Title: PYRIDO' 1,2-ALPHA PYRAZINE AND PIPERIDINE DERIVATIVES AS LIGANDS FOR THE NEUROPEPTIDE Y Y5 RECEPTOR

Abstract: Compounds of formula (I) R₁₆—A—R₂ wherein R₁ and R₂ are selected from the following combinations: R₁ is R₂ and R₂ is —SO₂—R₃, R₁ is R₂ —SO₂— and R₂ is —R₃, R₁ is R₂ —SO₂— and R₂ is —SO₂—R₄; and R₁ is R₂ —SO₂— and R₂ is —R₄; A is selected from Group 1a, Group 1b, Group 1c or Group 1d and B, R₃, R₄, R₅, p, q and n are as described within, and their pharmaceutically-acceptable salts, prodrugs and solvates are described. Also described are processes for their preparation, pharmaceutical compositions containing them and their use in the treatment of disorders mediated by the neuropeptide Y5 receptor.
PYRIDO'1,2-A-PYRAZINE AND PIPERIDINE DERIVATIVES AS LIGANDS FOR THE NEUROPEPTIDE Y Y5 RECEPTOR

This invention relates to compounds which antagonise the interaction between neuropeptide Y (NPY) and the neuropeptide Y5 (NPY-5) receptor sub-type. This invention also relates to processes for the manufacture of NPY-5 receptor antagonists or agonists, pharmaceutically-acceptable salts thereof, and to novel pharmaceutical compositions of NPY-5 receptor antagonists or agonists.

NPY is a 36 amino acid polypeptide which is a member of the pancreatic polypeptide family of regulatory peptides with widespread distribution throughout the mammalian system. NPY is the most abundant neuropeptide in the central and peripheral nervous systems and has been shown to have powerful and complex effects on feeding, anxiety, circadian rhythms, reproduction, pituitary-adrenocortical axis function, memory retention, seizures, thermoregulation, and cardiovascular and gastrointestinal functions. NPY interacts with a heterogeneous population of at least six receptor subtypes, Y1-Y6, which activate adenylyl cyclase via a G-protein. For reviews of NPY see: CRC Critical Reviews in Neurobiology, (1988) 4, 97-135; Regulatory Peptides (1996) 62, 1-11.

One of the most striking actions of NPY is induction of feeding in a variety of vertebrate species. Direct injection of NPY into the hypothalamus of satiated rats can increase food intake up to 10-fold over a 4 hour period and NPY is the only known peptide which can cause animals to eat until they are obese. Recent studies on NPY have focussed on the identification of the NPY receptor responsible for the regulation of feeding. The NPY-5 receptor has been identified as the receptor most closely matching a proposed appetite receptor. The functional role of this receptor was addressed by receptor blockade studies. Intra-cerebro-ventricular injection of NPY-5 receptor antisense oligodeoxynucleotides prevented the increase in hypothalamic NPY levels during food deprivation and inhibited fasting-induced food intake in rats [Schaffhauser et al (1997) Diabetes 46, 1792 - 1798]. Thus the NPY-5 receptor is a potential pharmacological target in the modulation of feeding disorders such as obesity. For reviews on the association between NPY and feeding see: Zimanyi et al (1998) Current Pharm Des 4, 349-66; Heinrichs et al (1998) Vitamins and Hormones 54, 51-66.

Obesity is a large and ever expanding problem in affluent societies, which has reached epidemic proportions. According to the US Institute of Medicine, 59% of Americans are
clinically obese or at least 20% above their ideal body weight. Obesity is associated with susceptibility to a number of other conditions e.g. non-insulin-dependent diabetes, hypertension, dyslipidaemia and coronary heart disease. These conditions lead to reduction in life expectancy and decreased quality of life. The overall financial burden of obesity is difficult to quantify but it has been estimated that in the US it may account for 6-8% of total healthcare expenditure.

Thus there is need for pharmaceutical agents which have efficacy in the treatment of eating disorders such as obesity. Modulation of NPY activity through antagonism at the NPY-5 receptor offers one potential target for pharmacological intervention in these conditions.

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

\[ R_1 - A - R_2 \]

formula (I)

wherein:

15 \( R_1 \) and \( R_2 \) are selected from the following combinations:

- \( R_1 \) is \( R_4 - \) and \( R_2 \) is \( -SO_2 - R_5 \),
- \( R_1 \) is \( R_4 - SO_2 - \) and \( R_2 \) is \( -R_5 \),
- \( R_1 \) is \( R_5 - \) and \( R_2 \) is \( -SO_2 - R_4 \); and
- \( R_1 \) is \( R_5 - SO_2 - \) and \( R_2 \) is \( -R_4 \);

20 \( A \) is selected from Group 1a, Group 1b, Group 1c or Group 1d

Group 1a

\[ \text{N} \quad (\text{CH}_2)_p \quad \text{N} \quad (\text{CH}_2)_q \quad \text{N} \]

Group 1b

\[ \text{N} \quad (\text{CH}_2)_p \quad \text{N} \quad (\text{CH}_2)_q \quad \text{N} \]

Group 1c

\[ \text{N} \quad (\text{CH}_2)_p \quad \text{N} \quad (\text{CH}_2)_q \quad \text{N} \]

Group 1d

25 \( B \) is a direct bond, methylene or carbonyl;
\( R_3 \) is hydrogen, \( C_{1-4} \) alkyl or phenyl\( C_{1-4} \) alkyl;
R₁ is a monocyclic nitrogen-containing heteroaryl substituted with an amino group, a bicyclic nitrogen-containing heteroaryl, naphthyl or a carbocyclic ring, wherein any monocyclic heteroaryl, the bicyclic heteroaryl, the naphthyl and carbocyclic ring are optionally substituted by one or more substituents independently selected from halo, amino or C₁₋₄ alkyl, wherein the C₁₋₄ alkyl is optionally substituted by 3 substituents independently selected from halo and C₁₋₄ alkoxy;

R₂ is C₁₋₄ alkyl, aryl, arylC₁₋₄ alkyl, N-C₁₋₄ alkylamino or N,N-di-C₁₋₄ alkylamino, wherein any aryl is optionally substituted by one or more substituents independently selected from halo, alkyl, cyano, C₁₋₄ alkoxy, C₁₋₄ alkanoyl and amino; and

p is 1 or 2;

q is 1 or 2; and

n is 1 or 2;

or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

Novel compounds of formula (I) have not previously been proposed for use in therapy.

Thus, according to a further aspect of the invention there is provided the use of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or solvate thereof as a medicament.

According to a further aspect of the invention there is provided a method of treatment, in a warm-blooded animal, of disorders mediated by the neuropeptide Y5 receptor comprising administering to said warm-blooded animal a therapeutically effective amount of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or solvate thereof.

According to a further aspect of the invention there is provided the use of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or solvate thereof in the manufacture of a medicament for the treatment of a disorder mediated by the neuropeptide Y5 receptor, in a warm-blooded animal.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically-acceptable salt, pro-drug or solvate thereof, in admixture with a pharmaceutically-acceptable diluent or carrier for the treatment of a warm-blooded animal, in need of treatment of disorders mediated by the neuropeptide Y5 receptor.

To treat disorders mediated by the neuropeptide Y5 receptor, neuropeptide Y5 receptor agonists or antagonists can be administered.
According to a further aspect of the invention there is provided a method of treatment, in a warm-blooded animal, of eating disorders, comprising administering a therapeutically effective amount of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or solvate thereof.

According to a further aspect of the invention there is provided the use of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or solvate thereof in the manufacture of a medicament for the treatment of eating disorders in a warm-blooded animal.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically-acceptable salt, pro-drug or solvate thereof, in admixture with a pharmaceutically-acceptable diluent or carrier for the treatment of eating disorders in a warm-blooded animal.

According to a further aspect of the invention there is provided a method of promoting weight loss, in a warm-blooded animal, comprising administering a therapeutically effective amount of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or solvate thereof.

According to a further aspect of the invention there is provided the use of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or solvate thereof in the manufacture of a medicament for promoting weight loss in a warm-blooded animal.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically-acceptable salt, pro-drug or solvate thereof, in admixture with a pharmaceutically-acceptable diluent or carrier for promoting weight loss in a warm-blooded animal.

The invention also includes compositions comprising a mixture of components including a compound of formula (I). For example a composition comprising a mixture of a compound of formula (I) and the corresponding compound in the cis configuration.

Examples of disorders mediated by the neuropeptide Y5 receptor are eating disorders. Examples of eating disorders include obesity, bulimia or anorexia. Examples of eating disorders include obesity and related disorders, bulimia or anorexia. Examples of "related disorders" are diabetes dyslipidaemia, hypertension and sleep disturbances.

Preferably "related disorders" refers to diabetes.

For the avoidance of doubt the numbering of the ring positions on Groups 1a, 1b, 1c and 1d is as follows:
In this specification the generic term ‘alkyl’ includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as ‘propyl’ are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as ‘isopropyl’ are specific for the branched-chain version only. An analogous convention applies to other generic terms.

The term “aryl” refers to phenyl or naphthyl.

The term “monocyclic nitrogen-containing heteroaryl” refers to a 5-6 membered fully saturated monocyclic ring containing up to 3 nitrogen atoms, linked via ring carbon atoms. Examples include pyridine, pyrimidine, triazole, pyrrole, pyrazole or imidazole.

The term ‘carbocyclic ring’ refers to a totally saturated or partially saturated 5,6 or 6,6 bicyclic ring containing between 9-10 carbon atoms. Examples include indene, bicyclo[4.4.0]deca-1(6)-ene, and 1,2,3,4-tetrahydronaphthalene.

The term “bicyclic nitrogen-containing heteroaryl” refers to a 9-10 membered aromatic bicyclic ring containing up to 3 nitrogen atoms, linked via ring carbon atoms. Examples include: quinoline, isoquinoline, quinazoline, quinoxaline, phthalazine, cinnoline, 1H-cyclopentapyrazine, or 1H-cyclopenta[c]-1,2,4-triazine.

The term “halo” refers to fluoro, chloro, bromo or iodo.

Examples of \( C_{1-4} \text{alkyl} \) include methyl, ethyl, propyl, isopropyl, sec-butyl and tert-butyl; examples of \( C_{1-4} \text{alkoxy} \) include methoxy, ethoxy and propoxy; examples of \( C_{1-4} \text{alkanoyl} \) include formyl, acetyl and propionyl; examples of \( N-C_{1-4} \text{alkylamino} \) include \( N \)-methylamino and \( N \)-ethylamino; and examples of \( N,N \text{-diC}_{1-4} \text{alkylamino} \) include \( N,N \)-dimethylamino and \( N \)-methyl-N-ethylamino.

A suitable pharmaceutically-acceptable salt of a compound of formula (I) is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline
earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an
organic base which affords a physiologically-acceptable cation, for example a salt with
methylamine, dimethylamine, trimethylamine, piperidine, morpholine or
tris-(2-hydroxyethyl)amine.

The compounds of the formula (I) may be administered in the form of a pro-drug
which is broken down in the human or animal body to give a compound of the formula (I).
Examples of pro-drugs include in-vivo cleavable amides of a compound of the formula (I).
Various forms of pro-drugs are known in the art. For examples of such pro-drug
derivatives, see:

a) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in
b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and
H. Bundgaard, Chapter 5 “Design and Application of Pro-drugs”, by H. Bundgaard
p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and

Examples of in vivo cleavable amides of a compound of formula (I) include: an
N-C₄ alkylamide and an N,N-di-C₄ alkylamide such as N-methyl, N-ethyl, N-propyl,
N,N-dimethyl, N-ethyl-N-methyl or N,N-diethylamide.

It is to be understood that, insofar as certain of the compounds of formula (I) defined
above may exist in optically active or racemic forms by virtue of one or more asymmetric
carbon atoms, the invention includes in its definition any such optically active or racemic
form which possesses the property of being an agonist or antagonist at the neuropeptide Y5
receptor. The synthesis of optically active forms may be carried out by standard techniques of
organic chemistry well known in the art, for example by synthesis from optically active
starting materials or by resolution of a racemic form. Similarly, binding to the neuropeptide
Y5 receptor may be evaluated using the standard laboratory techniques referred to hereinafter.

The invention also relates to any and all tautomeric forms of the compounds of the
formula (I) that possess neuropeptide Y5 receptor agonist or antagonist activity.

It will also be understood that certain compounds of the present invention may exist in
solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the
present invention encompasses all such solvated forms which possess the property of interacting with the neuropeptide Y5 receptor.

Preferably A is Group 1a or Group 1b.

In another aspect of the invention, preferably A is Group 1c or Group 1d.

Preferably R₄ is R₅—and R₃ is—SO₂—R₅.

Preferably R₄ is a bicyclic nitrogen containing heteroaryl, naphthyl or a carbocyclic ring, optionally substituted as described above. More preferably R₄ is a bicyclic nitrogen containing heteroaryl or a carbocyclic ring, optionally substituted as described above. Even more preferably R₄ is quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxaliny1 or 1,2,3,4-tetrahydronaphthyl, optionally substituted as described above.

Particularly preferably R₄ is quinolinyl, quinazolinyl or 1,2,3,4-tetrahydronaphthyl, optionally substituted as described above.

Preferred optional substituents on R₄ are amino, C₄₋₅alkyl, halo-substituted-C₄₋₅alkyl, chloro, fluoro or amino.

More preferably optional substituents on R₄ are chloro, fluoro, methyl, ethyl, trifluoromethyl or amino.

