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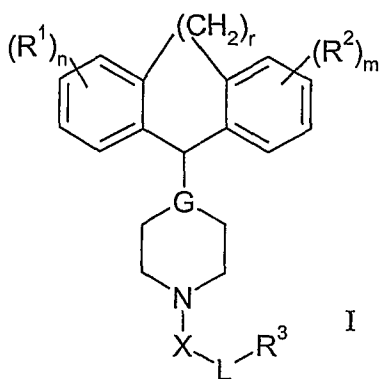
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(54) Title: THERAPEUTIC AGENTS



(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.

THERAPEUTIC AGENTS

Field of invention

5 The present invention relates to certain CB₁ 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.

10 Background of the invention

 It is known that certain CB₁ 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 CB₁ antagonists or inverse agonists with other
15 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
20 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
25 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
30 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, C₁₋₆alkyl 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, C₃₋₇cycloalkyl 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
5 "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
10 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,
15 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,
20 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,
25 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,
30 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
 5 and 7-oxabicyclo[2.2.1]heptane.

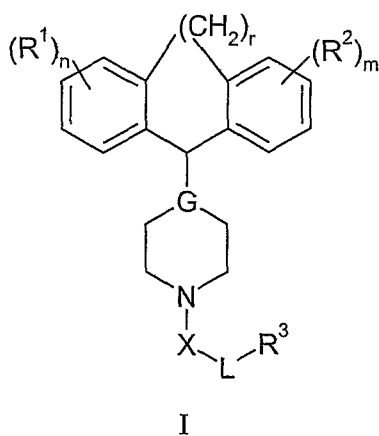
The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula $-O-R$, wherein R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

10 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
 15 pharmaceutically acceptable salts thereof



wherein

20 G is selected from CH and N;

r is selected from 0, 1 and 2;

R^1 and R^2 are independently selected from hydrogen, $-OH$, halogen, C_{1-6} alkyl, halogenated C_{1-6} alkyl, C_{1-6} alkoxy, halogenated C_{1-6} alkoxy, $-NR^4C(=O)-O-R^4$, $-S(=O)_2-$

NR^4R^4 and $-\text{O}-\text{S}(=\text{O})_2-\text{R}^4$; wherein each R^4 is independently selected from hydrogen, C_{1-6} alkyl, halogenated C_{1-6} alkyl, C_{3-6} cycloalkyl, and halogenated C_{3-6} cycloalkyl;

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

X is selected from a bond, $-\text{C}(=\text{O})-$, $-\text{S}(=\text{O})_2-$, $-\text{C}(=\text{O})-\text{N}-$, and $-\text{C}(=\text{S})-\text{N}-$;

5 L is selected from a bond, $-(\text{CH}_2)_p-$, $-(\text{CH}_2)_p-\text{O}-$, $-\text{C}(=\text{O})-\text{O}-$, $-(\text{CH}_2)_p\text{S}-$, $-\text{CH}_2\text{NHC}(=\text{O})-\text{CH}_2-$,

p is selected from 0, 1 and 2; and

R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and C_{3-9} heterocyclyl, wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and C_{3-9} heterocyclyl are optionally substituted with one or more group selected from C_{1-6} alkoxy, halogen, C_{1-6} alkyl, halogenated C_{1-6} alkyl, aryl, halogenated aryl, nitro, cyano, $-\text{C}(=\text{O})-\text{R}^5$, $-\text{CO}_2\text{R}^5$, $-\text{NHC}(=\text{O})-\text{R}^5$, wherein R^5 is selected from hydrogen, C_{1-6} alkyl, halogenated C_{1-6} alkyl, C_{3-6} cycloalkyl, halogenated C_{3-6} cycloalkyl, heterocyclyl, benzhydryl and aryl, wherein said heterocyclyl, benzhydryl and aryl are optionally substituted by one or more group selected from halogen, C_{1-3} alkyl, phenyl, and methoxy;

with a proviso that at least one of X and L is not a bond.

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

G is selected from CH and N ;

20 r is selected from 0, 1 and 2;

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

25 m and n are independently selected from 1 and 2;

X is selected from a bond, $-\text{C}(=\text{O})-$, $-\text{S}(=\text{O})_2-$, $-\text{C}(=\text{O})-\text{N}-$, and $-\text{C}(=\text{S})-\text{N}-$;

L is selected from a bond, $-(\text{CH}_2)_p-$, $-\text{C}(=\text{O})-\text{O}-$, $-(\text{CH}_2)_p-\text{O}-$, $-(\text{CH}_2)_p\text{S}-$, $-\text{CH}_2\text{NHC}(=\text{O})-\text{CH}_2-$,

p is selected from 1 and 2;

30 R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and C_{3-5} heteroaryl, wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and C_{3-5} heteroaryl are optionally substituted with

one or more group selected from C₁₋₃alkoxy, halogen, C₁₋₃alkyl, halogenated C₁₋₃alkyl, C₆₋₁₀aryl, halogenated C₆₋₁₀aryl, nitro, cyano, -C(=O)-R⁵, -CO₂R⁵, -NHC(=O)-R⁵, wherein R⁵ is selected from hydrogen, C₁₋₃alkyl, halogenated C₁₋₃alkyl, C₃₋₆cycloalkyl, halogenated C₃₋₆cycloalkyl, heterocyclyl, benzhydryl and phenyl, wherein said heterocyclyl, benzhydryl and
5 aryl are optionally substituted by one or more group selected from halogen, C₁₋₃alkyl, phenyl, and methoxy;

with a proviso that R³ is not unsubstituted phenyl; with a further proviso that at least one of X and L is not a bond.

