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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 June 2007 (07.06.2007)

PCT

(10) International Publication Number
WO 2007/064272 A1

(51) International Patent Classification:
C07D 213/75 (2006.01) *A61P 25/00* (2006.01)
A61K 31/4402 (2006.01) *A61P 3/04* (2006.01)
A61P 11/00 (2006.01) *C07C 237/52* (2006.01)

(21) International Application Number:
PCT/SE2006/001347

(22) International Filing Date:
28 November 2006 (28.11.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/740,508 29 November 2005 (29.11.2005) US

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

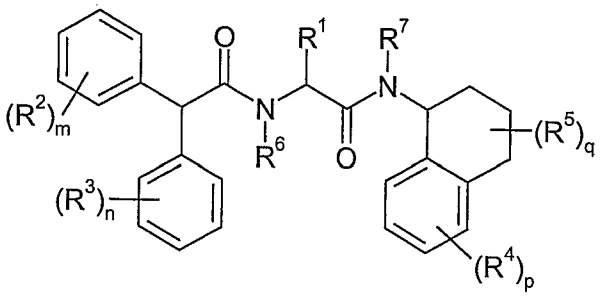
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BENZHYDRYL AMIDE DERIVATIVES AS CANNABINOID RECEPTOR ANTAGONISTS OR INVERSE AGONISTS

(57) Abstract: The present invention relates to compounds of formula I and processes for preparing such compounds, their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.



I

WO 2007/064272 A1

Benzhydryl amide derivatives as cannabinoid receptor antagonists or inverse agonists

Field of invention

The present invention relates to certain CB_1 antagonists or inverse agonists, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.

Background of the invention

It is known that certain CB_1 antagonists or inverse agonists (known as antagonists or inverse agonists) are useful in the treatment of obesity, psychiatric and neurological disorders (WO01/70700 and EP 656354).

However, there is a need for CB_1 antagonists or inverse agonists with other therapeutic effects, improved physicochemical properties and/or DMPK properties and/or pharmacodynamic properties.

Description of the invention

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

The term "alkyl" used alone or as a suffix or prefix, refers to a saturated monovalent straight or branched chain hydrocarbon radical comprising 1 to about 12

carbon atoms. Illustrative examples of alkyls include, but are not limited to, C_{1-6}alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, and hexyl, and longer alkyl groups, such as heptyl, and octyl. An alkyl can be unsubstituted or substituted with one or two suitable substituents.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a saturated monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms. Examples of cycloalkyls include, but are not limited to, C_{3-7}cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl can be unsubstituted or substituted by one or two suitable substituents. Preferably, the cycloalkyl is a monocyclic ring or bicyclic ring.

The term "aryl" used alone or as suffix or prefix, refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms.

The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-containing structure or molecule has an aromatic character (*e.g.*, 4n + 2 delocalized electrons).

The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term "heterocyclyl" used alone or as a suffix or prefix, refers a monovalent radical derived from a heterocycle by removing one hydrogen therefrom.

The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character.

Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4- oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings.

Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

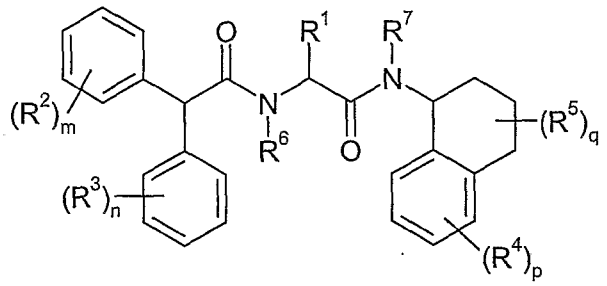
The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula –O-R, wherein R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on the group is replaced with one or more halogens.

"RT" or "rt" means room temperature.

In one aspect, the invention provides a compound of formula I, and pharmaceutically acceptable salts thereof



I

wherein

R^1 is selected from C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, C_{2-6}alkenyl, -$(CH_2)_r$-Ar^1, -$(CH_2)_r$-O-Ar^1, -$(CH_2)_r$-C(=O)-NH-Ar^1; -$(CH_2)_r$-NH-C(=O)-Ar^1, -$(CH_2)_r$-S(=O)$_2$-NH-Ar^1, -$(CH_2)_r$-NH-S(=O)$_2$-Ar^1, and -$(CH_2)_r$-NH-Ar^1, wherein said Ar^1 is independently selected from C_{1-5}heteroaryl and phenyl, wherein said C_{1-5}heteroaryl and phenyl used in defining Ar^1 and said C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, and C_{2-6}alkenyl used in defining R^1 are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy;

R^2, R^3, R^4 and R^5 are independently selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, halogenated C_{1-6}alkoxy, -NR^8C(=O)-

O-R^8, -S(=O)$_2$-NR^8R^8 and -O-S(=O)$_2$-R^8; wherein each R^8 is independently selected from hydrogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{3-6}cycloalkyl, and halogenated C_{3-6}cycloalkyl;

R^6 and R^7 are independently selected from hydrogen and C_{1-3}alkyl;

m, n, p, and q are independently selected from 1, 2, 3, and 4; and

r is selected from 0, 1, 2, 3 and 4.

In one embodiment, the compounds of the present invention are represented by formula I, wherein

R^1 is selected from -$(CH_2)_r$-Ar^1, -$(CH_2)_r$-O-Ar^1, -$(CH_2)_r$-C(=O)-NH-Ar^1; -$(CH_2)_r$-NH-C(=O)-Ar^1, -$(CH_2)_r$-S(=O)$_2$-NH-Ar^1, -$(CH_2)_r$-NH-S(=O)$_2$-Ar^1, and -$(CH_2)_r$-NH-Ar^1, wherein said Ar^1 is independently selected from C_{1-5}heteroaryl and phenyl, wherein said C_{1-5}heteroaryl and phenyl used in defining Ar^1 are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy;

R^2, R^3, R^4 and R^5 are independently selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, halogenated C_{1-6}alkoxy;

R^6 and R^7 are independently selected from hydrogen and C_{1-3}alkyl;

m, n, p, and q are independently selected from 1, 2, 3, and 4; and

r is selected from 0, 1, 2, 3 and 4.

In another embodiment, the compound of the invention may be represented by formula I, wherein

R^1 is selected from -$(CH_2)_r$-Ar^1, -$(CH_2)_r$-O-Ar^1, -$(CH_2)_r$-C(=O)-NH-Ar^1; -$(CH_2)_r$-NH-C(=O)-Ar^1, -$(CH_2)_r$-S(=O)$_2$-NH-Ar^1, -$(CH_2)_r$-NH-S(=O)$_2$-Ar^1, and -$(CH_2)_r$-NH-Ar^1, wherein said Ar^1 is independently selected from pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl, wherein said pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy;

R^2, R^3, R^4 and R^5 are independently selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, halogenated C_{1-6}alkoxy;

R^6 and R^7 are hydrogen;

m, n, p, and q are independently selected from 1, 2, 3, and 4; and

r is selected from 0, 1, 2, 3 and 4.

In a further embodiment, R^1 is selected from $-(CH_2)_r-Ar^1$, $-(CH_2)_r-O-Ar^1$, $-(CH_2)_r-C(=O)-NH-Ar^1$; $-(CH_2)_r-NH-C(=O)-Ar^1$, $-(CH_2)_r-S(=O)_2-NH-Ar^1$, $-(CH_2)_r-NH-S(=O)_2-Ar^1$, and $-(CH_2)_r-NH-Ar^1$, wherein said Ar^1 is independently selected from pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl, wherein said pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, $-NH_2$, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy, wherein r is selected from 1, 2 and 3.

Particularly, R^1 is selected from $-(CH_2)_r-C(=O)-NH-Ar^1$; $-(CH_2)_r-NH-C(=O)-Ar^1$, $-(CH_2)_r-S(=O)_2-NH-Ar^1$, $-(CH_2)_r-NH-S(=O)_2-Ar^1$, and $-(CH_2)_r-NH-Ar^1$, wherein said Ar^1 is independently selected from pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl, wherein said pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, $-NH_2$, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy, wherein r is selected from 1, 2 and 3.

More particularly, R^1 is selected from $-(CH_2)_r-C(=O)-NH-Ar^1$; $-(CH_2)_r-NH-C(=O)-Ar^1$, and $-(CH_2)_r-NH-Ar^1$, wherein said Ar^1 is independently selected from pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl, wherein said pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, $-NH_2$, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy, wherein r is selected from 2 and 3.

