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(21) International Application Number: PCT/EP92/00492 (22) International Filing Date: 4 March 1992 (04.03.92) (30) Priority data: 9104656.5 5 March 1991 (05.03.91) GB (71) Applicant (for all designated States except US): DR LO ZAMBELETTI S.P.A. [IT/IT]; Via Zambelletti, I-22021 Baranzate (IT). (72) Inventors; and (75) Inventors/Applicants (for US only) : GIARDINA, Giuseppe [IT/IT]; CLARKE, Geoffrey, Douglas [GB/IT]; Dr Lo Zambelletti S.p.A., Via Zambelletti, I-20021 Baranzate (IT). (74) Agent: RUSSELL, Brian, John; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).		(81) Designated States: AT, AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US. Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: PHARMACEUTICALS (57) Abstract Azacyclic and heterocyclic derivatives having kappa agonist activity are useful in the treatment of cerebral ischaemia.		

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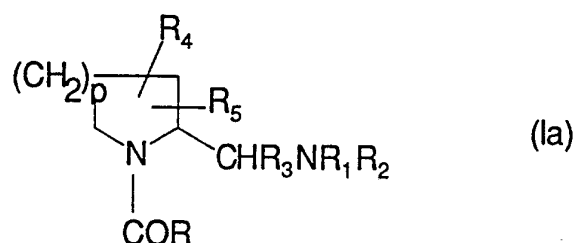
PHARMACEUTICALS

The present invention relates to the use of certain compounds for the manufacture of medicaments for the treatment of cerebral ischaemia; to a method of treatment of cerebral ischaemia; and to pharmaceutical compositions for the treatment of cerebral ischaemia.

EP-A-370732 and EP-A-361791 (both Dr. Lo. Zambelletti S.p.a.) describe classes of azacyclic and heterocyclic derivatives which exhibit kappa receptor agonism and are of potential therapeutic utility as analgesics.

It has now been found that compounds of these classes have pharmacological properties which indicate that they are effective neuroprotective agents and are therefore of potential use in the treatment of cerebral ischaemia.

According to the present invention there is provided the use of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of cerebral ischaemia, formula (Ia) being:



in which:

25

RCO is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring;

30 R_1 and R_2 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkylalkyl groups, or together form a C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group, optionally substituted with a hetero-atom,

R_3 is hydrogen, C_{1-6} alkyl, preferably methyl or ethyl, or phenyl, or R_3

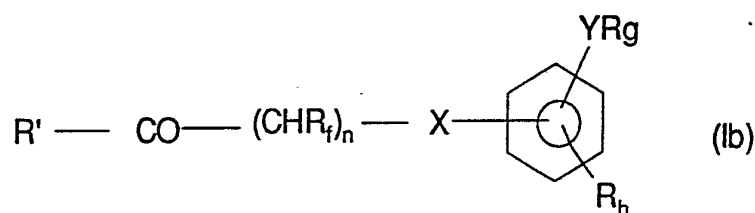
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together with R_1 form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

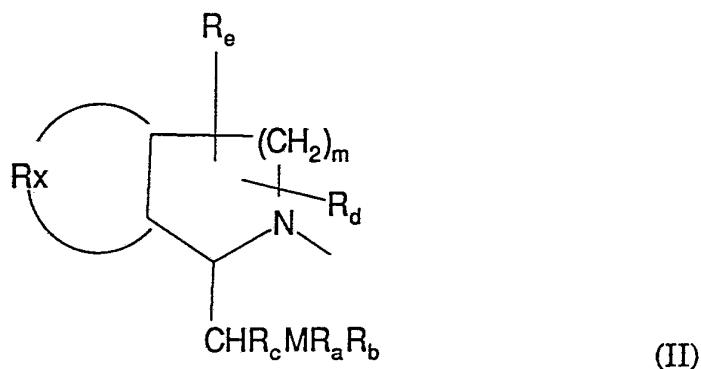
- R_4 and R_5 are independently hydrogen, hydroxyl, halogen, preferably fluorine, C_{1-6} alkyl, preferably methyl or ethyl, or aryl, preferably phenyl, provided both R_4 and R_5 are not simultaneously hydrogen; and p is an integer from 1 to 4, preferably 2;

and formula (Ib) being:

10



in which R' represents a group of formula (II)