Preferably p is 1 or 2 and q is 1. More preferably p is 1 and q is 1. Preferably n is 1.

Preferably B is a direct bond or methylene. More preferably B is a direct bond.

Preferably R₅ is aryl, optionally substituted as described above. More preferably R₅ is naphthyl, optionally substituted as described above.

Preferably R₃ is hydrogen, benzyl or C₁₋₅alkyl. More preferably R₃ is C₁₋₅alkyl. Even more preferably R₃ is ethyl or methyl.

A preferred group of compounds of the invention include a compound of formula (I) wherein:

R₁ and R₂ are selected from the following combinations:

R₁ is R₄—and R₂ is —SO₂—R₅,

R₁ is R₅—SO₂—and R₂ is —R₅,

R₁ is R₅—and R₂ is —SO₂—R₄; and

R₁ is R₅—SO₂—and R₂ is —R₄;

A is selected from Group 1a, Group 1b, Group 1c or Group 1d;

R₃ is hydrogen, C₁₋₅alkyl or phenylC₁₋₅alkyl;

p is 1;
q is 1;
n is 1;
B is a direct bond or methylene;
Rₚ is a monocyclic nitrogen-containing heteroaryl substituted with an amino group, a bicyclic nitrogen-containing heteroaryl, naphthyl or a carbocyclic ring, wherein any monocyclic heteroaryl, the bicyclic heteroaryl, the naphthyl and carbocyclic ring are optionally substituted by one or more substituents independently selected from halo, amino or C₁₋₄alkyl, wherein the C₁₋₄alkyl is optionally substituted by 3 substituents independently selected from halo and C₁₋₄alkoxy;
R₃ is naphthyl or phenyl;
or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.
A preferred group of compounds of the invention include a compound of formula (I) wherein:
R₁ and R₂ are selected from the following combination:
R₁ is R₄— and R₂ is —SO₂—R₃,
A is selected from Group 1a, Group 1b, Group 1c or Group 1d
p is 1;
q is 1;
n is 1;
B is a direct bond;
R₃ is hydrogen, C₁₋₄alkyl or phenylC₁₋₄alkyl;
R₄ is an optionally substituted bicyclic nitrogen-containing heteroaryl, naphthyl or 1,2,3,4-tetrahydronaphthyl; and
R₅ is naphthyl or phenyl;
or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.
A further preferred group of compounds of the invention include a compound of formula (I) wherein:
R₁ and R₂ are selected from the following combination:
R₁ is R₄— and R₂ is —SO₂—R₃,
A is Group 1a or 1b;
p is 1;
q is 1;
B is a direct bond or methylene;
R₃ is hydrogen, C₄₋alkyl or phenylC₄₋alkyl;
R₄ is an optionally substituted quinoline, quinazoline, naphthyl or 1,2,3,4-tetrahydronaphthyl; and

R₅ is naphthyl or phenyl;
or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

A further preferred group of compounds of the invention include a compound of formula (I) wherein:

R₁ and R₂ are selected from the following combinations:

R₁ is R₅— and R₂ is —SO₂—R₃,
R₁ is R₅—SO₂— and R₂ is —R₃,
R₁ is R₅— and R₂ is —SO₂—R₄; and
R₁ is R₅—SO₂— and R₂ is —R₄;
A is selected from Group 1a or Group 1b;

B is a direct bond, methylene or carbonyl;
R₃ is hydrogen, C₄₋alkyl or phenylC₄₋alkyl;
R₄ is a monocyclic nitrogen-containing heteroaryl substituted with an amino group, a bicyclic nitrogen-containing heteroaryl, naphthyl or a carbocyclic ring, wherein any monocyclic heteroaryl, the bicyclic heteroaryl, the naphthyl and carbocyclic ring are optionally substituted by one or more substituents independently selected from halo, amino or C₄₋alkyl, wherein the C₄₋alkyl is optionally substituted by 3 substituents independently selected from halo and C₄₋alkoxy;
R₅ is C₄₋alkyl, aryl, arylC₄₋alkyl, N-C₄₋alkylamino or N,N-di-C₄₋alkylamino, wherein any aryl is optionally substituted by one or more substituents independently selected from halo, alkyl, cyano, C₄₋alkoxy, C₄₋alkanoyl and amino; and
p is 1 or 2;
q is 1 or 2; and
n is 1 or 2;
or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

A further preferred group of compounds of the invention include a compound of formula (I) wherein:

R₁ and R₂ are selected from the following combinations:
R₁ is R₄— and R₂ is —SO₂—R₅,
R₁ is R₄—SO₂— and R₂ is —R₅,
R₁ is R₅— and R₂ is —SO₂—R₄; and
R₁ is R₅—SO₂— and R₂ is —R₄;

A is selected from Group 1c or Group 1d;
B is a direct bond, methylene or carbonyl;
R₃ is hydrogen, C₁₄-alkyl or phenylC₁₄-alkyl;
R₄ is a monocyclic nitrogen-containing heteroaryl substituted with an amino group, a bicyclic nitrogen-containing heteroaryl, naphthyl or a carbocyclic ring, wherein any

monocyclic heteroaryl, the bicyclic heteroaryl, the naphthyl and carbocyclic ring are optionally substituted by one or more substituents independently selected from halo, amino or C₁₄-alkyl, wherein the C₁₄-alkyl is optionally substituted by 3 substituents independently selected from halo and C₁₄-alkoxy;

R₃ is C₁₄-alkyl, aryl, arylC₁₄-alkyl, N-C₁₄-alkylamino or N,N-di-C₁₄-alkylamino, wherein any aryl is optionally substituted by one or more substituents independently selected from halo, alkyl, cyano, C₁₄-alkoxy, C₁₄-alkanoyl and amino; and

p is 1 or 2;
q is 1 or 2; and
n is 1 or 2;

or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

Particular compounds of the invention are:

trans-2-(naphth-1-ylsulphonyl)-7-[(4-aminooquinazolin-2-yl)aminomethyl]octahydro-2H-pyrido[1,2-α]pyrazine;
trans-1-benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(2-methylquinolin-4-yl)aminomethyl]piperidine;
trans-2-phenylsulphonylaminomethyl-5-[(2-methylquinolin-4-yl)aminomethyl]piperidine;
trans-2-(naphth-1-ylsulphonyl)-7-[(1,2,3,4-tetrahydronapth-2-yl)methylaminomethyl]octahydro-2H-pyrido[1,2-α]pyrazine;
trans-2-(naphth-1-ylsulphonyl)-7-[(4-aminooquinazolin-2-yl)aminomethyl]octahydro-2H-pyrido[1,2-α]pyrazine; and

trans-1-benzyl-2-(phenylsulphonylaminomethyl)-5-[(4-aminooquinazolin-2-yl)aminomethyl]piperidine.
More particular compounds of the invention are:

*trans*-1-ethyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(2-methylquinolin-4-yl)aminomethyl]piperidine;

*trans*-2-(naphth-1-ylsulphonyl)-7-[(2-methyl-7-chloroquinolin-4-yl)aminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine;

*trans*-2-(naphth-1-ylsulphonyl)-7-[(2-methyl-4-fluoroquinolin-4-yl)aminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine;

*trans*-2-(naphth-1-ylsulphonyl)-7-[(2-methylquinolin-4-yl)aminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine; and

*trans*-1-ethyl-2-phenylsulphonylaminomethyl-5-[(2-methylquinolin-4-yl)aminomethyl]piperidine.

A compound of formula (I), or a pharmaceutically-acceptable salt or *in vivo* hydrolysable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically related compounds. Such processes, when used to prepare compounds of formula (I), or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, are provided as a further feature of the invention and are illustrated by the following representative examples in which *R*₁, *R*₂, *R*₃, *R*₄, *R*₅, *A*, *B*, *n*, *p* and *q* have the same meaning as herein before defined. *R*₄ and *R*₅ bears the same optional substituents as described herein unless another substituent is drawn thereon (optionally protected as necessary). The reader is referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents. The reader is referred to Protective Groups in Organic Synthesis 2nd Edition, by Green et al, published by John Wiley & Sons for general guidance on protecting groups.

According to another aspect of the invention there is provided a process for preparing a compound of formula (I) wherein *R*₁, *R*₂, *R*₃, *R*₄, *R*₅, *A*, *B*, *n*, *p* and *q* are, unless otherwise specified as defined in formula (I) which comprises:

(a) reacting an amine of formula (II), wherein *B* is a direct bond and *R*₂ is selected from

\[ \text{H} - \text{A} - \text{R}_2 \]

formula (II)

with a compound of the formula *R*₅₁ wherein *L* is a displaceable group;

(b) reacting an amine of formula (III) wherein *R*₄ is selected from *R*₅₁ or *R*₅₂—
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\[ R_1 - A - H \]

formula (III)

with a sulphonyl compound of the formula \( LR_2 \), wherein \( L \) is a displaceable group and \( R_2 \) is selected from \( -SO_2 - R_4 \) or \( -SO_2 - R_5 \);

(c) for a compound of formula (I) wherein \( A \) is Group 1a or Group 1b and \( R_3 \) is other than hydrogen, reacting a group of formula (I) wherein \( A \) is Group 1a or Group 1b and \( R_3 \) is hydrogen, with a group of the formula \( LR_3 \) wherein \( L \) is a displaceable group;

(d) for a compound of formula (I) wherein \( A \) is Group 1c or Group 1d and \( B \) is carbonyl, reacting an amine of formula (IV)

\[ H_2 N - A' - SO_2 - R_2 \]

formula (IV)

wherein \( A' \) is selected from Group 1c' or Group 1d'

\[ \text{Group 1c'} \quad \text{Group 1d'} \]

15 with an acid of formula (V)

\[ R_1 - C - O \]

formula (V)

or an activated derivative thereof;

(e) for a compound of formula (I) wherein \( A \) is Group 1c or Group 1d and \( B \) is methylene, reacting a compound of formula (I) wherein \( A \) is Group 1c or Group 1d and \( B \) is carbonyl with a suitable reducing agent;

And thereafter if necessary

(i) converting a compound of formula (I) into another compound of formula (I);

(ii) removing any protecting groups;

25 (iii) forming a pharmaceutically-acceptable salt.

\( L \) is a displaceable group, suitable values for \( L \) include halo, for example chloro or bromo.
Specific reaction conditions for the above reactions are as follows:

*Process a)* an amine of formula (II) and a compound of formula R₃L can be reacted together:

(i) at a temperature of about 100 to 140°C in a high boiling point aliphatic alcohol, such as pentanol or isoamyl alcohol; or

(ii) under standard Buchwald conditions (for example see *J. Am. Chem. Soc.*, 118, 7215; *J. Am. Chem. Soc.*, 119, 8451; *J. Org. Chem.*, 62, 1568 and 6066) for example in the presence of a suitable palladium catalyst, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as sodium-t-butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and at a temperature in the range of 70 to 100°C.

*Process b)* an amine of formula (III) and a compound of formula LR₂ can be reacted together in the presence of a suitable base, such as pyridine, in a suitable solvent such as tetrahydrofuran or dichloromethane, at a temperature in the range 0 to 30°C;

*Process c)* a compound of formula (I), wherein A is Group 1a or 1b and R₃ is hydrogen and a compound of formula LR₃ can be reacted together in the presence of a suitable base, for example potassium carbonate, in a suitable solvent such as dimethylformamide, at a temperature between 0 to 30°C. A compound of formula (I), wherein A is Group 1a or Group 1b and R₃ is hydrogen can be prepared from a compound of formula (I) wherein A is Group 1a or Group 1b and R₃ is a protecting group by deprotection;

*Process d)* Amines of formula (IV) and acids of formula (V) may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-alkyl-pyrindines such as 2,6-lutidine or 2,6-di-tert-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of 0 to 30°C.

Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of
compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of 0 to 30°C.

5 Process e) a compound of formula (I) wherein A is Group 1c or Group 1d and B is carbonyl, as prepared in (d) above, can be converted to a compound of formula (I) wherein A is Group 1c or Group 1d and B is methylene under suitable reducing conditions such as using lithium aluminium hydride or borane/tetrahydrofuran in an inert solvent such as tetrahydrofuran at a temperature of 0°C under argon, followed by refluxing.

10 Compounds of formula (II) wherein A is Group 1a, can be prepared according to Scheme 1, wherein P is a protecting group. The starting compound can be prepared as described in Urban (1995) Journal of Heterocyclic Chemistry 32, 857-861.

Compounds of formula (II) wherein A is Group 1d, can be prepared according to Scheme 2, wherein P is a protecting group . The starting compound can be prepared as described in Urban (1995) Journal of Heterocyclic Chemistry 32, 857-861.

In Scheme 1 and Scheme 2 the compounds are illustrated as one of the trans isomers, but are in fact a racemic mixture of the two trans isomers. Pure samples of the individual trans isomers can be obtained at the end of the synthesis using separation methods well known in the art. Alternatively the skilled man may separate the individual trans isomers of one of the intermediates and then convert to a compound of formula (I).
Scheme 1
Reaction conditions referred to in Scheme 1 and Scheme 2 are as described below.

Reaction Conditions (i) - an appropriate protecting agent can be added using reactions well known in the art, for example, reacting with benzyl bromide in the presence of a suitable base, such as potassium carbonate, in the presence of a suitable solvent, such as dimethylformamide, at a temperature in the range 0 to 30°C.