Even more particularly, R^1 is selected from $-(CH_2)_r-C(=O)-NH-Ar^1$; $-(CH_2)_r-NH-C(=O)-Ar^1$, and $-(CH_2)_r-NH-Ar^1$, wherein said Ar^1 is independently selected from pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl, wherein said pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, $-NH_2$, halogen, C_{1-}

$_3$alkyl, halogenated C_{1-3}alkyl, C_{1-3}alkoxy, and halogenated C_{1-3}alkoxy, wherein r is selected from 2 and 3.

In an even further embodiment, R^2, R^3, R^4 and R^5 are independently selected from hydrogen, -OH, -CN, $-NH_2$, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, halogenated C_{1-6}alkoxy.

Particularly, R^2, R^3, R^4 and R^5 are independently selected from hydrogen, -OH, -CN, $-NH_2$, halogen, C_{1-3}alkyl, halogenated C_{1-3}alkyl, C_{1-3}alkoxy, halogenated C_{1-3}alkoxy.

More particularly, R^2, R^3, R^4 and R^5 are hydrogen.

In a yet even further embodiment, m, n, p, and q are independently selected from 1, 2, 3, and 4.

Particularly, m, n, p, and q are 1.

In a further embodiment, r is selected from 1, 2, 3 and 4. Particularly, r is selected from 2, 3 and 4. More particularly, r is selected from 2 and 3. Even more particularly, r is 2.

"Pharmaceutically acceptable salt", where such salts are possible, includes both pharmaceutically acceptable acid and base addition salts. A suitable pharmaceutically acceptable salt of a compound of Formula I is, for example, an acid-addition salt of a compound of Formula I which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a sodium, calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates. Isomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional

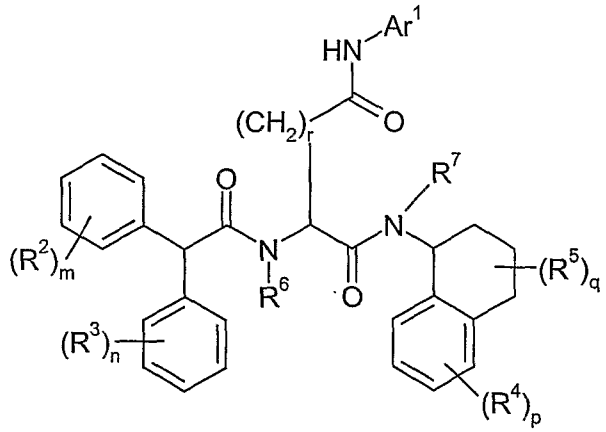
crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention. All tautomers, where possible, are included within the scope of the invention. The present invention also encompasses compounds containing one or more isotopes for example ^{14}C, ^{11}C or ^{19}F and their use as isotopically labelled compounds for pharmacological and metabolic studies.

The present invention also encompasses prodrugs of a compound of formula I that is compounds which are converted into a compound of formula I in vivo.

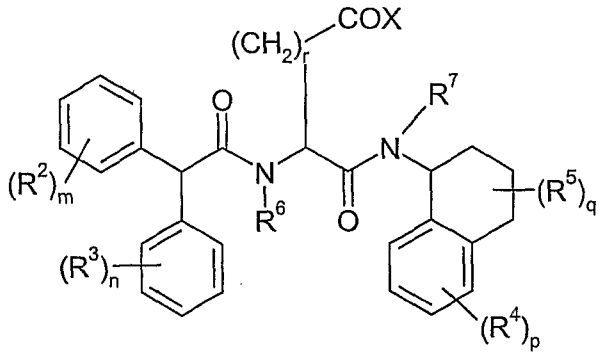
Methods of preparation

The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

Compounds of formula IA, wherein R^2, R^3, R^4, R^5, R^6, R^7, m, n, p, q and r are as defined above, may be prepared by reacting a compound of formula IIA



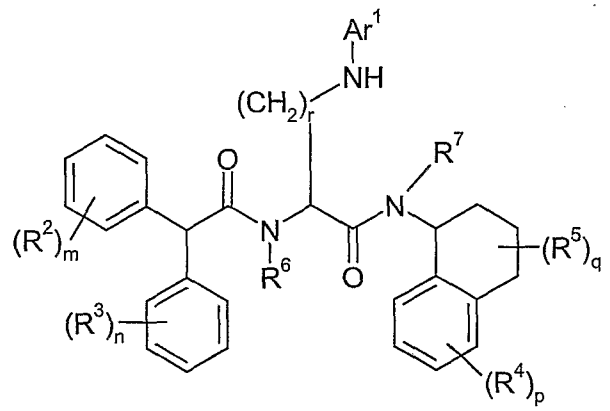
IA



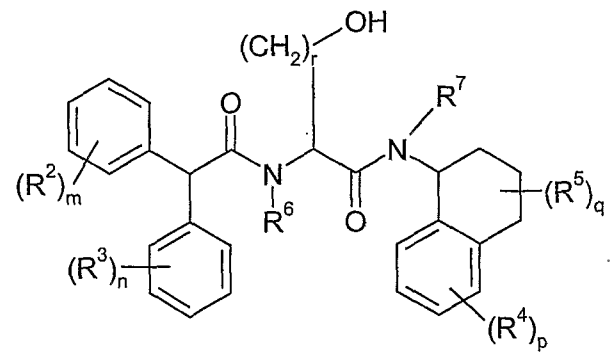
IIA

with Ar^1-NH_2, wherein X is selected from –OH and halogen, at a temperature in the range of –25 to 150°C, in the presence of an inert solvent, for example dimethylformamide, and optionally in the presence of one or more bases, for example, N, N-diisopropylethylamine or N-methylmorpholine, and optionally in the presence of HATU.

Compounds of formula IB, wherein R^2, R^3, R^4, R^5, R^6, R^7, m, n, p, q and r are as defined above, may be prepared by reacting a compound of formula IIB,