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

G is selected from CH and N;

r is selected from 0, 1 and 2;

R¹ and R² are independently selected from hydrogen, -OH, halogen, C₁₋₃alkyl, halogenated C₁₋₃alkyl, C₁₋₃alkoxy, and halogenated C₁₋₃alkoxy;

15 m and n are independently selected from 1 and 2;

X is selected from a bond, -C(=O)-, and -S(=O)₂-;

L is selected from a bond and -(CH₂)_p-,

p is selected from 1 and 2;

R³ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl, wherein
20 said C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl are optionally substituted with one or more group selected from C₁₋₃alkoxy, halogen, cyano, C₁₋₃alkyl, halogenated C₁₋₃alkyl, and benzhydryl;

with a proviso that R³ is not unsubstituted phenyl; with a further proviso that at least one of X and L is not a bond.

25 In a further embodiment, X is -C(=O)-.

In an even further embodiment, L is selected from a bond and -CH₂-.

In a yet even further embodiment, R³ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl, wherein said C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl are optionally substituted with one or more group selected from fluoro, chloro,
30 bromo, nitro, methyl, trifluoromethyl, cyano, methoxy, and benzhydryl.

In a further embodiment, compounds of the invention may be represented by formula I, wherein

G is selected from CH and N;

r is selected from 0, 1 and 2;

5 R^1 and R^2 are independently selected from hydrogen, fluoro, chloro, bromo, methyl, trifluoromethyl, and methoxy;

m and n are independently selected from 1 and 2;

X is $-C(=O)-$;

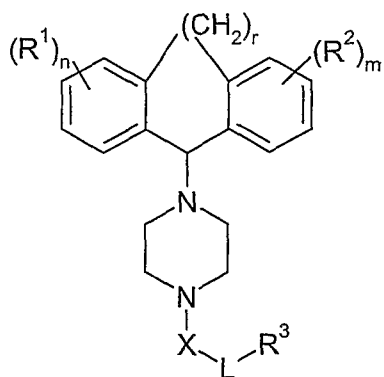
L is selected from a bond and $-CH_2-$,

10 R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and C_{3-5} heteroaryl, wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and C_{3-5} heteroaryl are optionally substituted with one or more group selected from fluoro, chloro, bromo, nitro, methyl, trifluoromethyl, cyano, methoxy, and benzhydryl;

with a proviso that R^3 is not unsubstituted phenyl.

15

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



20

IA

wherein

R^1 and R^2 are independently selected from hydrogen, $-OH$, halogen, C_{1-6} alkyl, halogenated C_{1-6} alkyl, C_{1-6} alkoxy, halogenated C_{1-6} alkoxy, $-NR^4C(=O)-O-R^4$, $-S(=O)_2-$

NR^4R^4 and $-\text{O}-\text{S}(=\text{O})_2-\text{R}^4$; wherein each R^4 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 is selected from 0, 1 and 2;

m and n are independently selected from 1, 2, 3, 4 and 5;

5 X is selected from a bond, $-\text{C}(=\text{O})-$, $-\text{S}(=\text{O})_2-$, $-\text{C}(=\text{O})-\text{N}-$, and $-\text{C}(=\text{S})-\text{N}-$;

L is selected from a bond, $-(\text{CH}_2)_p-$, $-(\text{CH}_2)_p-\text{O}-$, $-\text{C}(=\text{O})-\text{O}-$, $-(\text{CH}_2)_p\text{S}-$, $-\text{CH}_2\text{NHC}(=\text{O})-\text{CH}_2-$,

p is selected from 0, 1 and 2;

R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and C_{3-9} heterocyclyl,

10 wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and C_{3-9} heterocyclyl are optionally substituted with one or more group selected from C_{1-6} alkoxy, halogen, C_{1-6} alkyl, halogenated C_{1-6} alkyl, aryl, halogenated aryl, nitro, cyano, $-\text{C}(=\text{O})-\text{R}^5$, $-\text{CO}_2\text{R}^5$, $-\text{NHC}(=\text{O})-\text{R}^5$, wherein R^5 is selected from hydrogen, C_{1-6} alkyl, halogenated C_{1-6} alkyl, C_{3-6} cycloalkyl, halogenated C_{3-6} cycloalkyl, heterocyclyl, benzhydryl and aryl, wherein said
15 heterocyclyl, benzhydryl and aryl are optionally substituted by one or more group selected from halogen, C_{1-3} alkyl, phenyl, and methoxy;

with a proviso that at least one of X and L is not a bond;

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

20 R^1 and R^2 are independently selected from hydrogen, $-\text{OH}$, halogen, C_{1-3} alkyl, halogenated C_{1-3} alkyl, C_{1-3} alkoxy, halogenated C_{1-3} alkoxy, $-\text{NR}^4\text{C}(=\text{O})-\text{O}-\text{R}^4$, $-\text{S}(=\text{O})_2-\text{NR}^4\text{R}^4$ and $-\text{O}-\text{S}(=\text{O})_2-\text{R}^4$; wherein each R^4 is independently selected from hydrogen and C_{1-3} alkyl;

r is selected from 0, 1 and 2;

25 m and n are independently selected from 1, 2 and 3;

X is selected from a bond, $-\text{C}(=\text{O})-$, $-\text{S}(=\text{O})_2-$, $-\text{C}(=\text{O})-\text{N}-$, and $-\text{C}(=\text{S})-\text{N}-$;

L is selected from a bond, $-(\text{CH}_2)_p-$, $-\text{C}(=\text{O})-\text{O}-$, $-(\text{CH}_2)_p-\text{O}-$, $-(\text{CH}_2)_p\text{S}-$, $-\text{CH}_2\text{NHC}(=\text{O})-\text{CH}_2-$,

p is selected from 1 and 2;

30 R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and C_{3-5} heteroaryl, wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and C_{3-5} heteroaryl are optionally substituted with

one or more group selected from C₁₋₃alkoxy, halogen, C₁₋₃alkyl, halogenated C₁₋₃alkyl, C₆₋₁₀aryl, halogenated C₆₋₁₀aryl, nitro, cyano, -C(=O)-R⁵, -CO₂R⁵, -NHC(=O)-R⁵, wherein R⁵ is selected from hydrogen, C₁₋₃alkyl, halogenated C₁₋₃alkyl, C₃₋₆cycloalkyl, halogenated C₃₋₆cycloalkyl, heterocyclyl, benzhydryl and phenyl, wherein said heterocyclyl, benzhydryl and aryl are optionally substituted by one or more group selected from halogen, C₁₋₃alkyl, phenyl, and methoxy;

with a proviso that R³ is not unsubstituted phenyl; with a further proviso that at least one of X and L is not a bond.

