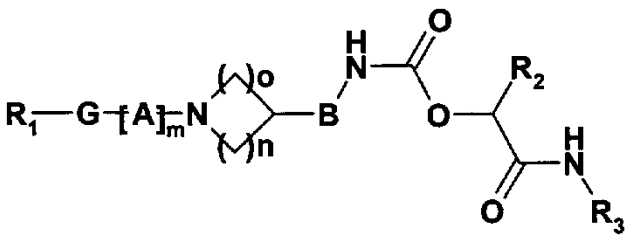
Derivatives of piperidinylalkylcarbamates, preparation method thereof and use of same as FAAH enzyme inhibitors

The invention relates to piperidinylalkylcarbamate derivatives, to their preparation and to their application in therapy.

Already known are phenylalkylcarbamate derivatives, dioxane-2-alkylcarbamate derivatives and piperidinyl- and piperazinyl-alkylcarbamate derivatives, described respectively in the documents WO 2004/067498 A, WO 2004/020430 A and WO 2004/099176, which are inhibitors of the enzyme FAAH (fatty acid amide hydrolase).

There is still a need to find and to develop products which inhibit the enzyme FAAH. The compounds of the invention meet this goal.

The compounds of the invention are of the general formula (I)



in which

m represents an integer from 1 to 4;

n represents an integer 1, 2 or 3;

o an integer 1 or 2;

A is selected from one or more groups X, Y and/or Z;

X represents a methylene group optionally substituted by one or two C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene groups;

Y represents either a C_2 alkenylene group optionally substituted by one or two C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene groups, or a C_2 alkynylene group;

Z represents a group of formula:



p represents an integer from 1 to 5;

q and r represent integers and are defined such that r+q is a number from 1 to 5;

B represents a covalent bond or a C_{1-6} alkylene group;

G represents a covalent bond, an oxygen or sulphur atom or a -CH(OH)-, CO, SO or SO_2 group;

R_1 represents a group R_4 optionally substituted by one or more groups R_5 and/or R_6;

R_4 represents a group selected from a furanyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, thiadiazolyl, isothiadiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, naphthalenyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl,

cinnolinyl, naphthyridinyl, imidazopyrimidinyl, thienopyrimidinyl, benzofuranyl, dihydrobenzofuranyl, benzothienyl, dihydrobenzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, indolyl, isoindolyl, indazolyl, pyrrolopyridinyl, furopyridinyl, dihydrofuropyridinyl, thienopyridinyl, dihydrothienopyridinyl, imidazopyridinyl, pyrazolopyridinyl, oxazolopyridinyl, isoxazolopyridinyl, thiazolopyridinyl;

R_5 represents a halogen atom, a cyano, nitro, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} thioalkyl, C_{1-6} fluoroalkyl, C_{1-6} fluoroalkoxy, C_{1-6} fluorothioalkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene group or a group NR_7R_8, NR_7COR_8, $NR_7CO_2R_8$, $NR_7SO_2R_8$, COR_7, CO_2R_7, $CONR_7R_8$, SO_2R_7, $SO_2NR_7R_8$ or -O-(C_{1-3} alkylene)-O-;

R_6 represents a phenyl, phenyloxy, benzyloxy, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl or pyrimidinyloxy group; it being possible for the group or groups R_6 to be substituted by one or more groups R_5 identical to or different from one another;

R_7 and R_8 represent independently of one another a hydrogen atom or a C_{1-6} alkyl group, or, with the atom or atoms which carry them, form a ring

selected from an azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine, azepine or piperazine ring, this ring being optionally substituted by a C_{1-6} alkyl or benzyl group;

R_2 represents a hydrogen atom or a C_{1-6} alkyl group;

R_3 represents a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene group.

In the context of the invention the compounds of general formula (I) may therefore comprise two or more groups A identical to or different from one another.

Among the compounds of general formula (I) a first subgroup of compounds is composed of the compounds for which:

m represents an integer from 1 to 4;

n represents an integer 1 or 2;

o an integer 1 or 2;

A is selected from one or more groups X and/or Y;

X represents a methylene group optionally substituted by one or two C_{1-6} alkyl groups, more particularly methyl;

Y represents a C_2 alkynylene group;

B represents a covalent bond or a C_{1-6} alkylene group, more particularly a methylene or an ethylene;

G represents a covalent bond or an oxygen atom;

R_1 represents a group R_4 optionally substituted by one or more groups R_5 and/or R_6, more particularly by

one or two groups R_5 and/or R_6;

R_4 represents a group selected from an oxazolyl, isoxazolyl, thiazolyl, phenyl, pyridinyl, naphthalenyl, quinolinyl, isoquinolinyl;

R_5 represents a halogen atom, more particularly a chlorine, a bromine or a fluorine, a cyano group, a group NR_7R_8, or a C_{1-6} alkyl group, more particularly a methyl or an isopropyl, a C_{1-6} alkoxy group, more particularly a methoxy or an ethoxy, a C_{1-6} fluoroalkyl group, more particularly a trifluoromethyl, or a C_{1-6} fluoroalkoxy group, more particularly a trifluoromethoxy;

R_6 represents a phenyl, phenyloxy or pyrimidinyloxy group; it being possible for the group or groups R_6 to be substituted by one or more groups R_5 identical to or different from one another;

R_7 and R_8 represent independently of one another a C_{1-6} alkyl group, more particularly a methyl;

R_2 represents a hydrogen atom or a C_{1-6} alkyl group;

R_3 represents a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene group.

Among the compounds of general formula (I) and of the first subgroup, a second subgroup of compounds is composed of the compounds for which:

n, o, A, B, G, R_1, R_2 and R_3 are as defined in the formula (I) or in the subgroup above;

m represents an integer 1 or 2, more particularly 1.

Among the compounds of general formula (I) and of the subgroups above, a third subgroup of compounds is composed of the compounds for which:
m, A, B, G, R_1, R_2 and R_3 are as defined in the formula (I) or in the subgroups above;
n is 2;
o is 2.

Among the compounds of general formula (I) and of the subgroups above, a fourth subgroup of compounds is composed of the compounds for which:
m, n, o, A, B, G, R_2 and R_3 are as defined in the formula (I) or in the subgroups above;
R_1 represents a group R_4 optionally substituted by one or more groups R_5 and/or R_6, more particularly by one or two groups R_5 and/or R_6;

R_4 represents a group selected from an oxazolyl, isoxazolyl, phenyl or naphthalenyl;

R_5 represents a halogen atom, more particularly a chlorine, a bromine or a fluorine, a cyano group, a group NR_7R_8, a C_{1-6} alkyl group, more particularly a methyl or an isopropyl, a C_{1-6} alkoxy group, more particularly a methoxy or an ethoxy, a C_{1-6} fluoro-alkyl group, more particularly a trifluoromethyl, or a C_{1-6} fluoroalkoxy group, more particularly a trifluoromethoxy;

R_6 represents a phenyl, phenyloxy or pyrimidinyloxy group; it being possible for the group or groups R_6

to be substituted by one or more groups R_5 identical to or different from one another;

R_7 and R_8 represent independently of one another a C_{1-6} alkyl group, more particularly a methyl.

Among the compounds of general formula (I) a fifth subgroup of compounds is composed of the compounds for which:

m, n, o, A, B, G, and R_1 are as defined in the formula (I) or in the subgroups above;

R_2 represents a hydrogen atom;

R_3 represents a hydrogen atom or a C_{1-6} alkyl group, more particularly a methyl.

Among the compounds of general formula (I) mention may be made of the following compounds:

- 2-(methylamino)-2-oxoethyl {1-[(3,4'-difluorobiphenyl-4-yl)methyl]piperidin-4-yl}methylcarbamate;
- 2-(methylamino)-2-oxoethyl {1-[(3-chloro-4'-fluorobiphenyl-4-yl)methyl]piperidin-4-yl}methylcarbamate;
- 2-(methylamino)-2-oxoethyl {1-[3-(4-fluorophenoxy)-benzyl]piperidin-4-yl}methylcarbamate;
- 2-(methylamino)-2-oxoethyl {1-[4-(4-chloro-3-fluorophenoxy)benzyl]piperidin-4-yl}methylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-{1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl}ethylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-{1-[4-(trifluoromethoxy)benzyl]piperidin-4-yl}ethylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-[1-(3-*tert*-butoxy-

benzyl)piperidin-4-yl]ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-[1-(3-*tert*-butoxy-benzyl)piperidin-4-yl]methylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-[1-(2,4-dichloro-benzyl)piperidin-4-yl]ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-[1-(2,5-dichloro-benzyl)piperidin-4-yl]ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-[1-(3,5-dichloro-benzyl)piperidin-4-yl]ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-[1-(2-chloro-5-fluoro-benzyl)piperidin-4-yl]ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-[1-(3-chloro-2-fluoro-benzyl)piperidin-4-yl]ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-[1-(3-chloro-5-methyl-benzyl)piperidin-4-yl]ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-{1-[(3,4'-difluorobi-phenyl-4-yl)methyl]piperidin-4-yl}ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-{1-[(3-chloro-4'-fluoro-biphenyl-4-yl)methyl]piperidin-4-yl}ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-{1-[4-(4-chloro-3-fluorophenoxy)benzyl]piperidin-4-yl}ethylcarbamate;

- 2-(methylamino)-2-oxoethyl {1-[3-(4-fluorophenoxy)-benzyl]piperidin-4-yl}carbamate;

- 2-(methylamino)-2-oxoethyl {1-[3-(trifluoromethoxy)-benzyl]piperidin-4-yl}methylcarbamate;

- 2-(methylamino)-2-oxoethyl {1-[4-(trifluoromethoxy)-benzyl]piperidin-4-yl}methylcarbamate;

- 2-(methylamino)-2-oxoethyl {1-[3-(pyrimidin-2-yloxy)-benzyl]piperidin-4-yl}methylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-[1-(2-chloro-4-fluoro-benzyl)piperidin-4-yl]ethylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-[1-(3-chloro-4-fluoro-benzyl)piperidin-4-yl]ethylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-[1-(3-cyano-5-fluoro-benzyl)piperidin-4-yl]ethylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-{1-[3-(4-fluorophenoxy)-benzyl]piperidin-4-yl}ethylcarbamate;
- 2-(methylamino)-2-oxoethyl (1-{[3-(4-chlorophenyl)-isoxazol-5-yl]methyl}piperidin-4-yl)methylcarbamate;
- 2-(methylamino)-2-oxoethyl (1-{[5-(4-chlorophenyl)-1,3-oxazol-2-yl]methyl}piperidin-4-yl)methylcarbamate;
- 2-(methylamino)-2-oxoethyl [1-({4-[4-(trifluoro-methyl)phenyl]-1,3-thiazol-2-yl}methyl)piperidin-4-yl]-methylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-(1-{[3-(4-chlorophenyl)-isoxazol-5-yl]methyl}piperidin-4-yl)ethylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-(1-{[5-(4-chlorophenyl)-1,3-oxazol-2-yl]methyl}piperidin-4-yl)ethylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-[1-({4-[4-(trifluoro-methyl)phenyl]-1,3-thiazol-2-yl}methyl)piperidin-4-yl]-ethylcarbamate;
- 2-(methylamino)-2-oxoethyl (1-{2-[5-(4-chlorophenyl)-isoxazol-3-yl]ethyl}piperidin-4-yl)methylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-(1-{2-[3-(4-chloro-

phenyl)isoxazol-5-yl]ethyl}piperidin-4-yl)ethyl-carbamate;

