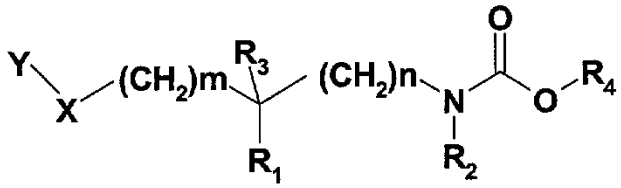
Aryloxyalkylcarbamate-type derivatives, preparation method thereof and use of same in therapeutics

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

The compounds of the invention conform to the general formula (I):



(I)

in which

m represents 0, 1, 2 or 3;

n represents 0, 1, 2 or 3;

X represents an oxygen or sulphur atom or an SO or SO_2 group;

R_1 and R_2 represent independently of one another a hydrogen atom or a C_{1-3} alkyl group, or R_1 and R_2 together form a group $-(CH_2)_p-$, where p represents an integer ranging from 1 to 5 such that n + p is an integer ranging from 2 to 5;

R_3 represents a hydrogen or fluorine atom or a hydroxyl or methyl group;

R_4 represents a group of general formula

CHR_5CONHR_6 in which

R_5 represents a hydrogen atom or a C_{1-6} alkyl group and

R_6 represents a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-6} alkylene group;

Y represents

a group Y_1 selected from in particular a phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, thiazolyl, naphthyl, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, cinnolinyl, benzofuranyl, dihydrobenzofuranyl, benzothienyl, dihydrobenzothienyl, indolyl, isoindolyl, indolinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzotriazolyl, benzoxadiazolyl and benzothiadiazolyl; the group Y_1 being optionally substituted by one or more substituents Y_2, which are identical to or different from one another, or by a group Y_3;

Y_2 represents a halogen atom or a cyano, nitro, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} thioalkyl, C_{1-8} fluoroalkyl, C_{1-8} fluoroalkoxy, C_{1-8} fluorothioalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{3-7} cycloalkyl-C_{1-8} alkylene, C_{3-7} cycloalkyl-C_{1-8} alkyloxy, hydroxyl, NR_7R_8, $NHCOR_7$, $NHSO_2R_7$, COR_7, CO_2R_7, $CONR_7R_8$, SO_2R_7, $SO_2NR_7R_8$, -O-(C_{1-3} alkylene)-O-, phenyloxy, phenylthio, phenyl-C_1-C_8 alkylene, phenyl-C_1-C_8 alkyloxy or phenyl-C_1-C_8 alkylthio

group;

Y_3 represents a group selected from in particular a phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl;

it being possible for the group or groups Y_3 to be substituted by one or more groups Y_2 which are 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 nitrogen atom carrying them form an azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine, azepine or piperazine ring optionally substituted by a C_{1-3} alkyl or benzyl group.

Among the compounds of general formula (I) a first group of compounds is that for which:

Y represents

a group Y_1 selected from in particular a phenyl, pyridinyl, pyrimidinyl, thiazolyl, naphthyl, quinolinyl, isoquinolinyl and benzoxazolyl; the group Y_1 being optionally substituted by one or more substituents, more particularly by one or two substituents, Y_2, which are identical to or different from one another, or by a group Y_3;

Y_2 represents a halogen atom, more particularly a chlorine, a fluorine or a bromine, a cyano, C_{1-8} alkyl, more particularly a methyl, isopropyl, butyl, tert-butyl or tetramethylbutyl, C_{1-8}

alkoxy, more particularly a methoxy, ethoxy or propoxy, C_{1-8} fluoroalkyl, more particularly a trifluoromethyl, C_{1-8} fluoroalkoxy, more particularly a trifluoromethoxy, phenyloxy or phenyl-C_1-C_8 alkylene group, more particularly a phenyl(1,1-dimethylmethylene);

Y_3 represents a phenyl group; it being possible for Y_3 to be substituted by one or more groups, more particularly by one or two groups, Y_2 which are identical to or different from one another.

Among the compounds of the first group as defined above a second group of compounds is that for which:

Y represents

a group Y_1 selected from in particular a phenyl or a naphthyl; the group Y_1 being optionally substituted by one or more substituents, more particularly by one or two substituents, Y_2, which are identical to or different from one another, or by a group Y_3;

Y_2 represents a halogen atom, more particularly a chlorine, a fluorine or a bromine, a cyano, C_{1-8} alkyl, more particularly a methyl, isopropyl, butyl, tert-butyl or tetramethylbutyl, C_{1-8} alkoxy, more particularly a methoxy, ethoxy or propoxy, C_{1-8} fluoroalkyl, more particularly a trifluoromethyl, C_{1-8} fluoroalkoxy, more particularly a trifluoromethoxy, phenyloxy or phenyl-C_1-C_8 alkylene group, more particularly a phenyl(1,1-dimethylmethylene);

Y_3 represents a phenyl group; it being possible for Y_3 to be substituted by one or more groups, more particularly by one or two groups, Y_2 which are identical to or different from one another.

Among the compounds of general formula (I) a third group of compounds is that for which:

m represents 0, 1, 2 or 3; and/or

n represents 0, 1, 2 or 3; and/or

R_1 and R_2 represent independently of one another a hydrogen atom or a C_{1-3} alkyl group, or R_1 and R_2 together form a group $-(CH_2)_p-$, where p represents an integer ranging from 1 to 5 such that n + p is an integer ranging from 2 to 5;

with the proviso that, when R_1 and R_2 represent independently of one another a hydrogen atom or a C_{1-3} alkyl group, m + n > 1.

Among the compounds of the third group as defined above, a fourth group of compounds is that for which:

m represents 0, 1, 2 or 3; and/or

n represents 0, 1, 2 or 3; and/or

R_1 and R_2 together form a group $-(CH_2)_p-$, where p represents an integer ranging from 1 to 4 such that n + p is equal to 4.

Among the compounds of general formula (I), a fifth group of compounds is that for which X represents an oxygen atom.

Among the compounds of general formula (I), a sixth group of compounds is that for which R_3 represents a hydrogen atom.

A seventh group is formed of the compounds for which simultaneously R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, X, Y, Y_1, Y_2, Y_3, n and m are as defined in the subgroups of compounds above.

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 8, 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_{1-3} alkyl group represents a linear or branched carbon chain of 1 to 3 carbon atoms, more particularly a methyl, ethyl, propyl or 1-methylethyl;

- 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-methylethylene, propylene or 1,1-dimethyl-methylene;

- cycloalkyl is a cyclic alkyl group; for example, a C_{3-5} cycloalkyl group represents a cyclic carbon group of 3 to 5 carbon atoms, more particularly a cyclopropyl, cyclobutyl or cyclopentyl;

- alkenylene is a divalent unsaturated aliphatic group containing 2 carbons, more particularly an ethylene;

- 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 in which one or more hydrogen atoms have been substituted by a fluorine atom;

- fluoroalkoxy is an alkoxy group in which one or more hydrogen atoms have been substituted by a fluorine atom;

- fluorothioalkyl is a thioalkyl group in which one or more hydrogen atoms have been substituted by a fluorine atom; and

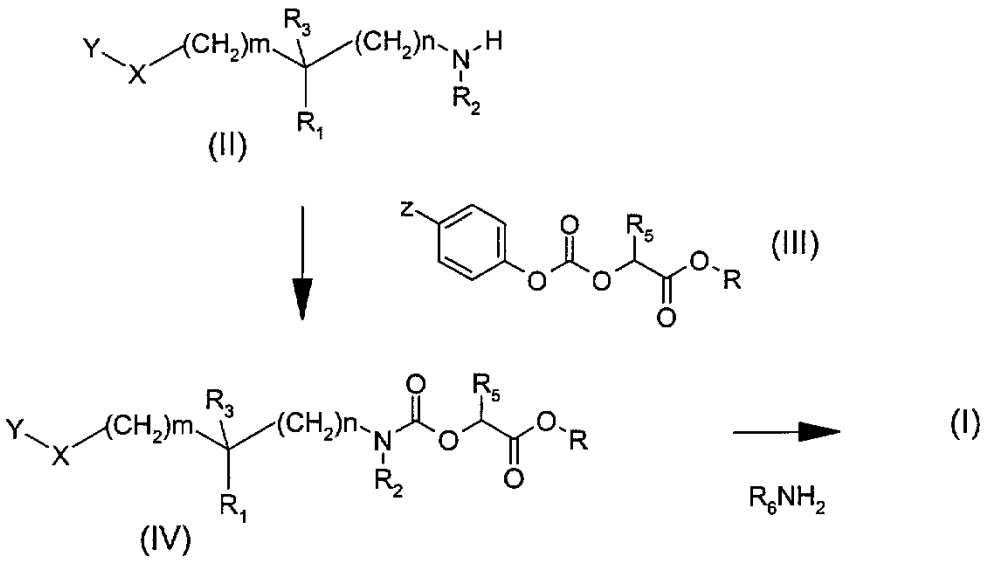
- a halogen atom is a fluorine, a chlorine, a bromine or an iodine.

The compounds of the invention may be prepared according to different methods, which are illustrated by the schemes which follow.

Thus one method of preparation (Scheme 1) consists in reacting an amine of general formula (II), in which Y, X, R_1, R_2, R_3, m and n are as defined in the general formula (I), with a carbonate of general formula (III), in which Z represents a hydrogen atom or a nitro group, R_5 is as defined in the general formula (I) and R represents a methyl or ethyl group, in a solvent such as toluene or dichloroethane, at a temperature of between 0 and 80°C . The resultant carbamate esters of general formula (IV) are subsequently converted into compounds of general formula (I) by aminolysis, by means of an amine of general formula R_6NH_2 where R_6 is as defined in the

general formula (I). The aminolysis reaction may be carried out in a solvent such as methanol or ethanol, or a mixture of solvents such as methanol and tetrahydrofuran.

