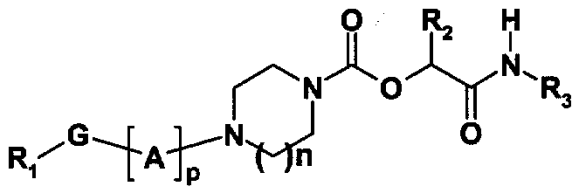
DERIVATIVES OF ALKYLPIPERAZINE- AND ALKYLHOMOPIPERAZINE-CARBOXYLATES, PREPARATION METHOD THEREOF AND USE OF SAME AS FAAH ENZYME INHIBITORS

The invention relates to alkylpiperazine- and alkylhomopiperazine-carboxylate derivatives, to their preparation and to their application in therapy.

Already known are phenylalkylcarbamate, dioxane-2-alkylcarbamate and 1-piperazine- and 1-homopiperazine-carboxylate derivatives, described respectively in the documents WO 2004/067498 A, WO 2004/020430 A and WO2005/070910, which are inhibitors of the enzyme FAAH (fatty acid amide hydrolase).

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

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



(I)

in which

n represents an integer 1 or 2;

p represents an integer ranging from 1 to 7;

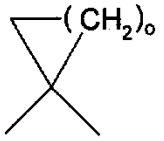
A is selected from one or more groups X, Y and/or Z;

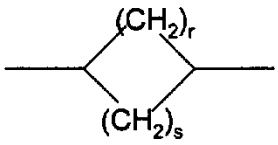
X represents a methylene group optionally substituted by one or two C_{1-6}-alkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-3}-

alkylene groups;

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

Z represents a group of formula:





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;

G represents a single bond, an oxygen or sulphur atom or an SO, SO_2, C=O or CH(OH) group;

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

R_4 represents a group selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, naphthalenyl, diphenylmethyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, cinnolinyl, naphthyridinyl, benzofuranyl, dihydrobenzofuranyl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indanyl, indazolyl,

isoindolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl, pyrrolopyridinyl, furopyridinyl, thienopyridinyl, imidazopyridinyl, oxazolopyridinyl, thiazolopyridinyl, pyrazolopyridinyl, isoxazolopyridinyl and isothiazolopyridinyl;

R_5 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 or C_1-C_6-fluorothioalkyl group, a group NR_7R_8, NR_7COR_8, $NR_7CO_2R_8$, $NR_7SO_2R_8$, COR_7, CO_2R_7, $CONR_7R_8$, SO_2R_7 or $SO_2NR_7R_8$, or an -O-(C_{1-3}-alkylene)-O group;

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

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

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

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

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

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

n represents an integer 1 or 2;

p represents an integer ranging from 1 to 7;

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

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

Y represents either a C_2-alkenylene group or a C_2-alkynylene group;

G represents a single bond, an oxygen atom or a C=O group;

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

R_4 represents a group selected from a phenyl, naphthalenyl, diphenylmethyl, quinolinyl, indolyl, pyrazolyl, isoxazolyl, pyrimidinyl and thiazolyl;

R_5 represents a halogen atom, more particularly a chlorine, a fluorine, a bromine or an iodine, or a cyano group, a C_{1-6}-alkyl group, more particularly a methyl, an isopropyl or a *tert*-butyl, a C_{1-6}-alkoxy group, more particularly a methoxy, a C_{1-6}-fluoroalkyl group, more particularly a trifluoromethyl, a C_1-C_6-fluoroalkoxy group, more particularly a trifluoromethoxy, or an -O-(C_{1-3}-alkylene)-O group, more particularly an $-OCH_2O-$;

R_6 represents a phenyl, naphthalenyl or benzyloxy group;

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

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

or C_{3-7}-cycloalkyl-C_{1-3}-alkyl group.

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

n represents an integer 1;

p represents an integer ranging from 1 to 4;

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

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

Y represents a C_2-alkynylene group;

G represents a single bond or an oxygen atom;

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

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

R_5 represents a halogen atom, more particularly a chlorine or a fluorine, or a cyano group, a C_{1-6}-alkoxy group, more particularly a methoxy, a C_{1-6}-fluoroalkyl group, more particularly a trifluoromethyl;

R_6 represents a phenyl group;

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

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

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

n, p, A, X, Y, Z, o, r, s, G, R_1, R_4, R_5, R_6, R_7 and R_8 are as

defined in the general formula (I) or in the subgroups as defined above;

R_2 represents a hydrogen atom;

R_3 represents a hydrogen atom or a C_{1-6}-alkyl group, more particularly a methyl, a C_{3-7}-cycloalkyl group, more particularly a cyclopropyl or a C_{3-7}-cycloalkyl-C_{1-3}-alkyl group, more particularly a -CH_2-cyclopropyl.

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

- 2-(methylamino)-2-oxoethyl 4-(2-biphenyl-3-ylethyl)-piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-(2-biphenyl-4-ylethyl)-piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[2-(1-naphthyl)ethyl]-piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-{2-[3-(4-chlorophenyl)-isoxazol-5-yl]ethyl}piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-{2-[5-(4-chlorophenyl)-isoxazol-3-yl]ethyl}piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-(3-biphenyl-3-ylpropyl)-piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-(3-biphenyl-4-ylpropyl)-piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-(3-biphenyl-3-yl-1,1-dimethylpropyl)piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(3'-chlorobiphenyl-3-yl)propyl]piperazine-1-carboxylate

- 2-(methylamino)-2-oxoethyl 4-[3-(4'-chlorobiphenyl-3-yl)propyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(3'-methoxybiphenyl-3-yl)propyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(4'-methoxybiphenyl-3-yl)propyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(3'-chlorobiphenyl-4-yl)propyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(4'-chlorobiphenyl-4-yl)propyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(2-naphthyl)propyl]-piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-{3-[5-(4-chlorophenyl)-isoxazol-3-yl]propyl}piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-{3-[3-(4-chlorophenyl)-isoxazol-5-yl]propyl}piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[4-(3-chlorophenyl)-butyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[4-(4-chlorophenyl)butyl]-piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-{4-[3-(trifluoromethyl)-phenyl]butyl}piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-{4-[4-(trifluoromethyl)-phenyl]butyl}piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-{4-[4-(trifluoromethyl-phenyl]but-3-yn-1-yl}piperazine-1-carboxylate

- 2-(methylamino)-2-oxoethyl 4-[5-(3-chlorophenyl)pent-4-yn-1-yl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[5-(2,4-dichlorophenyl)pent-4-yn-1-yl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[5-(2,5-dichlorophenyl)pent-4-yn-1-yl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[5-(3,4-dichlorophenyl)pent-4-yn-1-yl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[5-(3-chloro-4-fluorophenyl)pent-4-yn-1-yl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(2-chlorophenoxy)propyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(3-chlorophenoxy)-propyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(4-chlorophenoxy)-propyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(2,3-dichloro-phenoxy)propyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(2,4-dichloro-phenoxy)propyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(2,5-dichloro-phenoxy)propyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(2,6-dichloro-phenoxy)propyl]piperazine-1-carboxylate
- 2-(methylamino)-2-oxoethyl 4-[3-(3,5-dichlorophenoxy)-propyl]piperazine-1-carboxylate.