Reaction Conditions (ii) - selective hydrolysis can be facilitated using 1 equivalent of sodium hydroxide in a suitable solvent, such as an aliphatic alcohol, for example, methanol at a temperature in the range 0 to 30°C.

Reaction Conditions (iii) - the free carboxylic acid can be converted to the amide, for example by reacting with an alkylchboroformate in a suitable solvent, such as methylene chloride, chloroform or dry tetrahydrofuran, in the presence of a suitable base, such as triethylamine or pyridine, at a temperature between -10°C and 0°C to form the mixed anhydride, followed by reacting with the ammonium hydroxide at temperature in the range 0 to 30°C.

Reaction Conditions (iv) - reduction of the carbonyl to a methylene can be facilitated by reactions well known in the art, for example using lithium aluminium hydride or
borane/tetrahydrofuran in an inert solvent such as tetrahydrofuran at a temperature of 0°C under argon, followed by refluxing.

Reaction Conditions (v) - an appropriate protecting agent can be added using reactions well known in the art, for example by reacting with di-tert-butyl dicarbonate in a suitable solvent, such as tetrahydrofuran or dichloromethane, at room temperature.

Reaction Conditions (vi) - a hydroxyl group can be converted to an amino group as follows:

a) activation of the hydroxyl by reaction with methane sulphonyl chloride or tosyl chloride, in the presence of a suitable base such as pyridine or triethylamine, in a suitable solvent such as dichloromethane or pyridine at a temperature in the range 0 to 30°C followed by;

b) reaction with sodium azide in a suitable solvent such as dimethylformamide at a temperature of about 60°C, followed by;

c) reaction with triphenylphosphine in a suitable solvent such as tetrahydrofuran in the presence of water at temperature in the range 0 to 30°C.

Reaction Condition (vii) - reaction with the appropriate sulphonyl halide using a suitable base, such as pyridine or triethylamine, in a suitable solvent, such as tetrahydrofuran or dichloromethane, at temperature in the range 0 to 30°C.

Reaction Condition (viii) - protecting group P can be removed can be removed by reactions well known in the art, for example when P is tert-butyloxycarbonyl this can be removed, for example, by a strong acid, such as trifluoroacetic acid, at temperature in the range 0 to 30°C, in a suitable solvent, such as dichloromethane or tetrahydrofuran.

A compound of formula (III) can be prepared using analogous reactions to those illustrated in Scheme 1 and Scheme 2 except at Reaction Condition (vii) the free amino groups is reacted with a compound of the formula R,L, wherein L is a leaving group, as described for (a) above.

A compound of formula (IV) can be prepared as described in process (a) and process (b) above. A compound of formula (V) can be prepared by processes well known in the art.

In order to use a compound of the formula (I) or a pharmaceutically-acceptable salt, pro-drug or solvate thereof, for the therapeutic treatment (including prophylactic treatment) of warm-blooded animals, including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

According to this aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically-acceptable
salt, pro-drug or solvate thereof, as defined herein before in association with a 
pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example 
as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible 
powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, 
gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for 
example as a finely divided powder or a liquid aerosol), for administration by insufflation (for 
example as a finely divided powder) or for parenteral administration (for example as a sterile 
aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing 
or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using 
conventional pharmaceutical excipients, well known in the art. Thus, compositions intended 
for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or 
preservative agents.

Suitable pharmaceutically-acceptable excipients for a tablet formulation include, for 
example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium 
carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding 
agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; 
preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as 
ascorbic acid. Tablet formulations may be uncoated or coated either to modify their 
disintegration and the subsequent absorption of the active ingredient within the 
gastrointestinal tract, or to improve their stability and/or appearance, in either case, using 
conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the 
active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium 
phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with 
water or an oil such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form 
together with one or more suspending agents, such as sodium carboxymethylcellulose, 
methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum 
tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation 
products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or
condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxyacetol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, antioxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable
aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butandiol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedures well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μm or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent
compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

The compounds of this invention may be used in combination with other drugs and therapies used in the treatment of disease states which would benefit from antagonism at the neuropeptide Y5 receptor. For example, the compounds of the formula (I) or a pharmaceutically-acceptable salt, pro-drug or solvate thereof, could be used in combination with drugs and therapies used in the treatment of eating disorders, including, but not limited to, obesity, bulimia or anorexia.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

Although the compounds of the formula (I) are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to antagonise binding at the neuropeptide Y5 receptor. Thus, they are useful as
pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

**Biological Assays**

The activity of compounds of the invention was measured in a neuropeptide Y5 receptor binding assay as follows. Compounds were also tested in binding assays for the neuropeptide Y1 and neuropeptide Y2 receptors. Activity against these 2 receptors is contraindicated for a neuropeptide Y5 antagonist.

a) expression of human neuropeptide Y5 receptor in High 5TM insect cells.

High 5TM insect cells were obtained from Invitrogen (catalogue N° B855-02) and stored in liquid nitrogen. Cells were revived from liquid nitrogen storage and grown at 28°C in 100 ml ExCell 405 (JRH Biosciences) serum free medium in a 250 ml conical flask (Corning) agitated at 140 rpm in an Innova 4330 orbital shaker (New Brunswick Scientific). Cultures were routinely sub-cultured every 3 - 4 days.

High 5TM insect cells were transfected with the human NPY5 receptor as follows.

PCR primers were designed against the huNPY5 receptor sequence, Genbank Accession Number U56079 [Gerald et. al (1996) Nature 382, 168-171], but starting at base 56 through to base 1393, to express the protein 10 amino acid residues shorter at the amino terminal end [see Borowsky et al (1998) Regulatory Peptides 75-76, 45-53]. These primers were used to amplify the huNPY5 receptor from human placenta genomic DNA by PCR.

This was then sub-cloned into pZERO2 (obtained from Invitrogen) for sequencing and re-cloned into pFASTBAC1(obtained from GIBCO BRL Life Technologies) for expression. Human NPYr was isolated from pZERO2 on BamHI fragment and sub-cloned into pFastbac1 on BamHI restriction site. The junctions were sequenced to ensure correct prior to expression.

A baculovirus containing the pFASTBAC1 was then generated using the Bac-to-BacTM baculovirus expression system [Anderson et al (1996) FASEB Journal 10(6), 727-726] (obtained from GIBCO BRL Life Technologies) following the protocol supplied with this expression system by GIBCO BRL Life Technologies.

High 5TM insect cells were infected with the baculovirus to transfect the cells with the human neuropeptide Y5 receptor as follows: Batches were grown for membrane preparation by inoculating 5 L of ExCell 405TM medium in a 7 L Bioreactor (FT-Applikon) with 1.75 x 10⁹ mid log High 5TM cells. After 2-3 days growth at 28°C the mid log culture was infected with Baculovirus expressing the human NPY5 receptor at a multiplicity of infection (MOI) of
1.0. Cells (typically 1x10^10) were harvested 48 hours post infection by centrifugation (Heraeus Omnifuge 2.0RS 30 min, 296g, 4°C) and flash frozen in liquid nitrogen for storage at -80°C.

b) Membrane preparation procedure

The following buffer was prepared daily and stored at 4°C. 50mM Tris HCl pH 7.4, 5mM EDTA and 10% w.v. sucrose. A protease inhibitor cocktail (Boehringer Mannheim) was added to both buffers according to the manufacturers instruction. Cells were thawed rapidly in three times their packed cell volume of hypotonic buffer (3:1 mix of water and buffer) and lysed routinely on ice using five Vibra Cell Sonicator (Sonics and Materials Inc.) bursts of ten seconds for the High 5™ insect cells. The cell lysate (typically 10-15 ml) was carefully loaded onto a 10 ml 41% sucrose cushion which was topped off with lysis buffer and spun at 150,000g for 1 hour at 4°C in a Beckman Optima LE-80K Ultracentrifuge. The membrane fraction was carefully removed from the inter-phase and diluted at least four fold with lysis buffer. The membrane pellets were recovered by centrifugation at 150,000g for 20 min at 4°C in a Beckman Optima LE-80K Ultracentrifuge and re-suspended at 5x10^7 cell equivalents per ml. The re-suspended membranes were divided into working aliquots, routinely 1ml, flash frozen in liquid nitrogen and stored frozen at -80°C until use.

Prior to use the 1ml High 5™ membranes were thawed and resuspended in 8ml binding buffer (see below). Membranes are used at approximately 7 μg/ml of protein per incubate.

c) neuropeptide Y5 receptor binding assay

The following reagents were used:

Binding buffer: 50mM HEPES, 2.5mM CaCl₂, 1mM MgCl₂, 0.5% BSA, pH=7.4
Binding wash buffer: 50mM HEPES, 2.5mM CaCl₂, 1mM MgCl₂, 0.5M NaCl, 0.5% BSA, pH=7.4

Unifilter GFC filter plates: 50μl of 0.5% polyethyleneimine was added to each well and left to equilibrate for four hours before use
Incubation plates: 96 well polypropylene plates, siliconised prior to use
Test Compounds: Compounds were dissolved in DMSO at a concentration of 1mM. Final concentration of DMSO in the assay did not exceed 1%.

Peptide PYY (pancreatic polypeptide Y) - 10μM stock solution in binding buffer.

^125I PYY - 10μCi/ml stock solution, diluted 1:10 dilution, into binding buffer.
Assays were performed in 96 well microtitre plates. 10μl of diluted test compound was added to each well of a plate, followed by 80μl of membranes and 10μl of radiolabelled 125I PYY (0.01μCi per well). Total and non-specific binding controls were included in each plate. The non-specific binding wells received 10μl of Peptide PYY from the 10μM stock solution, whilst the total binding wells received 10μl of binding buffer. For each assay, a duplicate dose response of peptide PYY was included, top concentration 1μM.

The plates were incubated for two hours at room temperature with mixing, and then filtered onto the pre-treated filter plates. The incubation plates were washed twice with 150μl of cold binding wash buffer per well, then the filter plates were further washed with approximately 2.5ml per well. The filter plates were dried overnight at room temperature, the bottoms were sealed, and 20μl of Scintillant (Microscint 40, Canberra Packard) was added to each well. The tops of the plates were sealed and the plates were counted for 1 minute on a protocol set up for 125I on a 96 well plate liquid scintillation counter (Top Count, Canberra Packard).

Compounds were considered to be active if they inhibited the binding by more than 50% at a concentration of 10μM. Dose responses were carried out on all compounds found to be active (8 point curves in duplicate).

Although the pharmacological properties of the compounds of the formula (I) vary with structural change as expected, in general compounds of the formula (I) possess an IC₅₀ in the above test in the range, for example, 0.0002 to 200μM. For example trans-2-phenylsulphonylaminomethyl-5-[(2-methylquinolin-4-yl)aminomethyl]piperidine has an IC₅₀ for the neuropeptide Y5 receptor of 123nM and trans-2-((naphth-1-ylsulphonyl)-7-[(1,2,3,4-tetrahydronaphth-2-yl)methylaminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine has an IC₅₀ for the neuropeptide Y5 receptor of 150nM.

The invention will now be illustrated by the following non-limiting Examples in which, unless otherwise stated:
(i) all commercially available reagents and solvents were used without further purification;
(ii) organic solvent extracts were dried over anhydrous Na₂SO₄ or MgSO₄ where appropriate;
(iii) concentrations and evaporations were carried out by rotary evaporation in vacuo;
(iv) operations were carried out at room temperature, that is in the range 18-26°C;
(v) yields, when given, are intended for the assistance of the reader only and are not necessarily the maximum attainable by diligent process development;
(vi) $^1$H and $^{13}$C NMR were recorded on Bruker DPX-300, DPX-400 or Varian Gemini 2000 instruments using CDCl$_3$ or Me$_2$SO-d$_6$ with Me$_4$Si as internal reference, chemical shifts are in $\delta$ (ppm) and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplets; q, quartet; m, multiplet; br, broad;

(vii) mass spectra were recorded on Micromass Platform positive and negative electrospray spectrometers;

(viii) for TLC analysis, Merck precoated TLC plates (silica gel 60 F254, d = 0.25 mm) were used. Flash chromatography was performed on silica (Merck Keiselgel: Art.9385);

**Solvent Systems (v/v/v)**

1. A1: dichloromethane
2. A2: dichloromethane / methanol 49:1
3. A3: dichloromethane / methanol 24:1
4. A4: dichloromethane / methanol 19:1
5. A5: dichloromethane / methanol 9:1
6. A6: dichloromethane / methanol 4:1
7. A7: dichloromethane / methanol / ammonium hydroxide 89:10:1
8. A8: dichloromethane / methanol / ammonium hydroxide 78:20:2
10. A10: dichloromethane / ethyl acetate 8:2
11. A11: ethyl acetate / isohexane 1:2
12. A12: ethyl acetate / isohexane 1:1
13. A13: ethyl acetate
14. A14: ethyl acetate / methanol 9:1

where a gradient solvent system is used, for example A1 to A13, this means a gradient between 100% A1 to 100% A13, i.e. 100% dichloromethane to 100% ethyl acetate and A1 to A13 then to A14 means a gradient between 100% A1 to 100% A13 followed by 100% A14;

(ix) the following abbreviations are used;

- DMAP = 4-dimethylaminopyridine;
- EDAC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide;
- DMF = N,N-dimethylformamide;
- THF = tetrahydrofuran;
- IPA = isopropyl alcohol;
TEA = triethylamine.

