

20

that $m + n$ is an integer ranging from 2 to 5;

p represents an integer ranging from 1 to 7;

A represents a single bond or is chosen from one or more groups X , Y and/or Z ;

5 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
10 C_{3-7} -cycloalkyl- C_{1-3} -alkylene groups; or a C_2 -alkynylene group;

Z represents a group of formula:



o represents an integer ranging from 1 to 5;

r and s represent integers and are defined such that

15 $r+s$ is a number ranging from 1 to 5;

R_1 represents an R_5 group optionally substituted by one or more R_6 and/or R_7 groups;

R_2 represents a hydrogen or fluorine atom or a hydroxyl, C_{1-6} -alkoxy or NR_8R_9 group;

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

R_4 represents a hydrogen atom or a C_{1-6} -alkyl, C_{3-7} -cycloalkyl or C_{3-7} -cycloalkyl- C_{1-3} -alkyl group;

R_5 represents a group chosen from a phenyl, pyridyl,
 pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl,
 pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl,
 thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl,
 5 oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl,
 naphthyl, quinolinyl, tetrahydroquinolinyl,
 isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl,
 quinoxalinyl, phthalazinyl, cinnolinyl, naphthyridinyl,
 benzofuranyl, dihydrobenzofuranyl, benzothienyl,
 10 dihydrobenzothienyl, indolyl, indolinyl, indazolyl,
 isoindolyl, benzimidazolyl, benzoxazolyl,
 benzisoxazolyl, benzothiazolyl, benzisothiazolyl,
 benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl,
 pyrrolOPYRIDYL, furoPYRIDYL, thienOPYRIDYL,
 15 imidazOPYRIDYL, oxazOPYRIDYL, thiazOPYRIDYL,
 pyrazOPYRIDYL, isoxazOPYRIDYL or
 isothiazOPYRIDYL;

R_6 represents a halogen atom or a cyano, nitro,
 C_{1-6} -alkyl, C_{3-7} -cycloalkyl, C_{1-6} -alkoxy, hydroxyl,
 20 C_{1-6} -thioalkyl, C_{1-6} -fluoroalkyl, C_{1-6} -fluoroalkoxy,
 C_{1-6} -fluorothioalkyl, NR_8R_9 , NR_8COR_9 , $NR_8CO_2R_9$, $NR_8SO_2R_9$,
 COR_8 , CO_2R_8 , $CONR_8R_9$, SO_2R_8 , $SO_2NR_8R_9$ or $-O-(C_{1-3}\text{-alkylene})-$
 $O-$ group or a ring chosen from the azetidine,
 pyrrolidine, piperidine, morpholine, thiomorpholine,

azepine or piperazine rings, this ring optionally being substituted by a C₁₋₆-alkyl or benzyl group;

R₇ represents a phenyl, phenyloxy, benzyloxy, naphthyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl group;

5 it being possible for the R₇ group or groups to be substituted by one or more R₆ groups which are identical to or different from one another;

R₈ and R₉ represent, independently of one another, a hydrogen atom or a C₁₋₆-alkyl group.

10 In the context of the invention, the compounds of general formula (I) can thus comprise several groups A which are identical to or different from one another.

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

m and n represent integers equal to 1 or 2 such that

m + n is an integer ranging from 2 to 4;

p represents an integer ranging from 1 to 3;

20 A represents a single bond or a methylene or C₂-alkynylene group;

R₁ represents an R₅ group optionally substituted by one or more R₆ and/or R₇ groups;

R₂ represents a hydrogen atom or a hydroxyl group;

- R_3 represents a hydrogen atom or a C_{1-6} -alkyl group;
- R_4 represents a hydrogen atom or a C_{1-6} -alkyl, C_{3-7} -cycloalkyl or C_{3-7} -cycloalkyl- C_{1-3} -alkyl group;
- R_5 represents a group chosen from a phenyl, pyridyl, pyrimidinyl, imidazolyl, thiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, naphthyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, indolinyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzotriazolyl or pyrrolopyridyl;
- R_6 represents a halogen atom, more particularly a bromine, a chlorine or a fluorine, or a cyano, C_{1-6} -alkyl, more particularly a methyl, a butyl or an isobutyl, C_{3-7} -cycloalkyl, more particularly a cyclopentyl, C_{1-6} -alkoxy, more particularly a methoxy or an ethoxy, or C_{1-6} -fluoroalkyl, more particularly a trifluoromethyl, group or a pyrrolidine or piperidine ring, this ring optionally being substituted by a C_{1-6} -alkyl group, more particularly an isopropyl;
- R_7 represents a phenyl group which can be substituted by one or more R_6 groups which are identical to or different from one another.

Among the compounds of general formula (I), a second subgroup of compounds is composed of the

compounds for which:

- m and n represent integers equal to 1 or 2 such that
 m + n is an integer ranging from 2 to 4;
 p represents an integer ranging from 1 to 3;
- 5 A represents a single bond or a methylene or C₂-alkynylene group;
- R₁ represents an R₅ group optionally substituted by one or more R₆ and/or R₇ groups;
- R₂ represents a hydrogen atom or a hydroxyl group;
- 10 R₃ represents a hydrogen atom or a C₁₋₆-alkyl group;
- R₄ represents a hydrogen atom or a C₁₋₆-alkyl, C₃₋₇-cycloalkyl or C₃₋₇-cycloalkyl-C₁₋₃-alkyl group;
- R₅ represents a group chosen from a phenyl, pyridyl, pyrimidinyl, thiazolyl, isoxazolyl, naphthyl or
- 15 isoquinolinyl;
- R₆ represents a halogen atom, more particularly a bromine, a chlorine or a fluorine, or a cyano, C₁₋₆-alkyl, more particularly a methyl, a butyl or an isobutyl, C₃₋₇-cycloalkyl, more particularly a
- 20 cyclopentyl, C₁₋₆-alkoxy, more particularly a methoxy or an ethoxy, or C₁₋₆-fluoroalkyl, more particularly a trifluoromethyl, group or a pyrrolidine or piperidine ring, this ring optionally being substituted by a C₁₋₆-alkyl group, more particularly an isopropyl;

R₇ represents a phenyl group which can be substituted by one or more R₆ groups which are identical to or different from one another.

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

m, n, p, A and R₁ are as defined in the first subgroup defined above;

R₃ represents a hydrogen atom;

10 R₄ represents a hydrogen atom or a C₁₋₆-alkyl group, more particularly a methyl.

Mention may be made, among the compounds of the subgroups defined above, of the following compounds:

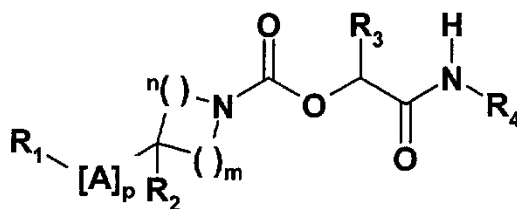
- 15 - 2-(methylamino)-2-oxoethyl 4-{5-[4-(trifluoromethyl)phenyl]pyrid-2-yl}piperidine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-(4'-chlorobiphenyl-4-yl)-4-hydroxypiperidine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-(4'-ethoxybiphenyl-4-yl)-4-hydroxypiperidine-1-carboxylate
- 20 - 2-(methylamino)-2-oxoethyl 4-(3',4'-dichlorobiphenyl-4-yl)-4-hydroxypiperidine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-(3'-chloro-4'-fluorobiphenyl-4-yl)-4-hydroxypiperidine-1-carboxylate

- 2-(methyamino)-2-oxoethyl 4-[(6-cyclopentylpyrid-2-yl)methyl]piperidine-1-carboxylate
- 2-(methyamino)-2-oxoethyl 4-[2-(3-chlorophenyl)ethyl]piperidine-1-carboxylate
- 5 - 2-(methyamino)-2-oxoethyl 4-[2-(4-chlorophenyl)ethyl]piperidine-1-carboxylate
- 2-(methyamino)-2-oxoethyl 4-{2-[3-(trifluoromethyl)phenyl]ethyl}piperidine-1-carboxylate
- 2-(methyamino)-2-oxoethyl 4-{2-[4-(trifluoromethyl)phenyl]ethyl}piperidine-1-carboxylate
- 10 - 2-(methyamino)-2-oxoethyl 4-(2-(biphenyl-3-yl)ethyl)-piperidine-1-carboxylate
- 2-(methyamino)-2-oxoethyl 4-[2-(1-naphthyl)ethyl]piperidine-1-carboxylate
- 15 - 2-(methyamino)-2-oxoethyl 4-[2-(2-naphthyl)ethyl]piperidine-1-carboxylate
- 2-(methyamino)-2-oxoethyl 4-[2-(6-cyclopentylpyrid-2-yl)ethyl]piperidine-1-carboxylate
- 2-(methyamino)-2-oxoethyl 4-[2-(6-(pyrrolidin-1-yl)pyrid-2-yl)ethyl]piperidine-1-carboxylate
- 20 - 2-(methyamino)-2-oxoethyl 4-(2-(isoquinolin-1-yl)ethyl)piperidine-1-carboxylate
- 2-(methyamino)-2-oxoethyl 4-[3-(3-chlorophenyl)propyl]piperidine-1-carboxylate

- 2-(methylamino)-2-oxoethyl 4-[3-(4-chloro-phenyl)propyl]piperidine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-{3-[3-(trifluoro-methyl)phenyl]propyl}piperidine-1-carboxylate
- 5 - 2-(methylamino)-2-oxoethyl 4-{3-[4-(trifluoro-methyl)phenyl]propyl}piperidine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(3-cyano-phenyl)propyl]piperidine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-(3-(biphenyl-2-yl)propyl)piperidine-1-carboxylate
- 10 - 2-(methylamino)-2-oxoethyl 4-(3-(biphenyl-3-yl)propyl)piperidine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(1-naphthyl)-propyl]piperidine-1-carboxylate
- 15 - 2-(methylamino)-2-oxoethyl 4-[3-(2-naphthyl)-propyl]piperidine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(1,3-thiazol-2-yl)propyl]piperidine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[(3-chloro-phenyl)ethynyl]piperidine-1-carboxylate
- 20 - 2-(methylamino)-2-oxoethyl 4-[(4-chloro-phenyl)ethynyl]piperidine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-(biphenyl-3-ylethynyl)piperidine-1-carboxylate

- 2-(methylamino)-2-oxoethyl 4-(1-naphthylethynyl)-piperidine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-(2-naphthylethynyl)-piperidine-1-carboxylate
- 5 - 2-(methylamino)-2-oxoethyl 4-(3-(biphenyl-2-yl)prop-2-yn-1-yl)piperidine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[(6-(pyrrolidin-1-yl)pyrid-2-yl)methyl]piperidine-1-carboxylate

Among the compounds of general formula (I),
 10 one subfamily of compounds is composed of the compounds corresponding to the general formula (I'):



(I')

15 in which

- m and n represent integers ranging from 1 to 3 such that m + n is an integer ranging from 2 to 5;
- p represents an integer ranging from 1 to 7;
- A represents a single bond or is chosen from one or
- 20 more groups X, Y and/or Z;
- X represents a methylene group optionally substituted by one or two C₁₋₆-alkyl, C₃₋₇-cycloalkyl or C₃₋₇-

cycloalkyl-C₁₋₃-alkylene groups;

