N-AROYL CYCLIC AMINES

This invention relates to *N*-aroyl cyclic amine 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; nausea and vomiting; 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.

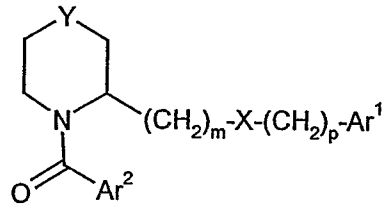
There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. It has been estimated that 5.7% of all healthcare costs in the USA are a consequence of obesity. About 85% of 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, 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 *N*-aroyl cyclic amine 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. Additionally these compounds are useful in the treatment of stroke, particularly ischemic or haemorrhagic stroke, and/or blocking the emetic response, i.e. useful in the treatment of nausea and vomiting.

International Patent Applications WO99/09024, WO99/58533, WO00/47577 and WO00/47580 disclose phenyl urea derivatives and WO00/47576 discloses quinolinyl cinnamide derivatives as orexin receptor antagonists. WO01/96302 discloses N-aroyl cyclic amine derivatives.

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



(I)

wherein:

Y represents a bond, oxygen, or a group $(CH_2)_n$, wherein n represents 1, 2 or 3

m represents 1, 2, or 3;

p represents 0 or 1;

X is NR, wherein R is H or (C_{1-4})alkyl;

Ar^1 is aryl, or a mono or bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S; any of which may be optionally substituted;

Ar^2 represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R^1 and further optional substituents; or Ar^2 represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

R^1 represents hydrogen, optionally substituted$(C_{1-4}$)alkoxy, halo, cyano, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S;

wherein when Y is a bond Ar^2 can not be 2-naphthyl;

when Ar^1 is aryl p is not 1;

or a pharmaceutically acceptable salt thereof.

X is preferably NH.

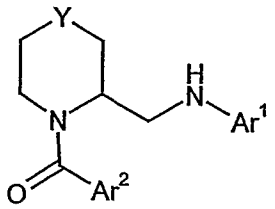
m is preferably 1.

p is preferably 0.

Even more preferably m is 1 when p is 0.

Preferably R is hydrogen.

Alternatively compounds of formula (I) are compounds of formula (Ia);



(Ia)

wherein:

Y represents a bond, oxygen, or a group $(CH_2)_n$, wherein n represents 1, 2 or 3

Ar^1 is a mono or bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S; any of which may be optionally substituted;

Ar^2 represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R^1 and further optional substituents; or Ar^2 represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

R^1 represents hydrogen, optionally substituted(C_{1-4})alkoxy, halo, cyano, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S;

wherein when Y is a bond then Ar^2 can not be 2-naphthyl;

or pharmaceutically acceptable salts thereof.

Preferably where Ar^2 represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, the R^1 group is situated adjacent to the point of attachment to the amide carbonyl.

Y is preferably a bond, oxygen or $(CH_2)_n$ wherein n is 1 or 2.

Even more preferably Y is a bond, oxygen or $(CH_2)_n$ wherein n is 1

Alternatively R^1 represents hydrogen, optionally substituted(C_{1-4})alkoxy, halo, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S.

Alternatively R^1 represents optionally substituted(C_{1-4})alkoxy, halo, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S.

Preferably R^1 is selected from trifluoromethoxy, methoxy, ethoxy, halo, cyano or an optionally substituted phenyl, pyridyl, pyrazolyl, pyrimidinyl, or oxadiazolyl group.

More preferably R^1 is selected from trifluoromethoxy, methoxy, ethoxy, halo, or an optionally substituted phenyl, pyridyl, pyrazolyl, pyrimidinyl, or oxadiazolyl group.

When Ar^1 is optionally substituted aryl it is preferably phenyl. Ar^1 may have up to 5, preferably 1, 2 or 3 optional substituents.

Examples of when Ar^1 is a mono or bicyclic heteroaryl are quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, naphthyridinyl, pyridinyl, pyrimidinyl, or thiazolyl. Additionally Ar^1 can be selected from pyridazinyl, pyrazinyl, oxazolyl, triazolyl, imidazolyl, pyrazolyl, quinolinyl, benzofuranyl, indolyl, benzothiazolyl, oxazolyl[4,5-b]pyridiyl, pyridopyrimidinyl or isoquinolinyl. Furthermore Ar^1 can be furanyl or thienyl.

Preferably Ar^1 is benzoxazolyl, benzimidazolyl, quinoxalinyl, quinazolinyl, pyrimidinyl, pyridinyl, naphthyridinyl, Additionally Ar^1 can be quinolinyl, pyridopyrimidine, thiazolyl, oxazolylpyridinyl, benzothiazolyl, isoquinolinyl or pyrazinyl.

More preferably Ar^1 is benzoxazolyl, benzimidazolyl, quinoxalinyl, quinazolinyl, pyrimidinyl, pyridinyl, naphthyridinyl or oxazolyl[4,5-b]pyridinyl.

When Ar^2 is a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, it may be furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl or pyrazolyl.

When R^1 is a 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S, it may be furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl or pyrazolyl. Additionally it can be tetrazoyl, piperazinyl, piperidinyl, morpholinyl or thiomorpholinyl.

Preferably when R^1 is a 5- or 6-membered heterocyclic ring containing up to 4 heteroatoms selected from N, O and S, it is furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl or pyrazolyl.

Preferably R^1 is a 5- or 6-membered heterocyclic ring it contains up to 3 heteroatoms selected from N, O and S.

When Ar^2 is an optionally substituted bicyclic aromatic or bicyclic heteroaromatic it is selected from benzofuryl, benzimidazolyl, quinolinyl, quinoxalinyl or naphthyl. Additionally it may be benzotriazolyl, benzothienyl, benzoxazolyl, naphthyridinyl, isoquinolinyl or quinazolinyl. Furthermore it can be indolyl, benzothiazolyl, or benzothiadiazolyl.

Preferably Ar^2 represents optionally substituted phenyl, pyridyl, thiazolyl, pyrazolyl, benzofuryl, naphthyl, triazolyl, quinoxalinyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothienyl, benzotriazolyl, benzothiazolyl, indolyl or thienyl.

Alternatively Ar^2 represents optionally substituted phenyl, pyridyl, thiazolyl, pyrazolyl, benzofuryl, naphthyl or triazolyl. Preferably the triazolyl is 1,2,3-triazolyl.

More preferably Ar^2 represents optionally substituted thiazolyl, pyrazolyl or quinolinyl.

Alternatively R^1 is selected from trifluoromethoxy, methoxy, halo, or an optionally substituted phenyl, pyridyl, pyrazolyl or oxadiazolyl group

Even more preferably R^1 represents a trifluoromethoxy group, methoxy group, iodo, or an optionally substituted phenyl, pyridyl, or oxadiazolyl group.

Optional substituents for the groups Ar^1, Ar^2, R and R^1 include halogen, hydroxy, oxo, cyano, nitro, (C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy(C_{1-4})alkyl, hydroxy(C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, aryl(C_{1-4})alkoxy, (C_{1-4})alkylthio, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{3-6})cycloalkyl(C_{1-4})alkoxy, (C_{1-4})alkanoyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylsulfonyl, (C_{1-4})alkylsulfonyloxy, (C_{1-4})alkylsulfonyl(C_{1-4})alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonyl(C_{1-4})alkyl, (C_{1-4})alkylsulfonamido, (C_{1-4})alkylamido, (C_{1-4})alkylsulfonamido(C_{1-4})alkyl, (C_{1-4})alkylamido(C_{1-4})alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamido(C_{1-4})alkyl, arylcarboxamido(C_{1-4})alkyl, aroyl, aroyl(C_{1-4})alkyl, or aryl(C_{1-4})alkanoyl group; a group R^aR^bN-, $R^aOCO(CH_2)_r$, $R^aCON(R^a)(CH_2)_r$, $R^aR^bNCO(CH_2)_r$, $R^aR^bNSO_2(CH_2)_r$ or $R^aSO_2NR^b(CH_2)_r$ where each of R^a and R^b independently represents a hydrogen atom or a (C_{1-4})alkyl group or where appropriate R^aR^b forms part of a (C_{3-6})azacyloalkane or (C_{3-6})(2-oxo)azacycloalkane ring and r represents zero or an integer from 1 to 4. Additional substituents are (C_{1-4})acyl, aryl, aryl(C_{1-4})alkyl, (C_{1-4})alkylamino(C_{1-4})alkyl, $R^aR^bN(CH_2)n$-, $R^aR^bN(CH_2)nO$-, wherein n represents an

integer from 1 to 4. Additionally when the substituent is $R^aR^bN(CH_2)n$- or $R^aR^bN(CH_2)nO$, R^a with at least one CH_2 of the $(CH_2)n$ portion of the group form a (C_{3-6})azacycloalkane and R^b represents hydrogen, a (C_{1-4})alkyl group or with the nitrogen to which it is attached forms a second (C_{3-6})azacycloalkane fused to the first (C_{3-6})azacycloalkane.

Preferred optional substituents for Ar^2 are halogen, cyano, (C_{1-4})alkyl. Additional preferred optional substituents are hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, $R^aR^bN(CH_2)n$, R^aR^bN . Further optional substituents for Ar^2 can also be halogen, cyano, (C_{1-4})alkyl, $R^aR^bN(CH_2)nO$ or (C_{1-4})alkoxy.

Preferred optional substituents for Ar^1 are halogen, cyano, (C_{1-4})alkanoyl. Other preferred substituents are hydroxy(C_{1-4})alkyl, (C_{1-4})alkyl or CF_3.

Preferred optional substituents for R^1 are halogen, (C_{1-4})alkoxy(C_{1-4})alkyl, R^aR^bN, $R^aR^bN(CH_2)nO$ and $R^aR^bN(CH_2)n$. Other preferred substituents are (C_{1-4})alkoxy or (C_{1-4})alkanoyl.

In the groups Ar^1 and Ar^2, substituents positioned *ortho* to one another may be linked to form a ring.

Illustrative compounds of formula (I) are selected from:

Example	Compound Name
1	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone.
2	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-biphenyl-2-yl-methanone
3	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
4	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
5	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-naphthalen-1-yl-methanone
6	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-methoxy-phenyl)-methanone
7	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-iodo-phenyl)-methanone
8	1-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
9	1-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
10	1-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-biphenyl-2-yl-methanone
11	1-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-iodo-phenyl)-methanone
12	1-[2-Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-phenyl-methanone

Example	Compound Name
13	1-{2-[(1H-Benzoimidazol-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
14	1-{2-[(1H-Benzoimidazol-2-ylamino)-methyl]-piperidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
15	1-[2-(Benzothiazol-2-ylaminomethyl)-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
16	1-[2-(Benzothiazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
17	1-[2-(Benzothiazol-2-ylaminomethyl)-piperidin-1-yl]-1-biphenyl-2-yl-methanone
18	1-[2-(Benzothiazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone
19	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(isoquinolin-1-ylaminomethyl)-piperidin-1-yl]-methanone
20	1-[2-(Isoquinolin-1-ylaminomethyl)-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
21	1-[2-(Isoquinolin-1-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
22	1-(2-Iodo-phenyl)-1-[2-(isoquinolin-1-ylaminomethyl)-piperidin-1-yl]-methanone
23	1-[2-(Isoquinolin-1-ylaminomethyl)-piperidin-1-yl]-1-naphthalen-1-yl-methanone
24	1-[2-(Quinoxalin-2-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
25	1-[2-(Quinoxalin-2-ylaminomethyl)-piperidin-1-yl]-1-(3-trifluoromethoxy-phenyl)-methanone
26	1-(2-Iodo-phenyl)-1-[2-(quinoxalin-2-ylaminomethyl)-piperidin-1-yl]-methanone
27	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(quinoxalin-2-ylaminomethyl)-piperidin-1-yl]-methanone
28	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[2-(quinoxalin-2-ylaminomethyl)-piperidin-1-yl]-methanone
29	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(R)-2-(quinazolin-2-ylaminomethyl)-piperidin-1-yl]-methanone
30	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-([1,5]naphthyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone
31	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-([1,8]naphthyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone
32	1-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
33	1-[3-(Benzooxazol-2-ylaminomethyl)-morpholin-4-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

Example	Compound Name
34	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(quinolin-2-ylaminomethyl)-piperidin-1-yl]-methanone
35	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[2-(quinolin-2-ylaminomethyl)-piperidin-1-yl]-methanone
36	1-[2-(Quinolin-2-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
37	1-[2-(Benzothiazol-2-ylaminomethyl)-piperidin-1-yl]-1-naphthalen-1-yl-methanone
38	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(quinolin-2-ylaminomethyl)-piperidin-1-yl]-methanone
39	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(pyrimidin-2-ylaminomethyl)-piperidin-1-yl]-methanone
40	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[2-(pyrimidin-2-ylaminomethyl)-piperidin-1-yl]-methanone
41	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(pyrazin-2-ylaminomethyl)-piperidin-1-yl]-methanone
42	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
43	1-[5-(4-Fluoro-phenyl)-thiazol-4-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
44	1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
45	1-[4-(4-Fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
46	1-[4-(4-Fluoro-phenyl)-1H-pyrazol-3-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
47	1-[5-(3-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
48	1-[5-(3-Fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
49	1-Naphthalen-1-yl-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
50	1-(5-Bromo-2-methoxy-phenyl)-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
51	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
52	1-[(S)-2-(Quinazolin-4-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
53	1-{(S)-2-[(6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
54	1-{(S)-2-[(6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone

Example	Compound Name
55	1-{(S)-2-[(6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
56	1-{(S)-2-[(6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
57	1-{(S)-2-[(6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[2-(4-fluoro-phenyl)-5-methyl-2H-pyrazol-3-yl]-methanone
58	1-{(S)-2-[(6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-methanone
59	1-{(S)-2-[(6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-naphthalen-1-yl-methanone
60	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-quinolin-4-yl-methanone
61	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-oxazol-4-yl]-methanone
62	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
63	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
64	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-(2-trifluoromethoxy-phenyl)-methanone
65	1-Biphenyl-2-yl-1-{(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanone
66	1-(5-Bromo-2-methoxy-phenyl)-1-{(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanone
67	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
68	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-methanone
69	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-methanone
70	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-naphthalen-1-yl-methanone
71	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
72	1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[(R)-2-(quinazolin-2-ylaminomethyl)-piperidin-1-yl]-methanone
73	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[2-(oxazolo[4,5-b]pyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone
74	1-[2-(Oxazolo[4,5-b]pyridin-2-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
75	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(oxazolo[4,5-b]pyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone

Example	Compound Name
76	1-(2-Iodo-phenyl)-1-[2-(oxazolo[4,5-b]pyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone
77	1-{3-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-morpholin-4-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
78	1-{3-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-morpholin-4-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
79	1-{3-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-morpholin-4-yl}-1-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-methanone
80	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(pyrido[2,3-b]pyrazin-2-ylaminomethyl)-piperidin-1-yl]-methanone
81	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(pyrido[2,3-b]pyrazin-3-ylaminomethyl)-piperidin-1-yl]-methanone
82	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[(4-phenyl-thiazol-2-ylamino)-methyl]-piperidin-1-yl}-methanone
93	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-methanone
94	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
95	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(4-fluoro-phenyl)-5-methyl-2H-pyrazol-3-yl]-methanone
96	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-methanone
97	2-(1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanoyl)-benzonitrile
98	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-naphthalen-1-yl-methanone
99	1-(5-Bromo-2-methoxy-phenyl)-1-{2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
100	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
101	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
102	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
103	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
104	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
105	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[(S)-2-(oxazolo[4,5-b]pyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone
106	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-{(S)-2-[(methyl-oxazolo[4,5-b]pyridin-2-yl-amino)-methyl]-piperidin-1-yl}-methanone

Example	Compound Name
83	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-quinoxalin-2-yl-methanone
84	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-quinolin-3-yl-methanone
85	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-isoquinolin-3-yl-methanone
86	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-(2-methoxy-pyridin-3-yl)-methanone
87	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-quinoxalin-6-yl-methanone
88	6-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-nicotinonitrile
89	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(4-trifluoromethyl-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-methanone
90	1-(1H-Benzoimidazol-5-yl)-1-[(S)-2-(pyrido[2,3-b]pyrazin-2-ylaminomethyl)-piperidin-1-yl]-methanone Duplicate of Example 161
91	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[2-dimethylamino-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
92	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[2-(3-dimethylamino-propoxy)-phenyl]-methanone
107	6-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-methyl-amino]-nicotinonitrile
108	1-((S)-2-{[(6,7-Difluoro-quinoxalin-2-yl)-methyl-amino]-methyl}-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone

and pharmaceutically acceptable salts thereof.

Additional compounds of formula (I) are selected from:

Example	Compund Name
109	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-(4-fluoro-benzofuran-2-yl)-methanone
110	2-[((S)-1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-nicotinonitrile
111	2-[((S)-1-{1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanoyl}-piperidin-2-ylmethyl)-amino]-nicotinonitrile
112	2-[((S)-1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-isonicotinonitrile
113	1-Benzo[b]thiophen-2-yl-1-{(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanone
114	1-(1H-Benzoimidazol-5-yl)-1-{(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanone

Example	Compound Name
115	1-(1H-Benzotriazol-5-yl)-1-{(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanone
116	1-Benzothiazol-6-yl-1-{(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanone
117	1-(3,4-Dichloro-phenyl)-1-{(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanone
118	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-(3,4-dimethoxy-phenyl)-methanone
121	1-Isoquinolin-3-yl-1-[(S)-2-(pyrido[2,3-b]pyrazin-2-ylaminomethyl)-piperidin-1-yl]-methanone
122	1-(1H-Indol-5-yl)-1-[(S)-2-(pyrido[2,3-b]pyrazin-2-ylaminomethyl)-piperidin-1-yl]-methanone
123	1-[(S)-2-(Pyrido[2,3-b]pyrazin-2-ylaminomethyl)-piperidin-1-yl]-1-quinolin-4-yl-methanone
124	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-(2-methoxy-ethyl)-1H-pyrazol-3-yl]-methanone
125	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-(2,4-dimethyl-thiazol-5-yl)-methanone
126	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-1-methyl-1H-[1,2,3]triazol-4-yl]-methanone
127	6-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-(2-methoxy-ethyl)-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-nicotinonitrile
128	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
129	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
130	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2H-[1,2,3]triazol-4-yl]-methanone
131	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-quinolin-2-yl-methanone
132	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-1-methyl-1H-[1,2,3]triazol-4-yl]-methanone
133	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
134	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
135	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-quinolin-8-yl-methanone
136	2-{[(S)-1-(1-1H-Benzoimidazol-5-yl-methanoyl)-piperidin-2-ylmethyl]-amino}-6,7-difluoro-quinoline-3-carbonitrile
137	6,7-Difluoro-2-{[(S)-1-(1-isoquinolin-3-yl-methanoyl)-piperidin-2-ylmethyl]-amino}-quinoline-3-carbonitrile

Example	Compound Name
138	6,7-Difluoro-2-[((S)-1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-quinoline-3-carbonitrile
139	6,7-Difluoro-2-{[(S)-1-(1-naphthalen-2-yl-methanoyl)-piperidin-2-ylmethyl]-amino}-quinoline-3-carbonitrile
140	6,7-Difluoro-2-[((S)-1-{1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-quinoline-3-carbonitrile
141	6,7-Difluoro-2-{[(S)-1-(1-1H-indol-6-yl-methanoyl)-piperidin-2-ylmethyl]-amino}-quinoline-3-carbonitrile
142	2-{[(S)-1-(1-Benzothiazol-6-yl-methanoyl)-piperidin-2-ylmethyl]-amino}-6,7-difluoro-quinoline-3-carbonitrile
143	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-naphthalen-2-yl-methanone
144	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-(6-fluoro-benzofuran-2-yl)-methanone
145	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-(5-fluoro-benzofuran-2-yl)-methanone
146	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-(7-fluoro-benzofuran-2-yl)-methanone
147	1-(5,7-Difluoro-benzofuran-2-yl)-1-{(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanone
148	2-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-nicotinonitrile
149	2-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-nicotinonitrile
150	2-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-isonicotinonitrile
151	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-{2-[3-(3-dimethylamino-propoxy)-phenyl]-thiophen-3-yl}-methanone
152	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-{2-[3-(3-dimethylamino-propoxy)-phenyl]-thiophen-3-yl}-methanone
153	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-quinolin-8-yl-methanone
154	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-(1-methyl-1H-indol-2-yl)-methanone
155	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-(1H-indol-6-yl)-methanone
156	1-Benzo[1,2,3]thiadiazol-5-yl-1-{(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanone
157	3-(1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanoyl)-benzoic acid methyl ester
158	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone

Example	Compound Name
159	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
160	1-[4-(4-Fluoro-phenyl)-1-(2-methoxy-ethyl)-1H-pyrazol-3-yl]-1-[(S)-2-(pyrido[2,3-b]pyrazin-2-ylaminomethyl)-piperidin-1-yl]-methanone
162	1-(1H-Benzoimidazol-5-yl)-1-{(S)-2-[(5-bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-methanone
163	1-Benzofuran-2-yl-1-{(S)-2-[(5-bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-methanone
164	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(2-methoxy-phenyl)-methanone
165	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-quinolin-4-yl-methanone
166	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-[3-(3-dimethylamino-propoxy)-phenyl]-methanone
170	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
119	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[1-ethyl-4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
120	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2H-[1,2,3]triazol-4-yl]-methanone
167	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
168	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(2-fluoro-phenyl)-thiazol-4-yl]-methanone
169	1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
171	1-{2-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-pyrimidin-5-yl}-ethanone
172	1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-((S)-2-{[5-(1-hydroxy-ethyl)-pyrimidin-2-ylamino]-methyl}-piperidin-1-yl)-methanone
173	2-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile
174	3-(1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanoyl)-N-methyl-benzamide

and pharmaceutically acceptable salts thereof.