IB

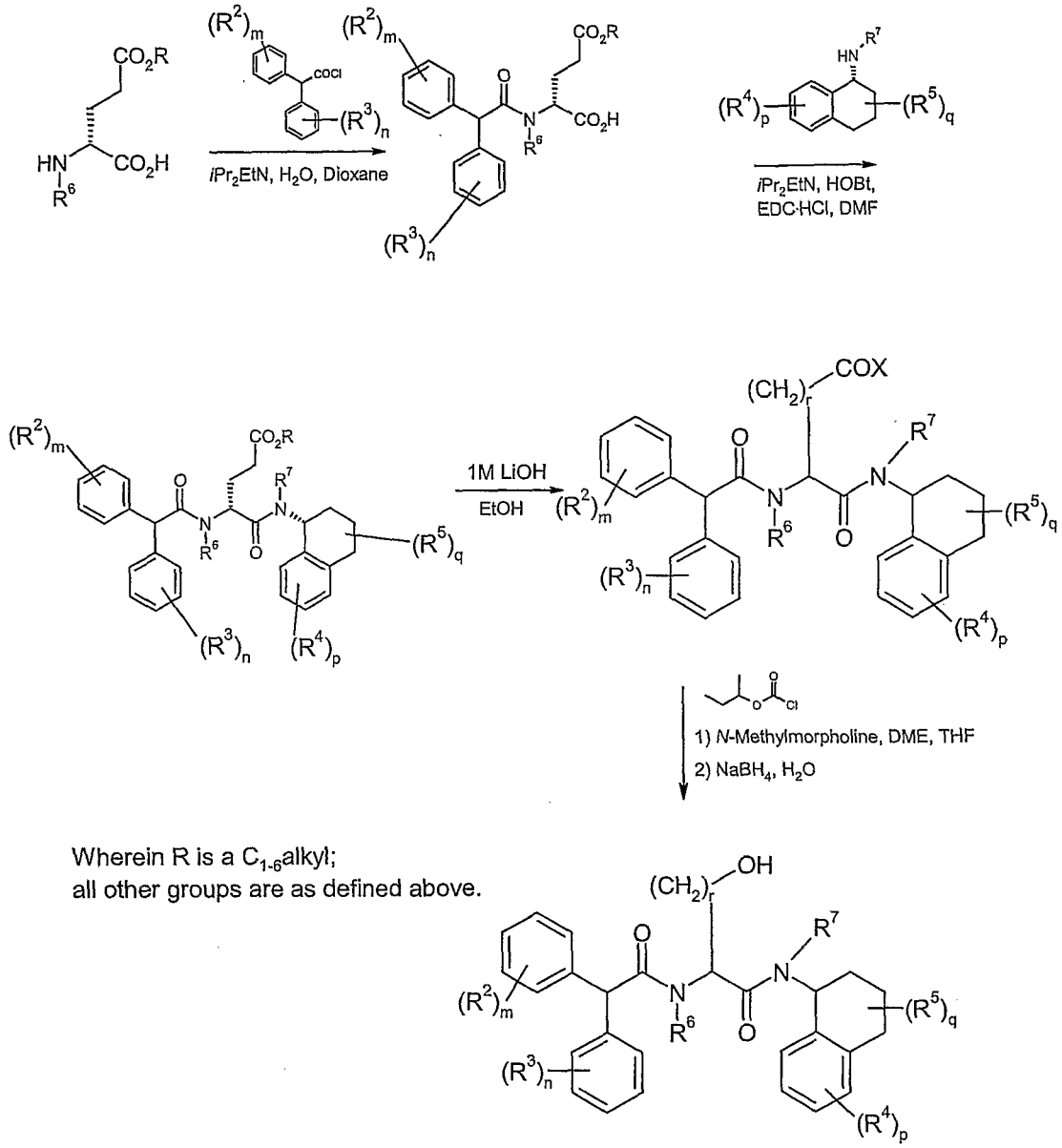


IIB

with methanesulfonyl chloride to form an intermediate, optionally in the presence of a base such as N,N-diisopropylethylamine, followed by reacting the intermediate with Ar^1-NH_2, at a temperature in the range of –25 to 150°C, in the presence of an inert solvent, for example, dimethylformamide, and optionally in the presence of one or more bases, for example, triethylamine, N, N-diisopropylethylamine or N-methylmorpholine.

Compounds of formula IIA or IIB may be prepared by the following general synthetic scheme (Scheme I) and adaptations thereof or by analogous methods known to those skilled in the art. It will be appreciated by those skilled in the art that during the reaction sequence certain functional groups will require protection followed by deprotection at an appropriate stage, see "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

Scheme I



Wherein R is a C_{1-6}alkyl;
all other groups are as defined above.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of

pharmaceutical preparations comprising the active ingredient or a pharmaceutically acceptable addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight. Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The compounds of formula I are useful for the treatment of obesity or being overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention of weight gain (e.g., medication-induced or subsequent to cessation of smoking), for modulation of appetite and/or satiety, eating disorders (e.g. binge eating, anorexia, bulimia and compulsive), cravings (for drugs, tobacco, alcohol, any appetizing macronutrients or non-essential food items), for the treatment of psychiatric disorders such as psychotic and/or mood disorders, schizophrenia, cognitive deficiency associated with schizophrenia, schizo-affective disorder, bipolar disorders, anxiety, anxio-depressive disorders, depression, mania, obsessive-compulsive disorders, impulse control disorders (e.g., Gilles de la Tourette's syndrome), attention disorders like ADD/ADHD, stress, and neurological disorders such as dementia and cognitive and/or memory dysfunction (e.g., amnesia, Alzheimer's disease, Pick´s dementia, dementia of ageing, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild dementia of ageing), neurological and/or neurodegenerative disorders (e.g. Multiple Sclerosis, Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease), demyelinisation-related disorders, neuroinflammatory disorders (e.g., Guillain-Barré syndrome).

The compounds are also potentially useful for the prevention or treatment of dependence and addictive disorders and behaviours (e.g., alcohol and/or drug abuse, pathological gambling, kleptomania), drug withdrawal disorders (e.g., alcohol withdrawal with or without perceptual disturbances; alcohol withdrawal delirium; amphetamine withdrawal; cocaine withdrawal; nicotine withdrawal; opioid withdrawal; sedative, hypnotic or anxiolytic withdrawal with or without perceptual disturbances; sedative, hypnotic or anxiolytic withdrawal delirium; and withdrawal symptoms due to other substances), alcohol and/or drug-induced mood, anxiety and/or sleep disorder with onset during withdrawal, and alcohol and/or drug relapse.

The compounds are also potentially useful for the prevention or treatment of neurological dysfunctions such as dystonias, dyskinesias, akathisia, tremor and spasticity, treatment of spinal cord injury, neuropathy, migraine, vigilance disorders, sleep disorders (e.g., disturbed sleep architecture, sleep apnea, obstructive sleep apnea, sleep apnea syndrome), pain disorders, cranial trauma.

The compounds are also potentially useful for the treatment of immune, cardiovascular disorders (e.g. atherosclerosis, arteriosclerosis, angina pectoris, abnormal heart rhythms, and arrhythmias, congestive heart failure, coronary artery disease, heart disease, hypertension, prevention and treatment of left ventricular hypertrophy, myocardial infarction, transient ischaemic attack, peripheral vascular disease, systemic inflammation of the vasculature, septic chock, stroke, cerebral apoplexy, cerebral infarction, cerebral ischaemia, cerebral thrombosis, cerebral embolism, cerebral hemorrhagia, metabolic disorders (e.g. conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, diabetes mellitus, dyslipidemia, fatty liver, gout, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, hyperuricacidemia, impaired glucose tolerance, impaired fasting glucose, insulin resistance, insulin resistance syndrome, metabolic syndrome, syndrome X, obesity-hypoventilation syndrome (Pickwickian syndrome), type I diabetes, type II diabetes, low HDL- and/or high LDL-cholesterol levels, low adiponectin levels), reproductive and endocrine disorders (e.g. treatment of hypogonadism in males, treatment of infertility or as contraceptive, menstrual abnormalities/emmeniopathy, polycystic ovarian disease, sexual and reproductive dysfunction in women and men (erectile dysfunction), GH-deficient subjects, hirsutism in females, normal variant short stature) and diseases related to the

respiratory (e.g. asthma and chronic obstructive pulmonary disease) and gastrointestinal systems (e.g. dysfunction of gastrointestinal motility or intestinal propulsion, diarrhea, emesis, nausea, gallbladder disease, cholelithiasis, obesity-related gastro-esophageal reflux, ulcers).

The compounds are also potentially useful as agents in treatment of dermatological disorders, cancers (e.g. colon, rectum, prostate, breast, ovary, endometrium, cervix, gallbladder, bile duct), craniopharyngioma, Prader-Willi syndrome, Turner syndrome, Frohlich's syndrome, glaucoma, infectious diseases, urinary tract disorders and inflammatory disorders (e.g. arthritis deformans, inflammation, inflammatory sequelae of viral encephalitis, osteoarthritis) and orthopedic disorders. The compounds are also potentially useful as agents in treatment of (esophageal) achalasia.

In another aspect the present invention provides a compound of formula I as previously defined for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity or being overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention of weight gain (e.g., medication-induced or subsequent to cessation of smoking), for modulation of appetite and/or satiety, eating disorders (e.g. binge eating, anorexia, bulimia and compulsive), cravings (for drugs, tobacco, alcohol, any appetizing macronutrients or non-essential food items), for the treatment of psychiatric disorders such as psychotic and/or mood disorders, schizophrenia, cognitive deficiency associated with schizophrenia, cognitive deficiency associated with schizophrenia, schizo-affective disorder, bipolar disorders, anxiety, anxio-depressive disorders, depression, mania, obsessive-compulsive disorders, impulse control disorders (e.g., Gilles de la Tourette's syndrome), attention disorders like ADD/ADHD, stress, and neurological disorders such as dementia and cognitive and/or memory dysfunction (e.g., amnesia, Alzheimer's disease, Pick´s dementia, dementia of ageing, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild dementia of ageing), neurological and/or neurodegenerative disorders (e.g. Multiple Sclerosis, Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease), demyelinisation-related disorders, neuroinflammatory disorders (e.g., Guillain-Barré syndrome).