- 2-(methylamino)-2-oxoethyl (1-{2-[3-(4-chlorophenyl)-isoxazol-5-yl]ethyl}piperidin-4-yl)methylcarbamate;

- 2-(methylamino)-2-oxoethyl (1-{3-[3-(4-chlorophenyl)-isoxazol-5-yl]propyl}piperidin-4-yl)methylcarbamate;

- 2-(methylamino)-2-oxoethyl (1-{3-[5-(4-chlorophenyl)-isoxazol-3-yl]propyl}piperidin-4-yl)methylcarbamate;

- 2-(methylamino)-2-oxoethyl {1-[1-(2-chloro-4-fluoro-phenyl)ethyl]piperidin-4-yl}methylcarbamate;

- 2-(methylamino)-2-oxoethyl (1-{1-[3-(4-chloro-phenoxy)phenyl]ethyl}piperidin-4-yl)methylcarbamate;

- 2-(methylamino)-2-oxoethyl (1-{1-[2-chloro-3-(4-chlorophenoxy)phenyl]ethyl}piperidin-4-yl)methyl-carbamate;

- 2-(methylamino)-2-oxoethyl 2-(1-{1-[3-(trifluoro-methoxy)phenyl]ethyl}piperidin-4-yl)ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-{1-[1-(2-chloro-4-fluorophenyl)ethyl]piperidin-4-yl}ethylcarbamate;

- 2-(methylamino)-2-oxoethyl {1-[4-(4-chlorophenyl)but-3-yn-1-yl]piperidin-4-yl}carbamate;

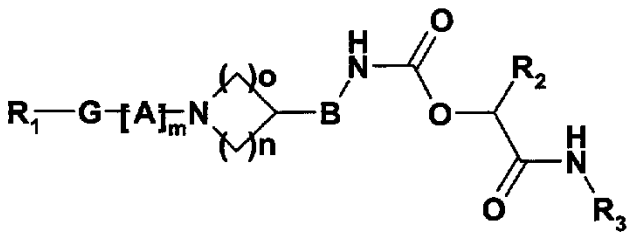
- 2-(methylamino)-2-oxoethyl {1-[5-(4-chlorophenyl)-pent-4-yn-1-yl]piperidin-4-yl}carbamate;

- 2-(methylamino)-2-oxoethyl {1-[5-(2,5-dichloro-phenyl)pent-4-yn-1-yl]piperidin-4-yl}carbamate;

- 2-(methylamino)-2-oxoethyl {1-[4-(4-chlorophenyl)but-3-yn-1-yl]piperidin-4-yl}methylcarbamate;

- 2-(methylamino)-2-oxoethyl {1-[4-(4-chloro-2-fluoro-phenyl)but-3-yn-1-yl]piperidin-4-yl}methylcarbamate;
- 2-(methylamino)-2-oxoethyl {1-[4-(2,5-dichloro-phenyl)but-3-yn-1-yl]piperidin-4-yl}methylcarbamate.

Among the compounds of general formula (I) a subclass of compounds is composed of the compounds of the general formula (I'):



(I')

in which

m represents an integer from 1 to 4;

n represents an integer 1, 2 or 3;

o an integer 1 or 2;

A is selected from one or more groups X, Y and/or Z;

X represents a methylene group optionally substituted by one or two C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene groups;

Y represents either a C_2 alkenylene group optionally substituted by one or two C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene groups, or a C_2 alkynylene group;

Z represents a group of formula:



p represents an integer from 1 to 5;

q and r represent integers and are defined such that r+q is a number from 1 to 5;

B represents a covalent bond or a C_{1-6} alkylene group;

G represents a covalent bond, an oxygen or sulphur atom or a -CH(OH)-, CO, SO or SO_2 group;

R_1 represents a group R_4 optionally substituted by one or more groups R_5 and/or R_6;

R_4 represents a group selected from a furanyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, thiadiazolyl, isothiadiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, naphthalenyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, imidazopyrimidinyl, thienopyrimidinyl, benzofuranyl, dihydrobenzofuranyl, benzothienyl, dihydrobenzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, indolyl, isoindolyl, indazolyl, pyrrolopyridinyl, furopyridinyl, dihydrofuropyridinyl, thienopyridinyl, dihydrothienopyridinyl, imidazopyridinyl, pyrazolopyridinyl, oxazolopyridinyl, isoxazolopyridinyl,

thiazolopyridinyl;

R_5 represents a halogen atom, a cyano, nitro, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} thioalkyl, C_{1-6} fluoroalkyl, C_{1-6} fluoroalkoxy, C_{1-6} fluorothioalkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene group or a group NR_7R_8, NR_7COR_8, $NR_7CO_2R_8$, $NR_7SO_2R_8$, COR_7, CO_2R_7, $CONR_7R_8$, SO_2R_7, $SO_2NR_7R_8$ or -O-(C_{1-3} alkylene)-O-;

R_6 represents a phenyl, phenyloxy, benzyloxy, pyridinyl, pyrazinyl, pyridazinyl or pyrimidinyl group; it being possible for the group or groups R_6 to be substituted by one or more groups R_5 identical to or different from one another;

R_7 and R_8 represent independently of one another a hydrogen atom or a C_{1-6} alkyl group, or, with the atom or atoms which carry them, form a ring selected from an azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine, azepine or piperazine ring, this ring being optionally substituted by a C_{1-6} alkyl or benzyl group;

R_2 represents a hydrogen atom or a C_{1-6} alkyl group;

R_3 represents a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene group.

Among the compounds of general formula (I') a first subgroup of compounds is composed of the compounds for which:

m represents an integer from 1 to 3;

n represents an integer 1 or 2;

o an integer 2;

A is a methylene group;

B represents a covalent bond or a C_{1-6} alkylene group, more particularly a methylene or an ethylene;

G represents a covalent bond or an oxygen atom;

R_1 represents a group R_4 optionally substituted by one or more groups R_5 and/or R_6, more particularly by one or two groups R_5 and/or R_6;

R_4 represents a group selected from a phenyl, pyridinyl, naphthalenyl, isoquinolinyl;

R_5 represents a halogen atom, more particularly a chlorine, a bromine or a fluorine, a cyano group, an *N,N*-dimethylamino group, a C_{1-6} alkyl group, more particularly an isopropyl, a C_{1-6} alkoxy group, more particularly a methoxy or an ethoxy, or a C_{1-6} fluoroalkyl group, more particularly a trifluoromethyl;

R_6 represents a phenyl group;

R_2 represents a hydrogen atom or a C_{1-6} alkyl group;

R_3 represents a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene group.

Among the compounds of general formula (I') a second subgroup of compounds is composed of the compounds for which:

m, n, o, A, B, G and R_1 are as defined in subgroup 1;

R_2 represents hydrogen atom;

R_3 represents a hydrogen atom or a C_{1-6} alkyl group, more particularly a methyl.

Among the compounds of general formula (I') mention may be made of the following compounds:

- 2-(methylamino)-2-oxoethyl {1-[(2-chlorophenyl)-methyl]piperidin-4-yl}methylcarbamate;
- 2-(methylamino)-2-oxoethyl {1-[(4-chlorophenyl)-methyl]piperidin-4-yl}methylcarbamate;
- 2-(methylamino)-2-oxoethyl {1-[(4-chlorophenyl)-methyl]piperidin-4-yl}carbamate;
- 2-(methylamino)-2-oxoethyl (1-[4-(1-methylethyl)-phenyl]methyl piperidin-4-yl)methylcarbamate;
- 2-(methylamino)-2-oxoethyl [1-(biphenyl-4-ylmethyl)-piperidin-4-yl]carbamate;
- 2-(methylamino)-2-oxoethyl [1-(biphenyl-4-ylmethyl)-piperidin-4-yl]methylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-[1-(biphenyl-4-yl-methyl)piperidin-4-yl]ethylcarbamate;
- 2-(methylamino)-2-oxoethyl [1-(2-biphenyl-4-ylethyl)-piperidin-4-yl]carbamate;
- 2-(methylamino)-2-oxoethyl [1-(naphthalen-2-yl-methyl)piperidin-4-yl]methylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-{1-[(4-bromophenyl)-methyl]piperidin-4-yl}ethylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-(1-{[3-(trifluoro-methyl)phenyl]methyl}piperidin-4-yl)ethylcarbamate;
- 2-(methylamino)-2-oxoethyl 2-(1-{[4-(trifluoro-

methyl)phenyl]methyl}piperidin-4-yl)ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-{1-[(2,3-dichloro-phenyl)methyl]piperidin-4-yl}ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-{1-[(3,4-dichloro-phenyl)methyl]piperidin-4-yl}ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-[1-(naphthalen-1-yl-methyl)piperidin-4-yl]ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-[1-(naphthalen-2-yl-methyl)piperidin-4-yl]ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-[1-(pyridin-2-yl-methyl)piperidin-4-yl]ethylcarbamate;

- 2-(methylamino)-2-oxoethyl (1-{2-[4-fluoro-2-(methyloxy)phenyl]ethyl}piperidin-4-yl)methylcarbamate;

- 2-(methylamino)-2-oxoethyl (1-{2-[(4-fluorophenyl)-oxy]ethyl}piperidin-4-yl)carbamate;

- 2-(methylamino)-2-oxoethyl (1-{2-[(4-chlorophenyl)-oxy]ethyl}piperidin-4-yl)carbamate;

- 2-(methylamino)-2-oxoethyl (1-{2-[(2,4-dichloro-phenyl)oxy]ethyl}piperidin-4-yl)carbamate;

- 2-(methylamino)-2-oxoethyl (1-{2-[(4-chlorophenyl)-oxy]ethyl}piperidin-4-yl)methylcarbamate;

- 2-(methylamino)-2-oxoethyl 1-{2-[(2,4-dichloro-phenyl)oxy]ethyl} piperidin-4-yl)methylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-(1-{2-[(4-fluorophenyl)-oxy]ethyl}piperidin-4-yl)ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-(1-{2-[(4-chlorophenyl)-oxy]ethyl}piperidin-4-yl)ethylcarbamate;