15

in which R_x is the remainder of a heterocyclic group, or an optionally substituted phenyl group;

- R_a and R_b are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkylalkyl groups, or together form a C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group, optionally substituted with a hetero-atom;

- R_c is hydrogen, C_{1-6} alkyl, preferably methyl or ethyl, or phenyl, or R_c together with R_a form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

25

R_d and R_e , which may be located on the same or different carbon atoms, are independently hydrogen, C_{1-6} alkyl, preferably methyl or ethyl, or

phenyl; m is 1, 2 or 3, preferably 2;

R_f is hydrogen or C_{1-6} alkyl, such as methyl or ethyl; n is 0, 1 or 2 preferably 1;

5

X is a direct bond, or O, S or NR_k in which R_k is hydrogen or C_{1-6} alkyl, preferably a direct bond and preferably linked in the meta- or para-position with respect to YR_g or R_h ;

- 10 Y is $>C=O$, $>CHOH$, $-S=O$ or $-SO_2$;
each of R_g and R_h is C_{1-6} alkyl, or
 R_g and R_h are linked together and R_g represents $-(Z)_p-$ where p is 0 or 1
and Z is O, S or NR_z where R_z is hydrogen or C_{1-6} alkyl,
and R_h represents $-(CH_2)_q-$ where q is an integer of from 1 to 4,
15 preferably 2 or 3.

In the compounds of formula (Ia), R_4 and R_5 may be located on the same or different carbon atoms of the azacyclic nucleus.

- 20 When used herein, the term 'carbocyclic aromatic group' includes single or fused rings, having 6 to 12 ring carbon atoms, and the term 'heterocyclic aromatic group' includes single or fused rings having 5 to 12 ring atoms, comprising up to four hetero-atoms in the or each ring, selected from oxygen, nitrogen and sulphur.

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When the carbocyclic or heterocyclic group is a fused two ring system, one or both rings may be aromatic in character.

Suitably, one of the rings is aromatic and the other is non-aromatic.

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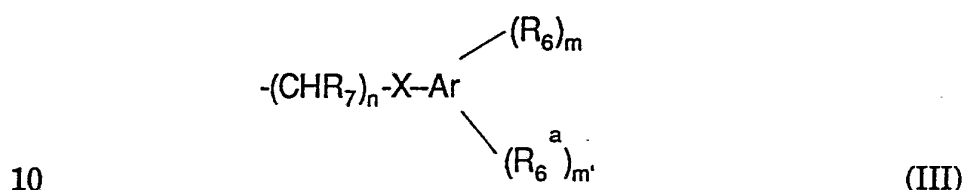
The C_{1-6} alkyl groups may be either straight or branched chain and examples are methyl, ethyl, propyl, n-butyl, n-pentyl or n-hexyl, preferably methyl.

- 35 Examples of C_{2-6} alkenyl groups are 1- and 2-propenyl; an example of a C_{3-6} cycloalkyl group is cyclopropyl, and an example of a C_{4-12} cycloalkylalkyl group is cyclopropyl methyl.

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- When R_1 and R_2 together form a linear or branched polymethylene group, examples are propylene, butylene, pentylene or hexylene, preferably butylene or 1-methyl-butylene. As an alkylene group, R_1 - R_2 may be typically $-\text{CH}_2\text{-CH=CH-CH}_2-$. Examples of hetero-atoms are oxygen and sulphur, particularly oxygen, and a suitable hetero-atom substituted polymethylene group is $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$.

The group R in formula (Ia) preferably has the formula (III):



in which n is 0, 1 or 2;

m is 0, 1 or 2;

m' is 0, 1 or 2, provided $m + m' \leq 2$

- X is a direct bond, or O, S or NR_8 in which R_8 is hydrogen or C_{1-6} alkyl,

Ar is a substituted or unsubstituted carbocyclic or heterocyclic group,

- each of R_6 and R_6^a is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, optionally substituted phenyl, optionally substituted phenyl C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, thiol, C_{1-6} alkylthio, C_{1-6} haloalkoxy, C_{1-6} haloalkylthio, halogen, NO_2 , CN, CF_3 , $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCF}_2\text{CF}_2\text{H}$, $-\text{OCCl}_2\text{CF}_3$, $-\text{COOR}_9$, $-\text{CONR}_{10}\text{R}_{11}$, $-\text{SO}_3\text{R}_{12}$, $-\text{SO}_2\text{NR}_{13}\text{R}_{14}$ and $-\text{COR}_{15}$ in which each of R_9 to R_{15} is independently hydrogen, C_{1-6} alkyl, optionally substituted phenyl or optionally substituted phenyl C_{1-6} alkyl;
- or, when m is 2 and m' is 0, two R_6 's form a C_{3-6} polymethylene group, and R_7 is hydrogen or C_{1-6} alkyl, such as methyl or ethyl.