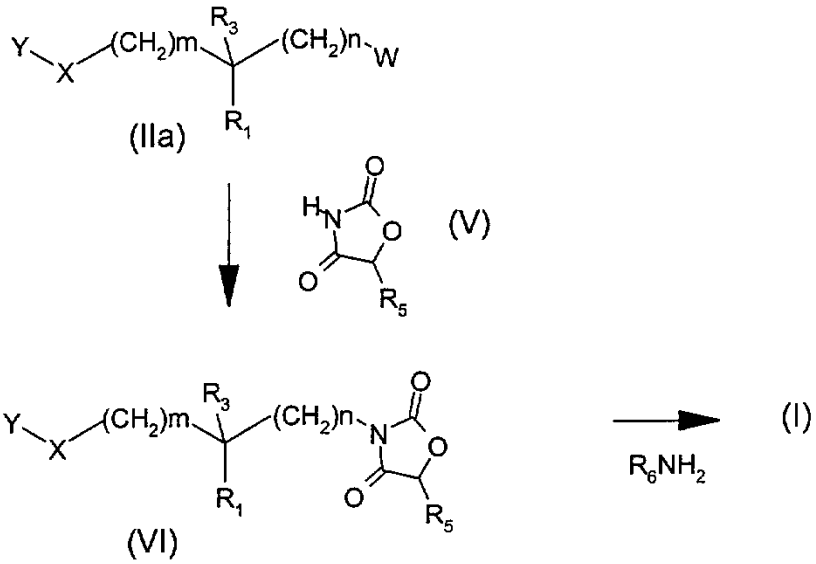
Scheme 1



Another method (Scheme 2) of obtaining the compounds of general formula (I) in which R_2 represents more particularly a hydrogen atom consists in reacting a derivative of general formula (IIa) in which W represents a hydroxyl, mesylate or tosylate group or a chlorine, bromine or iodine atom, and in which Y, X, R_1, R_3, m and n are as defined in the general formula (I), with an oxazolidine dione of general structure (V), in which R_5 is as defined in the general formula (I), to give the oxazolidine dione derivative of general structure (VI). In the case where W represents a hydroxyl group the reaction may be conducted according

to the conditions of Mitsunobu (Synthesis, 1981, 1-28); for example, by the action of diethyl or diisopropyl azodicarboxylate in the presence of triphenylphosphine. In the case where W represents a chlorine, bromine or iodine atom or a mesylate or tosylate group the reaction may be conducted in the presence of a base such as 1,1,3,3-tetramethylguanidine, sodium hydride or sodium *tert*-butoxide in a solvent such as tetrahydrofuran, acetonitrile or dimethylformamide at a temperature of between 0°C and the reflux temperature of the solvent. The resultant oxazolidine dione derivative of general formula (VI) is subsequently converted into a compound of general formula (I) by aminolysis, by means of an amine of general formula R_6NH_2 where R_6 is as defined in the general formula (I).

Scheme 2

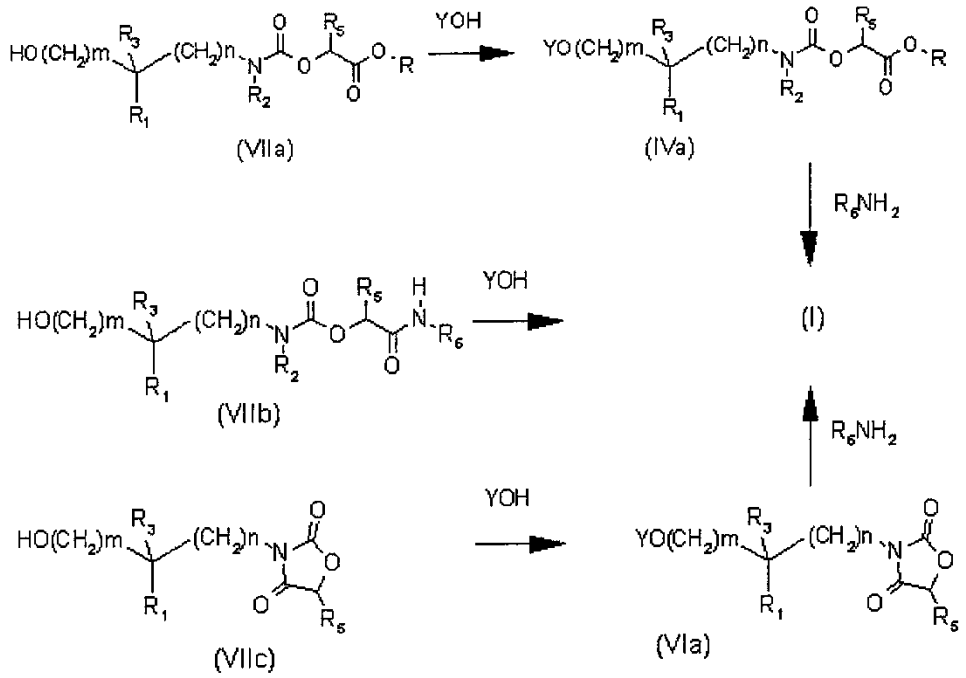


Another variant (Scheme 3), for obtaining the

compounds of general formula (I) in which X represents more particularly an oxygen atom, consists in reacting an alcohol derivative of general formula (VIIa), (VIIb) or (VIIc) with a phenol derivative of general structure YOH, in which the Y is as defined in the general formula (I), for example in accordance with the Mitsunobu reaction conditions (Synthesis, 1981, 1-28) or modified conditions (Tetrahedron Letters 1993, 34, 1639-1642), the carbamate ester (IVa) and oxazolidine dione (VIa) derivatives being subsequently converted into compounds of general formula (I) by aminolysis reaction by means of an amine of general structure R_6NH_2 where R_6 is as defined in the general formula (I).

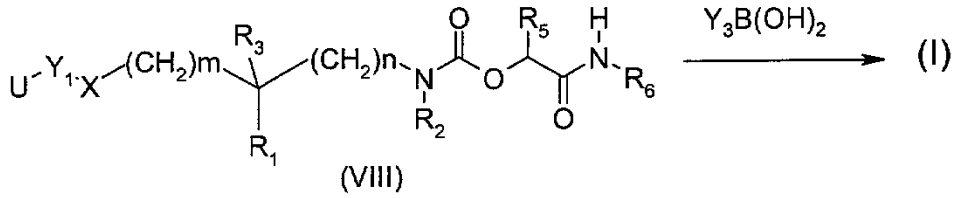
In the general formulae (VIIa), (VIIb) and (VIIc), the groups R_1, R_2, R_3, R_5, R_6, m, n and R are as defined above.

Scheme 3



Another variant (Scheme 4) for obtaining the compounds of general formula (I) in which Y represents more particularly a group Y_1-Y_3 of aryl-aryl, aryl-heteroaryl, heteroaryl-aryl or heteroaryl-heteroaryl type, consists in reacting an aryl halide derivative of general structure (VIII), in which U is a bromine or iodine atom and Y_1, X, R_1, R_2, R_3, R_5, R_6, n and m are as defined in the general formula (I), with an arylboronic or heteroarylboronic acid derivative of formula $Y_3B(OH)_2$, where Y_3 is as defined in the general formula (I), in accordance with the Suzuki reation conditions (Chem. Rev. 1995, 95, 2457-2483) or with an aryl- or heteroaryl-tri-alkylstannane derivative of formula $Y_3Sn(R')_3$, where Y_3 is as defined in the general formula (I) and R' is a C_{1-4} alkyl, in accordance with the Stille reaction conditions (Angew. Chem. Int. Ed. 1986, 25, 504-524).

Scheme 4



(VIII)

The compounds of general formulae (II), (IIa), (III), (V), (VIIa), (VIIb), (VIIc) and (VIII) and the phenol derivatives of general structure YOH, when the method by which they are prepared is not described, are available commercially or are described in the literature, or else may be prepared according to methods which are described therein or which are known to the person skilled in the art.

The amines of general formula R_6NH_2 are available commercially.

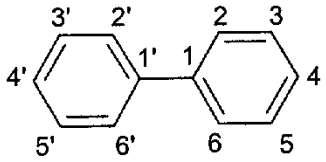
The examples which follow illustrate the preparation of some compounds of the invention. These examples are not limitative, and merely illustrate the invention. The microanalyses, the IR and NMR spectra and/or the LC-MS (Liquid Chromatography coupled to Mass Spectroscopy) confirm the structures and purities of the compounds obtained.

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

The numbers indicated in parentheses in the titles of the examples correspond to those from the 1st

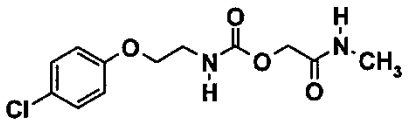
column of the table thereafter.

The IUPAC (International Union of Pure and Applied Chemistry) nomenclature has been used for naming the compounds in the following examples. For example, for the biphenyl group, the following numbering has been respected:



Example 1 (Compound 1)

2-(methylamino)-2-oxoethyl {2-[(4-chlorophenyl)-oxy]ethyl}carbamate



1.1 ethyl [(phenyloxycarbonyl)oxy]acetate

A solution of 25 g (240 mmol) of ethyl glycolate and of 55 ml (315 mmol) of diisopropylethylamine in 500 ml of toluene is admixed slowly at ambient temperature with 32 ml (256 mmol) of phenyl chloroformate. Stirring is continued at ambient temperature for 2 hours. The salt formed is separated off and the filtrate is concentrated under reduced

pressure. This gives 53.7 g of oily product, used as it is in the following step.

1.2. ethyl {[({2-[(4-chlorophenyl)oxy]ethyl}-amino)carbonyl]oxy}acetate

A solution of 0.6 g (3.5 mmol) of [(4-chlorophenyl)oxy]ethylamine (Chim. Ther. 1973, 8, 259-270) and 1.3 g (5.8 mmol) of ethyl [(phenyloxycarbonyl)oxy]acetate, prepared in Step 1.1., in 30 ml of toluene is heated at 60°C overnight. It is evaporated to dryness and the product is purified by chromatography on silica gel, eluting with a 30/70 mixture of ethyl acetate and cyclohexane. This gives 0.7 g of oily product, containing ~10% of cyclized oxazolidine dione product, used as it is in the following step.