The compounds of general formula (I) may include

one or more asymmetric carbons. They may exist in the form of enantiomers or diastereoisomers. The compounds of general formula (I) may also exist in the form of *cis (Z)* or *trans (E)* stereoisomers. These stereoisomers , enantiomers and diastereoisomers, and also their mixtures, 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. Addition salts of this kind form part of the invention.

These salts are advantageously prepared with pharmaceutically acceptable acids, although the salts of other acids useful, 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. Hydrates and solvates of this kind likewise form part of the invention.

In the context of the invention the terms have the following meanings:

- C_{t-z}, where t and z may take the values from 1 to 7, is a carbon chain which may have from t to z carbon atoms; for example, C_{1-3} is a carbon chain which may have 1 to 3 carbon atoms;
- alkyl is a linear or branched saturated aliphatic group; for example, a C_{1-6}-alkyl group represents a carbon

chain of 1 to 6 carbon atoms which is linear or branched, more particularly a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl or hexyl;

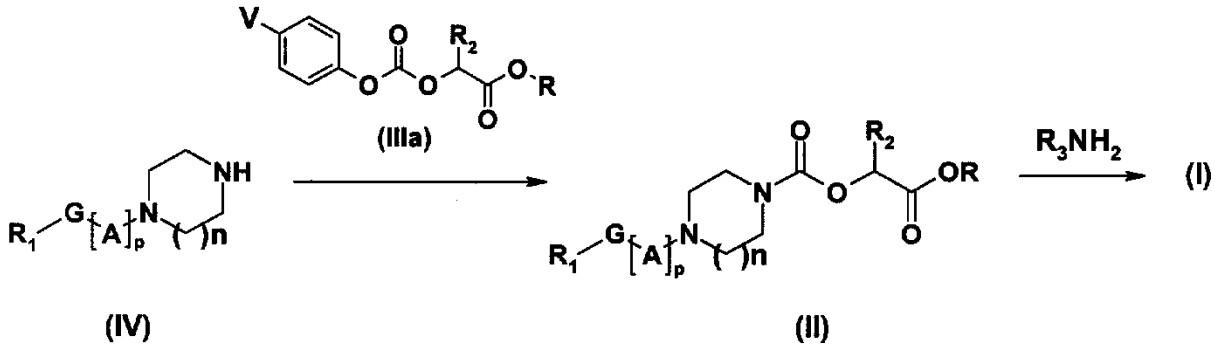
- alkylene is a linear or branched, saturated divalent alkyl group; for example, a C_{1-3}-alkylene group represents a divalent carbon chain of 1 to 3 carbon atoms which is linear or branched, more particularly methylene, ethylene, 1-methylethylene or propylene;
- cycloalkyl is a cyclic alkyl group; for example, C_{3-7}-cycloalkyl group represents a cyclic carbon group of 3 to 7 carbon atoms, more particularly a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;
- alkenylene is a divalent unsaturated aliphatic group having 2 carbons, more particularly an ethylene,
- C_2-alkynylene is a -C≡C- group;
- alkoxy is an -O-alkyl group having a linear or branched, saturated aliphatic chain;
- thioalkyl is an -S-alkyl group having a linear or branched, saturated aliphatic chain;
- fluoroalkyl is an alkyl group of which one or more hydrogen atoms have been substituted by a fluorine atom;
- fluoroalkoxy is an alkoxy group of which one or more hydrogen atoms have been substituted by a fluorine atom;
- fluorothioalkyl is a thioalkyl group of which one or more hydrogen atoms have been substituted by a fluorine atom; and
- a halogen atom is a fluorine, a chlorine, a bromine or

an iodine.

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

Thus according to a first method (scheme 1) the compounds of general formula (I) may be prepared by reacting an amine of general formula (IV), in which R_1, G, A, p and n are as defined in the general formula (I), with a carbonate of general formula (IIIa), in which V represents a hydrogen atom or nitro group, R_2 is as defined in the general formula (I) and R represents a methyl or ethyl group. The carbamate-ester of general formula (II) thus obtained is subsequently converted into a compound of general formula (I) by aminolysis using an amine of general formula R_3NH_2, in which R_3 is as defined in the general formula (I). The aminolysis reaction may be carried out in a solvent such as methanol or ethanol or in a mixture of solvents such as methanol and tetrahydrofuran.

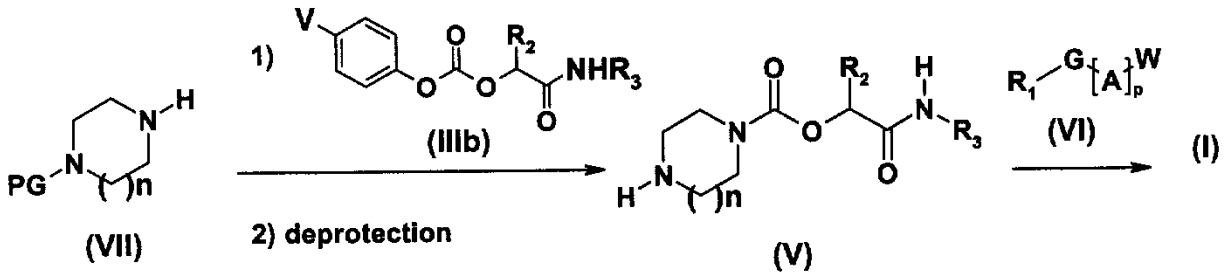
Scheme 1



Another method (scheme 2) of obtaining compounds of general formula (I) involves reacting a piperazine or

homopiperazine derivative of general formula (VII), in which PG represents a protective group such as a *tert*-butyloxycarbonyl (Boc), with a carbonate of general formula (IIIb), in which V represents a hydrogen atom or a nitro group and R_2 and R_3 are as defined in the general formula (I), then deprotecting the resultant compound, in the presence for example of a solution of hydrochloric acid in a solvent such as isopropanol. The carbamate-amide of general formula (V) thus obtained is subsequently converted into a compound of general formula (I) by reaction with a derivative of general formula (VI), in which R_1, G, p and A are as defined in the general formula (I) and W represents a chlorine, bromine or iodine atom or a mesylate or tosylate group. The N-alkylation reaction may be carried out in a solvent such as acetonitrile or toluene in the presence of a base such as potassium carbonate or diisopropylethylamine.