(x) compounds are a racemic mixture of the 2 \textit{trans}-isomers;

(xii) where a Mega Bond Elut cartridge is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI"; "Mega Bond Elut" is a trademark;

(xii) where an ‘isolute’ cartridge is referred to, this means an "ion exchange" extraction cartridge for adsorption of basic or acid material, i.e. a polypropylene tube containing a special grade of ion exchange sorbent, high purity, surface to pH ~7, incorporating a phase-separation filtering material, used according to the manufacturers instructions, obtained from Varian, Harbor City, California, USA under the name of "Extube, Chem Elut, ISOLUTE";

"Extube" is a registered trademark of International Sorbent Technology Limited;

(xiii) a soxhlet apparatus is a piece of equipment for the continuous extraction of a solid by a hot solvent. It is described in detail in 'Vogel's Textbook of Practical Organic Chemistry, Fifth Edition, page 164, Publisher: Longman Scientific and Technical;

(xiv) retention times are quoted for the following hplc column and gradient system

<table>
<thead>
<tr>
<th>Column</th>
<th>Solvent A</th>
<th>Solvent B</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.6mm x10cm</td>
<td>0.1% Formic Acid/ Water</td>
<td>0.1% Formic Acid / Acetonitrile</td>
</tr>
</tbody>
</table>

| Flow rate    | 1ml/min                        |

<table>
<thead>
<tr>
<th>Gradient</th>
<th>Time (mins)</th>
<th>A%</th>
<th>B%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.00</td>
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</tr>
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</tr>
<tr>
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<td>95</td>
<td>5</td>
</tr>
</tbody>
</table>

The examples are preceded by some general procedures and examples of synthesis of key intermediates which can be used in the synthesis of compounds of formula (I).
Intermediate XI

**trans-7-Aminomethyl-2-(naphth-1-ylsulphonyloctahydro-2H-pyrido[1,2-a]pyrazine**
can be prepared as follows:

a) **trans-7-chloromethyl-2-(naphth-1-ylsulphonyloctahydro-2H-pyrido[1,2-a]pyrazine**

1. Napthalene sulphonyl chloride (7.92g, 34.91mM) was added to a suspension of
   **trans-7-(hydroxymethyl)-1,3,4,6,7,8,9aoctahydro-2H-pyrido[1,2-a]pyrazine**
   (J. Heterocyclic Chem., 1995, 32, 857)(2.96g, 17.45 mM) in dichloromethane (10 ml) and
   pyridine (10ml). After allowing to warm to room temperature the mixture was stirred for 72
   hours. The mixture was diluted with dichloromethane, washed with aqueous potassium
   carbonate solution, dried over sodium sulphate and concentrated. Chromatography on silica
   gel (eluent gradient of A1 to A13) gave **trans-7-chloromethyl-2-(naphth-1-
   ylsulphonyloctahydro-2H-pyrido[1,2-a]pyrazine** as a yellow solid. Yield 5.66g (86%); Rf
   (A10) 0.47; MS (ES+) 379/381 [MH]+.

b) **trans-7-azidomethyl-2-(naphth-1-ylsulphonyloctahydro-2H-pyrido[1,2-a]pyrazine**

Sodium azide (4.18g, 64.30 mM) was added to **trans-7-chloromethyl-2-(naphth-1-
ysulphonyloctahydro-2H-pyrido[1,2-a]pyrazine** (4.87g, 12.87 mM) in DMF (70ml) and the
mixture heated at 65°C for 24 hours under an argon atmosphere. After allowing to cool, the
mixture was diluted with dichloromethane, washed with water, dried over sodium sulphate
and concentrated. The crude **trans-7-azidomethyl-2-(naphth-1-ylsulphonyloctahydro-2H-
pyrido[1,2-a]pyrazine** was obtained as an oil and used without further purification. Rf (A13)
0.49; MS (ES+) 386 [MH]+.

c) **trans-7-aminomethyl-2-(naphth-1-ylsulphonyloctahydro-2H-pyrido[1,2-a]pyrazine (X1)**

**trans-7-azidomethyl-2-(naphth-1-ylsulphonyloctahydro-2H-pyrido[1,2-a]pyrazine** in
ethyl acetate (100ml) and ethanol (40ml) was hydrogenated over platinum oxide (500mg) at
ambient temperature under atmospheric pressure of hydrogen. The catalyst is filtered off
through celite and the filtrate concentrated. Chromatography on silica gel (eluent gradient of
A1 to A5, A7 then A8) gave **trans-7-aminomethyl-2-(naphth-1-ylsulphonyloctahydro-2H-
pyrido[1,2-a]pyrazine** as a pale brown foam. Yield 3.00g (65%); Rf (A7) 0.12; Yield 3.00g
(65%); Rf (A7) 0.12; 1H NMR (300MHz, CDCl3) δ 8.78 (d, 1H), 8.20 (d, 1H), 8.07 (d, 1H),
7.92 (d, 1H), 7.60 (3H, m), 3.74 (dd, 1H), 3.62 (dt, 1H), 2.87 (d, 1H), 2.70 (m, 2H), 2.50 (m,
2H), 2.27 (m, 2H), 1.94 (m, 1H), 1.85-1.45 (m, 4H), 1.25-0.85 (m, 2H); $^{13}$C NMR (300MHz, CDCl$_3$) δ 134.87, 134.75, 132.62, 130.97, 129.50, 129.23, 128.41, 127.24, 125.64, 124.50, 60.72, 59.59, 54.68, 51.10, 46.65, 45.95, 39.96, 29.37, 28.31; MS (ES$^+$) 360 [MH]$^+$.  

5 **Intermediate X2**

**trans-7-Aminomethyl-2-(isopropylsulphonyl)octahydro-2H-pyrido[1,2-a]pyrazine**

This was prepared by a similar process to that described for intermediate X1, using isopropylsulphonyl chloride in place of 1-naphthalene sulphonyl chloride.

10 **Intermediate X3**

**trans-7-Aminomethyl-2-(N,N-dimethylsulphamoyl)octahydro-2H-pyrido[1,2-a]pyrazine**

This was prepared by a similar process to that described for X1, using dimethylsulphamoyl chloride was used in place of 1-naphthalene sulphonyl chloride.

15 **Intermediate X4**

**trans-7-[(Naphth-2-ylsulphonyl)aminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine**

was prepared as follows:

a) **trans-7-Hydroxymethyl-2-(tert-butoxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine**

A solution of di-tert-butyl dicarbonate (1.03g, 4.71 mM) in dichloromethane (5ml) was added to *trans-7-(hydroxymethyl)-1,3,4,6,7,8,9,9aoctahydro-2H-pyrido[1,2-a]pyrazine* (J. Heterocyclic Chem., 1995, 32, 857) (801mg, 4.71 mM) in dichloromethane (10ml) followed by triethylamine (0.66ml, 4.74mM). After 24 hours the mixture was diluted with dichloromethane, washed with water, dried over sodium sulphate and concentrated.

Chromatography on silica gel (eluent gradient of A1 to A5 then A7) gave

25 **trans-7-hydroxymethyl-2-(tert-butoxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine** as a white solid. Yield 0.86g (68%); Rf (A5) 0.19; $^1$H NMR (300MHz, CDCl$_3$) δ 3.95 (m, 2H), 3.50 (m, 2H), 2.96 (m, 2H), 2.75 (d, 1H), 2.55 (t, 1H), 2.16 (dt, 1H), 1.95-1.55 (m, 5H), 1.46 (s, 9H), 1.25 (m, 1H), 1.04 (m, 1H); MS (ES$^+$) 271 [MH]$^+$.  


b) trans-7-[(para-Toluenesulphonyl)oxymethyl]-2-( tert-butyloxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine

A solution of para-toluenesulphonyl chloride (608mg, 3.19 mM) in dichloromethane (2 ml) was added to trans-7-hydroxymethyl-2-(tert-butyloxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine (0.86g, 3.19 mM) in anhydrous pyridine (8 ml) in an ice bath under an argon atmosphere. After 4 hours para-toluenesulphonyl chloride (300mg, 1.57 mM) was added and the mixture was allowed to warm to room temperature. After 24 hours the mixture was concentrated under reduced pressure and then partitioned between ethyl acetate and water. The organic was dried over sodium sulphate, filtered and concentrated.

Chromatography on silica gel (eluent gradient of A1 to A5) gave trans-7-[(para-toluenesulphonyl)oxymethyl]-2-(tert-butyloxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine as a pale red solid. Yield 1.20g (89%); Rf (A5) 0.57; ¹H NMR (300MHz, CDCl₃) δ 7.76 (d, 2H), 7.35 (d, 2H), 4.05-3.77 (m, 4H), 3.00-2.80 (m, 2H), 2.65 (d, 1H), 2.46 (s, 3H), 2.15-1.90 (m, 2H), 1.80-1.55 (m, 4H), 1.45 (s, 9H), 1.25-0.90 (m, 2H); MS (ES+) 425 [MH⁺].

c) trans-7-Azidomethyl-2-(tert-butyloxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine

Sodium azide (0.56g, 8.49 mM) was added to trans-7-[(para-toluenesulphonyl)oxymethyl]-2-(tert-butyloxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine (1.20g, 8.49 mM) in DMF (20ml) and heated to 50°C for 5 hours under an argon atmosphere. After allowing to cool, the mixture was diluted with dichloromethane, washed with water, dried over sodium sulphate and concentrated. The crude trans-7-azidomethyl-2-(tert-butyloxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine was given as an orange oil and used without further purification. Rf (A13) 0.33.

d) trans-7-Aminomethyl-2-(tert-butyloxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine

trans-7-Azidomethyl-2-(tert-butyloxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine in ethyl acetate (35ml) is hydrogenated over platinum oxide (100mg) at ambient temperature under atmospheric pressure of hydrogen. The catalyst is filtered off through celite and the filtrate concentrated to give the crude product as a dark oil. Rf (A7) 0.07.
e) *trans*-7-(naphth-2-ylsulphonylaminomethyl)-2-((tert-butyloxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine

A solution of naphth-2-ylsulphonyl chloride (0.69g, 3.05 mM) in dichloromethane (2 ml) was added to a solution of *trans*-7-aminomethyl-2-((tert-butyloxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine (0.82g, 3.05 mM) in dichloromethane (10 ml) and pyridine (0.25 ml, 3.05 mM) in an ice bath under argon. After complete addition the mixture was allowed to warm to room temperature for 24 hours. The mixture was diluted with dichloromethane, washed with water, dried over sodium sulphate and concentrated. Chromatography on silica gel (eluent gradient of A1 to A13 then to A14) gave *trans*-7-(naphth-2-ylsulphonylaminomethyl)-2-((tert-butyloxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine as an off white solid. Yield 0.82g (63%); Rf (A13) 0.23; ^1H NMR (300MHz, CDCl₃) δ 8.45 (s, 1H), 7.96 (m, 2H), 7.93 (dd, 1H), 7.84 (dd, 1H), 7.65 (m, 2H), 4.70 (t, 1H), 3.95 (m, 2H), 2.85 (m, 4H), 2.60 (dd, 1H), 2.05 (dt, 1H), 1.90-1.65 (m, 5H), 1.47 (s, 9H), 1.18 (m, 1H), 0.95 (m, 1H); MS (ES+) 460 [MH]^+.

15

f) *trans*-7-(Naphth-2-ylsulphonylaminomethyl)octahydro-2H-pyrido[1,2-a]pyrazine (X4)

Trifluoroacetic acid (2 ml) was added to a solution of *trans*-7-(naphth-2-ylsulphonylaminomethyl)-2-((tert-butyloxycarbonyl)octahydro-2H-pyrido[1,2-a]pyrazine (0.88g) in dichloromethane (10 ml) in an ice bath. After complete addition the mixture was allowed to warm to room temperature. The mixture was diluted with dichloromethane, washed with aqueous potassium carbonate, dried over sodium sulphate and concentrated to give *trans*-7-(naphth-2-ylsulphonylaminomethyl)octahydro-2H-pyrido[1,2-a]pyrazine as a pale brown solid. Yield 690 mg (100%); Rf (A7) 0.24; MS (ES+) 360 [MH]^+.

