias al nombre con el cual fue re-registrada.

De acuerdo con las reglas, las palabras "sociedad anónima" (o en inglés *public limited company*) pueden ser reemplazadas por las letras p.l.c, plc. P.L.C ó PLC.

El re-registro bajo la Ley de Compañías no constituye una nueva entidad legal sino simplemente somete a la compañía a ciertas normas de ley adicionales.

(FIRMA) ANDREW CRESSEY

FECHA: 30 de noviembre de 1999

(SELLO DE LACRE)

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11/18

OFICINA DE PATENTES

SOLICITUD DE PATENTE

1. Su referencia: **AJB/PS/P32240**

2. Solicitud No. **9903266.6** 12 de febrero de 1999

3. Nombre completo y código postal de cada solicitante:

Dirección: SMITHKLINE BEECHAM
New Horizons Court
Brentford,
Middlesex TW8 9EP

Si el solicitante es una entidad, indique el país/estado de constitución:

GRAN BRETAÑA

ADP No.: 5776299002

4. TITULO DEL INVENTO:

COMPUESTOS

5. NOMBRE DE SU AGENTE:

Nombre del Agente: CORPORATE INTELLECTUAL PROPERTY

Dirección para notificaciones: SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

NO. ADP Patentes 05800974003

6. N/A

7. N/A

8. SI

9. Número de hojas radicadas (En inglés). Descripción: 15 Reivindicaciones: 4

Resumen : - Dibujos: -

10. Solicitud de examen preliminar y búsqueda

11. Solicitamos se nos adjudique una patente con base en esta solicitud.

A. J. BLAKEY

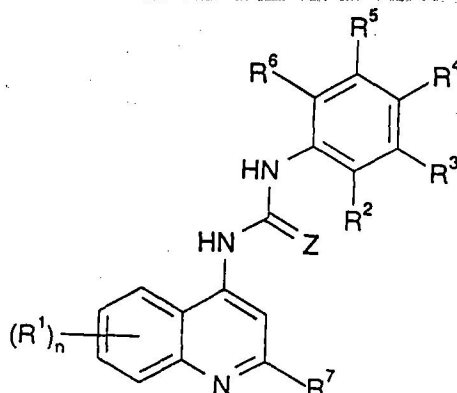
12 de febrero de 1998

12. Nombre y teléfono del contacto en el Reino Unido Nombre y teléfono del contacto en el
Reino Unido (FIRMA) A. J. BLAKEY 01279 644355

COMPUESTOS

REIVINDICACIONES:

1. Un compuesto de la fórmula (I):



en la cual:

Z representa oxígeno o azufre;

R^1 representa alquil(C_{1-6}), alquenil(C_{2-6}) o alcoxi(C_{1-6}), cualquiera de los cuales puede ser sustituido opcionalmente; halógeno, R^8CO- o $NR^9R^{10}CO-$;

R^2 , R^3 , R^4 , R^5 y R^6 representan independientemente alquil(C_{1-6}), alquenil(C_{2-6}), alcoxi(C_{1-6}) o alquiltio(C_{1-6}), cualquiera de los cuales puede ser sustituido opcionalmente; hidrógeno, halógeno, nitro, ciano, ariloxi, aril-alquiloxi(C_{1-6}), aril-alquil(C_{1-6}), R^8CO- , R^8SO_2NH- , $R^8CON(R^{11})-$, $NR^9R^{10}-$, $NR^9R^{10}CO-$, $-COOR^9$, heterociclil o heterociclil-alquil(C_{1-6});

o un par adyacente de R^2 , R^3 , R^4 , R^5 y R^6 junto con los átomos de carbono a los que están fijos forman un anillo carbocíclico o heterocíclico sustituido opcionalmente;

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R⁷ es alquil(C1-6), alquenil(C2-6), alcoxi(C1-6) o alquiltio(C1-6), cualquiera de los cuales puede ser sustituido opcionalmente; halógeno, hidroxilo, nitro, ciano, NR⁹R¹⁰- o NR⁹R¹⁰CO-, N₃, -OCOR⁹ o R⁸CON(R¹¹)-;

R⁸ es alquil(C1-6) o aril;

R⁹ y R¹⁰ representan independientemente hidrógeno, alquil(C₁₋₆), aril o arilalquil(C₁₋₆);

R¹¹ es hidrógeno o alquil(C₁₋₆); y

n es 0, 1, 2, 3 ó 4;

o una sal farmacéuticamente aceptable de lo mismo;

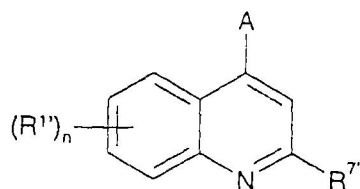
siempre y cuando que el compuesto no sea:

- a) N-(2-metil-4-quinolinil)-N'-[3-(trifluorometil)fenil]urea;
- b) N-(4-metoxi)-N'-(2-metil-4-quinolinil)urea;
- c) N-[3-(dimetilamino)fenil]-N'-(2-metil-4-quinolinil)urea;
- d) N-(3-metoxifenil)-N'-(2-metil-4-quinolinil)urea;
- e) Benzoato de etil 3-[[[(2-metil-4-quinolinil)amino]carbonil]amino];
- f) N-[3-hidroxifenil]-N'-(2-metil-4-quinolinil)urea;
- g) N-[2,3-diclorofenil]-N'-(2-metil-4-quinolinil)urea;
- h) N-benzo[b]tiazol-5-il-N'-(2-metil-4-quinolinil)urea;
- i) N-(1-metil-1H-indol-5-il)-N'-(2-metil-4-quinolinil)urea;
- j) N-(2-metil-4-quinolinil)-N'-(5,6,7,8-tetrahidro-1-naftalenil)urea;
- k) N-(2-metil-4-quinolinil)-N'-(3,4,5-trimetoxifenil)urea;
- l) N-(2-metilfenil)-N'-(2-metil-4-quinolinil)urea;
- m) N-(4-metilfenil)-N'-(2-metil-4-quinolinil)urea;
- n) N-(3,5-dimetilfenil)-N'-(2-metil-4-quinolinil)urea;

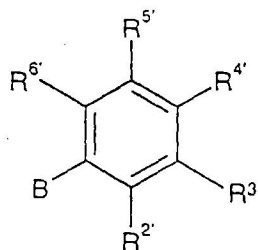
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- o) N-(4-clorofenil)-N'-(2-metil-4-quinolinil)urea;
- p) N-(2-metil-4-quinolinil)-N'-[3-(triflurometil)fenil]urea;
- q) N-(2-metoxifenil)-N'-(2-metil-4-quinolinil)urea;
- r) N-(2-metil-4-quinolinil)-N'-fewnileurea;
- s) N-(3,4-dimetilfenil)-N'-(2-metil-4-quinolinil)urea;
- t) N-(4-metil-2-nitrofenil)-N'-(2-metil-4-quinolinil)urea;
- u) N-(3-cloro-4-metilfenil)-Nñ-(2-metil-4-quinolinil)urea;
- v) N-(5-cloro-2-metoxifenil)-N'-(2-metil-4-quinolinil)urea;
- w) 1-(6-amino-2-metil-4-quinolinil)-3-(o-nitrofenil)urea; o
- x) N-(1,2-dihidro-6-metil-2-oxo-4-quinolinil)-N'-feniltiurea.

- 2. Un compuesto según la reivindicación 1, donde Z representa oxígeno.
- 3. Un compuesto según la reivindicación 1 ó 2, en donde n es 0 o 1.
- 4. Un compuesto según cualquiera de las reivindicaciones anteriores donde R^2 a R^6 representan independientemente hidrógeno, halógeno, alcoxi(C_{1-6}), alquiltio(C_{1-6}) o NR^9R^{10} , y al menos uno de R^2 a R^6 es diferente de hidrógeno; o un par adyacente de R^2 a R^6 junto con los átomos de carbono a los que están fijos forman un anillo heterocíclico sustituido opcionalmente de 5 a 7 miembros.
- 5. Un compuesto según cualquiera de las reivindicaciones anteriores en donde R^2 , R^4 y R^6 representan hidrógeno.
- 6. Un compuesto según cualquiera de las reivindicaciones 1 a 5 en donde R^2 , R^4 y R^6 representan hidrógeno.
- 7. Un proceso para la preparación de un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones anteriores o sales de lo mismo, que comprende acoplar un compuesto de la fórmula (II):

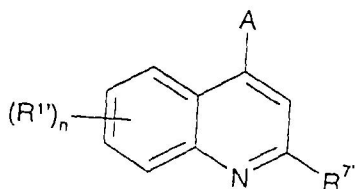


con un compuesto de la fórmula (III):



donde A y B son grupos funcionales adecuados para formar el medio -NHCONH- o -NHCSHN- cuando están acoplados; n es según se define en la fórmula (I); y R^{1'} a R^{7'} son R¹ a R⁷ según se define en la fórmula (I) o grupos convertibles a ello; y en seguida, opcionalmente y según sea necesario y en cualquier orden apropiado, convertir cualquiera de R^{1'} a R^{7'} cuando otro diferente de R¹ a R⁷ respectivamente a R¹ a R⁷, y/o formar una sal farmacéuticamente aceptable de lo mismo.

8. Una librería de compuestos que comprende al menos de 2 compuestos de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 6, o sales farmacéuticamente aceptables de lo mismo.
9. Un compuesto de la fórmula (II):



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donde A es -CON₃, -NH₂, -CO₂H, -N=C=O, -N=C=S, -NHCOL o halógeno, L es un grupo saliente, n es según se define en la fórmula (I), y R1' y R7' son R1 y R7 según se define en la fórmula (I) o grupos convertibles a ello.

10. Una composición farmacéutica que comprende un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable de lo mismo, y un vehículo farmacéuticamente aceptable.
11. Un método para el tratamiento o prevención de enfermedades o trastornos donde se requiere un antagonista de un receptor de orexina humana, que consiste en administrar a un sujeto que lo requiera, una cantidad efectiva de un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable de lo mismo, sin las salvedades anteriores.
12. Un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable de lo mismo, sin las salvedades a)-x), para uso en el tratamiento o profilaxis de enfermedades o trastornos donde se requiere un antagonista de un receptor de orexina humana.
13. El uso de un compuesto de la fórmula (I) según se define en las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable de lo mismo, sin las salvedades a)-x), para la fabricación de un medicamento para el tratamiento o profilaxis de enfermedades o trastornos donde se requiere un antagonista de un receptor de orexina humana.



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INVESTOR IN PEOPLE

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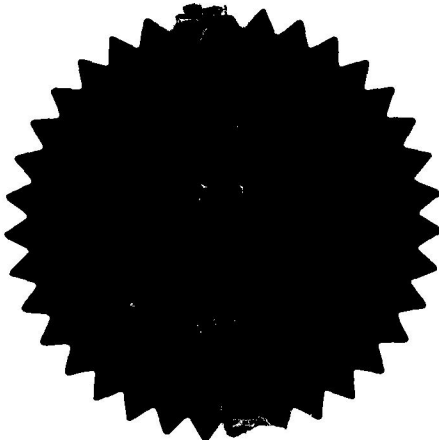
The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

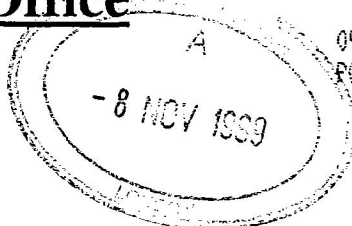
Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed *Andrew Gersey*
Dated 17 February 2000

The
Patent
Office

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09NOV99 E490344-1 D02029
P01/7700 0.00-9926430.1

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1. Your reference

AJB/NM/P32461

2. Patent application number

(The Patent Office will fill in his part)

9926430.1

08 NOV 1999

3. Full name, address and postcode of the or of each applicant (underline all surnames)

SmithKline Beecham plc
New Horizons Court, Brentford, Middx TW8 9EP.
Great Britain

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

577624002

4. Title of the invention

Compounds

5. Name of your agent (if you have one)

CORPORATE INTELLECTUAL PROPERTY

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

Patents ADP number (if you know it)

447223 1005

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (if you know it) the or each application number

Country	Priority application number (if you know it)	Date of filing (day / month / year)
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)
-------------------------------	--

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer yes if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is named as an applicant, or
 - c) any named applicant is a corporate body
- See note (d)

9. Enter the number of sheets for any of the following items you are filing with this form.
Do not count copies of the same document

Continuation sheets of this form

Description
Claim(s)
Abstract
Drawings

19

4

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10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 1/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11.

We request the grant of a patent on the basis of this application

Signature

A J Blakey

Date 8-Nov-99

A J Blakey

12. Name and daytime telephone number of person to contact in the United Kingdom

A J Blakey 01279 644355

Warning

After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

- a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
- b) Write your answers in capital letters using black ink or you may type them.
- c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- d) If you have answered 'Yes' *Patents Form 7/77* will need to be filed.
- f) For details of the fee and ways to pay please contact the Patent Office.

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120COMPOUNDS

This invention relates to phenyl urea and phenyl thiourea derivatives and their use as pharmaceuticals.

5 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 EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides
10 and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP-A-893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.

Orexin receptors are found in the mammalian host and may be responsible for
15 many biological functions, including pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression;
20 delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourett's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma;
25 hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea;
30 hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain and restless
35 leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid

haemorrhage; head injury such as sub-arachnoid haemorrhage associated with traumatic head injury; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders, which includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

Experiments have shown that central administration of the ligand orexin-A (described in more detail below) 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. Therefore, antagonists of its receptor may be useful in the treatment of obesity and diabetes, see *Cell*, 1998, 92, 573-585.

There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. 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, and 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.

Rat sleep/EEG studies have also 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,

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when administered at the onset of the normal sleep period. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

The present invention provides phenyl urea and phenyl thiourea derivatives which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity including obesity observed in Type 2 (non-insulin-dependent) diabetes patients and/or sleep disorders.