Further compounds of formula (I) are selected from:

Example	Compound Name
175	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-phenyl-methanone

Example	Compound Name
176	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
177	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
178	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-quinolin-8-yl-methanone
179	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-ethoxy-phenyl)-methanone
180	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone
181	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-{5-[3-(3-dimethylamino-propoxy)-phenyl]-2-methyl-thiazol-4-yl}-methanone
182	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-propoxy-phenyl)-methanone
183	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-isopropoxy-phenyl)-methanone
184	1-(2-Benzyloxy-phenyl)-1-{(S)-2-[(5-bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
185	1-[3-(1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanoyl)-4-ethoxy-phenyl]-ethanone
186	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-ethoxy-6-methoxy-phenyl)-methanone
187	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-ethoxy-6-methyl-phenyl)-methanone
188	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-ethoxy-naphthalen-1-yl)-methanone
189	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(2-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
190	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(3-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
191	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(2-fluoro-phenyl)-thiazol-4-yl]-methanone
192	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(5-phenyl-thiazol-4-yl)-methanone

Example	Compound Name
193	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-methyl-4-phenyl-thiazol-5-yl)-methanone
194	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
195	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
196	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-chloro-phenyl)-2-methyl-thiazol-4-yl]-methanone
197	1-{(S)-2-[(5-Bromo-pyridin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
198	1-{(S)-2-[(5-Bromo-pyridin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
199	1-[3-(Benzooxazol-2-ylaminomethyl)-morpholin-4-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
200	1-{3-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-morpholin-4-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
201	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(3-fluoro-phenyl)-thiazol-4-yl]-methanone
202	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-methoxy-phenyl)-2-methyl-thiazol-4-yl]-methanone
203	3,5-Difluoro-4-[((S)-1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-benzonitrile
204	3,5-Difluoro-4-[((S)-1-{1-[4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-benzonitrile
205	3,5-Difluoro-4-[((S)-1-{1-[4-(4-fluoro-phenyl)-1*H*-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-benzonitrile
206	3,5-Difluoro-4-[((S)-1-{1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanoyl}-piperidin-2-ylmethyl)-amino]-benzonitrile
207	4-{[(S)-1-(1-Benzofuran-7-yl-methanoyl)-piperidin-2-ylmethyl]-amine}-3,5-difluoro-benzonitrile
208	3,5-Difluoro-4-[((S)-1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-benzonitrile
209	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-dimethylamino-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
210	1-(2-Amino-5-phenyl-thiazol-4-yl)-1-{(S)-2-[(5-bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone

Example	Compound Name
211	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(3-methoxy-phenyl)-2-methyl-thiazol-4-yl]-methanone
212	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(4-fluoro-phenyl)-thiophen-3-yl]-methanone
213	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-pyridin-2-yl-phenyl)-methanone
214	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-fluoro-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
215	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(4-methoxy-phenyl)-thiophen-3-yl]-methanone
216	1-{(S)-2-[(5-Ethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
217	1-((S)-2-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-pyrrolidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
218	1-((S)-2-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-pyrrolidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazol-3-yl]-methanone
219	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methoxy-thiazol-4-yl]-methanone
220	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-fluoro-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
221	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-phenyl-thiophen-3-yl)-methanone
222	2'-(1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)methyl]-pyrrolidin-1-yl}-methanoyl)-biphenyl-4-carbonitrile
223	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methoxy-phenyl)-thiophen-3-yl]-methanone
224	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-pyrazol-1-yl-phenyl)-methanone
225	1-{2-[((S)-1-{1-[5-(4-Chloro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-pyrimidin-5-yl}-ethanone
226	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
227	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
228	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2[(5-methyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
229	6-[((S)-1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]methanoyl}-pyrrolidin-2-ylmethyl)-amino]-nicotinonitrile
230	5-(1-{2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-methanoyl-)4*H*-benzo[1,4]oxazin-3-one
231	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-(2-piperidin-1-yl-ethyl)-1*H*-pyrazol-3-yl]-methanone

Example	Compound Name
232	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1*H*-pyrazol-3-yl]-methanone
233	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-ethyl-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
234	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(6-methyl-2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
235	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
236	1-{(S)-2-[(Dimethyl-trifluoromethyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
237	1-{(S)-2-[(2,6-Dimethyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
238	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(6-trifluoromethyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
239	1-(3-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-morpholin-4-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
240	1-(3-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-morpholin-4-yl)-1-[2-(4-fluoro-phenyl)-thiophen-3-yl]-methanone
241	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(4-ethyl-quinolin-8-yl)-methanone
242	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-isoquinolin-1-yl-methanone
243	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(2-methyl-quinolin-5-yl)-methanone
244	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1- yl}-1-(3-methyl-quinolin-4-yl)-methanone
245	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1- yl}-1-(2,3-dichloro-phenyl)-methanone
246	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(7-chloro-3-methyl-quinolin-8-yl)-methanone
247	1-[5-(4-Chloro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(5-chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
248	1-{2-[((S)-1-{1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-pyrimindin-5-yl}-ethanone
249	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(5-trifluoromethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
250	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(4-ethyl-quinolin-8-yl)-methanone
251	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-dimethylamino-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
252	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-pyridin-2-yl-phenyl)-methanone

Example	Compound Name
253	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-ethyl-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
254	1-Biphenyl-2-yl-1-{(S)-2-[(5-chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
255	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2,3-dichloro-phenyl)-methanone
256	1-{5-[3-(4-Chloro-butoxy)-phenyl]-2-methyl-thiazol-4-yl}-1-{(S)-2-[(5-chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
257	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
258	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
259	1-{3-[(5-Bromo-pyridin-2-ylamino)-methyl]-morpholin-4-yl}-1-[2-(4-fluoro-phenyl)-thiophen-3-yl]-methanone
260	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[2,4-dimethyl-quinolin-8-yl)-methanone
261	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(2-phenyl-quinolin-4-yl)-methanone
262	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(2-methyl-quinolin-4-yl)-methanone
263	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(6-bromo-quinolin-4-yl)-methanone
264	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(2-methyl-quinolin-8-yl)-methanone
265	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(8-bromo-quinolin-4-yl)-methanone
266	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[1-(3-dimethylamino-propyl)-4-(4-fluorophenyl)-1*H*-pyrazol-3-yl]-methanone
267	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[1-(2-dimethylamino-ethyl)-4-(4-fluorophenyl)-1*H*-pyrazol-3-yl]-methanone
268	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-(2-piperidine-1-yl-ethyl)-1*H*-pyrazol-3-yl]-methanone
269	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-(3-piperidine-1-yl-propyl)-1*H*-pyrazol-3-yl]-methanone
270	1-((S)-2-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-piperidin-1-yl)-1-isoquinolin-1-yl-methanone
271	1-((S)-2-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-piperidin-1-yl)-1-(2,3-dichloro-phenyl)-methanone
272	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[2-dimethylaminomethyl-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
273	1-((S)-2-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-piperidin-1-yl)-1-(3-methyl-quinolin-4-yl)-methanone

Example	Compound Name
274	1-((S)-2-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-piperidin-1-yl)-1-(2-methyl-quinolin-5-yl)-methanone
275	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

and pharmaceutically acceptable salts thereof.

Preferred compounds of formula (I) are selected from:

Example	Compound Name
1	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone
32	1-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
93	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-methanone
105	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[(R)-2-(oxazolo[4,5-b]pyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone
106	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-{(R)-2-[(methyl-oxazolo[4,5-b]pyridin-2-yl-amino)-methyl]-piperidin-1-yl}-methanone
107	6-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-methyl-amino]-nicotinonitrile
108	1-((S)-2-{[(6,7-Difluoro-quinoxalin-2-yl)-methyl-amino]-methyl}-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
171	1-{2-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-pyrimidin-5-yl}-ethanone
172	1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-((S)-2-{[5-(1-hydroxy-ethyl)-pyrimidin-2-ylamino]-methyl}-piperidin-1-yl)-methanone
173	2-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile
174	3-(1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanoyl)-N-methyl-benzamide
194	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
195	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
196	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-chloro-phenyl)-2-methyl-thiazol-4-yl]-methanone

Example	Compound Name
197	1-{(S)-2-[(5-Bromo-pyridin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
198	1-{(S)-2-[(5-Bromo-pyridin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
200	1-{3-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-morpholin-4-yl}-1-[4(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
203	3,5-Difluoro-4-[((S)-1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-benzonitrile
208	3,5-Difluoro-4-[((S)-1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-benzonitrile
216	1-{(S)-2-[(5-Ethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
217	1-((S)-2-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-pyrrolidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
218	1-((S)-2-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-pyrrolidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazol-3-yl]-methanone
225	1-{2-[((S)-1-{1-[5-(4-Chloro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-pyrimidin-5-yl}-ethanone
226	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
227	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
228	1-[5-(4-Fluoro-phenyl)-2-methyl-thaizol-4-yl]-1-{(S)-2-[(5-methyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
229	6-[((S)-1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanyol}-pyrrolidin-2-ylmethyl)-amino]-nicotinonitrile
234	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(6-methyl-2-methylsulfanyl-primidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
235	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
239	1-(3-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-morpholin-4-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
240	1-(3-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-morpholin-4-yl)-1-[2-(4-fluoro-phenyl)-thiophen-3-yl]-methanone
249	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(5-trifluoromethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone

and pharmaceutically acceptable salts thereof.

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

When the compound of formula (I) contains an 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 is preferably methyl or ethyl.

When used herein the term aryl means a 5- to 6- membered aromatic ring for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic for example naphthyl.

It will be appreciated that compounds of formula (I) may exist as *R* or *S* enantiomers. The present invention includes within its scope all such isomers, including mixtures. Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoismers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

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

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

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

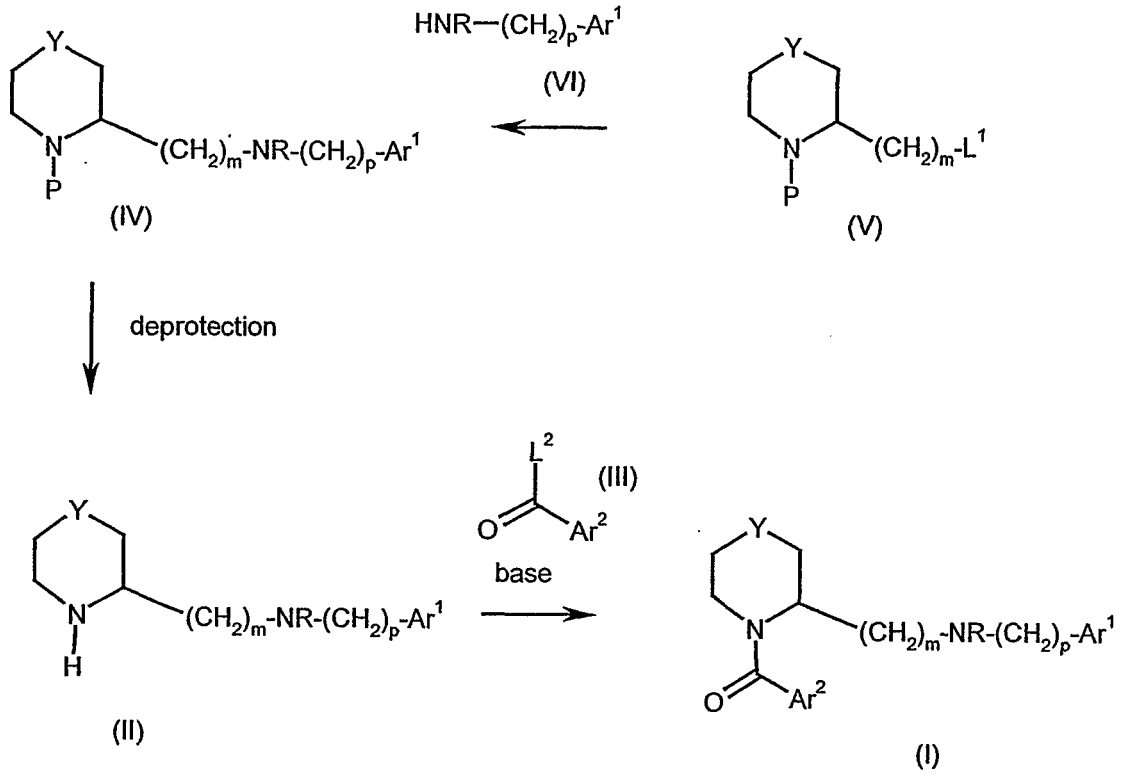
It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic,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

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

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 there is provided a process for the preparation of compounds of formula (I) and derivatives thereof. The following schemes detail some synthetic routes to compounds of the invention.

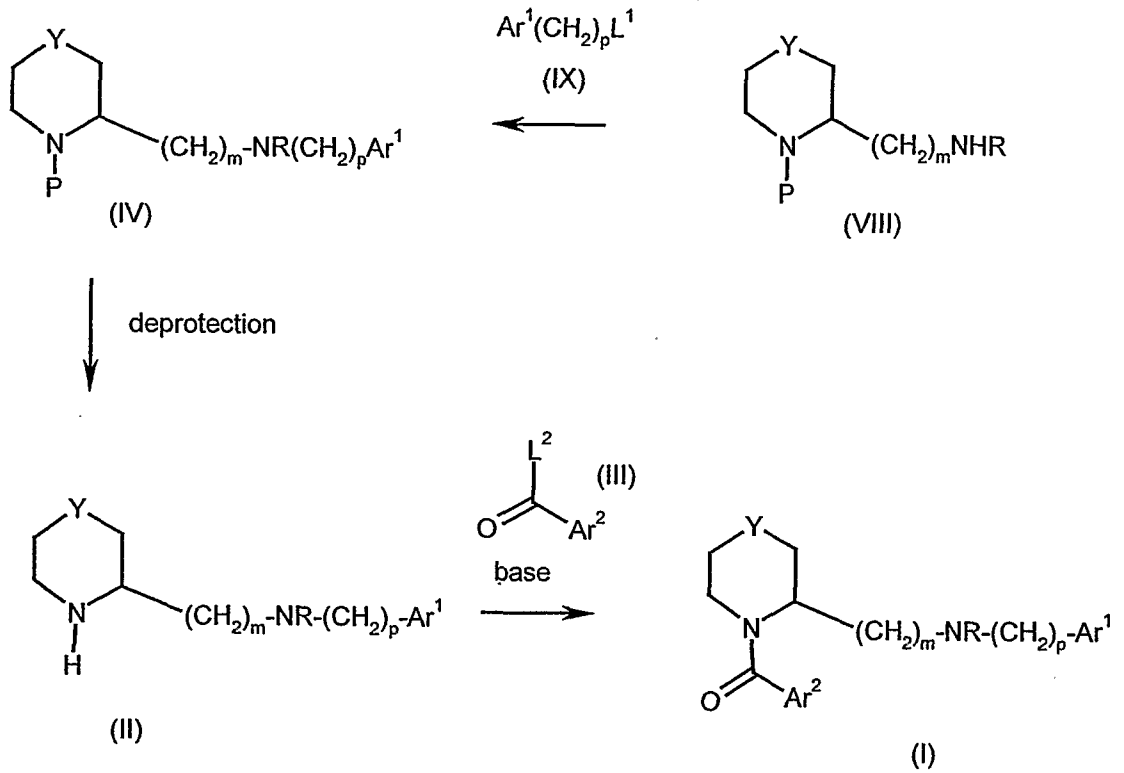
Scheme 1a



wherein Ar^1, Ar^2, Y, m, p and R are as defined for formula (I), L^1 and L^2 are leaving groups, and P is a protecting group.

Examples of suitable leaving groups L^1 include halogen, hydroxy, OSO_2Me, OSO_2(4-tolyl). The reaction of (V) with (VI) preferably proceeds in an inert solvent such as N,N-dimethylformamide in the presence of a base such as triethylamine, sodium hydride or potassium t-butoxide.

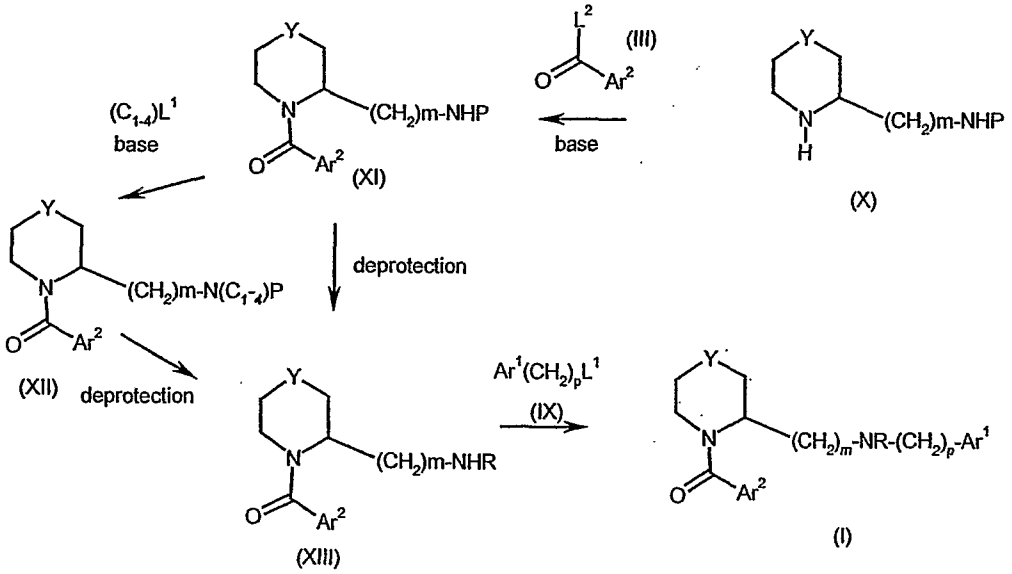
Scheme 1b



Reaction of (VIII) with (IX) proceeds in an inert solvent such as dimethylformamide or xylene in the presence of a base such as potassium carbonate or diisopropylethylamine, preferably at elevated temperatures.

Alternatively where m is 1 and p is 0 or 1 compounds maybe prepared as shown in scheme 1c.

Scheme 1c



Reaction of (XI) with an alkylating agent $(C_{1-4})L^1$ proceeds in the presence of a base such as sodium hydride in an inert solvent such as dimethylformamide.

Examples of suitable leaving groups L^2 include halogen, hydroxy, OC(=O)alkyl and OC(=O)O-alkyl. The transformation (II) to (I) may be carried out in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine. Alternatively this step

may be carried out when L^2 represents hydroxy, in which case reaction with (II) takes place in an inert solvent such as dichloromethane in the presence of a diimide reagent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and an activator such as 1-hydroxybenzotriazole.

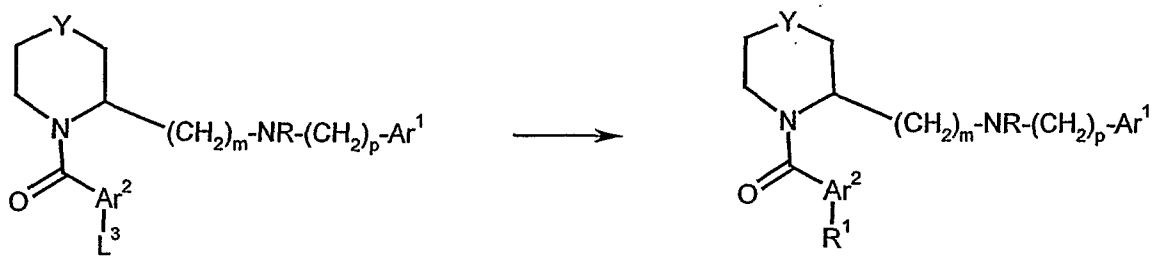
Examples of protecting groups P include *t*-butyloxycarbonyl, trifluoroacetyl, optionally substitued benzyl and benzyloxycarbonyl. Deprotection conditions are respectively, acid (e.g. trifluoroacetic acid in dichloromethane), base (e.g. sodium hydroxide in a solvent such as aqueous methanol) and catalytic hydrogenolysis in an inert solvent (e.g using palladium on charcoal in a lower alcohol or ethyl acetate).

Compounds of formula (V), (VI) and (IX) are known in the literature or can be prepared by known methods. Compounds (VIII) can be prepared by known methods.

Within the schemes above there is scope for functional group interconversion; for example in compound (V), conversion of one value of L^1 to another value of L^1; or in compounds (IV) conversion of protecting group P for another protecting group P, or conversion of one compound of formula (I) to another of formula (I) by interconversion of substituents.

When R^1 is an aromatic group, the substituent R^1 may be introduced at the final stage as illustrated in Scheme 2 by reaction of a compound of formula (VII) where L^3 represents a leaving group such as halogen (preferably bromo or iodo) or trifluoromethylsulfonyloxy, and all other variables are as previously defined, with a reagent R^1M, where M is the residue of an organometallic species e.g. $B(OH)_2$ or trialkylstannyl. Such a process may be carried out in an inert solvent such as 1,2-dimethoxyethane or 1,4-dioxan, in the presence of a transition metal catalyst such as $Pd(PPh_3)_4$.

Scheme 2



(VII) (I)

Wherein Y, Ar^2, m, p, Ar^1, R, R^1 and Y are as defined for compounds of formula (I). L^3 is a leaving group.

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

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

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

The compounds of formula (I) and their pharmaceutically acceptable derivatives are useful for the treatment of diseases or disorders where an antagonist of a human Orexin receptor is required 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; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and 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; delerium; dementia; bulimia and hypopituitarism. Additionally the compounds of formula (I) and pharmaceutically acceptable derivatives are useful for the treatment of stroke, particularly ischemic or haemorrhagic and/or in blocking an emetic response i.e. nausea and vomiting.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, and sleep disorders. Additionally the compounds of formula (I) and pharmaceutically acceptable derivatives are useful for the treatment of stroke, particularly ischemic or haemorrhagic and/or in blocking an emetic response i.e. nausea and vomiting.

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 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 derivative thereof.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Another method involves screening for compounds which inhibit activation of the receptor by determining inhibition of binding of a labelled orexin-1 receptor ligand to cells which have the receptor on their surface. This method involves transfecting a eukaryotic cell with DNA encoding the orexin-1 receptor such that the cell expresses the receptor on its

surface and contacting the cell or cell membrane preparation with a compound in the presence of a labelled form of an orexin-1 receptor ligand. The ligand may contain a radioactive label. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity.

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

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

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The Descriptions D1-D105 illustrate the preparation of intermediates to compounds of the invention.

In the Examples ^{1}H NMR's were measured at 250MHz in $CDCl_3$ unless otherwise stated.

Description 1: (S) 2-Aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester

a) 2,2,2-Trifluoro-N-[(S)-1-((R)-2-hydroxy-1-phenyl-ethyl)-piperidin-2-ylmethyl]-acetamide

(R)-2-[(S)-2-Aminomethyl-piperidin-1-yl])-2-phenyl-ethanol (20.0g) (Froelich, Olivier; Desos, Patrice; Bonin, Martine; Quirion, Jean-Charles; Husson, Henri-Philippe; Zhu, Jieping., J. Org. Chem. 1996, **61**, 6700) and triethylamine (13.0ml) were dissolved in dichloromethane (500ml), cooled to 0°C and trifluoroacetic anhydride (12.66ml) added dropwise. The mixture was warmed to room temperature and stirred overnight. The organic phase was washed with water, separated, dried and solvent removed at reduced pressure. The residue was column chromatographed [silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant] to give the title compound (28.0g) as a yellow oil.

Mass Spectrum (API$^+$): Found 331 (MH^+). $C_{16}H_{21}F_3N_2O_2$ requires 330.

$[\alpha]_D$ -55°@ 28° 1% in chloroform

b) 2,2,2-Trifluoro-N-(S)-1-piperidin-2-ylmethyl-acetamide

2,2,2-Trifluoro-N-[(S)-1-((R)-2-hydroxy-1-phenyl-ethyl)-piperidin-2-ylmethyl]-acetamide (28.0g) was dissolved in ethanol (200ml) containing Pearlmans catalyst (2.0g) and shaken under a hydrogen atmosphere (50psi) at 50°C for 3 hours. The reaction mixture was filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title compound (14.18g) as a colourless oil.

Mass Spectrum (API$^+$): Found 211 (MH^+). $C_8H_{13}F_3N_2O$ requires 210.

$[\alpha]_D$ +18°@ 28° 1% in chloroform

^{1}H NMR δ: (d^6-DMSO) 1.07 (1H, m), 1.32 (2H, m), 1.35 – 1.60 (2H, m), 1.72 (1H, m), 2.54 (1H, t), 2.70 (1H, m), 3.00 (1H, d), 3.17 (3H, m), 9.30 (1H, br. s.)

c) (S)-2-[(2,2,2-Trifluoro-ethanoylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester

2,2,2-Trifluoro-N-(S)-1-piperidin-2-ylmethyl-acetamide (14.18g) was dissolved in dichloromethane (250ml) and treated with di-*tert*-butyl dicarbonate (14.95g). The mixture was stirred for 16h, washed with water, 2N hydrochloric acid and saturated brine, dried and solvent removed at reduced pressure to give the title compound (18.3g)

Mass Spectrum (API$^+$): Found 311 (MH^+). $C_{13}H_{21}F_3N_2O_3$ requires 310.

$[\alpha]_D$ -94°@ 28° 1% in chloroform

^{1}H NMR δ: (d^6-DMSO) 1.27 (1H, m), 1.36, 1.47 (9H, s), 1.49 – 1.58 (5H, m), 2.88 (1H, m), 3.22 (1H, m), 3.49 (1H, m), 3.84 (1H, m), 4.34 (1H, m) and 9.42 (1H, br. s.).

d) (S) 2-Aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester

(S)-2-[(2,2,2-Trifluoro-ethanoylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester (18.2g) was dissolved in methanol (500ml) and treated with potassium carbonate (16.1g). After stirring for 16h solvent was removed at reduced pressure and the residue partitioned between dichloromethane/water. The organic phase was separated, washed with brine, dried and solvent removed at reduced pressure. the residue was column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title compound (8.82g) of description 1.

Mass Spectrum (API$^+$): Found 215 (MH^+). $C_{11}H_{22}N_2O_2$ requires 214.

$[\alpha]_D$ -32.2°@ 28° 1% in chloroform

^{1}H NMR δ: 1.44 (2H, m), 1.50 (9H, s), 2.64 – 2.80 (2H, m), 2.94 (1H, dd), 3.99 (1H, m) and 4.15 (1H, m).

Description 2: (RS) 2-(Benzoxazol-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

(RS) 2-Aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (0.21g) and 2-chlorobenzoxazole (0.153g) and triethylamine (0.1g) were combined in tetrahydrofuran (10ml) and stirred at room temperature for 4 hours. The mixture was partitioned between ethyl acetate and water, the organic phase dried and solvent removed at reduced pressure to give the title compound (0.36g) as an oil that solidified on standing.

Mass Spectrum (API$^+$): Found 332 (MH^+). $C_{18}H_{25}N_3O_3$ requires 331.

Description 3: (RS) Benzoxazol-2-yl-piperidin-2-ylmethyl-amine

The compound of description 2 (0.36g) was stirred in trifluoroacetic acid (10ml) containing water (1 drop) for 3 hours. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title compound (0.23g).

Mass Spectrum (API$^+$): Found 232 (MH^+). $C_{13}H_{17}N_3O$ requires 231.

Description 4: (R)-2-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-2-phenyl-ethanol

A mixture of (R)-2-[(S)-2-Aminomethyl-piperidin-1-yl])-2-phenyl-ethanol (1.0g) (Froelich, Olivier; Desos, Patrice; Bonin, Martine; Quirion, Jean-Charles; Husson, Henri-Philippe;

Zhu, Jieping. J. Org. Chem. 1996, **61**, 6700) and 2-chlorobenzoxazole (0.66g) were combined in tetrahydrofuran (40ml) containing triethylamine (0.43g) and stirred at room temperature for 1 hours. The mixture was partitioned between ethyl acetate and water, the organic phase separated, dried and solvent removed at reduced pressure. the residue was column chromatographed (silica gel, 30% pentane in ethyl acetate – ethyl acetate) to give the title compound (1.1g).
^{1}H NMR δ: 1.59 – 1.71 (4H, m), 1.91 (1H, t), 2.73 (1H, m), 2.95 (1H, m), 3.71 (2H, m), 4.0 (1H, m), 4.10 (1H, m), 4.26 (1H, m), 5.7 (1H, m), 7.03 (1H, m), 7.17 (1H, m), 7.23 – 7.26 (3H, m) and 7.32 – 7.40 (4H, m). Mass Spectrum (API$^+$): Found 352 (MH^+). $C_{21}H_{25}N_3O_2$ requires 351.