- 2-(methylamino)-2-oxoethyl (1-{2-[(4-fluorophenyl)-oxy]ethyl} pyrrolidin-3-yl)methylcarbamate;

- 2-(methylamino)-2-oxoethyl (1-{2-[(4-chlorophenyl)-oxy]ethyl}pyrrolidin-3-yl)methylcarbamate;

- 2-(methylamino)-2-oxoethyl (1-{2-[3-(trifluoro-methyl)phenyl]ethyl}piperidin-4-yl)carbamate;

- 2-(methylamino)-2-oxoethyl {1-[2-(4-chlorophenyl)-ethyl]piperidin-4-yl}carbamate;

- 2-(methylamino)-2-oxoethyl {1-[2-(4-cyanophenyl)-ethyl]piperidin-4-yl}carbamate;

- 2-(methylamino)-2-oxoethyl (1-{2-[(isoquinolin-5-yl)oxy]ethyl}piperidin-4-yl)carbamate;

- 2-(methylamino)-2-oxoethyl [1-(2-naphthalen-1-yl-ethyl)piperidin-4-yl]carbamate;

- 2-(methylamino)-2-oxoethyl [1-(2-naphthalen-2-yl-ethyl)piperidin-4-yl]carbamate;

- 2-(methylamino)-2-oxoethyl {1-[3-(4-chlorophenyl)-propyl]piperidin-4-yl}carbamate;

- 2-(methylamino)-2-oxoethyl (1-{3-[4-(methyloxy)-phenyl]propyl}piperidin-4-yl)carbamate;

- 2-(methylamino)-2-oxoethyl {1-[2-(3-chlorophenyl)-ethyl]piperidin-4-yl}methylcarbamate;

- 2-(methylamino)-2-oxoethyl (1-{2-[4-(ethyloxy)-phenyl]ethyl}piperidin-4-yl)methylcarbamate;

- 2-(methylamino)-2-oxoethyl (1-{2-[4-(dimethylamino)-phenyl]ethyl}piperidin-4-yl)methylcarbamate;

- 2-(methylamino)-2-oxoethyl {1-[2-(2,4-dichloro-

phenyl)ethyl]piperidin-4-yl}methylcarbamate;

- 2-(methylamino)-2-oxoethyl [1-(2-naphthalen-1-yl-ethyl)piperidin-4-yl]methylcarbamate;

- 2-(methylamino)-2-oxoethyl [1-(2-naphthalen-2-yl-ethyl)piperidin-4-yl]methylcarbamate;

- 2-(methylamino)-2-oxoethyl (1-{3-[4-(methyloxy)-phenyl]propyl}piperidin-4-yl)methylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-{1-[2-(2-chlorophenyl)-ethyl]piperidin-4-yl}ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-{1-[2-(4-fluorophenyl)-ethyl]piperidin-4-yl}ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-(1-{2-[4-(ethyloxy)-phenyl]ethyl}piperidin-4-yl)ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-{1-[2-(2-chloro-6-fluorophenyl)ethyl]piperidin-4-yl}ethylcarbamate;

- 2-(methylamino)-2-oxoethyl 2-(1-{3-[4-(methyloxy)-phenyl]propyl}piperidin-4-yl)ethylcarbamate.

The compounds of general formula (I) may include one or more asymmetric carbons. They may exist in the form of enantiomers or diastereoisomers. These enantiomers and diastereoisomers, and also mixtures thereof, including the racemic mixtures, form part of the invention.

The compounds of formula (I) may exist in the form of bases or of addition salts with acids. Such addition salts form part of the invention.

These salts are advantageously prepared with

pharmaceutically acceptable acids, although the salts of other acids which are of use, for example, for purifying or isolating compounds of formula (I) likewise form part of the invention.

The compounds of general formula (I) may be in the form of hydrates or solvates, namely in the form of associations or combinations with one or more molecules of water or with a solvent. Such hydrates and solvates likewise form part of the invention.

In the context of the invention the terms are understood as follows:

- C_{t-z}, where t and z may take the values from 1 to 7, is a carbon chain which may have from t to z carbon atoms; for example, C_{1-3} is a carbon chain which may have from 1 to 3 carbon atoms;
- alkyl is a saturated, linear or branched aliphatic group; for example, a C_{1-6} alkyl group represents a linear or branched carbon chain of 1 to 6 carbon atoms, more particularly a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl or hexyl;
- alkylene is a saturated, linear or branched divalent alkyl group; for example, a C_{1-3} alkylene group represents a linear or branched, divalent carbon chain of 1 to 3 carbon atoms, more particularly a methylene, ethylene, 1-methyl-ethylene or propylene;

- cycloalkyl is a cyclic alkyl group; for example, a C_{3-7} cycloalkyl group represents a cyclic carbon group of 3 to 7 carbon atoms, more particularly a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;
- alkenylene is a divalent unsaturated aliphatic group having 2 carbons, more particularly an ethylene;
- C_2 alkynylene is a -C≡C- group;
- alkoxy is an -O-alkyl group having a saturated, linear or branched aliphatic chain;
- thioalkyl is an -S-alkyl group having a saturated, linear or branched aliphatic chain;
- fluoroalkyl is an alkyl group of which one or more hydrogen atoms have been substituted by a fluorine atom;
- fluoroalkoxy is an alkoxy group of which one or more hydrogen atoms have been substituted by a fluorine atom;
- fluorothioalkyl is a thioalkyl group of which one or more hydrogen atoms have been substituted by a fluorine atom; and
- halogen atom is a fluorine, a chlorine, a bromine or an iodine.

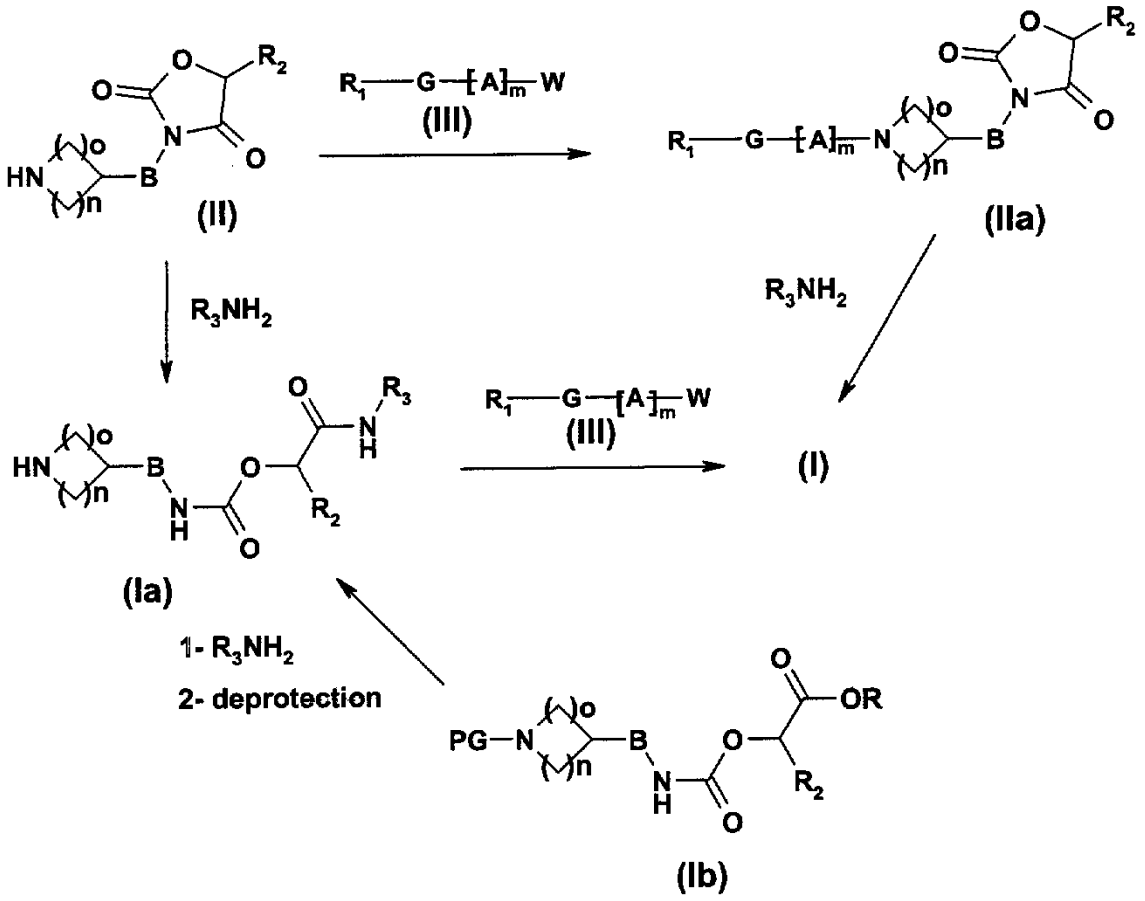
In the text below, a protective group Pg is understood to be a group which makes it possible on the one hand for a reactive function such as a hydroxyl or

an amine to be protected during a synthesis and on the other hand for the reactive function to be regenerated intact at the end of synthesis. Examples of protective groups and also of methods of protection and deprotection are given in "Protective Groups in Organic Synthesis", Green *et al.*, 2nd Edition (John Wiley & Sons, Inc., New York).

The compounds of the invention may be prepared according to various methods, which are illustrated by scheme 1 below.

Thus a first method (scheme 1) involves reacting a compound of general formula (II), in which B, R_2, n and o are as defined in the general formula (I), with a derivative of general formula (III), in which W represents a mesylate or tosylate group or a chlorine, bromine or iodine atom and m, G, A and R_1 are as defined in the general formula (I), in the presence of a base such as triethylamine, sodium hydride, sodium tert-butoxide or sodium carbonate in a solvent such as tetrahydrofuran, acetonitrile, dimethyl sulphoxide or dimethylformamide at a temperature between 0°C and the reflux temperature of the solvent.

Scheme 1



The oxazolidine-dione of general formula (IIa) thus obtained is subsequently converted into a compound of general formula (I), by aminolysis using an amine of general formula R_3NH_2 in which R_3 is as defined in the general formula (I). The aminolysis reaction may be carried out in a solvent such as methanol, ethanol or a solvent mixture such as methanol and tetrahydrofuran or methanol and dioxane.