25 Intermediate X5

*trans*-1-Benzyl-2-(aminomethyl)-5-[(1-naphthalen-ylsulphonyl)aminomethyl]piperidine

This can be prepared as follows:

a) Dimethyl-*trans*-1-benzylpiperidine-2,5-dicarboxylate

Benzyl bromide (15ml, 126.3mmol) was added dropwise to a suspension of dimethyl transpiperidine-2,5-dicarboxylate hydrochloride (J. Heterocyclic Chem., 1995, 32, 857) and potassium carbonate (35g, 253mmol) in methanol (400ml). The reaction mixture was stirred at room temperature for 24 hours before the white solid was filtered and washed with
methanol. The filtrate solvent was removed in vacuo and the residue dissolved in ethyl acetate, washed with water and brine, dried over magnesium sulphate and concentrated to leave a clear liquid. Chromatography on silica gel (eluent A13) gave dimethyl-trans-1-benzylpiperidine-2,5-dicarboxylate as a white solid. Yield 35.14g (96%); Rf (A11) 0.8; 1H NMR (300 MHz, CDCl₃) 7.30 (m, 5H), 3.75 (s, 3H), 3.60 (s, 3H), 3.60 (dd, 2H), 3.13 (dd, 1H), 3.08 (dd, 1H), 3.58 (m, 1H), 2.25 (dd, 1H), 2.02 (m, 1H), 1.95 (m, 1H), 1.80 (m, 1H), 1.55 (m, 1H); 13C NMR (300 MHz, CDCl₃) 174.39, 174.30, 137.76, 129.56, 128.54, 127.57, 64.93, 60.70, 52.13, 52.09, 51.91, 41.17, 28.55, 25.73; MS (ES+) 292.4 [MH]+.

b) trans-1-Benzyl-2-(methoxycarbonyl)piperidine-5-carboxylic acid

Sodium hydroxide (210ml, 1M solution) was added to a solution of the above product (35.14g, 120.76mmol) in methanol (150ml) and water (100ml). The reaction mixture was allowed to stir at room temperature for 72 hours before acidification (pH 5) with hydrochloric acid (1M solution) followed by dilution with dichloromethane, washed with water and dried over magnesium sulphate. The solvent was removed in vacuo to give trans-1-benzyl-2-(methoxycarbonyl)piperidine-5-carboxylic acid as a yellow oil. Yield 28.92g (86%); Rf (A11) 0.37; 1H NMR (300 MHz, CDCl₃) 10.75 (brs, 1H), 7.30 (m, 5H), 3.75 (s, 3H), 3.70 (dd, 2H), 3.32 (dd, 1H), 3.28 (dd, 1H), 2.67 (m, 1H), 2.52 (m, 1H), 2.05 (m, 1H), 1.95 (m, 1H), 1.90 (m, 1H), 1.70 (m, 1H); 13C NMR (300 MHz, CDCl₃) 178.74, 173.73, 136.93, 130.24, 129.31, 128.54, 62.69, 60.71, 52.67, 51.21, 41.05, 27.64, 25.28; MS (ES+) 278.1 [MH]+, (ES-) 276.2 [M]+.

c) Methyl-trans-1-benzyl-5-(aminocarbonyl)piperidine-2-carboxylate

Ethyl chloroformate (10.04ml, 105mmol) was slowly added to solution of the above product (28.92g, 104.4mmol) in dry THF (100ml) and triethylamine (14.64ml, 105mmol) at 0°C under an argon atmosphere. The white suspension was stirred at room temperature for 24 hours before concentrated ammonia solution (100ml) was added. The mixture was allowed to stir for 4 hours and then diluted with dichloromethane, washed with water, dried over magnesium sulphate and concentrated to give methyl-trans-1-benzyl-5-(aminocarbonyl)piperidine-2-carboxylate as a white solid. Yield 19.22g (67%); Rf (A11) 0.26; 1H NMR (300 MHz, CDCl₃) 7.30 (m, 5H), 6.72 (brs, 1H), 5.48 (brs, 1H), 3.76 (s, 3H), 3.70 (dd, 2H), 3.42 (dd, 1H), 3.25 (dd, 1H), 2.55 (m, 1H), 2.47 (m, 1H), 2.03 (m, 1H), 1.90
(m, 1H), 1.82 (m, 2H); \(^{13}\text{C}\) NMR (300 MHz, CDCl\(_3\)) 177.51, 173.65, 137.69, 129.74, 128.91, 127.99, 62.39, 60.72, 51.98, 50.28, 41.77, 26.83, 24.80; MS (ES\(^{+}\)) 277.1 [MH]\(^{+}\), (ES\(^{-}\)) 275.2 [M].

d) \textit{trans-1-Benzyl-2-(hydroxymethyl)-5-(aminomethyl)piperidine}

Lithium aluminium hydride (140ml, 1M solution in THF) was added slowly to the above product (19.22, 69.94mmol) in dry THF (200ml) at 0°C under an argon atmosphere. The reaction mixture was heated at reflux for 24 hours then cooled to room temperature before water (140ml) then sodium hydroxide (140ml, 15% w/v solution) and finally water (140ml) was added. The mixture was filtered and the solid extracted with acetonitrile using Soxhlet apparatus for 72 hours. The extract was combined with the filtrate and solvent removed \textit{in vacuo}. The product was used without further purification. MS (ES\(^{+}\)) 235.4 [MH]\(^{+}\).

e) \textit{trans-1-Benzyl-2-hydroxymethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine}

1-Naphthalenesulphonyl chloride (1.16g, 5.1mmol) was added to a solution of the above product (5.1mmol approx.) and pyridine (412\(\mu\)l, 5.1mmol) in dichloromethane (5ml) at 0°C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 24 hours before being diluted with dichloromethane, washed with water, dried over magnesium sulphate and concentrated. Chromatography on silica gel (eluent gradient of A1 to A5) yielded \textit{trans-1-benzyl-2-hydroxymethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine} as a gum. Yield 589mg. Rf (A5) 0.43; MS (ES\(^{+}\)) 425.3 [MH]\(^{+}\).

f) \textit{trans-1-Benzyl-2-chloromethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine}

Methanesulphonyl chloride (378\(\mu\)l, 4.9mmol) was added to a solution of \textit{trans-1-benzyl-2-hydroxymethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine} (589mg, 1.39mmol) and triethylamine (682\(\mu\)l, 4.9mmol) in dichloromethane (5ml) at 0°C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 72 hours before being diluted with dichloromethane, washed with water, dried over magnesium sulphate and concentrated. Chromatography on silica gel (eluent gradient of A1 to A5) yielded \textit{trans-1-benzyl-2-chloromethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine} as a brown solid. Yield 449mg. Rf (A5) 0.77; MS (ES\(^{+}\)) 443.3 (R-Cl)[MH]\(^{+}\).
g) trans-1-Benzyl-2-azidomethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine

The above product (0.88mmol) was stirred with sodium azide (172mg, 2.64mmol) in dry DMF at 70-75°C for 3 hours under an argon atmosphere. The reaction mixture was allowed to cool before being diluted with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulphate and solvent removed in vacuo to yield trans-1-benzyl-2-azidomethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine as a gum. Yield 431mg. Rf (A12) 0.76; MS (ES+) 450.2 [MH]+.

h) trans-1-Benzyl-2-aminomethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine (X5)

Triphenylphosphine (393mg, 1.5mmol) was added to a solution of the above product (431mg, 0.96mmol) in dry THF (5ml) at room temperature. The reaction mixture was stirred for 24 hours before adding water (2ml), followed by stirring for a further 24 hours and then concentration in vacuo. Chromatography on silica gel (eluent gradient of A1 to A5) gave trans-1-benzyl-2-aminomethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine as a gum. Yield 135mg. Rf (A7) 0.40; MS (ES+) 424.4 [MH]+.

Intermediate X6
trans-1-Benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-aminomethylpiperidine

a) trans-1-Benzyl-2-hydroxymethyl-5-[(tert-butyloxyacarbonyl)aminomethyl]piperidine

Di-tert-butyl dicarbonate (15.26g, 70mmol) in dichloromethane (50ml) was added slowly to a stirred solution of trans-1-benzyl-2-hydroxymethyl-5-aminomethylpiperidine (16.3g, 69.64mmol) in dichloromethane (150ml) and allowed to stir under an argon atmosphere for 24 hours. The solvent was removed in vacuo. Chromatography on silica gel (eluent A5) gave trans-1-benzyl-2-hydroxymethyl-5-[(tert-butyloxyacarbonyl)aminomethyl]piperidine as a gum. Yield 18.7g. Rf (A5) 0.55; 1H NMR (300 MHz, CDCl3) 7.30 (m, 5H), 4.58 (brt, 1H), 4.00 (dd, 1H), 3.63 (dd, 2H), 3.49 (m, 1H), 2.90 (m, 2H), 2.32 (m, 1H), 1.83-1.33 (m, 6H), 1.40 (s, 9H), 1.00 (m, 1H); MS (ES+) 335.4 [MH]+, (ES-) 333.4 [M].
b) **trans-1-Benzyl-2-chloromethyl-5-[(tert-butylloxycarbonyl)aminomethyl]piperidine**

**trans-1-Benzyl-2-chloromethyl-5-[(tert-butylloxycarbonyl)aminomethyl]piperidine** was prepared by a similar process to that described for **trans-1-benzyl-2-chloromethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine**, using **trans-1-benzyl-2-hydroxymethyl-5-[(tert-butylloxycarbonyl)aminomethyl]piperidine** instead of **trans-1-benzyl-2-hydroxymethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine**. MS (ES+) 353.3 (R-CI) [MH]+.

c) **trans-1-Benzyl-2-(azidomethyl)-5-[(tert-butylloxycarbonyl)aminomethyl]piperidine**

**trans-1-Benzyl-2-azidomethyl-5-[(tert-butylloxycarbonyl)aminomethyl]piperidine** was prepared by a similar process to that described for **trans-1-benzyl-2-azidomethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine**, using **trans-1-benzyl-2-chloromethyl-5-[(tert-butylloxycarbonyl)aminomethyl]piperidine** instead of **trans-1-benzyl-2-chloromethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine**. MS (ES+) 360.4 [MH]+.

d) **trans-1-Benzyl-2-aminomethyl-5-[(tert-butylloxycarbonyl)aminomethyl]piperidine**

**trans-1-Benzyl-2-aminomethyl-5-[(tert-butylloxycarbonyl)aminomethyl]piperidine** was prepared by a similar process to that described for **trans-1-benzyl-2-aminomethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine** (X5), using **trans-1-benzyl-2-azidomethyl-5-[(tert-butylloxycarbonyl)aminomethyl]piperidine** instead of **trans-1-benzyl-2-azidomethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine**. Rf (A7) 0.33; MS (ES+) 334.5 [MH]+.

e) **trans-1-Benzyl-2-naphth-1-ylsulphonylaminomethyl)-5-[(tert-butylloxycarbonyl)aminomethyl]piperidine**

Prepared by a similar process to that described for **trans-1-benzyl-2-hydroxymethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine**, using **trans-1-benzyl-2-aminomethyl-5-[(tert-butylloxycarbonyl)aminomethyl]piperidine**. Chromatography on silica gel (eluent A1 to A2) gave **trans-1-benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(tert-butylloxycarbonyl)aminomethyl]piperidine**. Rf (A7) 0.71; MS (ES+) 524.3 [MH]+.

f) **trans-1-Benzyl-2-(naphth-1-ylsulphonyl)aminomethyl]-5-(aminomethyl)piperidine**
Trifluoroacetic acid (1.6ml) was added slowly to a stirred solution of \textit{trans}-1-benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(\textit{tert}-butyloxy carbonyl)aminomethyl]piperidine (343mg, 0.66mmol) at 0°C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours before being washed with potassium carbonate solution, diluted with dichloromethane, washed with water, dried over sodium sulphate and concentrated to give a white gum. Rf (A13) 0.13; $^1$H NMR (300 MHz, CDCl$_3$) 8.50 (d, 1H), 8.09 (d, 1H), 7.98 (d, 1H), 7.87 (d, 1H), 7.47 (m, 3H), 7.20 (m, 3H), 7.10 (d, 2H), 5.21 (brs, 2H), 3.31 (m, 1H), 3.21 (dd, 2H), 2.69 (dd, 1H), 2.25 (m, 4H), 1.89 (m, 1H), 1.75-0.75 (m, 6H); MS (ES+) 424.4 [MH]$^+$. 

\textbf{Intermediate X7} 

\textit{trans}-1-Benzyl-2-(phenylsulphonylaminomethyl)-5-aminomethylpiperidine

Prepared by a similar process to that described for \textit{trans}-1-benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-aminomethylpiperidine (X6), using \textit{trans}-1-benzyl-2-aminomethyl-5-[(\textit{tert}-butyloxy carbonyl)aminomethyl]piperidine and phenyl sulphonyl chloride. Rf (A13) 0.13; MS (ES+) 374.4 [MH]$^+$. 

\textbf{Intermediate X8} 

\textit{trans}-1-Ethyl-2-(naphth-1-ylsulphonylaminomethyl)-5-aminomethylpiperidine

\textbf{a) trans-2-(naphth-1-ylsulphonylaminomethyl)-5-[(tert-butyloxy carbonyl)-aminomethyl]piperidine}

10% Palladium on carbon (80mg) was added to a stirred solution of \textit{trans}-1-benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(\textit{tert}-butyloxy carbonyl)aminomethyl]piperidine (307mg, 0.587mmol) in ethanol (20ml) and cyclohexene (20ml) under an argon atmosphere. The reaction mixture was heated at 90°C for 75 hours before being filtered through celite and washed with ethanol. The filtrate was concentrated to give a yellow gum. Chromatography on a 5 gram isolute cartridge (eluent A13 to A14) gave a white foam. Yield 121mg (48%). Rf (A7) 0.29; $^1$H NMR (300 MHz, CDCl$_3$) 8.63 (d, 1H), 8.29 (d, 1H), 8.05 (d, 1H), 7.94 (d, 1H), 7.60 (m, 3H), 4.60 (m, 1H), 3.35 (m, 1H), 2.88 (m, 3H), 2.60 (m, 2H), 2.27 (m, 1H), 1.75-0.98 (m, 7H), 1.41 (s, 9H); MS (ES+) 434.4 [MH]$^+$. 


b) trans-1-Ethyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(tert-butyloxycarbonyl)aminomethyl]piperidine

Sodium cyanoborohydride (50mg, 0.80mmol) was added to a stirred solution of trans-2-(naphth-1-ylsulphonylaminomethyl)-5-[(tert-butyloxycarbonyl)aminomethyl]piperidine (115mg, 0.27mmol) and acetaldehyde solution (0.1M in ethanol) (2.7ml, 0.27mmol) in ethanol (5ml) and acetic acid (0.5ml) at 0°C under an argon atmosphere. The reaction mixture was stirred at room temperature for 24 hours before concentration in vacuo. The residue was washed with potassium carbonate solution, diluted with dichloromethane, washed with water and dried over magnesium sulphate before concentration gave a gum. Chromatography on a 5g isolute cartridge (eluent A13) gave a white solid. Rf (A13) 0.38; 1H NMR (300 MHz, CDCl3) 8.63 (d, 1H), 8.28 (d, 1H), 8.07 (d, 1H), 7.95 (d, 1H), 7.62 (m, 3H), 4.80 (m, 1H), 3.47 (m, 1H), 2.92 (m, 2H), 2.73 (m, 2H), 2.58 (m, 2H), 2.35 (m, 1H), 1.93 (brs, 1H), 1.68 (m, 1H), 1.52 (m, 1H), 1.47-1.05 (m, 4H), 1.40 (s, 9H), 0.98 (t, 3H); MS (ES+) 462.4 [MH]+.

c) trans-1-Ethyl-2-(naphth-1-ylsulphonylaminomethyl)-5-(aminomethyl)piperidine

Prepared by a similar process to that described for trans-1-benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-aminomethylpiperidine (X6), using trans-1-ethyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(tert-butyloxycarbonyl)aminomethyl]piperidine. Rf (A7) 0.30; MS (ES+) 362.4 [MH]+.