Several phenyl urea derivatives are known in the literature, viz:

WO 93/18028, WO 94/14801 and WO 94/18170 disclose indolylurea, benzo[b]thienylurea and N-phenyl-N'-heteroarylurea derivatives respectively [compounds a)-i) below] as 5HT_{2C} receptor antagonists;

JP 04178362 discloses the compound N-(2-methyl-4-quinolinyl)-N'-(5,6,7,8-tetrahydro-1-naphthalenyl)urea [compound j) below] as an agrochemical pesiticide;

EP 123146 discloses the compound N-(2-methyl-4-quinolinyl)-N'-(3,4,5-trimethoxyphenyl)urea [compound k) below] as an anti-inflammatory agent;

GB 2009155 and *J. Am. Chem. Soc.*, 1956, **78**, 3703, disclose various N-phenyl-N'-(2-methyl-4-quinolinyl)urea derivatives [compounds m)-r) and compounds s)-w) below respectively];

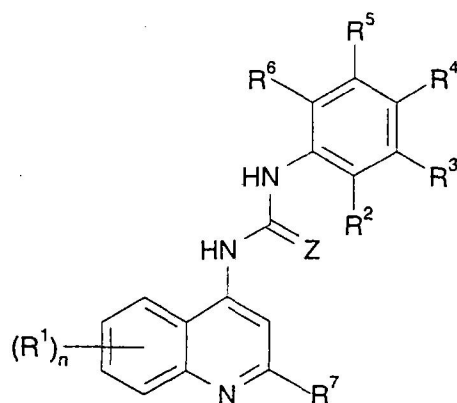
J. Serb. Chem. Soc., 1993, **58**(10), 737-43, discloses the synthesis of the compound N-(1,2-dihydro-6-methyl-2-oxo-4-quinolinyl)-N'-phenylthiourea [compound x) below];

none of these documents suggest the use of phenyl urea derivatives as orexin receptor antagonists.

International Patent Applications PCT/GB98/02437 and PCT/EP99/03100 (published after the priority date of the present application) disclose various phenyl urea derivatives as orexin receptor antagonists.

The present invention relates to N-phenyl-N'-(2-substituted-quinolinyl)urea derivatives. Thus according to the invention there is provided a compound of formula (I):

30



(I)

in which :

Z represents oxygen or sulphur;

- 5 R^1 represents (C_{1-6}) alkyl, (C_{2-6}) alkenyl or (C_{1-6}) alkoxy, any of which may be optionally substituted; halogen, R^8CO- or $NR^9R^{10}CO-$;

- R^2 , R^3 , R^4 , R^5 and R^6 independently represent (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy or (C_{1-6}) alkylthio, any of which may be optionally substituted; hydrogen, halogen, nitro, cyano, aryloxy, aryl (C_{1-6}) alkyloxy, aryl (C_{1-6}) alkyl, R^8CO- , R^8SO_2NH- , R^8SO_2O- , $R^8CON(R^{11})-$, $NR^9R^{10}-$, $NR^9R^{10}CO-$, $-COOR^9$, $R^{11}C(=NOR^8)$, heterocyclyl or heterocyclyl (C_{1-6}) alkyl;

or an adjacent pair of R^2 , R^3 , R^4 , R^5 and R^6 together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

- 15 R^7 is (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy or (C_{1-6}) alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano, $NR^9R^{10}-$, $NR^9R^{10}CO-$, N_3 , $-OCOR^9$ or $R^8CON(R^{11})-$;

R^8 is (C_{1-6}) alkyl, (C_{2-6}) alkenyl, heterocyclyl, heterocyclyl (C_{1-6}) alkyl, aryl or aryl (C_{1-6}) alkyl, any of which maybe optionally substituted;

- 20 R^9 and R^{10} independently represent hydrogen, (C_{1-6}) alkyl, (C_{2-6}) alkenyl, heterocyclyl, heterocyclyl (C_{1-6}) alkyl, aryl or aryl (C_{1-6}) alkyl, any of which maybe optionally substituted;

R^{11} is hydrogen or (C_{1-6}) alkyl; and

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

- 25 provided that the compound is not:

- N-(2-methyl-4-quinolinyl)-N'-[3-(trifluoromethyl)phenyl]urea;
- N-(4-methoxy)-N'-(2-methyl-4-quinolinyl)urea;
- N-[3-(dimethylamino)phenyl]-N'-(2-methyl-4-quinolinyl)urea;
- N-(3-methoxyphenyl)-N'-(2-methyl-4-quinolinyl)urea;

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- e) Ethyl 3-[[[(2-methyl-4-quinolinyl)amino]carbonyl]amino]benzoate;
- f) N-[3-hydroxyphenyl]-N'-(2-methyl-4-quinolinyl)urea;
- g) N-[2,3-dichlorophenyl]-N'-(2-methyl-4-quinolinyl)urea;
- h) N-benzo[b]thien-5-yl-N'-(2-methyl-4-quinolinyl)urea;
- 5 i) N-(1-methyl-1H-indol-5-yl)-N'-(2-methyl-4-quinolinyl)urea;
- j) N-(2-methyl-4-quinolinyl)-N'-(5,6,7,8-tetrahydro-1-naphthalenyl)urea;
- k) N-(2-methyl-4-quinolinyl)-N'-(3,4,5-trimethoxyphenyl)urea;
- l) N-(2-methylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- m) N-(4-methylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- 10 n) N-(3,5-dimethylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- o) N-(4-chlorophenyl)-N'-(2-methyl-4-quinolinyl)urea;
- p) N-(2-methyl-4-quinolinyl)-N'-[3-(trifluoromethyl)phenyl]urea;
- q) N-(2-methoxyphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- r) N-(2-methyl-4-quinolinyl)-N'-phenylurea;
- 15 s) N-(3,4-dimethylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- t) N-(4-methyl-2-nitrophenyl)-N'-(2-methyl-4-quinolinyl)urea;
- u) N-(3-chloro-4-methylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- v) N-(5-chloro-2-methoxyphenyl)-N'-(2-methyl-4-quinolinyl)urea;
- w) 1-(6-amino-2-methyl-4-quinolinyl)-3-(o-nitrophenyl)urea; or
- 20 x) N-(1,2-dihydro-6-methyl-2-oxo-4-quinolinyl)-N'-phenylthiourea.

In formula (I) Z is preferably oxygen.

When a halogen atom is present in the compound of formula (I) this may be fluorine, chlorine, bromine or iodine.

n is preferably 1 or 2, more preferably 2.

- 25 When n is 1, the group R¹ is preferably in the 6- or 8-position, particularly the 8-position.

When n is 2, the groups R¹ are preferably in the 5,8- or 6,8-positions, particularly the 5,8-positions.

- 30 R¹ is preferably halogen e.g. fluoro, or (C₁₋₆)alkoxy e.g. methoxy. R¹ is most preferably fluoro.

When any one of R¹ to R¹¹ comprise a (C₁₋₆)alkyl group, whether alone or forming part of a larger group, e.g. alkoxy or alkylthio, the alkyl group may be straight chain, branched or cyclic, or combinations thereof, it preferably contains 1 to 4 carbon atoms, and is most preferably methyl or ethyl.

- 35 When any one of R¹ to R¹⁰ comprise a (C₂₋₆)alkenyl group, whether alone or forming part of a larger group, the alkenyl group may be straight chain, branched or

cyclic, or combinations thereof, it preferably contains 2 to 4 carbon atoms and is most preferably allyl.

Suitable optional substituents for (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxy and (C₁₋₆)alkylthio groups include one or more substituents selected from halogen e.g. fluoro, (C₁₋₄)alkoxy e.g. methoxy, hydroxy, carboxy and (C₁₋₆)alkyl esters and (C₁₋₆)alkylamides thereof, amino, mono- or di-(C₁₋₆)alkylamino, N(R¹¹)COR⁸, N(R¹¹)SO₂R⁸, CONR⁹R¹⁰ and cyano. For example one or more substituents selected from halogen e.g. fluoro, (C₁₋₄)alkoxy e.g. methoxy, hydroxy, carboxy and (C₁₋₆)alkyl esters thereof, amino, mono- or di-(C₁₋₆)alkylamino and cyano.

When used herein the term "aryl", whether alone or forming part of a larger group, includes optionally substituted aryl groups such as phenyl and naphthyl, preferably phenyl. The aryl group may contain up to 5, more preferably 1, 2 or 3 optional substituents. Suitable substituents for aryl groups include halogen, (C₁₋₄)alkyl e.g. methyl, (C₁₋₄)haloalkyl e.g. trifluoromethyl, (C₁₋₄)alkoxy e.g. methoxy, (C₁₋₄)alkoxy(C₁₋₄)alkyl e.g. methoxymethyl, hydroxy, =O, carboxy and (C₁₋₆)alkyl esters and (C₁₋₆)mono and dialkylamides thereof, nitro, arylsulfonyl e.g. p-toluenesulfonyl, (C₁₋₄)alkylsulfonyl e.g. methanesulfonyl, aryl(C₁₋₄)alkyl e.g. benzyl or 3-phenylpropyl, aryl e.g. phenyl, hydroxy(C₁₋₄)alkyl e.g. hydroxyethyl, R^aCO₂⁻, R^aCO₂ (C₁₋₄)alkyl e.g. carboethoxypropyl, cyano, cyano(C₁₋₄)alkyl e.g. 3-cyanopropyl, R^aR^bN, R^aR^bN(C₁₋₄)alkyl, R^aR^bNCO(C₁₋₄)alkyl in which R^a and R^b are independently selected from hydrogen and (C₁₋₄)alkyl.

When any one of R² to R⁶, R⁸, R⁹ or R¹⁰ represent heterocyclyl or heterocyclyl(C₁₋₆)alkyl the heterocyclyl group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may be saturated or unsaturated, for example containing 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur; for example pyrrolidine, oxazole, morpholine, pyrimidine or phthalimide. A ring containing one or two nitrogen atoms is especially preferred. The heterocyclyl group may contain up to 5, more preferably 1, 2 or 3 optional substituents. Suitable substituents for heterocyclyl groups include those mentioned above for aryl groups.

When an adjacent pair of R² to R⁶ together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring this is preferably a 5- to 7-membered ring, which may be aromatic or non-aromatic. Heterocyclic rings preferably contain 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur; for example oxazole, imidazole, thiophene, pyran, dioxan, pyrrole or pyrrolidine. A ring containing one nitrogen atom and one oxygen atom is preferred. It is particularly preferred for the nitrogen to be attached directly to the R⁴ position. A carbocyclic or heterocyclic ring formed by an adjacent pair of R² to R⁶ together with the carbon atoms

to which they are attached may be optionally substituted on carbon or nitrogen by one or more substituents, e.g. up to 3 substituents. Suitable substituents for the carbocyclic or heterocyclic ring include those mentioned above for aryl groups.

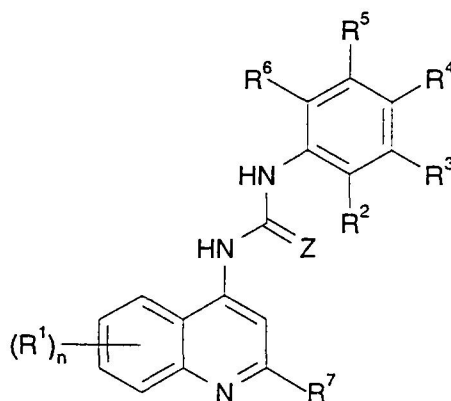
A preferred group of compounds are those in which R^2 to R^6 independently represent hydrogen, R^8CO- , $NR^9R^{10}CO-$, halogen, (C_{1-6}) alkoxy e.g. methoxy, (C_{1-6}) alkylthio e.g. methylthio, or NR^9R^{10} wherein R^9 and R^{10} preferably represent (C_{1-6}) alkyl e.g. dimethylamino, and at least one of R^2 to R^6 is other than hydrogen; or an adjacent pair of R^2 to R^6 together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered carbocyclic or heterocyclic ring, e.g. a 6- or 7-membered non-aromatic heterocyclic ring, a 5- or 6-membered non-aromatic carbocyclic ring or a 5- or 6-membered aromatic heterocyclic ring.

A further preferred group of compounds are those in which R^2 , R^5 and R^6 represent hydrogen.

A further preferred group of compounds are those in which R^2 , R^4 and R^6 represent hydrogen.

A preferred group of compounds are those in which either R^3 and R^4 , or R^3 and R^5 are other than hydrogen.