Scheme 2



The compounds of general formula (I), (II) and (IV), in which R_1 represents a group of aryl-aryl, aryl-heteroaryl, heteroaryl-aryl or heteroaryl-heteroaryl type may also be prepared by reacting corresponding compounds of general formula (I), (II) or (IV) for which R_4 is

substituted by a chlorine, bromine or iodine atom or by a triflate group, in the position where the group R_6 is to be introduced, with an aryl- or heteroaryl-boronic acid derivative in accordance with the Suzuki reaction conditions (Chem. Rev. 1995, 95, 2457-2483) or with an aryl- or heteroaryl-trialkylstannane derivative in accordance with the Stille reaction conditions (Angew. Chem. Int. Ed. 1986, 25, 504-524).

The carbonates of general formula (IIIa) and (IIIb) may be prepared according to any method described in the literature, for example by reacting an alcohol of respective general formula $HOCHR_2COOR$ where R represents a methyl or ethyl group, or $HOCHR_2CONHR_3$ where R_3 is as defined in the general formula (I), with phenyl chloroformate or 4-nitrophenyl chloroformate, in the presence of a base such as triethylamine or diisopropylethylamine.

The compounds of general formula (IV), (VI) and (VII), and also the amines of general formula R_3NH_2, when their preparation method is not described, are available commercially or are described in the literature, or may be prepared according to various methods described in the literature or known to the skilled person.

The invention, according to another of its aspects, likewise provides the compounds of formula (II) and (V). These compounds are useful as intermediates in the synthesis of the compounds of formula (I).

The examples which follow illustrate the

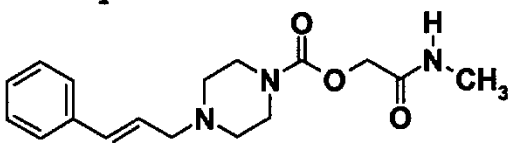
preparation of some compounds of the invention. These examples are not limitative and merely illustrate the invention. The microanalyses, IR and NMR spectra and/or the LC-MS (liquid chromatography coupled to mass spectroscopy) confirm the structures and the purities of the compounds obtained.

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

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

Example 1 (compound 85)

2-(methylamino)-2-oxoethyl *trans*-4-(3-phenylprop-2-en-1-yl)piperazine-1-carboxylate



1.1. 2-(ethoxy)-2-oxoethyl *trans*-4-(3-phenylprop-2-en-1-yl)piperazine-1-carboxylate

A solution of 1.40 g (6.93 mmol) of *trans*-1-cinnamylpiperazine and 1.74 g (7.76 mmol) of ethyl {[(phenoxy)carbonyl]oxy}acetate (J. Med. Chem., 1999, 42, 277-290) in 15 ml of toluene is heated at 80°C overnight. It is evaporated to dryness and the residue is taken up in 50 ml of ethyl acetate. It is washed with 2 times 20 ml of water and 1 times 10 ml of saturated aqueous sodium chloride

solution. It is dried over sodium sulphate and evaporated to dryness. The residue is purified by chromatography on silica gel, eluting with a 50/50 mixture of cyclohexane and ethyl acetate, then with ethyl acetate, to give 0.814 g of product in the form of a pale yellow oil.

1.2. 2-(methylamino)-2-oxoethyl *trans*-4-(3-phenylprop-2-en-1-yl)piperazine-1-carboxylate

0.8 g (2.4 mmol) of 2-(ethoxy)-2-oxoethyl *trans*-4-(3-phenylprop-2-en-1-yl)piperazine-1-carboxylate, obtained in step 1.1., is dissolved in 10 ml of a 2M solution of methylamine (20 mmol) in methanol. The solution is left to react for an hour and a half at ambient temperature and is then evaporated to dryness. The residue is purified by chromatography on silica gel, eluting first with ethyl acetate and then with a mixture 90/10 mixture of ethyl acetate and methanol. This gives 0.548 g of a white powder.

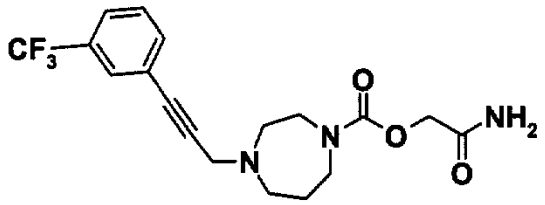
Melting point (°C): 109-111

LC-MS : M+H = 318

^{1}H NMR (DMSO-d_6): δ (ppm): 7.80 (broad s, 1H); 7.50-7.15 (m, 5H); 6.55 (d, 1H); 6.25 (td, 1H); 4.40 (s, 2H); 3.40 (m, 4H); 3.10 (d, 2H); 2.60 (d, 3H); 2.40 (m, 4H).

Example 2 (compound 99)

2-amino-2-oxoethyl 4-{3-[3-(trifluoromethyl)phenyl]prop-2-yn-1-yl}-1,4-diazepane-1-carboxylate



2.1. 4-{3-[3-(trifluoromethyl)phenyl]prop-2-yn-1-yl}-1,4-diazepane-1-carbaldehyde

A mixture of 1.28 g (10 mmol) of 1,4-diazepane-1-carbaldehyde and 0.33 g (11 mmol) of paraformaldehyde in 13 ml of dioxane is heated at 80°C until a homogeneous solution is obtained. 1.70 g (10 mmol) of 3-trifluoromethylphenylacetylene in solution in 7 ml of dioxane and 1.81 g (10 mmol) of copper diacetate are added. The mixture is heated at 80°C for 4 hours. It is cooled to ambient temperature and diluted with 75 ml of ethyl acetate. The organic phase is washed with 25 ml of 30% ammonia solution and with saturated aqueous sodium chloride solution. It is dried over sodium sulphate and evaporated to dryness. The residue is purified by chromatography on silica gel, eluting with a 98/2/0.2 then 96/4/0.4 and 94/6/0.6 mixture of dichloromethane, methanol and 30% ammonia, to give 2.67 g of product in the form of a yellow oil.