Y represents either a C₂-alkenylene group optionally substituted by one or two C₁₋₆-alkyl, C₃₋₇-cycloalkyl or C₃₋₇-cycloalkyl-C₁₋₃-alkylene groups; or a C₂-alkynylene

5 group;

Z represents a group of formula:



o represents an integer ranging from 1 to 5;

r and s represent integers and are defined such that

r+s is a number ranging from 1 to 5;

10 R₁ represents an R₅ group optionally substituted by one or more R₆ and/or R₇ groups;

R₂ represents a hydrogen or fluorine atom or a hydroxyl, C₁₋₆-alkoxy or NR₈R₉ group;

R₃ represents a hydrogen atom or a C₁₋₆-alkyl group;

15 R₄ represents a hydrogen atom or a C₁₋₆-alkyl, C₃₋₇-cycloalkyl or C₃₋₇-cycloalkyl-C₁₋₃-alkyl group;

R₅ represents a group chosen from a phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl,

20 thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, naphthyl, quinolinyl, tetrahydroquinolinyl,

- isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl,
 quinoxalinyl, phthalazinyl, cinnolinyl, naphthyridinyl,
 benzofuranyl, dihydrobenzofuranyl, benzothienyl,
 dihydrobenzothienyl, indolyl, indolinyl, indazolyl,
 5 isoindolyl, benzimidazolyl, benzoxazolyl,
 benzisoxazolyl, benzothiazolyl, benzisothiazolyl,
 benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl,
 pyrrolopyridyl, furopyridyl, thienopyridyl,
 imidazopyridyl, oxazolopyridyl, thiazolopyridyl,
 10 pyrazolopyridyl, isoxazolopyridyl or
 isothiazolopyridyl;

- R_6 represents a halogen atom or a cyano, nitro, C_{1-6} -
 alkyl, C_{1-6} -alkoxy, hydroxyl, C_{1-6} -thioalkyl, C_{1-6} -
 fluoroalkyl, C_{1-6} -fluoroalkoxy, C_{1-6} -fluorothioalkyl,
 15 NR_8R_9 , NR_8COR_9 , $NR_8CO_2R_9$, $NR_8SO_2R_9$, COR_8 , CO_2R_8 , $CONR_8R_9$,
 SO_2R_8 , $SO_2NR_8R_9$ or $-O-(C_{1-3}\text{-alkylene})-O-$ group;

- R_7 represents a phenyl, phenyloxy, benzyloxy, naphthyl,
 pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl group;
 it being possible for the R_7 group or groups to be
 20 substituted by one or more R_6 groups which are identical
 to or different from one another;

R_8 and R_9 represent, independently of one another, a
 hydrogen atom or a C_{1-6} -alkyl group or form, with the
 atom or atoms which carry them, a ring chosen from an

azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine, azepine or piperazine ring optionally substituted by a C₁₋₆-alkyl or benzyl group.

- Among the compounds of general formula (I'),
- 5 a first subgroup of compounds is composed of the compounds for which:
- m and n represent integers equal to 1 or 2 such that m + n is an integer ranging from 2 to 4;
- p represents an integer equal to 1 or 2;
- 10 A represents a single bond or a methylene group;
- R₁ represents an R₅ group optionally substituted by one or more R₆ and/or R₇ groups;
- R₂ represents a hydrogen or fluorine atom or a hydroxyl, C₁₋₆-alkoxy or NR₈R₉ group;
- 15 R₃ represents a hydrogen atom or a C₁₋₆-alkyl group;
- R₄ represents a hydrogen atom or a C₁₋₆-alkyl, C₃₋₇-cycloalkyl or C₃₋₇-cycloalkyl-C₁₋₃-alkyl group;
- R₅ represents a group chosen from a phenyl, imidazolyl, naphthyl, tetrahydroquinoliny, tetrahydroiso-
- 20 quinoliny, indolyl, indoliny, benzimidazolyl, benzotriazolyl or pyrrolopyridyl;
- R₆ represents a halogen atom, more particularly a bromine, a chlorine or a fluorine, or a C₁₋₆-alkyl, more particularly a methyl or a butyl, C₁₋₆-alkoxy, more

particularly a methoxy or an ethoxy, or C₁₋₆-fluoroalkyl, more particularly a trifluoromethyl, group;

R₇ represents a phenyl group which can be substituted by
5 one or more R₆ groups which are identical to or different from one another.

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

10 m, n, p, A and R₁ are as defined in the first subgroup defined above;

R₃ represents a hydrogen atom;

R₄ represents a hydrogen atom or a C₁₋₆-alkyl group, more particularly a methyl.

15 Mention may be made, among the compounds of general formula (I'), of the following compounds:

- 2-amino-2-oxoethyl 4-phenylpiperidine-1-carboxylate;
- 2-(methylamino)-2-oxoethyl 4-phenylpiperidine-1-carboxylate;
- 20 - 2-amino-2-oxoethyl 4-[3-(trifluoromethyl)-phenyl]piperidine-1-carboxylate;
- 2-(methylamino)-2-oxoethyl 4-[3-(trifluoromethyl)phenyl]piperidine-1-carboxylate;
- 2-(methylamino)-2-oxoethyl 4-(4-phenyl-1H-imidazol-1-

- yl)piperidine-1-carboxylate;
- 2-(methylamino)-2-oxoethyl 4-(1H-1,2,3-benzotriazol-1-yl)piperidine-1-carboxylate;
- 2-(methylamino)-2-oxoethyl 4-(4-bromophenyl)-4-
- 5 hydroxypiperidine-1-carboxylate;
- 2-(methylamino)-2-oxoethyl 4-(4'-fluorobiphenyl-4-yl)-4-hydroxypiperidine-1-carboxylate;
- 2-(methylamino)-2-oxoethyl 4-(4'-chlorobiphenyl-4-yl)-4-hydroxypiperidine-1-carboxylate;
- 10 - 2-(methylamino)-2-oxoethyl 4-hydroxy-4-(4'-methylbiphenyl-4-yl)piperidine-1-carboxylate;
- 2-(methylamino)-2-oxoethyl 4-(4'-butylbiphenyl-4-yl)-4-hydroxypiperidine-1-carboxylate;
- 2-(methylamino)-2-oxoethyl 4-hydroxy-4-[4'-(trifluoromethyl)biphenyl-4-yl]piperidine-1-
- 15 carboxylate;
- 2-(methylamino)-2-oxoethyl 4-hydroxy-4-[4'-(methyloxy)biphenyl-4-yl]piperidine-1-carboxylate;
- 2-(methylamino)-2-oxoethyl 4-[4'-(ethyloxy)biphenyl-
- 20 4-yl]-4-hydroxypiperidine-1-carboxylate;
- 2-(methylamino)-2-oxoethyl 4-(3',4'-dichlorobiphenyl-4-yl)-4-hydroxypiperidine-1-carboxylate;
- 2-(methylamino)-2-oxoethyl 4-[3'-fluoro-4'-(methyloxy)biphenyl-4-yl]-4-hydroxypiperidine-1-

carboxylate;

- 2-(methylamino)-2-oxoethyl 4-(3'-chloro-4'-fluoro-biphenyl-4-yl)-4-hydroxypiperidine-1-carboxylate;

- 2-(methylamino)-2-oxoethyl 4-(naphth-2-ylmethyl)-

5 piperidine-1-carboxylate;

- 2-(methylamino)-2-oxoethyl 4-(biphenyl-4-ylmethyl)piperidine-1-carboxylate;

- 2-amino-2-oxoethyl 4-(1H-indol-1-ylmethyl)piperidine-1-carboxylate;

10 - 2-amino-2-oxoethyl 4-(2,3-dihydro-1H-indol-1-ylmethyl)piperidine-1-carboxylate;

- 2-amino-2-oxoethyl 4-(3,4-dihydroquinolin-1(2H)-ylmethyl)piperidine-1-carboxylate;

- 2-amino-2-oxoethyl 4-(3,4-dihydroisoquinolin-2(1H)-

15 ylmethyl)piperidine-1-carboxylate;

- 2-amino-2-oxoethyle 4-(1H-pyrrolo[2,3-b]pyrid-1-ylmethyl)piperidine-1-carboxylate;

- 2-amino-2-oxoethyl 4-(1H-benzimidazol-1-ylmethyl)piperidine-1-carboxylate;

20 - 2-amino-2-oxoethyl 4-[(4-phenyl-1H-imidazol-1-yl)methyl]piperidine-1-carboxylate;

- 2-amino-2-oxoethyl 3-(2-phenylethyl)pyrrolidine-1-carboxylate;

- 2-amino-2-oxoethyl 4-[2-(3,4-dihydroquinolin-1(2H)-

- yl)ethyl]piperidine-1-carboxylate;
- 2-amino-2-oxoethyl 4-[2-(3,4-dihydroisoquinolin-2(1H)-yl)ethyl]piperidine-1-carboxylate;
 - 2-amino-2-oxoethyl 4-[2-(1H-indol-1-yl)ethyl]-
- 5 piperidine-1-carboxylate;
- 2-amino-2-oxoethyl 4-[2-(2,3-dihydro-1H-indol-1-yl)ethyl]piperidine-1-carboxylate;
 - 2-amino-2-oxoethyl 4-[2-(1H-pyrrolo[2,3-b]pyrid-1-yl)ethyl]piperidine-1-carboxylate;
- 10 - 2-amino-2-oxoethyl 4-[2-(1H-benzimidazol-1-yl)ethyl]piperidine-1-carboxylate;
- 2-amino-2-oxoethyl 4-[2-(4-phenyl-1H-imidazol-1-yl)ethyl]piperidine-1-carboxylate.

The compounds of general formula (I) can

15 comprise one or more asymmetric carbons. They can exist in the form of enantiomers or of diastereoisomers. These enantiomers and diastereoisomers, and their mixtures, including the racemic mixtures, form part of the invention.

20 The compounds of formula (I) can 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 but the salts of

other acids, of use, for example, in the purification or the isolation of the compounds of formula (I), also form part of the invention. The compounds of general formula (I) can exist in the form of hydrates or of
5 solvates, namely in the form of combinations or of associations with one or more molecules of water or with a solvent. Such hydrates and solvates also form part of the invention.