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

R¹ and R² are independently selected from hydrogen, -OH, halogen, C₁₋₃alkyl, halogenated C₁₋₃alkyl, C₁₋₃alkoxy, and halogenated C₁₋₃alkoxy;

r is selected from 0, 1 and 2;

m and n are independently selected from 1 and 2;

X is selected from a bond, -C(=O)-, and -S(=O)₂-;

L is selected from a bond and -(CH₂)_p-,

p is selected from 1 and 2;

R³ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl, wherein said C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl are optionally substituted with one or more group selected from C₁₋₃alkoxy, halogen, nitro, cyano, C₁₋₃alkyl, halogenated C₁₋₃alkyl, and benzhydryl;

with a proviso that R³ is not unsubstituted phenyl; with a further proviso that at least one of X and L is not a bond.

In a further embodiment, X is -C(=O)-.

In an even further embodiment, L is selected from a bond and -CH₂-.

In a yet even further embodiment, R³ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl, wherein said C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl are optionally substituted with one or more group selected from fluoro, chloro, bromo, methyl, trifluoromethyl, cyano, methoxy, and benzhydryl.

In a further embodiment, compounds of the invention may be represented by formula IA, wherein

R^1 and R^2 are independently selected from hydrogen, fluoro, chloro, bromo, methyl, trifluoromethyl, and methoxy;

r is selected from 0, 1 and 2;

m and n are independently selected from 1 and 2;

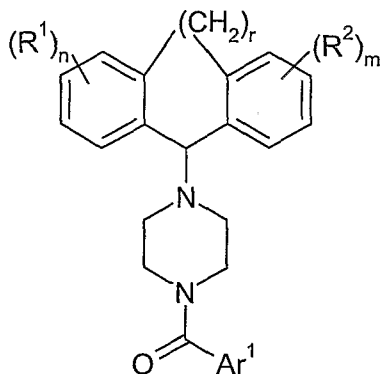
5 X is $-C(=O)-$;

L is selected from a bond and $-CH_2-$,

R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and C_{3-5} heteroaryl, wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and C_{3-5} heteroaryl are optionally substituted with one or more group selected from fluoro, chloro, bromo, nitro, methyl, trifluoromethyl, cyano, methoxy, and benzhydryl; and

10 with a proviso that R^3 is not unsubstituted phenyl.

In a further embodiment, the invention provides a compound of formula IB or pharmaceutically acceptable salts thereof:



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IB

wherein

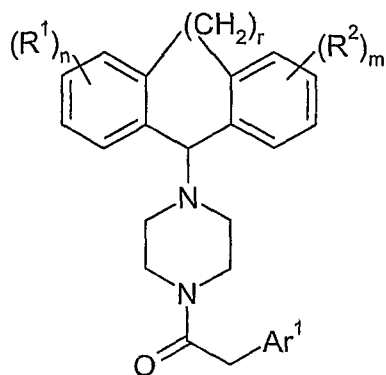
R^1 and R^2 are independently selected from hydrogen, fluoro, chloro, bromo, methyl, trifluoromethyl, and methoxy;

r is selected from 0, 1 and 2;

20 m and n are independently selected from 1 and 2; and

Ar^1 is selected from phenyl, and C_{3-5} heteroaryl, wherein said phenyl, and C_{3-5} heteroaryl are substituted with one or more group selected from fluoro, chloro, bromo, nitro, methyl, trifluoromethyl, cyano, methoxy, and benzhydryl.

In an even further embodiment, the invention provides a compound of formula IC or pharmaceutically acceptable salts thereof:



IC

5 wherein

R^1 and R^2 are independently selected from hydrogen, fluoro, chloro, bromo, methyl, trifluoromethyl, and methoxy;

r is selected from 0, 1 and 2;

m and n are independently selected from 1 and 2; and

10 Ar^1 is selected from phenyl, and C_{3-5} heteroaryl, wherein said phenyl, and C_{3-5} heteroaryl are substituted with one or more group selected from fluoro, chloro, bromo, nitro, methyl, trifluoromethyl, cyano, methoxy, and benzhydryl.

15 “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, IA, IB or IC is, for example, an acid-addition salt of a compound of Formula I, IA, IB or IC 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
20 Formula I, IA, IB or IC 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.

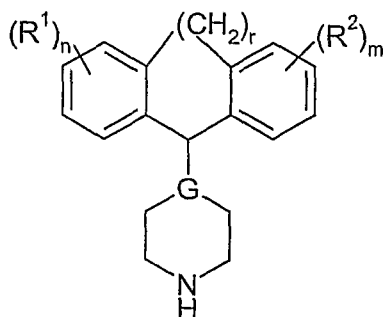
Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable 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, IA, IB or IC that is compounds which are converted into a compound of formula I, IA, IB or IC 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.

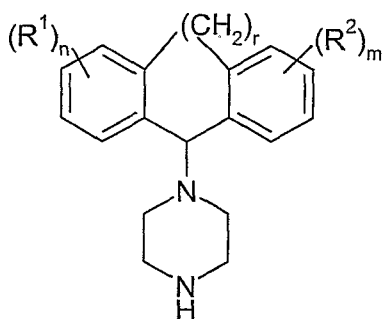
Compounds of formula I, wherein R^1 , R^2 , R^3 , r , n , m , G , X and L are as defined above, may be prepared by reacting a compound of formula IIA



IIA

with Y-X-L-R³, wherein Y represents a leaving group, for example, halo or -OH, at a temperature in the range of -25 to 150⁰C, in the presence of an inert solvent, for example dichloromethane, and optionally in the presence of a base for example triethylamine or pyridine, and optionally in the presence of DMAP.