A group of compounds which may be mentioned are the compounds of formula (Ia):



(Ia)

in which :

Z represents oxygen or sulphur;

R^1 represents (C_{1-6}) alkyl, (C_{2-6}) alkenyl or (C_{1-6}) alkoxy, any of which may be optionally substituted; halogen, R^8CO- or $NR^9R^{10}CO-$;

R^2 , R^3 , R^4 , R^5 and R^6 independently represent (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy or (C_{1-6}) alkylthio, any of which may be optionally substituted; hydrogen,

halogen, nitro, cyano, aryloxy, aryl(C₁₋₆)alkyloxy, aryl(C₁₋₆)alkyl, R⁸CO-, R⁸SO₂NH-, R⁸CON(R¹¹)-, NR⁹R¹⁰-, NR⁹R¹⁰CO-, -COOR⁹, heterocyclyl or heterocyclyl(C₁₋₆)alkyl;

or an adjacent pair of R², R³, R⁴, R⁵ and R⁶ together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

- 5 R⁷ is (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxy or (C₁₋₆)alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano, NR⁹R¹⁰-, NR⁹R¹⁰CO-, N₃, -OCOR⁹ or R⁸CON(R¹¹)-;

R⁸ is (C₁₋₆)alkyl or aryl;

- R⁹ and R¹⁰ independently represent hydrogen, (C₁₋₆)alkyl, aryl or aryl(C₁₋₆)alkyl;

- 10 R¹¹ is hydrogen or (C₁₋₆)alkyl; and
n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof;

provided that the compound is not:

- 15 a) N-(2-methyl-4-quinoliny)-N'-[3-(trifluoromethyl)phenyl]urea;
b) N-(4-methoxy)-N'-(2-methyl-4-quinoliny)urea;
c) N-[3-(dimethylamino)phenyl]-N'-(2-methyl-4-quinoliny)urea;
d) N-(3-methoxyphenyl)-N'-(2-methyl-4-quinoliny)urea;
e) Ethyl 3-[[[(2-methyl-4-quinoliny)amino]carbonyl]amino]benzoate;
20 f) N-[3-hydroxyphenyl]-N'-(2-methyl-4-quinoliny)urea;
g) N-[2,3-dichlorophenyl]-N'-(2-methyl-4-quinoliny)urea;
h) N-benzo[b]thien-5-yl-N'-(2-methyl-4-quinoliny)urea;
i) N-(1-methyl-1H-indol-5-yl)-N'-(2-methyl-4-quinoliny)urea;
j) N-(2-methyl-4-quinoliny)-N'-(5,6,7,8-tetrahydro-1-naphthalenyl)urea;
25 k) N-(2-methyl-4-quinoliny)-N'-(3,4,5-trimethoxyphenyl)urea;
l) N-(2-methylphenyl)-N'-(2-methyl-4-quinoliny)urea;
m) N-(4-methylphenyl)-N'-(2-methyl-4-quinoliny)urea;
n) N-(3,5-dimethylphenyl)-N'-(2-methyl-4-quinoliny)urea;
o) N-(4-chlorophenyl)-N'-(2-methyl-4-quinoliny)urea;
30 p) N-(2-methyl-4-quinoliny)-N'-[3-(trifluoromethyl)phenyl]urea;
q) N-(2-methoxyphenyl)-N'-(2-methyl-4-quinoliny)urea;
r) N-(2-methyl-4-quinoliny)-N'-phenylurea;
s) N-(3,4-dimethylphenyl)-N'-(2-methyl-4-quinoliny)urea;
t) N-(4-methyl-2-nitrophenyl)-N'-(2-methyl-4-quinoliny)urea;
35 u) N-(3-chloro-4-methylphenyl)-N'-(2-methyl-4-quinoliny)urea;
v) N-(5-chloro-2-methoxyphenyl)-N'-(2-methyl-4-quinoliny)urea;
w) 1-(6-amino-2-methyl-4-quinoliny)-3-(o-nitrophenyl)urea; or

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x) N-(1,2-dihydro-6-methyl-2-oxo-4-quinoliny)-N'-phenylthiourea.

In the compounds of formula (Ia) suitable substituents for aryl groups and for heterocyclyl groups when any one of R^2 to R^6 represent heterocyclyl or heterocyclyl(C_{1-6})alkyl include halogen, (C_{1-4})alkyl e.g. methyl, (C_{1-4})haloalkyl e.g. trifluoromethyl, (C_{1-4})alkoxy e.g. methoxy, (C_{1-4})alkoxy(C_{1-4})alkyl e.g. methoxymethyl, hydroxy, carboxy and (C_{1-6})alkyl esters, amino, nitro, arylsulfonyl e.g. p-toluenesulfonyl, and (C_{1-4})alkylsulfonyl e.g. methanesulfonyl. Suitable substituents for carbocyclic or heterocyclic rings when an adjacent pair of R^2 to R^6 together with the carbon atoms to which they are attached form carbocyclic or heterocyclic ring include (C_{1-4})alkyl e.g. methyl, (C_{1-4})alkoxy, (C_{1-4})alkoxy(C_{1-4})alkyl e.g. methoxymethyl, hydroxy, =O, aryl(C_{1-4})alkyl e.g. benzyl or 3-phenylpropyl, aryl e.g. phenyl, hydroxy(C_{1-4})alkyl e.g. hydroxyethyl, R^aCO_2 -, R^aCO_2 (C_{1-4})alkyl e.g. carboethoxypropyl, cyano, cyano(C_{1-4})alkyl e.g. 3-cyanopropyl, R^aR^bN and $R^aR^bN(C_{1-4})$ alkyl in which R^a and R^b are independently selected from hydrogen and (C_{1-4})alkyl.

A further group of compounds of formula (Ia) are those in which R^2 to R^6 independently represent hydrogen, halogen, (C_{1-6})alkoxy e.g. methoxy, (C_{1-6})alkylthio e.g. methylthio, or NR^9R^{10} wherein R^9 and R^{10} preferably represent (C_{1-6})alkyl e.g. dimethylamino, and at least one of R^2 to R^6 is other than hydrogen; or an adjacent pair of R^2 to R^6 together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring, e.g. a 6- or 7-membered non-aromatic heterocyclic ring or a 5- or 6-membered aromatic heterocyclic ring.

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

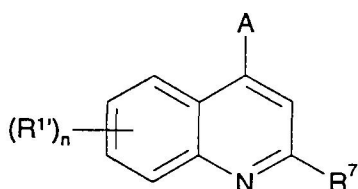
It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids e.g. hydrochloric, 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, 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).

The invention extends to all isomeric forms including stereoisomers and geometric isomers of the compounds of formula (I) including enantiomers and mixtures thereof e.g. racemates. 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.

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.

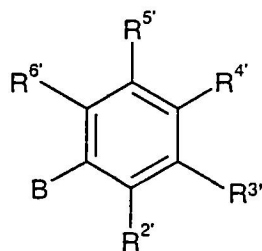
According to a further feature of the invention we provide a process for the preparation of the compounds of formula (I) and salts thereof which comprises coupling a compound of formula (II);



(II)

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with a compound of formula (III);



(III)

wherein A and B are appropriate functional groups to form the -NHCONH- or -NHCSNH- moiety when coupled; n is as defined in formula (I); and $R^{1'}$ to $R^{7'}$ are R^1 to R^7 as defined in formula (I) or groups convertible thereto; and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$ to $R^{7'}$ when other than R^1 to R^7 respectively to R^1 to R^7 , and/or forming a pharmaceutically acceptable salt thereof.

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Suitable examples of groups A and B are:

- (i) A and B are $-NH_2$
- (ii) one of A and B is $-CON_3$ and the other is $-NH_2$
- (iii) one of A and B is $-CO_2H$ and the other is $-NH_2$

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- (iv) one of A and B is $-N=C=O$ and the other is $-NH_2$
(v) one of A and B is $-N=C=S$ and the other is $-NH_2$
(vi) one of A and B is $-NHCOL$ and the other is $-NH_2$
(vii) one of A and B is halogen and the other is $-NHCONH_2$
5 (viii) one of A and B is $NHCOCBr_3$ and the other is NH_2

Wherein L is a leaving group such as chloro or bromo, imidazole or phenoxy or phenylthio optionally substituted for example with halogen, for example chlorine.

When A and B are both $-NH_2$, the reaction is generally effected in the presence of a urea coupling agent such as carbonyldiimidazole or triphosgene.

- 10 When one of A and B is $-CO_2H$ and the other is $-NH_2$ the reaction is generally effected in the presence of an agent such as diphenylphosphoryl azide and in the presence of a base such as triethylamine.

- 15 When one of A and B is $-N=C=O$ or $-N=C=S$ and the other is $-NH_2$ the reaction is suitably carried out in an inert solvent for example dimethylformamide or dichloromethane and/or toluene at ambient or elevated temperature, preferably ambient.

When one of A and B is $-CON_3$ or $-CO_2H$ and the other is $-NH_2$ the reaction is suitably carried out in an inert solvent for example toluene or dimethylformamide at elevated temperature.

- 20 Where one of A and B is $-NHCOL$ and the other is $-NH_2$, the reaction is suitably carried out in an inert solvent such as dichloromethane at ambient temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature.

- 25 When one of A and B is halogen and the other is $-NHCONH_2$ the reaction is suitably carried out in an inert solvent such as toluene at elevated temperature, optionally in the presence of base.

When one of A and B is $NHCOBr_3$ and the other is NH_2 the reaction is suitably carried out in an inert solvent such as dimethylsulfoxide or pyridine at elevated temperatures in the presence of a base such as DBU.

- 30 Suitable examples of compounds having groups $R^{1'}$ to $R^{7'}$ which are convertible to $R^{1'}$ to $R^{7'}$ respectively include compounds where one or more of $R^{2'}$ to $R^{7'}$ are OH or NH_2 ; and compounds where an adjacent pair of $R^{2'}$ to $R^{6'}$ together with the carbon atoms to which they are attached represent a fused pyrrole ring which is unsubstituted on nitrogen, where treatment with a base, e.g. sodium hydride, and
35 reaction with an electrophile, e.g. methyl iodide, benzyl chloride or benzenesulfonyl chloride, affords the corresponding substituent on the pyrrole nitrogen.

Compounds of formula (II) and (III) where A or B is -NH_2 , -N=C=S or halogen are known compounds or can be prepared analogously to known compounds.

- Compounds of formula (II) and (III) where A or B is -N=C=O may be prepared by treating a compound of formula (II) or (III) in which:
- (i) A or B is amino, with phosgene or a phosgene equivalent, in the presence of excess base or an inert solvent.
 - (ii) A or B is acylazide (i.e. -CON_3), via the nitrene, by thermal rearrangement using conventional conditions (ref. L.S. Trifonov *et al*, *Helv. Chim. Acta*, 1987, **70**, 262).
 - (iii) A or B is -CONH_2 , via the nitrene intermediate using conventional conditions.

Compounds of formula (II) and (III) where A or B is -NHCOL may be prepared by reacting a compound of formula (II) or (III) in which A or B is -NH_2 with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of a base such as triethylamine.

Examples of phosgene equivalents include triphosgene, carbonyldiimidazole, phenyl chloroformate and phenyl chlorothioformate.

Compounds of formula (II) and (III) where A or B is -NHCONH_2 can be prepared from compounds of formula (II) or (III) where A or B is -NH_2 by reaction with an isocyanate under conventional conditions.

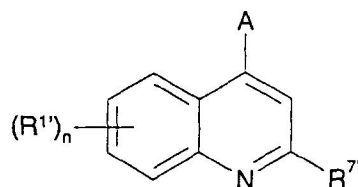
Compounds of formula (II) and (III) where A or B is -NHCOCBr_3 can be prepared from compounds of formula (II) or (III) where A or B is -NH_2 by reaction with tribromoacetyl chloride in an inert solvent such as dichloromethane in the presence of a base such as triethylamine.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) 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 salts thereof.

Novel intermediates of formulae (II) and (III) are also part of this invention.

According to a further feature of the invention we provide a compound of formula (II):

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(II)

wherein A is $-\text{CON}_3$, $-\text{NH}_2$, $-\text{CO}_2\text{H}$, $-\text{N}=\text{C}=\text{O}$, $-\text{N}=\text{C}=\text{S}$, $-\text{NHCOL}$ or halogen, L is a leaving group, n is as defined in formula (I) and $\text{R}^{1'}$ and $\text{R}^{7'}$ are R^1 and R^7 as defined in formula (I) or groups convertible thereto.

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

As indicated above the compounds of formula (I) and their pharmaceutically acceptable salts, without provisos a)-x), are useful for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required especially feeding disorders, such as obesity and diabetes; prolactinoma; hypoprolactinemia, hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; Cushings syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases, mental illness such as depression or schizophrenia, and addictions; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; bulimia; and hypopituitarism.

The compounds of formula (I) and their pharmaceutically acceptable salts, without provisos a)-x), are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, and sleep disorders.

Other diseases or disorders which may be treated in accordance with the invention include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and tolerance to narcotics or withdrawal from narcotics.

The present invention also provides a method of treating or preventing diseases or disorders 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 of formula (I), or a pharmaceutically acceptable salt thereof, without
5 provisos a)-x).

The present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, without provisos a)-x), for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

10 The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, without provisos a)-x), 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 use in medicine, the compounds of the present invention are usually
15 administered as a pharmaceutical composition. The present 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) and their pharmaceutically acceptable salts, without provisos a)-x), may be administered by any convenient method, for example
20 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 salts, without provisos a)-x), which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and
25 lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example 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
30 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. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine
35 encapsulation procedures. For example, 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

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pharmaceutical carrier(s), for example 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 compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example 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 substance in a physiologically 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 unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein 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 salt thereof, without provisos a)-x), 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 500.0 mg; such 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; and such therapy may extend for a number of weeks or

months. In the case of physiologically acceptable salts the above figures are calculated as the parent compound of formula (I), without provisos a)-x).

No toxicological effects are indicated/expected when a compound of formula (I), without provisos a)-x), is administered in the above mentioned dosage range.

5 Human orexin-A referred to above has the amino acid sequence:

pyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu

1 5 10 15

Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr

20 25 30

10 Leu-NH₂

Orexin-A can be employed in a process for screening for compounds (antagonists) which inhibit the ligand's activation of the orexin-1 receptor.

In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on the surface thereof. Such cells include cells from mammals, yeast, *Drosophila* or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is employed to transfect cells to thereby 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 procedure involves the use of melanophores which are transfected to express the orexin-1 receptor. Such a screening technique is described in WO 92/01810.

Another such screening technique involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes may then be contacted with a receptor ligand and a compound to be screened, 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 the surface thereof. Such a 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 can be labelled, e.g. by radioactivity. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity of the receptors. If the compound binds to the receptor as determined by a reduction of labelled ligand which binds to the receptors, the binding of labelled ligand to the receptor is inhibited.

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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. The ligand used in the screening method described below to determine the antagonist activity of compounds according to the invention is orexin-A which has the amino acid sequence shown above.

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. In the Examples ¹H NMR's were measured at 250MHz in d₆-DMSO unless otherwise stated. All hydrochloride salts unless otherwise stated were prepared by dissolving/suspending the free-base in methanol and treating with an excess of ethereal HCl (1M).

Example 1: 1-(2-Methylbenzoxazol-6-yl)-3-(2-methylquinolin-4-yl)urea

A slurry of 4-amino-2-methylquinoline (0.158 g) in dichloromethane (10 ml) was added to solution of carbonyl diimidazole (0.162 g) in dichloromethane (5 ml). The mixture was stirred for 2.5h, solvent removed at reduced pressure and the residue dissolved in dimethylformamide (15 ml). 6-Amino-2-methylbenzoxazole (0.148 g) was added and the mixture warmed to 100°C for 1h. Solvent was removed at reduced pressure and triturated with diethyl ether and methanol to give the title compound (0.035 g) as a colourless solid.