2.2. 4-{3-[3-(trifluoromethyl)phenyl]prop-2-yn-1-yl}-1,4-diazepane

2.63 g (8.48 mmol) of 4-{3-[3-(trifluoromethyl)phenyl]prop-2-yn-1-yl}-1,4-diazepane-1-carbaldehyde, obtained in step 2.1., are dissolved in 7.5 ml of methanol.

3.5 ml of a 35% aqueous sodium hydroxide (30 mmol) solution are added and the mixture is heated at reflux for 3 hours. It is cooled to ambient temperature. It is diluted with 20 ml of water and 75 ml of dichloromethane. The phases are separated and then the aqueous phase is extracted with 2 times 25 ml of dichloromethane. The organic phases are washed with 25 ml of water and then with 25 ml of saturated aqueous sodium chloride solution. They are dried over sodium sulphate and evaporated to dryness, to give 2.25 g of product in the form of a red oil, which is used as it is in the following step.

2.3. 2-(ethyloxy)-2-oxoethyl 4-{3-[3-(trifluoromethyl)phenyl]prop-2-yn-1-yl}-1,4-diazepane-1-carboxylate

A solution of 2.25 g (7.95 mmol) of 4-{3-[3-(trifluoromethyl)phenyl]prop-2-yn-1-yl}-1,4-diazepane, obtained in step 2.2., and 2.68 g (11.9 mmol) of ethyl {[(phenyloxy)carbonyl]oxy}acetate in 10 ml of toluene is heated at 60°C overnight. 5 g of silica are added and the mixture is evaporated to dryness. The residue is purified by chromatography on silica gel, eluting with a 60/40 then 40/60 mixture of cyclohexane and ethyl acetate and then with ethyl acetate, to give 2.42 g of product in the form of an orange-coloured oil.

2.4. 2-amino-2-oxoethyl 4-{3-[3-(trifluoromethyl)phenyl]prop-2-yn-1-yl}-1,4-diazepane-1-carboxylate

0.77 g (1.87 mmol) of 2-(ethyloxy)-2-oxoethyl 4-{3-[3-(trifluoromethyl)phenyl]prop-2-yn-1-yl}-1,4-diazepane-1-carboxylate, obtained in step 2.3., is dissolved in 14 ml of a 7M solution of ammonia (98 mmol) in methanol. The solution is left to react at ambient temperature overnight and then 2 g of silica are added and it is evaporated to dryness. The residue is purified by chromatography on silica gel, eluting with a 97/3/0.3 then 95/5/0.5 and 93/7/0.7 mixture of dichloromethane, methanol and 30% ammonia. The eluate is subsequently recrystallized from a mixture of ethyl acetate and diisopropyl ether, to give 0.57 g of white crystals.

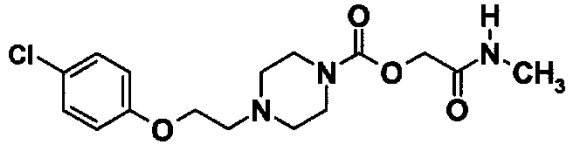
Melting point (°C): 102-104

LC-MS : M+H = 384

^{1}H NMR ($CDCl_3$) δ(ppm): 7.70 (s, 1H); 7.55 (m, 2H); 7.45 (d, 1H); 6.15 (broad m, 1H); 5.50 (broad m, 1H); 4.65 (s, 2H); 3.65 (m+s, 6H); 2.85 (m, 4H); 1.95 (m, 2H).

Example 3 (compound 130)

2-(methylamino)-2-oxoethyl 4-{2-[(4-chlorophenyl)-oxy]ethyl}piperazine-1-carboxylate



3.1. 4-nitrophenyl 2-(methylamino)-2-oxoethyl carbonate

A suspension of 2.62 g (29.4 mmol) of 2-hydroxy-N-methylacetamide and 16.5 g (58.7 mmol) of supported diisopropylethylamine (Ps-DIEA from Argonaut, loading = 3.56 mmol/g) in 250 ml of dichloromethane is admixed in small portions and at ambient temperature with 5.93 g (29.4 mmol) of 4-nitrophenyl chloroformate. Orbital stirring is continued at ambient temperature for 16 hours. The resin is filtered off and rinsed with 150 ml of dichloromethane and the filtrate is concentrated under reduced pressure. This gives 6 g of product in the form or a light yellow solid, which is used as it is in the following step.

3.2. 1,1-dimethylethyl 2-(methylamino)-2-oxoethyl piperazine-1,4-dicarboxylate

A solution, cooled to 0°C, of 1.1 g (3 mmol) of 4-nitrophenyl 2-(methylamino)-2-oxoethyl carbonate, prepared in step 3.1., in 10 ml of 1,2-dichloroethane is admixed dropwise at about 0°C with a solution of 0.53 g (2.85 mmol) of 1,1-dimethylethyl piperazine-1-carboxylate in 5 ml of 1,2-dichloroethane. Stirring is continued at 0°C for 1 hour, then at ambient temperature for 3 hours.

The mixture is concentrated under reduced pressure. The residue is purified by chromatography on silica gel, eluting with a 20/80 mixture of ethyl acetate and cyclohexane and then gradually increasing the gradient to end with elution with ethyl acetate. The eluate is triturated in diisopropyl ether, to give 0.61 g of product in the form of a white solid, which is used as it is in the

following step.

3.3. 2-(methylamino)-2-oxoethyl piperazine-1-carboxylate hydrochloride

A solution of 2.68 g (8.9 mmol) of 1,1-dimethylethyl 2-(methylamino)-2-oxoethyl piperazine-1,4-dicarboxylate, obtained according to step 3.2., in 25 ml of dichloromethane is admixed with 25 ml of a 6N solution of hydrochloric acid in isopropanol. Stirring is continued at ambient temperature for 1 hour. The organic phase is separated by filtration through a hydrophobic cartridge and is concentrated under reduced pressure. Trituration in isopropanol gives 2.05 g of product.

Melting point (°C): 167-169°C

3.4. 2-(methylamino)-2-oxoethyl 4-{2-[(4-chlorophenyl)oxy]ethyl}piperazine-1-carboxylate

A solution of 0.073 g (0.3 mmol) of 2-(methylamino)-2-oxoethyl piperazine-1-carboxylate hydrochloride, prepared in step 3.3., 0.13 g (0.9 mmol) of potassium carbonate and 0.069 g (0.29 mmol) of 1-(2-bromoethoxy)-4-chlorobenzene in 3 ml of acetonitrile is heated at 85°C for 16 hours. After cooling to ambient temperature, the inorganic components are filtered off through a cartridge fitted with a frit and containing celite. The cartridge is rinsed with acetone and the filtrate is concentrated under reduced pressure. Chromatography on silica gel, eluting with a 95/5 mixture of dichloromethane and methanol, followed by crystallization

from diisopropyl ether give 0.089 g of product in the form of a white solid.