In the context of the invention:

- 10 - C_{t-z} , where t and z can take the values from 1 to 7, is understood to mean a carbon chain which can have from t to z carbon atoms, for example C_{1-3} a carbon chain which can have from 1 to 3 carbon atoms;
- 15 - alkyl is understood to mean 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,
20 butyl, isobutyl, tert-butyl, pentyl or hexyl;
- alkylene is understood to mean 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-methylethylene or propylene;

- cycloalkyl is understood to mean a cyclic alkyl group, for example a C₃₋₇-cycloalkyl group
5 represents a cyclic carbon group of 3 to 7 carbon atoms, more particularly a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

- alkenylene is understood to mean an
10 unsaturated divalent aliphatic group comprising 2 carbons, more particularly an ethylene;

- C₂-alkynylene is understood to mean a -C≡C- group;

- alkoxy is understood to mean an -O-alkyl
15 group comprising a saturated, linear or branched, aliphatic chain;

- thioalkyl is understood to mean an -S-alkyl group comprising a saturated, linear or branched, aliphatic chain;

20 - fluoroalkyl is understood to mean an alkyl group, one or more hydrogen atoms of which have been substituted by a fluorine atom;

- fluoroalkoxy is understood to mean an alkoxy group, one or more hydrogen atoms of which have

been substituted by a fluorine atom;

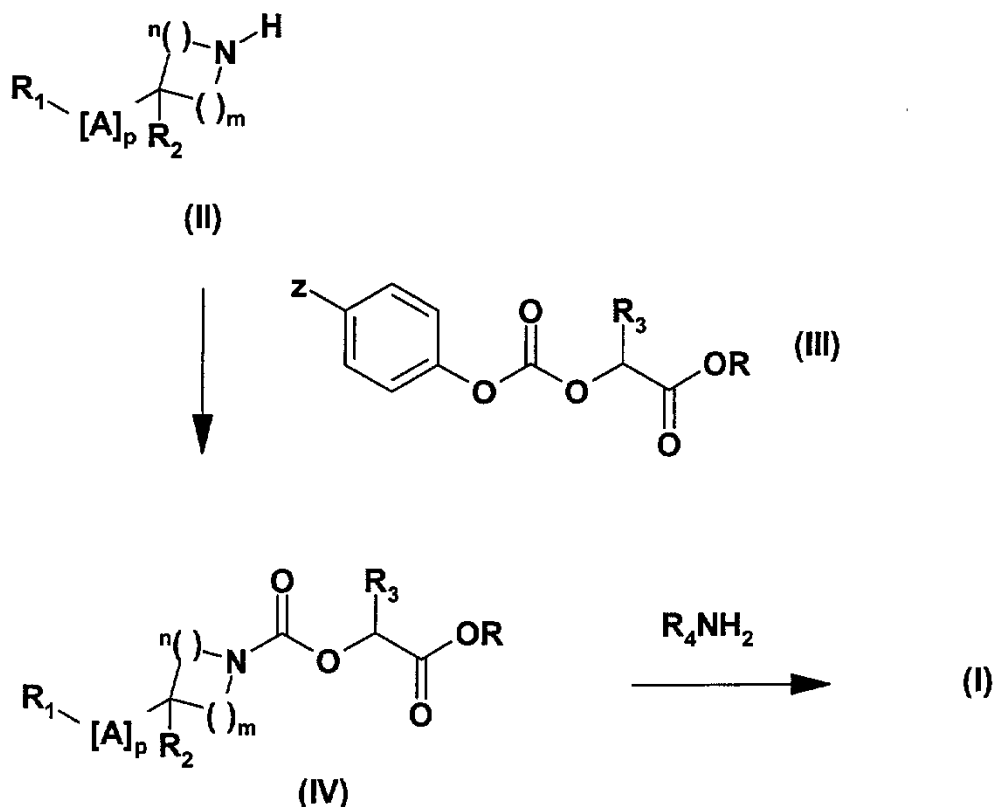
- fluorothioalkyl is understood to mean a thioalkyl group, one or more hydrogen atoms of which have been substituted by a fluorine atom;

5 - halogen atom is understood to mean a fluorine, a chlorine, a bromine or an iodine.

The compounds of the invention can be prepared according to the method illustrated by the following scheme.

10

Scheme



The compounds of the invention can be prepared by reacting an amine of general formula (II),

15 in which R_1 , A , R_2 , p , m and n are as defined in the

general formula (II), with a carbonate of general formula (III), in which Z represents a hydrogen atom or a nitro group, R_3 is as defined in the general formula (I) and R represents a methyl or ethyl group, in a
5 solvent, such as toluene, dichloroethane, acetonitrile or a mixture of these solvents, at a temperature of between 0°C and 80°C. The carbamate-esters of general formula (IV) thus obtained are subsequently converted to compounds of general formula (I) by aminolysis using
10 an amine of general formula R_4NH_2 , where R_4 is as defined in the general formula (I). The aminolysis reaction can be carried out in a solvent, such as methanol or ethanol, or a mixture of solvents, such as methanol and tetrahydrofuran.

15 The compounds of general formula (I) or (IV) in which R_1 represents a group of aryl-aryl, aryl-heteroaryl, heteroaryl-aryl or heteroaryl-heteroaryl type can also be prepared by reaction of the corresponding compounds of general formula (I) or (IV)
20 for which R_5 is substituted by a chlorine, bromine or iodine atom or by a triflate group in the position where the R_7 group has to be introduced with an aryl- or heteroarylboronic acid derivative according to the Suzuki reaction conditions (Chem. Rev., 1995, 95, 2457-

2483) or with an aryl- or heteroaryltrialkylstannane derivative according to the Stille reaction conditions (Angew. Chem. Int. Ed., 1986, 25, 504-524).

The carbonates of general formula (III) can
5 be prepared according to any method described in the literature, for example by reaction of an alcohol of general formula $\text{HOCHR}_3\text{COOR}$, where R represents a methyl or ethyl group, with phenyl or 4-nitrophenyl chloroformate in the presence of a base, such as
10 triethylamine or diisopropylethylamine.

The compounds of general formula (II) and the amines of general formula R_4NH_2 , when their method of preparation is not described, are commercially available or are described in the literature or can be
15 prepared according to various methods described in the literature or known to a person skilled in the art.

The compounds of general formula (IV) in which R_1 , A, R_2 , R_3 , p, m and n are as defined in the general formula (I) and R represents a methyl or ethyl
20 group are novel and also form part of the invention. They are of use as synthetic intermediates in the preparation of the compounds of general formula (I).

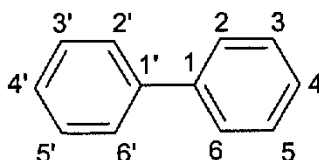
The examples which will follow illustrate the preparation of a few compounds of the invention. These

examples are not limiting and only 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
 5 of the compounds obtained.

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

The numbers shown in brackets in the titles of the examples correspond to those in the 1st column in the
 10 table below.

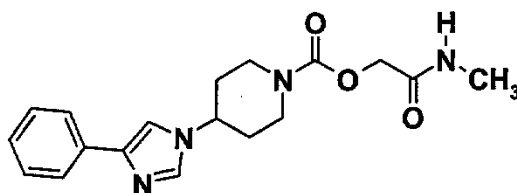
The IUPAC nomenclature was used to name the compounds in the following examples. For example, for the biphenyl group, the following notation was observed:



15

Example 1 (compound No. 14)

2-(Methylamino)-2-oxoethyl 4-(4-phenyl-1H-imidazol-1-yl)piperidine-1-carboxylate



20

1.1. 1,1-Dimethylethyl 4-[(methylsulphonyl)oxy]-

piperidine-1-carboxylate

1.4 ml (17.9 mmol) of methanesulphonyl chloride are added dropwise with stirring to a solution, cooled with an ice bath, of 3.0 g (14.9 mmol) of 1,1-dimethylethyl 4-hydroxypiperidine-1-carboxylate and of 2.2 ml (17.9 mmol) of triethylamine in 60 ml of dichloromethane. Stirring is continued at 0°C for one hour and then at ambient temperature for 4 hours. The reaction mixture is diluted with 100 ml of dichloromethane and is washed successively with 100 ml of an aqueous sodium hydrogencarbonate solution, with a saturated aqueous ammonium chloride solution and then with a saturated aqueous sodium chloride solution. The organic phase is dried over sodium sulphate and evaporated to dryness. The residue is subsequently triturated from a 50/50 mixture of cyclohexane and of diethyl ether to produce 3.7 g of product in the form of a white solid.

1.2. 1,1-Dimethylethyl 4-(4-phenyl-1*H*-imidazol-1-yl)-piperidine-1-carboxylate

A solution of 4.0 g (27.9 mmol) of 4-phenyl-imidazole in 40 ml of *N,N*-dimethylformamide is added dropwise to a suspension, cooled with an ice bath, of

1.1 g (27.9 mmol) of sodium hydride (60% suspension in oil) in 30 ml of *N,N*-dimethylformamide. The mixture is subsequently stirred at ambient temperature for one hour, is then cooled to 0°C and 2.6 g (9.3 mmol) of 1,1-dimethylethyl 4-[(methylsulphonyl)oxy]piperidine-1-carboxylate, obtained in stage 1.1., in solution in 20 ml of *N,N*-dimethylformamide, are added dropwise. The reaction mixture is subsequently heated at 80°C for 2 hours. It is cooled to ambient temperature and diluted with 150 ml of water and 150 ml of ethyl acetate. Separation by settling is carried out and the aqueous phase is extracted twice with 100 ml of ethyl acetate. The organic phases are washed with two times 100 ml of water and then with 100 ml of a saturated aqueous sodium chloride solution. They are dried over sodium sulphate and evaporated to dryness. The residue is purified by chromatography on silica gel, elution being carried out with a 98/2 mixture of dichloromethane and of methanol, to produce 1.0 g of product in the form of a yellow oil.

1.3. 4-(4-Phenyl-1*H*-imidazol-1-yl)piperidine

5.6 ml (76.3 mmol) of trifluoroacetic acid are added dropwise to a solution, cooled with an ice

bath, of 1.0 g (3.05 mmol) of 1,1-dimethylethyl
4-(4-phenyl-1*H*-imidazol-1-yl)piperidine-1-carboxylate,
obtained in stage 1.2., in 60 ml of dichloromethane.

The mixture is subsequently stirred at ambient

5 temperature for one hour and is evaporated to dryness.

The residue is taken up in 25 ml of water, and 2 ml of
a 30% aqueous sodium hydroxide solution are added. The
mixture is stirred for 30 minutes and is then extracted
four times with 80 ml of dichloromethane. The organic
10 phases are subsequently washed with a saturated aqueous
sodium chloride solution, dried over sodium sulphate
and evaporated to dryness to produce 0.7 g of product
in the form of a yellow oil used as is in the following
stage.

15

1.4. 2-(Ethyloxy)-2-oxoethyl 4-(4-phenyl-1*H*-imidazol-1-
yl)piperidine-1-carboxylate

A solution of 1.0 g (4.4 mmol) of 4-(4-
phenyl-1*H*-imidazol-1-yl)piperidine, prepared according
20 to stage 1.3., and of 1.18 g (5.2 mmol) of ethyl
[(phenyloxycarbonyl)oxy]acetate (J. Med. Chem., 1999,
42, 277-290) in 50 ml of toluene is heated at 60°C
overnight. The mixture is subsequently evaporated to
dryness and the residue is taken up in 80 ml of ethyl

acetate and 80 ml of water. Separation by settling is carried out and the aqueous phase is extracted with three times 80 ml of ethyl acetate. The organic phases are subsequently washed with 80 ml of a saturated aqueous sodium chloride solution. They are dried over sodium sulphate and evaporated to dryness. The residue is purified by chromatography on silica gel, elution being carried out with a 98/2 mixture of dichloromethane and of methanol, to produce 0.35 g of product.