1.3. 2-(methylamino)-2-oxoethyl {2-[(4-chlorophenyl)oxy]ethyl}carbamate

3.5 ml (7 mmol) of a 2M solution of methylamine in tetrahydrofuran are added to a solution of 0.7 g (2.3 mmol) of ethyl {[({2-[(4-chlorophenyl)-oxy]ethyl}amino)carbonyl]oxy}acetate, prepared in Step 1.2., in 5 ml of methanol. The mixture is left to react at ambient temperature overnight. It is evaporated to dryness and the residual solid is washed with hexane and then with diisopropyl ether, to give 0.59 g of product in powder form.

Melting point (°C): 147-149

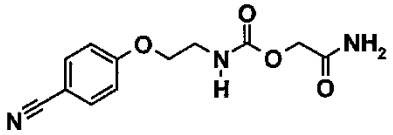
LC-MS: M+H = 287

^{1}H NMR (DMSO) δ(ppm): 7.75 (m, 1H), 7.40 (m, 1H), 7.25 (d, 2H), 6.95 (d, 2H), 4.35 (s, 2H), 3.95 (t, 2H), 3.35 (m, 2H), 2.60 (d, 3H).

Example 2 (compound 11)

2-amino-2-oxoethyl (2-[(4-cyanophenyl)oxy]ethyl)-carbamate

2.1 3-(2-hydroxyethyl)-1,3-oxazolidine-2,4-dione



A solution of 3 ml (39.6 mmol) of methyl glycolate in 25 ml of tetrahydrofuran is added dropwise over 2 hours to a solution of 49 ml (95 mmol) of phosgene, 1.9M in toluene, which is diluted in 50 ml of tetrahydrofuran and cooled using an ice bath. The mixture is subsequently stirred at ambient temperature for 16 hours and evaporated to dryness. Coevaporation is carried out 4 times with 30 ml of dichloromethane. The residue is taken up with 40 ml of acetonitrile and added dropwise over 1 hour to a solution of 3.4 ml (59.4 mmol) of ethanolamine and 30 ml (178 mmol) of diisopropylethylamine in a 50/10 mixture of acetonitrile and dichloromethane, cooled using an ice bath. The mixture is subsequently stirred at ambient temperature for 16 hours. It is filtered over celite and evaporated to dryness and the product is purified

by chromatography on silica gel, eluting with a 70/30 then 80/20 mixture of ethyl acetate and n-hexane, to give 4.9 g of product in white solid form.

2.2. 2-amino-2-oxoethyl (2-[(4-cyanophenyl)-oxy]ethyl)carbamate

0.61 ml (1.35 mmol) of a 2.2M solution of diethyl azodicarboxylate in toluene is added dropwise to a solution of 0.13 g (0.88 mmol) of 3-(2-hydroxyethyl)-1,3-oxazolidine-2,4-dione, prepared in Step 2.1., 0.35 g (1.35 mmol) of triphenylphosphine and 0.10 g (0.89 mmol) of 4-hydroxybenzonitrile in 2 ml of benzene, cooled using an ice bath. The reaction mixture is subsequently stirred at ambient temperature for 16 hours. It is evaporated to dryness and the product is purified by chromatography on silica gel, eluting with a 99/1 then 98/2 mixture of dichloromethane and ethyl acetate. The product is taken up in 1.5 ml of a 7M solution of ammonia (10.5 mmol) in methanol. This solution is stirred for one hour. The precipitate is filtered off and washed with ethyl acetate, to give 0.035 g of white solid.

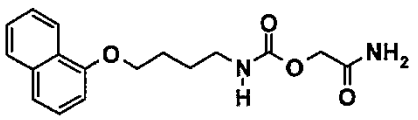
Melting point (°C): 204-206

LC-MS: M+H = 264

^{1}H NMR (DMSO) δ(ppm): 7.55 (d, 2H), 7.05 (m, 1H), 6.90-6.80 (m+d, 4H), 4.35 (s, 2H), 4.05 (t, 2H), 3.45 (m, 2H)

Example 3 (compound 58)

2-amino-2-oxoethyl [4-(1-naphthalenyloxy]butyl]-carbamate



3.1. 3-[4-(1-naphthalenyloxy]butyl]-1,3-oxazolidine-2,4-dione

A solution of 3.1 g (11.1 mmol) of 1-[(4-bromobutyl)oxy]naphthalene (Eur. J. Med. Chem. 1997, 32, 175-179) and 1.35 g (13.3 mmol) of 1,3-oxazolidine-2,4-dione (J. Med. Chem. 1991, 34, 1542-1543) in 30 ml of tetrahydrofuran is admixed dropwise with a solution of 2.55 g (22.2 mmol) of 1,1,3,3-tetramethylguanidine in 15 ml of tetrahydrofuran. The mixture is heated at reflux for 8 hours. 0.28 g (2.7 mmol) of 1,3-oxazolidine-2,4-dione and 0.32 g (2.7 mmol) of 1,1,3,3-tetramethylguanidine are added and the mixture is heated at reflux for 4 more hours. The reaction mixture is cooled using an ice bath, and 100 ml of ethyl acetate and then 50 ml of 1M aqueous hydrochloric acid are added. The system is decanted and the aqueous phase is extracted with 2 × 80 ml of ethyl acetate. The organic phases are subsequently washed with 80 ml of water and then with 80 ml of saturated aqueous sodium chloride solution. They are dried over sodium sulphate and then evaporated to dryness. The product is purified by chromatography on silica gel, eluting with an 80/20

mixture of cyclohexane and ethyl acetate, to give 2.0 g of product, which is used as it is in the following step.

3.2. 2-amino-2-oxoethyl [4-(1-naphthalenyl-oxy)butyl]carbamate

1.50 g (5.0 mmol) of 3-[4-(1-naphthalenyl-oxy)butyl]-1,3-oxazolidine-2,4-dione, prepared in Step 3.1., are dissolved in a mixture of 10 ml of tetrahydrofuran and 28 ml of a 7N solution of ammonia (200 mmol) in methanol. The solution is left to react overnight at ambient temperature and then evaporated to dryness. The product is purified by chromatography on silica gel, eluting with a 97/3 mixture of dichloromethane and methanol. It is recrystallized from ethyl acetate and then washed with diethyl ether, to give 0.73 g of product in white solid form.

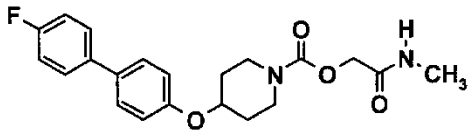
Melting point (°C): 80-82

LC-MS: M+H = 317

^{1}H NMR ($CDCl_3$) δ(ppm): 8.25 (dd, 1H), 7.80 (dd, 1H), 7.55-7.30 (m, 4H), 6.80 (d, 1H), 6.00 (m, 1H), 5.65 (m, 1H), 5.05 (m, 1H), 4.65 (s, 2H), 4.20 (t, 2H), 3.35 (m, 2H), 2.00 (m, 2H), 1.90 (m, 2H)

Example 4 (compound 85)

2-(methylamino)-2-oxoethyl 4-[(4'-fluoro-4-biphenyl)-oxy]-1-piperidinecarboxylate



4.1. 1,1-dimethylethyl 4-[(4-bromophenyl)-oxy]-1-piperidinecarboxylate

A solution of 2.01 g (10 mmol) of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate in 20 ml of dimethylformamide is admixed with 7 g (40 mmol) of 1-bromo-4-fluorobenzene and 2.5 g (50 mmol) of sodium hydride at 50% in mineral oil. The mixture is stirred at 100°C for 3 hours and then evaporated to dryness. The residue is taken up in 50 ml of ice-water and extracted with dichloromethane. The organic extracts are evaporated to dryness, to give 3.5 g of an oily product, which is used as it is in the following step.

4.2. 4-[(4-bromophenyl)oxy]piperidine

A solution of 3.5 g (9.83 mmol) of 1,1-dimethylethyl 4-[(4-bromophenyl)oxy]-1-piperidine-carboxylate, prepared in Step 4.1., in 20 ml of dichloromethane is admixed with 10 ml of trifluoroacetic acid and the solution is stirred at ambient temperature for 1 hour. It is evaporated to dryness and then the residue is taken up in 30 ml of toluene, which is evaporated again to dryness. The residue is subsequently washed with pentane and then taken up in a mixture of 60 ml of dichloromethane and 20 ml of 4N aqueous ammonia solution. It is stirred

vigorously for 15 minutes and then the organic phase is decanted, dried over sodium sulphate and evaporated to dryness, to give 2.7 g of product in oil form, which is used as it is in the following step.

4.2. 2-(ethyloxy)-2-oxoethyl 4-[(4-bromophenyl)oxy]-1-piperidinecarboxylate

2.7 g (7.58 mmol) of 4-[(4-bromophenyl)oxy]piperidine, prepared in Step 4.2., and 1.70 g (7.6 mmol) of ethyl {[(phenyloxy)carbonyl]oxy}acetate, prepared in accordance with Example 1.1, are mixed in 40 ml of toluene and the solution is heated at 50°C for 20 hours. After cooling, it is evaporated to dryness and the product is purified by chromatography on silica gel, eluting with a 40/60 mixture of ethyl acetate and cyclohexane. The eluate is subsequently triturated in diisopropyl ether, to give 2.9 g of product in powder form.

Melting point (°C): 87-88

4.3. 2-(methylamino)-2-oxoethyl 4-[(4-bromophenyl)oxy]-1-piperidinecarboxylate

2.9 g (7.5 mmol) of 2-(ethyloxy)-2-oxoethyl 4-[(4-bromophenyl)oxy]-1-piperidinecarboxylate, prepared in Step 4.3., in solution in 10 ml of a 33% ethanolic solution of methylamine are stirred at ambient temperature for 20 hours. Following evaporation, the product is purified by chromatography on silica gel, eluting with ethyl acetate, to give

0.8 g of product in gum form, which is used as it is in the following step.