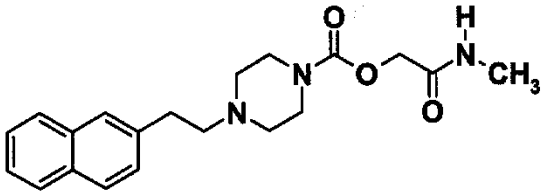
LC-MS: M+H = 356

Melting point: 159-161°C

^{1}H NMR ($CDCl_3$) δ (ppm): 7.25 (dd, 2H); 6.85 (dd, 2H); 6.05 (broad s, 1H); 4.60 (s, 2H); 4.10 (t, 2H); 3.55 (m, 4H); 2.90 (d, 3H); 2.85 (t, 2H); 2.60 (m, 4H).

Example 4 (compound 25)

2-(methylamino)-2-oxoethyl 4-(2-naphthalen-2-ylethyl)-piperazine-1-carboxylate



A solution, cooled to 0°C, of 0.13 g (0.75 mmol) of 2-naphthalen-2-ylethanol and 0.19 ml (1.13 mmol) of diisopropylethylamine in 7.5 ml of dichloromethane is admixed with 0.07 ml (0.9 mmol) of methanesulphonyl chloride. Stirring is continued in the cold for 0.5 hour, then at ambient temperature for 2 hours. The solution is concentrated under reduced pressure.

The residue is taken up in 5 ml of acetonitrile, and 0.12 g (0.5 mmol) of 2-(methylamino)-2-oxoethyl piperazine-1-carboxylate hydrochloride, prepared in accordance with Example 3.3., and 0.20 g (1.5 mmol) of potassium carbonate are added. The mixture is heated at 70°C

for 16 hours. After cooling to ambient temperature, it is concentrated under reduced pressure. The residue is suspended in dichloromethane and washed with saturated sodium bicarbonate solution and then with water. The organic phase is recovered by filtration on a hydrophobic membrane and is concentrated under reduced pressure. Chromatography on silica gel, eluting with a 95/5 mixture of dichloromethane and methanol, followed by crystallization from diisopropyl ether, give 0.069 g of product in the form of a white solid.

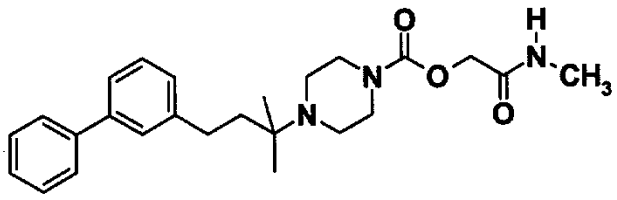
LC-MS: M+H = 356

Melting point: 133-135°C

^{1}H NMR ($CDCl_3$) δ(ppm): 7.85 (m, 3H); 7.65 (s, 1H); 7.55-7.30(m, 3H); 6.05 (broad s, 1H); 4.60 (s, 2H); 3.55 (m, 4H); 3.05-2.65 (m, 7H); 2.55 (m, 4H).

Example 5 (compound 50)

2-(methylamino)-2-oxoethyl 4-(3-biphenyl-3-yl-1,1-dimethylpropyl)piperazine-1-carboxylate hydrochloride



5.1. 1-(2,2-dimethylpropanoyl)-4-(1,1-dimethylprop-2-yn-1-yl)piperazine

0.756 g (6 mmol) of 1,1-dimethylprop-2-yn-1-yl acetate (J. Org. Chem. 1994, 59, 2282-4) and 2.235 g (12 mmol) of 1,1-dimethylethyl piperazine-1-carboxylate are dissolved in 9 ml of tetrahydrofuran and then 0.059 g (0.6 mmol) of cuprous chloride is added. The mixture is heated at reflux for 3 hours. After cooling to ambient temperature, 100 ml of ethyl acetate, 10 ml of 1N aqueous sodium hydroxide and 2 ml of 30% ammonia are added. The organic phase is separated off and washed with 2 times 10 ml of water and then with 10 ml of saturated aqueous sodium chloride solution. It is dried over sodium sulphate and evaporated. The product is purified by chromatography on silica gel, eluting with an 85/15 then 75/25 and 65/35 mixture of cyclohexane and ethyl acetate, to give 1.19 g (4.71 mmol) of product in the form of a pale yellow solid. Melting point: 106-109°C

5.2. 1-(3-biphenyl-3-yl-1,1-dimethylprop-2-yn-1-yl)-4-(2,2-dimethylpropanoyl)piperazine

1.05 g (4.5 mmol) of 3-bromobiphenyl and 0.9 g (3.6 mmol) of 1-(2,2-dimethylpropanoyl)-4-(1,1-dimethylprop-2-yn-1-yl)piperazine, prepared in step 5.1., 0.75 ml (5.38 mmol) of triethylamine and 0.028 g (0.11 mmol) of triphenylphosphine are dissolved in 8 ml of tetrahydrofuran. Under an argon atmosphere, 0.126 g (0.18 mmol) of the dichloride complex of bis(triphenylphosphine) palladium is added. The mixture is stirred for 15 minutes and then 0.014 g (0.07 mmol) of cuprous iodide is added. The mixture

is stirred at ambient temperature for 4 hours and then at 60°C overnight. After cooling to temperature it is diluted with 25 ml of ethyl acetate and filtered on paper. The solid is rinsed with 4 times 10 ml of ethyl acetate. 4 g of silica are added to the filtrate, which is evaporated to dryness. The residue is purified by chromatography on silica gel, eluting with a 90/10 then 80/20 and 70/30 mixture of cyclohexane and ethyl acetate, to give 0.90 g (2.22 mmol) of product in the form of a orange-coloured oil.

5.3. 1,1-dimethylethyl 4-(3-biphenyl-3-yl-1,1-dimethylpropyl)piperazine-1-carboxylate

0.87 g (2.15 mmol) of 1-(3-biphenyl-3-yl-1,1-dimethylprop-2-yn-1-yl)-4-(2,2-dimethylpropanoyl)piperazine, prepared in step 5.2., is dissolved in a mixture of 5 ml of methanol and 15 ml of ethyl acetate. 0.2 g of platinum oxide is added and the mixture is stirred under a hydrogen atmosphere at 40 psi for 6 hours. It is filtered on paper and the filter product is rinsed with 3 times 10 ml of ethyl acetate. 2 g of silica are added to the filtrate, which is evaporated to dryness. The residue is purified by chromatography on silica gel, eluting with a 90/10 then 85/15 and 80/20 mixture of cyclohexane and ethyl acetate, to give 0.36 g (0.88 mmol) of product in the form of a colourless oil.