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of dependence and addictive disorders and behaviours (e.g., alcohol and/or drug abuse, pathological gambling, kleptomania), drug withdrawal disorders (e.g., alcohol withdrawal with or without perceptual disturbances; alcohol withdrawal delirium; amphetamine withdrawal; cocaine withdrawal; nicotine withdrawal; opioid withdrawal; sedative, hypnotic or anxiolytic withdrawal with or without perceptual disturbances; sedative, hypnotic or anxiolytic withdrawal delirium; and withdrawal symptoms due to other substances), alcohol and/or drug-induced mood, anxiety and/or sleep disorder with onset during withdrawal, and alcohol and/or drug relapse.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of neurological dysfunctions such as dystonias, dyskinesias, akathisia, tremor and spasticity, treatment of spinal cord injury, neuropathy, migraine, vigilance disorders, sleep disorders (e.g., disturbed sleep architecture, sleep apnea, obstructive sleep apnea, sleep apnea syndrome), pain disorders, cranial trauma.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of immune, cardiovascular disorders (e.g. atherosclerosis, arteriosclerosis, angina pectoris, abnormal heart rhythms, and arrhythmias, congestive heart failure, coronary artery disease, heart disease, hypertension, prevention and treatment of left ventricular hypertrophy, myocardial infarction, transient ischaemic attack, peripheral vascular disease, systemic inflammation of the vasculature, septic chock, stroke, cerebral apoplexy, cerebral infarction, cerebral ischaemia, cerebral thrombosis, cerebral embolism, cerebral hemorrhagia, metabolic disorders (e.g. conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, diabetes mellitus, dyslipidemia, fatty liver, gout, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, hyperuricacidemia, impaired glucose tolerance, impaired fasting glucose, insulin resistance, insulin resistance syndrome, metabolic syndrome, syndrome X, obesity-hypoventilation syndrome (Pickwickian syndrome), type I diabetes, type II diabetes, low HDL- and/or high LDL-cholesterol levels, low adiponectin levels), reproductive and endocrine disorders (e.g. treatment of hypogonadism in males, treatment of infertility or as

contraceptive, menstrual abnormalities/emmeniopathy, polycystic ovarian disease, sexual and reproductive dysfunction in women and men (erectile dysfunction), GH-deficient subjects, hirsutism in females, normal variant short stature) and diseases related to the respiratory (e.g. asthma and chronic obstructive pulmonary disease) and gastrointestinal systems (e.g. dysfunction of gastrointestinal motility or intestinal propulsion, diarrhea, emesis, nausea, gallbladder disease, cholelithiasis, obesity-related gastro-esophageal reflux, ulcers).

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of dermatological disorders, cancers (e.g. colon, rectum, prostate, breast, ovary, endometrium, cervix, gallbladder, bile duct), craniopharyngioma, Prader-Willi syndrome, Turner syndrome, Frohlich's syndrome, glaucoma, infectious diseases, urinary tract disorders and inflammatory disorders (e.g. arthritis deformans, inflammation, inflammatory sequelae of viral encephalitis, osteoarthritis) and orthopedic disorders.

In a still further aspect the present invention provides a method comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof for the prophylaxis or treatment of obesity or being overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention of weight gain (e.g., medication-induced or subsequent to cessation of smoking), for modulation of appetite and/or satiety, eating disorders (e.g. binge eating, anorexia, bulimia and compulsive), cravings (for drugs, tobacco, alcohol, any appetizing macronutrients or non-essential food items), for the treatment of psychiatric disorders such as psychotic and/or mood disorders, schizophrenia, cognitive deficiency associated with schizophrenia, schizo-affective disorder, bipolar disorders, anxiety, anxio-depressive disorders, depression, mania, obsessive-compulsive disorders, impulse control disorders (e.g., Gilles de la Tourette's syndrome), attention disorders like ADD/ADHD, stress, and neurological disorders such as dementia and cognitive and/or memory dysfunction (e.g., amnesia, Alzheimer's disease, Pick´s dementia, dementia of ageing, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild dementia of ageing), neurological and/or neurodegenerative disorders (e.g. Multiple Sclerosis, Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease),

demyelinisation-related disorders, neuroinflammatory disorders (e.g., Guillain-Barré syndrome).

In a still further aspect the present invention provides a method comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof for the prophylaxis or treatment of dependence and addictive disorders and behaviours (e.g., alcohol and/or drug abuse, pathological gambling, kleptomania), drug withdrawal disorders (e.g., alcohol withdrawal with or without perceptual disturbances; alcohol withdrawal delirium; amphetamine withdrawal; cocaine withdrawal; nicotine withdrawal; opioid withdrawal; sedative, hypnotic or anxiolytic withdrawal with or without perceptual disturbances; sedative, hypnotic or anxiolytic withdrawal delirium; and withdrawal symptoms due to other substances), alcohol and/or drug-induced mood, anxiety and/or sleep disorder with onset during withdrawal, and alcohol and/or drug relapse.

In a still further aspect the present invention provides a method comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof for the prophylaxis or treatment of neurological dysfunctions such as dystonias, dyskinesias, akathisia, tremor and spasticity, treatment of spinal cord injury, neuropathy, migraine, vigilance disorders, sleep disorders (e.g., disturbed sleep architecture, sleep apnea, obstructive sleep apnea, sleep apnea syndrome), pain disorders, cranial trauma.

In a still further aspect the present invention provides a method comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof for the prophylaxis or treatment of immune, cardiovascular disorders (e.g. atherosclerosis, arteriosclerosis, angina pectoris, abnormal heart rhythms, and arrhythmias, congestive heart failure, coronary artery disease, heart disease, hypertension, prevention and treatment of left ventricular hypertrophy, myocardial infarction, transient ischaemic attack, peripheral vascular disease, systemic inflammation of the vasculature, septic chock, stroke, cerebral apoplexy, cerebral infarction, cerebral ischaemia, cerebral thrombosis, cerebral embolism, cerebral hemorrhagia, metabolic disorders (e.g. conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, diabetes mellitus, dyslipidemia, fatty liver, gout, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia,

hyperuricacidemia, impaired glucose tolerance, impaired fasting glucose, insulin resistance, insulin resistance syndrome, metabolic syndrome, syndrome X, obesity-hypoventilation syndrome (Pickwickian syndrome), type I diabetes, type II diabetes, low HDL- and/or high LDL-cholesterol levels, low adiponectin levels), reproductive and endocrine disorders (e.g. treatment of hypogonadism in males, treatment of infertility or as contraceptive, menstrual abnormalities/emmeniopathy, polycystic ovarian disease, sexual and reproductive dysfunction in women and men (erectile dysfunction), GH-deficient subjects, hirsutism in females, normal variant short stature) and diseases related to the respiratory (e.g. asthma and chronic obstructive pulmonary disease) and gastrointestinal systems (e.g. dysfunction of gastrointestinal motility or intestinal propulsion, diarrhea, emesis, nausea, gallbladder disease, cholelithiasis, obesity-related gastro-esophageal reflux, ulcers).

In a still further aspect the present invention provides a method comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof for the prophylaxis or treatment of dermatological disorders, cancers (e.g. colon, rectum, prostate, breast, ovary, endometrium, cervix, gallbladder, bile duct), craniopharyngioma, Prader-Willi syndrome, Turner syndrome, Frohlich's syndrome, glaucoma, infectious diseases, urinary tract disorders and inflammatory disorders (e.g. arthritis deformans, inflammation, inflammatory sequelae of viral encephalitis, osteoarthritis) and orthopedic disorders..

The compounds of the present invention are particularly suitable for the treatment of obesity or being overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention or reversal of weight gain (e.g., rebound, medication-induced or subsequent to cessation of smoking), for modulation of appetite and/or satiety, eating disorders (e.g. binge eating, anorexia, bulimia and compulsive), cravings (for drugs, tobacco, alcohol, any appetizing macronutrients or non-essential food items).

The compounds of formula I are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders(e.g. Multiple Sclerosis), Raynaud's syndrome, Parkinson's disease, Huntington's chorea and

Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, septic shock and diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea). The compounds are also potentially useful as agents in treatment of extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms. The compounds may also eliminate the increase in weight that normally accompanies the cessation of smoking.

In another aspect the present invention provides a compound of formula I as previously defined for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders such as schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine,

opiates, etc) withdrawal symptoms comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

The compounds of the present invention are particularly suitable for the treatment of obesity, e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound.

The compounds of the present invention may also be used to prevent or reverse medication-induced weight gain, e.g. weight gain caused by antipsychotic (neuroleptic) treatment(s). The compounds of the present invention may also be used to prevent or reverse weight gain associated with smoking cessation.

The compounds of the present invention are suitable for use in treating the above indications in juvenile or adolescent patient populations.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of obesity such as other anti-obesity drugs, that affect energy expenditure, glycolysis, gluconeogenesis, glucogenolysis, lipolysis, lipogenesis, fat absorption, fat storage, fat excretion, hunger and/or satiety and/or craving mechanisms, appetite/motivation, food intake, or G-I motility.