Description 5: Benzoxazol-2-yl-(S)-1-piperidin-2-ylmethyl-amine
The compound of description 4 (1.15g) in ethanol (60 ml) containing Pearlmans catalyst (0.23g) was shaken under an atmosphere of hydrogen (50psi) for 24 hours. Additional Pearlmans catalyst was added and shaking under hydrogen at 50psi continued for a further 12 hours. The reaction was filtered through kiesel guhr, the filtrate evaporated at reduced pressure and the residue column chromatographed (silica gel, ethyl acetate – ethyl acetate/methanol 1:1 eluant) to give the title compound (0.49g) as an oil.
^{1}H NMR δ: 1.16 – 1.85 (7H, m), 2.64 (1H, m), 2.85 – 2.99 (1H, m), 3.11 (1H, m), 3.31 (1H, m), 3.55 (1H, m), 7.00 (1H, dd), 7.12 (1H, m), 7.20 (1H, d) and 7.30 (1H, m). Mass Spectrum (API$^+$): Found 232 (MH^+). $C_{13}H_{17}N_3O$ requires 231.

Description 6: (RS)-Benzoxazol-2-yl-(4-benzyl-morpholin-3-ylmethyl)-amine
From (4-benzyl-morpholin-3-yl)-methylamine (1g) (Morie, Toshiya; Kato, Shiro; Harada, Hiroshi; Yoshida, Naoyuki; Fujiwara, Iwao; Matsumoto, Jun-ichi., Chem. Pharm. Bull. 1995, 43, 1137-47) and 2-chlorobenzoxazole (0.78g), the title compound (0.77g) was prepared according to the method of D4.
^{1}H NMR δ: 2.33 (1H, m), 2.73 – 2.80 (2H, m), 3.33 (1H, d), 3.51 – 3.90 (6H, m), 4.10 (1H, d), 5.58 (1H, s), 7.04 (1H, m), 7.17 (1H, m) and 7.24 – 7.39 (7H, m).
Mass Spectrum (API$^+$): Found 324 (MH^+). $C_{19}H_{21}N_3O_2$ requires 323.

Description 7: (RS)-Benzoxazol-2-yl-morpholin-3-ylmethyl-amine
From the compound of D6 (0.77g) the title compound (0.55g) was prepared according to the method of D5.
^{1}H NMR δ: 2.93 – 3.23 (2H, m), 3.46 – 4.03 (7H, m), 6.95 – 7.23 (4H, m). Mass Spectrum (API$^+$): Found 234 (MH^+). $C_{12}H_{15}N_3O_2$ requires 233.

Description 8: (RS) 2-(*1H*-Benzoimidazol-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester
(RS)-2-Aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (0.25g) and 2-chlorobenzimidazole (0.15g) were combined and warmed to 100°C for 48 hours. After cooling to room temperature the mixture was column chromatographed (silica gel, ethyl acetate/pentane 1:4 – ethyl acetate/pentane 1:1 eluant) to give the title compound (0.1g).

^{1}H NMR δ: 1.47 (9H, m), 1.65 – 1.81 (7H, m), 2.85 (1H, t), 3.47 (2H, m), 3.91 (1H, d), 4.32 (1H, s), 5.78 (1H, s), 7.04 (3H, m) and 7.29 (1H, s).
Mass Spectrum (API$^+$): Found 331 (MH^+). $C_{18}H_{26}N_4O_2$ requires 330.

Description 9: (RS)-(*1H*-Benzoimidazol-2-yl)-piperidin-2-ylmethyl-amine dihydrochloride.
The compound of D8 (0.39g) was stirred in a mixture of 4M HCl in dioxan/methanol (1:1) for 4 hours. Solvent was removed at reduced pressure to give the title compound (0.28g) as a foam.
Mass Spectrum (API$^+$): Found 231 (MH^+). $C_{13}H_{18}N_4$ requires 230.

Description 10: (RS) 2-(Quinolin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester
The title compound (0.1g) was prepared from (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (0.5ml) and 2-chloroquinoline (0.5g) according to the procedure of D8.
Mass Spectrum (API$^+$): Found 342 (MH^+). $C_{20}H_{27}N_3O_2$ requires 341.

Description 11: (RS)-Piperidin-2-ylmethyl-quinolin-2-yl-amine
The title compound (0.29g) was prepared from the compound of D10 according to the method of D9. After removal of solvent the residue was dissolved in dichloromethane, washed with saturated sodium hydrogen carbonate, the organic phase separated, dried and solvent removed at reduced pressure to give the title compound.
^{1}H NMR δ: 1.20 – 1.96 (6H, m), 2.64 (1H, m), 2.85 (1H, m), 3.10 (1H, m), 3.35 (1H, m), 3.60 (1H, m), 5.17 (1H, m), 6.66 (1H, d), 7.19 (1H, dt), 7.48 – 7.58 (2H, m), 7.66 (1H, d) and 7.78 (1H, d).
Mass Spectrum (API$^+$): Found 242 (MH^+). $C_{15}H_{19}N_3$ requires 241.

Description 12: (RS)-2-(Benzothiazol-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester
The title compound (1.2g) after column chromatography (silica gel, 5% diethyl ether/hexane – diethyl ether eluant) was prepared from (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (2.0g) and 2-chlorobenzothiazole (1.58g) according to the method of D2.
Mass Spectrum (API$^+$): Found 348 (MH^+). $C_{18}H_{25}N_3O_2S$ requires 347.

Description 13: (RS)-Benzothiazol-2-yl-piperidin-2-ylmethyl-amine
The compound of D12 (1.2g) was dissolved in methanol (60ml) and treated with 4N HCl in dioxan (12 ml). the mixture was stirred for 4h, added to water containing sodium hydrogen carbonate and extracted with ethyl acetate (x 3). The combined organic phase was dried and solvent removed at reduced pressure to give the title compound (0.70g).
Mass Spectrum (API$^+$): Found 348 (MH^+). $C_{13}H_{17}N_3S$ requires 347.

Description 14: 2-(RS)-(Isoquinolin-1-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

The title compound (0.76g) was prepared from (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (1.6ml) and 1-chloroisoquinoline (0.8g) according to the method used for the preparation of the compound of D8.
Mass Spectrum (API$^+$): Found 342 (MH^+). $C_{20}H_{27}N_3O_2$ requires 341.

Description 15: Isoquinolin-1-yl-piperidin-2-ylmethyl-amine
The title compound (0.39g) was prepared according to the method of description 13 from the compound of D14 (0.75g).
Mass Spectrum (API$^+$): Found 242 (MH^+). $C_{15}H_{19}N_3$ requires 241.

Description 16: (S) 2-(Quinolin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester
The title compound (0.11g) was prepared from (S) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (1.23g) and 2-chloroquinoline (1g) according to the procedure of D8.
Mass Spectrum (API$^+$): Found 342 (MH^+). $C_{20}H_{27}N_3O_2$ requires 341.

Description 17: (S)-Piperidin-2-ylmethyl-quinolin-2-yl-amine
The compound of D16 (0.11g) was dissolved in dichloromethane (10ml) and trifluoroacetic acid (1ml) added. The mixture was stirred for 4h, poured into ice containing potassium carbonate and extracted with 10% methanol/dichloromethane (x 3). The combined organic extracts were dried and solvent removed at reduced pressure to give the title compound (0.05g).
Mass Spectrum (API$^+$): Found 242 (MH^+). $C_{15}H_{19}N_3$ requires 241.

Description 18: (RS) 2-(Quinoxalin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester
The title compound (0.73g) was prepared from (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (1ml) and 2-chloroquinoxaline (0.5g) according to the procedure of D8.
Mass Spectrum (API$^+$): Found 343 (MH^+). $C_{19}H_{26}N_4O_2$ requires 342

Description 19: (RS)-Piperidin-2-ylmethyl-quinoxalin-2-yl-amine
The title compound (0.36g) was prepared from the compound of D18 (0.71g) according to the method of D17.
Mass Spectrum (API$^+$): Found 243 (MH^+). $C_{14}H_{18}N_4$ requires 242.

Description 20: (RS) 2-(Pyrimidin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester
A mixture of (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (1.28g) and 2-chloropyrimidine was heated at 100°C for 48 hours. After cooling to room temperature the mixture was column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title compound (0.42g) as an oil.
Mass Spectrum (API$^+$): Found 293 (MH^+). $C_{15}H_{24}N_4O_2$ requires 292.

Description 21: (RS)-Piperidin-2-ylmethyl-pyrimidin-2-yl-amine
The title compound (0.350g) was prepared from the compound of D20 (0.4g) according to the method of D17.
Mass Spectrum (API$^+$): Found 193 (MH^+). $C_{10}H_{16}N_4$ requires 192.

Description 22: (RS) 2-(Pyrazin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester
The title compound (0.18g) was prepared from (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (0.54g) and 2-chloropyrazine according to the method of D20.
Mass Spectrum (API$^+$): Found 293 (MH^+). $C_{15}H_{24}N_4O_2$ requires 292.

Description 23: (RS)-Piperidin-2-ylmethyl-pyrazin-2-yl-amine
The title compound (0.18g) was prepared from the compound of D22 (0.08g) according to the method of D17.
Mass Spectrum (API$^+$): Found 193 (MH^+). $C_{10}H_{16}N_4$ requires 192.

Description 24: (S)-2-(Quinazolin-4-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester
(S)-2-Aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.0g), 4-chloroquinoxaline (0.768g) and diisopropylethylamine (0.816ml) were dissolved in tetrahydrofuran (75ml) and heated to reflux for 6 hours under an atmosphere of argon. After cooling, the reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium hydrogen carbonate solution, saturated brine, dried and evaporated. The residue was chromatographed over silica gel, eluting with a gradient of 50 to 100% ethyl acetate in hexane. The title compound was obtained as a white foam (1.44g).
^{1}H NMR δ: 1.40 (3H, s), 2.90 (1H, dt), 3.35-3.50 (1H, br.), 3.9-4.05 (1H, br.), 4.15-4.3 (1H, br.), 4.68-4.82 (1H, br.), 6.9-7.2 (1H, br.), 7.40 (1H, t), 7.65-7.85 (3H, m), 8.65(1H, s).

Description 25: (S)-2-(Quinazolin-4-ylaminomethyl)-piperidine
(S)-2-(Quinazolin-4-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester (1.2g) was dissolved in trifluoroacetic acid (60ml) and stirred at room temperature for 2 hours. The solution was then evaporated and the residue chromatographed over silica gel, eluting with 0 to 10% (9:1 methanol – concentrated ammonia solution) in dichloromethane. The title compound was obtained as a white foam (0.84g), MH^+ 243.

Description 26: (S)-2-[(6,7-Difluoro-3-methylquinoxalin-2-ylamino)methyl]-piperidine-1-carboxylic acid *tert* buty ester
(S)-2-Aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.14g), and 2-chloro-6,7-difluoro-3-methylquinoxaline *Teng et al PCT Int. Appl (2000), WO00/42026A1 20000720* (1.14g) were dissolved in DMF (2ml) and heated to 90°C for 3 days under an atmosphere of argon. After cooling, the reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with water, saturated brine, dried and evaporated. The

residue was chromatographed over silica gel, eluting with a gradient of 10 to 50% ethyl acetate in hexane. The title compound was obtained as a pink foam (0.524g), MH^+ 393.

Description 27: (S)-2-[(6,7-Difluoro-3-methylquinoxalin-2-ylamino)methyl]-piperidine

(S)-2-[(6,7-Difluoro-3-methylquinoxalin-2-ylamino)methyl]-piperidine-1-carboxylic acid *tert* butyl ester (0.524g) was dissolved in trifluoroacetic acid (15ml) and stirred at room temperature for 3 hours. The solution was then evaporated and the residue chromatographed over silica gel, eluting with 0 to 10% (9:1 methanol – concentrated ammonia solution) in dichloromethane. The title compound was obtained as a white solid (0.289g), MH^+ 293.

Description 28: (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-piperidine-1-carboxylic acid *tert* buty ester

(S)-2-Aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.607g), and 2-chloro-6,7-difluoroquinoxaline *McQuaid et. al. J. Med. Chem. (1992), 35(18), 3319-24* (0.569g) were dissolved in dimethylformamide (1ml) and heated to 90 °C for 5 days under an atmosphere of argon. After cooling, the reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with water, saturated brine, dried and evaporated. The residue was chromatographed over silica gel, eluting with a gradient of 10 to 50% ethyl acetate in hexane. The title compound was obtained as a pale yellow solid (0.460g), MH^+ 379.

Description 29: (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-piperidine

(S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-piperidine-1-carboxylic acid *tert* butyl ester (0.460g) was dissolved in trifluoroacetic acid (10ml) and stirred at room temperature for 3 hours. The solution was then evaporated and the residue chromatographed over silica gel, eluting with 0 to 10% (9:1 methanol – concentrated ammonia solution) in dichloromethane. The title compound was obtained as a pale yellow foam (0.286g), MH^+ 279.

Description 30: (R,S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert* butyl ester

(R,S)-2-Aminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3.0g) and 2-chloro-6,7-difluoroquinoxaline (3.0g) were combined in xylene (20ml) containing diisopropylethylamine (3ml) and heated at 130°C for 24 hours. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, diethyl ether:petroleum ether 1:1) to give the title compound (3.4g)
Mass Spectrum (API$^+$): Found 365 (MH^+). $C_{18}H_{22}F_2N_4O_2$ requires 364.

Description 31: (R,S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-pyrrolidine

The compound of D30 (3.4g) was dissolved in dichloromethane (100ml) and treated with trifluoroacetic acid (15ml). After 3h additional trifluoroacetic acid (40ml) and dichloromethane (100ml) was added. The mixture was stirred for 48h, poured into excess

aqueous sodium hydrogen carbonate, the organic phase separated, dried and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 5% (9:1 methanol/ammonia)/ dichloromethane to give the title compound (0.9g) Mass Spectrum (API$^+$): Found 265 (MH$^+$). $C_{13}H_{14}F_2N_4$ requires 264. ^{1}H NMR δ: 1.56 (1H, m), 1.72 – 1.93 (3H, m), 2.96 (2h, m), 3.28 (1H, m), 3.49 (1H, m), 3.64 (1H, m), 7.39 (1H, dd), 7.59 1H, dd) and 8.16 (1H, s).

Description 32: (S)-2-(quinazolin-2-ylamino)methyl-piperidine-1-carboxylic acid *tert* butyl ester

The title compound (0.6g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.68g) and 2-chloroquinazoline (0.53g) according to the method of D30.

Mass Spectrum (API$^+$): Found 343 (MH$^+$). $C_{19}H_{26}N_4O_2$ requires 342.

Description 33: (S)-1-Piperidin-2-ylmethyl-quinazolin-2-yl-amine

The title compound (0.384g) was prepared from the compound of D32 (0.6g) according to the method of D31

Mass Spectrum (API$^+$): Found 243 (MH$^+$). $C_{14}H_{18}N_4$ requires 242.

^{1}H NMR δ: 1.18 – 1.65 6H, m), 2.66 (1H, m), 3.08 – 3.23 (2H, m), 3.50 (1H, m), 3.69 (1H, m), 6.16 (1h, br. s), 7.20 (1H, t), 7.54 – 7.69 (3H, m) and 8.91 (1H, s).

Description 34: (S)-2-([1,5]Naphthyridin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

The title compound (0.48g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.59g) and 2-chloro-1,5-naphthyridine *Rapoport, et al J. Org. Chem. (1971), 36(3), 450-4* (0.40g) according to the method of D30.

Mass Spectrum (API$^+$): Found 343 (MH$^+$). $C_{19}H_{26}N_4O_2$ requires 342.

Description 35: [1,5]Naphthyridin-2-yl-(S)-1-piperidin-2-ylmethyl-amine

The title compound (0.30g) was prepared from the compound of D34 (0.48g) according to the method of D31.

Mass Spectrum (API$^+$): Found 243 (MH$^+$). $C_{14}H_{18}N_4$ requires 242.

^{1}H NMR δ: 1.25 – 1.88 (6H, m), 2.68 (1H, m), 2.98 (1H, m), 3.16 (1H, m), 3.37 – 3.50 (1H, m), 3.66 (1H, m), 6.85 (1H, d), 7.41 1H, dd), 7.95 (1H, t) and 8.58 (1H, m).

Description 36: (S)-2-(1,8-Naphthyridin-2-ylamino)methyl-piperidine-1-carboxylic acid *tert* butyl ester

The title compound (0.28g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.35g) and 2-chloro-1,8-naphthyridine (0.19g) according to the method of D30.

Mass Spectrum (API$^+$): Found 343 (MH$^+$). $C_{19}H_{26}N_4O_2$ requires 342.

Description 37: [1,8]Naphthyridin-2-yl-(S)-1-piperidin-2-ylmethyl-amine

The title compound (0.11g) was prepared from the compound of D36 (0.28g) according to the method of D31.
Mass Spectrum (API$^+$): Found 243 (MH^+). $C_{14}H_{18}N_4$ requires 242.

Description 38: (RS) 2-(4-Azabenzooxazol-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester
The title compound (0.7g) was prepared from (RS)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.64g) and 2-methylthio-4-azabenzoxazole *Chu-Moyeret al J. Org. Chem. (1995), 60(17), 5721-5.* (0.5g) according to the method of D30.
Mass Spectrum (API$^+$): Found 333 (MH^+). $C_{17}H_{24}N_4O_3$ requires 332.

Description 39: (RS)-Oxazolo[4,5-b]]pyridin-2-yl-piperidin-2-ylmethyl-amine
The title compound (0.55g) was prepared from the compound of D38 (0.7g) according to the method of D31.
Mass Spectrum (API$^+$): Found 233 (MH^+). $C_{12}H_{16}N_4O$ requires 232.

Description 40: ((S)-1-{1-[2-(3-Methyl-[1,2,4]-oxadiazol-5-yl)-phenyl]-methanoyl}-piperidin-2-ylmethyl)-carbamic acid *tert* butyl ester
A mixture of (S)-1-piperidin-2-ylmethyl-carbamic acid tert butyl ester (2.0g) and 2-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (1.9) in dimethylformaide (10ml containing diisopropylethylamine (2.4ml) was treated with [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (3.55g) and stirred at 90°C for 16 hours. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, diethyl ether eluant) to give the title compound (3.4g).
Mass Spectrum (API$^+$): Found 401 (MH^+). $C_{21}H_{28}N_4O_4$ requires 400.

Description 41: 1-((S)-2-Aminomethyl-piperidin-1-yl)-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
The title compound (0.53g) was prepared from the compound of D40 according to the method of D13.
Mass Spectrum (API$^+$): Found 301 (MH^+). $C_{16}H_{20}N_4O_2$ requires 300.

Description 42: Methyl-((S)-1-{1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanoyl}-piperidin-2-ylmethyl)-carbamic acid dimethyl-ethyl ester
((S)-1-{1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanoyl}-piperidin-2-ylmethyl)-carbamic acid *tert* butyl ester (0.4g) in tetrahydrofuran (5ml) was treated with sodium hydride (0.1g). After evolution of hydrogen had ceased iodomethane (0.1ml) was added and the reaction stirred for 16 hours. The reaction was quenched with ice/water, extracted with diethyl ether (x 3), the combined organic extracts dried and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, diethyl ether) to give the title compound (0.2g).
Mass Spectrum (API$^+$): Found 415 (MH^+). $C_{22}H_{30}N_4O_4$ requires 414.

Description 43: 1-[(R)-2-Methylaminomethyl-piperidin-1-yl])-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

The title compound (0.15g) was prepared from the compound of D42 according to the method of D13.

Mass Spectrum (API$^+$): Found 315 (MH$^+$). $C_{11}H_{12}N_4$ requires 314.

Description 44: (S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert* butyl ester

The title compound (0.53g) was prepared from (S)-2-aminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.5g) and 2-chloro-6,7-difluoroquinoxaline (0.5g) according to the method of D30.

Mass Spectrum (API$^+$): Found 365 (MH$^+$). $C_{18}H_{22}F_2N_4O_2$ requires 364.

Description 45: (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-pyrrolidine

The title compound (0.38g) was prepared from the compound of D44 (0.53g) according to the method of D31.

Mass Spectrum (API$^+$): Found 265 (MH$^+$). $C_{13}H_{14}F_2N_4$ requires 264.

Description 46: (RS)-3-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-morpholine-4-carboxylic acid *tert* butyl ester

The title compound (0.58g) was prepared from 2-aminomethylmorpholine-4-carboxylic acid tert-butyl ester (0.82g) and 2-chloro-6,7-difluoroquinoxaline (0.76g) according to the method of D30.

Mass Spectrum (API$^+$): Found 381 (MH$^+$). $C_{18}H_{22}F_2N_4O_3$ requires 380.

Description 47: (6,7-Difluoro-quinoxalin-2-yl)-morpholin-3-ylmethyl-amine

The compound of D46 (0.58g) was dissolved in trifluoroacetic acid and stirred for 3hours. Solvent was removed at reduced pressure and the residue partitioned between aqueous sodium hydrogen carbonate and ethyl acetate. The organic phase was separated dried, solvent removed at reduced pressure and the residue column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane, eluant) to give the title compound (0.327g).

Mass Spectrum (API$^+$): Found 281 (MH$^+$). $C_{13}H_{14}F_2N_4O$ requires 280.

Description 48: 2-(Pyrido[2,3-*b*]pyrazin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert*-butyl ester and 2-(Pyrido[2,3-*b*]-pyrazin-3-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

A mixture of (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (1.0g) and a 2:1 mixture of 2-chloro-pyrido[2,3-b]pyrazine and 3-chloro-pyrido[2,3-b]pyrazine (0.8g) was combined and warmed to 90°C for 18 hours. The mixture was diluted with ethyl acetate, washed with aqueous sodium hydrogen carbonate and water, the organic phase dried and solvent was removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane 0 to 6% ethanol in dichloromethane, 1%

increments) to give as the faster running component 2-(pyrido[2,3-*b*]pyrazin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester (0.48g). mass spectrum (API$^+$): Found 344 (MH$^+$). $C_{17}H_{25}N_5O2$ requires 343 and 2-(pyrido[2,3-*b*]pyrazin-3-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester (0.3g) mass spectrum (API$^+$): Found 344 (MH$^+$). $C_{17}H_{25}N_5O2$ requires 343.

Description 49: Piperidin-2-ylmethyl-pyrido[2,3-*b*]pyrazin-2-yl-amine trifluoroacetate salt

2-(Pyrido[2,3-*b*]pyrazin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester (0.48g) was dissolved in dichloromethane (3ml), cooled (ice bath) and treated with trifluoroacetic acid (2ml). The mixture was stirred for 3hours at room temperature, solvent removed at reduced pressure and the residue co-evaporated with toluene to give the title compound (0.45g).

Mass spectrum (API$^+$): Found 244 (MH$^+$). $C_{13}H_{17}N_5$ requires 243.

Description 50: Piperidin-2-ylmethyl-pyrido[2,3-*b*]pyrazin-3-yl-amine trifluoroacetate salt

The title compound (0.3g) was prepared from 2-(pyrido[2,3-*b*]pyrazin-3-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester (0.3g) according to the method of description 49

Mass spectrum (API$^+$): Found 244 (MH$^+$). $C_{13}H_{17}N_5$ requires 243.

Description 51: 2-Thioureidomethyl-piperidine-1-carboxylic acid *tert* butyl ester

Benzoyl chloride (1.2ml) was added dropwise to sodium thiocyanate (0.90g) in acetone (50ml). When the addition was complete the mixture was refluxed for 15 minutes, cooled to room temperature and (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (2.0g) in acetone (5ml) added. The mixture was refluxed for 2 hours, cooled to room temperature and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title product (1.95g).

Mass spectrum (API$^+$): Found 274 (MH$^+$). $C_{12}H_{23}N_3O_2S$ requires 273.

Description 52: 2-[(4-Phenyl-thiazol-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester

The compound of description 51 (1.95g) was dissolved in ethanol (100ml) containing triethylamine (0.99ml). Phenacyl bromide (1.42g) was added and the mixture stirred for 16 hours. Solvent was removed at reduced pressure and the residue partitioned between ethyl acetate and water. The organic phase was separated and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane eluant) to give the title compound (2.42g).

Mass spectrum (API$^+$): Found 274 (MH$^+$). $C_{20}H_{27}N_3O_2S$ requires 273.

Description 53: (4-Phenyl-thiazol-2-yl)-piperidin-2-ylmethyl-amine

The title compound (1.55g) was prepared from the compound of D52 (2.42g) according to the method of D47.
Mass spectrum (API$^+$): Found 174 (MH$^+$). $C_{15}H_{19}N_3O_2S$ requires 173.