- Preferred halogens are F, Cl and Br.

When two R_6 's are linked they preferably form a fused cyclopentyl or cyclohexyl ring.

- Preferably Ar is phenyl and R_6 or R_6^a is preferably in the meta and/or

para position.

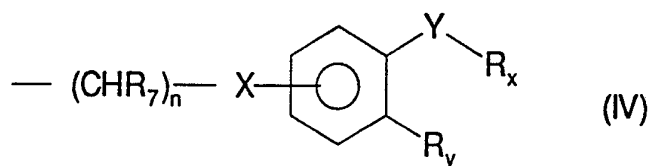
Preferably R_6 or R_6^a is bromine, chlorine, or CF_3 , particularly in the meta- or para- position.

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X is typically oxygen or a direct bond, and n is typically 0 or 1.

A further preferred group R has the formula (IV)

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15 in which the group $-(\text{CHR}_7)_n\text{---X}$, which is as defined in formula III, is in the meta- or para- position with respect to YR_x or R_y ,

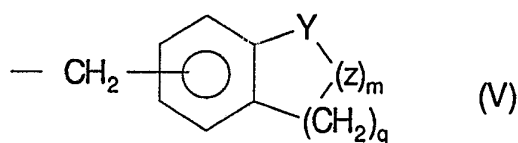
Y is $>\text{C}=\text{O}$, $>\text{CHOH}$, $-\text{S}=\text{O}$ or $-\text{SO}_2$;

each of R_x and R_y is C_{1-6} alkyl, or

20 R_x and R_y are linked together and R_x represents $-(\text{Z})_m\text{---}$ where m is 0 or 1 and Z is O, S or NR_z where R_z is hydrogen or C_{1-6} alkyl, and R_y represents $-(\text{CH}_2)_q\text{---}$ where q is an integer of from 1 to 4, preferably 2 or 3.

A preferred sub-group of formula (IV) is a group of formula (V)

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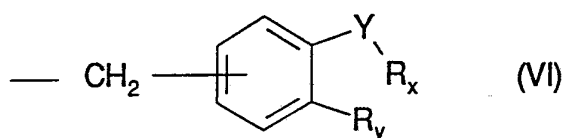
in which Y, Z, m, q and the position of $-\text{CH}_2\text{---}$ are as defined in formula (IV).

30

Preferably, q is 2 when Z is oxygen and m is 1, and q is 3 when m is 0.

A further preferred sub-group of formula (IV) is the group of formula (VI)

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in which Y is C=O or CHOH, each of R_x and R_y is C₁₋₆ alkyl, preferably methyl, and the position of -CH₂- is as defined in formula (IV)

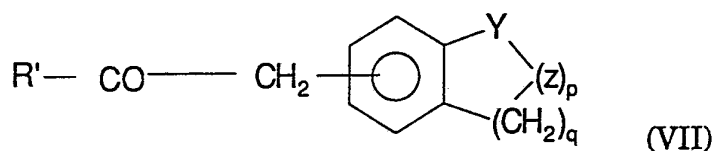
In the compounds of formula (Ib), when R_x forms an optionally substituted phenyl ring, examples of substituents are one or more of C₁₋₆ alkyl, preferably methyl, halogen, hydroxy, C₁₋₆ alkoxy, thiol or C₁₋₆ alkyl thio. Suitably R_x represents unsubstituted phenyl.

When R_x forms a heterocyclic group, it may be a single or fused ring group, preferably having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur.

When R_x forms a fused two ring system, one or both rings may be aromatic in character. Suitably one of the rings is aromatic and the other is non-aromatic.

When R_x is a single ring heterocyclic group, examples are thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl and pyridyl; and when R_x is a fused ring heterocyclic group, examples are benzofuranyl, benzo thienyl, indolyl and quinolyl.