Compounds of formula IA, wherein R¹, R², R³, r, n, m, X and L are as defined above, may be prepared by reacting a compound of formula II



II

with Y-X-L-R³, wherein Y represents a leaving group, for example, halo or -OH, at a temperature in the range of -25 to 150⁰C, in the presence of an inert solvent, for example dichloromethane, and optionally in the presence of a base for example triethylamine or pyridine, and optionally in the presence of DMAP.

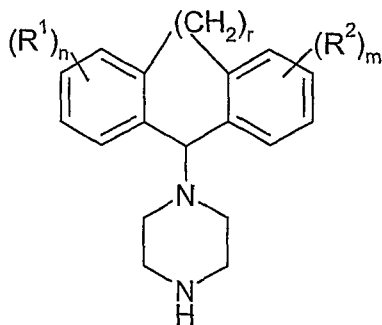
Compounds of formula IB, wherein R¹ and R² are independently selected from hydrogen, fluoro, chloro, bromo, methyl, trifluoromethyl, and methoxy;

r is selected from 0, 1 and 2;

m and n are independently selected from 1 and 2; and

Ar¹ is selected from phenyl, and C₃₋₅-heteroaryl, wherein said phenyl, and C₃₋₅-heteroaryl are substituted with one or more group selected from fluoro, chloro, bromo, nitro, methyl, trifluoromethyl, cyano, methoxy, and benzhydryl,

may be prepared by reacting a compound of formula II



5

II

with Y-C(=O)-Ar¹, wherein Y represents a leaving group, for example, halo or -OH, at a temperature in the range of -25 to 150°C, in the presence of an inert solvent, for example dichloromethane, and optionally in the presence of a base for example triethylamine or pyridine, and optionally in the presence of DMAP.

10

Compounds of formula IC, wherein R¹ and R² are independently selected from hydrogen, fluoro, chloro, bromo, methyl, trifluoromethyl, and methoxy;

r is selected from 0, 1 and 2;

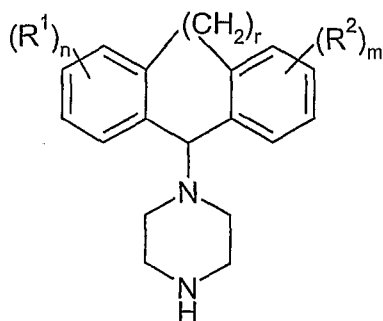
15

m and n are independently selected from 1 and 2; and

Ar¹ is selected from phenyl, and C₃₋₅-heteroaryl, wherein said phenyl, and C₃₋₅-heteroaryl are substituted with one or more group selected from fluoro, chloro, bromo, nitro, methyl, trifluoromethyl, cyano, methoxy, and benzhydryl,

may be prepared by reacting a compound of formula II

20



II

with $Y-C(=O)-Ar^1$, wherein Y represents a leaving group, for example, halo or $-OH$, at a temperature in the range of -25 to $150^\circ C$, in the presence of an inert solvent, for example dichloromethane, and optionally in the presence of a base for example triethylamine or pyridine, and optionally in the presence of DMAP.

Compounds of formula II or IIA may be prepared by the general synthetic route shown at the end of the examples 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.

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, IA, IB or IC 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), demyelination-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
5 potentially useful as agents in treatment of (esophageal) achalasia.

In another aspect the present invention provides a compound of formula I, IA, IB or IC as previously defined for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I, IA, IB or IC in the preparation of a medicament for the treatment or prophylaxis of
10 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
15 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
20 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), demyelination-related disorders, neuroinflammatory
25 disorders (e.g., Guillain-Barré syndrome).

In a further aspect the present invention provides the use of a compound of formula I, IA, IB or IC 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
30 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.

5 In a further aspect the present invention provides the use of a compound of formula I, IA, IB or IC 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
10 syndrome), pain disorders, cranial trauma.

In a further aspect the present invention provides the use of a compound of formula I, IA, IB or IC 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,
15 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
20 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
25 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
30 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, IA, IB or IC 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, IA, IB or IC 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), demyelination-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, IA, IB or IC 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, IA, IB or IC 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, IA, IB or IC 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, IA, IB or IC 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, IA, IB or IC 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
5 cessation of smoking.

In another aspect the present invention provides a compound of formula I, IA, IB or IC as previously defined for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I, IA, IB or IC in the preparation of a medicament for the treatment or prophylaxis of
10 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
15 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,
20 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
25 amount of a compound of formula I, IA, IB or IC 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.

10 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, IA, IB or IC, 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, IA, IB or IC, 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;
- 5 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
- 10 (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;
- 15 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, ERR α , β , PPAR α , β , γ and ROR α ;
- 20 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 antidepressant agent (TCA), a noradrenergic and specific serotonergic antidepressant (NaSSA);
- 25 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
5 a combination treatment comprising the administration of an effective amount of a compound of the formula I, IA, IB or IC, 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).

10 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, IA, IB or IC, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an
15 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
20 treatment which comprises administering to said animal an effective amount of a compound of formula I, IA, IB or IC, 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
25 thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, IA, IB or IC, 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,
30 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, IA, IB or IC, 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, IA, IB or IC, 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, IA, IB or IC, 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, IA, IB or IC, 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 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, IA, IB or IC, 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, IA, IB or IC, 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 MgCl₂, 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 [³⁵S]-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 MgCl₂, 50mM NaCl). Filters were then covered with scintillant and counted for the amount of [³⁵S]-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 $y=A+((B-A)/(1+((C/x)^D)))$ 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.