Description 54: 2-[(5-Cyano-pyridin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester.
The title compound (1.54g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (2.0g) and 2-chloro-5-cyanopyridine (1.29g) in the presence of diisopropylethylamine (1.21g) according to the method of D28.
Mass spectrum (API$^+$): Found 317 (MH$^+$). $C_{17}H_{24}N_4O_2$ requires 316.

Description 55: 6-[(Piperidin-2-ylmethyl)-amino]-nicotinonitrile
The title compound (1.56g) was prepared from the compound of D54 (1.53g) and trifluoroacetic acid according to the method of D29.
Mass spectrum (API$^+$): Found 217 (MH$^+$). $C_{12}H_{16}N_4$ requires 216.

Description 56: 2-[(4-Trifluoromethyl-pyrimidin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester
The title compound (0.298g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.0g) and 2-chloro-4-trifluoropyrimidine (0.85g) according to the method of D28.
Mass spectrum (API$^+$): Found 361 (MH$^+$). $C_{16}H_{23}F_3N_4O_2$ requires 360.

Description 57: Piperidin-2-ylmethyl-(4-trifluoromethyl-pyrimidin-2-yl)-amine.
The title compound (0.25g) was prepared from the compound of D56 (0.29g) and trifluoroacetic acid according to the method of D29.
Mass spectrum (API$^+$): Found 261 (MH$^+$). $C_{11}H_{15}F_3N_4$ requires 260.

Description 58: ((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1*H*--pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-carbamic acid *tert* butyl ester
The title compound (3.96g) was prepared from (S)-1-piperidin-2-ylmethyl-carbamic acid *tert* butyl ester (2.14g) and 4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazol-3-yl carboxylic acid (2.20g) according to the method of D40.
Mass spectrum (API$^+$): Found 417 (MH$^+$). $C_{22}H_{29}FN_4O_3$ requires 416.

Description 59: ((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-methyl-carbamic acid dimethyl-ethyl ester.
The title compound (2.0g) was prepared from the compound of description 58 (3.85g) according to the method of D42.
Mass spectrum (API$^+$): Found 431 (MH$^+$). $C_{23}H_{31}FN_4O_3$ requires 430

Description 60: 1-[4-(4-Fluoro-phenyl)-1-methyl-1*H*-pyrazol-3-yl]-1-((S)-2-methylaminomethyl-piperidin-1-yl)-methanone

The title compound (0.15g) was prepared for the compound of D59 (0.50g) according to the method of D29.

Description 61: (S)-2-[(3-Cyano-pyridin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester

The title compound (0.66g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.55g) and 2-chloro-3-cyanopyridine (1.0g) according to the method of D28.

Mass spectrum (API$^+$): Found 317 (MH^+). $C_{17}H_{24}N_4O_2$ requires 316

Description 62: 2-[((S)-1-Piperidin-2-ylmethyl)-amino]-nicotinonitrile

The title compound (0.53g) was prepared from the compound of D61 (0.663g) and trifluoroacetic acid according to the method of D29.

Mass spectrum (API$^+$): Found 217 (MH^+). $C_{12}H_{16}N_4$ requires 216

Description 63: (S)-2-[(4-Cyano-pyridin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester

The title compound (0.24g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.14g) and 2-chloro-4-cyanopyridine (0.74g) according to the method of D28.

Mass spectrum (API$^+$): Found 317 (MH^+). $C_{17}H_{24}N_4O_2$ requires 316

Description 64: 4-Cyano-2-[((S)-1-Piperidin-2-ylmethyl)-amino]-pyridine

The title compound (0.17g) was prepared from the compound of D63 (0.243g) and trifluoroacetic acid according to the method of D29.

Mass spectrum (API$^+$): Found 217 (MH^+). $C_{12}H_{16}N_4$ requires 216

Description 65: (S)2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert butyl carbonate.

(S)-2-Aminomethyl-piperidine-1-carboxylic acid tert butyl ester (1g), 5-bromo-2-chloropyrimidine (0.9g) were combined in xylene (20ml) containing potassium carbonate (1.29g) and diisopropylethylamine (2.43g) and warmed to reflux for 48h. The mixture was cooled to room temperature, filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, pentane – 25% ethyl acetate/pentane). The appropriate fractions were collected, solvent removed at reduced pressure to give the title compound (1.43g) as a colourless gum

Mass spectrum (API$^+$): Found 272 (MH^+ - tert BOC). $C_{10}H_{14}N_4Br$ requires 371

Description 66: (S) (5-Bromo-pyrimidin-2-yl)-piperidin-2-ylmethyl-amine

The title compound (1.40g) was prepared from the compound of D65 (2.1 g) according to the method of D9.

Mass spectrum (API$^+$): Found 272 (MH^+). $C_{10}H_{14}N_4Br$ requires 271.

Description 67: (S) 2-[(3-Cyano-6,7-difluoro-quinolin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester.

(S)-2-Aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.1g) and 2-chloro-3-cyano-5,6-difluoroquinoline (1.12g) according to the method of D28 were combined in xylene (15ml) containing potassium carbonate (4.0g) and diisopropylethylamine (4ml) and boiled for 20 hours. The reaction mixture was cooled to room temperature, filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane eluant) to give after combining appropriate fractions the title compound (1.8g).

Mass spectrum (API$^+$): Found 403 (MH^+). $C_{21}H_{24}F_2N_4O_2$ requires 402

Description 68: (S) 6,7-Difluoro-2-[(piperidin-2-ylmethyl)-amino]-quinoline-3-carbonitrile

The title compound (1.40g) was prepared from the compound of D67 (1.8g) according to the method of D9.

Mass spectrum (API$^+$): Found 303 (MH^+). $C_{16}H_{16}F_2N_4$ requires 302

Description 69: (S)2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-carboxylic acid tert butyl carbonate.

(S)-2-Aminomethyl-pyrrolidine-1-carboxylic acid tert butyl ester (2g), 5-bromo-2-chloropyrimidine (1.93g) were combined in xylene (40ml) containing potassium carbonate (2.76g) and diisopropylethylamine (5.23ml) and warmed to reflux for 20h. The mixture was cooled to room temperature, filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, pentane – 25% ethyl acetate/pentane). The appropriate fractions were collected, solvent removed at reduced pressure to give the title compound (1.78g) as a colourless gum

Mass spectrum (API$^+$): Found 257 (MH^+ - tert BOC). $C_{14}H_{21}BrN_4O_2$ requires 357

Description 70: (S) (5-Bromo-pyrimidin-2-yl)-pyrrolidin-2-ylmethyl-amine

The title compound (1.40g) was prepared from the compound of D69 (1.78 g) according to the method of D9.

Mass spectrum (API$^+$): Found 258 (MH^+). $C_9H_{12}N_4Br$ requires 257.

Description 71: 3-(1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanoyl)-benzoic acid

3-(1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanoyl)-benzoic acid methy ester (0.5g) was dissolved in methanol (15ml) and treated with 1M sodium hydroxide (1.7ml). The reaction mixture was stirred for 12 h, additional 1M sodium hydroxide (1.7ml) added and stirring continued for a further 24h. The reaction mixture was diluted with water and washed with ethyl acetate. The aqueous phase was acidified with 2M hydrochloric acid and extracted with ethyl aceate (x 3). the combined organic phase was dried ($MgSO_4$), fioltered and solvent removed at reduced pressure to give the title compound (0.463g) as a yellow solid.

Mass spectrum (API$^+$): Found 427 (MH^+). $C_{22}H_{20}F_2N_4O_3$ requires 426.

Description 72: 1,1,1-Trifluoromethanesulphonic acid, 5-bromo-pyridin-2-yl ester

To a solution of 5-bromo-2-pyridone (3g) in dichloromethane (60ml) and pyridine (60ml) at 0°C under argon was added dropwise trifluoromethane sulphonic anhydride (5.4g). The resulting mixture was warmed to ambient temperature and after 20h was evaporated and the residue chromatographed on silica gel eluting with ethyl acetate to afford the title product (3.5g) as a yellow oil. ^{1}H NMR δ: 7.10 (1H, d, J = 8 Hz), 8.00 (1H, dd, 2.4 and 8 Hz), 8.46 (1H, d, J = 2.4 Hz).

Description 73: (S)-2-[(5-Bromopyridin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

The title product (0.22g) was obtained from (S)-2-aminomethyl-pyrrolidine-1-carboxylic acid tert butyl ester (1g) and the compound of D72 (1.7g) according to the method of D69. Mass Spectrum (Electrospray LC/MS), API$^+$: Found 356 (MH^+). $C_{15}H_{22}{}^{79}BrN_3O_2$ requires 355.

Description 74: (5-Bromo-pyridin-2-yl)-(S)-1-pyrrolidin-2-ylmethylamine

To a solution of the compound from D73 (0.49g) in dichloromethane (40ml) at ambient temperature was added trifluoroacetic acid (5ml). After 48h, the reaction mixture was evaporated and partitioned between chloroform and 1M sodium hydroxide. The aqueous layer was extracted with chloroform and the combined organic extracts dried and evaporated to afford the title compound (0.33g) as an orange oil. ^{1}H NMR δ: 1.44 - 1.48 (1H, m), 1.71 - 1.81 (3H, m), 2.05 (1H, br s), 2.93 (2H, m), 3.09 - 3.13 (1H, m), 3.35 - 3.41 (2H, m), 4.99 (1H, br s), 6.32 (1H, d, J = 9 Hz), 7.43 (1H, dd, J = 3 and 9 Hz), 8.08 (1H, d, J = 3 Hz).

Description 75: *N*-(4-Benzyl-morpholin-3-ylmethyl)-2,2,2-trifluoroacetamide

To (4-benzyl-morpholin-3-yl)-methylamine (7.34g) in dichloromethane (240ml) was added triethylamine (5.83ml), followed by dropwise addition of trifluoroacetic anhydride (8.23g) over 25 min at 0°C under argon. The reaction mixture was allowed to reach ambient temperature and after stirring for 18h, was diluted in dichloromethane and washed with saturated aqueous sodium hydrogencarbonate. The organic phase was separated, dried and evaporated to afford a brown gum that was purified on silica gel, eluting with ethyl acetate-pentane mixtures to afford the title product (5.17g) as an orange gum. Mass Spectrum (API$^+$): Found 303 (MH^+). $C_{14}H_{17}F_3N_2O_2$ requires 302.

Description 76: 2,2,2-Trifluoro-*N*-morpholin-3-ylmethyl acetamide

To the compound from D75 (1.62g) in methanol (40ml) was added palladium black (0.45g) and formic acid (10 drops) and the mixture stirred at ambient temperature for 16h. Further palladium black (0.225g) and formic acid (10 drops) were added and after 1h, the reaction mixture was filtered through kieselguhr and the filtrate evaporated to an orange gum. Re-

evaporation from dichloromethane provided the title compound (1.4g) as a pink solid. Mass Spectrum (API$^+$): Found 213 (MH$^+$). $C_7H_{11}F_3N_2O_2$ requires 212.

Description 77: 3-[(2,2,2-Trifluoro-ethanoylamino)-methyl]-morpholine-4-carboxylic acid *tert*-butyl ester

A mixture of the compound from D76 (1.75g), triethylamine (2.25ml) and di-*tert*-butyl dicarbonate (3.59g) in dichloromethane (75ml) was stirred at ambient temperature for 18h. The reaction mixture was diluted with dichloromethane and washed successively with 2M hydrochloric acid, water and brine, dried and evaporated to a gum. Chromatography on silica gel eluting with ethyl acetate-pentane mixtures afforded the title compound (1.70g) as a pale yellow solid. Mass Spectrum (API$^+$): Found 213 (MH-^{t}Boc)$^+$. $C_{12}H_{19}F_3N_2O_4$ requires 312.

Description 78: 3-Aminomethyl-morpholine-4-carboxylic acid *tert*-butyl ester

A mixture of the compound from D77 (1.7g) and potassium carbonate (3.77g) in methanol (80 ml) and water (27 ml) was stirred at ambient temperature for 4h and then heated at 50°C for a further 2h. The reaction mixture was concentrated to remove methanol, diluted with water and extracted with ethyl acetate (x3) and dichloromethane (x4). The combined extracts were dried and evaporated to afford the title product (0.97g) as a yellow gum. Mass Spectrum (API$^+$): Found 116 (MH-^{t}Boc)$^+$. $C_{10}H_{20}N_2O_3$ requires 216.

Description 79: 3-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-morpholine-4-carboxylic acid *tert*-butyl ester

The title compound (1.19g) was obtained from the compound of D78 (0.97g) and 5-bromo-2-chloropyrimidine (0.87g) according to the method of D30. Mass spectrum (API$^+$): Found 273 (MH$^+$-^{t}Boc). $C_{14}H_{21}{}^{79}BrN_4O_3$ requires 372.

Description 80: (5-Bromo-pyrimidin-2-yl)-morpholin-3-ylmethyl amine

To the compound of D79 (1.15g) in dichloromethane (45 ml) at 0°C was added trifluoroacetic acid (5 ml) and the reaction mixture then stirred at ambient temperature for 2h. The resulting solution was poured onto ice and saturated aqueous potassium carbonate solution, and then extracted with dichloromethane (x2). The organic extracts were dried and evaporated to afford the title product (0.85g) as an off white solid. Mass Spectrum (API$^+$): Found 273 (MH$^+$). $C_9H_{13}{}^{79}BrN_4O$ requires 272.

Description 81: (S)-2-[(4-Cyano-2,6-difluoro-phenylamino)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester

(S)-2-Aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.36g) and 3,4,5-trifluorobenzonitrile (1.00g) were heated under argon in xylene (10 ml) containing diisopropylethylamine (3.3 ml) for 16h. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic phase was washed with brine, dried and evaporated to give a solid which was triturated with pentane-ether to afford the title product (0.16 g) as an off white powder. Chromatography of the mother liquors on silica gel eluting

with ethyl acetate-pentane mixtures afforded further title product (0.92 g). Mass Spectrum (API^+): Found 252 (MH^+-^{t}Boc). $C_{18}H_{23}F_2N_3O_2$ requires 351.

Description 82: 3,5-Difluoro-4-[((S)-1-piperidin-2-ylmethyl)-amino]-benzonitrile

Trifluoroacetic acid (3 ml) was added to a solution of D81 (1.05 g) in dichloromethane (27 ml) at 0 °C. The reaction was allowed to reach ambient temperature, stirred for 4 h and then poured into saturated aqueous potassium carbonate. The aqueous phase was extracted with dichloromethane and the combined extracts dried and evaporated to afford the title compound (0.59g) as an off white solid. Mass Spectrum (API^+): Found 252 (MH^+). $C_{13}H_{15}F_2N_3$ requires 251.

Description 83: (S)-2-[(4-Cyano-2,6-difluoro-phenylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

The title compound (0.295g) was obtained from (S)-2-aminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.402g) and 3,4,5-trifluorobenzonitrile (0.314g) using a similar procedure to that described in Description 81. Mass Spectrum (API^+): Found 238 (MH^+-^{t}Boc) $C_{17}H_{21}F_2N_3O_2$ requires 337.

Description 84: 3,5-Difluoro-4-[((S)-1-pyrrolidin-2-ylmethyl)-amino]-benzonitrile

The title compound (0.19g) was obtained from the compound of D83 (0.28g) using a similar procedure to that described in Description 82.

Description 85: (S)-2-[(5-Ethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

The title compound (0.10g) was obtained from (S)-2-aminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.75g) and 2-chloro-5-ethyl pyrimidine (0.53g) using a similar procedure to that described in description 81. Mass Spectrum (Electrospray LC/MS): Found 307 (MH^+). $C_{16}H_{26}N_4O_2$ requires 306.

Description 86: (5-Ethyl-pyrimidin-2-yl)-(S)-1-pyrrolidin-2-ylmethylamine

The title compound (0.07g) was obtained from the compound of D85 (0.10g) using the method of D9. Mass Spectrum (Electrospray LC/MS): Found 207 (MH^+). $C_{11}H_{18}N_4$ requires 206.

Description 87: (S)-2-[(2,2,2-Trifluoro-ethanoylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

To a solution of (S)-2-aminomethyl pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.3g) in dichloromethane (50 ml) containing triethylamine (1.4 ml) was added trifluoroacetic anhydride (1.6g) dropwise under argon. After 16h at ambient temperature the reaction mixture was diluted with dichloromethane and washed with brine. The aqueous layer was extracted with dichloromethane and the combined extracts dried and evaporated. Chromatography of the residue on silica gel eluting with pentane-ethyl acetate mixtures afforded the title compound (1.43g) as an orange oil. ^{1}H NMR δ: 1.30 - 1.50 (1H, m), 1.47

(9H, s), 1.60 - 1.75 (1H, m), 1.80 - 1.95 (2H, m), 2.00 - 2.10 (1H, m), 3.22 - 3.30 (1H, m), 3.30 - 3.55 (3H, m), 9.03 (1H, br s).

Description 88: (S)-2-{[Methyl-(2,2,2-trifluoro-ethanoyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

Sodium hydride (0.23g, 60 % dispersion in oil) was added to a solution of the compound of D87 (1.4g) in dimethylformamide (30 ml) under argon. After 1h, iodomethane (0.32 ml) was added and the reaction mixture stirred for a further 16h before being partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined extracts washed with brine, dried and evaporated to give the title compound (1.6g) as an orange oil. Mass Spectrum (API^+): Found 311 (MH^+). $C_{13}H_{21}F_3N_2O_3$ requires 310.

Description 89: (S)-2-Methylaminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester

A mixture of the compound of D88 (1.47g) and 1M potassium carbonate (20 ml) in methanol (50 ml) was stirred at ambient temperature for 20 h. After removal of the methanol *in vacuo*, the residue was partitioned between chloroform and water. The aqueous layer was extracted with chloroform and the combined extracts dried and evaporated to afford the title product (0.82g) as an orange oil.

Description 90: (S)-2-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

The title product (0.85g) was obtained from the compound of D89 (0.82g) and 5-bromo-2-chloro pyrimidine (0.77g) in a similar manner to that described in the procedure of description 81. Mass Spectrum (API^+): Found 371 (MH^+). $C_{15}H_{23}{}^{79}BrN_4O_2$ requires 370.

Description 91: (5-Bromo-pyrimidin-2-yl)-methyl-(S)-1-pyrrolidin-2-yl)methylamine

A solution of the compound from D90 (0.82g) in dichloromethane (50 ml) and trifluoroacetic acid (10 ml) was stirred at ambient temperature for 20 h. evaporated and partitioned between ethyl acetate and 1M sodium hydroxide. The organic phase was separated, dried and evaporated to afford the title product as an orange oil (0.54g). Mass Spectrum (API^+): Found 271 (MH^+). $C_{10}H_{15}{}^{79}BrN_4$ requires 270.

Description 92: (S)-2-[(5-Acetyl-pyrimidin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

The title compound (0.57g) was prepared from the compound of D69 (1.06g) (1-ethoxyvinyl)tributyl tin (1.2 ml) and tetrakis (triphenylphosphine)palladium (0) (0.172g) according to the method of Example 171. Mass Spectrum (API^+): Found 321 (MH^+). $C_{16}H_{24}N_4O_3$ requires 320.

Description 93: 1-{2-[((S)-1-Pyrrolidin-2-ylmethyl)-amino]-pyrimidin-5-yl}-ethanone trifluoroacetate

To a solution of the compound of D92 (0.57g) in dichloromethane (18ml) at 0°C was added trifluoroacetic acid (2ml) dropwise. The reaction mixture was stirred at ambient temperature for 2h, and evaporated to afford the title compound as a yellow gum (1.13g). Mass Spectrum (API$^+$): Found 221 (MH^+). $C_{11}H_{16}N_4O$ requires 220.

Description 94: (S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

(S)-2-Aminomethyl pyrrolidine-1-carboxylic acid *tert*-butyl ester (3.38g), 2,5-dichloropyrimidine (2.50g), potassium carbonate (4.67g) and diisopropylethylamine (8.79ml) were heated in xylene (60 ml) at 100°C for 3.75h. The cooled reaction mixture was filtered and the filtrate evaporated to a gum which was chromatographed on silica gel, eluting with ethyl acetate-pentane fractions, to afford the title compound as a pale yellow solid (2.55g). Mass Spectrum (API$^+$): Found 213 (MH^+-^{t}Boc). $C_{14}H_{21}{}^{35}ClN_4O_2$ requires 312.

Description 95: (5-Chloro-pyrimidin-2-yl)-(S)-1-pyrrolidin-2-ylmethylamine

The compound of D94 (2.5g) was dissolved in dichloromethane (63 ml), cooled to 0°C and trifluoroacetic acid (7 ml) added dropwise. The reaction mixture was stirred at ambient temperature for 2h, recooled to 0°C and further trifluoroacetic acid (3 ml) added. After 2h at ambient temperature the mixture was carefully poured into ice-saturated potassium carbonate and the organic layer separated. The aqueous phase was extracted with dichloromethane (x4) and the combined extracts dried and evaporated to afford the title product (1.74g) as an orange solid. Mass Spectrum (Electrospray LC/MS): Found 213 (MH^+). $C_9H_{13}{}^{35}ClN_4$ requires 212.

Description 96: (S)-2-[(5-Cyano-pyridin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

(S)-2-Aminomethyl pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.3g), 6-chloronicotinonitrile (0.21g), potassium carbonate (0.41g) and diisopropylethylamine (0.78 ml) were heated in xylene at 130°C for 26h, cooled and the mixture filtered through kieselguhr. The filtrate was evaporated and the residue chromatographed on silica gel, eluting with ethyl acetate-hexane mixtures to afford the title compound (0.2g). Mass Spectrum (API$^+$): Found 303 (MH^+). $C_{16}H_{22}N_4O_2$ requires 302.

Description 97: 6-[((S)-1-Pyrrolidin-2-ylmethyl)-amino]-nicotinonitrile

A solution of the compound of D96 (0.2g) in dichloromethane (20 ml) and trifluoroacetic acid (2.5 ml) was stirred at ambient temperature for 2h., evaporated and partitioned between dichloromethane and 1M sodium hydroxide. The aqueous phase was extracted with dichloromethane and the combined extracts dried and evaporated to afford the title compound as a gum (0.137g). Mass Spectrum (Electrospray LC/MS): Found 203 (MH^+). $C_{11}H_{14}N_4$ requires 202.

Description 98: 1,1,1-Trifluoromethanesulfonic acid 6-methyl-2-methylsulfanyl-pyrimidin-4-yl ester

To a solution of 6-methyl-2-methylsulfanyl-pyrimidin-4-ol (1g) in dichloromethane (40 ml) containing triethylamine (1.35 ml) at 0°C under argon was added trifluoromethanesulphonic anhydride (1.46 ml) dropwise. The resulting solution was allowed to reach ambient temperature and stirred for 16h. before being partitioned between dichloromethane and saturated aqueous sodium hydrogen carbonate solution. The organic phase was washed with brine, dried and evaporated and the residue chromatographed on silica gel, eluting with ethyl acetate-pentane mixtures, to afford the title compound (0.8g). ^{1}H NMR δ: 2.53 (3H, s), 2.55 (3H, s), 6.63 (1H, s).

Description 99: 2,2,2-Trifluoro-*N*-(S)-1-pyrrolidin-2-ylmethyl-acetamide

The title compound (2.31g) was obtained from the compound of D87 (5.5g) using the method of D97. ^{1}H NMR δ: 1.30 - 1.50 (1H, m), 1.70 - 1.95 (3H, m), 2.20 (1H, br s), 2.85 - 2.90 (1H, m), 2.94 - 2.97 (1H, m), 3.07 - 3.12 (1H, m), 3.37 - 3.39 (1H, m), 3.44 - 3.48 (1H, m), 7.15 (1H, br s).

Description 100: 2,2,2-Trifluoro-*N*-((S)-1-{1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-acetamide

The title compound (3.84g) was obtained from the compound of D99 (2.31g) and 5-(4-fluorophenyl)-2-methyl-thiazole-4-carboxylic acid (3.08g) using the method of Example 229. Mass Spectrum (Electrospray LC/MS): Found 416 (MH^+). $C_{18}H_{17}F_4N_3O_2S$ requires 415.

Description 101: 1-((S)-2-Aminomethyl-pyrrolidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (2.45g) was obtained from the compound of D100 (3.84g) using a similar procedure to that described in D78. Mass Spectrum (Electrospray LC/MS): Found 320 (MH^+). $C_{16}H_{18}FN_3OS$ requires 319.

Description 102: 3-[(2,2,2-Trifluoro-ethanoylamino)-methyl]-morpholine-4-carboxylic acid *tert*-butyl ester

The title compound (0.56g) was obtained from the compound of D77 (0.55g) and iodomethane (0.12 ml) using a method similar to that of Description 88. Mass Spectrum (API$^+$): Found 227 (MH^+-^{t}Boc). $C_{13}H_{21}F_3N_2O_4$ requires 326.