The compounds of the invention may further be combined with another therapeutic agent that is useful in the treatment of disorders associated with obesity such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes, sleep apnea, asthma, heart disorders, atherosclerosis, macro and micro vascular diseases, liver steatosis, cancer, joint disorders, and gallbladder disorders. For example, a compound of the present invention may be used in combination with a another therapeutic agent that lowers blood pressure or that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of obesity and its associated complications the metabolic syndrome and type 2 diabetes, these include biguanide drugs, insulin (synthetic insulin analogues) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors).

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt thereof may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art.

In addition the combination of the invention may be used in conjunction with a sulfonylurea. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin.

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The present invention also includes a compound of the present invention in combination with a bile acid binding resin.

The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor;

a cholesterol absorption antagonist;

a MTP (microsomal transfer protein) inhibitor ;

a nicotinic acid derivative, including slow release and combination products;

a phytosterol compound ;

probucol;

an anti-coagulant;

an omega-3 fatty acid ;

another anti-obesity compound for example sibutramine, phentermine, orlistat, bupropion, ephedrine, thyroxine;

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha adrenergic blocker, a beta adrenergic blocker, a mixed alpha/beta adrenergic blocker, an adrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a melanin concentrating hormone (MCH) modulator;

an NPY receptor modulator;

an orexin receptor modulator;

a phosphoinositide-dependent protein kinase (PDK) modulator; or

modulators of nuclear receptors for example LXR, FXR, RXR, GR, ERRα, β, PPARα, β, γ and RORalpha;

a monoamine transmission-modulating agent, for example a selective serotonin reuptake inhibitor (SSRI), a noradrenaline reuptake inhibitor (NARI), a noradrenaline-serotonin reuptake inhibitor (SNRI), a monoamine oxidase inhibitor (MAOI), a tricyclic antidepressive agent (TCA), a noradrenergic and specific serotonergic antidepressant (NaSSA);

an antipsychotic agent for example olanzapine and clozapine;

a serotonin receptor modulator;

a leptin/leptin receptor modulator;

a ghrelin/ghrelin receptor modulator;

a DPP-IV inhibitor;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a

compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of very low calorie diets (VLCD) or low-calorie diets (LCD).

Therefore in an additional feature of the invention, there is provided a method for the treatment of obesity and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of obesity and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically

acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in the treatment of disorders or conditions associated with obesity (such as type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension, coronary heart disease, non-alcoholic steatohepatitis, osteoarthritis and some cancers) and psychiatric and neurological conditions.

It will be understood that there are medically accepted definitions of obesity and being overweight. A patient may be identified by, for example, measuring body mass index (BMI), which is calculated by dividing weight in kilograms by height in metres squared, and comparing the result with the definitions.

Pharmacological Activity

Compounds of the present invention are active against the receptor product of the CB1 gene. The affinity of the compounds of the invention for central cannabinoid receptors is demonstrable in methods described in Devane et al , Molecular Pharmacology, 1988, 34,605 or those described in WO01/70700 or EP 656354. Alternatively the assay may be performed as follows.

10μg of membranes prepared from cells stably transfected with the CB1 gene were suspended in 200μl of 100mM NaCl, 5mM $MgCl_2$, 1mM EDTA, 50mM HEPES (pH 7.4), 1mM DTT, 0.1% BSA and 100μM GDP. To this was added an EC80 concentration of agonist (CP55940), the required concentration of test compound and 0.1μCi [^{35}S]-GTPγS.

The reaction was allowed to proceed at 30°C for 45 min. Samples were then transferred on to GF/B filters using a cell harvester and washed with wash buffer (50mM Tris (pH 7.4), 5mM $MgCl_2$, 50mM NaCl). Filters were then covered with scintilant and counted for the amount of [^{35}S]-GTPγS retained by the filter.

Activity is measured in the absence of all ligands (minimum activity) or in the presence of an EC80 concentration of CP55940 (maximum activity). These activities are set as 0% and 100% activity respectively. At various concentrations of novel ligand, activity is calculated as a percentage of the maximum activity and plotted. The data are fitted using the equation y=A+((B-A)/1+((C/x) ÙD)) and the IC50 value determined as the concentration required to give half maximal inhibition of GTPγS binding under the conditions used.

The compounds of the present invention are active at the CB1 receptor (IC50 <1 micromolar). Most preferred compounds have IC50 <200 nanomolar.

The compounds of the invention are believed to be selective CB1 antagonists or inverse agonists. The potency, selectivity profile and side effect propensity may limit the clinical usefulness of hitherto known compounds with alleged CB1 antagonistic/inverse agonistic properties. In this regard, preclinical evaluation of compounds of the present invention in models of gastrointestinal and/or cardiovascular function indicates that they offer significant advantages compared to representative reference CB1 antagonist/inverse agonist agents.

The compounds of the present invention may provide additional benefits in terms of potency, selectivity profile, bioavailability, half-life in plasma, blood brain permeability, plasma protein binding (for example increasing the free fraction of drug) or solubility compared to representative reference CB1 antagonists/inverse agonist agents.

The utility of the compounds of the present invention in the treatment of obesity and related conditions is demonstrated by a decrease in body weight in cafeteria diet-induced obese mice. Female C57Bl/6J mice were given ad libitum access to calorie-dense 'cafeteria' diet (soft chocolate/cocoa-type pastry, chocolate, fatty cheese and nougat) and standard lab chow for 8-10weeks. Compounds to be tested were then administered systemically (iv, ip, sc or po) once daily for a minimum of 5 days, and the body weights of the mice monitored on a daily basis. Simultaneous assessment of adiposity was carried by means of DEXA imaging at baseline and termination of the study. Blood sampling was also carried out to assay changes in obesity-related plasma markers.

Examples

Abbreviations

DMF	dimethylformamide
DMSO	Dimethyl Sulfoxide
DEA	Diethylamine
EtOAc	ethyl acetate
THF	tetrahydrofuran
DMAP	4-Dimethylaminopyridine
TLC	thin layer chromatography

t	triplet
s	singlet
d	doublet
q	quartet
quint	quintet
m	multiplet
br	broad
bs	broad singlet
dm	doublet of multiplet
bt	broad triplet
dd	doublet of doublet

Example 1: (R)-2-Diphenylacetylamino-pentanedioic acid 5-pyridin-4-ylamide 1-[(R)-(1,2,3,4-tetrahydro-naphthalen-1-yl)-amide].

(R)-2-Diphenylacetylamino-pentanedioic acid 5-methyl ester.

N,N-Diisopropylethylamine (3.33 mL, 19.2 mmol) was added to a solution of (R)-2-amino-pentanedioic acid 5-methyl ester (1.54 g, 9.60 mmol) in H_2O (5 mL) and dioxane (10 mL) at 0 °C, followed by a solution of diphenylacetyl chloride (2.00 g, 8.70 mmol). The reaction was stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in EtOAc and 5% $KHSO_4$ in water. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* and used directly in the next reaction.

(R)-4-Diphenylacetylamino-4-[(R)-(1,2,3,4-tetrahydro-naphthalen-1yl)carbamoyl]-butyric acid methyl ester.

(R)-2-Diphenylacetylamino-pentanedioic acid 5-methyl ester prepared above was dissolved in DMF (10 mL) and added to a solution of the (R)-1,2,3,4-tetrahydro-1-naphthylamine (1.41 g, 9.60 mmol), iPr$_2$EtN (7.56 mL, 43.5 mmol) and HOBt (1.41 g, 10.4 mmol) in DMF (80 mL) at 0 °C under nitrogen. EDC (1.99 g, 10.4 mmol) was added to the reaction mixture and the reaction was stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in EtOAc. The organic phase was washed with 5% $KHSO_4$ in water, saturated $NaHCO_3$ and brine, dried over Na_2SO_4,

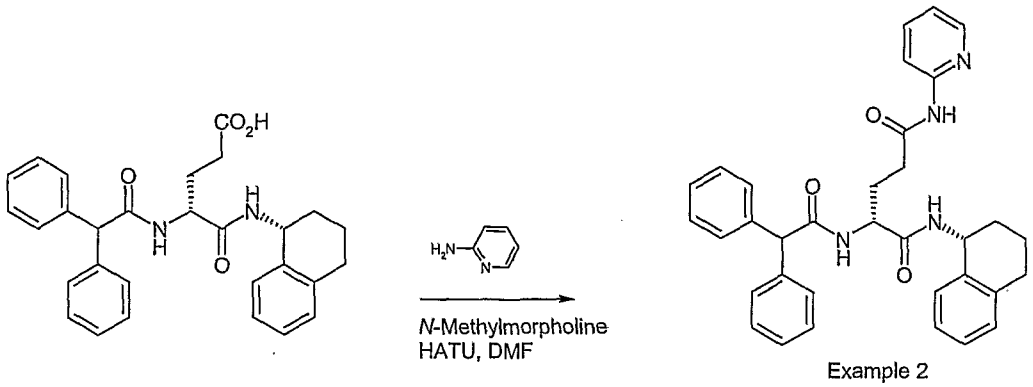
filtered, and concentrated *in vacuo*. The crude product was used directly in the next reaction.