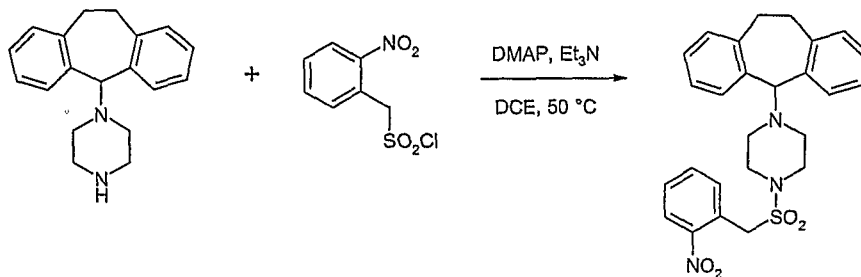
Examples

5 Abbreviations

	DMF	dimethylformamide
	DMSO	Dimethyl Sulfoxide
	DEA	Diethylamine
	EtOAc	ethyl acetate
10	THF	tetrahydrofuran
	DMAP	4-Dimethylaminopyridine
	TLC	thin layer chromatography
	t	triplet
	s	singlet
15	d	doublet
	q	quartet
	qvint	quintet
	m	multiplet
	br	broad
20	bs	broad singlet
	dm	doublet of multiplet
	bt	broad triplet
	dd	doublet of doublet

25 Example 1: 1-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-4-(2-nitro-phenylmethanesulfonyl)-piperazine.

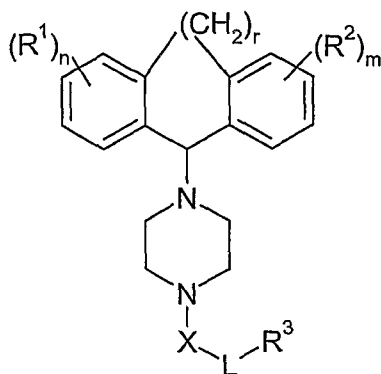
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To a solution of 1-(dibenzosuberonyl)-piperazine (0.118 g, 0.42 mmol) in 1,2-dichloroethane (10 mL) was added a solution of 2-nitro- α -toluenesulfonyl chloride (2.8 mL of a 0.15 M
5 1,2-dichloroethane solution, 0.42 mmol), triethylamine (69 μL , 0.50 mmol) and DMAP (5 mg, 0.042 mmol). The mixture was stirred at 50 °C overnight, then evaporated to dryness (100 mg). The crude compound was redissolved in DMF (2 mL) and purified by prep LC/MS to yield 67 mg (33%) of the title compound as the TFA salt. +ES MS ($M + 1$) 478.2.

We Claim:

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



IA

5

wherein

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

10

r is selected from 0, 1 and 2;

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

X is selected from a bond, $-C(=O)-$, $-S(=O)_2-$, $-C(=O)-N-$, and $-C(=S)-N-$;

L is selected from a bond, $-(CH_2)_p-$, $-(CH_2)_p-O-$, $-C(=O)-O-$, $-(CH_2)_pS-$,

15

$-CH_2NHC(=O)-CH_2-$,

p is selected from 0, 1 and 2;

R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and C_{3-9} heterocyclyl,

wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and C_{3-9} heterocyclyl are optionally substituted with one or more group selected from C_{1-6} alkoxy, halogen, C_{1-6} alkyl,

20

halogenated C_{1-6} alkyl, aryl, halogenated aryl, nitro, cyano, $-C(=O)-R^5$, $-CO_2R^5$, $-NHC(=O)-R^5$, wherein R^5 is selected from hydrogen, C_{1-6} alkyl, halogenated C_{1-6} alkyl, C_{3-6} cycloalkyl, halogenated C_{3-6} cycloalkyl, heterocyclyl, benzhydryl and aryl, wherein said heterocyclyl, benzhydryl and aryl are optionally substituted by one or more group selected from halogen, C_{1-3} alkyl, phenyl, and methoxy;

with a proviso that at least one of X and L is not a bond.

2. A compound as claimed in claim 1, wherein

R¹ and R² are independently selected from hydrogen, -OH, halogen, C₁₋₃alkyl, halogenated C₁₋₃alkyl, C₁₋₃alkoxy, halogenated C₁₋₃alkoxy, -NR⁴C(=O)-O-R⁴, -S(=O)₂-NR⁴R⁴ and -O-S(=O)₂-R⁴; wherein each R⁴ is independently selected from hydrogen and C₁₋₃alkyl;

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

X is selected from a bond, -C(=O)-, -S(=O)₂-, -C(=O)-N-, and -C(=S)-N-;

L is selected from a bond, -(CH₂)_p-, -C(=O)-O-, -(CH₂)_p-O-, -(CH₂)_pS-, -CH₂NHC(=O)-CH₂-,

p is selected from 1 and 2;

R³ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl, wherein said C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl are optionally substituted with one or more group selected from C₁₋₃alkoxy, halogen, C₁₋₃alkyl, halogenated C₁₋₃alkyl, C₆₋₁₀aryl, halogenated C₆₋₁₀aryl, nitro, cyano, -C(=O)-R⁵, -CO₂R⁵, -NHC(=O)-R⁵, wherein R⁵ is selected from hydrogen, C₁₋₃alkyl, halogenated C₁₋₃alkyl, C₃₋₆cycloalkyl, halogenated C₃₋₆cycloalkyl, heterocyclyl, benzhydryl and phenyl, wherein said heterocyclyl, benzhydryl and aryl are optionally substituted by one or more group selected from halogen, C₁₋₃alkyl, phenyl, and methoxy;

with a further proviso that R³ is not unsubstituted phenyl.