Description 103: 3-Methylaminomethyl-morpholine-4-carboxylic acid *tert*-butyl ester

The title compound (0.29g) was obtained from the compound of D102 (0.56g) using the method of Description 89.

Description 104: 3-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-morpholine-4-carboxylic acid *tert*-butyl ester

The title compound (0.3g) was obtained from the compound of D103 (0.29g) and 5-bromo-2-chloropyrimidine (0.26g) using the method of Description 81. Mass Spectrum (Electrospray LC/MS): Found 287 (MH^+-^{t}Boc). $C_{15}H_{23}{}^{79}BrN_4O_3$ requires 386.

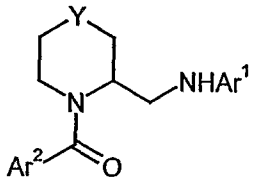
Description 105: (5-Bromo-pyrimidin-2-yl)-methyl-morpholin-3-ylmethyl-amine

The title compound (0.19g) was obtained from the compound of D104 (0.3g) according to the method of Description 91. Mass Spectrum (API$^+$): Found 287 (MH^+). $C_{10}H_{15}{}^{79}BrN_4O$ requires 286.

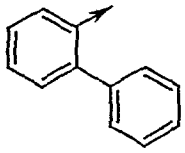
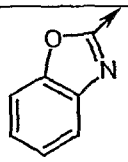
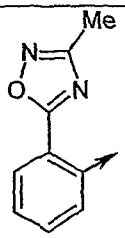
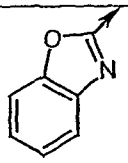
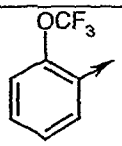
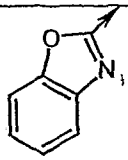
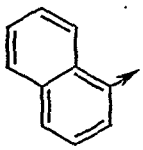
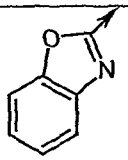
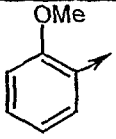
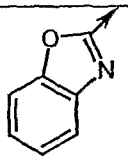
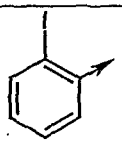
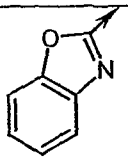
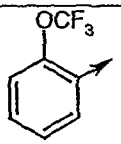
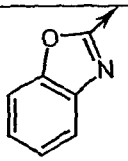
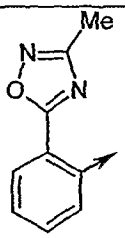
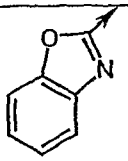
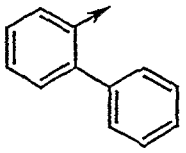
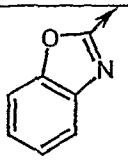
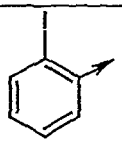
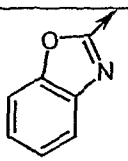
Example 1: 1-[2-(Benzoxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone

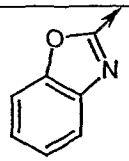
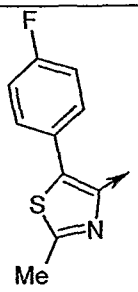
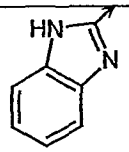
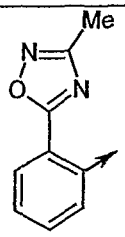
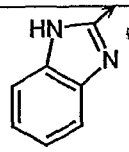
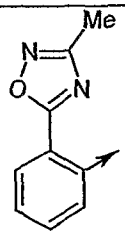
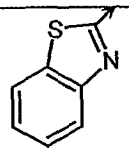
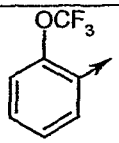
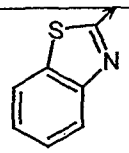
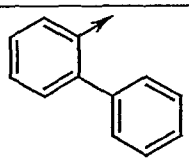
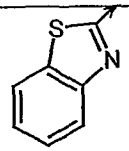
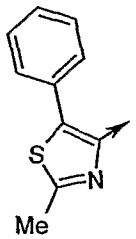
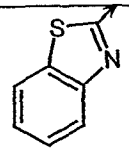
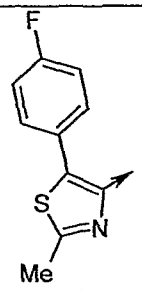
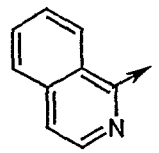
The amine of D3 (0.11g), triethylamine (0.05g) and 2-methyl-5-phenyl-thiazole-4-carbonyl chloride (0.12g) were combined in dichloromethane (5ml) and shaken for 16 hours. The organic phase was washed with water, filtered through a Whatman phase-separation filter tube, solvent removed at reduced pressure to give after column chromatography (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) the title compound (0.13g). Mass Spectrum (API$^+$): Found 433 (MH^+). $C_{24}H_{24}N_4O_2S$ requires 432.

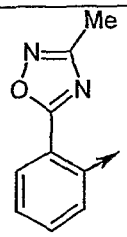
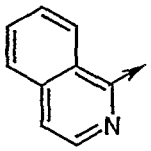
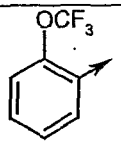
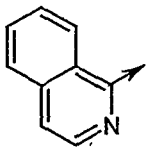
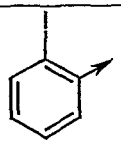
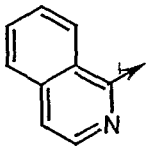
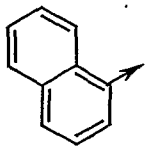
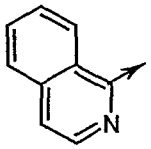
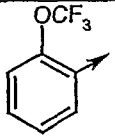
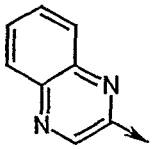
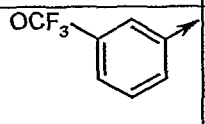
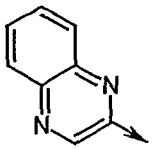
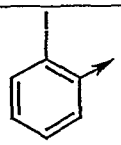
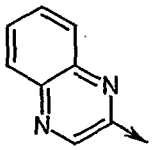
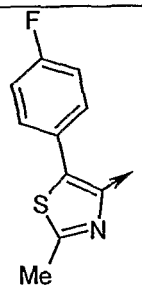
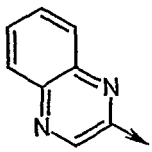
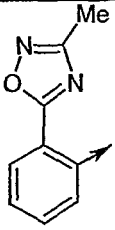
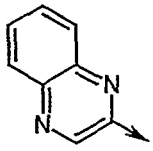
The compounds of the Examples below were prepared from the appropriate amine and acid chloride using a similar procedure to that described in Example 1.

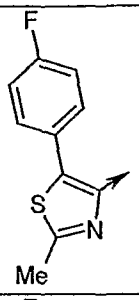
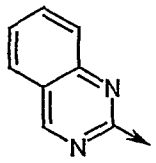
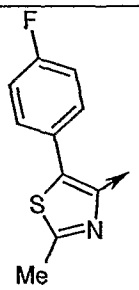
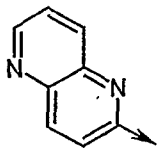
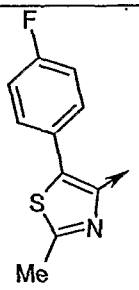
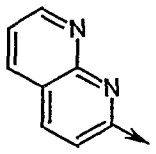


Example	Amine	Y	Ar^2	Ar^1	Mass Spectrum (Electrospray LC/MS) API$^+$

2	D3	CH_2			Found 412 (MH^+). $C_{26}H_{25}N_3O_2$ requires 411
3	D3	CH_2			Found 418 (MH^+). $C_{23}H_{23}N_5O_3$ requires 417
4	D3	CH_2			Found 420 (MH^+). $C_{21}H_{20}F_3N_3O_3$ requires 419
5	D3	CH_2			Found 386 (MH^+). $C_{24}H_{23}N_3O_2$ requires 385
6	D3	CH_2			Found 366 (MH^+). $C_{21}H_{23}N_3O_3$ requires 365
7	D3	CH_2			Found 462 (MH^+). $C_{20}H_{20}IN_3O_2$ requires 461
8	D5	CH_2			Found 420 (MH^+). $C_{21}H_{20}F_3N_3O_3$ requires 419
9	D5	CH_2			Found 418 (MH^+). $C_{23}H_{23}N_5O_3$ requires 417
10	D5	CH_2			Found 412 (MH^+). $C_{26}H_{25}N_3O_2$ requires 411
11	D5	CH_2			Found 462 (MH^+). $C_{20}H_{20}IN_3O_2$ requires 461

12	D3	CH_2	Ph		Found 336 (MH^+). $C_{20}H_{21}N_3O_2$ requires 335
13	D9	CH_2			Found 450 (MH^+). $C_{24}H_{24}FN_5OS$ requires 449
14	D9	CH_2			Found 417 (MH^+). $C_{23}H_{24}N_6O_2$ requires 416
15	D13	CH_2			Found 434 (MH^+). $C_{23}H_{23}N_5O_2S$ requires 433
16	D13	CH_2			Found 436 (MH^+). $C_{21}H_{20}F_3N_3O_2S$ requires 435
17	D13	CH_2			Found 428 (MH^+). $C_{26}H_{25}N_3OS$ requires 427
18	D13	CH_2			Found 449 (MH^+). $C_{24}H_{24}N_4OS_2$ requires 448
19	D15	CH_2			Found 461 (MH^+). $C_{26}H_{25}FN_4OS$ requires 460

20	D15	CH_2			Found 428 (MH^+). $C_{25}H_{25}N_5O_2$ requires 427
21	D15	CH_2			Found 430 (MH^+). $C_{23}H_{22}F_3N_3O_2$ requires 429
22	D15	CH_2			Found 472 (MH^+). $C_{22}H_{22}IN_3O$ requires 471
23	D15	CH_2			Found 396 (MH^+). $C_{26}H_{25}N_3O$ requires 395
24	D19	CH_2			Found 431 (MH^+). $C_{22}H_{21}F_3N_4O_2$ requires 430
25	D19	CH_2			Found 431 (MH^+). $C_{22}H_{21}F_3N_4O_2$ requires 430
26	D19	CH_2			Found 473 (MH^+). $C_{21}H_{21}IN_4O$ requires 472
27	D19	CH_2			Found 462 (MH^+). $C_{25}H_{24}FN_5OS$ requires 461
28	D19	CH_2			Found 429 (MH^+). $C_{24}H_{24}N_6O_2$ requires 428

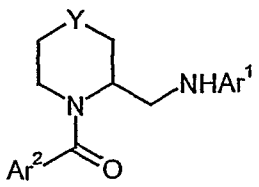
29	D33	CH_2			Found 462 (MH^+). $C_{25}H_{24}FN_5OS$ requires 461
30	D35	CH_2			Found 462 (MH^+). $C_{25}H_{24}FN_5OS$ requires 461
31	D37	CH_2			Found 462 (MH^+). $C_{25}H_{24}FN_5OS$ requires 461

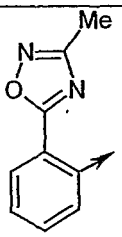
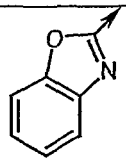
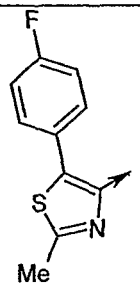
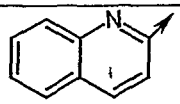
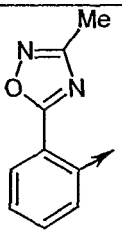
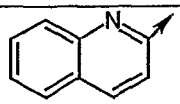
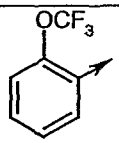
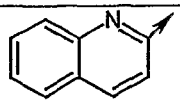
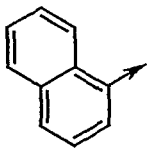
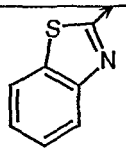
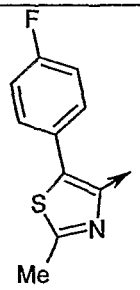
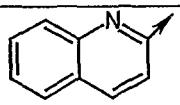
Example 32: 1-[(S)-2-(Benzoxazol-2-ylaminomethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

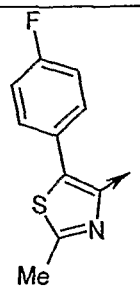
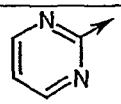
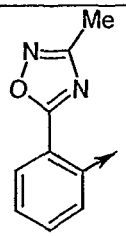
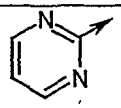
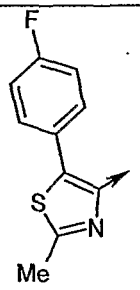
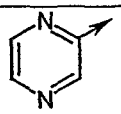
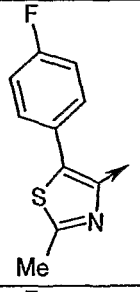
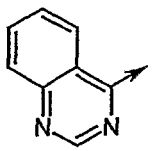
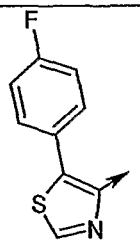
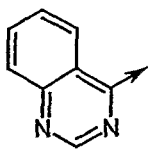
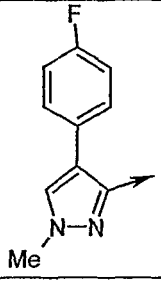
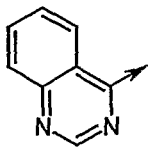
A mixture of amine D5 (0.05g), 2-methyl-5-phenyl-thiazole-4-carboxylic acid (0.026g) and diisopropylethylamine (0.06ml) in dimethylformamide (5ml) was treated with [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (0.042g) and the mixture stirred for 48 hours. The mixture was diluted with ethyl acetate, washed with sodium hydrogen carbonate and water, dried, solvent removed at reduced pressure and the residue column chromatographed (silica gel, dichloromethane – 1% methanol/dichloromethane) to give the title compound (0.05g).

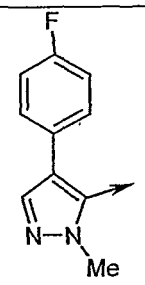
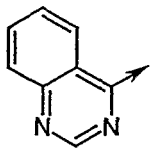
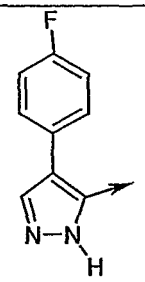
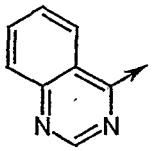
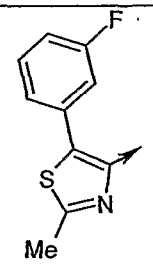
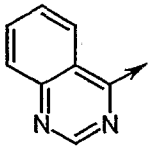
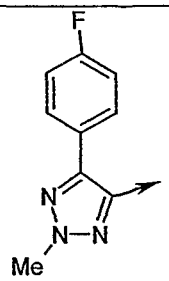
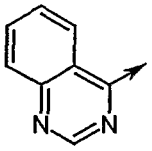
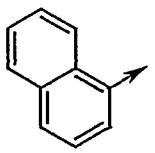
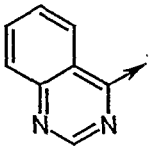
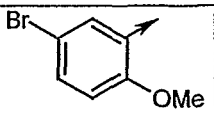
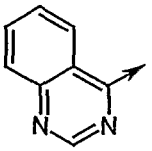
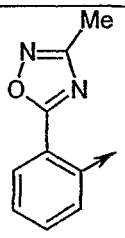
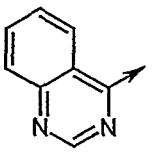
Mass Spectrum (API^+): Found 451 (MH^+). $C_{24}H_{23}FN_4O_2S$ requires 450.

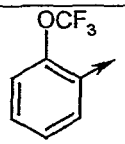
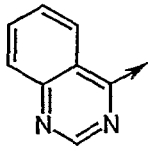
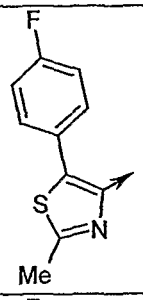
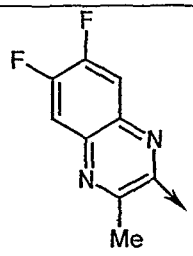
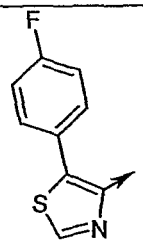
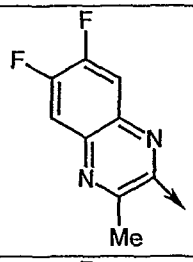
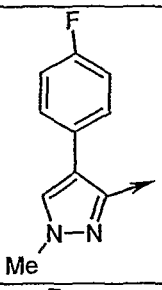
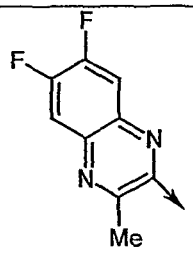
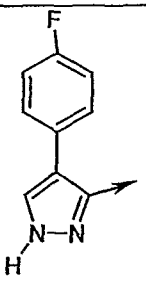
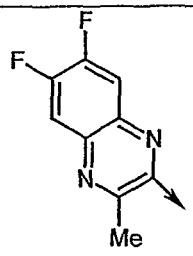
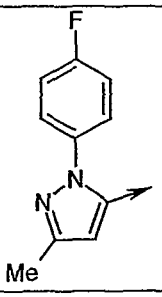
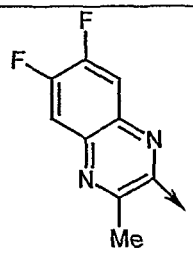
The compounds of the Examples below were prepared from the appropriate amine and acid using similar procedures to that described in Example 32.

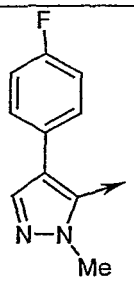
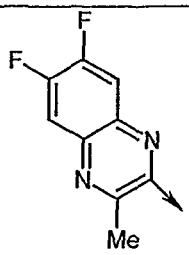
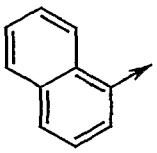
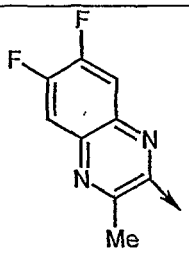
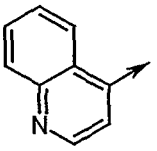
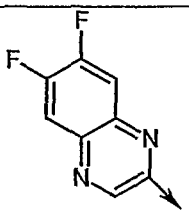
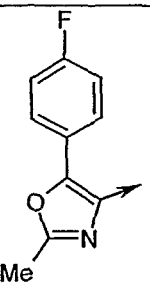
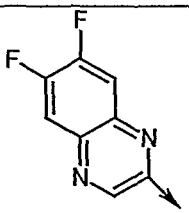
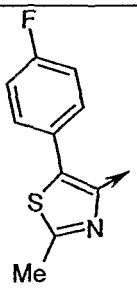
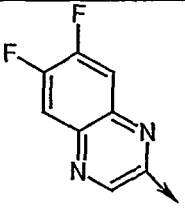
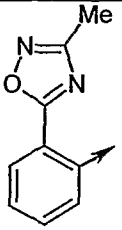
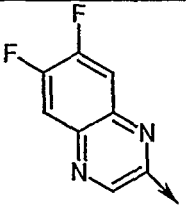
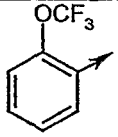
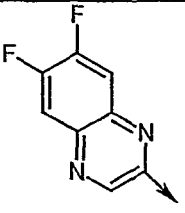


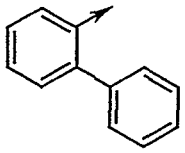
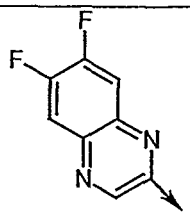
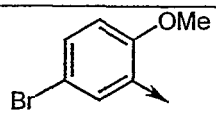
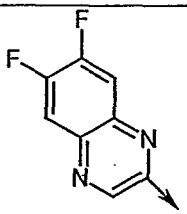
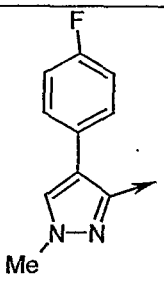
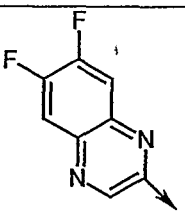
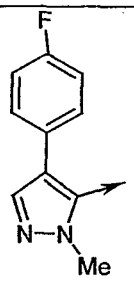
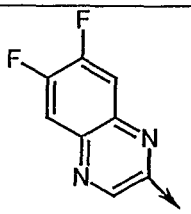
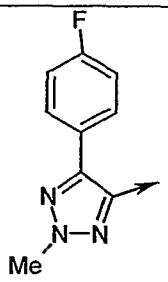
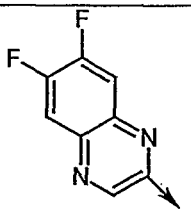
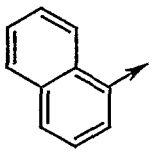
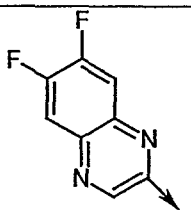
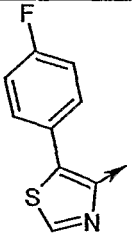
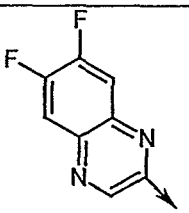
Example	Amine	Y	Ar^2	Ar^1	Mass Spectrum (Electrospray LC/MS), API^+
33	D7	O			Found 420 (MH^+). $C_{22}H_{21}N_5O_4$ requires 419
34	D11	CH_2			Found 461 (MH^+). $C_{26}H_{25}FN_4OS$ requires 460
35	D11	CH_2			Found 428 (MH^+). $C_{25}H_{25}N_5O_2$ requires 427 Prepared as the HCl salt
36	D11	CH_2			Found 430 (MH^+). $C_{23}H_{22}F_3N_3O_2$ requires 429 Prepared as the HCl salt
37	D13	CH_2			Found 402 (MH^+). $C_{24}H_{23}N_3OS$ requires 401
38	D17	CH_2			Found 461 (MH^+). $C_{26}H_{25}FN_4OS$ requires 460

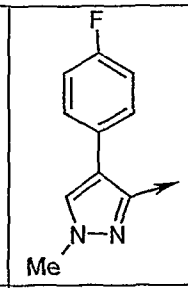
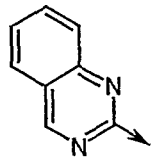
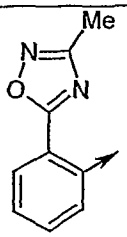
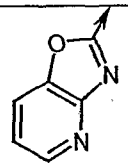
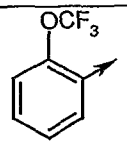
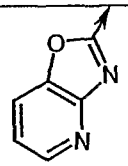
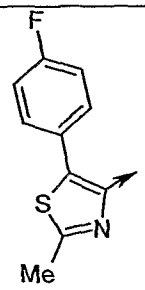
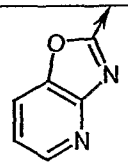
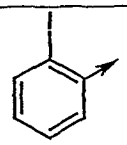
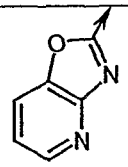
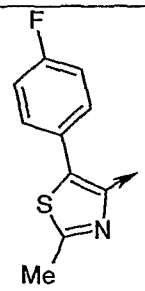
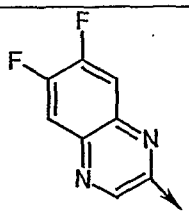
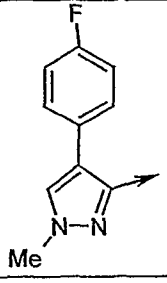
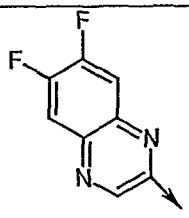
39	D21	CH_2			Found 412 (MH^+). $C_{21}H_{22}FN_5OS$ requires 411
40	D21	CH_2			Found 379 (MH^+). $C_{20}H_{22}N_6O_2$ requires 378
41	D23	CH_2			Found 412 (MH^+). $C_{21}H_{22}FN_5OS$ requires 411
42	D25	CH_2			Found 462 (MH^+). $C_{25}H_{24}FN_5OS$ requires 461
43	D25	CH_2			Found 448 (MH^+). $C_{24}H_{22}FN_5OS$ requires 447
44	D25	CH_2			Found 445 (MH^+). $C_{25}H_{25}FN_6O$ requires 444