4.5. 2-(methylamino)-2-oxoethyl 4-[(4'-fluoro-4-biphenyl)oxy]-1-piperidinecarboxylate

0.1 g (0.27 mmol) of 2-(methylamino)-2-oxoethyl 4-[(4-bromophenyl)oxy]-1-piperidinecarboxylate, prepared in Step 4.4., 0.01 g of tetrakis(triphenylphosphine)palladium(0) and 0.057 g (0.4 mmol) of 4-fluorophenylboronic acid are placed in a glass tube with stopper. 4 ml of toluene, 2 ml of a 2N aqueous solution of sodium carbonate and 0.5 ml of ethanol are added. The mixture is heated at 80°C with stirring for 2 hours. After it has cooled, 1 ml of water and 2 ml of toluene are added. The organic phase is withdrawn and the product is purified by chromatography on silica gel, eluting with a 95/5 mixture of dichloromethane and methanol. The product is redissolved in 1 ml of ethanol and then reprecipitated by adding 2 ml of water, to give 0.031 g of product in powder form.

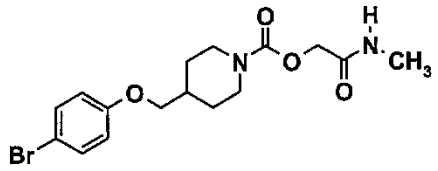
Melting point (°C): 117-119

LC-MS: M+H 387

^{1}H NMR ($CDCl_3$) δ(ppm): 7.70 (dd, 2H), 7.65 (d, 2H), 7.30 (dd, 2H), 7.20 (d, 2H), 6.25 (broad s, 1H), 4.80 (s + m, 3H), 4.00-3.70 (m, 4H), 3.05 (d, 3H), 2.25-2.00 (m, 4H)

Example 5 (compound 120)

2-(methylamino)-2-oxoethyl 4-{[(4-bromophenyl)oxy]-methyl}-1-piperidinecarboxylate



5.1. 1,1-dimethylethyl 4-{[(4-bromophenyl)-oxy]methyl}-1-piperidinecarboxylate

The procedure described in Example 4.1. is repeated. Starting from 2.5 g (11.6 mmol) of 1,1-dimethylethyl 4-(hydroxymethyl)-1-piperidine-carboxylate and 8.13 g (46.4 mmol) of 1-bromo-4-fluorobenzene gives 5.75 g of crude product in oil form.

5.2. 4-{[(4-bromophenyl)oxy]methyl}piperidine

The procedure described in Example 4.2 is repeated. Starting from 5.75 g of 1,1-dimethylethyl 4-{[(4-bromophenyl)oxy]methyl}-1-piperidinecarboxylate, prepared in Step 5.1, gives 3 g of product in oil form.

5.3. 2-(ethyloxy)-2-oxoethyl 4-{[(4-bromophenyl)oxy]methyl}-1-piperidinecarboxylate

The procedure described in Example 4.3. is repeated. Starting from 1.6 g (5.9 mmol) of 4-{[(4-bromophenyl)oxy]methyl}piperidine, prepared in Step 5.2., and from 1.32 g (5.9 mmol) of ethyl {[(phenyloxy)carbonyl]oxy}acetate, prepared in accordance with Example 1.1., gives the product in oil form.

5.4. 2-(methylamino)-2-oxoethyl 4-{[(4-bromophenyl)oxy]methyl}-1-piperidinecarboxylate

The procedure described in Example 4.4. is repeated. Starting from 2-(ethyloxy)-2-oxoethyl 4-{[(4-bromophenyl)oxy]methyl}-1-piperidinecarboxylate, prepared in Step 5.3, gives 1.1 g of product in powder form.

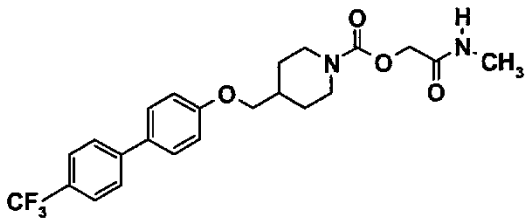
Melting point (°C): 163-165

LC-MS: M+H = 386

^{1}H NMR ($CDCl_3$) δ(ppm): 7.35 (d, 2H), 6.75 (d, 2H), 6.05 (broad s, 1H), 4.70-4.50 (m, 2H), 4.30-4.10 (m, 2H), 3.80 (d, 2H), 3.00-2.75 (m, 2H), 2.85 (d, 3H), 2.10-1.80 (m, 3H), 1.45-1.20 (m, 2H)

Example 6 (compound 154)

2-(methylamino)-2-oxoethyl 4-{[(4'-(trifluoromethyl)-4-biphenyl)oxy]methyl}-1-piperidinecarboxylate



The procedure described in Example 4.5. is repeated. Starting from 0.1 g (0,26 mmol) of 2-(methylamino)-2-oxoethyl 4-{[(4-bromophenyl)oxy]methyl}-1-piperidine-carboxylate, prepared in accordance with Example 5, and from 0.074 g (0.389 mmol) of 4-trifluoromethylphenyl-boronic acid gives 0.049 g of product in powder form.

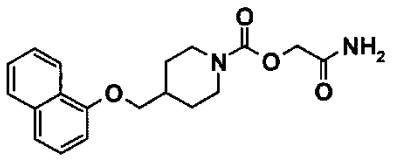
Melting point (°C): 197-199

LC-MS: M+H = 451

^{1}H NMR (DMSO) δ(ppm) : 7.85-7.65 (m, 7H), 7.05 (d, 2H), 4.35 (s, 2H), 4.05 (broad d, 2H), 3.90 (d, 2H), 2.85 (m, 2H), 2.60 (d, 3H), 2.00 (m, 1H), 1.80 (broad d, 2H), 1.35-1.10 (m, 2H).

Example 7 (compound 137)

2-amino-2-oxoethyl 4-[(1-naphthalenyloxy)methyl]-1-piperidinecarboxylate



7.1. 1,1-dimethylethyl 4-[(1-naphthalenyloxy)methyl]-1-piperidinecarboxylate

A solution of 5.0 g (23.2 mmol) of 1,1-dimethylethyl 4-(hydroxymethyl)-1-piperidinecarboxylate, 4.3 g (29.8 mmol) of 1-naphthalenol and 7.82 g (29.8 mmol) of triphenylphosphine in 120 ml of tetrahydrofuran, cooled under nitrogen by means of an ice bath, is admixed dropwise with a solution of 6.03 g (29.8 mmol) of diisopropyl azodicarboxylate. The reaction mixture is allowed to return to ambient temperature and stirring is continued overnight. 2 ml of methanol are added and then the mixture is evaporated to dryness. The residue is taken up in 200 ml of dichloromethane and washed in succession with

a 10% aqueous potassium hydrogen sulphate solution, water and a 1M aqueous solution of sodium hydroxide. The system is dried over sodium sulphate and evaporated to dryness. The product is purified by chromatography on silica gel, eluting with an 80/20 then 70/30 and 50/50 mixture of cyclohexane and dichloromethane, to give 7.96 g of product in oil form, which solidifies. Melting point (°C): 97-100

7.2. 4-[(1-naphthalenyloxy)methyl]piperidine

A solution of 7.96 g (29.1 mmol) of 1,1-dimethylethyl 4-[(1-naphthalenyloxy)methyl]-1-piperidinecarboxylate, prepared in Step 7.1., in 120 ml of methanol and 28 ml of 35% aqueous hydrochloric acid is heated at 60°C for 6 hours. It is cooled to ambient temperature and evaporated to dryness, and then coevaporation is carried out twice with ethanol. The solid residue is washed with diethyl ether and then dried under vacuum in the presence of phosphorus pentoxide, to give 3.1 g of white solid.

The solid is taken up in 80 ml of water and a 30% aqueous sodium hydroxide solution is added until a basic pH is obtained, after which the system is extracted twice with 150 ml of diethyl ether. The extracts are dried over sodium sulphate and concentrated to dryness, to give 2.75 g of oily product, which is used as it is in the following step.

7.3. 2-(ethyloxy)-2-oxoethyl 4-[(1-

naphthalenyloxy)methyl]-1-piperidinecarboxylate

A solution of 2.75 g (11.4 mmol) of 4-[(1-naphthalenyloxy)methyl]piperidine, prepared in Step 7.2., and 2.56 g (11.4 mmol) of ethyl [(phenyloxycarbonyl)oxy]acetate, prepared in accordance with Example 1.1, in 80 ml of toluene is heated at 50°C overnight. It is evaporated to dryness and the residue is taken up in a mixture of water, dichloromethane and saturated aqueous sodium hydrogen carbonate solution. The organic phase is decanted, dried over sodium sulphate and evaporated to dryness. The product is purified by chromatography on silica gel, eluting with a 50/50 mixture of cyclohexane and dichloromethane and then with dichloromethane and with a 95/5 mixture of dichloromethane and ethyl acetate. This gives 2.05 g of product in oil form, which is used as it is in the following step.

7.4. 2-amino-2-oxoethyl 4-[(1-naphthalenyloxy)methyl]-1-piperidinecarboxylate

1.0 g (2.69 mmol) of 2-(ethyloxy)-2-oxoethyl 4-[(1-naphthalenyloxy)methyl]-1-piperidinecarboxylate, prepared in Step 7.3., is dissolved in 12 ml of a 7N solution of ammonia (84 mmol) in methanol. The solution is left to react at ambient temperature for 3 days. It is evaporated to dryness and the residue is purified by chromatography on silica gel, eluting with a 90/10 then 80/20, 70/30 and 50/50 mixture of dichloromethane and

ethyl acetate and then with a 95/5 mixture of ethyl acetate and methanol. The eluate is subsequently recrystallized from ethyl acetate, to give 0.77 of product.