3. A compound as claimed in claim 1, wherein

R¹ and R² are independently selected from hydrogen, -OH, halogen, C₁₋₃alkyl, halogenated C₁₋₃alkyl, C₁₋₃alkoxy, and halogenated C₁₋₃alkoxy;

m and n are independently selected from 1 and 2;

X is selected from a bond, -C(=O)-, and -S(=O)₂-;

L is selected from a bond and -(CH₂)_p-;

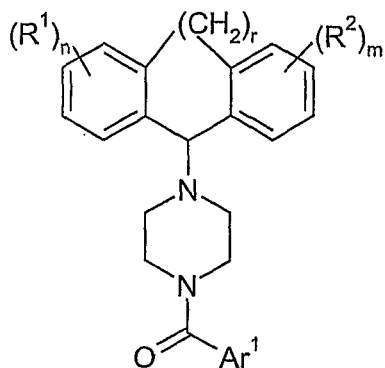
p is selected from 1 and 2;

R³ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl, wherein said C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl are optionally substituted with

one or more group selected from C₁₋₃alkoxy, halogen, nitro, cyano, C₁₋₃alkyl, halogenated C₁₋₃alkyl, and benzhydryl;

with a proviso that R³ is not unsubstituted phenyl.

- 5 4. A compound as claimed in any one of claims 1-3, wherein
R¹ and R² are independently selected from hydrogen, fluoro, chloro, bromo,
methyl, trifluoromethyl, and methoxy.
5. A compound as claimed in any one of claims 1-3, wherein X is -C(=O)-.
- 10 6. A compound as claimed in any one of claims 1-3, wherein L is selected from a
bond and -CH₂-.
7. A compound as claimed in any one of claims 1-3, wherein R³ is selected from C₁₋₆
15 alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl, wherein said C₁₋₆alkyl, C₃₋₆cycloalkyl,
phenyl, and C₃₋₅heteroaryl are optionally substituted with one or more group selected from
fluoro, chloro, bromo, nitro, methyl, trifluoromethyl, cyano, methoxy, and benzhydryl.
8. A compound as claimed in claim 1, wherein
20 R¹ and R² are independently selected from hydrogen, fluoro, chloro, bromo,
methyl, trifluoromethyl, and methoxy;
m and n are independently selected from 1 and 2;
X is -C(=O)-;
L is selected from a bond and -CH₂-,
25 R³ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl, wherein
said C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl are optionally substituted with
one or more group selected from fluoro, chloro, bromo, nitro, methyl, trifluoromethyl,
cyano, methoxy, and benzhydryl.
- 30 9. A compound of formula IB or pharmaceutically acceptable salts thereof:

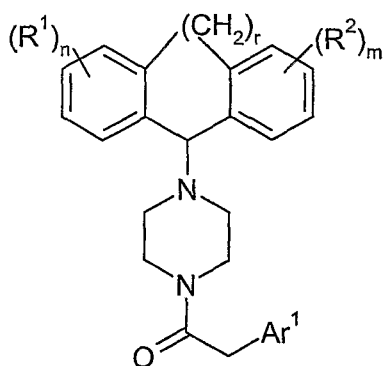


IB

wherein

- R^1 and R^2 are independently selected from hydrogen, fluoro, chloro, bromo,
 5 methyl, trifluoromethyl, and methoxy;
 r is selected from 0, 1 and 2;
 m and n are independently selected from 1 and 2;
 Ar^1 is selected from phenyl, and C_{3-5} heteroaryl, wherein said phenyl, and
 C_{3-5} heteroaryl are substituted with one or more group selected from fluoro, chloro, bromo,
 10 nitro, methyl, trifluoromethyl, cyano, methoxy, and benzhydryl.

10. A compound of formula IC or pharmaceutically acceptable salts thereof:



IC

15

wherein

R^1 and R^2 are independently selected from hydrogen, fluoro, chloro, bromo, methyl, trifluoromethyl, and methoxy;

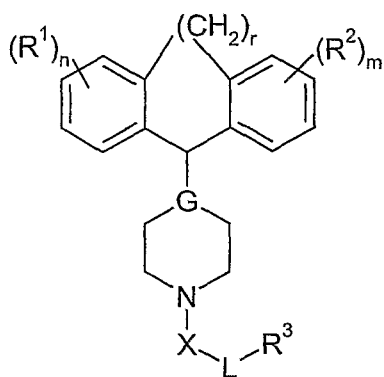
r is selected from 0, 1 and 2;

m and n are independently selected from 1 and 2;

5 Ar^1 is selected from phenyl, and C_{3-5} -heteroaryl, wherein said phenyl, and C_{3-5} -heteroaryl are substituted with one or more group selected from fluoro, chloro, bromo, nitro, methyl, trifluoromethyl, cyano, methoxy, and benzhydryl.

11. A compound selected from 1-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-4-(2-nitro-phenylmethanesulfonyl)-piperazine and pharmaceutically acceptable salts thereof.

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



15

I

wherein

G is selected from CH and N;

R^1 and R^2 are independently selected from hydrogen, -OH, halogen, C_{1-6} alkyl, halogenated C_{1-6} alkyl, C_{1-6} alkoxy, halogenated C_{1-6} alkoxy, $-NR^4C(=O)-O-R^4$, $-S(=O)_2-$
 20 NR^4R^4 and $-O-S(=O)_2-R^4$; wherein each R^4 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 is selected from 0, 1 and 2;

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

X is selected from a bond, $-C(=O)-$, $-S(=O)_2-$, $-C(=O)-N-$, and $-C(=S)-N-$;

L is selected from a bond, $-(\text{CH}_2)_p-$, $-(\text{CH}_2)_p\text{-O-}$, $-\text{C}(=\text{O})\text{-O-}$, $-(\text{CH}_2)_p\text{S-}$,
 $-\text{CH}_2\text{NHC}(=\text{O})\text{-CH}_2-$,

p is selected from 0, 1 and 2;

R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and C_{3-9} heterocyclyl,
 5 wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and C_{3-9} heterocyclyl are optionally
 substituted with one or more group selected from C_{1-6} alkoxy, halogen, C_{1-6} alkyl,
 halogenated C_{1-6} alkyl, aryl, halogenated aryl, nitro, cyano, $-\text{C}(=\text{O})\text{-R}^5$, $-\text{CO}_2\text{R}^5$,
 $-\text{NHC}(=\text{O})\text{-R}^5$, wherein R^5 is selected from hydrogen, C_{1-6} alkyl, halogenated C_{1-6} alkyl, C_3 -
 C_{6-10} cycloalkyl, halogenated C_{3-6} cycloalkyl, heterocyclyl, benzhydryl and aryl, wherein said
 10 heterocyclyl, benzhydryl and aryl are optionally substituted by one or more group selected
 from halogen, C_{1-3} alkyl, phenyl, and methoxy;

with a proviso that at least one of X and L is not a bond.