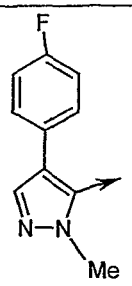
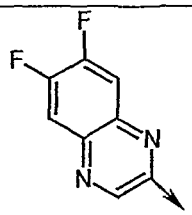
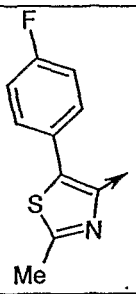
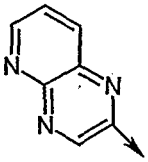
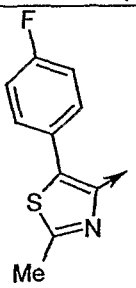
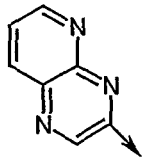
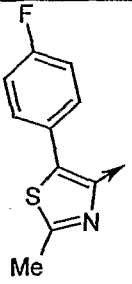
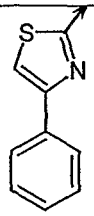
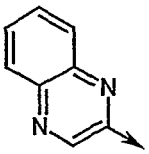
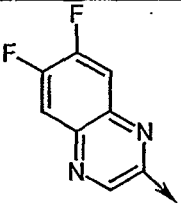
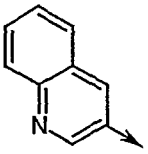
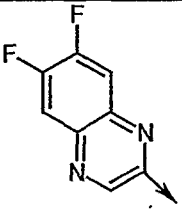
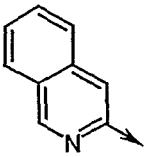
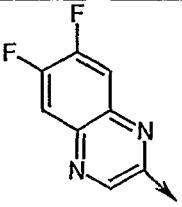
45	D25	CH_2			Found 445 (MH^+). $C_{25}H_{25}FN_6O$ requires 444
46	D25	CH_2			Found 431 (MH^+). $C_{24}H_{23}FN_6O$ requires 430
47	D25	CH_2			Found 462 (MH^+). $C_{25}H_{24}FN_5OS$ requires 461
48	D25	CH_2			Found 446 (MH^+). $C_{24}H_{24}FN_7O$ requires 445
49	D25	CH_2			Found 397 (MH^+). $C_{25}H_{24}N_4O$ requires 396
50	D25	CH_2			Found 456 (MH^+). $C_{22}H_{23}{}^{79}BrN_4O_2$ requires 455
51	D25	CH_2			Found 429 (MH^+). $C_{24}H_{24}N_6O_2$ requires 428

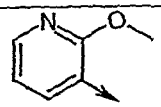
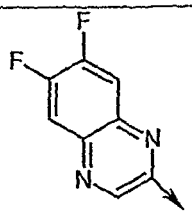
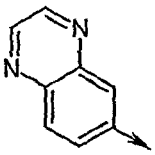
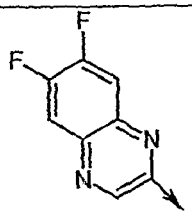
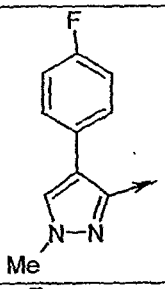
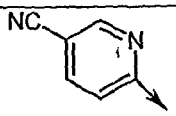
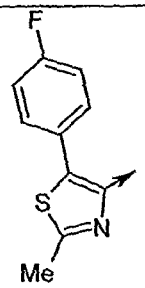
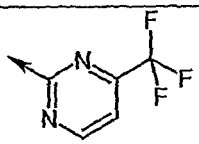
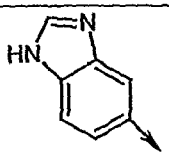
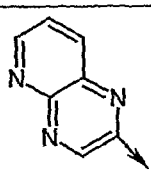
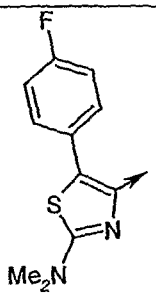
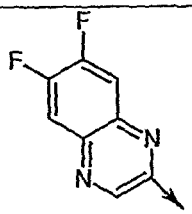
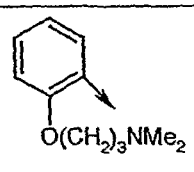
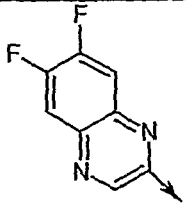
52	D25	CH_2			Found 431 (MH^+). $C_{22}H_{21}F_3N_4O_2$ requires 430
53	D27	CH_2			Found 512 (MH^+). $C_{26}H_{24}F_3N_5OS$ requires 511
54	D27	CH_2			Found 498 (MH^+). $C_{25}H_{22}F_3N_5OS$ requires 497
55	D27	CH_2			Found 495 (MH^+). $C_{26}H_{25}F_3N_6O$ requires 494
56	D27	CH_2			Found 481 (MH^+). $C_{25}H_{23}F_3N_6O$ requires 480
57	D27	CH_2			Found 495 (MH^+). $C_{26}H_{25}F_3N_6O$ requires 494

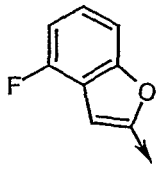
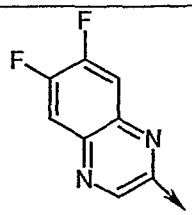
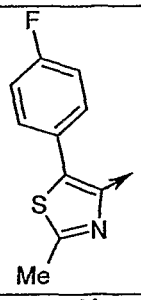
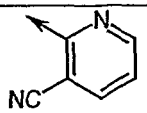
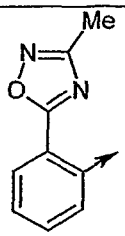
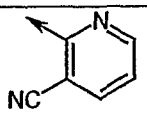
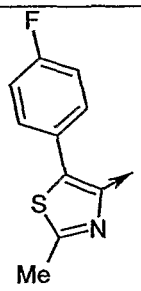
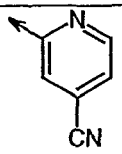
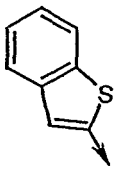
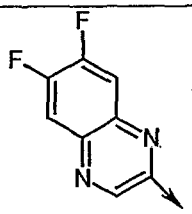
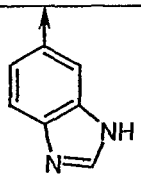
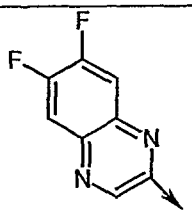
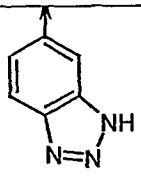
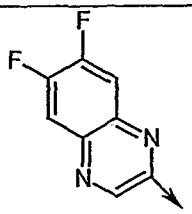
58	D27	CH_2			Found 495 (MH^+). $C_{26}H_{25}F_3N_6O$ requires 494
59	D27	CH_2			Found 447 (MH^+). $C_{26}H_{24}F_2N_4O$ requires 446
60	D29	CH_2			Found 434 (MH^+). $C_{24}H_{21}F_2N_5O$ requires 433
61	D29	CH_2			Found 482 (MH^+). $C_{25}H_{22}F_3N_5O_2$ requires 481
62	D29	CH_2			Found 498 (MH^+). $C_{25}H_{22}F_3N_5OS$ requires 497
63	D29	CH_2			Found 465 (MH^+). $C_{24}H_{22}F_2N_6O_2$ requires 464
64	D29	CH_2			Found 467 (MH^+). $C_{22}H_{19}F_5N_4O_2$ requires 466

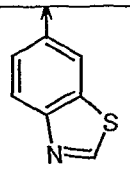
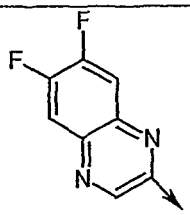
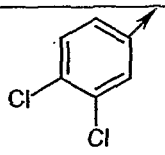
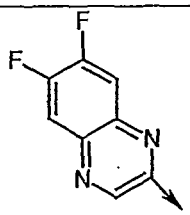
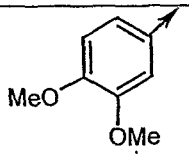
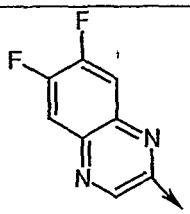
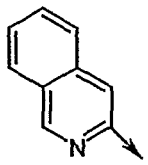
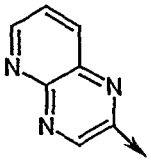
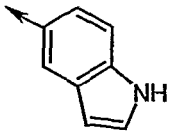
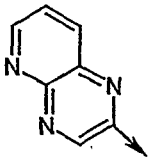
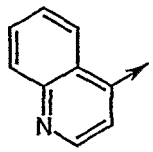
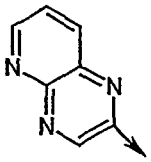
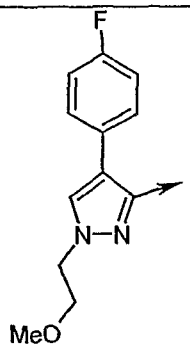
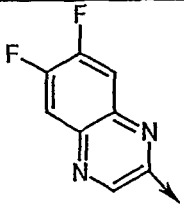
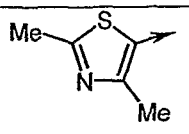
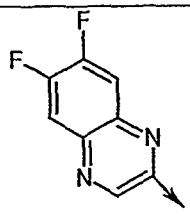
65	D29	CH_2			Found 459 (MH^+). $C_{27}H_{24}F_2N_4O$ requires 458
66	D29	CH_2			Found 491 (MH^+). $C_{22}H_{21}{}^{79}BrF_2N_4O_2$ requires 490
67	D29	CH_2			Found 481 (MH^+). $C_{25}H_{23}F_3N_6O$ requires 480
68	D29	CH_2			Found 481 (MH^+). $C_{25}H_{23}F_3N_6O$ requires 480
69	D29	CH_2			Found 482 (MH^+). $C_{24}H_{22}F_3N_7O$ requires 481
70	D29	CH_2			Found 433 (MH^+). $C_{25}H_{22}F_2N_4O$ requires 432
71	D29	CH_2			Found 484 (MH^+). $C_{24}H_{20}F_3N_5OS$ requires 483

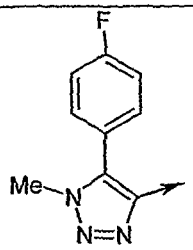
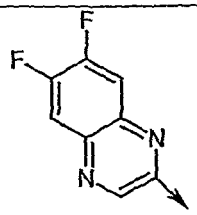
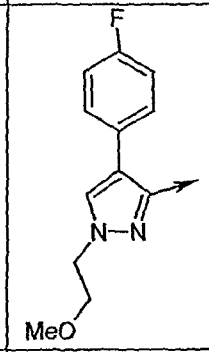
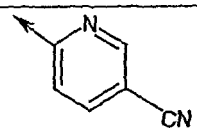
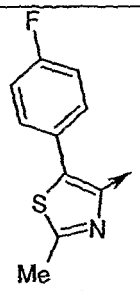
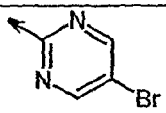
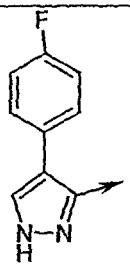
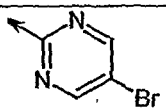
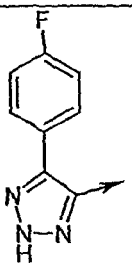
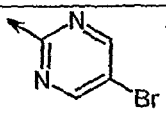
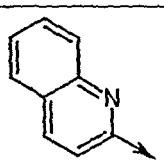
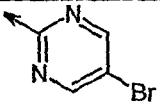
72	D33	CH_2			Found 445 (MH^+). $C_{25}H_{25}FN_6O$ requires 444
73	D39	CH_2			Found 419 (MH^+). $C_{22}H_{22}N_6O_3$ requires 418
74	D39	CH_2			Found 421 (MH^+). $C_{20}H_{19}F_3N_4O_3$ requires 420
75	D39	CH_2			Found 452 (MH^+). $C_{23}H_{22}FN_5O_2S$ requires 451
76	D39	CH_2			Found 463 (MH^+). $C_{19}H_{19}IN_4O_2$ requires 462
77	D47	O			Found 500 (MH^+). $C_{24}H_{20}F_3N_5O_2S$ requires 499
78	D47	O			Found 483 (MH^+). $C_{24}H_{21}F_3N_6O_2$ requires 482

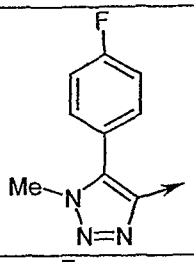
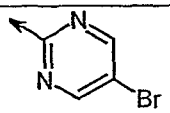
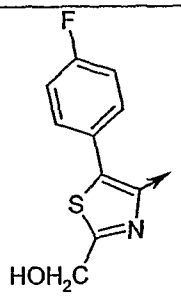
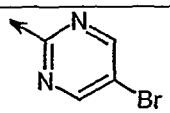
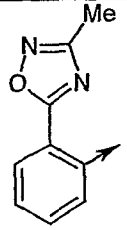
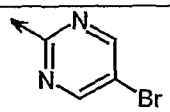
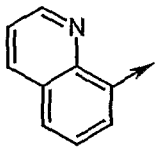
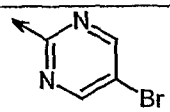
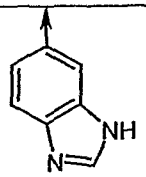
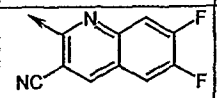
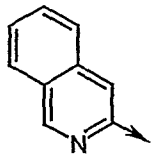
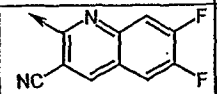
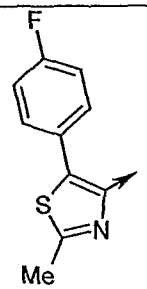
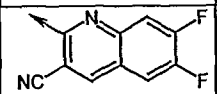
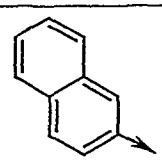
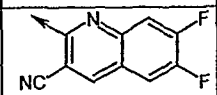
79	D47	O			Found 483 (MH^+). $C_{24}H_{21}F_3N_6O_2$ requires 482
80	D49	CH_2			Found 463 (MH^+). $C_{24}H_{23}FN_6OS$ requires 462
81	D50	CH_2			Found 463 (MH^+). $C_{24}H_{23}FN_6OS$ requires 462
82	D53	CH_2			Found 493 (MH^+). $C_{26}H_{25}FN_4OS_2$ requires 492
83	D29	CH_2			Found 435 (MH^+). $C_{23}H_{20}F_2N_6O$ requires 434
84	D29	CH_2			Found 434 (MH^+). $C_{24}H_{21}F_2N_5O$ requires 433
85	D29	CH_2			Found 434 (MH^+). $C_{24}H_{21}F_2N_5O$ requires 433

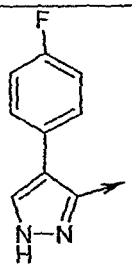
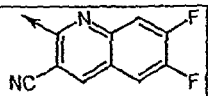
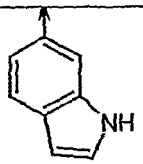
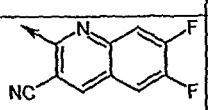
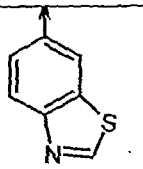
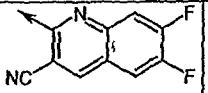
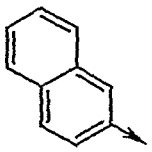
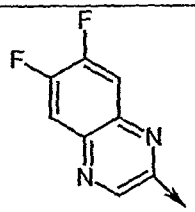
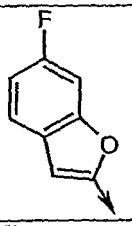
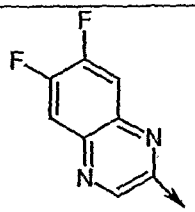
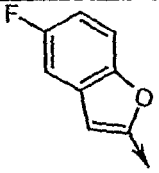
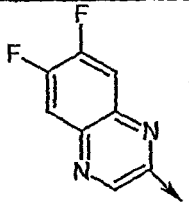
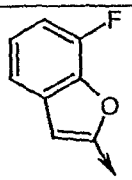
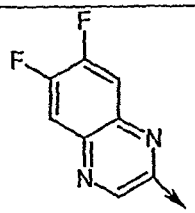
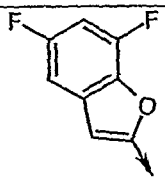
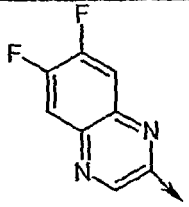
86	D29	CH_2			Found 414 (MH^+). $C_{21}H_{21}F_2N_5O_2$ requires 413
87	D29	CH_2			Found 435 (MH^+). $C_{23}H_{20}F_2N_6O$ requires 434
88	D55	CH_2			Found 419 (MH^+). $C_{23}H_{23}FN_6O$ requires 418
89	D57	CH_2			Found 480 (MH^+). $C_{22}H_{21}F_4N_5OS$ requires 479
90	D49	CH_2			Found 388MH^+). $C_{21}H_{21}N_7O$ requires 387
91	D29	CH_2			Found 527 (MH^+). $C_{26}H_{25}F_3N_6OS$ requires 526
92	D29	CH_2			Found 484 (MH^+). $C_{26}H_{31}F_2N_5O_2$ requires 483

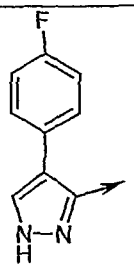
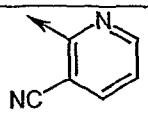
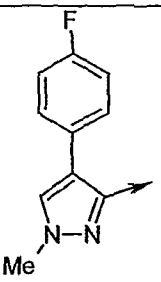
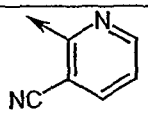
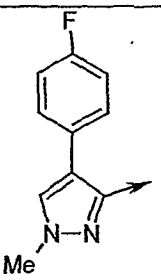
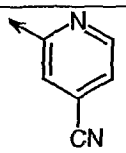
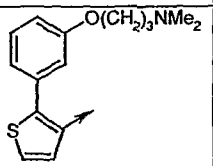
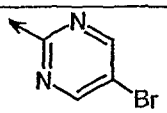
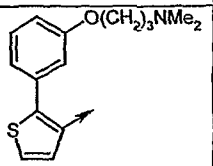
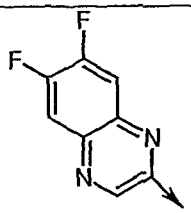
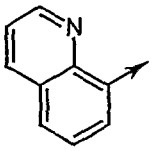
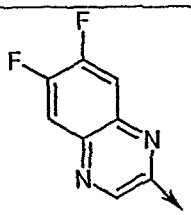
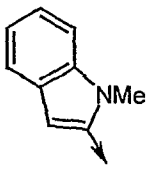
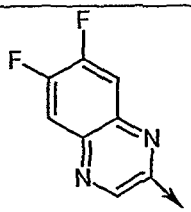
109	D29	CH_2			Found 441 (MH^+). $C_{23}H_{19}F_3N_4O_2$ requires 440
110	D62	CH_2			Found 436 (MH^+). $C_{23}H_{22}FN_5OS$ requires 435
111	D62	CH_2			Found 403 (MH^+). $C_{22}H_{22}N_6O_2$ requires 402
112	D64	CH_2			Found 436 (MH^+). $C_{23}H_{22}FN_5OS$ requires 435
113	D29	CH_2			Found 439 (MH^+). $C_{23}H_{20}F_2N_4OS$ requires 438
114	D29	CH_2			Found 423 (MH^+). $C_{22}H_{20}F_2N_6O$ requires 422
115	D29	CH_2			Found 424 (MH^+). $C_{21}H_{19}F_2N_7O$ requires 423

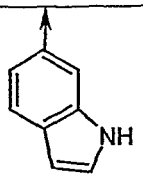
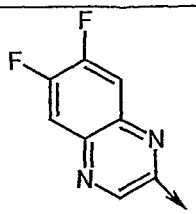
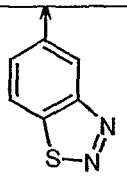
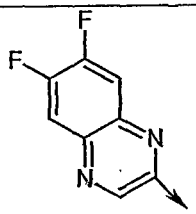
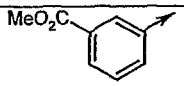
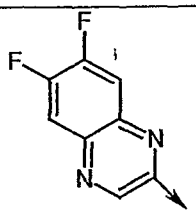
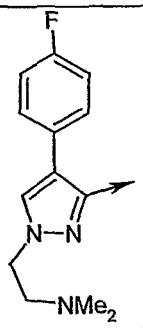
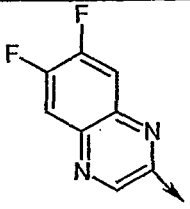
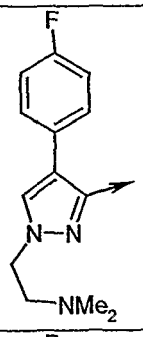
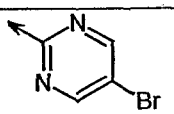
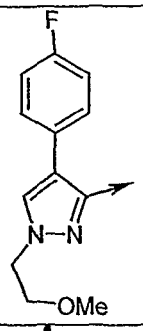
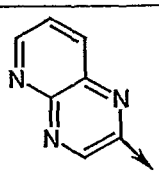
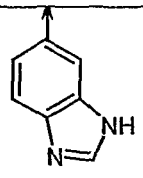
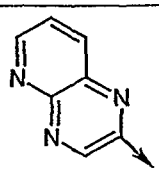
116	D29	CH_2			Found 440 (MH^+). $C_{22}H_{19}F_2N_5OS$ requires 439
117	D29	CH_2			Found 452 (MH^+). $C_{21}H_{18}Cl_2F_2N_4O$ requires 451
118	D29	CH_2			Found 443 (MH^+). $C_{23}H_{24}F_2N_4O_3$ requires 442
121	D49	CH_2			Found 399 (MH^+). $C_{23}H_{22}N_6O$ requires 398
122	D49	CH_2			Found 387 (MH^+). $C_{22}H_{22}N_6O$ requires 386
123	D49	CH_2			Found 399 (MH^+). $C_{23}H_{22}N_6O$ requires 398
124	D29	CH_2			Found 525 (MH^+). $C_{27}H_{27}F_3N_6O_2$ requires 524
125	D29	CH_2			Found 418 (MH^+). $C_{20}H_{21}F_2N_5OS$ requires 417

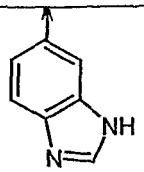
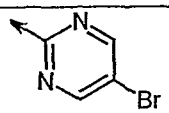
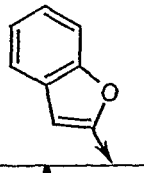
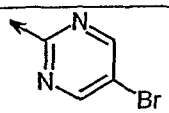
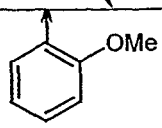
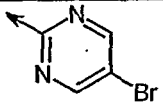
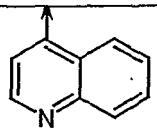
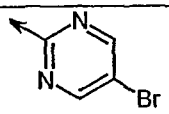
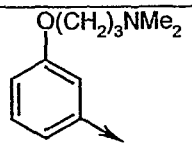
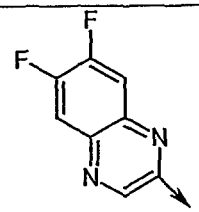
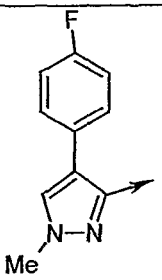
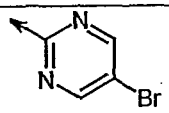
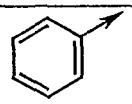
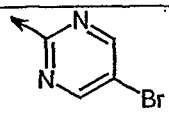
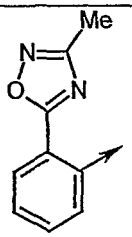
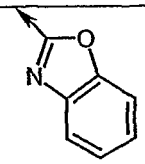
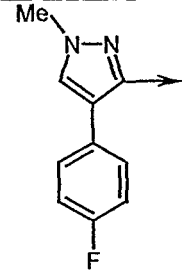
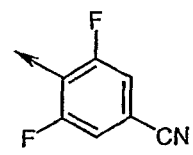
126	D29	CH_2			Found 482 (MH^+). $C_{24}H_{22}F_3N_7O$ requires 481
127	D55	CH_2			Found 463 (MH^+). $C_{25}H_{27}FN_6O_2$ requires 462
128	D66	CH_2			Found 490 (MH^+). $C_{21}H_{21}{}^{79}BrFN_5OS$ requires 489
129	D66	CH_2			Found 459 (MH^+). $C_{20}H_{20}{}^{79}BrFN_6O$ requires 458
130	D66	CH_2			Found 460 (MH^+). $C_{19}H_{19}BrFN_7O$ requires 459
131	D66	CH_2			Found 426 (MH^+). $C_{20}H_{20}{}^{79}BrN_5O$ requires 425