1.5. 2-(Methylamino)-2-oxoethyl 4-(4-phenyl-1H-imidazol-1-yl)piperidine-1-carboxylate

0.35 g (0.98 mmol) of 2-(ethyloxy)-2-oxoethyl 4-(4-phenyl-1H-imidazol-1-yl)piperidine-1-carboxylate, obtained in stage 1.4., is dissolved in 7 ml of methanol. 1.5 ml (3 mmol) of a 2M solution of methylamine in tetrahydrofuran are added. After 16 hours at ambient temperature, a further 1 ml (2 mmol) of a 2M solution of methylamine in tetrahydrofuran is added and reaction is allowed to take place for an additional 6 hours. The mixture is evaporated to dryness and the residue is purified by chromatography on silica gel, elution being carried out with a 98/2

then 97/3, 96/4 and 95/5 mixture of dichloromethane and of methanol. Trituration is subsequently carried out from diethyl ether to produce 0.20 g of product in the form of a white solid.

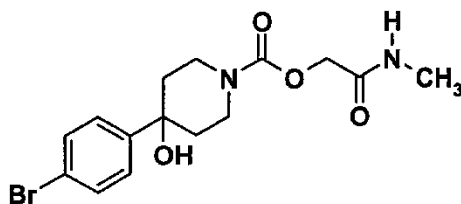
5 Melting point ($^{\circ}\text{C}$): 192-194

LC-MS : $\text{M}+\text{H} = 343$

^1H NMR (CDCl_3) δ (ppm) : 7.75 (d, 2H), 7.60 (s, 1H),
7.40 (m, 2H), 7.25 (m, 2H), 6.05 (broad s, 1H), 4.65
(s, 2H), 4.35 (m, 2H), 4.15 (m, 1H), 3.05 (m, 2H), 2.90
10 (d, 3H), 2.20 (m, 2H), 2.05-1.85 (m, 2H).

Example 2 (compound No. 32)

**2-(Methylamino)-2-oxoethyl 4-(4-bromophenyl)-4-hydroxy-
piperidine-1-carboxylate**



15

2.1. 2-(Ethoxy)-2-oxoethyl 4-(4-bromophenyl)-4-hydroxypiperidine-1-carboxylate

A mixture of 2.24 g (10 mmol) of ethyl [(phenyloxycarbonyl)oxy]acetate and 2.56 g (10 mmol) of
20 4-(4-bromophenyl)-4-piperidinol in solution in 40 ml of toluene is heated at 50°C for 20 hours. The solution is evaporated to dryness on a water bath under reduced

pressure. An oil is obtained and is used directly in the following stage.

2.2. 2-(Methylamino)-2-oxoethyl 4-(4-bromophenyl)-4-hydroxypiperidine-1-carboxylate

The 2-(ethyloxy)-2-oxyethyl 4-(4-bromophenyl)-4-hydroxypiperidine-1-carboxylate obtained in stage 2.1. is stirred for 3 hours in a 33% solution of methylamine in methanol. The solution is concentrated on a water bath under reduced pressure. The residue is purified by chromatography on silica gel, elution being carried out with ethyl acetate. 2.6 g of product are obtained in the form of an oil which gradually solidifies.

Melting point (°C): 57-60

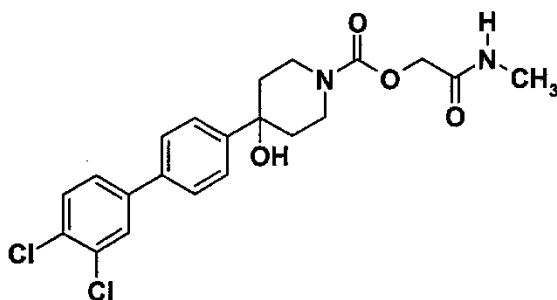
LC-MS : M+H = 371

¹H NMR (d₆-DMSO) δ (ppm) : 7.55 (broad s, 1H), 7.50 (d, 2H), 7.40 (d, 2H), 5.20 (s, 1H), 4.40 (s, 2H), 3.80 (m, 2H), 3.20 (m, 2H), 2.60 (d, 3H), 1.90-1.50 (m, 4H).

20

Example 3 (compound No. 40)

2-(Methylamino)-2-oxoethyl 4-(3',4'-dichlorobiphenyl-4-yl)-4-hydroxypiperidine-1-carboxylate



0.1 g (0.27 mmol) of 2-(methoxycarbonylmethylamino)-2-oxoethyl 4-(4-bromophenyl)-4-hydroxypiperidine-1-carboxylate, obtained according to Example 2, 0.077 g
 5 (0.4 mmol) of 3,4-dichlorophenylboronic acid, 10 mg of tetrakis(triphenylphosphine)palladium(0), 2 ml of 2M aqueous sodium carbonate solution, 0.5 ml of ethanol and 4 ml of toluene degassed beforehand with nitrogen are mixed. The mixture is heated at 80°C with stirring
 10 for 20 hours. It is filtered under hot conditions through a hydrophobic cartridge, rinsing is carried out with tetrahydrofuran (THF) and evaporation to dryness is carried out. The residue is purified by LC-MS chromatography on a silica phase, elution being carried
 15 out with a cyclohexane/ethyl acetate/methanol gradient, to produce 0.069 g of crystalline product.

Melting point (°C) : 156-158

LC-MS : M+H = 438

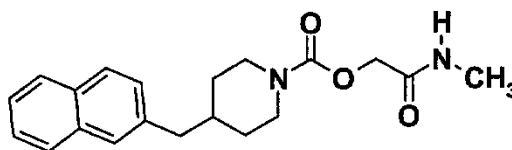
¹H NMR (d₆-DMSO) δ (ppm): 7.95 (s, 1H), 7.80 (m, 1H),
 20 7.70 (m, 4H), 7.60 (m, 2H), 5.20 (s, 1H), 4.45 (s, 2H), 4.00 (m, 2H), 3.25 (m, 2H), 2.60 (d, 3H), 1.95 (m, 2H),

1.65 (m, 2H).

Example 4 (compound No. 43)

2-(Methylamino)-2-oxoethyl 4-(naphth-2-ylmethyl)-

5 piperidine-1-carboxylate



4.1. 1,1-Dimethylethyl 4-(naphth-2-ylmethyl)piperidine-1-carboxylate

10 8.0 ml of a 0.5N solution (4 mmol) of 9-bora-bicyclo[3.3.1]nonane in tetrahydrofuran are added under an argon atmosphere to a solution of 0.789 g (4 mmol) of 1,1-dimethylethyl 4-methylidenepiperidine-1-carboxylate (Tetrahedron Letters, 1996, 37(30), 5233-15 5234) in solution in 5 ml of tetrahydrofuran. The mixture is heated at reflux for 3 hours. It is cooled to ambient temperature and 0.787 g (3,8 mmol) of 2-bromonaphthalene in solution in 9 ml of *N,N*-dimethylformamide, 0.829 g (6.0 mmol) of potassium carbonate in solution in 1 ml of water and 0.16 g 20 (0.20 mmol) of the [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)-dichloromethane complex are added. The mixture is

heated at reflux overnight. The reaction mixture is diluted with 150 ml of ethyl acetate and 50 ml of water. The organic phase is separated by settling and is washed with 25 ml of water and then with 25 ml of a saturated aqueous sodium chloride solution. It is dried over magnesium sulphate and evaporated under vacuum. The residue is purified by chromatography on silica gel, elution being carried out with a 99/1 then 95/5 and 90/10 mixture of cyclohexane and of ethyl acetate, to produce 0.79 g of product in the form of a colourless viscous liquid.

4.2. 4-(Naphth-2-ylmethyl)piperidine

0.79 g (2.43 mmol) of 1,1-dimethylethyl 4-(naphth-2-ylmethyl)piperidine-1-carboxylate, obtained in stage 4.1., is dissolved in 10 ml of dichloromethane, and 2 ml (25 mmol) of trifluoroacetic acid are added. The mixture is stirred at ambient temperature for 3 hours. It is evaporated under reduced pressure, then 4 ml of 1,2-dichloroethane are added and the mixture is again evaporated. The residue is taken up in a mixture of 50 ml of dichloromethane and of 15 ml of a 10% aqueous sodium hydroxide solution. The organic phase is separated by settling and the aqueous

phase is extracted twice with 25 ml of dichloromethane. The organic phases are washed with 15 ml of a saturated aqueous sodium chloride solution, then dried over sodium sulphate and evaporated under vacuum to provide
5 0.52 g of product in the form of an orange oil used as is in the following stage.

4.3. 2-(Ethoxy)-2-oxoethyl 4-(naphth-2-ylmethyl)-
piperidine-1-carboxylate

10 A mixture of 0.52 g (2.3 mmol) of 4-(naphth-2-ylmethyl)piperidine, obtained in stage 4.2., and of 0.69 g (3.11 mmol) of ethyl [(phenyloxycarbonyl)oxy]acetate in 10 ml of toluene and 5 ml of acetonitrile is heated at 60°C overnight. The
15 mixture is evaporated under vacuum. The residue is purified by chromatography on silica gel, elution being carried out with a 90/10 then 85/15 and 80/20 mixture of cyclohexane and of ethyl acetate, to produce 0.56 g of product in the form of a colourless viscous liquid.

20

4.4. 2-(Methylamino)-2-oxoethyl 4-(naphth-2-ylmethyl)-
piperidine-1-carboxylate

0.54 g (1.52 mmol) of 2-(ethoxy)-2-oxoethyl
4-(naphth-2-ylmethyl)piperidine-1-carboxylate, obtained

in stage 4.3., is dissolved in 3 ml of methanol, and
 3 ml (6.0 mmol) of a 2M solution of methylamine in
 tetrahydrofuran are added. Reaction is allowed to take
 place overnight at ambient temperature, then 1.5 g of
 5 silica are added and the mixture is evaporated. The
 residue is purified by chromatography on silica gel,
 elution being carried out with a 98.5/1.5 and then 97/3
 mixture of dichloromethane and of methanol. The product
 is subsequently recrystallized from a mixture of ethyl
 10 acetate and of diisopropyl ether to produce 0.43 g of
 product in the form of a white solid.

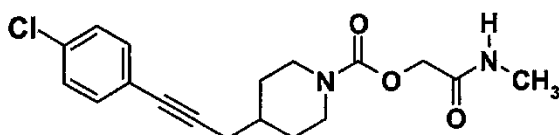
Melting point (°C): 150-152

LC-MS : M+H 341

¹H NMR (CDCl₃) δ (ppm) : 7.80 (m, 3H), 7.60 (s, 1H),
 15 7.45 (m, 2H), 7.30 (d, 1H), 6.10 (m, 1H), 4.60 (s, 2H),
 4.15 (m, 2H), 2.85 (d, 3H), 2.85-2.75 (m+d, 4H), 1.90-
 1.70 (m, 3H), 1.35-1.15 (m, 2H).

Example 5 (compound No. 107)

20 **2-(Methylamino)-2-oxoethyl 4-[3-(4-chlorophenyl)prop-2-
 yn-1-yl]piperidine-1-carboxylate**



5.1. *tert*-Butyl 4-(2-oxoethyl)piperidine-1-carboxylate

70.9 g (167 mmol) of 1,1,1-tris(acetyloxy)-
1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (Dess-Martin
5 reagent) are added portionwise to a solution, cooled to
0°C, of 30.4 g (132 mmol) of *tert*-butyl 4-(2-
hydroxyethyl)piperidine-1-carboxylate in 150 ml of
dichloromethane. The mixture is stirred at ambient
temperature for 2 hours, then 150 ml of a 10% aqueous
10 sodium thiosulphate (Na₂S₂O₃) solution are added and
stirring is continued for an additional 30 minutes. The
organic phase is separated by settling, washed with a
saturated aqueous sodium carbonate solution, dried over
sodium sulphate and evaporated to dryness to produce
15 30.1 g (132 mmol) of product in the form of a
colourless oil used as is in the following stage.