13. A compound as claimed in claim 12, wherein

15 R^1 and R^2 are independently selected from hydrogen, $-\text{OH}$, halogen, C_{1-3} alkyl,
 halogenated C_{1-3} alkyl, C_{1-3} alkoxy, halogenated C_{1-3} alkoxy, $-\text{NR}^4\text{C}(=\text{O})\text{-O-R}^4$, $-\text{S}(=\text{O})_2\text{-}$
 NR^4R^4 and $-\text{O-S}(=\text{O})_2\text{-R}^4$; wherein each R^4 is independantly selected from hydrogen and
 C_{1-3} alkyl;

m and n are independently selected from 1 and 2;

20 X is selected from a bond, $-\text{C}(=\text{O})-$, $-\text{S}(=\text{O})_2-$, $-\text{C}(=\text{O})\text{-N-}$, and $-\text{C}(=\text{S})\text{-N-}$;

L is selected from a bond, $-(\text{CH}_2)_p-$, $-\text{C}(=\text{O})\text{-O-}$, $-(\text{CH}_2)_p\text{-O-}$, $-(\text{CH}_2)_p\text{S-}$,
 $-\text{CH}_2\text{NHC}(=\text{O})\text{-CH}_2-$,

p is selected from 1 and 2;

R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and C_{3-5} heteroaryl, wherein
 25 said C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and C_{3-5} heteroaryl are optionally substituted with
 one or more group selected from C_{1-3} alkoxy, halogen, C_{1-3} alkyl, halogenated C_{1-3} alkyl, C_6 -
 C_{10} aryl, halogenated $\text{C}_6\text{-C}_{10}$ aryl, nitro, cyano, $-\text{C}(=\text{O})\text{-R}^5$, $-\text{CO}_2\text{R}^5$, $-\text{NHC}(=\text{O})\text{-R}^5$, wherein R^5
 is selected from hydrogen, C_{1-3} alkyl, halogenated C_{1-3} alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, halogenated C_3 -
 C_6 cycloalkyl, heterocyclyl, benzhydryl and phenyl, wherein said heterocyclyl, benzhydryl and
 30 aryl are optionally substituted by one or more group selected from halogen, C_{1-3} alkyl,
 phenyl, and methoxy;

with a further proviso that R³ is not unsubstituted phenyl.

14. A compound as claimed in claim 12, wherein

R¹ and R² are independently selected from hydrogen, -OH, halogen, C₁₋₃alkyl,

5 halogenated C₁₋₃alkyl, C₁₋₃alkoxy, and halogenated C₁₋₃alkoxy;

m and n are independently selected from 1 and 2;

X is selected from a bond, -C(=O)-, and -S(=O)₂-;

L is selected from a bond and -(CH₂)_p-,

p is selected from 1 and 2;

10 R³ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl, wherein said C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and C₃₋₅heteroaryl are optionally substituted with one or more group selected from C₁₋₃alkoxy, halogen, nitro, cyano, C₁₋₃alkyl, halogenated C₁₋₃alkyl, and benzhydryl;

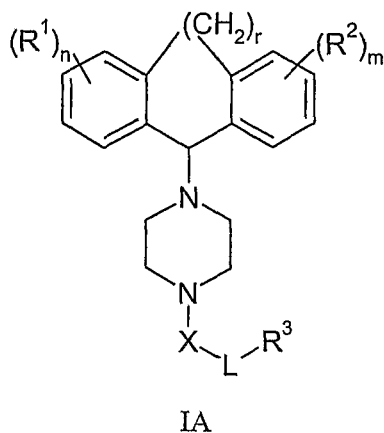
with a further proviso that R³ is not unsubstituted phenyl.

15 15. A compound as claimed in any of claims 1 to 14 for use as a medicament.

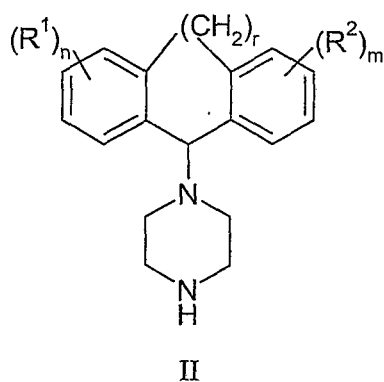
16. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 14 and a pharmaceutically acceptable adjuvant, diluent or carrier.

20 17. Use of a compound according to any one of claims 1 to 14 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
25 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.

18. 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 14 to a patient in need thereof.
19. A method of treating schizophrenia comprising administering a pharmacologically effective amount of a compound as claimed in any one of claims 1-14 to a patient in need thereof.
20. 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 1-14 to a patient in need thereof.
21. A compound as defined in any one of claims 1-14 for use in the treatment of obesity.
22. A compound as claimed in any one of claims 1-14 for use in the treatment of schizophrenia.
23. A compound as claimed in any one of claims 1-14 for use in the treatment of cognitive deficiency associated with schizophrenia.
24. A process for the preparation of a compound of formula IA,



comprising reacting a compound of formula II



with Y-X-L-R³,

wherein

Y represents a leaving group,

R¹ and R² are independently selected from hydrogen, -OH, halogen, C₁₋₆alkyl, halogenated C₁₋₆alkyl, C₁₋₆alkoxy, halogenated C₁₋₆alkoxy, -NR⁴C(=O)-O-R⁴, -S(=O)₂-NR⁴R⁴ and -O-S(=O)₂-R⁴; wherein each R⁴ is independently selected from hydrogen, C₁₋₆alkyl, halogenated C₁₋₆alkyl, C₃₋₆cycloalkyl, and halogenated C₃₋₆cycloalkyl;