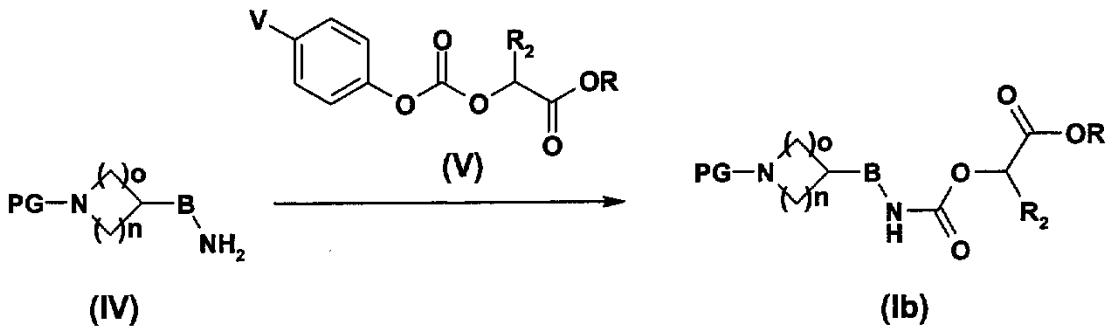
A variant form of obtaining compounds of general formula (I) (scheme 1) involves converting a compound of general formula (II) as defined above by

aminolysis, under the conditions described above, using an amine of general formula R_3NH_2 as defined above, to give a carbamate-amide derivative of general formula (Ia) in which B, R_2, R_3, n and o are as defined in the general formula (I). The compound of general formula (I) is then obtained by reacting the compound (Ia) with a derivative of general formula (III) as defined above, under the conditions described above.

The carbamate-amide derivative of general formula (Ia) as defined above may also be obtained from the carbamate-ester of general formula (Ib), in which B, R_2, n and o are as defined in the general formula (I), PG represents a protective group such as a Boc (*tert*-butyloxycarbonyl) and R represents a methyl or ethyl group, by aminolysis using an amine of general formula R_3NH_2 as defined above and under the conditions described above, then by deprotection, in the presence for example of a solution of hydrochloric acid (5N) in isopropanol.

The carbamate-esters (Ib) may be prepared according to the method illustrated by scheme 2 below.

Scheme 2



According to scheme 2 the carbamate-ester of general formula (Ib) is obtained by reacting an amine of general formula (IV), in which B, n and o are as defined in the general formula (I) and PG represents a protective group such as a Boc, with a carbonate of general formula (V), in which V represents a hydrogen atom or a nitro group, R_2 is as defined in the general formula (I) and R represents a methyl or ethyl group.

When the method of preparing them is not described the compounds of general formula (II) may be prepared according to methods which are described in the literature or according to methods similar to those described or known to the skilled person.

The carbonates of general formula (V) may be prepared according to any method described in the literature, by reaction for example of an alcohol of general formula $HOCHR_2COOR$ where R represents a methyl or ethyl group with phenyl chloroformate or 4-nitrophenyl chloroformate in the presence of a base such as triethylamine or diisopropylethylamine.

The compounds of general formulae (III) and (IV) and the amines of general formula R_3NH_2 are available commercially or are prepared according to methods which are described in the literature or which are known to the skilled person.

The compounds of general formula (Ia) in which B, R_2, R_3, n and o are as defined in the general

formula (I) are novel and likewise form part of the invention. They are useful as synthesis intermediates for the preparation of compounds of general formula (I).

The compounds of general formula (IIa) in which m, G, A, R_1, B, R_2, n and o are as defined in the general formula (I), with the exception of the compound 3-[1-(phenylmethyl)-4-piperidinyl]-2,4-oxazolidine-dione, are novel and likewise form part of the invention. They are useful as synthesis intermediates for preparing compounds of general formula (I).

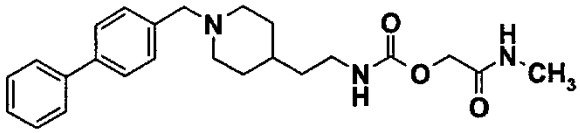
The examples which now follow illustrate the preparation of some compounds of the invention. These examples are not limitative and serve merely to illustrate the invention. The microanalyses, the IR and NMR spectra and/or the LC-MS (liquid chromatography coupled to mass spectroscopy) confirm the structures and the purities of the compounds obtained.

M.P. (°C) represents the melting point in degrees Celsius.

The numbers indicated between brackets in the titles of the examples correspond to those in the 1st column of the subsequent table.

Example 1 (compound 25)

2-(methylamino)-2-oxoethyl 2-[1-(biphenyl-4-ylmethyl)-piperidin-4-yl]ethylcarbamate



1.1. 3-(2-piperidin-4-ylethyl)-1,3-oxazolidine-2,4-dione hydrochloride

A solution of 10 g (77.40 mmol) of 2-piperidin-4-ylethanol, 22.33 g (85.14 mmol) of triphenylphosphine and 9.39 g (92.88 mmol) of 1,3-oxazolidine-2,4-dione (J. Med. Chem. 1991, 34, 1538-44) in 150 ml of tetrahydrofuran, cooled to approximately -10°C, is admixed dropwise under an inert atmosphere with a solution of 15.65 g (77.40 mmol) of diisopropyl azodicarboxylate (DIAD) in 25 ml of tetrahydrofuran, during which the temperature of the reaction mixture is held between -10°C and 0°C. Stirring is continued at 0°C for 1 hour and then at 25°C for 22 hours. The solid formed is collected by filtration, washed repeatedly with tetrahydrofuran and then dried under vacuum at approximately 70°C. This solid is then taken up in a solution of hydrochloric acid (5N) in isopropanol. The solid formed is collected by filtration and then washed with ethyl acetate and ether.

Drying under vacuum at approximately 70°C gives 6.45 g of hydrochloride in the form of a white solid.

M.P. (°C): 178°C

1.2. 3-{2-[1-(biphenyl-4-ylmethyl)piperidin-4-yl]ethyl}-1,3-oxazolidine-2,4-dione

A solution of 0.40 g (1.61 mmol) of 3-(2-piperidin-4-ylethyl)-1,3-oxazolidine-2,4-dione hydrochloride, prepared in step 1.1., 0.326 g (1.61 mmol) of 4-(chloromethyl)biphenyl and 0.51 g (4.82 mmol) of sodium carbonate in 3 ml of acetonitrile is heated at reflux for 17 hours. It is left to return to ambient temperature and filtered and the filtrate is concentrated under reduced pressure. The residue is taken up in dichloromethane and water and the aqueous phase is separated off and extracted twice with dichloromethane. The combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate. Following evaporation of the solvent, the residue obtained is purified by chromatography on silica gel, eluting with a 97/3 then 95/5 mixture of dichloromethane and methanol.

This gives 0.46 g of product in the form of a beige solid.

1.3. 2-(methylamino)-2-oxoethyl 2-[1-(biphenyl-4-ylmethyl)piperidin-4-yl]ethylcarbamate

A solution of 0.45 g (1.19 mmol) of 3-{2-[1-(biphenyl-4-ylmethyl)piperidin-4-yl]ethyl}-1,3-oxazolidine-2,4-dione, obtained in step 1.2., in 5 ml of methanol is admixed with 3 ml (5.97 mmol) of a solution of methylamine (2M) in tetrahydrofuran. Stirring is continued at ambient temperature for 17 hours. Following concentration under reduced pressure,

the residue obtained is purified by chromatography on silica gel, eluting with a 95/5 then 90/10 mixture of dichloromethane and methanol. A yellow paste is obtained which is crystallized from diisopropyl ether.

This gives 0.40 g of product in the form of a yellow solid.

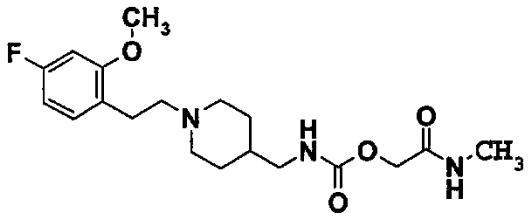
LC-MS: M+H = 410

M.P. (°C): 106-110°C

^{1}H NMR ($CDCl_3$) δ (ppm): 1.2-1.50 (unresolved complex, 5H); 1.70 (m, 2H); 2.0 (broad t, 2H); 2.90 (d, 3H); 3.0 (m, 2H); 3.30 (q, 2H); 3.55 (s, 2H); 4.60 (s, 2H); 4.80 (broad s, 1H); 6.15 (broad s, 1H); 7.40 (m, 5H); 7.60 (m, 4H).

Example 2 (compound 52)

2-(methylamino)-2-oxoethyl 1-{2-[4-fluoro-2-(methoxy)-phenyl]ethyl}piperidin-4-yl)methylcarbamate



2.1. 1,1-dimethylethyl 4-{[(methylsulphonyl)oxy]methyl}piperidine-1-carboxylate

A solution of 10.08 g (46.81 mmol) of 1,1-dimethylethyl 4-(hydroxymethyl)piperidine-1-carboxylate and 9.90 ml (70.21 mmol) of triethylamine in 100 ml of dichloromethane, cooled to approximately

0°C, is admixed dropwise under an inert atmosphere with a solution of 4 ml (51.49 mmol) of mesyl chloride in 10 ml of dichloromethane. The bath is removed and stirring is continued at ambient temperature for 30 minutes. Water is added to the reaction mixture, the aqueous phase is separated off and extracted once with dichloromethane, the combined organic phases are washed with water and dried over sodium sulphate and the filtrate is concentrated under reduced pressure.

This gives 13.7 g of product in the form of an orange-coloured oil, which is used as it is in the following step.

2.2. 1,1-dimethylethyl 4-[(2,4-dioxo-1,3-oxazolidin-3-yl)methyl]piperidine-1-carboxylate

A suspension of 13.60 g (46.36 mmol) of 1,1-dimethylethyl 4-{[(methylsulphonyl)oxy]methyl}-piperidine-1-carboxylate, prepared in step 2.1., 9.37 g (92.72 mmol) of 1,3-oxazolidine-2,4-dione and 16.02 g (139.08 mmol) of 1,1,3,3-tetramethylguanidine in a mixture of 180 ml of tetrahydrofuran and 30 ml of dimethylformamide is heated at reflux for 24 hours. It is allowed to return to ambient temperature and is concentrated under reduced pressure. The residue is taken up in dichloromethane and water and the aqueous phase is separated off and extracted twice with dichloromethane. The combined organic phases are washed with saturated aqueous sodium chloride solution and

dried over sodium sulphate. Following evaporation of the solvent, the residue obtained is purified by chromatography on silica gel, eluting with a 98/2 then 95/5 mixture of dichloromethane and methanol.

This gives 12.53 g of product in the form of an orange-brown solid.

2.3. 3-(piperidin-4-ylmethyl)-1,3-oxazolidine-2,4-dione hydrochloride

A suspension of 12.51 g (41.95 mmol) of 1,1-dimethylethyl 4-[(2,4-dioxo-1,3-oxazolidin-3-yl)-methyl]piperidine-1-carboxylate, obtained in step 2.2., in 65 ml of dioxane is admixed with 38.10 ml (209.75 mmol) of a solution of hydrochloric acid (5N) in isopropanol. Stirring is continued at approximately 60°C for 17 hours. The suspension is allowed to return to ambient temperature. The solid formed is collected by filtration and then washed repeatedly with ether and dried under vacuum at approximately 70°C.