A preferred sub-group of compounds of formula (Ib) is a group of compounds of formula (VII)



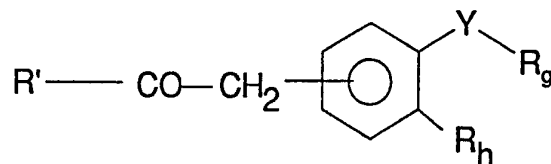
in which Y, Z, R', p, q and the position of -CH₂- are as defined in formula (Ib).

Preferably, q is 2 when Z is oxygen and p is 1, and q is 3 when p is 0.

Preferably, q is 2 when Z is oxygen and p is 1, and q is 3 when p is 0.

A further preferred sub-group of compounds of formula (Ib) is the group of compounds of formula (VIII)

5



(VIII)

- 10 in which R' is as defined in formula (Ib) and Y is $C=O$ or $CHOH$, each of R_g and R_h is C_{1-6} alkyl, preferably methyl, and the position of $-CH_2-$ is as defined in formula (Ib)

- The C_{1-6} alkyl groups mentioned above may be either straight or
 15 branched chain and examples are methyl, ethyl, propyl, n-butyl, n-pentyl or n-hexyl, preferably methyl.

- Examples of C_{2-6} alkenyl groups are 1- and 2-propenyl; an example of a
 20 C_{3-6} cycloalkyl group is cyclopropyl, and an example of a C_{4-12} cycloalkylalkyl group is cyclopropyl methyl.

- When R_a and R_b together form a linear or branched polymethylene group,
 examples are propylene, butylene, pentylene or hexylene, preferably
 butylene or 1-methyl-butylene. As an alkenylene group, $R_a - R_b$ may be
 25 typically $-CH_2-CH=CH-CH_2-$. Examples of hetero-atoms are oxygen and sulphur, particularly oxygen, and a suitable hetero-atom substituted polymethylene group is $-CH_2CH_2OCH_2CH_2-$.

- A particularly preferred group of compounds of formula (Ib) are those in
 30 which R_x represents phenyl or mono- or di- hydroxy substituted phenyl, or represents thieno.

- In a further aspect of the invention there is provided a pharmaceutical
 composition for use in the treatment of cerebral ischaemia in mammals
 35 which comprises a compound of formula (Ia) or (Ib) (as hereinbefore

defined) or a pharmaceutically acceptable salt or solvate thereof, (hereinafter referred to as the Compound) and a pharmaceutically acceptable carrier.

- 5 The invention further provides a method for the treatment and/or prophylaxis of cerebral ischaemia in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of the Compound.
- 10 The Compound is in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.
- 15 A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the Compound.
- 20 One preferred pharmaceutically acceptable form is the crystalline form, including such form in a pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.
- 25 Examples of the Compound in the form of a pharmaceutically acceptable salt include the acid addition salts with the conventional pharmaceutical acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.
- 30 An example of the Compound in the form of a pharmaceutically acceptable solvate includes the hydrate.
- The Compounds have at least two asymmetric centres and therefore exist in more than one stereoisomeric form. The invention extends to the use of all such forms and to mixtures thereof, including racemates.
- 35

The Compounds may be prepared as described in the aforementioned

EP-A-370732 and 361791 (the subject matter of which are incorporated herein by reference) or by analogous methods thereto.

Medicaments and compositions containing the Compounds may be
5 prepared by admixture of a Compound with an appropriate carrier, which may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the
10 preparation of compositions of known agents for treating cerebral ischaemia.

Preferably, a medicament or pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or
15 veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent for treating cerebral ischaemia.

The suitable dosage range for a Compound depends on the Compound to
20 be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The Compound may be formulated for administration by any route, and is
25 preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

30

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

35

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers,

for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable
5 setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large
10 quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical
15 practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for
20 example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel,
25 hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example
30 methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The Compounds may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may
35 be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a

- parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such
- 5 forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.
- 10 The effective dose of Compound depends on the particular Compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be
- 15 administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.
- 20 Specific examples of the compounds of formulae (Ia) and (Ib) are as follows:
- 1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 3-methyl
25 piperidine;
- 1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 4-methyl
piperidine;
- 30 1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 5-methyl
piperidine;
- 1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 6-methyl
piperidine;
- 35 1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 3-hydroxy
piperidine;