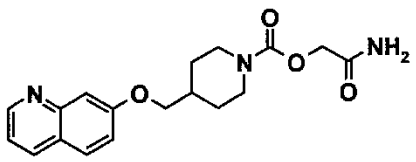
Melting point (°C): 135-136

LC-MS: M+H = 343

^{1}H NMR (DMSO) δ(ppm): 8.15 (dd, 1H), 7.80 (dd, 1H), 7.50-7.30 (m, 4H), 7.30 (m, 1H), 7.15 (m, 1H), 6.95 (d, 1H), 4.35 (s, 2H), 4.15-4.00 (m+d, 4H), 4.90 (m, 2H), 2.10 (m, 1H), 1.90 (d, 2H), 1.45-1.25 (m, 2H)

Example 8 (compound 148)

2-amino-2-oxoethyl 4-[(7-quinolinyloxy)methyl]-1-piperidinecarboxylate



8.1. 2-(methyloxy)-2-oxoethyl 4-(hydroxymethyl)-1-piperidinecarboxylate

The procedure described in Example 2.1. is repeated, using 6.84 g (59.4 mmol) of 4-(hydroxymethyl)piperidine, in place of ethanolamine, to give 7.85 g of product in colourless oil form.

8.2. 2-amino-2-oxoethyl 4-[(7-quinolinyloxy)methyl]-1-piperidinecarboxylate

0.26 g (1.03 mmol) of 1,1'-(azodicarbonyl)-dipiperidine (ADDP) is added to a solution of 0.16 g

(0.69 mmol) of 2-(methyloxy)-2-oxoethyl 4-(hydroxymethyl)-1-piperidinecarboxylate, prepared in Step 8.1., 0.26 ml (1.03 mmol) of tri-n-butylphosphine and 0.13 g (0.90 mmol) of 7-hydroxyquinoline in 2.5 ml of benzene, which is cooled by means of an ice bath. The mixture is stirred at 0°C for 15 minutes and then at ambient temperature for 16 hours. It is filtered over celite and rinsed with diethyl ether. The filtrates are evaporated to dryness and purified by chromatography on silica gel, eluting with a 70/30 mixture of ethyl acetate in n-hexane. The product obtained is dissolved in 3 ml (21 mmol) of a 7M solution of ammonia in methanol. The solution is stirred for 3 hours and then evaporated to dryness. The product is purified by chromatography on silica gel, eluting with a 90/10 mixture of ethyl acetate in ethanol, and recrystallized from ethyl acetate, to give 0.115 g of product in white solid form.

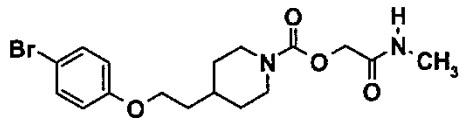
Melting point (°C): 137-139

LC-MS: M+H = 344

^{1}H NMR ($CDCl_3$) δ(ppm): 7.80 (dd, 1H), 8.05 (dd, 1H), 7.70 (d, 1H), 7.40 (d, 1H), 7.30-7,15 (m, 2H), 6.05 (m, 1H), 5.65 (m, 1H), 4.60 (s, 2H), 4.25 (m, 2H), 4.00 (d, 2H), 2.90 (m, 2H), 2.10 (m, 1H), 1.95 (d, 2H), 1.50-1.30 (m, 2H)

Example 9 (compound 168)

2-(methylamino)-2-oxoethyl 4-{2-[(4-bromophenyl)-oxy]ethyl}-1-piperidinecarboxylate



9.1. 1,1-dimethylethyl 4-{2-[(4-bromophenyl)-oxy]ethyl}-1-piperidinecarboxylate

The procedure described in Example 4.1. is repeated. Starting from 1.93 g (8.4 mmol) of 1,1-dimethylethyl 4-(2-hydroxyethyl)-1-piperidine-carboxylate and 5.88 g (33.6 mmol) of 1-bromo-4-fluorobenzene gives 4.1 g of crude product in oil form.

9.2. 4-{2-[(4-bromophenyl)oxy]ethyl}piperidine

The procedure described in Example 4.2. is repeated. Starting from 1,1-dimethylethyl 4-{2-[(4-bromophenyl)oxy]ethyl}-1-piperidinecarboxylate, prepared in Step 9.1., gives 1.79 g of product in powder form.

Melting point (°C): 100-102

9.3. 2-(ethyloxy)-2-oxoethyl 4-{2-[(4-bromophenyl)oxy]ethyl}-1-piperidinecarboxylate

The procedure described in Example 4.3. is repeated. Starting from 1.76 g (6.19 mmol) of 4-{2-[(4 bromophenyl)oxy]ethyl} prepared in Step 9.2., and 1.39 g (6.19 mmol) of ethyl {[(phenyloxy)carbonyl]oxy}-

acetate, prepared in accordance with Example 1.1., gives 1.4 g of product in oil form.

9.4. 2-(methylamino)-2-oxoethyl 4-{2-[(4-bromophenyl)oxy]ethyl}-1-piperidinecarboxylate

The procedure described in Example 4.4. is repeated. Starting from 1.3 g (3.14 mmol) of 2-(ethyloxy)-2-oxoethyl 4-{2-[(4-bromophenyl)oxy]ethyl}-1-piperidinecarboxylate, prepared in Step 9.3., gives 0.95 g of product in powder form.

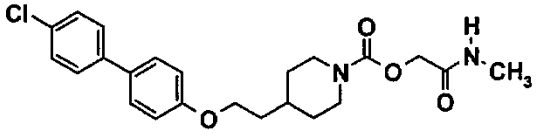
Melting point (°C): 101-103

LC-MS: M+H = 400

^{1}H NMR ($CDCl_3$) δ(ppm): 7.55 (d, 2H), 7.00 (d, 2H), 6.25 (broad s, NH), 4.90-4.70 (m, 2H), 4.50-4.25 (m, 2H), 4.20 (t, 2H), 3.20-2.90 (m, 2H), 3.10 (d, 3H), 2.05-1.90 (m, 5H), 1.55-1.30 (m, 2H)

Example 10 (compound 186)

2-(methylamino)-2-oxoethyl 4-{2-[(4'-chloro-4-biphenyl)oxy]ethyl}-1-piperidinecarboxylate



The procedure described in Example 4.5 is repeated. Starting from 0.1 g (0.25 mmol) of 2-(methylamino)-2-oxoethyl 4-{2-[(4-bromophenyl)-

oxy]ethyl}-1-piperidinecarboxylate, prepared in accordance with Example 9, and 0.117 g (0.75 mmol) of 4-chlorophenylboronic acid gives 0.087 g of product in powder form.

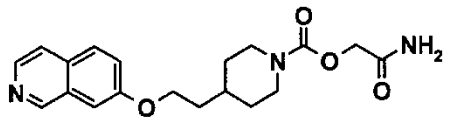
Melting point (°C): 104-106

LC-MS: M+H = 431

^{1}H NMR ($CDCl_3$) δ(ppm): 7.70-7.50 (m, 6H), 7.10 (d, 2H), 6.20 (broad s, NH), 4.85-4.60 (m, 2H), 4.45-4.15 (m, 2H), 4.20 (t, 2H), 3.15-2.95 (m, 2H), 3.05 (d, 3H), 2.10-1.85 (m, 5H), 1.50-1.25 (m, 2H)

Example 11 (compound 183)

2-amino-2-oxoethyl 4-[2-(7-isoquinolinyloxy)ethyl]-1-piperidinecarbamate



11.1. 2-(methyloxy)-2-oxoethyl 4-(2-hydroxyethyl)-1-piperidinecarboxylate

The procedure described in Example 2.1. is repeated, using7.6 g (59.4 mmol) of 4-(2-hydroxyethyl)piperidine, in place of ethanolamine, to give 7.1 g of product in colourless oil form.

11.2. 2-amino-2-oxoethyl 4-[2-(7-isoquinolinyloxy)ethyl]-1-piperidinecarbamate

The procedure described in Example 8.2. is repeated, starting from 0.46 g (1.84 mmol) of ADDP, 0.30 g (1.24 mmol) of 2-(methyloxy)-2-oxoethyl 4-(2-hydroxyethyl)-1-piperidinecarboxylate, prepared in

Step 11.1., 0.46 ml of tri-n-butylphosphine and 0.26 g (1.84 mmol) of 7-hydroxyisoquinoline in 4 ml of benzene. The product is purified by chromatography on silica gel, eluting with ethyl acetate and then with a 95/5 mixture of ethyl acetate and ethanol, to give 0.25 g of product in white solid form.

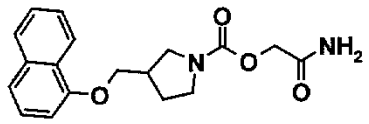
Melting point (°C): 179-181

LC-MS: M+H = 358

^{1}H NMR ($CDCl_3$) δ(ppm): 9.15 (s, 1H), 8.45 (d, 1H), 7.60 (d, 1H), 7.35 (dd, 1H), 7.20 (d, 1H), 6.05 (m, 1H), 5.75 (m, 1H), 4.60 (s, 2H), 4.20 (t, 4H), 2.90 (m, 2H), 1.90-1.70 (m, 5H), 1.40-1.20 (m, 2H)

Example 12 (compound 83)

2-amino-2-oxoethyl 3-[(1-naphthalenyloxy)methyl]-1-pyrrolidinecarboxylate



12.1. 1,1-dimethylethyl 3-[(1-naphthalenyloxy)methyl]-1-pyrrolidinecarboxylate

A solution of 1.0 g (4.9 mmol) of 1,1-dimethylethyl 3-(hydroxymethyl)-1-pyrrolidinecarboxylate (described in WO 0066557), 0.95 g (6.4 mmol) of 1-naphthalenol and 1.4 g (6.9 mmol) of tri-*n*-butylphosphine in 40 ml of toluene

and 20 ml of tetrahydrofuran, cooled under nitrogen by means of an ice bath, is admixed dropwise with a solution of 1.74 g (6.9 mmol) of ADDP. The reaction mixture is allowed to return to ambient temperature and stirring is continued for 24 hours. The mixture is filtered and the precipitate is rinsed with toluene. It is evaporated to dryness. The residue is taken up in dichloromethane and washed with a 1M aqueous sodium hydroxide solution. It is dried over sodium sulphate and evaporated to dryness. The residue is purified by chromatography on a silica gel column, eluting with dichloromethane and then with a 98/2 mixture of dichloromethane and methanol, to give 0.80 g of product in colourless oil form

12.2. 3-[(1-naphthalenyloxy)methyl]-pyrrolidine

A solution of 0.42 g (1.28 mmol) of 1,1-dimethylethyl 3-[(1-naphthalenyloxy)methyl]-1-pyrrolidinecarboxylate, prepared in Step 12.1., in 10 ml of 1,4-dioxane and 6 ml of a 2N solution of aqueous hydrochloric acid is stirred for 6 hours. It is evaporated to dryness and then coevaporation is carried out twice with toluene. The solid residue is washed with diethyl ether. The solid is taken up in dichloromethane and concentrated ammonia solution is added until a basic pH is obtained. The system is filtered on a Whatman PTFE cartridge and the organic

phase is concentrated, to give 0.21 g of oily product, which is used as it is in the following step.