5.4. 1-(3-biphenyl-3-yl-1,1-dimethylpropyl)-piperazine

0.65 ml (8.4 mmol) of trifluoroacetic acid is added to a solution of 0.35 g (0.86 mmol) of 1,1-dimethylethyl 4-(3-biphenyl-3-yl-1,1-dimethylpropyl)-piperazine-1-carboxylate, prepared in step 5.3., in 5 ml of dichloromethane. The mixture is stirred for 2 hours and then 0.65 ml of trifluoroacetic acid is added. It is stirred for 2 more hours and then diluted with 10 ml of 1,2-dichloroethane and evaporated to dryness. The residue is taken up in a mixture of 50 ml of dichloromethane and 20 ml of 15% aqueous sodium hydroxide solution. The phases are separated and the aqueous phase is extracted with 2 times 20 ml of dichloromethane. The organic phases are washed with 10 ml of water and then with 20 ml of saturated aqueous sodium chloride solution, dried over sodium sulphate and evaporated, to give 0.25 g (0.81 mmol) of product in the form of a yellow oil.

5.5. 2-(methylamino)-2-oxoethyl 4-(3-biphenyl-3-yl-1,1-dimethylpropyl)piperazine-1-carboxylate hydrocloride

A solution of 0.25 g (0.81 mmol) of 1-(3-biphenyl-3-yl-1,1-dimethylpropyl)piperazine, prepared in step 5.4., and 1.5 g (1.22 mmol) of ethyl {[(phenyloxy)carbonyl]oxy}acetate is heated at 60°C overnight and then evaporated to dryness. The residue is dissolved in a mixture of 4 ml of a 2M methylamine (8 mmol) solution in tetrahydrofuran and 2 ml of methanol. The solution is left to react overnight and then 1 g of silica is added and the mixture is evaporated. The product is

purified by chromatography on silica gel, eluting with a 98/2 then 96/4 and 94/6 mixture of dichloromethane and methanol, to give 0.23 g (0.54 mmol) of product in the form of a colourless gum.

The product is dissolved in 5 ml of ethyl acetate, and 1 ml of a 5N solution of hydrochloric acid in isopropanol is added. The mixture is evaporated to dryness. The residue is taken up in 15 ml of hot ethyl acetate. The solid is filtered off, rinsed with 2 times 3 ml of ethyl acetate and dried, to give 0.215 g (0.46 mmol) of product in the form of white powder.

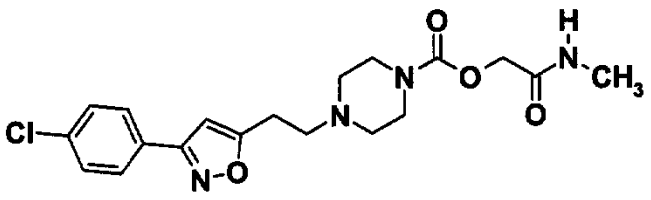
LC-MS: M+H = 424

Melting point: 212-216°C (dec.)

^{1}H NMR ($CDCl_3$) δ(ppm): 12.50 (broad s, 1H); 7.55 (d, 2H); 7.40 (m, 6H); 7.20 (d, 1H); 6.05 (broad s, 1H); 4.60 (s, 2H); 4.30-4.10 (m, 4H); 3.55 (broad d, 2H); 3.05-2.75 (m+d, 5H); 2.15 (m, 2H); 1.70 (s, 8H).

Example 6 (compound 29)

2-(methylamino)-2-oxoethyl 4-{2-[3-(4-chlorophenyl)isoxazol-5-yl]ethyl}piperazine-1-carboxylate



6.1. 2-[3-(4-chlorophenyl)isoxazol-5-yl]ethanol

1.63 ml (11.58 mmol) of triethylamine are added dropwise to a solution of 1.18 ml (15.57 mmol) of but-4-yn-1-ol and 2.0 g (10.52 mmol) of 4-chloro-N-hydroxybenzenecarboximidoyl chloride (J. Med. Chem. 1998, 41, 4556-66) in 30 ml of dichloromethane, cooled with an ice bath. The mixture is left to react at ambient temperature overnight. 50 ml of dichloromethane are added and the mixture is washed with 2 times 50 ml of water and then with 50 ml of saturated aqueous sodium chloride solution. After drying over sodium sulphate, the system is evaporated. The residue is purified by chromatography on silica gel, eluting with an 80/20 then 70/30 mixture of cyclohexane and ethyl acetate, to give 1.1 g (4.91 mmol) of product in the form of a white solid.

Melting point: 65-67°C

6.2. 2-(methylamino)-2-oxoethyl 4-{2-[3-(4-chlorophenyl)isoxazol-5-yl]ethyl}piperazine-1-carboxylate

A solution of 0.100 g (0.447 mmol) of 2-[3-(4-chlorophenyl)isoxazol-5-yl]ethanol, prepared in step 6.1., and 0.082 ml (0.47 mmol) of diisopropylethylamine in 5 ml of dichloromethane, is admixed with 0.036 ml (0.469 mmol) of methanesulphonyl chloride. The mixture is stirred at ambient temperature for 4 hours and then washed with saturated aqueous ammonium chloride solution and saturated aqueous sodium chloride solution. It is concentrated under reduced pressure. The residue is taken up in 5 ml of acetonitrile, and 0.107 g (0.45 mmol) of 2-(methylamino)-2-oxoethyl

piperazine-1-carboxylate hydrochloride, prepared in accordance with Example 3.3., and 0.186 g (1.35 mmol) of potassium carbonate are added. The mixture is heated at 75°C for 16 hours. After cooling to ambient temperature, it is concentrated under reduced pressure. The residue is taken up in ethyl acetate and washed with water and then with saturated aqueous sodium chloride solution. The mixture is evaporated and the residue is purified by chromatography on silica gel, eluting with dichloromethane and then with a 90/10 mixture of dichloromethane and methanol. This gives 0.054 g (0.132 mmol) of product in the form of a white solid.