This gives 8.41 g of product in the form of a white solid.

M.P. (°C): 195-200°C

2.4. 3-[(1-{2-[4-fluoro-2-(methoxy)phenyl]-ethyl}piperidin-4-yl)methyl]-1,3-oxazolidine-2,4-dione

The method described in Example 1 (step 1.2.) is used. Starting from 0.40 g (1.70 mmol) of 3-(piperidin-4-ylmethyl)-1,3-oxazolidine-2,4-dione hydrochloride, prepared in step 2.3., 0.423 g

(1.70 mmol) of 2-[4-fluoro-2-(methyloxy)phenyl]ethyl methanesulphonate [EP1340761] and 0.54 g (5.11 mmol) of sodium carbonate gives, after treatment, 0.590 g of product in the form of a viscous yellow oil, which is used as it is in the following step.

2.5. 2-(methylamino)-2-oxoethyl 1-{2-[4-fluoro-2-(methoxy)phenyl]ethyl]piperidin-4-yl)methyl-carbamate

The procedure described in Example 1 (step 1.3.) is followed. Starting from 0.58 g (1.66 mmol) of 3-[(1-{2-[4-fluoro-2-(methoxy)phenyl]ethyl}piperidin-4-yl)methyl]-1,3-oxazolidine-2,4-dione, prepared in step 2.4., and 8.28 ml (16.55 mmol) of a solution of methylamine (2M) in tetrahydrofuran, and after chromatography on silica gel, eluting with a 95/5/0.5 mixture of dichloromethane, methanol and 28% ammonia, followed by washing with diisopropyl ether, gives 0.315 g of product in the form of a white solid.

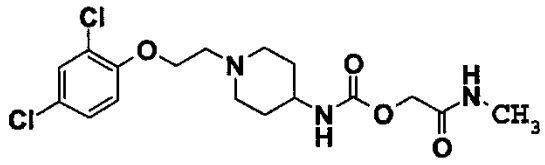
LC-MS: M+H = 382

M.P. (°C): 126-128°C

^{1}H NMR (DMSO) δ (ppm): 1.10 (m, 2H); 1.35 (broad s, 1H); 1.60 (broad d, 2H); 1.85 (broad t, 2H); 2.40 (m, 2H); 2.60 (m, 5H); 2.90 (m, 4H); 3.80 (s, 3H); 4.30 (s, 2H); 6.65 (td, 1H); 6.80 (dd, 1H); 7.15 (m, 2H); 7.70 (broad s, 1H).

Example 3 (compound 68)

2-(methylamino)-2-oxoethyl 1-{2-[(2,4-dichlorophenyl)-oxy]ethyl}piperidin-4-yl)carbamate



3.1. 1,1-dimethylethyl 4-[({[2-(ethyloxy)-2-oxoethyl]oxy}carbonyl)amino]piperidine-1-carboxylate

A suspension of 5.09 g (25.42 mmol) of 1,1-dimethylethyl 4-aminopiperidine-1-carboxylate and 13.45 g (59.99 mmol) of ethyl [(phenyloxycarbonyl)oxy]-acetate (J. Med. Chem., 1999, 42, 277-90) in 300 ml of toluene is heated at reflux for 30 hours.

The suspension is allowed to return to ambient temperature, the insoluble material is separated off by filtration and the filtrate is concentrated under reduced pressure. The residue thus obtained is purified by chromatography on silica gel, eluting with a 30/70 mixture of ethyl acetate and cyclohexane.

This gives 6.62 g of product in the form of a light-coloured yellow oil.

3.2. 1,1-dimethylethyl 4-[({[2-(methyl-amino)-2-oxoethyl]oxy}carbonyl)amino]piperidine-1-carboxylate

The procedure of Example 1 (step 1.3.) is

repeated. Starting from 6.33 g (19.16 mmol) of 1,1-dimethylethyl 4-[({[2-(ethyloxy)-2-oxoethyl]oxy}carbonyl)amino]piperidine-1-carboxylate, prepared in step 3.1., and 47.90 ml (95.81 mmol) of a solution of methylamine (2M) in tetrahydrofuran gives 5.90 g of product in the form of a sticky yellow paste.

3.3. 2-(methylamino)-2-oxoethyl piperidin-4-ylcarbamate hydrochloride

The method described in Example 2 (step 2.3.) is used. Starting from 5.90 g (18.71 mmol) of 1,1-dimethylethyl 4-[({[2-methylamino)-2-oxoethyl]oxy}carbonyl)amino]piperidine-1-carboxylate, prepared in step 3.2., and 17 ml (93.53 mmol) of a solution of hydrochloric acid (5N) in isopropanol gives 3.83 g of hydrochloride in the form of a white solid after washing with diisopropyl ether and drying under vacuum at approximately 70°C.

M.P. (°C): 153°C

3.4. 2-(methylamino)-2-oxoethyl 1-{2-[2,4-dichlorophenyl)oxy]ethyl}piperidin-4-yl)carbamate

The method described in Example 1 (step 1.2.) is used. Starting from 0.51 g (1.89 mmol) of 2-(methylamino)-2-oxoethyl piperidin-4-ylcarbamate hydrochloride, prepared in step 3.3., 0.50 g (1.99 mmol) of 1-[(2-bromoethyl)oxy]-2,4-dichlorobenzene and 0.60 g (5.68 mmol) of sodium carbonate, and after chromatography on silica gel, eluting with a 94/6/0.6

then 95/5/0.5 mixture of dichloromethane, methanol and 28% ammonia, followed by washing with diisopropyl ether, gives 0.44 g of product in the form of a white solid.

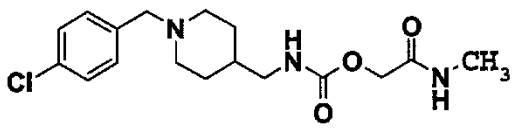
LC-MS: M+H = 404

M.P. (°C): 115-119°C

^{1}H NMR ($CDCl_3$) δ (ppm): 1.50 (m, 2H); 2.0 (broad d, 2H); 2.35 (broad t, 2H); 2.90 (d, 3H); 3.0 (m, 4H); 3.60 (m, 1H); 4.15 (t, 2H); 4.60 (s, 2H); 4.75 (broad d, 1H); 6.15 (broad s, 1H); 6.85 (d, 1H); 7.20 (dd, 1H); 7.40 (d, 1H).

Example 4 (compound 4)

2-(methylamino)-2-oxoethyl {1-[(4-chlorophenyl)methyl]-piperidin-4-yl}methylcarbamate hydrochloride



4.1. 2-(methylamino)-2-oxoethyl (piperidin-4-yl)methylcarbamate hydrochloride

A solution of 0.50 g (2.13 mmol) of 3-piperidin-4-ylmethyl)-1,3-oxozolidine-2,4-dione hydrochloride, obtained in step 2.3., and 5.30 ml (10.65 mmol) of a solution of methylamine (2M) in tetrahydrofuran in 10 ml of methanol is stirred at ambient temperature for 15 hours. Following concentration under reduced pressure, the residue obtained is treated with a solution of hydrochloric

acid (5N) in isopropanol. The hydrochloride obtained is collected by filtration, washed with diisopropyl ether and dried under vacuum at approximately 70°C. This gives 0.49 g of a white powder.

4.2. 2-(methylamino)-2-oxoethyl {1-[(4-chlorophenyl)methyl]piperidin-4-yl}methylcarbamate hydrochloride

A mixture of 0.118 g (0.44 mmol) of 2-(methylamino)-2-oxoethyl (piperidin-4-yl)methylcarbamate hydrochloride, 0.283 g (1.33 mmol) of sodium triacetoxyborohydride and 0.626 g (4.45 mmol) of 4-chlorobenzaldehyde in 5 ml of a 1% solution of acetic acid in N,N'-dimethylformamide is stirred at ambient temperature. After 24 hours of stirring, 2 g of DOWEX 50WX2 acidic resin (Fluka) are added and stirring is continued at ambient temperature for one hour. The mixture is filtered and the resin is rinsed with 3 times 5 ml of N,N'-dimethylformamide, 3 times 5 ml of dichloromethane and 3 times 5 ml of methanol. The resin is subsequently treated for an hour at ambient temperature with 8 ml of a solution (2M) of ammonia in methanol. The mixture is filtered and the filtrate is concentrated under vacuum. The product is purified by chromatography on silica gel, eluting with a 94/6 mixture of dichloromethane and methanol containing 2% of 28% aqueous ammonia solution. The oily residue obtained is treated with 5 ml of a solution of

hydrochloric acid (0.1N) in isopropanol. Concentration gives 0.067 g of a white powder.

M.P. (°C): 220-222°C

LC-MS: M+H = 354

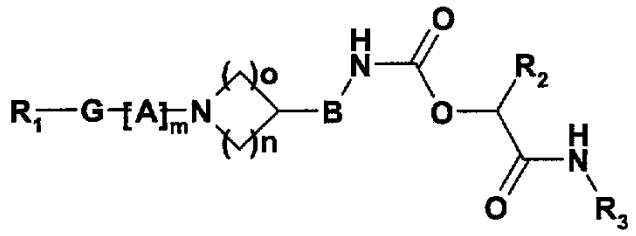
^{1}H NMR (DMSO-d_6 / D_2O): δ (ppm): 1.20 (m, 2H); 1.40 (m, 1H); 1.60 (m, 2H); 1.90 (t, 2H); 2.70 (s, 3H); 2.75 (d, 2H); 2.90 (d, 2H); 3.40 (s, 2H); 4.30 (s, 2H); 7.95 (m, 4H).

Table 1 below illustrates the chemical structures and the physical properties of some compounds according to the invention.

In this table:

- in the "base or salt" column, "base" signifies that the compound is in the form of the free base, whereas "HCl" represents a compound in hydrochloride form, and the ratio between brackets is the (acid:base) ratio,
- *t*-BuO, Me, Et and i-Pr represent, respectively, *tert*-butoxy, methyl, ethyl and isopropyl groups, and
- Ph represents a phenyl group.