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

X is selected from a bond, -C(=O)-, -S(=O)₂-, -C(=O)-N-, and -C(=S)-N-;

L is selected from a bond, -(CH₂)_p-, -(CH₂)_p-O-, -C(=O)-O-, -(CH₂)_pS-, -CH₂NHC(=O)-CH₂-,

p is selected from 0, 1 and 2;

R³ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₆₋₁₀aryl, and C₃₋₉heterocyclyl, wherein said C₁₋₆alkyl, C₃₋₆cycloalkyl, C₆₋₁₀aryl, and C₃₋₉heterocyclyl are optionally substituted with one or more group selected from C₁₋₆alkoxy, halogen, C₁₋₆alkyl, halogenated C₁₋₆alkyl, aryl, halogenated aryl, nitro, cyano, -C(=O)-R⁵, -CO₂R⁵,
5 -NHC(=O)-R⁵, wherein R⁵ is selected from hydrogen, C₁₋₆alkyl, halogenated C₁₋₆alkyl, C₃₋₆cycloalkyl, halogenated C₃₋₆cycloalkyl, heterocyclyl, benzhydryl and aryl, wherein said heterocyclyl, benzhydryl and aryl are optionally substituted by one or more group selected from halogen, C₁₋₃alkyl, phenyl, and methoxy.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000926

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.: 18-20
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 18-20 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods /Rule 39.1(iv). Nevertheless, a search has been for these claims, based on the alleged effects of the compounds.
2. Claims Nos.: 1-10, 12-17, 21-23
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:

See supplemental box

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.2

The initial phase of the search revealed a very large number of compounds relevant to the issue of novelty. So many compounds were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to:

For compounds, which are present in patents or other documents a full search has been done. However, as so many relevant compounds known only from STN file REGISTRY or CHEMCATS were retrieved, only a selection of such compounds has been given. The compound of claim 11 has been fully searched.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2006/000926

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, A61K

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.
X	WO 9900376 A1 (NOVO NORDISK A/S), 7 January 1999 (07.01.1999), abstract, claims, examples	1-2,4,6-7, 12-13,15-18, 21-24
	--	
X	WO 9726252 A1 (FMC CORPORATION), 24 July 1997 (24.07.1997), compounds 68 and 69	1-4,6-7, 12-14
	--	
X	WO 9501350 A1 (SUMITOMO METAL INDUSTRIES, LTD.), 12 January 1995 (12.01.1995), examples 26,27	1-4,6-7, 12-16,21-23
	--	
X	GB 1041536 A (RHONE-POULENC S.A.), 7 Sept 1966 (07.09.1966), example 2, page 3, line 25 - 33; example 8, page 4, line 57 - 63	1-4,6-7, 12-14
	--	

 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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"&" document member of the same patent family

Date of the actual completion of the international search

21 November 2006

Date of mailing of the international search report

23-11-2006

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Authorized officer

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Telephone No. +46 8 782 25 00

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20040034035 A1 (TERRANCE P. SNUTCH ET AL), 19 February 2004 (19.02.2004), compounds P31 and P32 --	1-2,4-6, 12-13,15-16, 21-23
X	WO 0140231 A1 (BRISTOL-MYERS SQUIBB COMPANY), 7 June 2001 (07.06.2001), compound 199, page 87 --	1-2,4-6,12, 15-16,21-23
X	US 2636032 A (ARTHUR W. WESTON ET AL), 21 April 1953 (21.04.1953), example XXI --	1-2,4,7, 12-13
X	US 4626542 A (STELLA W. KING ET AL), 2 December 1986 (02.12.1986), examples IX and XI --	12-16,21-23
X	STN International, File CAPLUS, accession number 1978:23339, document number DN 88:23339, Suehiro, Hideo et al: "2-Piperazinoethylthioadenosines" & Jpn. Kokai Tokkyo Koho, 5 pp. RN: 64966-89-8 --	1-4,6-7, 12-14
X	STN International, File CAPLUS, accession number 2004-753392, document number 141:260408, Amanomiya, Yoshiya et al: "Preparation of 3-amino- 2-hydroxy-4-phenylbutyric acid as protein tyrosin phosphatase inhibitors" & Jpn. Kokai Tokkyo Koho, 69 pp. RN: 756484-48-7, 756823-52-6, 756823-53-7, 756823-55-9, 756823-56-0, 756823-58-2, 756823-59-3, 756823-61-7 and 756823-62-8 --	1-2,4-6, 12-13
X	MASATOSHI YAMATO et al: "Synthesis and Structure-Activity Relationship of Spiro(isochroman-piperidine) Analogs for Inhibition of Histamine Release. III 1" Chem. Pharm. Bull. vol 31, no 2, 1983, page 521-526; compound (17) page 525 --	12-13,15-16

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MACK R. KUO et al: "Targeting Tuberculosis and Malaria through Inhibition of Enoyl Reductase" The Journal of Biological Chemistry, vol. 278, no 23,2003, page 20851-20859; see table II, compounds 10850, 12638, 12640, 12643, 12646, 13347, 13348, 13349 --	1,4-6,12, 15-16
X	JOHN J. PIWINSKI et al: "Dual antagonists of platelet activating factor and histamine 3. synthesis, biological activity and conformational implications of substituted N-Acyl-Bis-Arylcycloheptapiperazines 1" Bioorganic & Medicinal Chemistry Letters 8, 1998, page 3469-3474; compound 4, page 3470 --	1-8,12-14
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PX	JP 2005272354 A (POLA CHEM IND INC.), 6 October 2005 (06.10.2005), page 12, compound 16 ----- --	1-2,4,7, 12-13,15-16, 21-23

International patent classification (IPC)

C07D 295/26 (2006.01)
A61K 31/495 (2006.01)
A61P 25/00 (2006.01)
A61P 25/18 (2006.01)
A61P 3/04 (2006.01)
C07D 295/182 (2006.01)

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE2006/000926

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