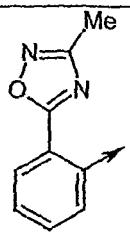
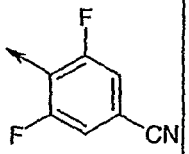
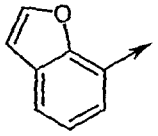
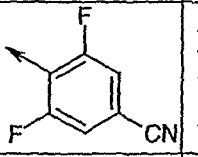
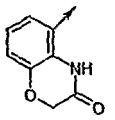
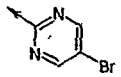
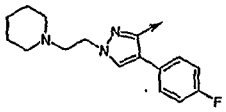
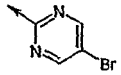
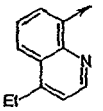
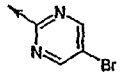
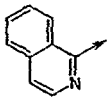
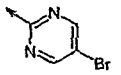
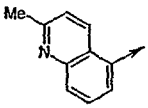
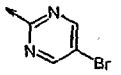
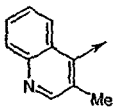
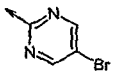
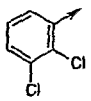
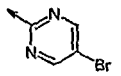
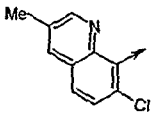
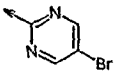
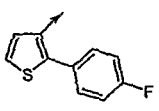
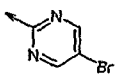
132	D66	CH_2			Found 474 (MH^+). $C_{20}H_{21}{}^{79}BrFN_7O$ requires 473
133	D66	CH_2			Found 506 (MH^+). $C_{21}H_{21}{}^{79}BrFN_5O_2S$ requires 505
134	D66	CH_2			Found 457 (MH^+). $C_{20}H_{21}{}^{79}BrN_6O_2$ requires 456
135	D66	CH_2			Found 426 (MH^+). $C_{20}H_{20}{}^{79}BrN_5O$ requires 425
136	D68	CH_2			Found 447 (MH^+). $C_{24}H_{20}F_2N_6O$ requires 446
137	D68	CH_2			Found 458 (MH^+). $C_{26}H_{21}F_2N_5O$ requires 457
138	D68	CH_2			Found 522 (MH^+). $C_{27}H_{22}F_3N_5OS$ requires 521
139	D68	CH_2			Found 457 (MH^+). $C_{27}H_{22}F_2N_4O$ requires 456

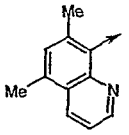
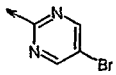
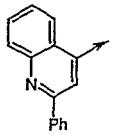
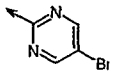
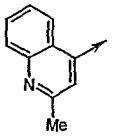
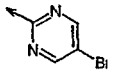
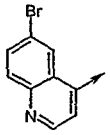
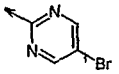
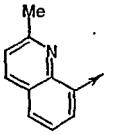
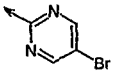
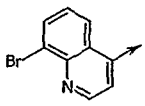
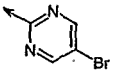
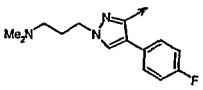
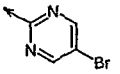
140	D68	CH_2			Found 491 (MH^+). $C_{26}H_{21}F_3N_6O$ requires 490
141	D68	CH_2			Found 446 (MH^+). $C_{25}H_{21}F_2N_5O$ requires 445
142	D68	CH_2			Found 464 (MH^+). $C_{24}H_{19}F_2N_5OS$ requires 463
143	D29	CH_2			Found 433 (MH^+). $C_{25}H_{22}F_2N_4O$ requires 432
144	D29	CH_2			Found 441 (MH^+). $C_{23}H_{19}F_3N_4O_2$ requires 440
145	D29	CH_2			Found 441 (MH^+). $C_{23}H_{19}F_3N_4O_2$ requires 440
146	D29	CH_2			Found 441 (MH^+). $C_{23}H_{19}F_3N_4O_2$ requires 440
147	D29	CH_2			Found 459 (MH^+). $C_{23}H_{18}F_4N_4O_2$ requires 458

148	D62	CH_2			Found 405 (MH^+). $C_{22}H_{21}FN_6O$ requires 404
149	D62	CH_2			Found 419 (MH^+). $C_{23}H_{23}FN_6O$ requires 418
150	D64	CH_2			Found 419 (MH^+). $C_{23}H_{23}FN_6O$ requires 418
151	D66	CH_2			Found 558 (MH^+). $C_{26}H_{32}{}^{79}BrN_5O_2S$ requires 557
152	D29	CH_2			Found 566 (MH^+). $C_{30}H_{33}F_2N_5O_2S$ requires 565
153	D29	CH_2			Found 427 (MH^+). $C_{20}H_{20}BrN_5O$ requires 426
154	D29	CH_2			Found 436 (MH^+). $C_{24}H_{23}F_2N_5O$ requires 435

155	D29	CH_2			Found 422 (MH^+). $C_{23}H_{21}F_2N_5O$ requires 421
156	D29	CH_2			Found 441 (MH^+). $C_{21}H_{18}F_2N_6OS$ requires 440
157	D29	CH_2			Found 441 (MH^+). $C_{23}H_{22}F_2N_4O_3$ requires 440
158	D29	CH_2			Found 538 (MH^+). $C_{28}H_{30}F_3N_7O$ requires 537
159	D66	CH_2			Found 530 (MH^+). $C_{24}H_{29}{}^{79}BrFN_7O$ requires 529
160	D49	CH_2			Found 490 (MH^+). $C_{26}H_{28}FN_7O_2$ requires 489
161	D49	CH_2			Found 388 (MH^+). $C_{21}H_{21}N_7O$ requires 387

162	D66	CH_2			Found 415 (MH^+) $C_{18}H_{19}{}^{79}BrN_6O$ requires 414
163	D66	CH_2			Found 415 (MH^+). $C_{19}H_{19}{}^{79}BrN_4O_2$ requires 414
164	D66	CH_2			Found (MH^+) 405 $C_{18}H_{21}{}^{79}BrN_4O_2$ requires 404
165	D66	CH_2			Found 426 (MH^+) $C_{20}H_{20}{}^{79}BrN_5O$ requires 425
166	D29	CH_2			Found 484 (MH^+). $C_{26}H_{31}F_2N_5O_2$ requires 483
170	D66	CH_2			Found 473 (MH^+) . $C_{21}H_{22}{}^{79}BrFN_6O$ requires 472
175	D66	CH_2			Found 375 (MH^+) $C_{17}H_{19}{}^{79}BrN_4O$ requires 374.
199	D7	O			Found 420 (MH^+) $C_{22}H_{21}N_5O_4$ requires 419.
204	D82	CH_2			Found 454 (MH^+). $C_{24}H_{22}F_3N_5O$ requires 453

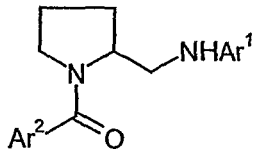
206	D82	CH_2			Found 438 (MH^+). $C_{23}H_{21}F_2N_5O_2$ requires 437.
207	D82	CH_2			Found 396 (MH^+). $C_{22}H_{19}F_2N_3O_2$ requires 395.
230	D66	CH_2			Found 446 (MH^+). $C_{19}H_{20}{}^{79}BrN_5O_3$ requires 445.
231	D66	CH_2			Found 570 (MH^+). $C_{27}H_{33}{}^{79}BrFN_7O$ requires 569.
241	D66	CH_2			Found 454 (MH^+). $C_{22}H_{24}{}^{79}BrN_5O$ requires 453
242	D66	CH_2			Found 448 (MNa^+). $C_{20}H_{20}{}^{79}BrN_5O$ requires 425.
243	D66	CH_2			Found 440 (MH^+). $C_{21}H_{22}{}^{79}BrN_5O$ requires 439.
244	D66	CH_2			Found 440 (MH^+). $C_{21}H_{22}{}^{79}BrN_5O$ requires 439.
245	D66	CH_2			Found 443 (MH^+). $C_{17}H_{17}{}^{79}Br^{35}Cl_2N_4O$ requires 442.
246	D66	CH_2			Found 474 (MH^+). $C_{21}H_{21}{}^{79}Br^{35}ClN_5O$ requires 473.
259	D80	O			Found 476 (MH^+). $C_{21}H_{19}{}^{79}BrFN_3O_2S$ requires 475.

260	D66	CH_2			Found 454 (MH^+). $C_{22}H_{24}{}^{79}BrN_5O$ requires 453.
261	D66	CH_2			Found 502 (MH^+). $C_{26}H_{24}{}^{79}BrN_5O$ requires 501.
262	D66	CH_2			Found 440 (MH^+). $C_{21}H_{22}{}^{79}BrN_5O$ requires 439.
263	D66	CH_2			Found 504 (MH^+). $C_{20}H_{19}{}^{79}Br_2N_5O$ requires 503.
264	D66	CH_2			Found 440 (MH^+). $C_{21}H_{22}{}^{79}BrN_5O$ requires 439.
265	D66	CH_2			Found 504 (MH^+). $C_{20}H_{19}{}^{79}Br_2N_5O$ requires 503.
266	D66	CH_2			Found 544 (MH^+). $C_{25}H_{31}{}^{79}BrFN_7O$ requires 543.

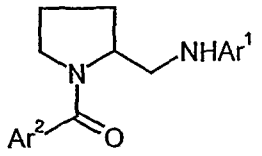
Example 93: 1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-2-H-pyrazol-3-yl]-methanone

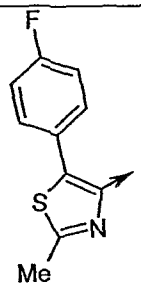
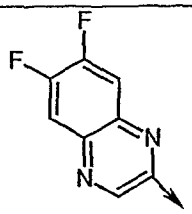
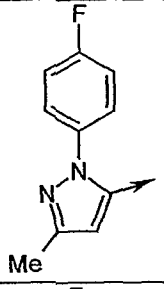
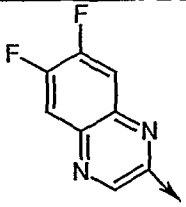
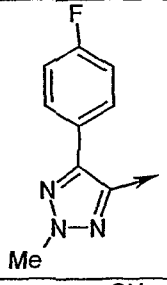
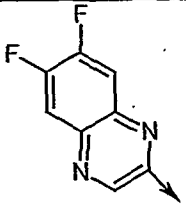
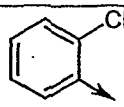
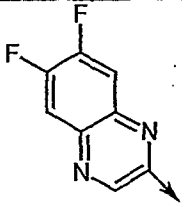
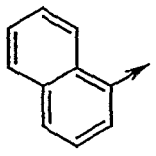
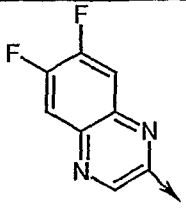
The amine of D31 (0.085g) in dimethylformamide (3ml) was treated with 4-(4-fluoro-phenyl)-2*H*-pyrazole-3-carboxylic acid (0.125g), diisopropylethylamine (0.07ml) and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (0.11g). the mixture was shaken for 48 hours. Solvent was removed at reduced pressure and the residue extracted with dichloromethane. The filtrate was evaporated under reduced pressure and the residue column chromatographed (silica gel, 3% methanol/diethyl ether) to give the title compound (0.1g).

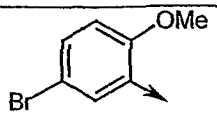
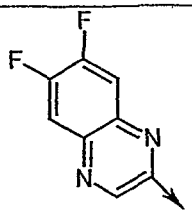
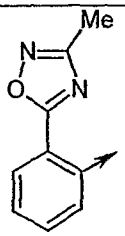
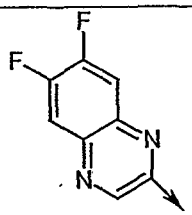
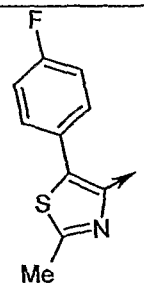
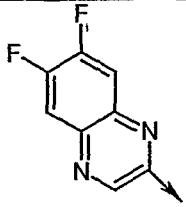
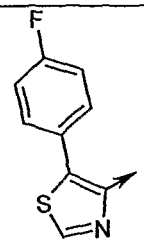
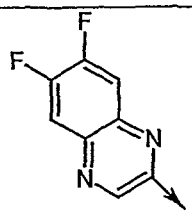
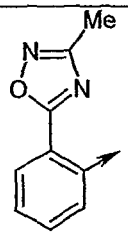
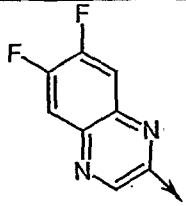
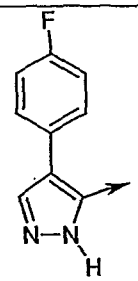
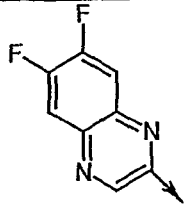
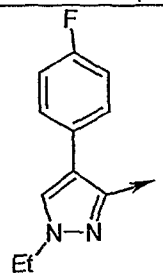
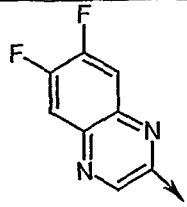
Mass Spectrum (API^+): Found 453 (MH^+). $C_{23}H_{19}F_3N_6O$ requires 452.

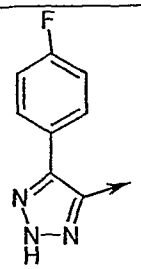
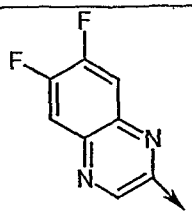
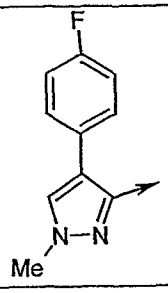
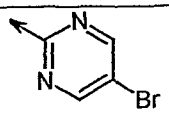
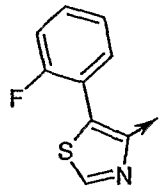
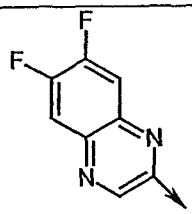
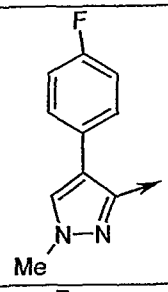
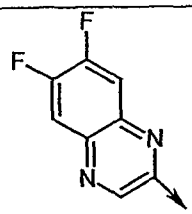
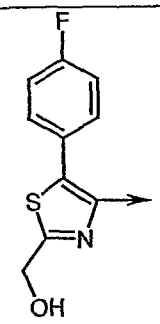
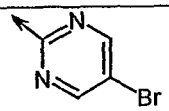
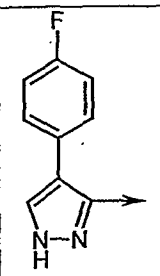
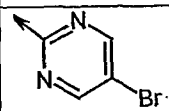
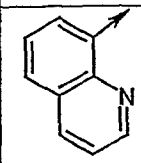
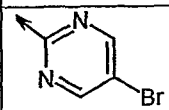


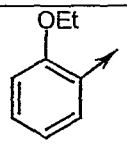
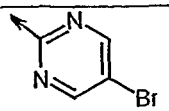
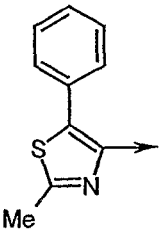
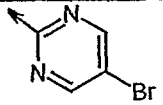
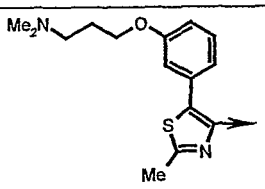
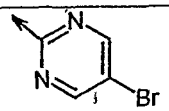
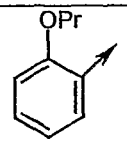
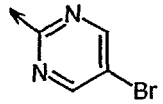
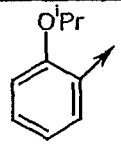
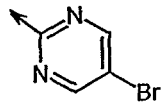
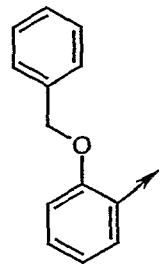
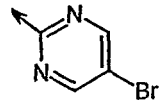
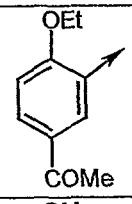
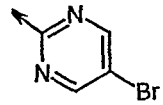
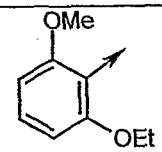
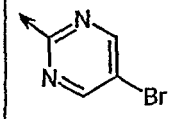
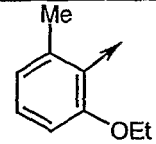
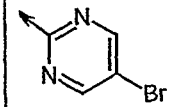
residue column chromatographed (silica gel, 3% methanol/diethyl ether) to give the title compound (0.1g).
Mass Spectrum (API$^+$): Found 453 (MH^+). $C_{23}H_{19}F_3N_6O$ requires 452.

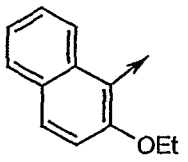
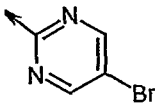
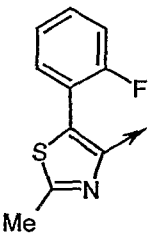
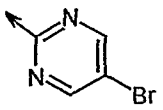
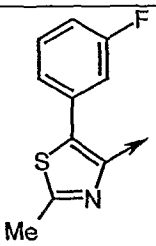
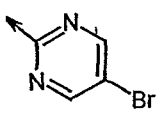
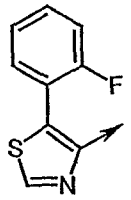
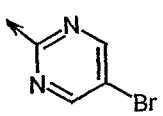
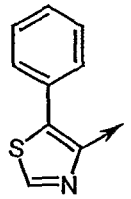
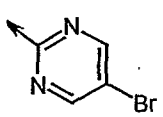
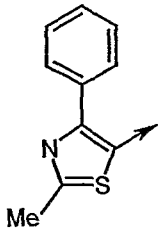
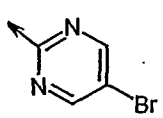
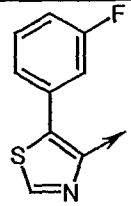
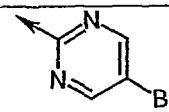
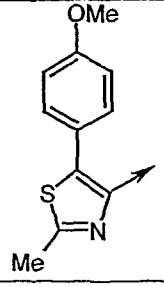
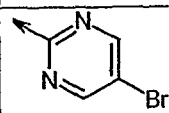


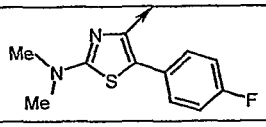
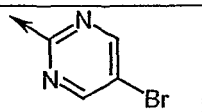
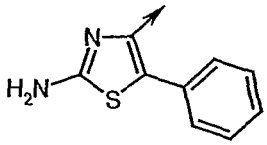
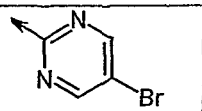
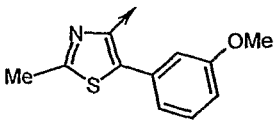
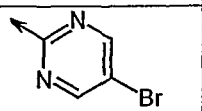
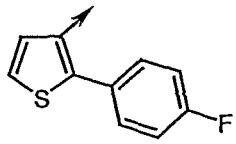
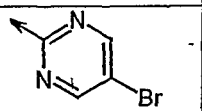
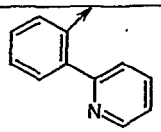
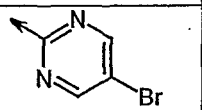
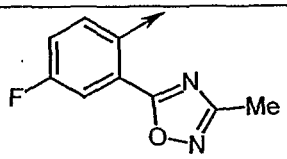
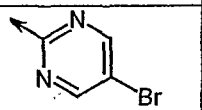
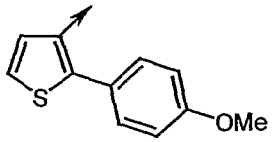
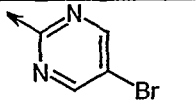
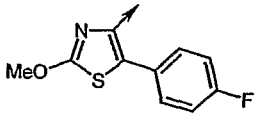
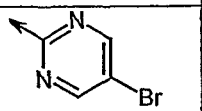
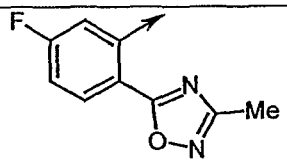
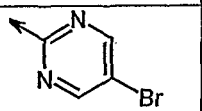
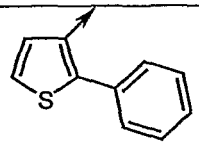
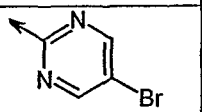
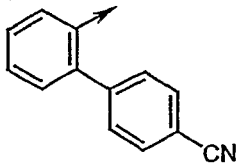
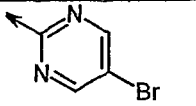
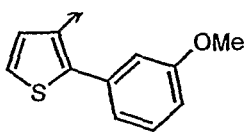
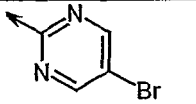
Example	Amine	Ar^2	Ar^1	Mass Spectrum (Electrospray LC/MS), API$^+$
94	D31			Found 484 (MH^+). $C_{24}H_{20}F_3N_5OS$ requires 483
95	D31			Found 467 (MH^+). $C_{24}H_{21}F_3N_6O$ requires 466
96	D31			Found 468 (MH^+). $C_{23}H_{20}F_3N_7O$ requires 467
97	D31			Found 394 (MH^+). $C_{21}H_{17}F_2N_5O$ requires 393
98	D31			Found 419 (MH^+). $C_{24}H_{20}F_2N_4O$ requires 418

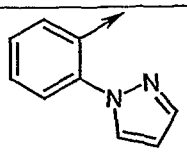
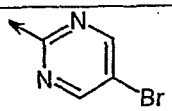
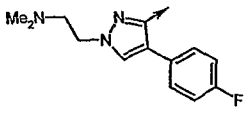
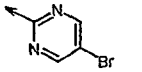
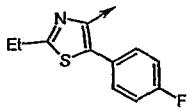
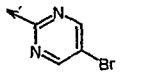
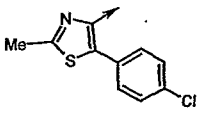
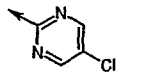
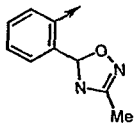
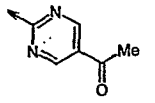
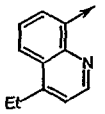
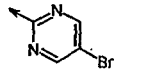
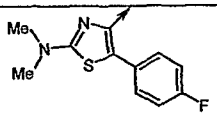
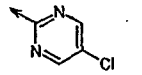
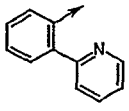
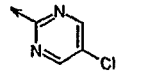
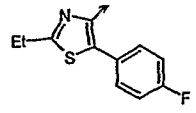
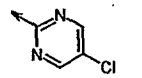
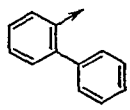
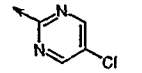
99	D31			Found 478 (MH^+). $C_{21}H_{19}BrF_2N_4O_2$ requires 477
100	D31			Found 451 (MH^+). $C_{23}H_{20}F_2N_6O_2$ requires 450
101	D45			Found 484 (MH^+). $C_{24}H_{20}F_3N_5OS$ requires 483
102	D45			Found 470 (MH^+). $C_{23}H_{18}F_3N_5OS$ requires 469
103	D45			Found 451 (MH^+). $C_{23}H_{20}F_2N_6O_2$ requires 450
104	D45			Found 453 (MH^+). $C_{23}H_{19}F_3N_6O$ requires 452
119	D45			Found 481 (MH^+). $C_{25}H_{23}F_3N_6O$ requires 480

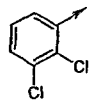
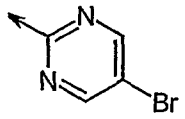
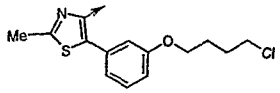
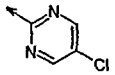
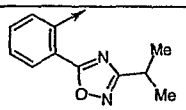
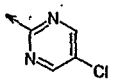
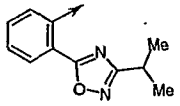
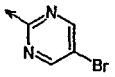
120	D45			Found 454 (MH^+). $C_{22}H_{18}F_3N_7O$ requires 453
167	D70			Found 459 (MH^+). $C_{20}H_{20}{}^{79}BrFN_6O$ requires 458
168	D45			Found 470 (MH^+). $C_{23}H_{18}F_3N_5OS$ requires 469
169	D45			Found 467 (MH^+). $C_{24}H_{21}F_3N_6O$ requires 466
176	D70			Found 514 (MNa^+) $C_{20}H_{19}{}^{79}BrFN_5O_2S$ requires 491.
177	D70			Found 445 (MH^+). $C_{19}H_{18}{}^{79}BrFN_6O$ requires 444.
178	D70			Found 434 (MNa^+). $C_{19}H_{18}{}^{79}BrN_5O$ requires 411.