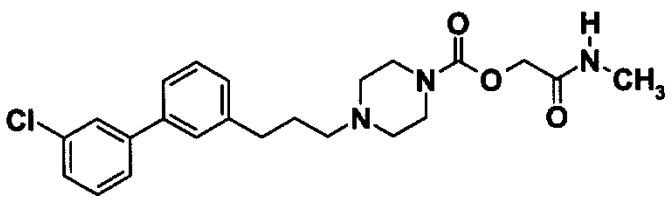
LC-MS: M+H = 407

Melting point: 130-132°C

^{1}H NMR (DMSO-d_6) δ (ppm): 7.85 (d, 2H); 7.75 (unresolved complex, 1H); 7.55 (d, 2H); 6.85 (s, 1H); 4.40 (s, 2H); 3.40 (m, 4H); 2.95 (t, 2H); 2.70 (t, 2H); 2.55 (d, 3H); 2.40 (m, 4H).

Example 7 (compound 52)

2-(methylamino)-2-oxoethyl 4-[3-(3'-chlorobiphenyl-3-yl)propyl]piperazine-1-carboxylate



7.1. 3-(3-bromophenyl)propan-1-ol

A suspension of 1.84 g (8 mmol) of 3-(3-bromophenyl)propionic acid and 0.91 g (24 mmol) of sodium borohydride in 20 ml of THF, cooled to 0°C, is admixed in small portions with 3.2 ml (25 mmol) of trifluoroborane-diethyl ether complex. Stirring is continued in the cold for 1 hour, and then at ambient temperature for 16 hours. The reaction mixture is cooled to 0°C and neutralized to a pH of 7-8 by adding a 1N solution of aqueous sodium hydroxide. It is concentrated under reduced pressure and then the residue is taken up in water. It is extracted with dichloromethane and dried over sodium sulphate. Following filtration, the organic phase is concentrated under reduced pressure. This gives 1.62 g (7.53 mmol) of product in the form of an oil, which is used as it is in the following step.

7.2. 2-(methylamino)-2-oxoethyl 4-[3-(3-bromophenyl)propyl]piperazine-1-carboxylate

A solution of 1.57 g (6.7 mmol) of 3-(3-bromophenyl)propan-1-ol, prepared in step 7.1., and 1.73 ml (10.1 mmol) of diisopropylethylamine in 38 ml of dichloromethane, cooled to 0°C, is admixed with 0.63 ml (8.14 mmol) of methanesulphonyl chloride. Stirring is continued in the cold for 0.5 hour and then at ambient temperature for 2 hours. The mixture is concentrated under reduced pressure and then the residue is suspended in 35 ml of acetonitrile. 1.34 g (5.35 mmol) of 2-(methylamino)-2-oxoethyl piperazine-1-carboxylate hydrochloride, prepared in

accordance with Example 3.3., and 2.2 g (16 mmol) of potassium carbonate are added. The mixture is heated at 75°C for 16 hours. After cooling to ambient temperature it is concentrated under reduced pressure and then the residue is taken up in water. It is extracted with ethyl acetate and dried over sodium sulphate. Following filtration, the organic phase is concentrated under reduced pressure. It is purified by chromatography on silica gel, eluting with a 98/2 mixture of dichloromethane and methanol. Crystallization from diisopropyl ether gives 0.84 g (2.10 mmol) of white crystals.

7.3. 2-(methylamino)-2-oxoethyl 4-[3-(3'-chlorobiphenyl-3-yl)propyl]piperazine-1-carboxylate

A suspension of 0.14 g (0.35 mmol) of 2-(methylamino)-2-oxoethyl 4-[3-(3-bromophenyl)propyl]piperazine-1-carboxylate, prepared in step 7.2., in a mixture of 4 ml of toluene and 0.6 ml of ethanol is admixed with 0.08 g (0.07 mol) of the tetrakis(triphenylphosphine)palladium complex, 1.05 ml (2.1 mmol) of a 2M aqueous solution of sodium carbonate and 0.22 g (1.4 mmol) of 3-chlorobenzeneboronic acid. The mixture is heated to 150°C under microwave irradiation for 5 minutes and the organic phase is recovered by filtration on a cartridge equipped with a frit and containing celite and sodium sulphate. The cartridge is rinsed with toluene and the filtrate is concentrated under reduced pressure. The product is purified by chromatography on silica gel, eluting with a 90/10

mixture of ethyl acetate and methanol. The eluate is subsequently taken up in n-heptane, to give 0.086 g (0.18 mmol) of product in the form of white crystals.

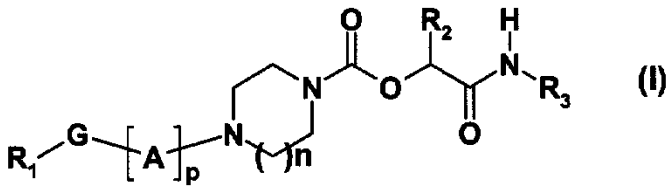
LC-MS: M+H = 430

Melting point: 82-85°C

^{1}H NMR δ (ppm): 7.35 (m, 8H); 6.05 (broad s, 1H); 4.6 (s, 2H); 3.55 (m, 4H); 2.85 (d, 3H); 2.75 (t, 2H); 2.45 (m, 6H); 1.9 (m, 2H).

Table 1 below illustrates the chemical structures and the physical properties of some compounds according to the invention. In the "base or salt" column, "base" represents a compound in the form of the free base, whereas "HCl" represents a compound in hydrochloride form.

Table 1



Cpd	R_1	G	$[A]_p$	n	R_2	R_3	m.p. (°C) (or M+H)	base or salt
1.	2-F-phenyl	bond	CH_2	1	H	CH_3	196-200	HCl
2.	2-Cl-phenyl	bond	CH_2	1	H	CH_3	212-217	HCl
3.	3-F-phenyl	bond	CH_2	1	H	CH_3	161-166	HCl
4.	3-I-phenyl	bond	CH_2	1	H	CH_3	(418)	base
5.	3-Cl-phenyl	bond	CH_2	1	H	CH_3	203-207	HCl
6.	4-Cl-phenyl	bond	CH_2	1	H	CH_3	112-115	HCl
7.	4-CH_3O-phenyl	bond	CH_2	1	H	CH_3	155-159	HCl