Intermediate X9

trans-1-Ethyl-2-phenylsulphonylaminomethyl-5-aminomethylpiperidine

Prepared by a similar process to that described for trans-1-benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-aminomethylpiperidine (X6), using trans-1-ethyl-2-phenylsulphonylaminomethyl-5-[(tert-butyloxycarbonyl)aminomethyl]piperidine. Rf (A7) 0.30.
Example 1

*trans*-2-(Naphth-1-ylsulphonyl)-7-[(4-aminoquinazolin-2-yl)aminomethyl]octahydro-2*H*-pyrido[1,2-\(a\)]pyrazine

*trans*-7-Aminomethyl-2-(naphth-1-ylsulphonyl)octahydro-2*H*-pyrido[1,2-\(a\)]pyrazine (XI) (428mg, 1.19 mM) and 2-chloro-4-aminoquinazoline (214mg, 1.19mM) were suspended in isoamyl alcohol (9 ml) and heated to 140°C for 24 hours under an argon atmosphere. After allowing to cool, the mixture was diluted with dichloromethane, washed with aqueous potassium carbonate, dried over sodium sulphate and concentrated. Chromatography on silica gel (eluent gradient of A1 to A5, then A7) gave *trans*-2-(naphth-1-ylsulphonyl)-7-[(4-aminoquinazolin-2-yl)aminomethyl]octahydro-2*H*-pyrido[1,2-\(a\)]pyrazine as a pale yellow solid. Yield 300mg (50%); Rf (A7) 0.48; 1H NMR (300MHz, CDCl₃) δ 8.75 (d, 1H), 8.20 (d, 1H), 8.07 (d, 1H), 7.90 (d, 1H), 7.55 (m, 5H), 7.41 (d, 1H), 7.10 (t, 1H), 5.42 (br s, 2H), 5.05 (br s, 1H), 3.72 (d, 1H), 3.60 (dt, 1H), 3.28 (t, 1H), 2.88 (d, 1H), 2.70 (m, 2H), 2.25 (m, 2H), 2.00-1.70 (m, 4H), 1.59 (d, 1H), 1.05 (m, 2H); 13C NMR (300MHz, CDCl₃) δ 162.36, 159.55, 152.5, 134.92, 134.74, 133.81, 132.59, 130.96, 129.45, 129.26, 128.45, 127.26, 125.58, 124.50, 122.46, 121.79, 110.64, 60.57, 59.41, 54.58, 51.02, 45.89, 45.48, 36.98, 29.29, 28.39; MS (ES+) 503 [MH]+.

Examples 2 and 3

*R- and S-* *trans*-2-(Naphth-1-ylsulphonyl)-7-[(4-aminoquinazolin-2-yl)aminomethyl]octahydro-2*H*-pyrido[1,2-\(a\)]pyrazine

The racemic mixture derived from Example 1 was separated using the conditions outlined below:-
Analysis Conditions:

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</tr>
<tr>
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<td>Ambient</td>
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<tr>
<td>Flow</td>
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<tr>
<td>Wavelength</td>
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<tr>
<td>Run Time</td>
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</tr>
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</table>

Examples 4-18

The following compounds were prepared using the intermediate X1 and the corresponding chloroheterocycle, using 1-pentanol as solvent, by a similar process to that described in Example 1. The compounds were obtained as a racemic mixture of the 2 trans isomers, although the figure below shows just one of the trans isomer to illustrate the structures.

![Chemical Structure]

<table>
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**Example 19**

trans-2-(Isopropylsulphonyl)-7-[(2-methyl-7-chlorquinolin-4-yl)aminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine

The following compound was prepared from trans-7-aminomethyl-2-(isopropylsulphonyl)octahydro-2H-pyrido[1,2-a]pyrazine (X2) and the corresponding chloroheterocycle, using 1-pentanol as solvent, by a similar process to that described in Example 1.

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**Examples 20 and 21**

The following compounds were prepared from trans-7-aminomethyl-2-(dimethylsulphamoyl)octahydro-2H-pyrido[1,2-a]pyrazine (X3) and the corresponding chloroheterocycles, and 1-pentanol as solvent, by a similar process to that described in Example 1. The compounds were obtained as a racemic mixture of the 2 trans isomers, although the figure below shows just one of the trans isomer to illustrate the structures.
Example 22

trans-2-(naphth-1-ylsulphonyl)-7-[(1,2,3,4-tetrahydronaphth-2-yl)carbonylaminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine

DMAP (180mg, 1.47 mM) was added to a suspension of trans-7-aminomethyl-2-(naphth-1-ylsulphonyl)octahydro-2H-pyrido[1,2-a]pyrazine (X1) (527mg, 1.47 mM) in dichloromethane (30 ml) followed by addition of EDAC (563 mg, 2.93 mM) under an argon atmosphere. After 30 minutes 1,2,3,4-tetrahydro-2-naphthoic acid (259mg, 1.47 mM) was added and the mixture was stirred for 24 hours. The mixture was diluted with dichloromethane, washed with aqueous ammonium chloride, dried over sodium sulphate and concentrated. Chromatography on silica gel (eluent gradient of A1 to A5) gave trans-2-(naphth-1-ylsulphonyl)-7-[(1,2,3,4-tetrahydronaphth-2-yl)carbonylaminomethyl] octahydro-2H-pyrido[1,2-a]pyrazine as a white foam. Yield 0.76g (100%); Rf (A5) 0.41; 'H NMR (300MHz, CDCl₃) δ 8.75 (d, 1H), 8.19 (d, 1H), 8.07 (d, 1H), 7.93 (d, 1H), 7.60 (m, 3H), 7.08 (m, 4H), 5.66 (t, 1H), 3.74 (d, 1H), 3.63 (d, 1H), 3.20-2.60 (m, 8H), 2.47 (m, 1H), 2.25 (m, 2H), 2.05 (m, 1H), 1.90 (m, 2H), 1.70 (m, 2H), 1.56 (m, 1H), 1.04 (m, 2H); ¹³C NMR (300MHz, CDCl₃) δ 175.70, 136.04, 135.33, 134.95, 134.76, 132.62, 130.99, 129.41, 129.27, 128.45, 127.28, 126.36, 126.25, 125.58, 124.50, 60.41, 59.25, 54.61, 51.00, 45.88, 43.22, 42.31, 37.43, 32.79, 32.76, 29.21, 28.88, 28.24, 27.03; MS (ES+) 518 [MH]+.
Example 23

*trans*-2-((Naphth-1-ylsulphonyl)-7-[[1,2,3,4-tetrahydronaphth-2-yl)methylaminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine

Borane THF complex (1M solution in THF) (4.20 ml, 4.20 mM) was added to a solution of *trans*-2-(naphth-1-ylsulphonyl)-7-[[1,2,3,4-tetrahydronaphth-2-yl]carbonylaminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine (Example 22) (414mg, 0.80 mM) in anhydrous THF (3 ml) under argon atmosphere and the mixture was refluxed for 24 hours. After allowing to cool, water (1.1 ml), 4M HCl aq. (4.4 ml) and methanol (8.8 ml) were added. After 24 hours dichloromethane (100 ml) was added and the aqueous layer basified with saturated aqueous potassium carbonate. The organic layer was dried over sodium sulphate and concentrated. Chromatography on silica gel (eluent gradient of A1 to A5) gave *trans*-2-(naphth-1-ylsulphonyl)-7-[[1,2,3,4-tetrahydronaphth-2-ylmethyl]aminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine as a white foam. Yield 290mg (72%); Rf (A7) 0.54; 1H NMR (300MHz, CDCl₃) δ 8.80 (d, 1H), 8.20 (d, 1H), 8.07 (d, 1H), 7.92 (d, 1H), 7.60 (m, 3H), 7.05 (m, 4H), 3.73 (d, 1H), 3.62 (dt, 1H), 2.95-2.65 (m, 5H), 2.62-2.18 (m, 7H), 2.00-0.80 (m, 11H); 13C NMR (300MHz, CDCl₃) δ 135.78, 135.19, 133.46, 133.35, 131.23, 129.56, 128.12, 127.81, 127.00, 125.83, 124.51, 124.24, 123.09, 59.36, 58.71, 54.76, 53.26, 53.08, 49.71, 44.55, 35.33, 33.50, 33.25, 28.02, 27.85, 27.54, 26.57; MS (ES+) 504 [MH]+.

Example 24

*trans*-7-((Quinolin-3-ylmethylaminomethyl)-2-(naphth-1-ylsulphonyl)octahydro-2H-pyrido[1,2-a]pyrazine

Sodium cyanoborohydride (67mg, 1.05 mM) was added to a solution of *trans*-7-aminomethyl-2-(naphth-1-ylsulphonyl)octahydro-2H-pyrido[1,2-a]pyrazine (X1) (343 mg, 0.96 mM), 3quinolinecarboxaldehyde (150 mg, 0.96 mM) and glacial acetic acid (60ul, 1.05 mM) in ethanol (5ml) in an ice bath under an argon atmosphere. After 1 hour the reaction was allowed to warm to room temperature and stirred overnight. The mixture was diluted with dichloromethane, washed with aqueous potassium carbonate solution, dried over sodium sulphate and concentrated. Chromatography on silica gel (eluent gradient of A1, A3, A5 then A6) gave *trans*-7-(quinolin-3-ylmethylaminomethyl)-2-(naphth-1-ylsulphonyl)octahydro-2H-pyrido[1,2-a]pyrazine as a white foam. Yield 0.35g (73%); Rf (A5) 0.18; 1H NMR (300MHz,
Example 25

*trans*-2-(4-Aminoquinazolin-2-yl)-7-(naphth-2-ylsulphonylaminomethyl)octahydro-2H-pyrido[1,2-α]pyrazine

*trans*-7-(Naphth-2-ylsulphonylaminomethyl)octahydro-2H-pyrido[1,2-α]pyrazine (X4)

(335 mg, 0.93 mM) and 2-chloro-4-aminoquinazoline (201 mg, 1.12 mM) were suspended in isoamyl alcohol (7 ml) and heated to 140°C for 24 hours under an argon atmosphere. After allowing to cool, the mixture was diluted with dichloromethane, washed with aqueous potassium carbonate solution, dried over sodium sulphate and concentrated. Chromatography on silica gel (eluent gradient of A1 to A5 then to A6) gave *trans*-2-(4-aminoquinazolin-2-yl)-7-(naphth-2-ylsulphonylaminomethyl)octahydro-2H-pyrido[1,2-α]pyrazine as a pale brown solid. Rf (A5) 0.25; ¹H NMR (300 MHz, CDCl₃) δ 8.45 (s, 1H), 8.15 (m, 2H), 8.05 (d, 1H), 7.97 (d, 1H), 7.90-7.60 (m, 3H), 7.50 (m, 1H), 7.40 (br s, 2H), 7.25 (d, 1H), 7.01 (m, 1H), 4.60 (m, 2H), 2.95-2.35 (m, 5H), 1.97 (t, 1H), 1.80-1.45 (m, 4H), 1.40-1.00 (m, 2H), 0.85 (m, 2H); ¹³C NMR (300 MHz, CDCl₃) δ 162.44, 158.87, 152.26, 137.86, 134.45, 132.95, 132.08, 129.71, 129.52, 128.99, 128.16, 127.89, 127.63, 125.13, 123.96, 122.62, 120.70, 110.47, 60.70, 59.11, 54.75, 49.06, 46.83, 43.61, 36.40, 28.93, 28.09; MS (ES+) 503 [MH]+.