179	D70			Found 405 (MH^+). $C_{18}H_{21}{}^{79}BrN_4O_2$ requires 404.
180	D70			Found 458 (MH^+). $C_{20}H_{20}{}^{79}BrN_5OS$ requires 457.
181	D70			Found 559 (MH^+). $C_{25}H_{31}{}^{79}BrN_6O_2S$ requires 558.
182	D70			Found 419 (MH^+). $C_{19}H_{23}{}^{79}BrN_4O_2$ requires 418.
183	D70			Found 419 (MH^+). $C_{19}H_{23}{}^{79}BrN_4O_2$ requires 418.
184	D70			Found 467 (MH^+). $C_{23}H_{23}{}^{79}BrN_4O_2$ requires 466.
185	D70			Found 447 (MH^+). $C_{20}H_{23}{}^{79}BrN_4O_3$ requires 446.
186	D70			Found 435 (MH^+). $C_{19}H_{23}{}^{79}BrN_4O_3$ requires 434.
187	D70			Found 419 (MH^+). $C_{19}H_{23}{}^{79}BrN_4O_2$ requires 418

188	D70			Found 455 (MH^+). $C_{22}H_{23}{}^{79}BrN_4O_2$ requires 454.
189	D70			Found 476 (MH^+). $C_{20}H_{19}{}^{79}BrFN_5OS$ requires 475.
190	D70			Found 476 (MH^+). $C_{20}H_{19}{}^{79}BrFN_5OS$ requires 475.
191	D70			Found 462 (MH^+). $C_{19}H_{17}{}^{79}BrFN_5OS$ requires 461.
192	D70			Found 444 (MH^+). $C_{19}H_{18}{}^{79}BrN_5OS$ requires 443.
193	D70			Found 458 (MH^+). $C_{20}H_{20}{}^{79}BrN_5OS$ requires 457.
201	D70			Found 462 (MH^+). $C_{20}H_{17}{}^{79}BrFN_5OS$ requires 461.
202	D70			Found 488 (MH^+). $C_{21}H_{22}{}^{79}BrN_5O_2S$ requires 487.

209	D70			Found 505 (MH^+) $C_{21}H_{22}{}^{79}BrFN_6OS$ requires 504
210	D70			Found 459 (MH^+). $C_{19}H_{19}{}^{79}BrN_6OS$ requires 458.
211	D70			Found 488 (MH^+). $C_{21}H_{22}{}^{79}BrN_5O_2S$ requires 487.
212	D70			Found 461 (MH^+) $C_{20}H_{18}{}^{79}BrFN_4OS$ requires 460.
213	D70			Found 460(MNa^+). $C_{21}H_{20}{}^{79}BrN_5O$ requires 437.
214	D70			Found 461 (MH^+). $C_{19}H_{18}{}^{79}Br\ FN_6O_2$ requires 460.
215	D70			Found 473 (MH^+). $C_{21}H_{21}{}^{79}Br\ N_4O_2$ requires 472.
219	D70			Found 492 (MH^+). $C_{20}H_{19}{}^{79}BrFN_5O_2S$ requires 491.
220	D70			Found 461 (MH^+). $C_{19}H_{18}{}^{79}BrFN_6O_2$ requires 460.
221	D70			Found 443 (MH^+). $C_{20}H_{19}{}^{79}BrN_4OS$ requires 442.
222.	D70			Found 462 (MH^+). $C_{23}H_{20}{}^{79}BrN_5O$ requires 461.
223	D70			Found 473 (MH^+). $C_{21}H_{21}{}^{79}BrN_4O_2S$ requires 472.

224	D70			Found 449 (MNa^+). $C_{19}H_{19}{}^{79}BrN_6O$ requires 426.
232	D70			Found 516 (MH^+). $C_{23}H_{27}{}^{79}BrFN_7O$ requires 515.
233	D70			Found 490 (MH^+). $C_{21}H_{21}{}^{79}BrFN_5OS$ requires 489.
247	D95			Found 448 (MH^+). $C_{20}H_{19}{}^{35}Cl_2N_5OS$ requires 447.
248	D93			Found 407 (MH^+). $C_{21}H_{22}N_6O_3$ requires 406.
250	D70			Found 440 (MH^+). $C_{21}H_{22}{}^{79}BrN_5O$ requires 439.
251	D95			Found 461 (MH^+). $C_{21}H_{22}{}^{35}ClFN_6OS$ requires 460.
252	D95			Found 416 (MNa^+). $C_{21}H_{20}{}^{35}ClN_5O$ requires 393.
253	D95			Found 468 (MNa^+). $C_{21}H_{21}{}^{35}ClFN_5OS$ requires 445.
254	D95			Found 393 (MH^+). $C_{22}H_{21}{}^{35}ClN_4O$ requires 392.

255	D70			Found 429 (MH^+). $C_{16}H_{15}{}^{79}Br^{35}Cl_2N_4O$ requires 428.
256	D95			Found 520 (MH^+). $C_{24}H_{27}{}^{35}Cl_2N_5O_2S$ requires 519.
257	D95			Found 427 (MH^+). $C_{21}H_{23}{}^{35}ClN_6O_2$ requires 426.
258	D70			Found 471 (MH^+). $C_{21}H_{23}{}^{79}BrN_6O_2$ requires 470.

Example 105: 1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[(S)-2-(oxazolo[4,5-b]]pyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone

The compound of D41 (0.51g) and 2-methylsulfanyl-oxazolo[4,5-*b*]pyridine (0.25g) were combined and heated under argon at 90°C for 18 hours The mixture was column chromatographed (5% methanol, diethyl ether eluant) to give the title compound (0.26g)
Mass Spectrum (API$^+$): Found 419 (MH^+). $C_{22}H_{22}N_6O_3$ requires 418.

Example 106: 1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-{(R)-2-[(methyl-oxazolo[4,5-b]pyridin-2-yl-amino)-methyl]piperidin-1-yl}-methanone

The title compound (0.015g) was prepared from the compound of D43 (0.15g) according to the method of Example 105.
Mass Spectrum (API$^+$): Found 433 (MH^+). $C_{23}H_{24}N_6O_3$ requires 432.

Example 107: 6-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-methyl-amino]-nicotinonitrile

The title compound (0.078g) was prepared from the compound of D60 (0.45g) and 2-chloro-5-cyanopyridine (0.189g) according to the method of D26
Mass Spectrum (API$^+$): Found 433 (MH^+). $C_{24}H_{25}FN_6O$ requires 432.

Example 108: 1-((S)-2-{[(6,7-Difluoro-quinoxalin-2-yl)-methyl-amino]-methyl}-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone

The title compound (0.031g) was prepared from the compound of D60 (0.15g) and 2-chloro-6,7-difluoroquinoxaline (0.091g) according to the method of D26
Mass Spectrum (API$^+$): Found 495 (MH^+). $C_{26}H_{25}F_3N_6O$ requires 494.

Example 171: 1-{2-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-pyrimidin-5-yl}-ethanone

A mixture of 1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazol-3-yl]-methanone (0.5g) and 1-ethoxyvinyl)tributyltin (0.42ml) tetrakis(triphenylphosphine)palladium[0} (0.06g) was boiled in dioxane (8ml) for 16h. 2N Hydrochloric acid was added, the mixtrue stirred for 90 min, water was added and the mixture extracted (x3) with ethyl acetate. The combined ethyl acetate extracts were dried, solvent removed at reduced pressure and the residue column chromatographed (silica gel, ethyl acetate → 2% methanol ethyl acetate to give the title compound (0.3g) as a yellow foam.

Mass Spectrum (API$^+$): Found 437 (MH$^+$). $C_{23}H_{25}FN_6O_2$ requires 436.

Example 172: 1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-((S)-2-{[5-(1-hydroxy-ethyl)-pyrimidin-2-ylamino]-methyl}-piperidin-1-yl)-methanone

1-{2-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-pyrimidin-5-yl}-ethanone (0.2g) was dissolved in methanol 20ml) and sodium borohydride (0.4g) added. The reaction was stirred overnight, water was added and stirring continued for 30min. The reaction mixture was extracted with ethyl acetate (x3), the organic extracts combined, dried ($MgSO_4$) and solvent removed at reduced pressure to give the title compound as a colourless foam.

Mass Spectrum (API$^+$): Found 439 (MH$^+$). $C_{23}H_{27}FN_6O_2$ requires 438.

Example 173: 2-[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile

1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazol-3-yl]-methanone (0.35g) in N-methylpyrrolidinone (10ml) containing copper(I)cyanide (0.13g) was heated to reflux for 5h. The reaction mixture was diluted with water, filtered (Kieselguhr) and the filtrate extracted with ethyl acetate. The ethyl acetate phase was washed with water and brine, dried (MgSO4), filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel; ethyl acetate:pentane 1:1 → ethyl acetate eluant), the appropriate fractions combined and solvent removed at reduced pressure to give the title compound (0.019g).

Mass Spectrum (API$^+$): Found 420 (MH$^+$). $C_{22}H_{22}FN_7O$ requires 419.

Example 174: 3-(1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanoyl)-N--methyl-benzamide

The compound of description 71 (0.10g) was dissolved in dimethylformamide (5ml) containing HATU (0.095g) and diisopropylethylamine (0.131ul) and stirred for 30 in. Methylamine (1M in tetrahydrofuran, 0.125ml) was added and stirring continued for 16. The reaction mixture was diluted with diethyl ether, washed with water (x3), saturated brine and dried (MgSO4). Solvent was removed at reduced pressure and the residue column chromatographed (silica gel; ethyl acetate → 10% methanol:ethyl acetate to give the title compound (0.018g).

Mass Spectrum (API$^+$): Found 440 (MH$^+$). $C_{23}H_{23}F_2N_5O_2$ requires 439.

Example 194: 1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

A mixture of the amine of D70 (0.070g), 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.065g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.042g) and 1-hydroxybenzotriazole hydrate (0.037g) in dimethylformamide (2ml) was stirred at ambient temperature for 18h, evaporated *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4), evaporated and the residue chromatographed on silica gel eluting with a 30% - 100% ethyl acetate in pentane gradient to afford the title product (0.083g) as a white solid. Mass Spectrum (Electrospray LC/MS), API$^+$: Found 476 (MH$^+$). $C_{20}H_{19}{}^{79}BrFN_5OS$ requires 475.

Example 195: 1-{(S)-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone The title compound (0.053g) was obtained from the amine of D70 (0.070g) and 2-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (0.056g) using the method of Example 194. Mass Spectrum (Electrospray LC/MS) : Found 443 (MH$^+$). $C_{19}H_{19}{}^{79}BrN_6O_2$ requires 442.

Example 196: 1-{(S)-2-[5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-chloro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (0.078g) was obtained from the amine of D70 (0.077g) and 5-(4-chloro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.076g) according to the method of Example 32. Mass spectrum (Electrospray LC/MS), API$^+$: Found 492 (MH$^+$). $C_{20}H_{19}{}^{79}Br{}^{35}ClN_5OS$ requires 491.

Example 197: 1-{(S)-2-[(5-Bromo-pyridin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (0.135g) was obtained from the amine of D74 (0.11g) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.12g) according to the method of Example 32. Mass Spectrum API$^+$: Found 475 (MH$^+$). $C_{21}H_{20}{}^{79}BrFN_4OS$ requires 474.

Example 198: 1-{(S)-2-[(5-Bromo-pyridin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazol-3-yl]-methanone

The title compound (0.10g) was obtained from the amine of D74 (0.11g) and 4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (0.12g) according to the method of Example 32. Mass Spectrum API$^+$: Found 458 (MH$^+$). $C_{21}H_{21}{}^{79}BrFN_5O$ requires 457.

Example 200: 1-{3-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-morpholin-4-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazol-3-yl]-methanone

The title compound (0.393g) was obtained from the compound of D80 (0.3g) and 4-(4-fluorophenyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (0.242g) according to the method of Example 32. Mass Spectrum (API$^+$): Found 475 (MH$^+$). $C_{20}H_{20}{}^{79}BrFN_6O_2$ requires 474.

Example 203: 3,5-Difluoro-4-[((S)-1-{1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-benzonitrile

The title compound (0.090g) was obtained from the compound of D82 (0.073g) and 5-(4-fluorophenyl)-2-methyl-thiazole-4-carboxylic acid (0.069g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 471. $C_{24}H_{21}F_3N_4OS$ requires 470.

Example 208: 3,5-Difluoro-4-[((S)-1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-benzonitrile

The title compound (0.09g) was obtained from the compound of D84 and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.095g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 457 (MH^+). $C_{23}H_{19}F_3N_4OS$ requires 456.

Example 216: 1-{(S)-2-[(5-Ethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (0.05g) was obtained from the compound of D86 (0.07g) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.068g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 426 (MH^+). $C_{22}H_{24}FN_5OS$ requires 425.

Example 217: 1-((S)-2-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-pyrrolidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (0.1g) was obtained from the compound of D91 (0.275g) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.285g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 490 (MH^+). $C_{21}H_{21}{}^{79}BrFN_5OS$ requires 489.

Example 218: 1-((S)-2-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-pyrrolidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazol-3-yl]-methanone

The title compound (0.02g) was obtained from the compound of D91 (0.275g) and 4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (0.260g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 473 (MH^+). $C_{21}H_{22}{}^{79}BrFN_6O$ requires 472.

Example 225: 1-{2-[((S)-1-{1-[5-(4-Chloro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-pyrimidin-5-yl}-ethanone

The title product (0.04g) was obtained from the compound of D93 (0.133g) and 5-(4-chloro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.076g) using a similar procedure to that described in Example 32. Mass Spectrum (Electrospray LC/MS): Found 456 (MH^+). $C_{22}H_{22}{}^{35}ClN_5O_2S$ requires 455.

Example 226: 1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title product (0.095g) was obtained from the amine of D95 (0.064g) and 5-(4-fluorophenyl)-2-methyl-thiazole-4-carboxylic acid (0.071g) using the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 432 (MH^+). $C_{20}H_{19}{}^{35}ClFN_5OS$ requires 431.

Example 227: 1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

The title compound (0.052g) was obtained from the amine of D95 (0.064g) and 2-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (0.061g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 399 (MH^+). $C_{19}H_{19}{}^{35}ClN_6O_2$ requires 398.

Example 228: 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(5-methyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone

To the compound of Example 194 (0.36g) in dimethylformamide was added lithium chloride (0.096g), tetramethyl tin (0.126 ml) and dichlorobis(triphenylphosphine) palladium (0) (0.035g) and the resulting mixture heated at 100°C under argon for 18h. The reaction was then evaporated, diluted with dichloromethane, filtered and the filtrate washed with water, dried and evaporated. Chromatography of the residue on silica gel, eluting with methanol-dichloromethane mixtures, afforded the title product (0.2g) as a yellow amorphous solid. Mass Spectrum (API^+): Found 412 (MH^+). $C_{21}H_{22}FN_5OS$ requires 411.

Example 229: 6-[((S)-1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-nicotinonitrile

A mixture of the amine of D97 (0.134g), 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.172g), EDC (0.139g) and 1-hydroxybenzotriazole (0.01g) in dichloromethane (8 ml) was stirred at ambient temperature for 7 days. The reaction was washed with saturated aqueous sodium bicarbonate solution, dried and evaporated. Chromatography of the residue on silica gel, eluting with ethyl acetate - hexane mixtures afforded the title product (0.196g). Mass Spectrum (Electrospray LC/MS): Found 422 (MH^+). $C_{22}H_{20}FN_5OS$ requires 421.

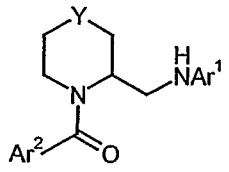
Example 234: 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(6-methyl-2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-methanone

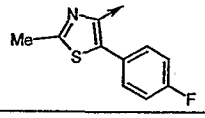
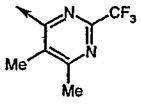
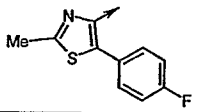
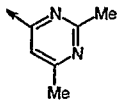
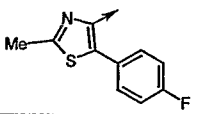
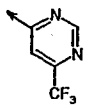
The title product (0.095g) was obtained from the amine of D101 (0.15g) and the compound of D98 (0.14g) using a similar method to that described in D69. Mass Spectrum (Electrospray LC/MS): Found 458 (MH^+). $C_{22}H_{24}FN_5OS_2$ requires 457.

Example 235: 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-methanone

The title compound (0.05g) was obtained from the amine of D101 (0.15g) and 4-chloro-2-methylsulfanyl-pyrimidine (0.076g) using a similar method to that described in D69. Mass Spectrum (Electrospray LC/MS): Found 444 (MH^+). $C_{21}H_{22}FN_5OS_2$ requires 443.

The following compounds were prepared using methods similar to that described in Examples 234 and 235.



Example	Amine	Y	Ar^2	Ar^1	Mass spectrum (Electrospray LC/MS), API^+
236	D101	Bond			Found 494 (MH^+). $C_{23}H_{23}F_4N_5OS$ requires 493.
237	D101	Bond			Found 426 (MH^+). $C_{22}H_{24}FN_5OS$ requires 425.
238	D101	Bond			Found 466 (MH^+). $C_{21}H_{19}F_4N_5OS$ requires 465.

Example 239: 1-(3-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-morpholin-4-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone The title compound (0.056g) was obtained from the compound of D105 (0.095g) and 5-(4-fluorophenyl)-2-methyl-thiazole-4-carboxylic acid (0.10g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 506 (MH^+). $C_{21}H_{21}{}^{79}BrFN_5O_2S$ requires 505.

Example 240: 1-(3-{[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-morpholin-4-yl)-1-[2-(4-fluoro-phenyl)-thiophen-3-yl]-methanone

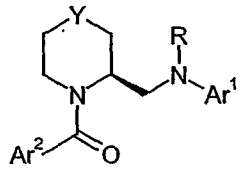
To the compound of D105 (0.095g) in dichloromethane (8ml) containing triethylamine (0.06ml) was added 2-(4-fluorophenyl)-thiophene-3-carbonyl chloride (0.084g). After 72h at ambient temperature the reaction mixture was washed with brine, dried and evaporated; the residue was chromatographed on silica gel, eluting with ethyl acetate-pentane mixtures to afford the title product (0.093g). Mass Spectrum (Electrospray LC/MS): Found 491 (MH^+). $C_{21}H_{20}{}^{79}BrFN_4O_2S$ requires 490.

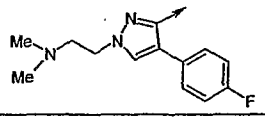
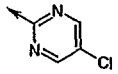
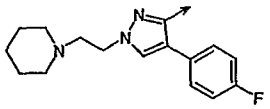
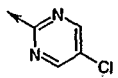
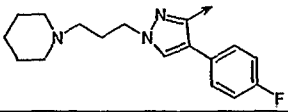
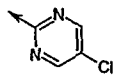
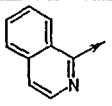
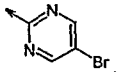
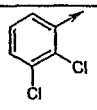
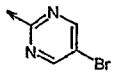
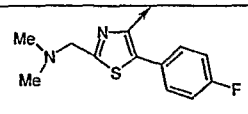
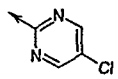
Example 249: 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(5-trifluoromethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone

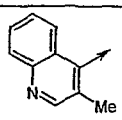
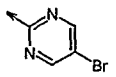
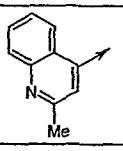
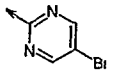
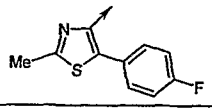
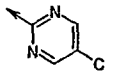
Example 249: 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(5-trifluoromethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone

To the compound from Example 194 (0.36g) in dimethylformamide (5ml) was added potassium trifluoroacetate (0.23g), copper iodide (0.3g) and toluene (5ml) and the resulting mixture heated at reflux under Dean-Stark conditions for 3h, before refluxing for a further 20h. The reaction mixture was cooled, poured into water/ether and filtered through kieselguhr. The aqueous layer from the filtrate was extracted with ether, and the combined ether extracts washed with water, dried and evaporated. The aqueous was re-extracted with dichloromethane and the extract evaporated. The combined extracts were chromatographed on silica gel, eluting with methanol-dichloromethane mixtures, to afford the title product (0.001g). Mass Spectrum (Electrospray LC/MS): Found 466 (MH^+). $C_{21}H_{19}F_4N_5OS$ requires 465.

The compounds in the table below were prepared using methods described above



Example	X	R	Ar^2	Ar^1	Mass Spectrum (Electrospray LC/MS), API^+
267	CH_2	H			Found 486 (MH^+). $C_{24}H_{29}{}^{35}ClFN_7O$ requires 485.
268	CH_2	H			Found 526 (MH^+). $C_{27}H_{33}{}^{35}ClFN_7O$ requires 525.
269	CH_2	H			Found 540 (MH^+). $C_{28}H_{35}{}^{35}ClFN_7O$ requires 539.
270	CH_2	Me			Found 440 (MH^+). $C_{21}H_{22}{}^{79}BrN_5O$ requires 439.
271	CH_2	Me			Found 457 (MH^+). $C_{18}H_{19}{}^{79}Br^{35}Cl_2N_4O$ requires 456.
272	CH_2	H			Found 489 (MH^+). $C_{23}H_{26}{}^{35}ClFN_6OS$ requires 488.

273	CH_2	Me			Found 454 (MH^+). $C_{22}H_{24}{}^{79}BrN_5O$ requires 453.
274	CH_2	Me			Found: 454 (MH^+). $C_{22}H_{24}{}^{79}BrN_5O$ requires 453.
275	CH_2	H			Found 446 (MH^+). $C_{21}H_{21}{}^{35}ClFN_5OS$ requires 445.

It is understood that the present invention covers all combinations of particular and preferred groups described herein above.

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

CHO-DG44 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 37C in 5% CO_2.

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 $CaCl_2$, 1.2 mM $MgCl_2$ 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 60 min at 37C 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 37C in 5% CO_2 for 30 minutes. Cell plates were then transferred to the Fluorescent

Imaging Plate Reader (FLIPR, Molecular Devices) instrument. 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 seconds (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, *TiPS*, 1995, **16**, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

Kb= IC50/(1+([3/EC50])

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

Compounds of Examples tested according to this method had pKb values in the range 6.7 – 9.7 at the human cloned orexin-1 receptor.

The orexin-2 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

CHO-DG44 cells expressing the human orexin-2 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 37C in 5% CO_2.

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 $CaCl_2$, 1.2 mM $MgCl_2$ 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 10.0 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 60 min at 37C in 5% CO_2. 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 37C in 5% CO_2 for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. 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, *TiPS*, 1995, **16**, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

$$Kb = IC50/(1+([3/EC50])$$

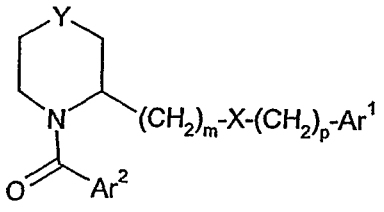
where EC50 was the potency of human orexin-A determined in the assay (in nM terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values in the range <6.3 – 9.1 at the human cloned orexin-2 receptor.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compound of formula (I):



(I)

wherein:

Y represents a bond, oxygen, or a group $(CH_2)_n$, wherein n represents 1, 2 or 3

m represents 1, 2, or 3;

p represents 0 or 1;

X is NR, wherein R is H or (C_{1-4})alkyl;

Ar^1 is aryl, or a mono or bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S; any of which may be optionally substituted;

Ar^2 represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R^1 and further optional substituents; or Ar^2 represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

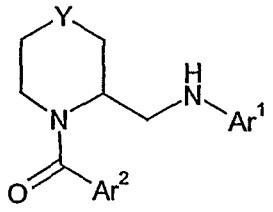
R^1 represents hydrogen, optionally substituted$(C_{1-4}$)alkoxy, halo, cyano, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S;

wherein when Y is a bond Ar^2 can not be 2-naphthyl;

when Ar^1 is aryl p is not 1;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (Ia);



(Ia)

wherein:

Y represents a bond, oxygen, or a group $(CH_2)_n$, wherein n represents 1, 2 or 3

Ar^1 is a mono or bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S; any of which may be optionally substituted;

Ar^2 represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R^1 and further optional substituents; or Ar^2 represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

R^1 represents hydrogen, optionally substituted(C_{1-4})alkoxy, halo, cyano, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S;

wherein when Y is a bond then Ar^2 can not be 2-naphthyl;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2 wherein Y is a bond, oxygen or $(CH_2)_n$ where n is 1 or 2.

4. A compound according to any preceding claim wherein Ar^2 represents an optionally substituted phenyl, pyridyl, thiazolyl, pyrazolyl, benzofuryl, naphthyl, triazolyl, quinoxalinyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothienyl, benzotriazolyl, benzothiazolyl, indolyl or thienyl.

5. A compound according to any preceding claim wherein Ar^1 represents an optionally substituted is benzoxazolyl, benzimidazolyl, quinoxalinyl, quinazolinyl, pyrimidinyl, pyridinyl, naphthyridinyl, quinolinyl, pyridopyrimidine, thiazolyl, oxazolylpyridinyl, benzothiazolyl, isoquinolinyl or pyrazinyl.

6. A compound according to any preceding claim wherein R^1 is selected from trifluoromethoxy, methoxy, ethoxy, halo, cyano or an optionally substituted phenyl, pyridyl, pyrazolyl, pyrimidinyl, or oxadiazolyl group.

7. A compound of formula (I) as defined in any one of Examples 1 to 275, or a pharmaceutically acceptable salt of any one thereof.

8. 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.

9. 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.