5.2. *tert*-Butyl 4-(3,3-dibromoprop-2-en-1-
yl)piperidine-1-carboxylate

20 47.6 ml (531 mmol) of tribromomethane and
then 59.6 g (531 mmol) of potassium *tert*-butoxide are
added to a solution, cooled to -20°C, of 139.4 g
(531 mmol) of triphenylphosphine in 440 ml of toluene.
Stirring is continued at -20°C for 15 minutes and then

a solution of 30.1 g (131 mmol) of *tert*-butyl 4-(2-oxoethyl)piperidine-1-carboxylate, prepared in stage 5.1., in 240 ml of toluene is added. Stirring is continued at ambient temperature for 3 hours. 300 ml of diethyl ether are added, the solid formed is filtered off and the filtrate is evaporated. The residue is purified by chromatography on silica gel, elution being carried out with dichloromethane, to produce 32.6 g (85 mmol) of product in the form of a yellow oil.

10

5.3. *tert*-Butyl 4-(prop-2-yn-1-yl)piperidine-1-carboxylate

32.6 g (85 mmol) of *tert*-butyl 4-(3,3-dibromoprop-2-en-1-yl)piperidine-1-carboxylate, prepared in stage 5.2., are dissolved in 420 ml of anhydrous tetrahydrofuran. The solution is cooled to -78°C and 106 ml of a 1.6M solution of *n*-butyllithium (170 mmol) in hexane, dissolved in 100 ml of anhydrous tetrahydrofuran, are added dropwise while stirring well. Stirring is continued at -78°C for 3 hours and then at -20°C for 1 hour. The mixture is cooled to -78°C and 130 ml of a 1.25M solution of hydrochloric acid in ethanol are added. The mixture is subsequently reheated to ambient temperature over 1 hour. Water and

20

ethyl acetate are added. The organic phase is separated by settling, washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and evaporated to dryness. The residue is purified by chromatography on silica gel, elution being carried out with dichloromethane and then with a 98/2 mixture of dichloromethane and of methanol, to produce 32.4 g (85.2 mmol) of product in the form of a colourless oil.

5.4. *tert*-Butyl 4-[3-(4-chlorophenyl)prop-2-yn-1-yl]-piperidine-1-carboxylate

2.29 g (9.6 mmol) of 1-chloro-4-iodobenzene and 1.7 ml (12 mmol) of triethylamine are dissolved in 5 ml of tetrahydrofuran. 0.076 g (0.40 mmol) of cuprous iodide and 0.168 g (0.24 mmol) of the bis(triphenylphosphine)palladium dichloride complex are added under argon, followed, dropwise, by a solution of 1.78 g (8 mmol) of *tert*-butyl 4-(prop-2-yn-1-yl)piperidine-1-carboxylate, prepared in stage 5.3., in 3 ml of tetrahydrofuran. Stirring is continued overnight. 25 ml of water and 100 ml of ethyl acetate are added. The organic phase is separated by settling, washed successively with 25 ml of 10% aqueous ammonia, 25 ml of water and 25 ml of a saturated aqueous sodium

chloride solution, dried over magnesium sulphate and evaporated to dryness. The residue is purified by chromatography on silica gel, elution being carried out with a 95/5 and then 90/10 mixture of cyclohexane and
5 of ethyl acetate, to produce 2.15 g (6.44 mmol) of product in the form of a yellow oil.

5.5. 4-[3-(4-Chlorophenyl)prop-2-yn-1-yl]piperidine

2.13 g (6.38 mmol) of *tert*-butyl 4-[3-(4-chlorophenyl)prop-2-yn-1-yl]piperidine-1-carboxylate,
10 obtained in stage 5.4., are dissolved in 15 ml of dichloromethane. A solution of 4.9 ml (63.8 mmol) of trifluoroacetic acid in 5 ml of dichloromethane is added dropwise. Reaction is allowed to take place at
15 ambient temperature overnight and then the mixture is evaporated to dryness. 25 ml of dichloromethane are added and the mixture is again evaporated to dryness. The residue is subsequently taken up in a mixture of 70 ml of ethyl acetate, 10 ml of a 1N aqueous sodium
20 hydroxide solution and 10 ml of 30% aqueous ammonia. The organic phase is separated by settling, washed with 2 times 10 ml of water and then with 10 ml of a saturated aqueous sodium chloride solution, dried over sodium sulphate and evaporated to dryness to produce

1.39 g (5.94 mmol) of product in the form of a brown oil used as is in the following stage.

5.6. 2-Ethoxy-2-oxoethyl 4-[3-(4-chlorophenyl)prop-2-yn-1-yl]piperidine-1-carboxylate

A solution of 1.39 g (5.94 mmol) of 4-[3-(4-chlorophenyl)prop-2-yn-1-yl]piperidine, prepared in stage 5.5, and of 1.86 g (8.33 mmol) of ethyl [(phenyloxycarbonyl)oxy]acetate in 12 ml of toluene is heated at 70°C for 5 hours. The mixture is evaporated to dryness and the residue is purified by chromatography on silica gel, elution being carried out with a 90/10 and then 80/20 mixture of cyclohexane and of ethyl acetate, to produce 1.89 g (5.19 mmol) of product in the form of a viscous oil.

5.7. 2-(Methylamino)-2-oxoethyl 4-[3-(4-chlorophenyl)prop-2-yn-1-yl]piperidine-1-carboxylate

0.91 g (2.51 mmol) of 2-ethoxy-2-oxoethyl 4-[3-(4-chlorophenyl)prop-2-yn-1-yl]piperidine-1-carboxylate, prepared in stage 5.6., is dissolved in 4 ml of methanol. 2.5 ml (25 mmol) of a 33% solution of methylamine in ethanol are added and the mixture is left overnight at ambient temperature. It is evaporated

to dryness and the residue is purified by chromatography on silica gel, elution being carried out with a 99.5/0.5 and then 98/2 and 96/4 mixture of dichloromethane and of methanol. The product is

5 crystallized from hexane and is then dried under vacuum to produce 0.50 g (1.43 mmol) of product in the form of a white powder.

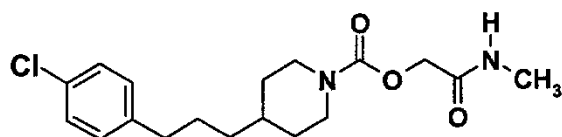
Melting point (°C): 101-103

LC-MS : M+H = 349

10 ¹H NMR (CDCl₃) δ (ppm): 7.20 (m, 4H), 6.30 (m, 1H), 4.50 (broad s, 2H), 4.10 (broad d, 2H), 2.75 (m+d, 5H), 2.30 (d, 2H), 1.85-1.60 (m, 3H), 1.35-1.15 (m, 2H).

Example 6 (compound No. 83)

15 **2-(Methylamino)-2-oxoethyl 4-[3-(4-chlorophenyl)propyl]piperidine-1-carboxylate**



0.156 g (0.448 mmol) of 2-(methylamino)-2-oxoethyl 4-[3-(4-chlorophenyl)prop-2-yn-

20 1-yl]piperidine-1-carboxylate, prepared according to Example 5, is dissolved in 2 ml of ethanol. 16 mg of platinum dioxide are added. The mixture is stirred under a hydrogen atmosphere at ambient pressure and

ambient temperature for 2 hours and then at 40°C for an additional 2 hours. The mixture is filtered through celite and the filtrate is evaporated. The residue is purified by HPLC chromatography on Nucleosil gel,
 5 elution being carried out with a 70/30/0 to 0/80/20 gradient of hexane, of ethyl acetate and of methanol, to produce 0.108 mg (0.306 mmol) of product in the form of a white solid.

Melting point (°C): 118-120

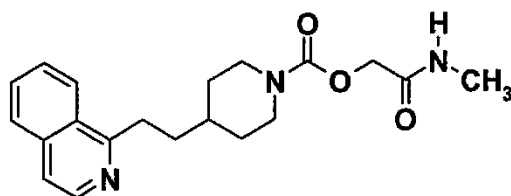
10 LC-MS : M+H = 353

¹H NMR (CDCl₃) δ (ppm): 7.25 (d, 2H), 7.10 (d, 2H), 6.05 (m, 1H), 4.60 (s, 2H), 4.10 (broad d, 2H), 2.90 (d, 3H), 2.80 (broad t, 2H), 2.60 (t, 2H), 1.75-1.55 (m, 4H), 1.45 (m, 1H), 1.35-1.05 (m, 4H).

15

Example 7 (compound No. 74)

2-(Methylamino)-2-oxoethyl 4-(2-(isoquinolin-1-yl)ethyl)-1-piperidinecarboxylate



20

7.1. tert-Butyl 4-(iodomethyl)-1-piperidinecarboxylate

14.15 g (55.74 mmol) of iodine (I₂) are added

in small portions to a solution, cooled to approximately 0°C, of 10 g (46.45 mmol) of tert-butyl 4-(hydroxymethyl)-1-piperidinecarboxylate, of 15.84 g (60.38 mmol) of triphenylphosphine and of 4.74 g (69.67 mmol) of imidazole in 200 ml of dichloromethane while keeping the temperature of the reaction medium between 0°C and 5°C. Stirring is continued at 0°C for 1 hour and then at ambient temperature for 4 hours.

100 ml of water and 300 ml of ethyl acetate are added. The organic phase is separated by settling, washed successively with a saturated aqueous sodium thiosulphate solution and a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure. The residue obtained is purified by chromatography on silica gel, elution being carried out with a 90/10 mixture of cyclohexane and of ethyl acetate. 13.70 g (42.13 mmol) of product are obtained in the form of a colourless oil.

20

7.2. tert-Butyl 4-(2-(isoquinolin-1-yl)ethyl)-1-piperidinecarboxylate

10 ml (20 mmol) of a solution (2M) of lithium diisopropylamide (LDA) in a mixture of tetrahydrofuran

and of n-hexane are added dropwise to a solution,
cooled to approximately -70°C , of 2.202 g (15.38 mmol)
of 1-methylisoquinoline in 150 ml of tetrahydrofuran.
Stirring is continued at -70°C for 10 minutes and then
5 a solution of 5 g (15.38 mmol) of tert-butyl 4-
(iodomethyl)-1-piperidinecarboxylate, obtained in stage
7.1., in 30 ml of tetrahydrofuran is added slowly.
After stirring at -70°C for 30 minutes, 100 ml of a
saturated aqueous ammonium chloride solution are added.
10 The mixture is allowed to return to ambient
temperature and the aqueous phase is separated and then
extracted 3 times with ethyl acetate. The combined
organic phases are washed with a saturated aqueous
sodium chloride solution, dried over sodium sulphate
15 and concentrated under reduced pressure. The residue
obtained is purified by chromatography on silica gel,
elution being carried out with a 99/1 and then 98/2
mixture of dichloromethane and of methanol. 1.80 g
(5.29 mmol) of product are obtained in the form of a
20 yellow oil.