(R)-4-Diphenylacetylamino-4-[(R)-(1,2,3,4-tetrahydro-naphthalen-1-yl)carbamoyl]-butyric acid.

A suspension of (R)-4-diphenylacetylamino-4-[(R)-(1,2,3,4-tetrahydro-naphthalen-1yl)carbamoyl]-butyric acid methyl ester prepared above in EtOH (50 mL) at 0 °C was treated with a 1M solution of LiOH in water (21.8 mL, 21.8 mmol). The reaction was stirred at room temperature for 5 hours. The mixture was acidified with 1N HCl and filtered. The solid was washed with water, then dried. The acid was obtained as a white solid (3.47 g, 85% for 3 steps) and used directly in the next reaction. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 1.54-1.66 (2H, m), 1.68-2.12 (4H, m), 2.10-2.12 (2H, m), 2.43-2.66 (2H, m), 4.23-4.26 (1H, m), 4.85-4.87 (1H, m), 5.06 (1H, s), 7.02-7.10 (4H, m), 7.13-7.24 (8H, m), 8.17 (1H, d), 8.41 (1H, d). MS (ESI) $(M+H)^+ = 471$.

(R)-2-Diphenylacetylamino-pentanedioic acid 5-pyridin-4-ylamide 1-[(R)-(1,2,3,4-tetrahydro-naphthalen-1-yl)-amide].

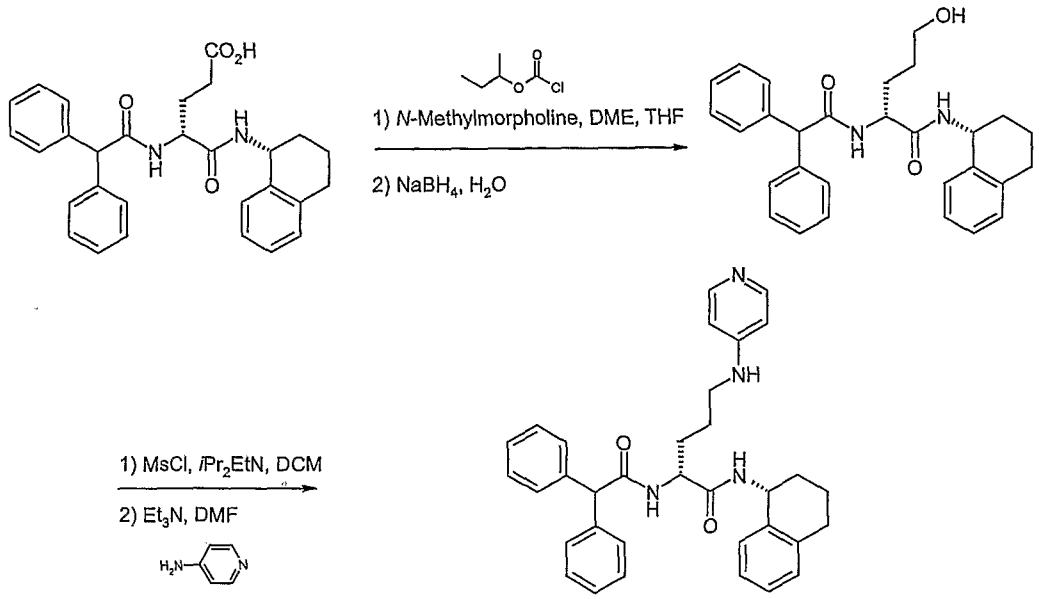
N,N-Diisopropylethylamine (0.11 mL, 0.64 mmol), HOBt (34 mg, 0.26 mmol), (R)-4-diphenylacetylamino-4-[(R)-(1,2,3,4-tetrahydro-naphthalen-1-yl)carbamoyl]-butyric acid (100 mg, 0.213 mmol) and EDC (49 mg, 0.26 mmol) were added to a solution of 4-aminopyridine (22 mg, 0.23 mmol) in DMF (3 mL). The reaction was stirred at room temperature overnight. The solvent was evaporated. The residue was purified by reverse phase HPLC (gradient 30-80% CH_3CN in H_2O) and lyophilized to provide the TFA salt of the title compound (20 mg, 14%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ1.38-1.47 (2H, m), 1.56-1.65 (4H, m), 1.74-1.77 (2H, m), 2.65 (1H, q), 4.00-4.04 (1H, m), 4.32-4.36 (1H, m), 4.86 (1H, q), 5.10 (1H, s), 6.72 (2H, d), 6.95-7.17 (3H, m), 7.18-7.25 (8H, m), 7.97-8.04 (3H, m), 8.27 (1H, d), 8.45 (1H, d); MS (ESI) $(M+H)^+ = 533.15$. Anal. Calcd for $C_{34}H_{34}N_4O_3$ + 1.5 TFA: C, 63.15; H, 5.37; N, 7.96. Found: C, 63.12; H, 5.40; N, 7.94.



Example 2

Example 2: (R)-2-Diphenylacetylamino-pentanedioic acid 5-pyridin-2-ylamide 1-[(R)-(1,2,3,4-tetrahydro-naphthalen-1-yl)-amide].

N-Methylmorpholine (0.030 mL, 0.28 mmol), (R)-4-diphenylacetylamino-4-[(R)-(1,2,3,4-tetrahydro-naphthalen-1-yl)carbamoyl]-butyric acid (100 mg, 0.213 mmol) and HATU (97 mg, 0.26 mmol) were added to a solution of 2-aminopyridine (22 mg, 0.23 mmol) in DMF (3 mL) under nitrogen. The reaction was stirred at room temperature overnight, then the solvent evaporated. The residue was purified by reverse phase HPLC (gradient 30-80% CH_3CN in H_2O) and lyophilized to provide the TFA salt of the title compound (87 mg, 62%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ1.55-1.67 (2H, m), 1.75-1.92 (3H, m), 1.94-2.04 (2H, m), 2.48 (2H, t), 2.60-2.72 (2H, m), 4.32-4.36 (1H, m), 4.85-4.92 (1H, m), 5.08 (1H, s), 7.05-7.26 (14H, m), 7.96 (2H, d), 8.19 (1H, d), 8.46 (1H, d), 8.64 (2H, d); MS (ESI) $(M+H)^+ = 547.21$. Anal. Calcd for $C_{34}H_{34}N_4O_3 + 1.5$ TFA + 2.5 H_2O: C, 58.26; H, 5.35; N, 7.35. Found: C, 58.17; H, 5.34; N, 6.86.



Example 3

Example 3: (R)-2-Diphenylacetylamino-5-(pyridin-4-ylamino)-pentanoic acid (R)-1,2,3,4-tetrahydro-naphthalen-1-yl-amide.

(R)-2-Diphenylacetylamino-5-hydroxy-pentanoic acid [(R)-1,2,3,4-tetrahydro-naphthalen-1-yl]-amide.

N-Methylmorpholine (0.066 mL, 0.60 mmol) was added to a solution of (R)-4-diphenylacetylamino-4-[(R)-(1,2,3,4-tetrahydro-naphthalen-1-yl)carbamoyl]-butyric acid (280 mg, 0.596 mmol) in DME (2 mL) and THF (2 mL) at -15 °C under nitrogen, followed by 2-butylchloroformate (0.077 mL, 0.60 mmol). The white precipitate that formed was filtered and washed with THF. The solution obtained was cooled to -15 °C and a solution of $NaBH_4$ (34 mg, 0.89 mmol) in water (0.3 mL) was added in one portion, followed by water (12 mL). The solid that formed was filtered and washed with water and hexanes, then dried under vacuum. The alcohol was obtained as a white solid (180 mg, 66%). MS (ESI) $(M+H)^+ = 457.04$.