- 1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 3,3-dimethyl
piperidine;
- 5 1-(4-trifluoromethylphenyl)acetyl-2-(pyrrolidin-1-yl)methyl-3,3-dimethyl
piperidine;
- 1-(3,4-dichloromethylphenyl)acetyl-2-(pyrrolidin-1-yl)methyl-5,5-dimethyl
piperidine;
- 10 1-(5,6,7,8-tetrahydronaphth-2-yl)acetyl-2-(pyrrolidin-
1-yl)methyl-3,3-dimethyl piperidine;
- 1-[1-oxo-3,4-dihydro-(2H)-naphth-6-yl]acetyl-2-
(pyrrolidin-1-yl)methyl-3,3-dimethyl piperidine;
- 15 1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 4,4-dimethyl
piperidine;
- 1-(4-trifluoromethylphenyl)acetyl-2-(pyrrolidin-1-yl)methyl-4,4-dimethyl
20 piperidine;
- (-)-1-(4-trifluoromethylphenyl)acetyl-2-(pyrrolidin-1-
yl)methyl-3,3-dimethyl piperidine;
- 25 (+)-1-(4-trifluoromethylphenyl)acetyl-2-(pyrrolidin-1-
yl)methyl-3,3-dimethyl piperidine;
- 1-(pyrrolidin-1-yl)methyl-2-(1-oxo-3,4-dihydro-(2H)-
naphth-6-yl)acetyl-1,2,3,4-tetrahydroisoquinoline;
- 30 1-(piperidin-1-yl)methyl-2-(1-oxo-3,4-dihydro-(2H)-
naphth-6-yl)acetyl-1,2,3,4-tetrahydroisoquinoline;
- 4-(pyrrolidin-1-yl)methyl-5-(1-oxo-3,4-dihydro-(2H)-
35 naphth-6-yl)acetyl-4,5,6,7-tetrahydrothieno [3,2-c]pyridine;
- 4-(piperidin-1-yl)methyl-5-(1-oxo-3,4-dihydro-(2H)-
naphth-6-yl)acetyl-4,5,6,7-tetrahydrothieno [3,2-c]pyridine;

(-)-4-(piperidin-1-yl)methyl-5-(1-oxo-3,4-dihydro-(2H)-naphth-6-yl)acetyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

- 5 (+)-4-(piperidin-1-yl)methyl-5-(1-oxo-3,4-dihydro-(2H)-naphth-6-yl)acetyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

These compounds may all be prepared according to the methods described in the aforementioned EP-A-370732 and 361791.

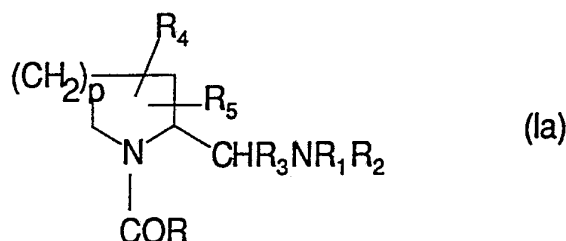
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The activity of the Compounds in treating cerebral ischaemia may be determined using the gerbil model of ischaemic stroke, as described in P. Lysko *et al* Stroke, 23(3), 1992.

- 14 -

Claims

1. Use of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of cerebral ischaemia, formula (Ia) being:



in which:

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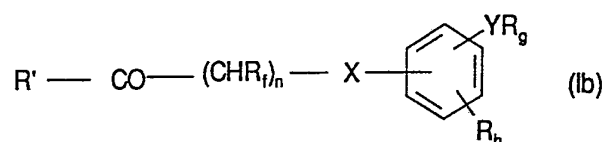
RCO is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring;

- 15 R_1 and R_2 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkylalkyl groups, or together form a C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group, optionally substituted with a hetero-atom,

- 20 R_3 is hydrogen, C_{1-6} alkyl, or phenyl, or R_3 together with R_1 form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

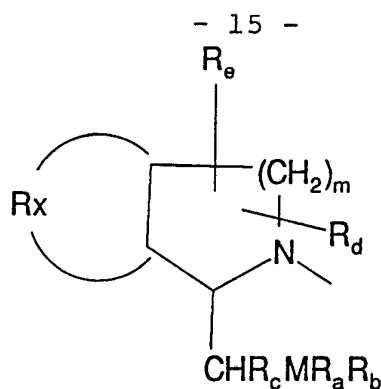
- 25 R_4 and R_5 are independently hydrogen, hydroxyl, halogen, C_{1-6} alkyl, or aryl, provided both R_4 and R_5 are not simultaneously hydrogen; and p is an integer from 1 to 4;

and formula (Ib) being:



30

in which R' represents a group of formula (II)



in which R_x is the remainder of a heterocyclic group, or an optionally substituted phenyl group;

5

R_a and R_b are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkylalkyl groups, or together form a C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group, optionally substituted with a hetero-atom;

10

R_c is hydrogen, C_{1-6} alkyl, or phenyl, or R_c together with R_a form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

15 R_d and R_e , which may be located on the same or different carbon atoms, are independently hydrogen, C_{1-6} alkyl, or phenyl; m is 1, 2 or 3;

R_f is hydrogen or C_{1-6} alkyl; n is 0, 1 or 2;

X is a direct bond, or O, S or NR_k in which R_k is hydrogen or C_{1-6} alkyl;

20

Y is $>C=O$, $>CHOH$, $-S=O$ or $-SO_2$;

each of R_g and R_h is C_{1-6} alkyl, or

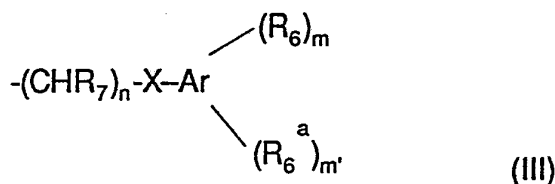
R_g and R_h are linked together and R_g represents $-(Z)_p-$ where p is 0 or 1 and Z is O, S or NR_z where R_z is hydrogen or C_{1-6} alkyl,

25

and R_h represents $-(CH_2)_q-$ where q is an integer of from 1 to 4;

2. A use according to Claim 1 in which the group R in formula (Ia) has the formula (III):

- 16 -



in which n is 0, 1 or 2;

m is 0, 1 or 2;

5 m' is 0, 1 or 2, provided $m + m' \leq 2$

X is a direct bond, or O, S or NR_8 in which R_8 is hydrogen or C_{1-6} alkyl,

Ar is a substituted or unsubstituted carbocyclic or heterocyclic group,

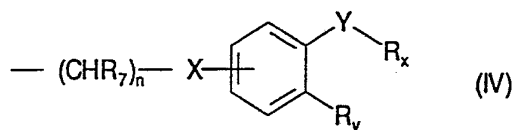
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each of R_6 and R_6^a is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, optionally substituted phenyl, optionally substituted phenyl C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, thiol, C_{1-6} alkylthio, C_{1-6} haloalkoxy, C_{1-6} haloalkylthio, halogen, NO_2 , CN , CF_3 , $-\text{OCF}_3$, $-\text{OCHF}_2$,
 15 $-\text{OCF}_2\text{CF}_2\text{H}$, $-\text{OCCl}_2\text{CF}_3$, $-\text{COOR}_9$, $-\text{CONR}_{10}\text{R}_{11}$, $-\text{SO}_3\text{R}_{12}$, $-\text{SO}_2\text{NR}_{13}\text{R}_{14}$ and $-\text{COR}_{15}$ in which each of R_9 to R_{15} is independently hydrogen, C_{1-6} alkyl, optionally substituted phenyl or optionally substituted phenyl C_{1-6} alkyl;

20 or, when m is 2 and m' is 0, two R_6 's form a C_{3-6} polymethylene group, and R_7 is hydrogen or C_{1-6} alkyl.

3. A use according to Claim 1 in which R in formula (Ia) has the formula (IV)

25



30 in which the group $-(\text{CHR}_7)_n\text{---X---}$, which is as defined in formula (III) in claim 2, is in the meta- or para- position with respect to YR_x or R_y ,

Y is $>\text{C}=\text{O}$, $>\text{CHOH}$, $-\text{S}=\text{O}$ or $-\text{SO}_2$;

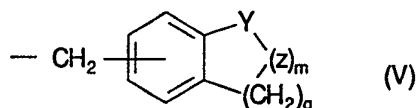
- 17 -

each of R_x and R_y is C_{1-6} alkyl, or

R_x and R_y are linked together and R_x represents $-(Z)_m-$ where m is 0 or 1 and Z is O, S or NR_z where R_z is hydrogen or C_{1-6} alkyl, and R_y represents $-(CH_2)_q-$ where q is an integer of from 1 to 4.