Example 26

*trans*-2-(1,2,3,4-Tetrahydronaphth-2-ylmethyl)-7-(naphth-2-ylsulphonylaminomethyl)octahydro-2H-pyrido[1,2-α]pyrazine

*trans*-7-(Naphth-2-ylsulphonylaminomethyl)octahydro-2H-pyrido[1,2-α]pyrazine (X4)

(335 mg, 0.93 mM) and 1,2,3,4-tetrahydro-2-naphthoic acid (165 mg, 0.93 mM) were condensed to give the corresponding amide by a similar process to that described in Example 22. Yield 475 mg (98%); Rf (A5) 0.42; ¹H NMR (300 MHz, CDCl₃) δ 8.44 (s, 1H), 7.90 (m, 3H), 7.80 (d, 1H), 7.60 (m, 2H), 7.10 (m, 4H), 4.76 (br s, 1H), 4.54 (m, 1H), 3.30-2.60 (m, 10H), 2.40-1.50 (m, 10H), 1.20 (m, 1H), 0.90 (m, 1H); MS (ES+) 518 [MH]+.
This material was reduced (by a similar process to that described in Example 23) to give trans-2-[1,2,3,4-tetrahydronaphth-2-ylmethyl]-7-(naphth-2-ylsulphonylaminomethyl)octahydro-2H-pyrido[1,2-a]pyrazine as a white solid. Yield 341mg (83%); Rf (A13) 0.16; 1H NMR (300MHz, CDCl₃) δ 8.40 (s, 1H), 7.95 (d, 2H), 7.90 (d, 1H), 7.85 (dd, 1H), 7.60 (m, 2H), 7.05 (m, 4H), 4.95-4.70 (br m, 1H), 2.95-2.60 (m, 8H), 2.40 (dd, 1H), 2.35-2.05 (m, 4H), 1.95 (m, 3H), 1.85-1.60 (m, 4H), 1.50 (m, 1H), 1.35-1.10 (m, 3H), 0.95 (m, 1H); 13C NMR (300MHz, CDCl₃) δ 137.28, 137.12, 136.83, 135.20, 132.57, 129.92, 129.62, 129.57, 129.22, 129.16, 128.78, 128.29, 127.95, 125.91, 125.87, 122.69, 64.95, 61.19, 59.27, 55.23, 47.55, 36.87, 35.05, 31.98, 29.52, 29.25, 28.54, 28.26; MS (ES+)) 504 [MH]+.

Example 27

**trans-7-(Quinolin-3-ylaminomethyl)-2-(naphth-1-ylsulphonyl)octahydro-2H-pyrido[1,2-a]pyrazine**

trans-7-Aminomethyl-2-(naphth-1-ylsulphonyl)octahydro-2H-pyrido[1,2-a]pyrazine

(X1) (359mg, 1 mM), 3-bromoquinoline (208mg, 1mM), Sodium tert-butoxide (134mg, 1.4 mM), tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (18mg, 0.02mM) and (S)-(-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (25mg, 0.04mM) in anhydrous toluene (9 ml) were heated at 70°C for 24 hours under an argon atmosphere. After allowing to cool, the mixture was diluted with dichloromethane, washed with aqueous potassium carbonate, dried over sodium sulphate and concentrated. Chromatography on silica gel (eluent gradient of A1 to A5) gave trans-7-(quinolin-3-ylaminomethyl)-2-(naphth-1-ylsulphonyl)octahydro-2H-pyrido[1,2-a]pyrazine as an off white foam. Yield 316mg (65%); Rf (A5) 0.38; 1H NMR (300MHz, CDCl₃) δ 8.77 (dd, 1H), 8.39 (dd, 1H), 8.22 (d, 1H), 8.06 (d, 1H), 7.94 (m, 2H), 7.55 (m, 4H), 7.40 (m, 2H), 6.93 (m, 1H), 3.98 (t, 1H), 3.75 (d, 1H), 3.65 (d, 1H), 3.05 (t, 2H), 2.95 (d, 1H), 2.75 (m, 2H), 2.30 (m, 2H), 2.05-1.75 (m, 3H), 1.62 (m, 1H), 1.10 (m, 2H); MS (ES+)) 487 [MH]+.

Example 28

**trans-1-Benzyl-2-[(4-aminoquinazolin-2-yl)aminomethyl]-5-(naphth-1-ylsulphonylaminomethyl)piperidine**

trans-1-Benzyl-2-aminomethyl-5-(naphth-1-ylsulphonylaminomethyl)piperidine (X5) (135mg, 0.32mmol) was stirred with 2-chloro-4-aminoquinazoline (63mg, 0.35mmol) in 1-
pentanol (3ml) at 140°C for 24 hours. The reaction mixture was concentrated and the residue dissolved in dichloromethane, washed with potassium carbonate solution then water and dried over magnesium sulphate before concentration. Chromatography on a 10 gram Mega Bond Elut cartridge (eluens A1 to A4) gave trans-1-benzyl-2-[(4-aminoquinazolin-2-y1)aminomethyl]-5-(naphth-1-ylsulphonyl)aminomethyl]piperidine as a brown solid. Yield 74mg (41%). Rf (A7) 0.54; 1H NMR (300 MHz, CDCl3) 8.60 (d, 1H), 8.21 (d, 1H), 8.03 (d, 1H), 7.92 (d, 1H), 7.70–7.05 (m, 12H), 4.00 (m, 1H), 3.47 (m, 3H), 2.90 (m, 1H), 2.60 (m, 3H), 2.32 (m, 1H), 1.85 (m, 1H), 1.72–0.85 (m, 8H); MS (ES+) 567.3 [MH]+.

Example 29

trans-1-Benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(4-aminoquinazolin-2-y1)aminomethyl]piperidine

Prepared by a similar process to that described for Example 28, using trans-1-benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-aminomethyl]piperidine (X6). Chromatography on a 5 gram isolate cartridge (eluens A1 to A4) gave trans-1-benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(4-aminoquinazolin-2-y1)aminomethyl]piperidine as a foam. Rf (A5) 0.25; 1H NMR (300 MHz, CDCl3) 8.56 (d, 1H), 8.17 (d, 1H), 8.03 (d, 1H), 7.91 (dd, 1H), 7.49 (m, 6H), 7.22 (m, 3H), 7.09 (m, 3H), 5.47 (brs, 2H), 3.36 (m, 1H), 3.28 (m, 2H), 3.19 (m, 2H), 2.80 (dd, 1H), 2.40 (dd, 1H), 2.25 (dd, 1H), 2.12 (dd, 1H), 1.90 (m, 1H), 1.69 (m, 2H), 1.51 (m, 2H), 1.22 (m, 2H); MS (ES+) 567.3 [MH]+.

Example 30

trans-1-Benzyl-2-(phenylsulphonylaminomethyl)-5-[(4-aminoquinazolin-2-y1)aminomethyl]piperidine

Prepared by a similar process to that described for Example 28 using trans-1-benzyl-2-phenylsulphonylaminomethyl-5-aminomethyl]piperidine (X7). Chromatography on silica gel (eluens A1 to A8) gave trans-1-benzyl-2-phenylsulphonylaminomethyl-5-[(4-aminoquinazolin-2-y1)aminomethyl]piperidine as a brown foam. Rf (A7) 0.63; 1H NMR (300 MHz, CDCl3) 7.75–7.07 (m, 14H), 3.50 (dd, 2H), 3.30 (m, 1H), 3.20 (m, 1H), 2.41 (m, 1H), 2.20 (m, 1H), 2.03 (m, 1H), 1.79 (m, 2H), 1.60 (m, 2H), 1.25 (m, 2H); MS (ES+) 517.4 [MH]+.
Example 31

\[ \text{trans-1-Benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(2-methylquinolin-4-y)laminomethyl]piperidine} \]

1-Benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-aminomethylpiperidine (X6)

(118mg, 0.28mmol), 4-chloroquinidine (50mg, 0.28mmol), sodium tert-butoxide (38mg, 0.39mmol), tris(dibenzylideneacetone)dipalladium(0) (31mg, 0.03mmol) and (S)-(−)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (42mg, 0.07mmol) in anhydrous toluene (10 ml) were heated at 70°C for 72 hours under an argon atmosphere. After allowing to cool, the mixture was diluted with dichloromethane, washed with water, dried over magnesium sulphate and concentrated. Chromatography on silica gel (eluent gradient of A1 to A8) gave \textit{trans}-1-benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(2-methylquinolin-4-yl)aminomethyl]piperidine as a yellow solid. Yield 44mg (28%); Rf (A7) 0.67; \(^1^H\) NMR (300 MHz, CDCl\(_3\)) 8.55 (d, 1H), 8.15 (d, 1H), 8.01 (d, 1H), 7.89 (m, 4H), 7.51 (m, 4H), 7.29 (m, 2H), 7.09 (m, 4H), 3.30 (m, 2H), 3.20 (m, 1H), 2.92 (m, 1H), 2.63 (m, 1H), 2.53 (s, 3H), 2.48 (m, 1H), 2.40 (m, 1H), 2.00 (m, 1H), 1.61 (m, 4H), 1.21 (m, 2H); MS (ES+) 565.3 [MH]^+.

Example 32

\[ \text{trans-1-Benzyl-2-phenylsulphonylaminomethyl-5-[(2-methylquinolin-4-y)laminomethyl]piperidine} \]

Prepared by a similar process to that described for Example 28 using \textit{trans}-1-benzyl-2-phenylsulphonylaminomethyl-5-aminomethylpiperidine (X7) and 4-chloroquinidine.

Chromatography on silica gel (eluent A1 to A8) gave \textit{trans}-1-benzyl-2-phenylsulphonylaminomethyl-5-[(2-methylquinolin-4-y)laminomethyl]piperidine as a brown gum. Rf (A7) 0.64; \(^1^H\) NMR (500 MHz, CDCl\(_3\)) 8.45 (m, 1H), 8.37 (d, 1H), 8.11 (d, 1H), 7.64 (d, 2H), 7.54 (t, 1H), 7.46 (t, 1H), 7.35 (m, 3H), 7.15 (m, 5H), 5.94 (s, 1H), 3.46 (dd, 2H), 3.32 (m, 1H), 3.14 (m, 2H), 2.79 (m, 1H), 2.66 (s, 3H), 2.58 (m, 1H), 2.41 (m, 1H), 2.34 (m, 1H), 2.24 (m, 1H), 1.82 (m, 2H), 1.67 (m, 1H), 1.33 (m, 1H); \(^1^H\) NMR (300 MHz, CDCl\(_3\)) 155.15, 154.13, 141.19, 139.25, 138.97, 132.74, 129.38, 128.75, 127.65, 127.11, 126.29, 123.26, 120.83, 116.37, 97.93, 64.07, 61.36, 59.71, 53.91, 50.93, 47.88, 38.04, 32.79, 27.10, 21.10; MS (ES+) 515.4 [MH]^+.
Example 33

*trans*-2-phenylsulphonylaminomethyl-5-[(2-methylquinolin-4-y1)aminomethyl]piperidine

Prepared by a similar process to that described for *trans*-2-(naphth-1-y1)sulphonylaminomethyl)-5-[(tert-butyloxy carbonyl)aminomethyl]piperidine, using *trans*-1-benzyl-2-phenylsulphonylaminomethyl-5-[(2-methylquinolin-4-y1)aminomethyl]piperidine. Chromatography on silica gel (eluent A4 to A9) gave

*trans*-2-phenylsulphonylaminomethyl-5-[(2-methylquinolin-4-y1)aminomethyl]piperidine as a yellow solid. Rf (A7) 0.40; $^1$H NMR (500 MHz, Methanol-d$_4$) 7.80 (m, 4H), 7.55 (m, 1H), 7.50 (m, 1H), 7.43 (m, 2H), 7.13 (m, 1H), 6.17 (s, 1H), 3.28 (m, 1H), 3.11 (m, 2H), 2.95 (m, 2H), 2.62 (m, 2H), 2.51 (s, 3H), 2.03 (m, 1H), 1.75 (m, 2H), 1.48 (m, 1H), 1.28 (m, 1H); $^{13}$C NMR (300 MHz, CDCl$_3$) 159.22, 151.11, 147.32, 141.47, 132.94, 129.86, 129.51, 128.18, 127.22, 124.50, 120.23, 117.61, 98.75, 57.34, 55.51, 54.38, 50.85, 48.54, 38.90, 32.66, 26.89, 25.36; MS (ES+) 425.99 [MH]$^+$.  

Example 34

*trans*-1-Ethyl-2-(naphth-1-y1)sulphonylaminomethyl)-5-[(2-methylquinolin-4-y1)aminomethyl]piperidine

Prepared by a similar process to that described for *trans*-1-benzyl-2-(naphth-1-y1)sulphonylaminomethyl)-5-[(2-methylquinolin-4-y1)aminomethyl]piperidine, using *trans*-1-ethyl-2-(naphth-1-y1)sulphonylaminomethyl)-5-aminomethylpiperidine (X8). Chromatography on silica gel (eluent gradient of A1 to A8) gave *trans*-1-ethyl-2-(naphth-1-y1)sulphonylaminomethyl)-5-[(2-methylquinolin-4-y1)aminomethyl]piperidine as a yellow solid. Rf (A7) 0.61; MS (ES+) 503.3 [MH]$^+$.  