12.3. 2-(ethyloxy)-2-oxoethyl 3-[(1-naphthalenyloxy)methyl]-1-pyrrolidinecarboxylate

A solution of 0.20 g (0.88 mmol) of 3-[(1-naphthalenyloxy)methyl]pyrrolidine, prepared in Step 12.2., and 0.35 g (1.5 mmol) of ethyl [(phenyloxycarbonyl)oxy]acetate, prepared in accordance with Example 1.1, in 6 ml of toluene is heated at 60°C overnight. It is evaporated to dryness and the residue is taken up in a mixture of water, dichloromethane and saturated aqueous sodium hydrogen carbonate solution. The organic phase is decanted, dried over sodium sulphate and evaporated to dryness. The residue is purified by chromatography on a silica gel column, eluting with dichloromethane and then with a 99/1 mixture of dichloromethane and methanol. This gives 0.24 g of product in oil form, which is used as it is in the following step.

12.4. 2-amino-2-oxoethyl 3-[(1-napthalenyl-oxy)methyl]-1-pyrrolidinecarboxylate

0.24 g (0.67 mmol) of 2-(ethyloxy)-2-oxoethyl 3-[(1-naphthenyloxy)methyl]-1-pyrrolidinecarboxylate, prepared in Step 12.3., is dissolved in 15 ml of a 7N solution of ammonia (105 mmol) in methanol. The solution is stirred in a stoppered tube at ambient temperature for 3 days. It is evaporated to dryness and

the residue is purified by chromatography on a silica gel column, eluting with a 97/3 then 94/6 mixture of dichloromethane and methanol. The solid obtained is triturated in diethyl ether and filtered, to give 0.15 g of product.

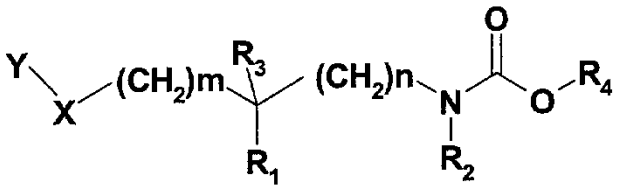
Melting point (°C): 161-163

LC-MS: M+H = 329

^{1}H NMR (DMSO) δ(ppm): 8.15 (m, 1H), 7.75 (m, 1H), 7.50-7.30 (m, 4H), 7.10-6.90 (s, 2H), 6.80 (m, 1H), 4.40 (s, 2H), 4.20-4.05 (m, 2H), 3.90-3.30 (m, 4H), 2.90-2.70 (m, 1H), 2.30-2.10 (m, 1H), 2.05-1.85 (m, 1H).

The table which follows the chemical structures and the physical properties of some compounds according to the invention.

Table



(I)

Cpd	Y	X	m	n	R_1	R_2	R_3	R_4	m.p.°C (or M+H)
1.	4-chlorophenyl	O	0	1	H	H	H	$CH_2CONHCH_3$	147-149
2.	4-chlorophenyl	O	0	1	H	H	H	CH_2CONH_2	128-130
3.	4-chlorophenyl	O	0	2	H	H	H	CH_2CONH_2	108-110
4.	4-chlorophenyl	O	0	3	H	H	H	CH_2CONH_2	116-118
5.	3-chlorophenyl	O	0	1	H	H	H	CH_2CONH_2	114-116
6.	3-chlorophenyl	O	0	2	H	H	H	CH_2CONH_2	90-92
7.	3-chlorophenyl	O	0	3	H	H	H	CH_2CONH_2	114-116
8.	2-chlorophenyl	O	0	1	H	H	H	CH_2CONH_2	128-130
9.	2-chlorophenyl	O	0	2	H	H	H	CH_2CONH_2	128-130
10.	2-chlorophenyl	O	0	3	H	H	H	CH_2CONH_2	110-112
11.	4-cyanophenyl	O	0	1	H	H	H	CH_2CONH_2	204-206
12.	4-cyanophenyl	O	0	2	H	H	H	CH_2CONH_2	173-175
13.	4-cyanophenyl	O	0	3	H	H	H	CH_2CONH_2	169-171
14.	3-cyanophenyl	O	0	1	H	H	H	CH_2CONH_2	142-143
15.	3-cyanophenyl	O	0	2	H	H	H	CH_2CONH_2	129-131
16.	3-cyanophenyl	O	0	3	H	H	H	CH_2CONH_2	123-125
17.	4-*iso*-propylphenyl	O	0	1	H	H	H	CH_2CONH_2	95-97
18.	4-*iso*-propylphenyl	O	0	2	H	H	H	CH_2CONH_2	(295)
19.	4-*iso*-propylphenyl	O	0	3	H	H	H	CH_2CONH_2	103-105

Cpd	Y	X	m	n	R_1	R_2	R_3	R_4	m.p.°C (or M+H)
20.	3-*iso*-propylphenyl	O	0	1	H	H	H	CH_2CONH_2	96-98
21.	3-*iso*-propylphenyl	O	0	2	H	H	H	CH_2CONH_2	(295)
22.	3-*iso*-propylphenyl	O	0	3	H	H	H	CH_2CONH_2	88-90
23.	4-tert-butylphenyl	O	0	2	H	H	H	CH_2CONH_2	90-92
24.	4-*tert*-butylphenyl	O	0	3	H	H	H	CH_2CONH_2	(323)
25.	3-*tert*-butylphenyl	O	0	2	H	H	H	CH_2CONH_2	(309)
26.	3-*tert*-butylphenyl	O	0	3	H	H	H	CH_2CONH_2	(323)
27.	4-(1,1,3,3-tetramethylbutyl)phenyl	O	0	2	H	H	H	CH_2CONH_2	(365)
28.	4-(1,1,3,3-tetramethylbuty)phenyl	O	0	3	H	H	H	CH_2CONH_2	(379)
29.	4-(1,1-dimethylphenyl methyl)phenyl	O	0	1	H	H	H	CH_2CONH_2	(357)
30.	4-(1,1-dimethylphenyl methyl)phenyl	O	0	2	H	H	H	CH_2CONH_2	(371)
31.	4-(1,1-dimethylphenyl methyl)phenyl	O	0	3	H	H	H	CH_2CONH_2	(385)
32.	4-phenylphenyl	O	0	1	H	H	H	CH_2CONH_2	196-198
33.	4-phenylphenyl	O	0	2	H	H	H	CH_2CONH_2	187-189
34.	4-phenylphenyl	O	0	3	H	H	H	CH_2CONH_2	192-194
35.	4-(4-chlorophenyl)phenyl	O	0	1	H	H	H	CH_2CONH_2	193-195
36.	4-(3-chlorophenyl)phenyl	O	0	1	H	H	H	CH_2CONH_2	168-170
37.	4-(2-chlorophenyl)phenyl	O	0	1	H	H	H	CH_2CONH_2	114-116
38.	4-(4-methoxyphenyl) phenyl	O	0	1	H	H	H	CH_2CONH_2	194-196

Cpd	Y	X	m	n	R_1	R_2	R_3	R_4	m.p.°C (or M+H)
39.	4-(3-methoxyphenyl) phenyl	O	0	1	H	H	H	CH_2CONH_2	(345)
40.	4-(2-methoxyphenyl) phenyl	O	0	1	H	H	H	CH_2CONH_2	127-129
41.	3-phenylphenyl	O	0	1	H	H	H	CH_2CONH_2	126-128
42.	3-phenylphenyl	O	0	2	H	H	H	CH_2CONH_2	110-112
43.	3-phenylphenyl	O	0	3	H	H	H	CH_2CONH_2	127-129
44.	3-(4-chlorophenyl)phenyl	O	0	1	H	H	H	CH_2CONH_2	137-139
45.	3-(3-chlorophenyl)phenyl	O	0	1	H	H	H	CH_2CONH_2	90-92
46.	3-(2-chlorophenyl)phenyl	O	0	1	H	H	H	CH_2CONH_2	55-57
47.	3-(4-methoxyphenyl) phenyl	O	0	1	H	H	H	CH_2CONH_2	168-170
48.	3-(3-methoxyphenyl) phenyl	O	0	1	H	H	H	CH_2CONH_2	86-88
49.	2-phenylphenyl	O	0	1	H	H	H	CH_2CONH_2	92-94
50.	2-phenylphenyl	O	0	2	H	H	H	CH_2CONH_2	(329)
51.	2-phenylphenyl	O	0	3	H	H	H	CH_2CONH_2	(343)
52.	2-(4-chlorophenyl)phenyl	O	0	1	H	H	H	CH_2CONH_2	130-132
53.	2-(3-chlorophenyl)phenyl	O	0	1	H	H	H	CH_2CONH_2	88-90
54.	2-(2-chlorophenyl)phenyl	O	0	1	H	H	H	CH_2CONH_2	(349)
55.	2-(4-methoxyphenyl) phenyl	O	0	1	H	H	H	CH_2CONH_2	74-76
56.	naphthalen-1-yl	O	0	1	H	H	H	CH_2CONH_2	(289)
57.	naphthalen-1-yl	O	0	2	H	H	H	CH_2CONH_2	(303)
58.	naphthalen-1-yl	O	0	3	H	H	H	CH_2CONH_2	80-82