5

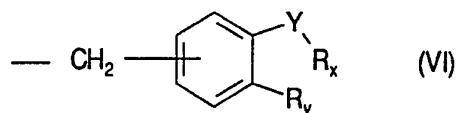
4. A use according to claim 3 in which R has the formula (V)



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in which Y, Z, m, q and the position of $-CH_2-$ are as defined in formula (IV) in claim 3.

15 5. A use according to claim 3 in which R has the formula (VI)



20 in which Y is $C=O$ or $CHOH$, each of R_x and R_y is C_{1-6} alkyl, and the position of $-CH_2-$ is as defined in formula (IV) in claim 3.

6. A use according to claim 1 in which the compound of formula (Ia) or (Ib) is selected from:

25 1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 3-methyl piperidine;

1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 4-methyl piperidine;

30

1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 5-methyl piperidine;

35 1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 6-methyl piperidine;

1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 3-hydroxy
piperidine;

- 5 1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 3,3-dimethyl
piperidine;

1-(4-trifluoromethylphenyl)acetyl-2-(pyrrolidin-1-yl)methyl-3,3-dimethyl
piperidine;

10

1-(3,4-dichloromethylphenyl)acetyl-2-(pyrrolidin-1-yl)methyl-5,5-dimethyl
piperidine;

- 15 1-(5,6,7,8-tetrahydronaphth-2-yl)acetyl-2-(pyrrolidin-
1-yl)methyl-3,3-dimethyl piperidine;

1-[1-oxo-3,4-dihydro-(2H)-naphth-6-yl]acetyl-2-
(pyrrolidin-1-yl)methyl-3,3-dimethyl piperidine;

- 20 1-(3,4-dichlorophenyl)acetyl-2-(pyrrolidin-1-yl)methyl- 4,4-dimethyl
piperidine;

1-(4-trifluoromethylphenyl)acetyl-2-(pyrrolidin-1-yl)methyl-4,4-dimethyl
piperidine;

25

(-)-1-(4-trifluoromethylphenyl)acetyl-2-(pyrrolidin-1-
yl)methyl-3,3-dimethyl piperidine;

- 30 (+)-1-(4-trifluoromethylphenyl)acetyl-2-(pyrrolidin-1-
yl)methyl-3,3-dimethyl piperidine;

1-(pyrrolidin-1-yl)methyl-2-(1-oxo-3,4-dihydro-(2H)-
naphth-6-yl)acetyl-1,2,3,4-tetrahydroisoquinoline;

- 35 1-(piperidin-1-yl)methyl-2-(1-oxo-3,4-dihydro-(2H)-
naphth-6-yl)acetyl-1,2,3,4-tetrahydroisoquinoline;

4-(pyrrolidin-1-yl)methyl-5-(1-oxo-3,4-dihydro-(2H)-

naphth-6-yl)acetyl-4,5,6,7-tetrahydrothieno [3,2-c]pyridine;

4-(piperidin-1-yl)methyl-5-(1-oxo-3,4-dihydro-(2H)-
naphth-6-yl)acetyl-4,5,6,7-tetrahydrothieno [3,2-c]pyridine;

5

(-)-4-(piperidin-1-yl)methyl-5-(1-oxo-3,4-dihydro-(2H)-
naphth-6-yl)acetyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

(+)-4-(piperidin-1-yl)methyl-5-(1-oxo-3,4-dihydro-(2H)-
10 naphth-6-yl)acetyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

7. A use according to any one of claims 1 to 6 in which the medicament
contains from 20 to 1000mg of active compound per unit dose.

15 8. A pharmaceutical composition for use in the treatment of cerebral
ischaemia in mammals, which comprises a compound of formula (Ia) or
(Ib) as defined in any one of claims 1 to 6, or a pharmaceutically
acceptable salt or solvate thereof, and a pharmaceutically acceptable
carrier.

20

9. A method of treatment and/or prophylaxis of cerebral ischaemia in
mammals, which comprises administering to a mammal in need of such
treatment and/or prophylaxis an effective amount of a compound of
formula (Ia) or (Ib) as defined in any one of claims 1 to 6, or a
25 pharmaceutically acceptable salt or solvate thereof.