¹H NMR δ: 2.59 (3H, s), 2.60 (3H, s), 7.24 (1H, dd, J = 1.9, 8.5Hz), 7.58-7.63 (2H, m), 7.73 (1H, t, J = 7.2Hz), 7.89 (1H, d, J = 7.7Hz), 8.06 (1H, d, J = 1.8Hz), 8.13-8.15 (2H, m), 9.22 (1H, bs), 9.55 (1H, bs).

m/z (AP⁺): 333 (MH⁺).

Example 2: 1-(4-Dimethylaminophenyl)-3-(2-methylquinolin-4-yl)urea

4-N,N-Dimethylaminophenyl isocyanate (0.162 g) was added to a stirred solution of 4-amino-2-methylquinoline (0.158 g) in dichloromethane (20 ml) containing 4-N,N-dimethylaminopyridine (2 mg). The mixture was stirred for 16h under argon, diluted with diethyl ether (20 ml), the precipitated solid collected by filtration and washed with diethyl ether to give the title compound (0.146 g) as a colourless solid.

¹H NMR δ: 2.61 (3H, s), 2.86 (6H, s), 6.74 (2H, d, J = 9.0Hz), 7.33 (2H, d, J = 9.0Hz), 7.58 (1H, t, J = 7.0Hz), 7.71 (1H, t, J = 7.6Hz), 7.87 (1H, d, J = 8.3Hz), 8.13 (1H, d, J = 8.5Hz), 8.15 (1H, s), 8.98 (1H, s), 9.04 (1H, s).

Example 3: 1-(2-Methylbenzoxazol-6-yl)-3-(2-chloroquinolin-4-yl)urea

2-Chloro-4-chlorocarbonylquinoline (0.5 g) was added to sodium azide in aqueous dioxan (2.1 ml, 1:3) at 0°C. Acetone was added and the mixture stirred for 16h. Water (10 ml) was added, the precipitated solid collected by filtration and air dried to give 2-chloroquinoline-4-carbonyl azide (0.455 g). The azide (0.232 g) in toluene (10 ml) was warmed from room temperature to 75°C then heated for 1h. After cooling to room temperature, 6-amino-2-methylbenzoxazole (0.148 g) in dichloromethane (15 ml) containing 4-N,N-dimethylaminopyridine (20 mg) was added and the mixture stirred for 16h. The precipitated solid was separated by filtration to give a solid (0.25g). Column chromatography (silica gel, dichloromethane:methanol:ammonia mixtures) gave the title compound (0.072 g). ¹H NMR δ: 2.60 (3H, s), 7.25 (1H, d, J = 8.5Hz), 7.61 (1H, d, J = 8.5Hz), 7.73 (1H, t, J = 7.0Hz), 7.84 (1H, t, J = 6.7Hz), 7.91 (1H, d, J = 8.0Hz), 8.05 (1H, s), 8.20 (1H, d, J = 8.25Hz), 8.28 (1H, s), 9.49 (1H, s), 9.61 (1H, s). m/z (API⁺): 353, 355 (MH⁺).

15 Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

HEK293 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37°C in 5% CO₂.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC₅₀ values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM CaCl₂, 1.2 mM MgCl₂ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC₅₀ values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 3.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well

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plates were incubated for 90 min at 37°C in 5% CO₂. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37°C in 5% CO₂ for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument and maintained at 37°C in humidified air. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, 1995, *TiPS*, 16, 413-417) to generate a concentration effect value. Antagonist K_b values were calculated using the equation:

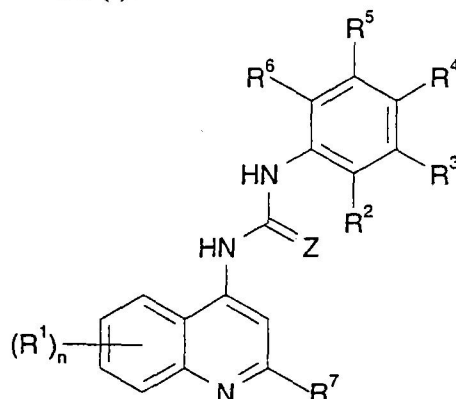
$$K_b = IC_{50} / (1 + ([3/EC_{50}]))$$

where EC₅₀ was the potency of human orexin-A determined in the assay (in nM terms) and IC₅₀ is expressed in molar terms.

As an illustration of the activity of the compounds of formula (I), the compounds of Examples 1 and 2 each had a pK_b > 6.0 in this assay.

CLAIMS

1. A compound of formula (I):



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(I)

in which :

Z represents oxygen or sulphur;

R¹ represents (C₁₋₆)alkyl, (C₂₋₆)alkenyl or (C₁₋₆)alkoxy, any of which may be optionally substituted; halogen, R⁸CO- or NR⁹R¹⁰CO-;

10 R², R³, R⁴, R⁵ and R⁶ independently represent (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxy or (C₁₋₆)alkylthio, any of which may be optionally substituted; hydrogen, halogen, nitro, cyano, aryloxy, aryl(C₁₋₆)alkyloxy, aryl(C₁₋₆)alkyl, R⁸CO-, R⁸SO₂NH-, R⁸SO₂O-, R⁸CON(R¹¹)-, NR⁹R¹⁰-, NR⁹R¹⁰CO-, -COOR⁹, R¹¹C(=NOR⁸), heterocyclyl or heterocyclyl(C₁₋₆)alkyl;

15 or an adjacent pair of R², R³, R⁴, R⁵ and R⁶ together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

R⁷ is (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxy or (C₁₋₆)alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano, NR⁹R¹⁰-, NR⁹R¹⁰CO-, N₃-, -OCOR⁹ or R⁸CON(R¹¹)-;

20 R⁸ is (C₁₋₆)alkyl, (C₂₋₆)alkenyl, heterocyclyl, heterocyclyl(C₁₋₆)alkyl, aryl or aryl(C₁₋₆)alkyl, any of which may be optionally substituted;

R⁹ and R¹⁰ independently represent hydrogen, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, heterocyclyl, heterocyclyl(C₁₋₆)alkyl, aryl or aryl(C₁₋₆)alkyl, any of which may be optionally substituted;

25 R¹¹ is hydrogen or (C₁₋₆)alkyl; and

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

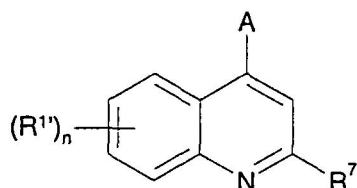
provided that the compound is not:

a) N-(2-methyl-4-quinoliny)-N'-[3-(trifluoromethyl)phenyl]urea;

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- b) N-(4-methoxy)-N'-(2-methyl-4-quinolinyl)urea;
 - c) N-[3-(dimethylamino)phenyl]-N'-(2-methyl-4-quinolinyl)urea;
 - d) N-(3-methoxyphenyl)-N'-(2-methyl-4-quinolinyl)urea;
 - e) Ethyl 3-[[[(2-methyl-4-quinolinyl)amino]carbonyl]amino]benzoate;
 - 5 f) N-[3-hydroxyphenyl]-N'-(2-methyl-4-quinolinyl)urea;
 - g) N-[2,3-dichlorophenyl]-N'-(2-methyl-4-quinolinyl)urea;
 - h) N-benzo[b]thien-5-yl-N'-(2-methyl-4-quinolinyl)urea;
 - i) N-(1-methyl-1H-indol-5-yl)-N'-(2-methyl-4-quinolinyl)urea;
 - j) N-(2-methyl-4-quinolinyl)-N'-(5,6,7,8-tetrahydro-1-naphthalenyl)urea;
 - 10 k) N-(2-methyl-4-quinolinyl)-N'-(3,4,5-trimethoxyphenyl)urea;
 - l) N-(2-methylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
 - m) N-(4-methylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
 - n) N-(3,5-dimethylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
 - o) N-(4-chlorophenyl)-N'-(2-methyl-4-quinolinyl)urea;
 - 15 p) N-(2-methyl-4-quinolinyl)-N'-[3-(trifluoromethyl)phenyl]urea;
 - q) N-(2-methoxyphenyl)-N'-(2-methyl-4-quinolinyl)urea;
 - r) N-(2-methyl-4-quinolinyl)-N'-phenylurea;
 - s) N-(3,4-dimethylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
 - t) N-(4-methyl-2-nitrophenyl)-N'-(2-methyl-4-quinolinyl)urea;
 - 20 u) N-(3-chloro-4-methylphenyl)-N'-(2-methyl-4-quinolinyl)urea;
 - v) N-(5-chloro-2-methoxyphenyl)-N'-(2-methyl-4-quinolinyl)urea;
 - w) 1-(6-amino-2-methyl-4-quinolinyl)-3-(o-nitrophenyl)urea; or
 - x) N-(1,2-dihydro-6-methyl-2-oxo-4-quinolinyl)-N'-phenylthiourea.
- 25 2. A compound according to claim 1 in which Z represents oxygen.
 3. A compound according to claim 1 or 2 in which n is 1 or 2.
 4. A compound according to any one of the preceding claims in which R² to R⁶ independently represent hydrogen, R⁸CO-, NR⁹R¹⁰CO-, halogen, (C₁₋₆)alkoxy, (C₁₋₆)alkylthio, or NR⁹R¹⁰, and at least one of R² to R⁶ is other than hydrogen; or an adjacent pair of R² to R⁶ together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered carbocyclic or heterocyclic ring.
 - 35 5. A compound according to any one of the preceding claims in which R², R⁵ and R⁶ represent hydrogen.

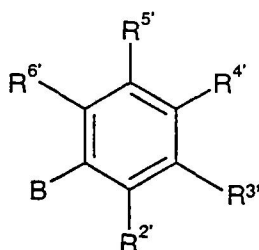
6. A compound according to any one of claims 1 to 4 in which R^2 , R^4 and R^6 represent hydrogen.

7. A process for the preparation of a compound of formula (I) as defined in any one of the preceding claims or a salt thereof which comprises coupling a compound of formula (II):



(II)

10 with a compound of formula (III):

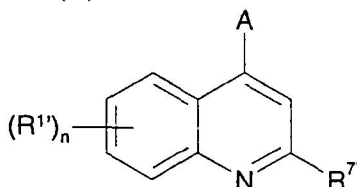


(III)

15 where A and B are appropriate functional groups to form the -NHCONH- or -NHCSNH- moiety when coupled; n is as defined in formula (I); and $R^{1'}$ to $R^{7'}$ are R^1 to R^7 as defined in formula (I) or groups convertible thereto; and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$ to $R^{7'}$ when other than R^1 to R^7 respectively to R^1 to R^7 , and/or forming a pharmaceutically acceptable salt thereof.

8. A compound library comprising at least 2 compounds of formula (I) as defined in any one of claims 1 to 6, or pharmaceutically acceptable salts thereof.

25 9. A compound of formula (II):



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(II)

wherein A is $-\text{CON}_3$, $-\text{NH}_2$, $-\text{CO}_2\text{H}$, $-\text{N}=\text{C}=\text{O}$, $-\text{N}=\text{C}=\text{S}$, $-\text{NHCOL}$ or halogen, L is a leaving group, n is as defined in formula (I) and $\text{R}^{1'}$ and $\text{R}^{7'}$ are R^1 and R^7 as defined in formula (I) or groups convertible thereto.

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10. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10 11. A method of treating or preventing diseases or disorders 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 of formula (I) as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, without provisos a)-x).

15 12. A compound of formula (I) as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, without provisos a)-x), for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

20 13. The use of a compound of formula (I) as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, without provisos a)-x), 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.

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LEGALIZACIONES

OFICINA DE PATENTES

Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

El suscrito, un funcionario debidamente autorizado conforme a los Artículos 74(1) y (4) de la Ley de Desreglamentación y Contratación de 1994 para firmar y expedir certificados en nombre del Contralor General, certifico que la copia adjunta es una copia correcta de los documentos archivados originalmente con respecto a la solicitud de patente que allí se identifica.

De acuerdo con las Reglamentaciones de Patentes de 1982 (Re-registro de Compañías), si una compañía nombrada en este certificado y en los documentos adjuntos se ha vuelto a registrar según la Ley de Compañías de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del re-registro, salvo la sustitución o inclusión como la última parte del nombre de las palabras "sociedad anónima" o su equivalente en galés, las referencias al nombre de la compañía y sus documentos adjuntos serán tratadas como referencias al nombre con el cual fue re-registrada.

De acuerdo con las reglas, las palabras "sociedad anónima" (o en inglés *public limited company*) pueden ser reemplazadas por las letras p.l.c, plc. P.L.C ó PLC.

El re-registro bajo la Ley de Compañías no constituye una nueva entidad legal sino simplemente somete a la compañía a ciertas normas de ley adicionales.