Cpd	Y	X	m	n	R_1	R_2	R_3	R_4	m.p.°C (or M+H)
59.	naphthalen-1-yl	O	0	3	H	H	H	$CH_2CONHCH_3$	90-92
60.	4-chloronaphthalen-1-yl	O	0	3	H	H	H	CH_2CONH_2	142-144
61.	4-chloronaphthalen-1-yl	O	0	3	H	H	H	$CH_2CONHCH_3$	108-110
62.	naphthalen-2-yl	O	0	1	H	H	H	CH_2CONH_2	(289)
63.	naphthalen-2-yl	O	0	2	H	H	H	CH_2CONH_2	158-160
64.	naphthalen-2-yl	O	0	3	H	H	H	CH_2CONH_2	171-173
65.	4-phenoxyphenyl	O	0	1	H	H	H	CH_2CONH_2	158-160
66.	4-phenoxyphenyl	O	0	2	H	H	H	CH_2CONH_2	141-143
67.	4-phenoxyphenyl	O	0	3	H	H	H	CH_2CONH_2	144-146
68.	pyridin-3-yl	O	0	1	H	H	H	CH_2CONH_2	135-137
69.	pyridin-3-yl	O	0	2	H	H	H	CH_2CONH_2	119-121
70.	pyridin-3-yl	O	0	3	H	H	H	CH_2CONH_2	96-98
71.	5-chloroquinolin-8-yl	O	0	1	H	H	H	CH_2CONH_2	232-234
72.	5-chloroquinolin-8-yl	O	0	2	H	H	H	CH_2CONH_2	183-185
73.	5-chloroquinolin-8-yl	O	0	3	H	H	H	CH_2CONH_2	184-186
74.	phenyl	O	1	0	H	H	CH_3	CH_2CONH_2	90-92
75.	4-CF_3-phenyl	O	0	2	$(CH_2)_2$		H	CH_2CONH_2	115-117
76.	4-Cl-phenyl	SO_2	0	2	$(CH_2)_2$		H	CH_2CONH_2	164-166
77.	4-Cl-phenyl	SO_2	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	168-170
78.	3-CF_3-phenyl	SO_2	0	2	$(CH_2)_2$		H	CH_2CONH_2	148-150
79.	3-CF_3-phenyl	SO_2	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	163-165
80.	naphthalen-1-yl	O	0	1	$(CH_2)_2$		H	$CH_2CONHCH_3$	111-113
81.	naphthalen-1-yl	O	1	1	CH_2		H	CH_2CONH_2	176-178
82.	naphthalen-1-yl	O	1	1	CH_2		H	$CH_2CONHCH_3$	112-114

Cpd	Y	X	m	n	R_1	R_2	R_3	R_4	m.p.°C (or M+H)
83.	naphthalen-1-yl	O	1	1	$(CH_2)_2$		H	CH_2CONH_2	161-163
84.	naphthalen-1-yl	O	1	1	$(CH_2)_2$		H	$CH_2CONHCH_3$	99-101
85.	4-(4-F-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	117-119
86.	4-(4-Cl-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	134-136
87.	4-(4-CH_3-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	121-123
88.	4-(4-*n*-butyl-phenyl) phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	105-107
89.	4-(4-CF_3-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	141-143
90.	4-(4-CH_3O-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	152-154
91.	4-(4-C_2H_5O-phenyl) phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	145-147
92.	4-(4-CF_3O-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	131-133
93.	4-(3-F,4-CH_3O-phenyl) phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(417)
94.	4-(3-Cl,4-F-phenyl) phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	124-126
95.	4-(3,4-Cl_2-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(438)
96.	3-(4-F-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(387)
97.	3-(4-Cl-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(403)
98.	3-(4-CH_3-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(383)
99.	3-(4-*n*-butylphenyl) phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(425)
100.	3-(4-CF_3-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(437)
101.	3-(4-CH_3O-phenyl) phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(399)

Cpd	Y	X	m	n	R_1	R_2	R_3	R_4	m.p.°C (or M+H)
102.	3-(4-C_2H_5O-phenyl) phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(413)
103.	3-(4-CF_3O-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(453)
104.	3-(3-F,4-CH_3O-phenyl) phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(417)
105.	3-(3-Cl,4-F-phenyl)- phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(421)
106.	3-(3,4-Cl_2-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(438)
107.	3-(2,4-Cl_2-phenyl)phenyl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(438)
108.	naphthalen-1-yl	O	0	2	$(CH_2)_2$		H	CH_2CONH_2	137-138
109.	naphthalen-1-yl	O	0	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	121-122
110.	naphthalen-2-yl	O	0	2	$(CH_2)_2$		H	CH_2CONH_2	118-120
111.	quinolin-8-yl	O	0	2	$(CH_2)_2$		H	CH_2CONH_2	(330)
112.	phenyl	O	1	2	$(CH_2)_2$		H	CH_2CONH_2	123-125
113.	4-Cl-phenyl	O	1	2	$(CH_2)_2$		H	CH_2CONH_2	152-154
114.	4-Cl-phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	166-168
115.	4-Cl-phenyl	S	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	130-132
116.	4-Cl-phenyl	SO_2	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	131-133
117.	3-Cl-phenyl	O	1	2	$(CH_2)_2$		H	CH_2CONH_2	131-133
118.	3-Cl-phenyl	S	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	94-96
119.	3-Cl-phenyl	SO_2	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	100-102
120.	4-Br-phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	163-165
121.	4-CH_3O-phenyl	O	1	2	$(CH_2)_2$		H	CH_2CONH_2	128-130
122.	3-CH_3O-phenyl	O	1	2	$(CH_2)_2$		H	CH_2CONH_2	119-121
123.	4-n-propyloxyphenyl	O	1	2	$(CH_2)_2$		H	CH_2CONH_2	141-143

Cpd	Y	X	m	n	R_1 R_2	R_3	R_4	m.p.°C (or M+H)
124.	4-CF_3-phenyl	O	1	2	$(CH_2)_2$	H	CH_2CONH_2	134-136
125.	4-CF_3-phenyl	S	1	2	$(CH_2)_2$	H	$CH_2CONHCH_3$	129-131
126.	4-CF_3-phenyl	SO_2	1	2	$(CH_2)_2$	H	$CH_2CONHCH_3$	103-105
127.	3-CF_3-phenyl	O	1	2	$(CH_2)_2$	H	CH_2CONH_2	120-121
128.	3-CF_3-phenyl	S	1	2	$(CH_2)_2$	H	$CH_2CONHCH_3$	167-169
129.	3-CF_3-phenyl	SO_2	1	2	$(CH_2)_2$	H	$CH_2CONHCH_3$	141-143
130.	4-CF_3O-phenyl	O	1	2	$(CH_2)_2$	H	CH_2CONH_2	118-120
131.	3-CF_3O-phenyl	O	1	2	$(CH_2)_2$	H	CH_2CONH_2	132-134
132.	4-isopropylphenyl	O	1	2	$(CH_2)_2$	H	CH_2CONH_2	113-115
133.	3-isopropylphenyl	O	1	2	$(CH_2)_2$	H	CH_2CONH_2	119-121
134.	2,3-Cl_2-phenyl	O	1	2	$(CH_2)_2$	H	$CH_2CONHCH_3$	160-162
135.	2,4-Cl_2-phenyl	O	1	2	$(CH_2)_2$	H	$CH_2CONHCH_3$	144-146
136.	3,4-Cl_2-phenyl	O	1	2	$(CH_2)_2$	H	CH_2CONH_2	113-115
137.	naphthalen-1-yl	O	1	2	$(CH_2)_2$	H	CH_2CONH_2	135-136
138.	naphthalen-1-yl	O	1	2	$(CH_2)_2$	H	$CH_2CONHCH_3$	151-152
139.	naphthalen-1-yl	O	1	1	$(CH_2)_3$	H	CH_2CONH_2	149-151
140.	naphthalen-1-yl	O	1	1	$(CH_2)_3$	H	$CH_2CONHCH_3$	(357)
141.	naphthalen-1-yl	S	1	2	$(CH_2)_2$	H	$CH_2CONHCH_3$	127-129
142.	naphthalen-1-yl	SO_2	1	2	$(CH_2)_2$	H	$CH_2CONHCH_3$	154-156
143.	naphthalen-2-yl	O	1	2	$(CH_2)_2$	H	CH_2CONH_2	142-144
144.	naphthalen-2-yl	S	1	2	$(CH_2)_2$	H	$CH_2CONHCH_3$	111-113
145.	naphthalen-2-yl	SO_2	1	2	$(CH_2)_2$	H	$CH_2CONHCH_3$	105-107
146.	4-chloronaphthalen-1-yl	O	1	2	$(CH_2)_2$	H	CH_2CONH_2	166-168

Cpd	Y	X	m	n	R_1	R_2	R_3	R_4	m.p.°C (or M+H)
147.	4-chloronaphthalen-1-yl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	163-165
148.	quinolin-7-yl	O	1	2	$(CH_2)_2$		H	CH_2CONH_2	137-139
149.	isoquinolin-7-yl	O	1	2	$(CH_2)_2$		H	CH_2CONH_2	162-164
150.	4-(4-F-phenyl)phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	150-152
151.	4-(4-Cl-phenyl)phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	167-169
152.	4-(4-CH_3-phenyl)phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	164-166
153.	4-(4-*n*-butyl-phenyl)-phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	171-173
154.	4-(4-CF_3-phenyl)phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	197-199
155.	4-(4-CH_3O-phenyl)phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	172-174
156.	4-(4-C_2H_5O-phenyl)phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	173-175
157.	4-(4-CF_3O-phenyl)phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	152-154
158.	4-(3-F,4-CH_3O-phenyl)-phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	156-158
159.	4-(3-Cl,4-F-phenyl)-phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	132-134
160.	4-(3,4-Cl_2-phenyl)phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	163-165
161.	4-(2,4-Cl_2-phenyl)phenyl	O	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	177-179
162.	pyrimidin-2-yl	S	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	109-111
163.	5-phenylthiazol-2-yl	S	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(406)
164.	benzoxazol-2-yl	S	1	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	(364)
165.	phenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	136-138
166.	4-Cl-phenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	115-117
167.	3-Cl-phenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	91-93