Table 1



(I)

Cpd	R_1	G	[A]m	n	o	B	R_2	R_3	Base or salt	M.P. (°C)
1.	4-Cl-phenyl	bond	CH_2	2	2	bond	H	CH_3	base	144-146
2.	4-Ph-phenyl	bond	CH_2	2	2	bond	H	CH_3	base	165-167
3.	2-Cl-phenyl	bond	CH_2	2	2	CH_2	H	CH_3	HCl (1/1)	173-175
4.	4-Cl-phenyl	bond	CH_2	2	2	CH_2	H	CH_3	HCl (1/1)	220-222
5.	4-iPr-phenyl	bond	CH_2	2	2	CH_2	H	CH_3	HCl (1/1)	159-161
6.	4-Ph-phenyl	bond	CH_2	2	2	CH_2	H	CH_3	HCl (1/1)	205-207
7.	[2-F,4-(4-F-phenyl)]-phenyl	bond	CH_2	2	2	CH_2	H	CH_3	base	156-158
8.	[2-Cl,4-(4-F-phenyl)]-phenyl	bond	CH_2	2	2	CH_2	H	CH_3	HCl (1/1)	163-169

Cpd	R_1	G	[A]m	n	o	B	R_2	R_3	Base or salt	M.P. (°C)
9.	3-(4-F-phenyloxy)-phenyl	bond	CH_2	2	2	CH_2	H	CH_3	HCl (1/1)	163-165
10.	4-[(3-F,4-Cl)-phenyl-oxy]phenyl	bond	CH_2	2	2	CH_2	H	CH_3	base	96-104
11.	naphthalen-2-yl	bond	CH_2	2	2	CH_2	H	CH_3	HCl (1/1)	156-157
12.	4-Br-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	107-111
13.	3-CF_3-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	90-92
14.	4-CF_3-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	116-120
15.	3-CF_3O-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	418*
16.	4-CF_3O-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	109-111
17.	(2-Cl,3-Cl)-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	114-116
18.	(2-Cl,4-Cl)-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	117-119
19.	(2-Cl,5-Cl)-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	125-127
20.	(3-Cl,4-Cl)-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	101-105

Cpd	R_1	G	[A]m	n	o	B	R_2	R_3	Base or salt	M.P. (°C)
21.	(3-Cl,5-Cl)-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	124-126
22.	(2-Cl,5-F)-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	102-104
23.	(2-F,3-Cl)-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	104-106
24.	(3-Cl,5-CH_3)-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	79-81
25.	4-Ph-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	106-110
26.	[2-F,4-(4-F-phenyl)]-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	143-145
27.	[2-Cl,4-(4-F-phenyl)]-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	98-102
28.	4-[(3-F,4-Cl)-phenyl-oxy]phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	109-111
29.	naphthalen-1-yl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	86-88
30.	naphthalen-2-yl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	87-93
31.	pyridin-2-yl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	104-106

Cpd	R_1	G	[A]m	n	o	B	R_2	R_3	Base or salt	M.P. (°C)
32.	3-CF_3-phenyl	bond	$(CH_2)_2$	2	2	bond	H	CH_3	HCl (1/1)	136-138
33.	4-Cl-phenyl	bond	$(CH_2)_2$	2	2	bond	H	CH_3	HCl (1/1)	168-170
34.	4-CN-phenyl	bond	$(CH_2)_2$	2	2	bond	H	CH_3	base	179-181
35.	(2-Cl,3-Cl)-phenyl	bond	$(CH_2)_2$	2	2	bond	H	CH_3	base	117-123
36.	(2-Cl,4-Cl)-phenyl	bond	$(CH_2)_2$	2	2	bond	H	CH_3	base	134-138
37.	(2-Cl,6-Cl)-phenyl	bond	$(CH_2)_2$	2	2	bond	H	CH_3	base	163-167
38.	(3-Cl,4-Cl)-phenyl	bond	$(CH_2)_2$	2	2	bond	H	CH_3	base	130-132
39.	4-Ph-phenyl	bond	$(CH_2)_2$	2	2	bond	H	CH_3	base	174-178
40.	4-phenyloxy-phenyl	bond	$(CH_2)_2$	2	2	bond	H	CH_3	base	144-146
41.	naphthalen-1-yl	bond	$(CH_2)_2$	2	2	bond	H	CH_3	HCl (1/1)	185-187
42.	4-F-naphthalen-1-yl	bond	$(CH_2)_2$	2	2	bond	H	CH_3	base	124-130
43.	naphthalen-2-yl	bond	$(CH_2)_2$	2	2	bond	H	CH_3	HCl (1/1)	198-202

Cpd	R_1	G	[A]m	n	o	B	R_2	R_3	Base or salt	M.P. (°C)
44.	3-Cl-phenyl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	93-95
45.	4-EtO-phenyl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	134-136
46.	4-Me_2N-phenyl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	130-132
47.	(2-Cl,3-Cl)-phenyl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	81-87
48.	(2-Cl,4-Cl)-phenyl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	125-127
49.	(2-Cl,4-Cl)-phenyl	bond	$(CH_2)_2$	2	2	CH_2	H	H	base	115-119
50.	(2-Cl,6-Cl)-phenyl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	144-148
51.	(3-Cl,4-Cl)-phenyl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	123-127
52.	(2-MeO,4-F)-phenyl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	126-128
53.	4-phenyloxy-phenyl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	120-124
54.	naphthalen-1-yl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	HCl (1/1)	148-150
55.	4-F-naphthalen-1-yl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	120-124

Cpd	R_1	G	[A]m	n	o	B	R_2	R_3	Base or salt	M.P. (°C)
56.	naphthalen-2-yl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	163-166
57.	2-Cl-phenyl	bond	$(CH_2)_2$	2	2	$(CH_2)_2$	H	CH_3	HCl (1/1)	121-123
58.	4-F-phenyl	bond	$(CH_2)_2$	2	2	$(CH_2)_2$	H	CH_3	base	122-124
59.	4-EtO-phenyl	bond	$(CH_2)_2$	2	2	$(CH_2)_2$	H	CH_3	base	118-120
60.	(2-Cl,6-F)-phenyl	bond	$(CH_2)_2$	2	2	$(CH_2)_2$	H	CH_3	base	88-90
61.	4-Cl-phenyl	bond	$(CH_2)_3$	2	2	bond	H	CH_3	HCl (1/1)	132-134
62.	4-MeO-phenyl	bond	$(CH_2)_3$	2	2	bond	H	CH_3	HCl (1/1)	175-177
63.	4-MeO-phenyl	bond	$(CH_2)_3$	2	2	CH_2	H	CH_3	HCl (1/1)	155-157
64.	4-MeO-phenyl	bond	$(CH_2)_3$	2	2	$(CH_2)_2$	H	CH_3	HCl (1/1)	118-120
65.	4-F-phenyl	O	$(CH_2)_2$	2	2	bond	H	CH_3	base	135-137
66.	4-Cl-phenyl	O	$(CH_2)_2$	2	2	bond	H	CH_3	base	141-145
67.	(2-Cl,3-Cl)-phenyl	O	$(CH_2)_2$	2	2	bond	H	CH_3	base	128-130
68.	(2-Cl,4-Cl)-phenyl	O	$(CH_2)_2$	2	2	bond	H	CH_3	base	115-119

Cpd	R_1	G	[A]m	n	o	B	R_2	R_3	Base or salt	M.P. (°C)
69.	(2-Cl,4-Cl)-phenyl	O	$CH(CH_3)CH_2$	2	2	bond	H	CH_3	HCl (1/1)	141-143
70.	(3-Cl,4-Cl)-phenyl	O	$(CH_2)_2$	2	2	bond	H	CH_3	base	146-148
71.	4-Cl-naphthalen-1-yl	O	$(CH_2)_2$	2	2	bond	H	CH_3	base	136-140
72.	4-Cl-naphthalen-1-yl	O	$(CH_2)_2$	2	2	bond	H	H	base	141-143
73.	quinolin-5-yl	O	$(CH_2)_2$	2	2	bond	H	CH_3	base	140-142
74.	isoquinolin-5-yl	O	$(CH_2)_2$	2	2	bond	H	CH_3	base	149-153
75.	4-Cl-phenyl	O	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	115-119
76.	(2-Cl,3-Cl)-phenyl	O	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	117-119
77.	(2-Cl,4-Cl)-phenyl	O	$(CH_2)_2$	2	2	CH_2	H	CH_3	HCl (1/1)	137-139
78.	(2-Cl,4-Cl)-phenyl	O	$CH(CH_3)CH_2$	2	2	CH_2	H	CH_3	HCl (1/1)	194-196
79.	(3-Cl,4-Cl)-phenyl	O	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	98-100

Cpd	R_1	G	[A]m	n	o	B	R_2	R_3	Base or salt	M.P. (°C)
80.	4-Cl-naphthalen-1-yl	O	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	116-120
81.	quinolin-5-yl	O	$(CH_2)_2$	2	2	CH_2	H	CH_3	HCl (1/1)	220-224
82.	isoquinolin-5-yl	O	$(CH_2)_2$	2	2	CH_2	H	CH_3	HCl (1/1)	74-78
83.	4-F-phenyl	O	$(CH_2)_2$	2	2	$(CH_2)_2$	H	CH_3	base	125-129
84.	4-Cl-phenyl	O	$(CH_2)_2$	2	2	$(CH_2)_2$	H	CH_3	base	109-113
85.	4-Cl-phenyl	O	$(CH_2)_3$	2	2	bond	H	CH_3	base	133-137
86.	4-F-phenyl	O	$(CH_2)_2$	1	2	CH_2	H	CH_3	HCl (1/1)	354*
87.	4-Cl-phenyl	O	$(CH_2)_2$	1	2	CH_2	H	CH_3	base	67-69
88.	3-(4-F-phenyloxy)-phenyl	bond	CH_2	2	2	bond	H	CH_3	base	107-109
89.	5-(4-Cl-phenyl)iso-xazol-3-yl	bond	$(CH_2)_3$	2	2	bond	H	CH_3	base	151-153
90.	3-CF_3O-phenyl	bond	CH_2	2	2	CH_2	H	CH_3	base	73-75
91.	4-CF_3O-phenyl	bond	CH_2	2	2	CH_2	H	CH_3	base	104-106

Cpd	R_1	G	[A]m	n	o	B	R_2	R_3	Base or salt	M.P. (°C)
92.	3-(pyrimidin-2-yloxy)-phenyl	bond	CH_2	2	2	CH_2	H	CH_3	HCl (1/1)	196-200
93.	3-(4-Cl-phenyl)isoxazol-5-yl	bond	CH_2	2	2	CH_2	H	CH_3	base	148-150
94.	5-(4-Cl-phenyl)-1,3-oxazol-2-yl	bond	CH_2	2	2	CH_2	H	CH_3	base	143-145
95.	4-(4-CF_3-phenyl)-1,3-thiazol-2-yl	bond	CH_2	2	2	CH_2	H	CH_3	base	172-174
96.	5-(4-Cl-phenyl)isoxazol-3-yl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	165-167
97.	3-(4-Cl-phenyl)isoxazol-5-yl	bond	$(CH_2)_2$	2	2	CH_2	H	CH_3	base	146-148
98.	3-(4-Cl-phenyl)isoxazol-5-yl	bond	$(CH_2)_3$	2	2	CH_2	H	CH_3	base	134-136