7.3. 1-(2-(Piperidin-4-yl)ethyl)isoquinoline

3.90 ml (23.50 mmol) of a solution of
hydrochloric acid (6N) in isopropanol are added at

ambient temperature to a solution of 1.60 g (4.70 mmol) of tert-butyl 4-(2-(isoquinolin-1-yl)ethyl)-1-piperidinecarboxylate, obtained in stage 7.2., in 15 ml of 1,4-dioxane. The reaction mixture is subsequently
5 brought to approximately 60°C for 12 hours.

The mixture is concentrated to dryness under reduced pressure. The hydrochloride obtained is taken up in 5 ml of water and then a 20% aqueous sodium hydroxide solution is slowly added with stirring to
10 pH 9. The aqueous phase is extracted twice with chloroform and the combined organic phases are washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure. 0.400 g (1.66 mmol) of product is
15 obtained in the form of a brown oil.

7.4. 2-Ethoxy-2-oxoethyl 4-(2-(isoquinolin-1-yl)ethyl)-1-piperidinecarboxylate

A solution of 0.320 g (1.33 mmol) of 1-(2-(piperidin-4-yl)ethyl)isoquinoline, obtained in stage
20 7.3., and of 0.388 g (1.73 mmol) of ethyl [(phenyloxycarbonyl)oxy]acetate in 10 ml of toluene is heated at 70°C for 18 hours.

The mixture is allowed to return to ambient

temperature and concentrated under reduced pressure and then the residue thus obtained is purified by chromatography on silica gel, elution being carried out with a 40/60 mixture of ethyl acetate and of cyclohexane. 0.390 g (1.05 mmol) of product is thus obtained in the form of a viscous oil.

7.5. 2-(Methylamino)-2-oxoethyl 4-(2-(isoquinolin-1-yl)ethyl)-1-piperidinecarboxylate

2.60 ml (5.13 mmol) of a solution of methylamine (2M) in tetrahydrofuran are added to a solution of 0.380 g (1.03 mmol) of 2-ethoxy-2-oxoethyl 4-(2-(isoquinolin-1-yl)ethyl)-1-piperidinecarboxylate, prepared in stage 7.4., in 10 ml of methanol. Stirring is continued at ambient temperature for 12 hours.

After concentrating under reduced pressure, the residue obtained is purified by chromatography on silica gel, elution being carried out with a 95/5 mixture of dichloromethane and of methanol. A solid is obtained and is recrystallized from a mixture of ethyl acetate and of diisopropyl ether. 0.315 g (0.88 mmol) of product is thus obtained in the form of a white solid.

LC-MS : M+H = 356

Melting point (°C): 126-128

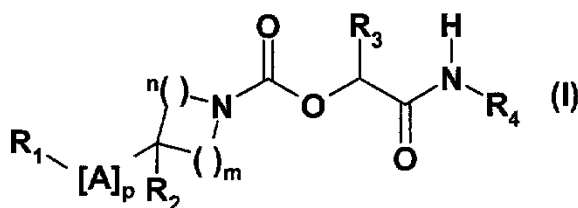
¹H NMR (CDCl₃) δ (ppm): 8.50 (d, 1H), 8.15 (d, 1H), 7.90 (d, 1H), 7.70 (m, 2H), 7.55 (d, 1H), 6.10 (broad s, 1H), 4.60 (broad s, 2H), 4.20 (m, 2H), 3.35 (dd, 2H),
 5 2.90 (m+d, 5H), 1.90 (m, 4H), 1.65 (m, 1H), 1.30 (m, 2H).

The chemical structures and the physical properties of a few compounds according to the invention are illustrated in the following table. In
 10 this table:

- all the compounds are in the free base form,
- n-butyl represents a linear butyl group.

Table

15



No.	R ₁	[A] _p	R ₂	n	m	R ₃	R ₄	M.p. (°C) (M+H)
1.	phenyl	bond	H	2	2	H	H	160-162
2.	phenyl	bond	H	2	2	H	CH ₃	76-78
3.	3-CF ₃ -phenyl	bond	H	2	2	H	H	(331)
4.	3-CF ₃ -phenyl	bond	H	2	2	H	CH ₃	(345)

No.	R ₁	[A] _p	R ₂	n	m	R ₃	R ₄	M.p. (°C) (M+H)
5.	5-isobutylpyrid-2-yl	bond	H	2	2	H	CH ₃	98-100
6.	6-isobutylpyrid-2-yl	bond	H	2	2	H	CH ₃	(334)
7.	6-cyclopentylpyrid-2-yl	bond	H	2	2	H	CH ₃	(346)
8.	5-(4-F-phenyl)pyrid-2-yl	bond	H	2	2	H	CH ₃	151-153
9.	6-(4-F-phenyl)pyrid-2-yl	bond	H	2	2	H	CH ₃	104-106
10.	6-(4-Cl-phenyl)pyrid-2-yl	bond	H	2	2	H	CH ₃	136-138
11.	5-(4-CF ₃ -phenyl)pyrid-2-yl	bond	H	2	2	H	CH ₃	203-205
12.	6-(4-CF ₃ -phenyl)pyrid-2-yl	bond	H	2	2	H	CH ₃	128-130
13.	5-(3-CF ₃ -phenyl)-1- methylpyrazol-3-yl	bond	H	2	2	H	CH ₃	160-162
14.	4-phenylimidazol-1-yl	bond	H	2	2	H	CH ₃	192-194
15.	5-phenyl-1,3,4-oxadiazol- 2-yl	bond	H	2	2	H	H	152-154
16.	5-phenyl-1,3,4-oxadiazol- 2-yl	bond	H	2	2	H	CH ₃	114-116
17.	5-(4-F-phenyl)-1,3,4-oxa- diazol-2-yl	bond	H	2	2	H	H	158-160
18.	5-(4-F-phenyl)-1,3,4-oxa- diazol-2-yl	bond	H	2	2	H	CH ₃	163-165
19.	5-(3-CF ₃ -phenyl)- 1,3,4-oxadiazol-2-yl	bond	H	2	2	H	H	130-130
20.	5-(3-CF ₃ -phenyl)- 1,3,4-oxadiazol-2-yl	bond	H	2	2	H	CH ₃	123-125
21.	3-(3-CF ₃ -phenyl)- 1,2,4-oxadiazol-5-yl	bond	H	2	2	H	H	133-135

No.	R ₁	[A] _p	R ₂	n	m	R ₃	R ₄	M.p. (°C) (M+H)
22.	3-(3-CF ₃ -phenyl)- 1,2,4-oxadiazol-5-yl	bond	H	2	2	H	CH ₃	119-121
23.	benzoxazol-2-yl	bond	H	2	2	H	CH ₃	137-139
24.	benzothiazol-2-yl	bond	H	2	2	H	H	148-150
25.	benzothiazol-2-yl	bond	H	2	2	H	CH ₃	120-122
26.	benzimidazol-2-yl	bond	H	2	2	H	CH ₃	213-215
27.	benzimidazol-1-yl	bond	H	2	2	H	H	206-208
28.	2-phenylbenzimidazol-1-yl	bond	H	2	2	H	CH ₃	193-195
29.	benzotriazol-1-yl	bond	H	2	2	H	CH ₃	129-131
30.	5-CF ₃ -benzotriazol-1-yl	bond	H	2	2	H	H	152-154
31.	indol-1-yl	bond	H	2	2	H	H	178-180
32.	4-Br-phenyl	bond	OH	2	2	H	CH ₃	57-60
33.	4-(4-F-phenyl)phenyl	bond	OH	2	2	H	CH ₃	212-214
34.	4-(4-Cl-phenyl)phenyl	bond	OH	2	2	H	CH ₃	223-225
35.	4-(4-CH ₃ -phenyl)phenyl	bond	OH	2	2	H	CH ₃	179-181
36.	4-(4-(n-butyl)phenyl)- phenyl	bond	OH	2	2	H	CH ₃	(425)
37.	4-(4-CF ₃ -phenyl)phenyl	bond	OH	2	2	H	CH ₃	191-193
38.	4-(4-CH ₃ O-phenyl)phenyl	bond	OH	2	2	H	CH ₃	175-176
39.	4-(4-C ₂ H ₅ O-phenyl)phenyl	bond	OH	2	2	H	CH ₃	165-167
40.	4-(3-Cl, 4-Cl-phenyl)- phenyl	bond	OH	2	2	H	CH ₃	156-158
41.	4-(3-F, 4-CH ₃ O-phenyl)- phenyl	bond	OH	2	2	H	CH ₃	(417)
42.	4-(3-Cl, 4-F-phenyl)phenyl	bond	OH	2	2	H	CH ₃	123-125

No.	R ₁	[A] _p	R ₂	n	m	R ₃	R ₄	M.p. (°C) (M+H)
43.	naphth-2-yl	CH ₂	H	2	2	H	CH ₃	150-152
44.	4-phenylphenyl	CH ₂	H	2	2	H	CH ₃	115-117
45.	6-cyclopentylpyrid-2-yl	CH ₂	H	2	2	H	CH ₃	(360)
46.	6-(4-F-phenyl)pyrid-2-yl	CH ₂	H	2	2	H	CH ₃	112-114
47.	indol-1-yl	CH ₂	H	2	2	H	H	158-159
48.	indolin-1-yl	CH ₂	H	2	2	H	H	115-116
49.	1,2,3,4-tetrahydro- quinolin-1-yl	CH ₂	H	2	2	H	H	158-159
50.	1,2,3,4-tetrahydro- isoquinolin-2-yl	CH ₂	H	2	2	H	H	(332)
51.	pyrrolo[2,3-b]pyrid-1-yl	CH ₂	H	2	2	H	H	(317)
52.	benzimidazol-1-yl	CH ₂	H	2	2	H	H	(317)
53.	4-phenylimidazol-1-yl	CH ₂	H	2	2	H	H	124-125
54.	phenyl	(CH ₂) ₂	H	1	2	H	CH ₃	(291)
55.	4-F-phenyl	(CH ₂) ₂	H	2	2	H	CH ₃	150-152
56.	3-Cl-phenyl	(CH ₂) ₂	H	2	2	H	CH ₃	86-88
57.	4-Cl-phenyl	(CH ₂) ₂	H	2	2	H	CH ₃	150-152
58.	3-CF ₃ -phenyl	(CH ₂) ₂	H	2	2	H	CH ₃	103-105
59.	4-CF ₃ -phenyl	(CH ₂) ₂	H	2	2	H	CH ₃	131-133
60.	3-CN-phenyl	(CH ₂) ₂	H	2	2	H	CH ₃	(330)
61.	4-CH ₃ -phenyl	(CH ₂) ₂	H	2	2	H	H	125-127
62.	4-CH ₃ -phenyl	(CH ₂) ₂	H	2	2	H	CH ₃	117-119
63.	4-CH ₃ O-phenyl	(CH ₂) ₂	H	2	2	H	H	123-125
64.	4-CH ₃ O-phenyl	(CH ₂) ₂	H	2	2	H	CH ₃	122-124