Cpd	Y	X	m	n	R_1	R_2	R_3	R_4	m.p.°C (or M+H)
168.	4-Br-phenyl	O	2	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	101-103
169.	4-CH_3O-phenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	108-110
170.	3-CH_3O-phenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	(337)
171.	4-n-propyloxy-phenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	121-123
172.	4-CF_3-phenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	112-114
173.	3-CF_3-phenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	94-96
174.	4-CF_3O-phenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	79-81
175.	3-CF_3O-phenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	(391)
176.	4-isopropylphenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	75-77
177.	3-isopropylphenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	(349)
178.	3,4-Cl_2-phenyl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	103-105
179.	naphthalen-1-yl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	134-135
180.	naphthalen-1-yl	O	2	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	108-109
181.	naphthalen-2-yl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	(357)
182.	quinolin-7-yl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	164-166
183.	isoquinolin-7-yl	O	2	2	$(CH_2)_2$		H	CH_2CONH_2	179-181
184.	4-phenylphenyl	O	2	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	124-126
185.	4-(4-F-phenyl)phenyl	O	2	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	120-122
186.	4-(4-Cl-phenyl)phenyl	O	2	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	104-106
187.	4-(4-CF_3-phenyl)phenyl	O	2	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	137-139
188.	4-(3-CF_3-phenyl)phenyl	O	2	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	98-100
189.	4-(4-CH_3O-phenyl)phenyl	O	2	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	141-143
190.	4-(4-CF_3O-phenyl)phenyl	O	2	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	116-118
191.	4-(4-*iso*-propyl-phenyl)phenyl	O	2	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	121-123

Cpd	Y	X	m	n	R_1	R_2	R_3	R_4	m.p.°C (or M+H)
192.	4-(2,4-Cl_2-phenyl)phenyl	O	2	2	$(CH_2)_2$		H	$CH_2CONHCH_3$	112-114

The compounds of the invention were subjected to pharmacological tests permitting 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 (ethanolamine [1-^{3}H]) of anandamide [ethanolamine 1-^{3}H] 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 enzyme 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 [ethanolamine 1-^{3}H] (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 enzyme 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 enzyme activity of FAAH) of between 0.001 and 1 μM. For example, compound 58 of the table exhibits an IC_{50} of 0.47 μM.

It is therefore apparent that the compounds according to the invention have an inhibitory effect 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 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 58 of the table reduces by 51% the number of stretches induced by PBQ, at a dose of 1 mg/kg at 2 hours.

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*-arachidonylethanolamine (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 the 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, osteoarthritis, spondylitis, gout, vasculitis, Crohn's diease, 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, epiphyseal 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, Sjögrer'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 tracts, bronchospasms, coughing, asthma, chronic bronchitis, chronic obstruction of the respiratory tracts, emphysema;

gastrointestinal diseases: irritable bowel syndrome, intestinal inflammatory disorders, ulcers, diarrhoea;

urinary incontinence and bladder inflammation.

The use of compounds 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.

In accordance with another of its aspects the present invention provides pharmaceutical compositions comprising as active principle at least one compound of formula (I). These pharmaceutical compositions include an effective dose of a compound according to the invention, or a salt or a hydrate or pharmaceutically acceptable solvate of the said compound, and optionally one or more pharmaceutically acceptable excipients.

Said excipients are selected, according to the pharmaceutical form and the desired mode of administration, from the customary excipients, which are known to the 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 salt, solvate or hydrate where appropriate, may be administered in 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 gelatin 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

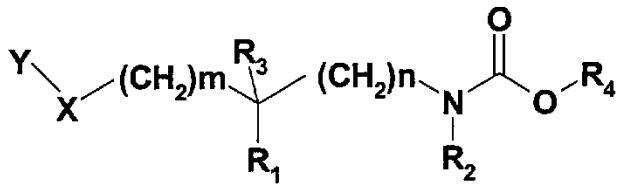
The said single-dose forms contain a dose permitting daily administration of from 0.01 to 20 mg of active principle per kg of bodyweight, depending on the pharmaceutical form.

There may be particular cases in which higher or lower dosages are appropriate; such dosages also belong to the invention. In accordance with common 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 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, or a solvate or a hydrate of the said compound.

Claims

1. Compound conforming to the formula (I)



(I)

in which

m represents 0, 1, 2 or 3;

n represents 0, 1, 2 or 3;

X represents an oxygen or sulphur atom or an SO or SO_2 group;

R_1 and R_2 represent independently of one another a hydrogen atom or a C_{1-3} alkyl group, or R_1 and R_2 together form a group $-(CH_2)_p-$, where p represents an integer ranging from 1 to 5 such that n + p is an integer ranging from 2 to 5;

R_3 represents a hydrogen or fluorine atom or a hydroxyl or methyl group;

R_4 represents a group of general formula CHR_5CONHR_6 in which

R_5 represents a hydrogen atom or a C_{1-6} alkyl group and

R_6 represents a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-6} alkylene group;

Y represents

a group Y_1 selected from in particular a phenyl,

pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, thiazolyl, naphthyl, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, cinnolinyl, benzofuranyl, dihydrobenzofuranyl, benzothienyl, dihydrobenzothienyl, indolyl, isoindolyl, indolinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzotriazolyl, benzoxadiazolyl and benzothiadiazolyl; the group Y_1 being optionally substituted by one or more substituents Y_2, which are identical to or different from one another, or by a group Y_3;

Y_2 represents a halogen atom or a cyano, nitro, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} thioalkyl, C_{1-8} fluoroalkyl, C_{1-8} fluoroalkoxy, C_{1-8} fluorothioalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{3-7} cycloalkyl-C_{1-8} alkylene, C_{3-7} cycloalkyl-C_{1-8} alkyloxy, hydroxyl, NR_7R_8, $NHCOR_7$, $NHSO_2R_7$, COR_7, CO_2R_7, $CONR_7R_8$, SO_2R_7, $SO_2NR_7R_8$, -O-(C_{1-3} alkylene)-O-, phenyloxy, phenylthio, phenyl-C_1-C_8 alkylene, phenyl-C_1-C_8 alkyloxy or phenyl-C_1-C_8 alkylthio group;

Y_3 represents a group selected from in particular a phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl;

it being possible for the group or groups Y_3 to be substituted by one or more groups Y_2 which are 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 nitrogen atom carrying them form an azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine, azepine or piperazine ring optionally substituted by a C_{1-3} alkyl or benzyl 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

Y represents

a group Y_1 selected from in particular a phenyl, pyridinyl, pyrimidinyl, thiazolyl, naphthyl, quinolinyl, isoquinolinyl and benzoxazolyl; the group Y_1 being optionally substituted by one or more substituents Y_2, which are identical to or different from one another, or by a group Y_3;

Y_2 represents a halogen atom, a cyano, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} fluoroalkyl, C_{1-8} fluoroalkoxy, phenyloxy or phenyl-C_1-C_8 alkylene group;

Y_3 represents a phenyl group; it being possible for Y_3 to be substituted by one or more groups Y_2 which are identical to or different from one another;

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

Y represents

a group Y_1 selected from in particular a phenyl or a naphthyl; the group Y_1 being optionally substituted by one or more substituents Y_2, which are identical to or different from one another, or by a group Y_3;

Y_2 represents a halogen atom, a cyano, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} fluoroalkyl, C_{1-8} fluoroalkoxy, phenyloxy or phenyl-C_1-C_8 alkylene group;

Y_3 represents a phenyl group; it being possible for Y_3 to be substituted by one or more groups Y_2 which are identical to or different from one another;

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

m represents 0, 1, 2 or 3;

n represents 0, 1, 2 or 3;

R_1 and R_2 represent independently of one another a hydrogen atom or a C_{1-3} alkyl group, or R_1 and R_2 together form a group $-(CH_2)_p-$, where p represents an integer ranging from 1 to 5 such that n + p is an integer ranging from 2 to 5;

with the proviso that, when R_1 and R_2 represent independently of one another a hydrogen atom or a C_{1-3} alkyl group, m + n > 1;

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

m represents 0, 1, 2 or 3; and/or

n represents 0, 1, 2 or 3; and/or

R_1 and R_2 together form a group $-(CH_2)_p-$, where p represents an integer ranging from 1 to 4 such that n + p is equal to 4;

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

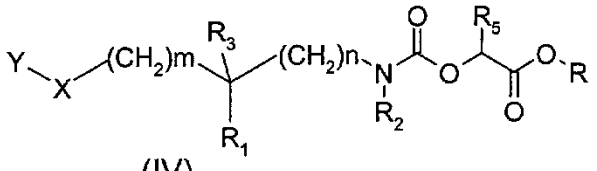
6. Compound of formula (I) according to any one of Claims 1 to 5, characterized in that X represents an oxygen atom;

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

7. Compound of formula (I) according to any one of Claims 1 to 6, characterized in that R_3 represents a hydrogen atom;

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

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



(IV)

in which Y, X, R_1, R_2, R_3, R_5, n and m are as defined

according to any one of Claims 1 to 7 and R represents a methyl or ethyl group,

by aminolysis by means of an amine of formula R_6NH_2 where R_6 is as defined in formula (I) according to Claim 1.

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

10. Compound of formula (I) according to any one of Claims 1 to 7, in base, salt, hydrate or pharmaceutically acceptable solvate form, for its use as a medicinal product.

11. Use of a compound of formula (I) according to any one of Claims 1 to 7, 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 substrates metabolized by the enzyme FAAH are involved.

12. Use of a compound of formula (I) according to any one of Claims 1 to 7, 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.