Cpd	R_1	G	[A]m	n	o	B	R_2	R_3	Base or salt	M.P.(°C)
99.	5-(4-Cl-phenyliso-xazol-3-yl	bond	$(CH_2)_3$	2	2	CH_2	H	CH_3	base	160-162
100	(2-Cl,4-F)-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	108-110
101	(3-Cl,4-F)-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	112-114
102	(3-CN,5-F)-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	132-134
103	3-(4-F-phenyloxy)-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	79-81
104	3-(4-Cl-phenyl)iso-xazol-5-yl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	169-171
105	5-(4-Cl-phenyl)-1,3-oxazol-2-yl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	124-126
106	4-(4-CF_3-phenyl)-1,3-thiazol-2-yl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	161-163
107	(2-Cl,4-F)-phenyl	bond	$CH(CH_3)$	2	2	CH_2	H	CH_3	HCl (1/1)	386*

Cpd	R_1	G	[A]m	n	o	B	R_2	R_3	Base or salt	M.P. (°C)
108	3-(4-Cl-phenyloxy)-phenyl	bond	$CH(CH_3)$	2	2	CH_2	H	CH_3	HCl (1/1)	130-134
109	[2-Cl,3-(4-Cl-phenyl-oxy)]phenyl	bond	$CH(CH_3)$	2	2	CH_2	H	CH_3	base	115-119
110	3-CF_3O-phenyl	bond	$CH(CH_3)$	2	2	$(CH_2)_2$	H	CH_3	HCl (1/1)	169-171
111	(2-Cl,4-F)-phenyl	bond	$CH(CH_3)$	2	2	$(CH_2)_2$	H	CH_3	HCl (1/1)	400*
112	4-Cl-phenyl	bond	$C\equiv C-(CH_2)_2$	2	2	bond	H	CH_3	base	189-191
113	4-Cl-phenyl	bond	$C\equiv C-(CH_2)_3$	2	2	bond	H	CH_3	base	137-139
114	(2-Cl,5-Cl)-phenyl	bond	$C\equiv C-(CH_2)_3$	2	2	bond	H	CH_3	base	426*
115	(2-Cl,4-F)-phenyl	bond	$C\equiv C-(CH_2)_3$	2	2	bond	H	CH_3	base	410*
116	4-Cl-phenyl	bond	$C\equiv C-(CH_2)_2$	2	2	CH_2	H	CH_3	base	151-153
117	(2-Cl,3-Cl)-phenyl	O	$(CH_2)_2$	1	1	bond	H	CH_3	base	138-140
118	(2-F,4-Cl)-phenyl	bond	$C\equiv C-(CH_2)_2$	2	2	CH_2	H	CH_3	base	144-146
119	(2-Cl,5-Cl)-phenyl	bond	$C\equiv C-(CH_2)_2$	2	2	CH_2	H	CH_3	base	128-130

Cpd	R_1	G	[A]m	n	o	B	R_2	R_3	Base or salt	M.P. (°C)
120	3-(4-Cl-phenyl)iso-xazol-5-yl	bond	$(CH_2)_2$	2	2	$(CH_2)_2$	H	CH_3	base	135-137
121	3-t-BuO-phenyl	bond	CH_2	2	2	CH_2	H	CH_3	base	392*
122	3-t-BuO-phenyl	bond	CH_2	2	2	$(CH_2)_2$	H	CH_3	base	66-70

* M+H

The compounds of the invention were subjected to pharmacological tests allowing determination of their inhibitory effect on the enzyme FAAH (fatty acid amide hydrolase).

The inhibitory activity was demonstrated in a radioenzymatic assay based on measuring the product of hydrolysis ([1-^{3}H] ethanolamine) of anandamide [1-^{3}H ethanolamine] by FAAH (*Life Sciences (1995), 56, 1999-2005* and *Journal of Pharmacology and Experimental Therapeutics (1997), 283, 729-734*). Accordingly, mouse brains (minus the cerebellum) are removed and stored at -80°C. Membrane homogenates are prepared at the time of use by homogenizing the tissues in a Polytron in a 10 mM Tris-HCl buffer (pH 8.0) containing 150 mM NaCl and 1 mM EDTA. The enzymatic reaction is subsequently conducted in 70 μl of buffer containing bovine serum

albumin without fatty acids (1 mg/ml). In succession the test compounds, at various concentrations, anandamide [1-^{3}H ethanolamine] (specific activity: 15-20 Ci/mmol) diluted to 10 μM with cold anandamide, and the membrane preparation (400 μg of frozen tissue per assay) are added. After 15 minutes at 25°C, the enzymatic reaction is terminated by adding 140 μl of chloroform/methanol (2:1). The mixture is stirred for 10 minutes and then centrifuged for 15 minutes at 3500 g. An aliquot (30 μl) of the aqueous phase containing the ethanolamine [1-^{3}H] is counted by liquid scintillation.

Under these conditions the most active compounds of the invention exhibit IC_{50} values (concentration inhibiting by 50% the control enzymatic activity of FAAH) of between 0.001 and 1 μM.

Table 2 below presents the IC_{50} values of some compounds according to the invention.

Table 2

Compound	IC_{50}
25	0.225 μM
77	0.049 μM

It is therefore apparent that the compounds according to the invention have an inhibitory activity on the FAAH enzyme.

The *in vivo* activity of the compounds of the invention was evaluated in an analgesia test.

Accordingly, intraperitoneal (i.p.) administration of PBQ (phenylbenzoquinone, 2 mg/kg in a 0.9% sodium chloride solution containing 5% of ethanol) to male OF1 mice weighing 25 to 30 g causes abdominal stretches, on average 30 twists or contractions during the period from 5 to 15 minutes after injection. The test compounds are administered orally (p.o.) or intraperitoneally (i.p.) in suspension in Tween 80 at 0.5%, 60 minutes or 120 minutes before the administration of PBQ. Under these conditions the most potent compounds of the invention reduce by 35% to 70% the number of stretches induced by PBQ, within a dose range of between 1 and 30 mg/kg.

For example, compound 26 of the table reduces by 56% the number of stretches induced by PBQ, at a dose of 10 mg/kg p.o. at 120 minutes.

The enzyme FAAH (*Chemistry and Physics of Lipids,* (2000), 108, 107-121) catalyses the hydrolysis of endogenous derivatives of amides and of esters of various fatty acids such as *N*-arachidonoylethanolamine (anandamide), *N*-palmitoylethanolamine, *N*-oleoyl-ethanolamine, oleamide or 2-arachidonoylglycerol. These derivatives exert various pharmacological activities by interacting, inter alia, with cannabinoid and vanilloid receptors.

The compounds of the invention block this degradation pathway and increase the tissue level of

these endogenous substances. They can be used in this respect in the prevention and treatment of pathologies in which endogenous cannabinoids and/or any other substrates metabolized by the FAAH enzyme are involved.

Mention may be made, for example, of the following diseases and conditions:

pain, especially acute or chronic pain of neurogenic type: migraine, neuropathic pain, including forms associated with the herpes virus and with diabetes;

acute or chronic pain associated with inflammatory diseases: arthritis, rheumatoid arthritis, osteo-arthritis, spondylitis, gout, vasculitis, Crohn's disease, irritable bowel syndrome;

acute or chronic peripheral pain;

dizziness, vomiting, nausea, especially those subsequent to chemotherapy;

eating disorders, especially anorexia and cachexia of various kinds;

neurological and psychiatric pathologies: shaking, dyskinesia, dystonia, spasticity, obsessive-compulsive behaviours, Tourette's syndrome, all forms of depression and anxiety of any kind and cause, mood disorders, psychoses;

acute and chronic neurodegenerative diseases: Parkinson's disease, Alzheimer's disease, senile dementia, Huntington's chorea, lesions associated with cerebral ischemia and with cranial and medullary

trauma;

epilepsy;

sleep disorders, including sleep apnoea;

cardiovascular diseases, especially hypertension, cardiac arrhythmias, arteriosclerosis, heart attack, cardiac ischemias;

renal ischemia;

cancers: benign skin tumours, papillomas and brain tumours, prostate tumours, brain tumours (glioblastomas, medulloepitheliomas, medulloblastomas, neuroblastomas, tumours of embryonic origin, astrocytomas, astroblastomas, ependyomas, oligodendrogliomas, plexus tumour, neuroepitheliomas, epiphysial tumour, ependymoblastomas, malignant meningiomas, sarcomatoses, malignant melanomas, schwannomas);

disorders of the immune system, especially autoimmune diseases: psoriasis, lupus erythematosis, diseases of the connective tissue or collagen diseases, Sjögren's syndrome, ankylosing spondylarthritis, undifferentiated spondylarthritis, Behcet's disease, haemolytic autoimmune anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amyloses, transplant rejection, diseases affecting the plasmocytic line;

allergic diseases: immediate or delayed hypersensitivity, allergic rhinitis or conjunctivitis, contact dermatitis;

parasitic, viral or bacterial infectious diseases:

AIDS, meningitis; inflammatory diseases, especially diseases of the joints: arthritis, rheumatoid arthritis, osteoarthritis, spondylitis, gout, vasculitis, Crohn's disease, irritable bowel syndrome; osteoporosis; ocular conditions: ocular hypertension, glaucoma;
pulmonary conditions: diseases of the respiratory tract, bronchospasms, coughing, asthma, chronic bronchitis, chronic obstruction of the respiratory tract, emphysema;
gastrointestinal diseases: irritable bowel syndrome, intestinal inflammatory disorders, ulcers, diarrhoea; urinary incontinence and bladder inflammation.

The use of a compound of formula (I) in base, salt, hydrate or pharmaceutically acceptable solvate form for preparing a medicinal product intended for treating the abovementioned pathologies forms an integral part of the invention.

The invention likewise provides medicinal products which comprise a compound of formula (I), or a salt or else a hydrate or a pharmaceutically acceptable solvate of the compound of formula (I). These medicinal products are employed in therapy, particularly in the treatment of the abovementioned pathologies.

According to another of its aspects the present invention provides pharmaceutical compositions comprising as active principle at least one compound

according to the invention. These pharmaceutical compositions include an effective dose of a compound according to the invention, or a salt or a hydrate or a pharmaceutically acceptable solvate of the said compound, and, optionally, one or more pharmaceutically acceptable excipients.

The said excipients are selected, according to the pharmaceutical form and the desired mode of administration, from the customary excipients, which are known to the skilled person.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, local, intrathecal, intranasal, transdermal, pulmonary, ocular or rectal administration, the active principle of formula (I) above, or its salt, solvate or hydrate where appropriate, may be administered in a single-dose administration form, in a mixture with conventional pharmaceutical excipients, to animals and to humans for the prophylaxis or treatment of the above disorders or diseases.

The unit-dose administration forms which are appropriate include oral forms such as tablets, soft or hard gelatine capsules, powders, granules, chewing gums and oral solutions or suspensions, forms for sublingual, buccal, intratracheal, intraocular and intranasal administration, and for administration by

inhalation, forms for subcutaneous, intramuscular or intravenous administration and forms for rectal or vaginal administration. For topical application the compounds according to the invention may be used in creams, ointments or lotions.