(FIRMA) ANDREW CRESSEY

FECHA: 17 de febrero de 2000

(SELLO DE LACRE)

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OFICINA DE PATENTES

SOLICITUD DE PATENTE

1. Su referencia: **AJB/NM/P32461**

2. Solicitud No. **9926430.1** **8 de noviembre de 1999**

3. Nombre completo y código postal de cada solicitante:

Dirección: **SMITHKLINE BEECHAM**
New Horizons Court
Brentford,
Middlesex TW8 9EP

Si el solicitante es una entidad, indique el país/estado de constitución:

GRAN BRETAÑA

ADP No.: 5776299002

4. TITULO DEL INVENTO:

COMPUESTOS

5. NOMBRE DE SU AGENTE:

Nombre del Agente: **CORPORATE INTELLECTUAL PROPERTY**

Dirección para notificaciones: **SMITHKLINE BEECHAM PLC**
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

NO. ADP Patentes **4422231005**

6. N/A

7. N/A

8. SI

9. Número de hojas radicadas (En inglés). Descripción: 19 Reivindicaciones: 4

Resumen : - Dibujos: -

10. Solicitud de examen preliminar y búsqueda

11. Solicitamos se nos adjudique una patente con base en esta solicitud.

A. J. BLAKEY

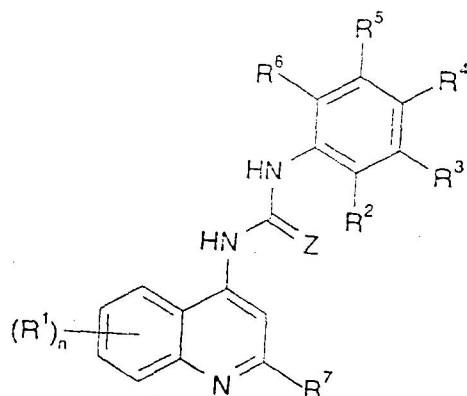
8 de noviembre de 1999

12. Nombre y teléfono del contacto en el Reino Unido Nombre y teléfono del contacto en el
Reino Unido (FIRMA) A. J. BLAKEY 01279 644355

COMPUESTOS

REIVINDICACIONES:

1. Un compuesto de la fórmula (I):



en la cual:

Z representa oxígeno o azufre;

R^1 representa alquil(C_{1-6}), alquenil(C_{2-6}) o alcoxi(C_{1-6}), cualquiera de los cuales puede ser sustituido opcionalmente; halógeno, R^8CO- o $NR^9R^{10}CO-$;

R^2 , R^3 , R^4 , R^5 y R^6 representan independientemente alquil(C_{1-6}), alquenil(C_{2-6}), alcoxi(C_{1-6}) o alquiltio(C_{1-6}), cualquiera de los cuales puede ser sustituido opcionalmente; hidrógeno, halógeno, nitro, ciano, ariloxi, aril-alquiloxi(C_{1-6}), aril-alquil(C_{1-6}), R^8CO- , R^8SO_2NH- , $R^8CON(R^{11})-$, $NR^9R^{10}-$, $NR^9R^{10}CO-$, $-COOR^9$, heterociclil o heterociclil-alquil(C_{1-6});

o un par adyacente de R^2 , R^3 , R^4 , R^5 y R^6 junto con los átomos de carbono a los que están fijos forman un anillo carbocíclico o heterocíclico sustituido opcionalmente;

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R⁷ es alquil(C₁₋₆), alquenil(C₂₋₆), alcoxi(C₁₋₆) o alquiltio(C₁₋₆), cualquiera de los cuales puede ser sustituido opcionalmente; halógeno, hidroxilo, nitro, ciano, NR⁹R¹⁰- o NR⁹R¹⁰CO-, N₃, -OCOR⁹ o R⁸CON(R¹¹)-;

R⁸ es alquil(C₁₋₆), alquenil(C₂₋₆), heterociclil, heterociclil-alquil(C₁₋₆), aril o aril-alquil(C₁₋₆), cualquiera de los cuales puede ser sustituido opcionalmente;

R⁹ y R¹⁰ representan independientemente hidrógeno, alquil(C₁₋₆), aril o aril-alquil(C₁₋₆), alquenil(C₂₋₆), heterociclil, heterociclil-alquil(C₁₋₆), aril o aril-alquil(C₁₋₆), cualquiera de los cuales puede ser sustituido opcionalmente;

R¹¹ es hidrógeno o alquil(C₁₋₆); y

n es 0, 1, 2, 3 ó 4;

o una sal farmacéuticamente aceptable de lo mismo;

siempre y cuando que el compuesto no sea:

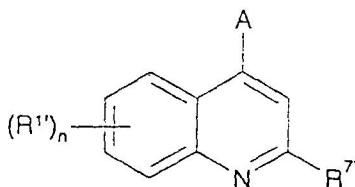
- a) N-(2-metil-4-quinolinil)-N'-[3-(trifluorometil)fenil]urea;
- b) N-(4-metoxi)-N'-(2-metil-4-quinolinil)urea;
- c) N-[3-(dimetilamino)fenil]-N'-(2-metil-4-quinolinil)urea;
- d) N-(3-metoxifenil)-N'-(2-metil-4-quinolinil)urea;
- e) Benzoato de etil 3-[[[(2-metil-4-quinolinil)amino]carbonil]amino];
- f) N-[3-hidroxifenil]-N'-(2-metil-4-quinolinil)urea;
- g) N-[2,3-diclorofenil]-N'-(2-metil-4-quinolinil)urea;
- h) N-benzo[b]tien-5-il-N'-(2-metil-4-quinolinil)urea;
- i) N-(1-metil-1H-indol-5-il)-N'-(2-metil-4-quinolinil)urea;
- j) N-(2-metil-4-quinolinil)-N'-(5,6,7,8-tetrahidro-1-naftalenil)urea;
- k) N-(2-metil-4-quinolinil)-N'-(3,4,5-trimetoxifenil)urea;
- l) N-(2-metilfenil)-N'-(2-metil-4-quinolinil)urea;

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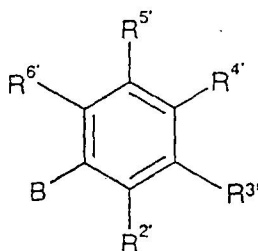
- m) N-(4-metilfenil)-N'-(2-metil-4-quinolinil)urea;
- n) N-(3,5-dimetilfenil)-N'-(2-metil-4-quinolinil)urea;
- o) N-(4-clorofenil)-N'-(2-metil-4-quinolinil)urea;
- p) N-(2-metil-4-quinolinil)-N'-[3-(triflurometil)fenil]urea;
- q) N-(2-metoxifenil)-N'-(2-metil-4-quinolinil)urea;
- r) N-(2-metil-4-quinolinil)-N'-fenvilurea;
- s) N-(3,4-dimetilfenil)-N'-(2-metil-4-quinolinil)urea;
- t) N-(4-metil-2-nitrofenil)-N'-(2-metil-4-quinolinil)urea;
- u) N-(3-cloro-4-metilfenil)-N'-(2-metil-4-quinolinil)urea;
- v) N-(5-cloro-2-metoxifenil)-N'-(2-metil-4-quinolinil)urea;
- w) 1-(6-amino-2-metil-4-quinolinil)-3-(o-nitrofenil)urea; o
- x) N-(1,2-dihidro-6-metil-2-oxo-4-quinolinil)-N'-feniltiourea.

- 2. Un compuesto según la reivindicación 1, donde Z representa oxígeno.
- 3. Un compuesto según la reivindicación 1 ó 2, en donde n es 1 o 2.
- 4. Un compuesto según cualquiera de las reivindicaciones anteriores donde R^2 a R^6 representan independientemente hidrógeno, R^8CO- , $NR^9R^{10}CO-$, halógeno, alcoxi(C_{1-6}), alquiltio(C_{1-6}) o NR^9R^{10} , y al menos uno de R^2 a R^6 es diferente de hidrógeno; o un par adyacente de R^2 a R^6 junto con los átomos de carbono a los que están fijos forman un anillo heterocíclico sustituido opcionalmente de 5 a 7 miembros.
- 5. Un compuesto según cualquiera de las reivindicaciones anteriores en donde R^2 , R^5 y R^6 representan hidrógeno.
- 6. Un compuesto según cualquiera de las reivindicaciones 1 a 4 en donde R^2 , R^4 y R^6 representan hidrógeno.

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7. Un proceso para la preparación de un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones anteriores o sales de lo mismo, que comprende acoplar un compuesto de la fórmula (II):



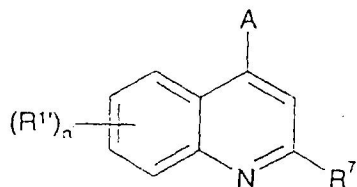
con un compuesto de la fórmula (III):



donde A y B son grupos funcionales adecuados para formar el medio -NHCONH- o -NHCSHN- cuando están acoplados; n es según se define en la fórmula (I); y $R^{1'}$ a $R^{7'}$ son R^1 a R^7 según se define en la fórmula (I) o grupos convertibles a ello; y en seguida, opcionalmente y según sea necesario y en cualquier orden apropiado, convertir cualquiera de $R^{1'}$ a $R^{7'}$ cuando otro diferente de R^1 a R^7 respectivamente a R^1 a R^7 , y/o formar una sal farmacéuticamente aceptable de lo mismo.

8. Una librería de compuestos que comprende al menos de 2 compuestos de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 6, o sales farmacéuticamente aceptables de lo mismo.

9. Un compuesto de la fórmula (II):



donde A es -CON₃, -NH₂, -CO₂H, -N=C=O, -N=C=S, -NHCOL o halógeno, L es un grupo saliente, n es según se define en la fórmula (I), y R¹ y R⁷ son R¹ y R⁷ según se define en la fórmula (I) o grupos convertibles a ello.

10. Una composición farmacéutica que comprende un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable de lo mismo, y un vehículo farmacéuticamente aceptable.
11. Un método para el tratamiento o prevención de enfermedades o trastornos donde se requiere un antagonista de un receptor de orexina humana, que consiste en administrar a un sujeto que lo requiera, una cantidad efectiva de un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable de lo mismo, sin las salvedades anteriores.
12. Un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable de lo mismo, sin las salvedades a)-x), para uso en el tratamiento o profilaxis de enfermedades o trastornos donde se requiere un antagonista de un receptor de orexina humana.
13. El uso de un compuesto de la fórmula (I) según se define en las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable de lo mismo, sin las salvedades a)-x), para la fabricación de un medicamento para el tratamiento o profilaxis de enfermedades o trastornos donde se requiere un antagonista de un receptor de orexina humana.



The
Patent
Office



INVESTOR IN PEOPLE

27/11/00
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The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

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Signed

Andrew Gersey

Dated 16 February 2000

The
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Office

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09NOV99 E490354-1 D02029
P01/7700 0.00-9926441.8



Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

AJB/NM/P32464

2. Patent application number

(The Patent Office will fill in this part)

9926441.8

08 NOV 1999

3. Full name, address and postcode of the or of each applicant (underline all surnames)

SmithKline Beecham plc
New Horizons Court, Brentford, Middx TW8 9EP,
Great Britain

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

5776299002

4. Title of the invention

Compounds

5. Name of your agent (if you have one)

CORPORATE INTELLECTUAL PROPERTY

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

Patents ADP number (if you know it)

4471231005

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (if you know it) the or each application number

Country	Priority application number (if you know it)	Date of filing (day / month / year)
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer yes if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is named as an applicant, or
 - c) any named applicant is a corporate body
- See note (d)

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form
Description
Claim(s)
Abstract
Drawings

20
3

20
3

10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 1/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11.

We request the grant of a patent on the basis of this application

Signature Alison Blakey Date 8-Nov-99
A J Blakey

12. Name and daytime telephone number of person to contact in the United Kingdom

A J Blakey 01279 644355

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15/11/94
142COMPOUNDS

This invention relates to phenyl urea and phenyl thiourea 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 EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP-A-893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.

Orexin receptors are found in the mammalian host and may be responsible for many biological functions, including pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourett's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid

haemorrhage; head injury such as sub-arachnoid haemorrhage associated with traumatic head injury; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders, which includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

Experiments have shown that central administration of the ligand orexin-A (described in more detail below) 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. Therefore, antagonists of its receptor may be useful in the treatment of obesity and diabetes, see *Cell*, 1998, **92**, 573-585.

There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. 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, and 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.

Rat sleep/EEG studies have also 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,

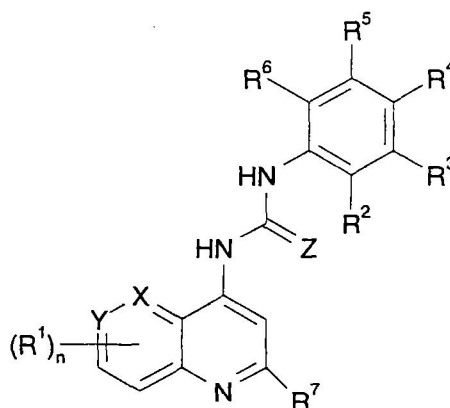
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when administered at the onset of the normal sleep period. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

International Patent Applications PCT/GB98/02437 and PCT/EP99/03100 (published after the priority date of the present application) disclose various phenyl urea derivatives as orexin receptor antagonists.

The present invention provides phenyl urea and phenyl thiourea derivatives which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity including obesity observed in Type 2 (non-insulin-dependent) diabetes patients and/or sleep disorders.

According to the invention there is provided a compound of formula (I):



(I)

in which:

one of X and Y is N and the other is CH;

Z represents oxygen or sulphur;

R¹ represents (C₁₋₆)alkyl, (C₂₋₆)alkenyl or (C₁₋₆)alkoxy, any of which may be optionally substituted; halogen, R⁸CO- or NR⁹R¹⁰CO-;

R², R³, R⁴, R⁵ and R⁶ independently represent (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxy or (C₁₋₆)alkylthio, any of which may be optionally substituted; hydrogen, halogen, nitro, cyano, aryloxy, aryl(C₁₋₆)alkyloxy, aryl(C₁₋₆)alkyl, R⁸CO-, R⁸SO₂NH-, R⁸SO₂O-, R⁸CON(R¹¹)-, NR⁹R¹⁰-, NR⁹R¹⁰CO-, -COOR⁹, R¹¹C(=NOR⁸), heterocyclyl or heterocyclyl(C₁₋₆)alkyl;

or an adjacent pair of R², R³, R⁴, R⁵ and R⁶ together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

R⁷ is (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxy or (C₁₋₆)alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano, NR⁹R¹⁰-, NR⁹R¹⁰CO-, N₃, -OCOR⁹ or R⁸CON(R¹¹)-;

R^8 is (C_{1-6}) alkyl, (C_{2-6}) alkenyl, heterocyclyl, heterocyclyl (C_{1-6}) alkyl, aryl or aryl (C_{1-6}) alkyl, any of which maybe optionally substituted;

R^9 and R^{10} independently represent hydrogen, (C_{1-6}) alkyl, (C_{2-6}) alkenyl, heterocyclyl, heterocyclyl (C_{1-6}) alkyl, aryl or aryl (C_{1-6}) alkyl, any of which maybe
5 optionally substituted;

R^{11} is hydrogen or (C_{1-6}) alkyl; and

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

In formula (I) Z is preferably oxygen.

10 When a halogen atom is present in the compound of formula (I) this may be fluorine, chlorine, bromine or iodine.

n is preferably 0 or 1, more preferably 0.

X is preferably N and Y is CH .

When n is 1, the group R^1 is preferably in the 6- or 8-position, particularly the
15 8-position.