Example 35

*trans*-1-Ethyl-2-phenylsulphonylaminomethyl-5-[(2-methylquinolin-4-y1)aminomethyl]piperidine

Prepared by a similar process to that described for *trans*-1-benzyl-2-[(4-aminooquinazolin-2-y1)aminomethyl]-5-(naphth-1-y1)sulphonylaminomethyl)piperidine, using *trans*-1-ethyl-2-phenylsulphonylaminomethyl-5-aminomethylpiperidine (X9) and 4-chloroquinaldine. Chromatography on silica gel (eluent A1 to A8) gave *trans*-1-ethyl-
2-phenylsulphonylaminomethyl-5-[(2-methylquinolin-4-yl)aminomethyl]piperidine as a foam. Rf (A7) 0.60; ¹H NMR (300 MHz, CDCl₃) 7.95 (d, 1H), 7.87 (d, 2H), 7.73 (d, 1H), 7.52 (m, 4H), 7.35 (t, 1H), 6.20 (s, 1H), 6.10 (brs, 1H), 3.45 (m, 1H), 3.19 (m, 2H), 2.85 (m, 1H), 2.75 (m, 1H), 2.61 (s, 3H), 2.45 (m, 4H), 2.11 (m, 1H), 1.82 (m, 2H), 1.52 (m, 2H), 0.94 (t, 3H); ¹³C NMR (300 MHz, CDCl₃) 159.09, 151.16, 147.11, 141.47, 132.93, 129.97, 129.48, 128.20, 127.27, 124.62, 120.05, 117.60, 98.87, 66.20, 61.79, 60.70, 54.46, 54.20, 48.80, 37.99, 32.94, 27.11, 25.29, 15.63, 12.21; MS (ES⁺) 453.35 [MH⁺].

**Example 36**

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically-acceptable salt, pro-drug or solvate thereof (hereafter compound Y), for therapeutic or prophylactic use in humans:

<table>
<thead>
<tr>
<th>(a): Tablet I</th>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound Y</td>
<td>100</td>
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<tr>
<td>Lactose Ph.Eur</td>
<td>182.75</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>12.0</td>
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<tr>
<td>Maize starch paste (5% w/v paste)</td>
<td>2.25</td>
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<tr>
<td>Magnesium stearate</td>
<td>3.0</td>
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</tbody>
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<table>
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<tr>
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<tr>
<td>Compound Y</td>
<td>50</td>
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<tr>
<td>Lactose Ph.Eur</td>
<td>223.75</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>6.0</td>
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<tr>
<td>Maize starch</td>
<td>15.0</td>
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<tr>
<td>Polyvinylpyrrolidone (5% w/v paste)</td>
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<td>Magnesium stearate</td>
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### (c): Tablet III

<table>
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### (d): Capsule

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<td>Magnesium stearate</td>
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### (e): Injection I

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<td>Compound Y</td>
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</tr>
<tr>
<td>1M Sodium hydroxide solution</td>
<td>15.0% v/v</td>
</tr>
<tr>
<td>0.1M Hydrochloric acid</td>
<td>(to adjust pH to 7.6)</td>
</tr>
<tr>
<td>Polyethylene glycol 400</td>
<td>4.5% w/v</td>
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<tr>
<td>Water for injection</td>
<td>to 100%</td>
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### (f): Injection II

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<td>Sodium phosphate BP</td>
<td>3.6% w/v</td>
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<tr>
<td>0.1M Sodium hydroxide solution</td>
<td>15.0% v/v</td>
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<td>Water for injection</td>
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<tr>
<td>(g): Injection III</td>
<td>(1mg/ml, buffered to pH6)</td>
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<td>----------------------------------------</td>
<td>---------------------------</td>
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<td>0.1% w/v</td>
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<td>Sodium phosphate BP</td>
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<td>0.38% w/v</td>
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<td>Polyethylene glycol 400</td>
<td>3.5% w/v</td>
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<td>Water for injection</td>
<td>to 100%</td>
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**Note**

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.
Claims

1. A compound of formula (I):

\[ R_1 - A - R_2 \]

wherein:

- \( R_1 \) and \( R_2 \) are selected from the following combinations:
  - \( R_1 \) is \( R_4 \) and \( R_2 \) is \( \text{SO}_2 \) \(- R_5 \),
  - \( R_1 \) is \( R_4 - \text{SO}_2 \) and \( R_2 \) is \( - R_5 \),
  - \( R_1 \) is \( R_5 \) and \( R_2 \) is \( \text{SO}_2 - R_4 \); and
  - \( R_1 \) is \( R_5 - \text{SO}_2 \) and \( R_2 \) is \( - R_4 \),

- \( A \) is selected from Group 1a, Group 1b, Group 1c or Group 1d

\[ \text{Group 1a} \]

\[ \text{Group 1b} \]

\[ \text{Group 1c} \]

\[ \text{Group 1d} \]

- \( B \) is a direct bond, methylene or carbonyl;
- \( R_3 \) is hydrogen, \( C_{1-4} \) alkyl or phenyl\( C_{1-4} \) alkyl;
- \( R_4 \) is a monocyclic nitrogen-containing heteroaryl substituted with an amino group, a bicyclic nitrogen-containing heteroaryl, naphthyl or a carbocyclic ring, wherein any monocyclic heteroaryl, the bicyclic heteroaryl, the naphthyl and carbocyclic ring are optionally substituted by one or more substituents independently selected from halo, amino or \( C_{1-4} \) alkyl, wherein the \( C_{1-4} \) alkyl is optionally substituted by 3 substituents independently selected from halo and \( C_{1-4} \) alkoxy;
- \( R_5 \) is \( C_{1-2} \) alkyl, aryl, aryl\( C_{1-2} \) alkyl, \( N\)-\( C_{1-4} \) alkylamino or \( N,N\)-di-\( C_{1-4} \) alkylamino, wherein any aryl is optionally substituted by one or more substituents independently selected from halo, alkyl, cyano, \( C_{1-4} \) alkoxy, \( C_{1-4} \) alkanoyl and amino; and
\[ p \text{ is } 1 \text{ or } 2; \]
\[ q \text{ is } 1 \text{ or } 2; \text{ and} \]
\[ n \text{ is } 1 \text{ or } 2; \]

or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

2. A compound of formula (I) according to claim 1 wherein A is Group 1a or Group 1b or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

3. A compound of formula (I) according to claim 1 wherein A is Group 1c or Group 1d or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

4. A compound of formula (I) according to any one of claims 1-3 wherein \( R_1 \) is \( R_4^- \) and \( R_2 \) is -SO\(_2\)-R\(_3\) or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

5. A compound of formula (I) according to any one of claims 1-4 wherein \( R_1 \) is quinolinyl, quinazolinyl or 1,2,3,4-tetrahydronaphthyl, optionally substituted by one or more substituents independently selected from halo, amino or \( C_{1-4} \) alkyl, wherein the \( C_{1-4} \) alkyl is optionally substituted by 3 substituents independently selected from halo and \( C_{1-4} \) alkoxy or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

6. A compound of formula (I) according to any one of claims 1-5 wherein \( R_4 \) is optionally substituted by one or more substituents independently selected from chloro, fluoro, methyl, ethyl, trifluoromethyl or amino or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

7. A compound of formula (I) according to any one of claims 1-6 wherein \( p \) is 1, \( q \) is 1 and \( n \) is 1 or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

8. A compound of formula (I) according to any one of claims 1-7 wherein B is a direct bond or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.
9. A compound of formula (I) according to any one of claims 1-8 wherein R₃ is naphthyl, optionally substituted by one or more substituents independently selected from halo, alkyl, cyano, C₄₋₅alkoxy, C₄₋₅alkanoyl and amino or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

10. A compound of formula (I) according to any one of claims 1-9 wherein R₃ is hydrogen, benzyl or C₄₋₅alkyl or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

11. A compound of formula (I) selected from:

- trans-2-(naphth-1-ylsulphonyl)-7-[(4-aminoquinazolin-2-yl)aminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine;
- trans-1-benzyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(2-methylquinolin-4-yl)aminomethyl]piperidine;
- trans-2-phenylsulphonylaminomethyl-5-[(2-methylquinolin-4-yl)aminomethyl]piperidine;
- trans-2-(naphth-1-ylsulphonyl)-7-[(1,2,3,4-tetrahydronaphth-2-yl)methylaminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine;
- trans-2-(naphth-1-ylsulphonyl)-7-[(4-aminoquinazolin-2-yl)aminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine; and

12. A compound of formula (I) selected from:

- trans-1-ethyl-2-(naphth-1-ylsulphonylaminomethyl)-5-[(2-methylquinolin-4-yl)aminomethyl]piperidine;
- trans-2-(naphth-1-ylsulphonyl)-7-[(2-methyl-7-chloroquinolin-4-yl)aminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine;
- trans-2-(naphth-1-ylsulphonyl)-7-[(2-methyl-4-fluoroquinolin-4-yl)aminomethyl]octahydro-2H-pyrido[1,2-a]pyrazine; and
trans-1-ethyl-2-phenylsulphonylaminomethyl-5-[(2-methylquinolin-4-
yl)aminomethyl]piperidine;
or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

A process for preparing a compound of formula (I) wherein \( R_1, R_2, R_3, R_4, R_5, A, B, n, p \) and \( q \) are, unless otherwise specified as defined in claim 1 which comprises:
(a) reacting an amine of formula (II), wherein \( B \) is a direct bond and \( R_2 \) is selected from

\[
\begin{align*}
-\text{SO}_2- & -R_4 \text{ or } -\text{SO}_2- & -R_4 \\
\text{H} & -A & -R_2
\end{align*}
\]

formula (II)

with a compound of the formula \( R_1L \) wherein \( L \) is a displaceable group;
(b) reacting an amine of formula (III) wherein \( R_1 \) is selected from \( R_4 \) or \( R_5 \):

\[
R_1-A-H
\]

formula (III)

with a sulphonyl compound of the formula \( LR_2 \), wherein \( L \) is a displaceable group and \( R_3 \) is selected from \(-\text{SO}_2- R_4 \) or \(-\text{SO}_2- R_5 \);
(c) for a compound of formula (I) wherein \( A \) is Group 1a or Group 1b and \( R_3 \) is other than hydrogen, reacting a group of formula (I) wherein \( A \) is Group 1a or Group 1b and \( R_3 \) is hydrogen, with a group of the formula \( LR_3 \) wherein \( L \) is a displaceable group;
(d) for a compound of formula (I) wherein \( A \) is Group 1c or Group 1d and \( B \) is carbonyl, reacting an amine of formula (IV)

\[
\begin{align*}
H_2N & -A'-\text{SO}_2- & -R_2 \\
\text{formula (IV)}
\end{align*}
\]

wherein \( A' \) is selected from Group 1c' or Group 1d'

with an acid of formula (V)
or an activated derivative thereof;
(e) for a compound of formula (I) wherein A is Group 1c or Group 1d and B is methylene,
reacting a compound of formula (I) wherein A is Group 1c or Group 1d and B is carbonyl
with a suitable reducing agent;
And thereafter if necessary
(i) converting a compound of formula (I) into another compound of formula (I);
(ii) removing any protecting groups;
(iii) forming a pharmaceutically-acceptable salt.

14. The use of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or
solvate thereof, according to any one of claims 1-12, as a medicament.

15. A pharmaceutical composition which comprises a compound of the formula (I) or a
pharmaceutically-acceptable salt, pro-drug or solvate thereof, according to any one of claims
1-12, in association with a pharmaceutically-acceptable diluent or carrier.

16. A method of treatment, in a warm-blooded animal, of disorders mediated by the
neuropeptide Y5 receptor comprising administering to said warm-blooded animal a
therapeutically effective amount of a compound of formula (I) or pharmaceutically-acceptable
salt, pro-drug or solvate thereof, according to any one of claims 1-12.

17. The use of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or
solvate thereof, according to any one of claims 1-12, in the manufacture of a medicament for
the treatment of a disorder mediated by the neuropeptide Y5 receptor, in a warm blooded
animal.

18. A pharmaceutical composition comprising a compound of formula (I), or a
pharmaceutically-acceptable salt, pro-drug or solvate thereof, according to any one of claims
1-12, in admixture with a pharmaceutically-acceptable diluent or carrier for the treatment of a warm-blooded animal, in need of treatment, of disorders mediated by the neuropeptide Y5 receptor.

19. A method of treatment, in a warm-blooded animal, of eating disorders, comprising administering a therapeutically effective amount of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or solvate thereof, according to any one of claims 1-12.

20. The use of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or solvate thereof, according to any one of claims 1-12, in the manufacture of a medicament for the treatment of eating disorders in a warm-blooded animal.

21. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically-acceptable salt, pro-drug or solvate thereof, according to any one of claims 1-12, in admixture with a pharmaceutically-acceptable diluent or carrier for the treatment of eating disorders in a warm-blooded animal.

22. The method, use or composition, according to claims 19-21 wherein the eating disorders are obesity and related disorders, bulimia or anorexia, wherein the related disorders are diabetes dyslipidaemia, hypertension and sleep disturbances.

23. A method of promoting weight loss, in a warm-blooded animal, comprising administering a therapeutically effective amount of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or solvate thereof, according to any one of claims 1-12.

24. The use of a compound of formula (I) or pharmaceutically-acceptable salt, pro-drug or solvate thereof, according to any one of claims 1-12, in the manufacture of a medicament for promoting weight loss in a warm-blooded animal.
25. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically-acceptable salt, pro-drug or solvate thereof, according to any one of claims 1-12, in admixture with a pharmaceutically-acceptable diluent or carrier for promoting weight loss in a warm-blooded animal.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 C07D403/12 A61K31/505 A61P3/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X Further documents are listed in the continuation of box C.

X Patent family members are listed in annex.

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* E* earlier document but published on or after the international filing date
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Date of the actual completion of the international search

5 July 2001

Date of mailing of the international search report

16/07/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax: (+31-70) 940-3018

Authorized officer

Grassi, D
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claim 1 | 1-12                              |
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