By way of example a single-dose administration form of a compound according to the invention in tablet form may comprise the following components:

Compound according to the invention	50.0 mg
Mannitol	223.75 mg
Croscaramellose sodium	6.0 mg
Maize starch	15.0 mg
Hydroxypropyl-methylcellulose	2.25 mg
Magnesium stearate	3.0 mg

The said single-dose forms contain a dose permitting daily administration of 0.01 to 20 mg of active principle per kg of body weight, depending on the pharmaceutical form.

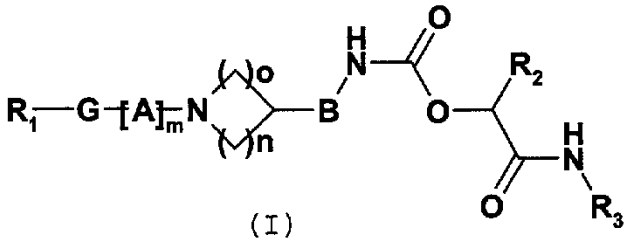
There may be particular cases in which higher or lower dosages are appropriate; such dosages also belong to the invention. In accordance with customary practice, the dosage appropriate to each patient is determined by the doctor according to the mode of administration, the weight and the response of the said patient.

According to another of its aspects the

invention also provides a method of treating the pathologies indicated above, which comprises administering an effective dose of a compound according to the invention, one of its pharmaceutically acceptable salts, a solvate or a hydrate of the said compound.

Claims

1. Compound of the formula (I)



(I)

in which

m represents an integer from 1 to 4;

n represents an integer 1, 2 or 3;

o an integer 1 or 2;

A is selected from one or more groups X, Y and/or Z;

X represents a methylene group optionally substituted by one or two C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene groups;

Y represents either a C_2 alkenylene group optionally substituted by one or two C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene groups, or a C_2 alkynylene group;

Z represents a group of formula:



p represents an integer from 1 to 5;

q and r represent integers and are defined such that r+q is a number from 1 to 5;

B represents a covalent bond or a C_{1-6} alkylene group;

G represents a covalent bond, an oxygen or sulphur atom or a -CH(OH)-, CO, SO or SO_2 group;

R_1 represents a group R_4 optionally substituted by one or more groups R_5 and/or R_6;

R_4 represents a group selected from a furanyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, thiadiazolyl, isothiadiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, naphthalenyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, imidazopyrimidinyl, thienopyrimidinyl, benzofuranyl, dihydrobenzofuranyl, benzothienyl, dihydrobenzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, indolyl, isoindolyl, indazolyl, pyrrolopyridinyl, furopyridinyl, dihydrofuropyridinyl, thienopyridinyl, dihydrothienopyridinyl, imidazopyridinyl, pyrazolopyridinyl, oxazolopyridinyl, isoxazolopyridinyl, thiazolopyridinyl;

R_5 represents a halogen atom, a cyano, nitro, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} thioalkyl, C_{1-6} fluoroalkyl, C_{1-6} fluoroalkoxy, C_{1-6} fluorothioalkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene group or a group NR_7R_8, NR_7COR_8, $NR_7CO_2R_8$, $NR_7SO_2R_8$, COR_7,

CO_2R_7, $CONR_7R_8$, SO_2R_7, $SO_2NR_7R_8$ or -O-(C_{1-3} alkylene)-O-;

R_6 represents a phenyl, phenyloxy, benzyloxy, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl or pyrimidinyloxy group; it being possible for the group or groups R_6 to be substituted by one or more groups R_5 identical to or different from one another;

R_7 and R_8 represent independently of one another a hydrogen atom or a C_{1-6} alkyl group, or, with the atom or atoms which carry them, form a ring selected from an azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine, azepine or piperazine ring, this ring being optionally substituted by a C_{1-6} alkyl or benzyl group;

R_2 represents a hydrogen atom or a C_{1-6} alkyl group;

R_3 represents a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene group;

in the form of a base, addition salt with an acid, hydrate or solvate.

2. Compound of formula (I) according to Claim 1, characterized in that:

m represents an integer from 1 to 4;

n represents an integer 1 or 2;

o an integer 1 or 2;

A is selected from one or more groups X and/or Y;

X represents a methylene group optionally

substituted by one or two C_{1-6} alkyl groups;

Y represents a C_2 alkynylene group;

B represents a covalent bond or a C_{1-6} alkylene group;

G represents a covalent bond or an oxygen atom;

R_1 represents a group R_4 optionally substituted by one or more groups R_5 and/or R_6;

R_4 represents a group selected from an oxazolyl, isoxazolyl, thiazolyl, phenyl, pyridinyl, naphthalenyl, quinolinyl, isoquinolinyl;

R_5 represents a halogen atom, a cyano group, a group NR_7R_8, or a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} fluoroalkyl group or a C_{1-6} fluoroalkoxy group;

R_6 represents a phenyl, phenyloxy or pyrimidinyloxy group; it being possible for the group or groups R_6 to be substituted by one or more groups R_5 identical to or different from one another;

R_7 and R_8 represent independently of one another a C_{1-6} alkyl group;

R_2 represents a hydrogen atom or a C_{1-6} alkyl group;

R_3 represents a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene group;

in the form of a base, addition salt with an acid, hydrate or solvate.

3. Compound of formula (I) according to Claim 1 or 2, characterized in that:

m represents an integer 1 or 2;

in the form of a base, addition salt with an acid,

hydrate or solvate.

4. Compound of formula (I) according to any one of Claims 1 to 3, characterized in that:

n is 2;

o is 2;

in the form of a base, addition salt with an acid, hydrate or solvate.

5. Compound of formula (I) according to any one of Claims 1 to 4, characterized in that:

R_1 represents a group R_4 optionally substituted by one or more groups R_5 and/or R_6;

R_4 represents a group selected from an oxazolyl, isoxazolyl, phenyl or naphthalenyl;

R_5 represents a halogen atom, a cyano group, a group NR_7R_8, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} fluoroalkyl group, or a C_{1-6} fluoroalkoxy group;

R_6 represents a phenyl, phenyloxy or pyrimidinyloxy group; it being possible for the group or groups R_6 to be substituted by one or more groups R_5 identical to or different from one another;

R_7 and R_8 represent independently of one another a C_{1-6} alkyl group;

in the form of a base, addition salt with an acid, hydrate or solvate.

6. Compound of formula (I) according to any one of Claims 1 to 5, characterized in that:

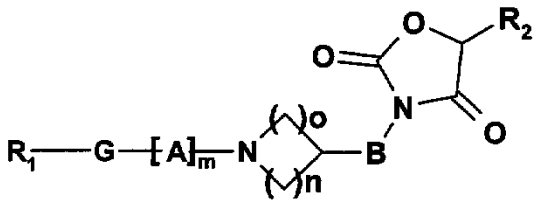
R_2 represents a hydrogen atom;

R_3 represents a hydrogen atom or a C_{1-6} alkyl group;

in the form of a base, addition salt with an acid, hydrate or solvate.

7. Process for preparing a compound of formula (I) according to any one of Claims 1 to 6, comprising the step consisting in

converting the oxazolidine-dione of general formula (IIa)



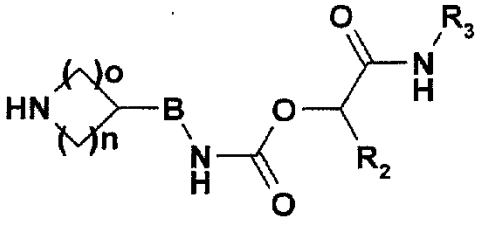
(IIa)

in which A, B, G, R_1, R_2, m, n and o are as defined in the formula (I) according to Claim 1

by aminolysis using an amine of general formula R_3NH_2 in which R_3 is as defined in the formula (I) according to Claim 1.

8. Process for preparing a compound of formula (I) according to any one of Claims 1 to 6, comprising the step consisting in

converting the carbamate-amide derivative of general formula (Ia)



(Ia)

in which B, R_2, R_3, n and o are as defined in the formula (I) according to Claim 1,

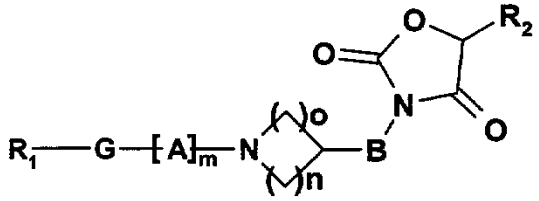
by reaction with a derivative of general formula (III)



(III)

in which W represents a mesylate or tosylate group or a chlorine, bromine or iodine atom and m, G, A and R_1 are as defined in the formula (I) according to Claim 1.

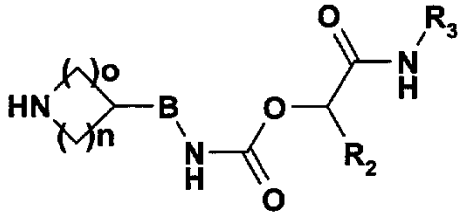
9. Compound of the general formula (IIa)



(IIa)

in which in which A, B, G, R_1, R_2, m, n and o are as defined in the formula (I) according to Claim 1, with the exception of 3-[1-(phenylmethyl)-4-piperidinyl]-2,4-oxazolidinedione.

10. Compound of the general formula (Ia)



(Ia)

in which B, R_2, R_3, n and o are as defined in the formula (I) according to Claim 1.

11. Pharmaceutical composition comprising at least one compound of formula (I) according to any one of Claims 1 to 6, in base, salt, hydrate or pharmaceutically acceptable solvate form, and, optionally, one or more pharmaceutically acceptable excipients.

12. Compound of formula (I) according to any one of Claims 1 to 6, in base, salt, hydrate or pharmaceutically acceptable solvate form, for its use as a medicinal product.

13. Use of a compound of formula (I) according to any one of Claims 1 to 6, in base, salt, hydrate or pharmaceutically acceptable solvate form, for preparing a medicinal product intended for preventing or treating a pathology in which endogenous cannabinoids and/or any other substances metabolized by the enzyme FAAH are involved.

14. Use of a compound of formula (I) according to any one of Claims 1 to 6, in base, salt, hydrate or pharmaceutically acceptable solvate form, for preparing a medicinal product intended for preventing or treating acute or chronic pain, dizziness, vomiting, nausea, eating disorders, neurological and psychiatric pathologies, acute or chronic neurodegenerative diseases, epilepsy, sleep disorders, cardiovascular diseases, renal ischemia, cancers, disorders of the immune system, allergic diseases, parasitic, viral or bacterial infectious diseases, inflammatory diseases, osteoporosis, ocular conditions, pulmonary conditions, gastrointestinal diseases or urinary incontinence.