R^1 is preferably halogen e.g. fluoro, or (C_{1-6}) alkoxy e.g. methoxy. R^1 is most preferably fluoro.

When any one of R^1 to R^{11} comprise a (C_{1-6}) alkyl group, whether alone or forming part of a larger group, e.g. alkoxy or alkylthio, the alkyl group may be straight
20 chain, branched or cyclic, or combinations thereof, it preferably contains 1 to 4 carbon atoms, and is most preferably methyl or ethyl.

When any one of R^1 to R^{10} comprise a (C_{2-6}) alkenyl group, whether alone or forming part of a larger group, the alkenyl group may be straight chain, branched or cyclic, or combinations thereof, it preferably contains 2 to 4 carbon atoms and is most
25 preferably allyl.

Suitable optional substituents for (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy and (C_{1-6}) alkylthio groups include one or more substituents selected from halogen e.g. fluoro, (C_{1-4}) alkoxy e.g. methoxy, hydroxy, carboxy and (C_{1-6}) alkyl esters and (C_{1-6}) alkylamides thereof, amino, mono- or di- (C_{1-6}) alkylamino, $N(R^{11})COR^8$,
30 $N(R^{11})SO_2R^8$, $CONR^9R^{10}$ and cyano. For example one or more substituents selected from halogen e.g. fluoro, (C_{1-4}) alkoxy e.g. methoxy, hydroxy, carboxy and (C_{1-6}) alkyl esters thereof, amino, mono- or di- (C_{1-6}) alkylamino and cyano.

When used herein the term "aryl", whether alone or forming part of a larger group, includes optionally substituted aryl groups such as phenyl and naphthyl,
35 preferably phenyl. The aryl group may contain up to 5, more preferably 1, 2 or 3 optional substituents. Suitable substituents for aryl groups include halogen, (C_{1-4}) alkyl e.g. methyl, (C_{1-4}) haloalkyl e.g. trifluoromethyl, (C_{1-4}) alkoxy e.g. methoxy, (C_{1-4})

- 4)alkoxy(C₁₋₄)alkyl e.g. methoxymethyl, hydroxy, =O, carboxy and (C₁₋₆)alkyl esters and (C₁₋₆)mono and dialkylamides thereof, nitro, arylsulfonyl e.g. p-toluenesulfonyl, (C₁₋₄)alkylsulfonyl e.g. methanesulfonyl, aryl(C₁₋₄)alkyl e.g. benzyl or 3-phenylpropyl, aryl e.g. phenyl, hydroxy(C₁₋₄)alkyl e.g. hydroxyethyl, R^aCO₂-, R^aCO₂ (C₁₋₄)alkyl e.g. carboethoxypropyl, cyano, cyano(C₁₋₄)alkyl e.g. 3-cyanopropyl, R^aR^bN, R^aR^bN(C₁₋₄)alkyl, R^aR^bNCO(C₁₋₄)alkyl in which R^a and R^b are independently selected from hydrogen and (C₁₋₄)alkyl.

- When any one of R² to R⁶, R⁸, R⁹ or R¹⁰ represent heterocyclyl or heterocyclyl(C₁₋₆)alkyl the heterocyclyl group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may be saturated or unsaturated, for example containing 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur; for example pyrrolidine, oxazole, morpholine, pyrimidine or phthalimide. A ring containing one or two nitrogen atoms is especially preferred. The heterocyclyl group may contain up to 5, more preferably 1, 2 or 3 optional substituents. Suitable substituents for heterocyclyl groups include those mentioned above for aryl groups.

- When an adjacent pair of R² to R⁶ together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring this is preferably a 5- to 7-membered ring, which may be aromatic or non-aromatic. Heterocyclic rings preferably contain 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur; for example oxazole, imidazole, thiophene, pyran, dioxan, pyrrole or pyrrolidine. A ring containing one nitrogen atom and one oxygen atom is preferred. It is particularly preferred for the nitrogen to be attached directly to the R⁴ position. A carbocyclic or heterocyclic ring formed by an adjacent pair of R² to R⁶ together with the carbon atoms to which they are attached may be optionally substituted on carbon or nitrogen by one or more substituents, e.g. up to 3 substituents. Suitable substituents for the carbocyclic or heterocyclic ring include those mentioned above for aryl groups.

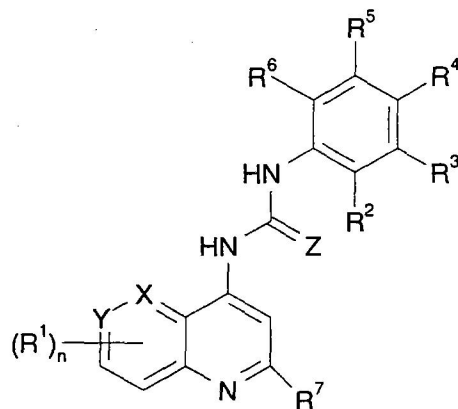
- A preferred group of compounds are those in which R² to R⁶ independently represent hydrogen, R⁸CO-, NR⁹R¹⁰CO-, halogen, (C₁₋₆)alkoxy e.g. methoxy, (C₁₋₆)alkylthio e.g. methylthio, or NR⁹R¹⁰ wherein R⁹ and R¹⁰ preferably represent (C₁₋₆)alkyl e.g. dimethylamino, and at least one of R² to R⁶ is other than hydrogen; or an adjacent pair of R² to R⁶ together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered carbocyclic or heterocyclic ring, e.g. a 6- or 7-membered non-aromatic heterocyclic ring, a 5- or 6-membered non-aromatic carbocyclic ring or a 5- or 6-membered aromatic heterocyclic ring.

- A further preferred group of compounds are those in which R², R⁵ and R⁶ represent hydrogen.

A further preferred group of compounds are those in which R^2 , R^4 and R^6 represent hydrogen.

A preferred group of compounds are those in which either R^3 and R^4 , or R^3 and R^5 are other than hydrogen.

- 5 A group of compounds which may be mentioned are the compounds of formula (Ia):



(Ia)

in which :

- 10 one of X and Y is N and the other is CH;
 Z represents oxygen or sulphur;
 R^1 represents (C_{1-6}) alkyl, (C_{2-6}) alkenyl or (C_{1-6}) alkoxy, any of which may be optionally substituted; halogen, R^8CO- or $NR^9R^{10}CO-$;
 R^2 , R^3 , R^4 , R^5 and R^6 independently represent (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy or (C_{1-6}) alkylthio, any of which may be optionally substituted; hydrogen,
 15 halogen, nitro, cyano, aryloxy, aryl (C_{1-6}) alkyloxy, aryl (C_{1-6}) alkyl, R^8CO- , R^8SO_2NH- , $R^8CON(R^{11})-$, $NR^9R^{10}-$, $NR^9R^{10}CO-$, $-COOR^9$, heterocyclyl or heterocyclyl (C_{1-6}) alkyl;
 or an adjacent pair of R^2 , R^3 , R^4 , R^5 and R^6 together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;
 20 R^7 is (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy or (C_{1-6}) alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano, $NR^9R^{10}-$, $NR^9R^{10}CO-$, N_3 , $-OCOR^9$ or $R^8CON(R^{11})-$;
 R^8 is (C_{1-6}) alkyl or aryl;
 R^9 and R^{10} independently represent hydrogen, (C_{1-6}) alkyl, aryl or aryl (C_{1-6}) alkyl;
 25 R^{11} is hydrogen or (C_{1-6}) alkyl; and
 n is 0, 1, 2, or 3;
 or a pharmaceutically acceptable salt thereof.

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In the compounds of formula (Ia) suitable substituents for aryl groups and for heterocyclyl groups when any one of R^2 to R^6 represent heterocyclyl or heterocyclyl(C_{1-6})alkyl include halogen, (C_{1-4})alkyl e.g. methyl, (C_{1-4})haloalkyl e.g. trifluoromethyl, (C_{1-4})alkoxy e.g. methoxy, (C_{1-4})alkoxy(C_{1-4})alkyl e.g.

- 5 methoxymethyl, hydroxy, carboxy and (C_{1-6})alkyl esters, amino, nitro, arylsulfonyl e.g. p-toluenesulfonyl, and (C_{1-4})alkylsulfonyl e.g. methanesulfonyl. Suitable substituents for carbocyclic or heterocyclic rings when an adjacent pair of R^2 to R^6 together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring include (C_{1-4})alkyl e.g. methyl, (C_{1-4})alkoxy, (C_{1-4})alkoxy(C_{1-4})alkyl e.g.
- 10 methoxymethyl, hydroxy, =O, aryl(C_{1-4})alkyl e.g. benzyl or 3-phenylpropyl, aryl e.g. phenyl, hydroxy(C_{1-4})alkyl e.g. hydroxyethyl, R^aCO_2 , R^aCO_2 (C_{1-4})alkyl e.g. carboethoxypropyl, cyano, cyano(C_{1-4})alkyl e.g. 3-cyanopropyl, R^aR^bN and $R^aR^bN(C_{1-4})$ alkyl in which R^a and R^b are independently selected from hydrogen and (C_{1-4})alkyl.

- A further group of compounds of formula (Ia) are those in which R^2 to R^6
- 15 independently represent hydrogen, halogen, (C_{1-6})alkoxy e.g. methoxy, (C_{1-6})alkylthio e.g. methylthio, or NR^9R^{10} wherein R^9 and R^{10} preferably represent (C_{1-6})alkyl e.g. dimethylamino, and at least one of R^2 to R^6 is other than hydrogen; or an adjacent pair of R^2 to R^6 together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring, e.g. a 6- or 7-membered
- 20 non-aromatic heterocyclic ring or a 5- or 6-membered aromatic heterocyclic ring.

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

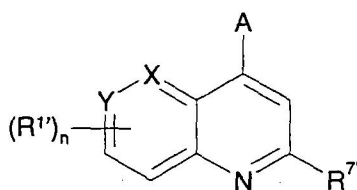
- It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically
- 25 acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids e.g. 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, may be used, for example in the
- 30 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).

- The invention extends to all isomeric forms including stereoisomers and geometric isomers of the compounds of formula (I) including enantiomers and
- 35 mixtures thereof e.g. racemates. 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.

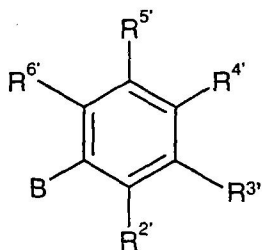
Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% 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 feature of the invention we provide a process for the preparation of the compounds of formula (I) and salts thereof which comprises coupling a compound of formula (II);



(II)

with a compound of formula (III);



(III)

wherein A and B are appropriate functional groups to form the -NHCONH- or -NHCSNH- moiety when coupled; n, X and Y are as defined in formula (I); and R' to R'' are R¹ to R⁷ as defined in formula (I) or groups convertible thereto; and thereafter optionally and as necessary and in any appropriate order, converting any R' to R'' when other than R¹ to R⁷ respectively to R¹ to R⁷, and/or forming a pharmaceutically acceptable salt thereof.

Suitable examples of groups A and B are:

- (i) A and B are -NH₂
- (ii) one of A and B is -CON₃ and the other is -NH₂
- (iii) one of A and B is -CO₂H and the other is -NH₂
- (iv) one of A and B is -N=C=O and the other is -NH₂

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- (v) one of A and B is $-N=C=S$ and the other is $-NH_2$
- (vi) one of A and B is $-NHCOL$ and the other is $-NH_2$
- (vii) one of A and B is halogen and the other is $-NHCONH_2$
- (viii) one of A and B is $NHCOCBr_3$ and the other is NH_2

5 Wherein L is a leaving group such as chloro or bromo, imidazole or phenoxy or phenylthio optionally substituted for example with halogen, for example chlorine.

When A and B are both $-NH_2$, the reaction is generally effected in the presence of a urea coupling agent such as carbonyldiimidazole or triphosgene.

When one of A and B is $-CO_2H$ and the other is $-NH_2$ the reaction is
10 generally effected in the presence of an agent such as diphenylphosphoryl azide and in the presence of a base such as triethylamine.

When one of A and B is $-N=C=O$ or $-N=C=S$ and the other is $-NH_2$ the reaction is suitably carried out in an inert solvent for example dimethylformamide or dichloromethane and/or toluene at ambient or elevated temperature, preferably
15 ambient.

When one of A and B is $-CON_3$ or $-CO_2H$ and the other is $-NH_2$ the reaction is suitably carried out in an inert solvent for example toluene or dimethylformamide at elevated temperature.

Where one of A and B is $-NHCOL$ and the other is $-NH_2$, the reaction is
20 suitably carried out in an inert solvent such as dichloromethane at ambient temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature.

When one of A and B is halogen and the other is $-NHCONH_2$ the reaction is suitably carried out in an inert solvent such as toluene at elevated temperature,
25 optionally in the presence of base.

When one of A and B is $NHCOBr_3$ and the other is NH_2 the reaction is suitably carried out in an inert solvent such as dimethylsulfoxide or pyridine at elevated temperatures in the presence of a base such as DBU.

Suitable examples of compounds having groups $R^{1'}$ to $R^{7'}$ which are
30 convertible to $R^{1'}$ to $R^{7'}$ respectively include compounds where one or more of $R^{2'}$ to $R^{7'}$ are OH or NH_2 ; and compounds where an adjacent pair of $R^{2'}$ to $R^{6'}$ together with the carbon atoms to which they are attached represent a fused pyrrole ring which is unsubstituted on nitrogen, where treatment with a base, e.g. sodium hydride, and reaction with an electrophile, e.g. methyl iodide, benzyl chloride or benzenesulfonyl
35 chloride, affords the corresponding substituent on the pyrrole nitrogen.

Compounds of formula (II) and (III) where A or B is $-NH_2$, $-N=C=S$ or halogen are known compounds or can be prepared analogously to known compounds.

- Compounds of formula (II) and (III) where A or B is $-N=C=O$ may be prepared by treating a compound of formula (II) or (III) in which:
- (i) A or B is amino, with phosgene or a phosgene equivalent, in the presence of excess base or an inert solvent.
 - (ii) A or B is acylazide (i.e. $-CON_3$), via the nitrene, by thermal rearrangement using conventional conditions (ref. L.S. Trifonov *et al*, *Helv. Chim. Acta*, 1987, **70**, 262).
 - (iii) A or B is $-CONH_2$, via the nitrene intermediate using conventional conditions.