No.	R ₁	[A] _p	R ₂	n	m	R ₃	R ₄	M.p. (°C) (M+H)
65.	2-phenylphenyl	(CH ₂) ₂	H	2	2	H	CH ₃	(381)
66.	3-phenylphenyl	(CH ₂) ₂	H	2	2	H	CH ₃	113-115
67.	naphth-1-yl	(CH ₂) ₂	H	2	2	H	CH ₃	112-114
68.	naphth-2-yl	(CH ₂) ₂	H	2	2	H	CH ₃	106-108
69.	pyrimidin-2-yl	(CH ₂) ₂	H	2	2	H	CH ₃	160-170
70.	pyrimidin-5-yl	(CH ₂) ₂	H	2	2	H	CH ₃	123-125
71.	6-cyclopentylpyrid-2-yl	(CH ₂) ₂	H	2	2	H	CH ₃	(374)
72.	6-(pyrrolidin-1-yl)- pyrid-2-yl	(CH ₂) ₂	H	2	2	H	CH ₃	130-132
73.	thiazol-2-yl	(CH ₂) ₂	H	2	2	H	CH ₃	97-99
74.	isoquinolin-1-yl	(CH ₂) ₂	H	2	2	H	CH ₃	126-128
75.	1,2,3,4-tetrahydro- quinolin-1-yl	(CH ₂) ₂	H	2	2	H	H	(346)
76.	1,2,3,4-tetrahydro- isoquinolin-2-yl	(CH ₂) ₂	H	2	2	H	H	112-114
77.	indol-1-yl	(CH ₂) ₂	H	2	2	H	H	(330)
78.	indolin-1-yl	(CH ₂) ₂	H	2	2	H	H	92-93
79.	pyrrolo[2,3-b]pyrid-1-yl	(CH ₂) ₂	H	2	2	H	H	(331)
80.	benzimidazol-1-yl	(CH ₂) ₂	H	2	2	H	H	181-182
81.	4-phenylimidazol-1-yl	(CH ₂) ₂	H	2	2	H	H	183-184
82.	3-Cl-phenyl	(CH ₂) ₃	H	2	2	H	CH ₃	92-94
83.	4-Cl-phenyl	(CH ₂) ₃	H	2	2	H	CH ₃	118-120
84.	3-CF ₃ -phenyl	(CH ₂) ₃	H	2	2	H	CH ₃	106-108
85.	4-CF ₃ -phenyl	(CH ₂) ₃	H	2	2	H	CH ₃	111-113

No.	R ₁	[A] _p	R ₂	n	m	R ₃	R ₄	M.p. (°C) (M+H)
86.	3-CN-phenyl	(CH ₂) ₃	H	2	2	H	CH ₃	118-120
87.	2-phenylphenyl	(CH ₂) ₃	H	2	2	H	CH ₃	(395)
88.	3-phenylphenyl	(CH ₂) ₃	H	2	2	H	CH ₃	116-118
89.	naphth-1-yl	(CH ₂) ₃	H	2	2	H	CH ₃	(369)
90.	naphth-2-yl	(CH ₂) ₃	H	2	2	H	CH ₃	112-114
91.	pyrimidin-2-yl	(CH ₂) ₃	H	2	2	H	CH ₃	105-107
92.	pyrimidin-5-yl	(CH ₂) ₃	H	2	2	H	CH ₃	105-107
93.	thiazol-2-yl	(CH ₂) ₃	H	2	2	H	CH ₃	(326)
94.	3-Cl-phenyl	C≡C	H	2	2	H	CH ₃	85-87
95.	4-Cl-phenyl	C≡C	H	2	2	H	CH ₃	122-124
96.	3-CF ₃ -phenyl	C≡C	H	2	2	H	CH ₃	(369)
97.	4-CF ₃ -phenyl	C≡C	H	2	2	H	CH ₃	134-136
98.	3-CN-phenyl	C≡C	H	2	2	H	CH ₃	(326)
99.	2-phenylphenyl	C≡C	H	2	2	H	CH ₃	(377)
100.	3-phenylphenyl	C≡C	H	2	2	H	CH ₃	(377)
101.	naphth-1-yl	C≡C	H	2	2	H	CH ₃	(351)
102.	naphth-2-yl	C≡C	H	2	2	H	CH ₃	(351)
103.	pyrimidin-2-yl	C≡C	H	2	2	H	CH ₃	(303)
104.	pyrimidin-5-yl	C≡C	H	2	2	H	CH ₃	136-138
105.	thiazol-2-yl	C≡C	H	2	2	H	CH ₃	(308)
106.	3-Cl-phenyl	C≡CCH ₂	H	2	2	H	CH ₃	91-93
107.	4-Cl-phenyl	C≡CCH ₂	H	2	2	H	CH ₃	101-103
108.	3-CF ₃ -phenyl	C≡CCH ₂	H	2	2	H	CH ₃	113-115

No.	R ₁	[A] _p	R ₂	n	m	R ₃	R ₄	M.p. (°C) (M+H)
109.	4-CF ₃ -phenyl	C≡CCH ₂	H	2	2	H	CH ₃	112-114
110.	3-CN-phenyl	C≡CCH ₂	H	2	2	H	CH ₃	112-114
111.	2-phenylphenyl	C≡CCH ₂	H	2	2	H	CH ₃	99-101
112.	3-phenylphenyl	C≡CCH ₂	H	2	2	H	CH ₃	(391)
113.	naphth-1-yl	C≡CCH ₂	H	2	2	H	CH ₃	98-100
114.	naphth-2-yl	C≡CCH ₂	H	2	2	H	CH ₃	99-101
115.	pyrimidin-2-yl	C≡CCH ₂	H	2	2	H	CH ₃	91-93
116.	pyrimidin-5-yl	C≡CCH ₂	H	2	2	H	CH ₃	113-115
117.	thiazol-2-yl	C≡CCH ₂	H	2	2	H	CH ₃	112-114
118.	6-(pyrrolidin-1-yl)- pyrid-2-yl	CH ₂	H	2	2	H	CH ₃	119-121
119.	6-(1-isopropylpiperidin- 4-yl)pyrid-2-yl	(CH ₂) ₂	H	2	2	H	CH ₃	(431)

The compounds of the invention have formed the subject of pharmacological trials which make it possible to determine their inhibitory effect on the enzyme FAAH (Fatty Acid Amido Hydrolase).

5 The inhibitory activity was demonstrated in a radioenzymatic test based on the measurement of the product of hydrolysis ((1-³H)ethanolamine) of ((1-³H)ethanolamine)-anandamide by FAAH (*Life Sciences* (1995), 56, 1999-2005 and *Journal of Pharmacology and*
10 *Experimental Therapeutics* (1997), 283, 729-734). Thus,

mouse brains (minus the cerebellum) are removed and stored at -80°C . The membrane homogenates are prepared at the time of use by homogenization of the tissues with a Polytron in a 10 mM Tris-HCl buffer (pH 8.0) comprising 150 mM NaCl and 1 mM EDTA. The enzymatic reaction is subsequently carried out in 70 μl of buffer comprising bovine serum albumin free from fatty acids (1 mg/ml). The test compounds, at various concentrations, the ((1- ^3H)ethanolamine)-anandamide (specific activity of 15-20 Ci/mmol), diluted to 10 μM with non-radiolabelled anandamide, and the membrane preparation (400 μg of frozen tissue per assay) are successively added. After 15 minutes at 25°C , the enzymatic reaction is halted by addition of 140 μl of chloroform/methanol (2:1). The mixture is stirred for 10 minutes and is then centrifuged at 3500 g for 15 minutes. An aliquot (30 μl) of the aqueous phase comprising the (1- ^3H)ethanolamine is counted by liquid scintillation.

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

For example, compounds Nos. 39 and 40 in the

table exhibit IC₅₀ values of 0.095 and 0.098 μ M respectively.

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

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

Thus, the intraperitoneal (i.p.) administration of PBQ (phenylbenzoquinone, 2 mg/kg in a
10 0.9% sodium chloride solution comprising 5% of ethanol) to male OF1 mice weighing 25 to 30 g causes abdominal tractions, on average 30 twisting or contracting motions during the period from 5 to 15 minutes after injection. The test compounds are administered, orally
15 (p.o.) or intraperitoneally (i.p.) in suspension in 0.5% Tween 80, 60 minutes or 120 minutes before the administration of PBQ. Under these conditions, the most powerful compounds of the invention reduce by 35 to 70% the number of tractions induced by the PBQ, within a
20 range of doses of between 1 and 30 mg/kg.

For example, compound No. 57 in the table reduces by 37% and by 74% the number of tractions induced by the PBQ, at a dose of 3 mg/kg p.o., at 60 minutes and at 120 minutes respectively.

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

10 The compounds of the invention block this decomposition pathway and increase the tissue level of these endogenous substances. They can therefore be used in the prevention and treatment of pathologies in which endogenous cannabinoids and/or any other substrate
15 metabolized by the enzyme FAAH are involved.

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

Pain, in particular acute or chronic pain of neurogenic type: migraine, neuropathic pain, including forms
20 associated with the herpes virus and with diabetes; acute or chronic pain associated with inflammatory diseases: arthritis, rheumatoid arthritis, osteoarthritis, spondylitis, gout, vasculitis, Crohn's disease, irritable bowel syndrome;

acute or chronic peripheral pain;
dizziness, vomiting, nausea, in particular resulting
from chemotherapy;
eating disorders, in particular anorexia and cachexia
5 of various natures;
neurological and psychiatric pathologies: tremors,
dyskinesias, dystonias, spasticity, obsessive-
compulsive behaviour, Tourette's syndrome, all forms of
depression and of anxiety of any nature and origin,
10 mood disorders, psychoses;
acute and chronic neurodegenerative diseases:
Parkinson's disease, Alzheimer's disease, senile
dementia, Huntington's chorea, lesions related to
cerebral ischaemia and to cranial and medullary trauma;
15 epilepsy;
sleep disorders, including sleep apnoea;
cardiovascular diseases, in particular hypertension,
cardiac arrhythmias, arteriosclerosis, heart attack,
cardiac ischaemia;
20 renal ischaemia;
cancers: benign skin tumours, brain tumours and
papillomas, prostate tumours, cerebral tumours
(glioblastomas, medullopitheliomas, medulloblastomas,
neuroblastomas, tumours of embryonic origin,

astrocytomas, astroblastomas, ependymomas,
 oligodendrogliomas, plexus tumour, neuroepitheliomas,
 epiphyseal tumour, ependymoblastomas, malignant
 meningiomas, sarcomatosis, malignant melanomas,
 5 schwannomas);

disorders of the immune system, in particular
 autoimmune diseases: psoriasis, lupus erythematosus,
 diseases of the connective tissue or collagen diseases,
 Sjögren's syndrome, ankylosing spondylitis,
 10 undifferentiated spondylitis, Behcet's disease,
 autoimmune haemolytic anaemia, multiple sclerosis,
 amyotrophic lateral sclerosis, amyloidosis, graft
 rejection, diseases affecting the plasmocytic line;
 allergic diseases: immediate or delayed
 15 hypersensitivity, allergic rhinitis or conjunctivitis,
 contact dermatitis;

parasitic, viral or bacterial infectious diseases:
 AIDS, meningitis;

inflammatory diseases, in particular joint diseases:
 20 arthritis, rheumatoid arthritis, osteoarthritis,
 spondylitis, gout, vasculitis, Crohn's disease,
 irritable bowel syndrome; osteoporosis;

eye conditions: ocular hypertension, glaucoma;
 pulmonary conditions: diseases of the respiratory

tract, bronchospasm, coughing, asthma, chronic
bronchitis, chronic obstruction of the respiratory
tract, emphysema;

gastrointestinal diseases: irritable bowel syndrome,
5 inflammatory intestinal disorders, ulcers, diarrhoea;
urinary incontinence and bladder inflammation.