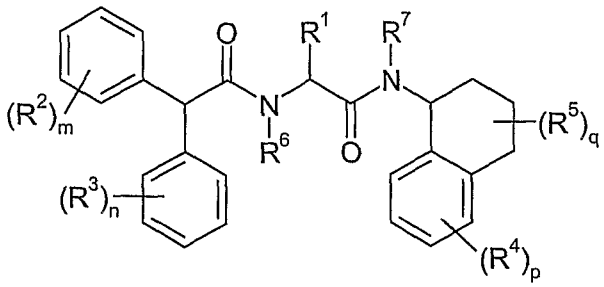
(R)-2-Diphenylacetylamino-5-(pyridin-4-ylamino)-pentanoic acid [(R)-1,2,3,4-tetrahydro-naphthalen-1-yl]-amide.

N,N-Diisopropylethylamine (0.060 mL, 0.35 mmol) was added to a solution of (R)-2-diphenylacetylamino-5-hydroxy-pentanoic acid [(R)-1,2,3,4-tetrahydro-naphthalen-1-yl]-amide (132 mg, 0.290 mmol) in DCM (3 mL) at 0 °C under nitrogen, followed by methanesulfonyl chloride (0.025 mL, 0.32 mmol). The reaction was stirred at room

temperature for 3 hours. The solvent was evaporated and the residue was dissolved in EtOAc. The organic phase was washed with 5% $KHSO_4$ in water and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. 4-Aminopyridine (136 mg, 1.45 mmol) and triethylamine (0.20 mL, 1.5 mmol) were added to a solution of the crude compound in DMF (2 mL) under nitrogen. The reaction was stirred at room temperature for 72 hours. The solvent was evaporated. The residue was purified by reverse phase HPLC (gradient 30-80% CH_3CN in H_2O) and lyophilized to provide the TFA salt of the title compound (38 mg, 21%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ1.38-1.47 (2H, m), 1.56-1.65 (4H, m), 1.74-1.77 (2H, m), 2.65 (2H, q), 4.00-4.04 (2H, m), 4.32-4.36 (1H, m), 4.86 (1H, q), 5.10 (1H, s), 6.72 (2H, d), 6.95-7.17 (3H, m), 7.18-7.25 (8H, m), 7.97-8.04 (3H, m), 8.27 (1H, d), 8.45 (1H, d); MS (ESI) $(M+H)^+ = 533.15$. Anal. Calcd for $C_{34}H_{36}N_4O_2$ + 1.5 TFA: C, 63.15; H, 5.37; N, 7.96. Found: C, 63.12; H, 5.40; N, 7.94.

We Claim:

1. A compound of formula I or pharmaceutically acceptable salts thereof



I

wherein

R^1 is selected from C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, C_{2-6}alkenyl, -$(CH_2)_r$-Ar^1, -$(CH_2)_r$-O-Ar^1, -$(CH_2)_r$-C(=O)-NH-Ar^1; -$(CH_2)_r$-NH-C(=O)-Ar^1, -$(CH_2)_r$-S(=O)$_2$-NH-Ar^1, -$(CH_2)_r$-NH-S(=O)$_2$-Ar^1, and -$(CH_2)_r$-NH-Ar^1, wherein said Ar^1 is independently selected from C_{1-5}heteroaryl and phenyl, wherein said C_{1-5}heteroaryl and phenyl used in defining Ar^1 and said C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, and C_{2-6}alkenyl used in defining R^1 are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy;

R^2, R^3, R^4 and R^5 are independently selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, halogenated C_{1-6}alkoxy, -NR^8C(=O)-O-R^8, -S(=O)$_2$-NR^8R^8 and -O-S(=O)$_2$-R^8; wherein each R^8 is independently selected from hydrogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{3-6}cycloalkyl, and halogenated C_{3-6}cycloalkyl;

R^6 and R^7 are independently selected from hydrogen and C_{1-3}alkyl;

m, n, p, and q are independently selected from 1, 2, 3, and 4; and

r is selected from 0, 1, 2, 3 and 4.

2. A compound as claimed in claim 1, wherein

R^1 is selected from -$(CH_2)_r$-Ar^1, -$(CH_2)_r$-O-Ar^1, -$(CH_2)_r$-C(=O)-NH-Ar^1; -$(CH_2)_r$-NH-C(=O)-Ar^1, -$(CH_2)_r$-S(=O)$_2$-NH-Ar^1, -$(CH_2)_r$-NH-S(=O)$_2$-Ar^1, and -$(CH_2)_r$-NH-Ar^1, wherein said Ar^1 is independently selected from C_{1-5}heteroaryl and phenyl, wherein said C_{1-5}heteroaryl and phenyl used in defining Ar^1 are optionally and independently substituted

with one or more groups selected from hydrogen, -OH, -CN, $-NH_2$, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy;

R^2, R^3, R^4 and R^5 are independently selected from hydrogen, -OH, -CN, $-NH_2$, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, halogenated C_{1-6}alkoxy;

R^6 and R^7 are independently selected from hydrogen and C_{1-3}alkyl;

m, n, p, and q are independently selected from 1, 2, 3, and 4; and

r is selected from 0, 1, 2, 3 and 4.

3. A compound as claimed in claim 1, wherein

R^1 is selected from $-(CH_2)_r-Ar^1$, $-(CH_2)_r-O-Ar^1$, $-(CH_2)_r-C(=O)-NH-Ar^1$; $-(CH_2)_r-NH-C(=O)-Ar^1$, $-(CH_2)_r-S(=O)_2-NH-Ar^1$, $-(CH_2)_r-NH-S(=O)_2-Ar^1$, and $-(CH_2)_r-NH-Ar^1$, wherein said Ar^1 is independently selected from pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl, wherein said pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, $-NH_2$, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy;

R^2, R^3, R^4 and R^5 are independently selected from hydrogen, -OH, -CN, $-NH_2$, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, halogenated C_{1-6}alkoxy;

R^6 and R^7 are hydrogen;

m, n, p, and q are independently selected from 1, 2, 3, and 4; and

r is selected from 0, 1, 2, 3 and 4.

4. A compound as claimed in any one of claims 1-3, wherein

R^1 is selected from $-(CH_2)_r-C(=O)-NH-Ar^1$; $-(CH_2)_r-NH-C(=O)-Ar^1$, $-(CH_2)_r-S(=O)_2-NH-Ar^1$, $-(CH_2)_r-NH-S(=O)_2-Ar^1$, and $-(CH_2)_r-NH-Ar^1$, wherein said Ar^1 is independently selected from pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl, wherein said pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, $-NH_2$, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy, wherein r is selected from 1, 2 and 3.

5. A compound as claimed in any one of claims 1-3, wherein R^1 is selected from -$(CH_2)_r$-C(=O)-NH-Ar^1; -$(CH_2)_r$-NH-C(=O)-Ar^1, and -$(CH_2)_r$-NH-Ar^1, wherein said Ar^1 is independently selected from pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl, wherein said pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy, wherein r is selected from 2 and 3.

6. A compound as claimed in any one of claims 1-3, wherein R^1 is selected from -$(CH_2)_r$-C(=O)-NH-Ar^1; -$(CH_2)_r$-NH-C(=O)-Ar^1, and -$(CH_2)_r$-NH-Ar^1, wherein said Ar^1 is independently selected from pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl, wherein said pyridyl, tetrazolyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, pyrazolyl, thiazolyl, pyridyl-N-oxide and phenyl are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-3}alkyl, halogenated C_{1-3}alkyl, C_{1-3}alkoxy, and halogenated C_{1-3}alkoxy, wherein r is selected from 2 and 3.

7. A compound selected from one or more of the following:
(R)-2-Diphenylacetylamino-pentanedioic acid 5-pyridin-4-ylamide 1-[(R)-(1,2,3,4-tetrahydro-naphthalen-1-yl)-amide];
(R)-2-Diphenylacetylamino-pentanedioic acid 5-pyridin-2-ylamide 1-[(R)-(1,2,3,4-tetrahydro-naphthalen-1-yl)-amide];
(R)-2-Diphenylacetylamino-5-(pyridin-4-ylamino)-pentanoic acid (R)-1,2,3,4-tetrahydro-naphthalen-1-yl-amide;
and pharmaceutically acceptable salts thereof.

8. A compound as claimed in any of claims 1 to 7 for use as a medicament.

9. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable adjuvant, diluent or carrier.