Compounds of formula (II) and (III) where A or B is $-NHCOL$ may be prepared by reacting a compound of formula (II) or (III) in which A or B is $-NH_2$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of a base such as triethylamine.

Examples of phosgene equivalents include triphosgene, carbonyldiimidazole, phenyl chloroformate and phenyl chlorothioformate.

Compounds of formula (II) and (III) where A or B is $-NHCONH_2$ can be prepared from compounds of formula (II) or (III) where A or B is $-NH_2$ by reaction with an isocyanate under conventional conditions.

Compounds of formula (II) and (III) where A or B is $-NHCOCBr_3$ can be prepared from compounds of formula (II) or (III) where A or B is $-NH_2$ by reaction with tribromoacetyl chloride in an inert solvent such as dichloromethane in the presence of a base such as triethylamine.

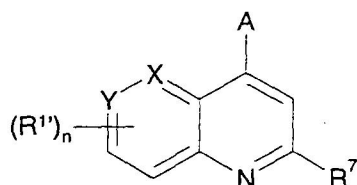
The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by a combinatorial 'split and mix' approach or by multiple 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 salts thereof.

Novel intermediates of formulae (II) and (III) are also part of this invention.

According to a further feature of the invention we provide a compound of formula (II):

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(II)

wherein A is $-\text{CON}_3$, $-\text{NH}_2$, $-\text{CO}_2\text{H}$, $-\text{N}=\text{C}=\text{O}$, $-\text{N}=\text{C}=\text{S}$, $-\text{NHCOL}$ or halogen and L is a leaving group, n, X and Y are as defined in formula (I), and $\text{R}^{1'}$ and $\text{R}^{7'}$ are R^1 and R^7 as defined in formula (I) or groups convertible thereto.

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

As indicated above the compounds of formula (I) and their pharmaceutically acceptable salts are useful for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required especially feeding disorders, such as obesity and diabetes; prolactinoma; hypoprolactinemia, hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; Cushings syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases; depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delirium; dementia; bulimia; and hypopituitarism.

The compounds of formula (I) and their pharmaceutically acceptable salts are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, and sleep disorders.

Other diseases or disorders which may be treated in accordance with the invention include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain;

post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and tolerance to narcotics or withdrawal from narcotics.

The present invention also provides a method of treating or preventing diseases or disorders 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 of formula (I), or a pharmaceutically acceptable salt thereof.

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

The present 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 diseases or disorders where an antagonist of a human orexin receptor is required.

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition. The present 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) and their pharmaceutically acceptable salts may be administered by any convenient method, for example 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 salts which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example 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. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, 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

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pharmaceutical carrier(s), for example 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 compound or physiologically acceptable salt in a sterile aqueous carrier or
5 parenterally acceptable oil, for example 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
10 solution or fine suspension of the active substance in a physiologically 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 unitary dispensing device such as a single dose nasal inhaler or an aerosol
15 dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. The aerosol dosage forms can also take the form of a pump-
20 atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein 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
25 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.

30 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 be 0.05 to 1000 mg, more suitably 0.05 to 500 mg; such
35 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; and such therapy may extend for a number of weeks or months. In the case of

physiologically acceptable salts 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.

5 Human orexin-A, referred to above, has the amino acid sequence:
 pyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu
 1 5 10 15
 Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr
 20 25 30
 10 Leu-NH₂

Orexin-A can be employed in a process for screening for compounds (antagonists) which inhibit the ligand's activation of the orexin-1 receptor.

In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on the surface thereof. Such cells include cells
 15 from mammals, yeast, *Drosophila* or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is employed to transfect cells to thereby 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 procedure involves the use of melanophores which are
 20 transfected to express the orexin-1 receptor. Such a screening technique is described in WO 92/01810.

Another such screening technique involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes may then be contacted with a receptor ligand and a compound to be
 25 screened, 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 the surface thereof. Such a method involves
 30 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 can be labelled, e.g. by radioactivity. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity of the
 35 receptors. If the compound binds to the receptor as determined by a reduction of labelled ligand which binds to the receptors, the binding of labelled ligand to the receptor is inhibited.

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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. The ligand used in the screening method described below to determine the antagonist activity of compounds according to the invention is orexin-A which has the amino acid sequence shown above.

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 invention.

Description 1: Trifluoromethane sulfonic acid 2-methyl-[1,5]naphthyridin-4-yl ester (D1)

A suspension of 4-hydroxy-2-methyl-[1,5]-naphthyridine contaminated with 4-hydroxy-2-methyl-[1,7]-naphthyridine (1.0g) (H.G.M. Walvaren *et al. J. Royal Netherlands Chem. Soc.* 1976, **95**, 220) in dichloromethane (45ml) was treated sequentially with 2,6-lutidine (1.2ml), 4-N,N-dimethylaminopyridine (0.075g) and trifluoromethanesulfonic anhydride (1.2ml). After the final addition was complete the mixture was stirred for 30 min the mixture washed with saturated aqueous ammonium chloride, dried (Na₂SO₄) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 0 – 20% ethyl acetate in pentane) to give after combining the appropriate fractions the title compound (0.588g) as a colourless solid.

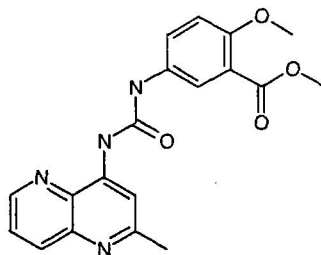
¹H NMR (CDCl₃) δ: 2.84 (3H, s), 7.42 (1H, s), 7.73 (1H, dd), 8.37 (1H, dd) and 9.04 (1H, m).

Description 2: 4-Amino-2-methyl-[1,5]-naphthyridine (D2)

D1 (2.2g) and propylamine hydrochloride (2.34g) were combined in pyridine (75ml) and the mixture refluxed for 8h. Solvent was removed at reduced pressure, the residue dissolved in 2N sodium hydroxide and extracted with diethyl ether (x 3) and dichloromethane (x 2). The combined organic phase was dried and solvent removed at reduced pressure. The residue was triturated with pentane to give the title compound (1.32g) as a pale orange solid.

¹H NMR (CDCl₃) δ: 2.60 (3H, s), 5.44 (2H, brs), 6.66 (1H, s), 7.54 (1H, dd), 8.17 (1H, dd) and 8.67 (1H, m).

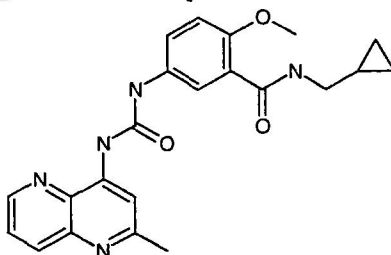
Example 1: 2-Methoxy-5-[3-(2-methyl-[1,5]-naphthyridin-4-yl)ureido]benzoic acid methyl ester



D2 (0.51g) was added in portions over 10 min to a solution of carbonyl diimidazole (0.536g) and 4-N,N-dimethylaminopyridine (0.004g) in dimethylformamide (10ml). The resulting solution was stirred for 16h, 5-amino-2-methoxybenzoic acid methyl ester (0.577g) added in dimethylformamide (2ml) and the mixture heated at 100°C for 2h. The mixture was diluted with ethyl acetate and washed with water (x 2) and brine, dried (Na₂SO₄) and solvent removed at reduced pressure. The pale pink solid was triturated with dichloromethane to give the desired product (0.58g).

¹H NMR (d⁶-DMSO) δ: 2.64 (3H, s), 3.34 (3H, s), 3.81 (3H, s), 7.15 (1H, d), 7.59 (1H, dd), 7.80 (1H, dd), 7.94 (1H, d), 8.29 (1H, dd), 8.34 (1H, s), 8.89 (1H, m), 9.85 (1H, s) and 10.05 (1H, s).

Example 2: N-Cyclopropylmethyl-2-methoxy-5-[3-(2-methyl-[1,5]-naphthyridin-4-yl)ureido]benzamide hydrochloride

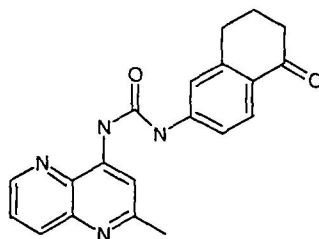


From D2 (0.16g) and 2-N-cyclopropylmethyl-2-methoxy-5-benzamide (0.22g) the title compound was prepared according to the method of Example 1. However the work-up was modified. The reaction mixture was added dropwise to water, chilled and the precipitated solid collected by filtration. The solid was triturated with methanol suspended in methanol and treated with 1M ethereal HCl to give the title compound (0.08g).

¹H NMR (d⁶-DMSO) δ: 0.25 (2H, m), 0.43 (2H, m), 2.89 (3H, s), 3.19 (2H, t), 3.90 (3H, s), 7.16 (1H, s), 7.65 (1H, dd), 7.96 (1H, d), 8.12 (1H, dd), 8.30 (1H, t), 8.64 (2H, m), 9.15 (1H, d), 10.54 (1H, s) and 10.69 (1H, s).

Example 3: 1-(2-Methyl-[1,5]-naphthyridin-4-yl)-3-(5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)urea

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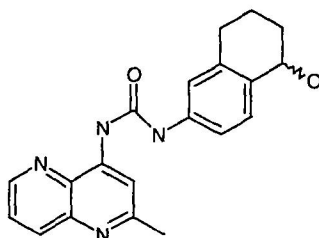


D2 (0.20g) was added in portions over 3h to a solution of carbonyl diimidazole (0.203g) in dichloromethane. When addition was complete the mixture was stirred for a further 2h, solvent removed at reduced pressure, the residue dissolved in dimethylformamide (5ml) and 6-amino-1,2,3,4-tetrahydronaphthalene-1-one (0.202g) added. The mixture was heated at 95°C for 5h, cooled and solvent removed at reduced temperature. The residue was triturated with water and the resultant solid chromatographed (silica gel, 20% ethyl acetate/pentane and 20 – 50% ethyl acetate in diethyl ether eluant) to give the title compound (0.134g) as an orange/yellow solid.

¹H NMR (d⁶-DMSO) δ: 2.04 (2H, m), 2.56 (2H, m), 2.65 (3H, s), 2.94 (2H, t), 7.41 (1H, dd), 7.60 (1H, m), 7.79 – 7.86 (2H, m), 8.30 (1H, dd), 8.36 (1H, s), 8.90 (1H, m), 10.03 (1H, s) and 10.36 (1H, s).

m/z (API⁺): 347 (MH⁺).

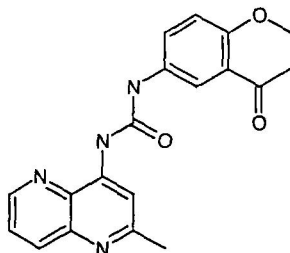
Example 4: 1-(5-Hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-3-(2-Methyl-[1,5]-naphthyridin-4-yl)urea



The compound of example 3 (0.093g) in methanol (100ml) was treated with sodium borohydride (0.3g) and the mixture stirred overnight. Solvent was removed at reduced pressure the residue dissolved in ethyl acetate and washed with water and brine. The organic phase was dried (Na₂SO₄) solvent removed at reduced pressure and the residue triturated with diethyl ether to give the title compound (0.06g) as a colourless solid.

¹H NMR (d⁶-DMSO) δ: 1.69 (2H, m), 1.87 (2H, m), 2.63 (3H, s), 2.67 (2H, m), 4.53 (1H, m), 5.01 (1H, d), 7.23 – 7.35 (3H, m), 7.79 (1H, dd), 8.29 (1H, dd), 8.36 (1H, s), 8.89 (1H, m), 9.90 (1H, s) and 9.93 (1H, s)

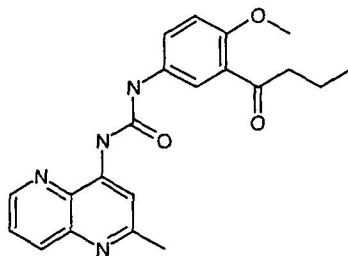
m/z (API⁺): 349 (MH⁺).

Example 5: 1-(3-Acetyl-4-methoxyphenyl)-3-(2-methyl-[1,5]-naphthyridin-4-yl)urea

3-Acetyl-4-methoxybenzoic acid (0.082g) in toluene (4ml) was treated with triethylamine (0.176ml) and subsequently with diphenylphosphoryl azide (0.092ml). The mixture was stirred for 16h at room temperature, D2 (0.067g) added and the mixture heated to reflux for 4h. After cooling to room temperature solvent was removed at reduced pressure and the residue column chromatographed (silica gel, 0 – 10% methanol in dichloromethane containing 1% ammonia) to give the title compound (0.03g) as a colourless solid.

¹H NMR (d⁶-DMSO) δ: 2.55 (3H, s), 2.63 (3H, s), 3.89 (3H, s), 7.18 (1H, d), 7.68 (1H, dd), 7.77 – 7.83 (2H, m), 8.28 (1H, dd), 8.34 (1H, s), 8.89 (1H, m), 9.85 (1H, s) and 10.03 (1H, s).

m/z (API⁺): (351, MH⁺).

Example 6: 1-(3-Butyryl-4-methoxyphenyl)-3-(2-methyl-[1,5]-naphthyridin-4-yl)urea

The title compound (0.075g) was prepared from compound D2 (0.08g) and 3-butyryl-4-methoxybenzoic acid (0.111g) according to the method of example 5.

¹H NMR (d⁶-DMSO) δ: 0.91 (3H, t), 1.53 – 1.68 (2H, m), 2.63 (3H, s), 2.91 (2H, t), 3.87 (3H, s), 7.15 (1H, d), 7.64 (1H, dd), 7.71 (1H, d), 7.80 (1H, dd), 8.28 (1H, dd), 8.34 (1H, s), 8.89 (1H, m), 9.85 (1H, s) and 10.03 (1H, s).

m/z (API⁺): (379, MH⁺).

Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

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HEK293 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37°C in 5% CO₂.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC₅₀ values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM CaCl₂, 1.2 mM MgCl₂ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC₅₀ values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 3.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 90 min at 37°C in 5% CO₂. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37°C in 5% CO₂ for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument and maintained at 37°C in humidified air. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, 1995, *TiPS*, 16, 413-417) to generate a concentration effect value. Antagonist K_b values were calculated using the equation:

$$K_b = IC_{50} / (1 + ([3/EC_{50}]))$$

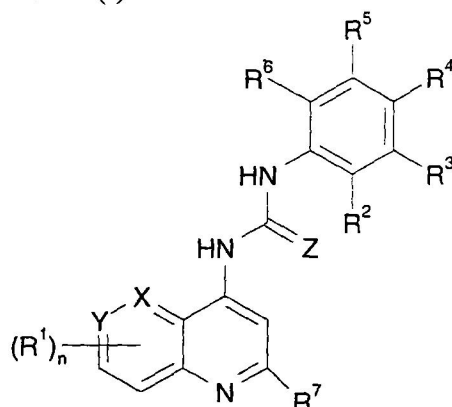
where EC_{50} was the potency of human orexin-A determined in the assay (in nM terms) and IC_{50} is expressed in molar terms.

As an illustration of the activity of the compounds of formula (I), the compound of Example 2 had a $pK_b > 7.5$ in this assay.

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CLAIMS

1. A compound of formula (I):



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(I)

in which :

one of X and Y is N and the other is CH ;

Z represents oxygen or sulphur;

- 10 R^1 represents (C_{1-6}) alkyl, (C_{2-6}) alkenyl or (C_{1-6}) alkoxy, any of which may be optionally substituted; halogen, R^8CO- or $NR^9R^{10}CO-$;

- 15 R^2 , R^3 , R^4 , R^5 and R^6 independently represent (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy or (C_{1-6}) alkylthio, any of which may be optionally substituted; hydrogen, halogen, nitro, cyano, aryloxy, aryl (C_{1-6}) alkyloxy, aryl (C_{1-6}) alkyl, R^8CO- , R^8SO_2NH- , R^8SO_2O- , $R^8CON(R^{11})-$, $NR^9R^{10}-$, $NR^9R^{10}CO-$, $-COOR^9$, $R^{11}C(=NOR^8)$, heterocyclyl or heterocyclyl (C_{1-6}) alkyl;

or an adjacent pair of R^2 , R^3 , R^4 , R^5 and R^6 together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

- 20 R^7 is (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxy or (C_{1-6}) alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano, $NR^9R^{10}-$, $NR^9R^{10}CO-$, N_3 , $-OCOR^9$ or $R^8CON(R^{11})-$;

R^8 is (C_{1-6}) alkyl, (C_{2-6}) alkenyl, heterocyclyl (C_{1-6}) alkyl, aryl or aryl (C_{1-6}) alkyl any of which maybe optionally substituted;

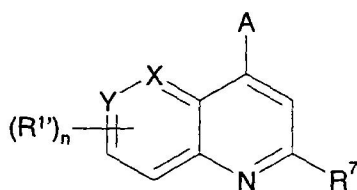
- 25 R^9 and R^{10} independently represent hydrogen, (C_{1-6}) alkyl, (C_{2-6}) alkenyl, heterocyclyl (C_{1-6}) alkyl, aryl or aryl (C_{1-6}) alkyl any of which maybe optionally substituted;

R^{11} is hydrogen or (C_{1-6}) alkyl; and

n is 0, 1, 2, or 3;

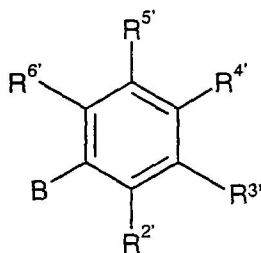
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which X is N and Y is CH.
3. A compound according to claim 1 or 2 in which Z represents oxygen.
- 5 4. A compound according to any one of the preceding claims in which n is 0 or 1.
5. A compound according to any one of the preceding claims in which R^2 to R^6 independently represent hydrogen, R^8CO- , $NR^9R^{10}CO-$, halogen, (C_{1-6}) alkoxy, (C_{1-6}) alkylthio, or NR^9R^{10} , and at least one of R^2 to R^6 is other than hydrogen; or an
 10 adjacent pair of R^2 to R^6 together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered carbocyclic or heterocyclic ring.
6. A compound according to any one of the preceding claims in which R^2 , R^5 and R^6 represent hydrogen.
- 15 7. A compound according to any one of claims 1 to 5 in which R^2 , R^4 and R^6 represent hydrogen.
8. A process for the preparation of a compound of formula (I) as defined in any
 20 one of the preceding claims or a salt thereof which comprises coupling a compound of formula (II):



(II)

- 25 with a compound of formula (III):



(III)

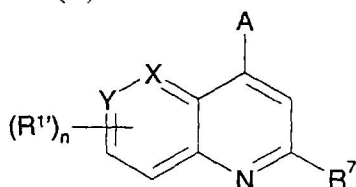
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where A and B are appropriate functional groups to form the -NHCONH- or -NHCSNH- moiety when coupled; n, X and Y are as defined in formula (I); and R^{1'} to R^{7'} are R¹ to R⁷ as defined in formula (I) or groups convertible thereto; and thereafter optionally and as necessary and in any appropriate order, converting any R^{1'} to R^{7'} when other than R¹ to R⁷ respectively to R¹ to R⁷, and/or forming a pharmaceutically acceptable salt thereof.

9. A compound library comprising at least 2 compounds of formula (I) as defined in any one of claims 1 to 7, or pharmaceutically acceptable salts thereof.

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10. A compound of formula (II):



(II)

wherein A is -CON₃, -NH₂, -CO₂H, -N=C=O, -N=C=S, -NHCOL or halogen and L is a leaving group, n, X and Y are as defined in formula (I), and R^{1'} and R^{7'} are R¹ and R⁷ as defined in formula (I) or groups convertible thereto.

11. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

12. A method of treating or preventing diseases or disorders 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 of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof.

13. A compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

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14. The use of a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt 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.

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LEGALIZACIONES

OFICINA DE PATENTES

Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

El suscrito, un funcionario debidamente autorizado conforme a los Artículos 74(1) y (4) de la Ley de Desreglamentación y Contratación de 1994 para firmar y expedir certificados en nombre del Contralor General, certifico que la copia adjunta es una copia correcta de los documentos archivados originalmente con respecto a la solicitud de patente que allí se identifica.

De acuerdo con las Reglamentaciones de Patentes de 1982 (Re-registro de Compañías), si una compañía nombrada en este certificado y en los documentos adjuntos se ha vuelto a registrar según la Ley de Compañías de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del re-registro, salvo la sustitución o inclusión como la última parte del nombre de las palabras "sociedad anónima" o su equivalente en galés, las referencias al nombre de la compañía y sus documentos adjuntos serán tratadas como referencias al nombre con el cual fue re-registrada.

De acuerdo con las reglas, las palabras "sociedad anónima" (o en inglés *public limited company*) pueden ser reemplazadas por las letras p.l.c, plc. P.L.C ó PLC.

El re-registro bajo la Ley de Compañías no constituye una nueva entidad legal sino simplemente somete a la compañía a ciertas normas de ley adicionales.

(FIRMA) ANDREW CRESSEY

FECHA: 16 de febrero de 2000

(SELLO DE LACRE)

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OFICINA DE PATENTES

SOLICITUD DE PATENTE

1. Su referencia: **AJB/NM/P32461**

2. Solicitud No. **9926441.8** 8 de noviembre de 1999

3. Nombre completo y código postal de cada solicitante:

Dirección: SMITHKLINE BEECHAM
New Horizons Court
Brentford,
Middlesex TW8 9EP

Si el solicitante es una entidad, indique el país/estado de constitución:

GRAN BRETAÑA

ADP No.: 5776299002

4. TITULO DEL INVENTO:

COMPUESTOS

5. NOMBRE DE SU AGENTE:

Nombre del Agente: CORPORATE INTELLECTUAL PROPERTY

Dirección para notificaciones: SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

NO. ADP Patentes 4471231005

6. N/A

7. N/A

8. SI

157
163

9. Número de hojas radicadas (En inglés). Descripción: 20 Reivindicaciones: 3

Resumen : - Dibujos: -

10. Solicitud de examen preliminar y búsqueda

11. Solicitamos se nos adjudique una patente con base en esta solicitud.

A. J. BLAKEY

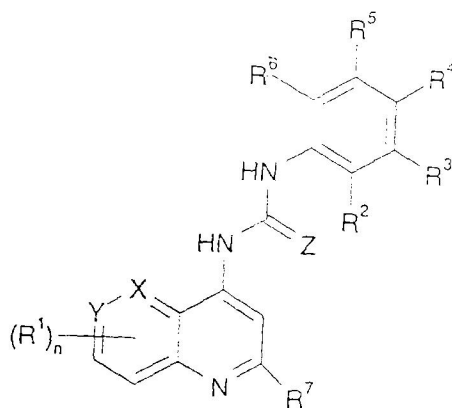
8 de noviembre de 1999

12. Nombre y teléfono del contacto en el Reino Unido Nombre y teléfono del contacto en el
Reino Unido (FIRMA) A. J. BLAKEY 01279 644355

COMPUESTOS

REIVINDICACIONES:

1. Un compuesto de la fórmula (I):



en la cual:

uno de X y Y es N y el otro es CH;

Z representa oxígeno o azufre;

R¹ representa alquil(C₁₋₆), alquenil(C₂₋₆) o alcoxi(C₁₋₆), cualquiera de los cuales puede ser sustituido opcionalmente; halógeno, R⁸CO- o NR⁹R¹⁰CO-;

R², R³, R⁴, R⁵ y R⁶ representan independientemente alquil(C₁₋₆), alquenil(C₂₋₆), alcoxi(C₁₋₆) o alquiltio(C₁₋₆), cualquiera de los cuales puede ser sustituido opcionalmente; hidrógeno, halógeno, nitro, ciano, ariloxi, aril-alquilo(C₁₋₆), aril-alquil(C₁₋₆), R⁸CO-, R⁸SO₂NH-, R⁸CON(R¹¹)-, NR⁹R¹⁰-, NR⁹R¹⁰CO-, -COOR⁹, heterociclil o heterociclil-alquil(C₁₋₆);

o un par adyacente de R², R³, R⁴, R⁵ y R⁶ junto con los átomos de carbono a los que están fijos forman un anillo carbocíclico o heterocíclico sustituido opcionalmente;

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R^7 es alquil(C_{1-6}), alquenal(C_{2-6}), alcoxi(C_{1-6}) o alquiltio(C_{1-6}), cualquiera de los cuales puede ser sustituido opcionalmente; halógeno, hidroxilo, nitrógeno, ciano, NR^9R^{10} - o $NR^9R^{10}CO$ -, N_3 , $-OCOR^9$ o $R^8CON(R^{11})$ -;

R^8 es alquil(C_{1-6}), alquenal(C_{2-6}), heterociclilo, heterociclilo-alquil(C_{1-6}), arilo o arilo-alquil(C_{1-6}), cualquiera de los cuales puede ser sustituido opcionalmente;

R^9 y R^{10} representan independientemente hidrógeno, alquil(C_{1-6}), arilo o arilo-alquil(C_{1-6}), alquenal(C_{2-6}), heterociclilo, heterociclilo-alquil(C_{1-6}), arilo o arilo-alquil(C_{1-6}), cualquiera de los cuales puede ser sustituido opcionalmente;

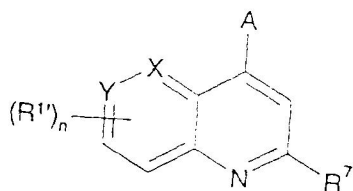
R^{11} es hidrógeno o alquil(C_{1-6}); y

n es 0, 1, 2, 3 ó 4;

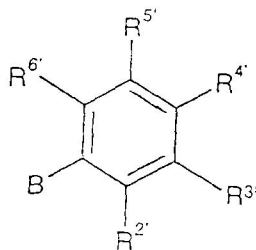
o una sal farmacéuticamente aceptable de lo mismo.

2. Un compuesto según la reivindicación 1, en donde X es N y Y es CH .
3. Un compuesto según la reivindicación 1 ó 2, donde Z representa oxígeno.
4. Un compuesto según la reivindicación 1 ó 2, en donde n es 0 o 1.
5. Un compuesto según cualquiera de las reivindicaciones anteriores donde R^2 a R^6 representan independientemente hidrógeno, R^8CO -, $NR^9R^{10}CO$ -, halógeno, alcoxi(C_{1-6}), alquiltio(C_{1-6}) o NR^9R^{10} , y al menos uno de R^2 a R^6 es diferente de hidrógeno; o un par adyacente de R^2 a R^6 junto con los átomos de carbono a los que están fijos forman un anillo heterocíclico sustituido opcionalmente de 5 a 7 miembros.
6. Un compuesto según cualquiera de las reivindicaciones anteriores en donde R^2 , R^5 y R^6 representan hidrógeno.
7. Un compuesto según cualquiera de las reivindicaciones 1 a 5 en donde R^2 , R^4 y R^6 representan hidrógeno.

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8. Un proceso para la preparación de un compuesto de la fórmula (I) según se define en cualquiera de las reivindicaciones anteriores o sales de lo mismo, que comprende acoplar un compuesto de la fórmula (II):



con un compuesto de la fórmula (III):



donde A y B son grupos funcionales adecuados para formar el medio -NHCONH- o -NHCSHN- cuando están acoplados; n es según se define en la fórmula (I); y R^{1'} a R^{7'} son R¹ a R⁷ según se define en la fórmula (I) o grupos convertibles a ello; y en seguida, opcionalmente y según sea necesario y en cualquier orden apropiado, convertir cualquiera de R^{1'} a R^{7'} cuando otro diferente de R¹ a R⁷ respectivamente a R¹ a R⁷, y/o formar una sal farmacéuticamente aceptable de lo mismo.

9. Una librería de compuestos que comprende al menos de 2 compuestos de la fórmula (I) según se define en cualquiera de las reivindicaciones 1 a 7, o sales farmacéuticamente aceptables de lo mismo.