The use of a compound of formula (I), in the
base or pharmaceutically acceptable salt, hydrate or
solvate form, in the preparation of a medicament
10 intended to treat the abovementioned pathologies forms
an integral part of the invention.

Another subject-matter of the invention is
medicaments which comprise a compound of formula (I) or
a pharmaceutically acceptable salt, hydrate or solvate
15 of the compound of formula (I). These medicaments are
used in therapeutics, in particular in the treatment of
the abovementioned pathologies.

According to another of its aspects, the
present invention relates to pharmaceutical
20 compositions including, as active principle, at least
one compound according to the invention. These
pharmaceutical compositions comprise an effective dose
of a compound according to the invention or a
pharmaceutically acceptable salt, hydrate or solvate of

the said compound and optionally one or more pharmaceutically acceptable excipients.

The said excipients are chosen, depending on the pharmaceutical form and the method of administration desired, from the usual excipients which are known to a person skilled in the art.

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 optional salt, solvate or hydrate can be administered in a single-dose administration form, as a mixture with conventional pharmaceutical excipients, to animals and to man for the prophylaxis or the treatment of the above disorders or diseases.

Appropriate single-dose administration forms comprise oral forms, such as tablets, soft or hard gelatin capsules, powders, granules, chewing gums and oral solutions or suspensions, forms for sublingual, buccal, intratracheal, intraocular or intranasal administration or 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 can be used in creams, ointments or lotions.

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

	Compound according to the invention	50.0 mg
10	Mannitol	223.75 mg
	Croscarmellose sodium	6.0 mg
	Maize starch	15.0 mg
	Hydroxypropylmethylcellulose	2.25 mg
	Magnesium stearate	3.0 mg

15 The said single-dose forms comprise a dose which makes possible a daily administration of 0.01 to 20 mg of active principle per kg of body weight, depending upon the pharmaceutical dosage form.

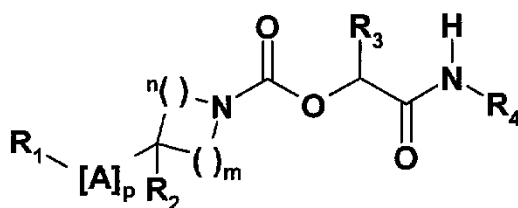
20 There may be specific cases where higher or lower dosages are appropriate; such dosages also come within the invention. According to the usual practice, the dosage appropriate to each patient is determined by the doctor according to the method of administration, the weight and the response of the said patient.

According to another of its aspects, the invention also relates to a method for the treatment of the pathologies indicated above which comprises the administration of an effective dose of a compound

5 according to the invention, of one of its pharmaceutically acceptable salts or of a solvate or of a hydrate of the said compound.

-

5



(I)

in which

10

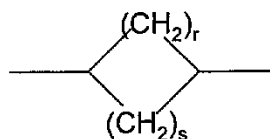
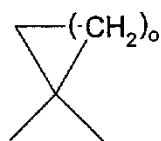
p represents an integer ranging from 1 to 7;

A represents a single bond or is chosen from one or more groups X, Y and/or Z;

15

Y represents either a C₂-alkenylene group optionally substituted by one or two C₁₋₆-alkyl, C₃₋₇-cycloalkyl or C₃₋₇-cycloalkyl-C₁₋₃-alkylene groups; or a C₂-alkynylene group;

Z represents a group of formula:



o represents an integer ranging from 1 to 5;

r and s represent integers and are defined such that

$r+s$ is a number ranging from 1 to 5;

- 5 R_1 represents an R_5 group optionally substituted by one or more R_6 and/or R_7 groups;
- R_2 represents a hydrogen or fluorine atom or a hydroxyl, C_{1-6} -alkoxy or NR_8R_9 group;
- R_3 represents a hydrogen atom or a C_{1-6} -alkyl group;
- 10 R_4 represents a hydrogen atom or a C_{1-6} -alkyl, C_{3-7} -cycloalkyl or C_{3-7} -cycloalkyl- C_{1-3} -alkyl group;
- R_5 represents a group chosen from a phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl,
- 15 thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, naphthyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, cinnolinyl, naphthyridinyl,
- 20 benzofuranyl, dihydrobenzofuranyl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, isoindolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl,

benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl,
 pyrrolopyridyl, furopyridyl, thienopyridyl,
 imidazopyridyl, oxazolopyridyl, thiazolopyridyl,
 pyrazolopyridyl, isoxazolopyridyl or

5 isothiazolopyridyl;

R_6 represents a halogen atom or a cyano, nitro, C_{1-6} -
 alkyl, C_{3-7} -cycloalkyl, C_{1-6} -alkoxy, hydroxyl, C_{1-6} -
 thioalkyl, C_{1-6} -fluoroalkyl, C_{1-6} -fluoroalkoxy, C_{1-6} -
 fluorothioalkyl, NR_8R_9 , NR_8COR_9 , $NR_8CO_2R_9$, $NR_8SO_2R_9$, COR_8 ,

10 CO_2R_8 , $CONR_8R_9$, SO_2R_8 , $SO_2NR_8R_9$ or $-O-(C_{1-3}\text{-alkylene})-O-$
 group or a ring chosen from the azetidine, pyrrolidine,
 piperidine, morpholine, thiomorpholine, azepine or
 piperazine rings, this ring optionally being
 substituted by a C_{1-6} -alkyl or benzyl group;

15 R_7 represents a phenyl, phenyloxy, benzyloxy, naphthyl,
 pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl group;
 it being possible for the R_7 group or groups to be
 substituted by one or more R_6 groups which are identical
 to or different from one another;

20 R_8 and R_9 represent, independently of one another, a
 hydrogen atom or a C_{1-6} -alkyl group;
 in the base form or in the form of an addition salt
 with an acid, of a hydrate or of a solvate.

2. Compound of formula (I) according to

Claim 1, characterized in that:

m and n represent integers equal to 1 or 2 such that

m + n is an integer ranging from 2 to 4;

p represents an integer ranging from 1 to 3;

- 5 A represents a single bond or a methylene or C₂-alkynylene group;

R₁ represents an R₅ group optionally substituted by one or more R₆ and/or R₇ groups;

R₂ represents a hydrogen atom or a hydroxyl group;

- 10 R₃ represents a hydrogen atom or a C₁₋₆-alkyl group;

R₄ represents a hydrogen atom or a C₁₋₆-alkyl, C₃₋₇-cycloalkyl or C₃₋₇-cycloalkyl-C₁₋₃-alkyl group;

R₅ represents a group chosen from a phenyl, pyridyl, pyrimidinyl, imidazolyl, thiazolyl, pyrazolyl,

- 15 isoxazolyl, oxadiazolyl, naphthyl,

tetrahydroquinolinyl, isoquinolinyl, tetrahydroiso-

quinolinyl, indolyl, indolinyl, benzimidazolyl,

benzoxazolyl, benzothiazolyl, benzotriazolyl or

pyrrolopyridyl;

- 20 R₆ represents a halogen atom or a cyano, C₁₋₆-alkyl, C₃₋₇-cycloalkyl, C₁₋₆-alkoxy or C₁₋₆-fluoroalkyl group or a pyrrolidine or piperidine ring, this ring optionally being substituted by a C₁₋₆-alkyl group;

R₇ represents a phenyl group which can be substituted by

one or more R_6 groups which are identical to or different from one another;
in the base form or in the form of an addition salt with an acid, of a hydrate or of a solvate.

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

m and n represent integers equal to 1 or 2 such that
m + n is an integer ranging from 2 to 4;

p represents an integer ranging from 1 to 3;

10 A represents a single bond or a methylene or C_2 -alkynylene group;

R_1 represents an R_5 group optionally substituted by one or more R_6 and/or R_7 groups;

R_2 represents a hydrogen atom or a hydroxyl group;

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

R_4 represents a hydrogen atom or a C_{1-6} -alkyl, C_{3-7} -cycloalkyl or C_{3-7} -cycloalkyl- C_{1-3} -alkyl group;

R_5 represents a group chosen from a phenyl, pyridyl, pyrimidinyl, thiazolyl, isoxazolyl, naphthyl or

20 isoquinolinyl;

R_6 represents a halogen atom or a cyano, C_{1-6} -alkyl, C_{3-7} -cycloalkyl, C_{1-6} -alkoxy or C_{1-6} -fluoroalkyl group or a pyrrolidine or piperidine ring, this ring optionally being substituted by a C_{1-6} -alkyl group;

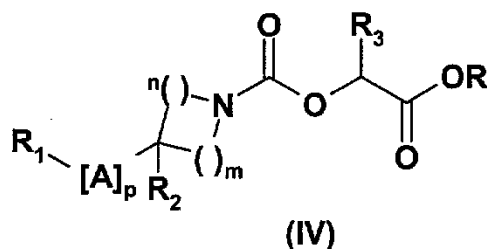
R_7 represents a phenyl group which can be substituted by one or more R_6 groups which are identical to or different from one another.

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

R_3 represents a hydrogen atom;

R_4 represents a hydrogen atom or a C_{1-6} -alkyl group; in the base form or in the form of an addition salt with an acid, of a hydrate or of a solvate.

5. Process for the preparation of a compound of formula (I) according to any one of Claims 1 to 4, comprising the stage consisting in converting the carbamate-ester of general formula (IV)



in which R_1 , A, R_2 , R_3 , p, m and n are as defined in the formula (I) according to Claim 1 and R represents a methyl or ethyl group, by aminolysis using an amine of general formula R_4NH_2 , in which R_4 is as defined in the formula (I) according to Claim 1.

6. Compound corresponding to the general formula (IV)

5 7. Pharmaceutical composition comprising at
least one compound of formula (I) according to any one
of Claims 1 to 4, in the base or pharmaceutically
acceptable salt, hydrate or solvate form, and
optionally one or more pharmaceutically acceptable
10 excipients.

8. Compound of formula (I) according to any one of Claims 1 to 4, in the base or pharmaceutically acceptable salt, hydrate or solvate form, for its use as medicament.

15 9. Use of a compound of formula (I)

according to any one of Claims 1 to 4, in the base or
pharmaceutically acceptable salt, hydrate or solvate
form, in the preparation of a medicament intended to
prevent or treat a pathology in which endogenous
20 cannabinoids and/or any other substrate metabolized by
the enzyme FAAH are involved.

10. Use of a compound of formula (I)

according to any one of Claims 1 to 4, in the base or pharmaceutically acceptable salt, hydrate or solvate form, in the preparation of a medicament intended to prevent or treat acute or chronic pain, dizziness, vomiting, nausea, eating disorders, neurological and psychiatric pathologies, acute or chronic neurodegenerative diseases, epilepsy, sleep disorders, cardiovascular diseases, renal ischaemia, cancers, disorders of the immune system, allergic diseases, parasitic, viral or bacterial infectious diseases, inflammatory diseases, osteoporosis, eye conditions, pulmonary conditions, gastrointestinal diseases or urinary incontinence.