10. Use of a compound according to any one of claims 1 to 7 in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse indications.

11. A method of treating obesity, psychiatric disorders, psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, neurological disorders, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal system, and extended abuse, addiction and/or relapse indications, comprising administering a pharmacologically effective amount of a compound according to any one of claims 1 to 7 to a patient in need thereof.

12. A method of treating schizophrenia comprising administering a pharmacologically effective amount of a compound as claimed in any one of claims 1-7 to a patient in need thereof.

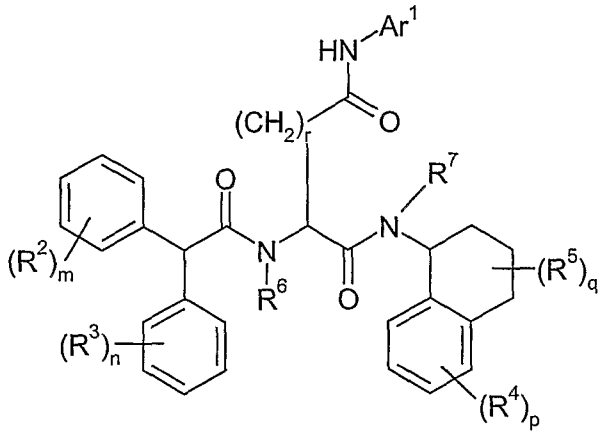
13. A method of treating cognitive deficiency associated with schizophrenia comprising administering a pharmacologically effective amount of a compound as claimed in any one of claims 1-7 to a patient in need thereof.

14. A compound as defined in any one of claims 1-7 for use in the treatment of obesity.

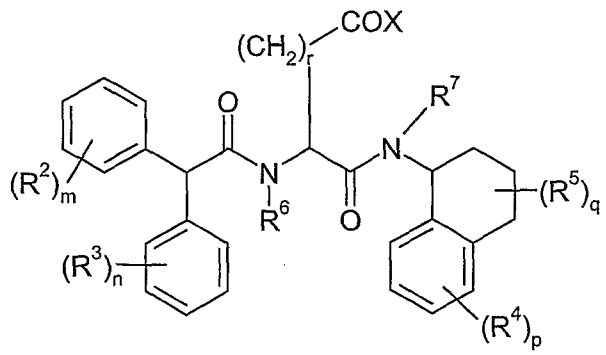
15. A compound as claimed in any one of claims 1-7 for use in the treatment of schizophrenia.

16. A compound as claimed in any one of claims 1-7 for use in the treatment of cognitive deficiency associated with schizophrenia.

17. A process for the preparation of a compound of formula IA, prepared by reacting a compound of formula IIA



IA



IIA

with Ar^1-NH_2, wherein X is selected from –OH and halogen, at a temperature in the range of –25 to 150^{0}C, in the presence of an inert solvent, wherein

R^1 is selected from C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, C_{2-6}alkenyl, -$(CH_2)_r$-Ar^1, -$(CH_2)_r$-O-Ar^1, -$(CH_2)_r$-C(=O)-NH-Ar^1; -$(CH_2)_r$-NH-C(=O)-Ar^1, -$(CH_2)_r$-S(=O)$_2$-NH-Ar^1, -$(CH_2)_r$-NH-S(=O)$_2$-Ar^1, and -$(CH_2)_r$-NH-Ar^1, wherein said Ar^1 is independently selected from C_{1-5}heteroaryl and phenyl, wherein said C_{1-5}heteroaryl and phenyl used in defining Ar^1 and said C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, and C_{2-6}alkenyl used in defining R^1 are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy;

R^2, R^3, R^4 and R^5 are independently selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, halogenated C_{1-6}alkoxy, -NR^8C(=O)-O-R^8, -S(=O)$_2$-NR^8R^8 and -O-S(=O)$_2$-R^8; wherein each R^8 is independently selected from hydrogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{3-6}cycloalkyl, and halogenated C_{3-6}cycloalkyl;

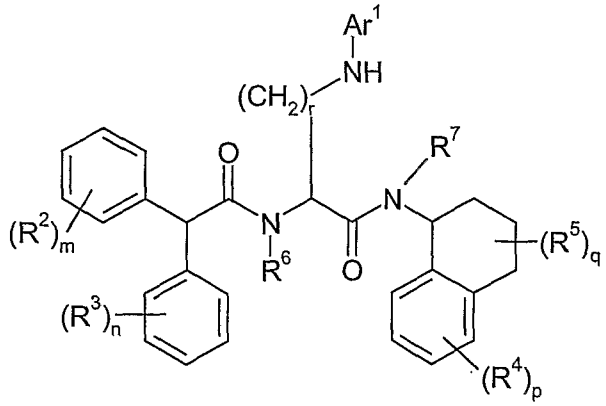
R^6 and R^7 are independently selected from hydrogen and C_{1-3}alkyl;

m, n, p, and q are independently selected from 1, 2, 3, and 4; and

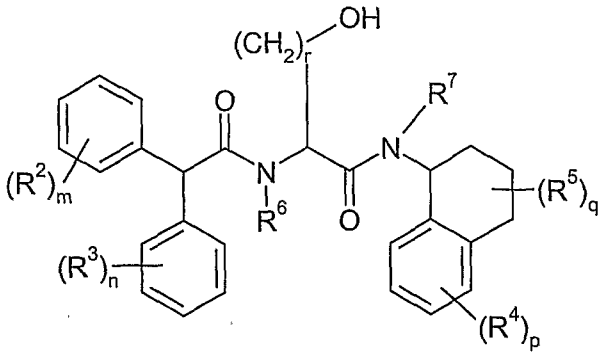
r is selected from 0, 1, 2, 3 and 4.

18. A process of preparing a compound of formula IB comprising

reacting a compound of formula IIB,



IB



IIB

with methanesulfonyl chloride to form an intermediate, and

reacting the intermediate with Ar^1-NH_2, at a temperature in the range of –25 to 150°C, in the presence of an inert solvent, wherein

R^1 is selected from C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, C_{2-6}alkenyl, -$(CH_2)_r$-Ar^1, -$(CH_2)_r$-O-Ar^1, -$(CH_2)_r$-C(=O)-NH-Ar^1; -$(CH_2)_r$-NH-C(=O)-Ar^1, -$(CH_2)_r$-S(=O)$_2$-NH-Ar^1, -$(CH_2)_r$-NH-S(=O)$_2$-Ar^1, and -$(CH_2)_r$-NH-Ar^1, wherein said Ar^1 is independently selected from C_{1-5}heteroaryl and phenyl, wherein said C_{1-5}heteroaryl and phenyl used in defining Ar^1 and said C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, and C_{2-6}alkenyl used in defining R^1 are optionally and independently substituted with one or more groups selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, and halogenated C_{1-6}alkoxy;

R^2, R^3, R^4 and R^5 are independently selected from hydrogen, -OH, -CN, -NH_2, halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{1-6}alkoxy, halogenated C_{1-6}alkoxy, -NR^8C(=O)-O-R^8, -S(=O)$_2$-NR^8R^8 and -O-S(=O)$_2$-R^8; wherein each R^8 is independently selected from hydrogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, C_{3-6}cycloalkyl, and halogenated C_{3-6}cycloalkyl;

R^6 and R^7 are independently selected from hydrogen and C_{1-3}alkyl;

m, n, p, and q are independently selected from 1, 2, 3, and 4; and

r is selected from 0, 1, 2, 3 and 4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/001347

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
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: C07D, C07C

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0102364 A1 (ASTRAZENECA AB), 11 January 2001 (11.01.2001) --	1-18
A	WO 9915498 A1 (ASTRA AKTIEBOLAG), 1 April 1999 (01.04.1999) --	1-18
A	WO 2005040355 A2 (EXELIXIS, INC.), 6 May 2005 (06.05.2005) --	1-18
A	WO 2005028456 A1 (SOLVAY PHARMACEUTICALS B.V.), 31 March 2005 (31.03.2005) --	1-18

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2007	23 -02- 2007
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Renzo C. Verboom/EÖ Telephone No. +46 8 782 25 00

International patent classification (IPC)

C07D 213/75 (2006.01)
A61K 31/4402 (2006.01)
A61P 11/00 (2006.01)
A61P 25/00 (2006.01)
A61P 3/04 (2006.01)
C07C 237/52 (2006.01)

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Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/001347

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11-13
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 11-13 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

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