Cpd	R_1	G	$[A]_p$	n	R_2	R_3	m.p. (°C) (or M+H)	base or salt
8.	4-(phenylCH_2O)-phenyl	bond	CH_2	1	H	CH_3	172-178	HCl
9.	4-$(CH_3)_2CH$-phenyl	bond	CH_2	1	H	CH_3	104-108	HCl
10.	3-phenyl-phenyl	bond	CH_2	1	H	CH_3	111-114	HCl
11.	4-phenyl-phenyl	bond	CH_2	1	H	CH_3	173-179	HCl
12.	naphthalen-1-yl	bond	CH_2	1	H	CH_3	143-145	base
13.	naphthalen-2-yl	bond	CH_2	1	H	CH_3	184-186	HCl
14.	phenyl	bond	$(CH_2)_2$	1	H	CH_3	167-169	base
15.	3-Br-phenyl	bond	$(CH_2)_2$	1	H	CH_3	(384)	base
16.	4-Br-phenyl	bond	$(CH_2)_2$	1	H	CH_3	(384)	base
17.	4-CH_3O-phenyl	bond	$(CH_2)_2$	1	H	CH_3	124-126	base
18.	3-phenyl-phenyl	bond	$(CH_2)_2$	1	H	CH_3	118-120	base
19.	4-phenyl-phenyl	bond	$(CH_2)_2$	1	H	CH_3	148-150	base
20.	naphthalen-1-yl	bond	$(CH_2)_2$	1	H	H	125-127	base
21.	naphthalen-1-yl	bond	$(CH_2)_2$	1	H	CH_3	109-112	base
22.	naphthalen-1-yl	bond	$(CH_2)_2$	1	H	CH_2CH_3	113-115	base
23.	naphthalen-1-yl	bond	$(CH_2)_2$	1	H	cyclo-propyl	125-127	base
24.	naphthalen-1-yl	bond	$(CH_2)_2$	1	H	CH_2-cyclo-propyl	113-115	base
25.	naphthalen-2-yl	bond	$(CH_2)_2$	1	H	CH_3	133-135	base
26.	naphthalen-2-yl	bond	$(CH_2)_2$	2	H	H	115-119	base
27.	indol-3-yl	bond	$(CH_2)_2$	1	H	CH_3	121-123	base
28.	3-(4-Cl-phenyl)-1*H*-methyl-pyrazol-5-yl	bond	$(CH_2)_2$	1	H	CH_3	141-143	base
29.	3-(4-Cl-phenyl)isoxazol-5-yl	bond	$(CH_2)_2$	1	H	CH_3	130-132	base
30.	5-(4-Cl-phenyl)isoxazol-3-yl	bond	$(CH_2)_2$	1	H	CH_3	146-148	base
31.	6-(4-Cl-phenyl)pyrimidin-4-yl	bond	$(CH_2)_2$	1	H	CH_3	132-134	base
32.	1,1-	bond	$(CH_2)_2$	1	H	CH_3	86-88	base

Cpd	R_1	G	$[A]_p$	n	R_2	R_3	m.p. (°C) (or M+H)	base or salt
	diphenylmethyl							
33.	phenyl	bond	$(CH_2)_3$	1	H	CH_3	315-317	HCl
34.	3-Cl-phenyl	bond	$(CH_2)_3$	1	H	CH_3	85-87	base
35.	4-Cl-phenyl	bond	$(CH_2)_3$	1	H	CH_3	115-117	base
36.	3-Br-phenyl	bond	$(CH_2)_3$	1	H	CH_3	(398)	base
37.	4-Br-phenyl	bond	$(CH_2)_3$	1	H	CH_3	(398)	base
38.	3-CN-phenyl	bond	$(CH_2)_3$	1	H	CH_3	107-109	base
39.	3-CF_3-phenyl	bond	$(CH_2)_3$	1	H	CH_3	98-100	base
40.	4-CF_3-phenyl	bond	$(CH_2)_3$	1	H	CH_3	85-87	base
41.	2-Cl,4-Cl-phenyl	bond	$(CH_2)_3$	1	H	CH_3	103-105	base
42.	2-Cl,5-Cl-phenyl	bond	$(CH_2)_3$	1	H	H	128-130	base
43.	2-Cl,5-Cl-phenyl	bond	$(CH_2)_3$	1	H	CH_3	121-123	base
44.	pyrimidin-2-yl	bond	$(CH_2)_3$	1	H	CH_3	103-105	base
45.	pyrimidin-5-yl	bond	$(CH_2)_3$	1	H	CH_3	116-118	base
46.	thiazol-2-yl	bond	$(CH_2)_3$	1	H	CH_3	83-85	base
47.	2-phenyl-phenyl	bond	$(CH_2)_3$	1	H	CH_3	(396)	base
48.	3-phenyl-phenyl	bond	$(CH_2)_3$	1	H	CH_3	99-101	base
49.	4-phenyl-phenyl	bond	$(CH_2)_3$	1	H	CH_3	110-113	base
50.	3-phenyl-phenyl	bond	$(CH_2)_2$-$C(CH_3)_2$	1	H	CH_3	212-216	HCl
51.	4-phenyl-phenyl	bond	$(CH_2)_2$-$C(CH_3)_2$	1	H	CH_3	101-103	base
52.	3-(3-Cl-phenyl)-phenyl	bond	$(CH_2)_3$	1	H	CH_3	82-85	base
53.	3-(4-Cl-phenyl)-phenyl	bond	$(CH_2)_3$	1	H	CH_3	136-138	base
54.	3-(3-CH_3O)phenyl)-phenyl	bond	$(CH_2)_3$	1	H	CH_3	(426)	base
55.	3-(4-CH_3O)phenyl)-phenyl	bond	$(CH_2)_3$	1	H	CH_3	135-137	base
56.	3-(3-CN-phenyl)-phenyl	bond	$(CH_2)_3$	1	H	CH_3	152-154	base
57.	3-(4-CN-phenyl)-phenyl	bond	$(CH_2)_3$	1	H	CH_3	137-139	base
58.	4-(3-Cl-	bond	$(CH_2)_3$	1	H	CH_3	101-103	base

Cpd	R_1	G	$[A]_p$	n	R_2	R_3	m.p. (°C) (or M+H)	base or salt
	phenyl)-phenyl							
59.	4-(4-Cl-phenyl)-phenyl	bond	$(CH_2)_3$	1	H	CH_3	125-128	base
60.	4-(3-CH_3O)phenyl)-phenyl	bond	$(CH_2)_3$	1	H	CH_3	97-100	base
61.	4-(4-CH_3O)phenyl)-phenyl	bond	$(CH_2)_3$	1	H	CH_3	128-130	base
62.	4-(3-CN-phenyl)-phenyl	bond	$(CH_2)_3$	1	H	CH_3	108-110	base
63.	4-(4-CN-phenyl)-phenyl	bond	$(CH_2)_3$	1	H	CH_3	148-150	base
64.	naphthalen-1-yl	bond	$(CH_2)_3$	1	H	CH_3	104-106	*HCl*
65.	naphthalen-2-yl	bond	$(CH_2)_3$	1	H	CH_3	110-112	base
66.	3-(4-Cl-phenyl)-1*H*-methyl-pyrazol-5-yl	bond	$(CH_2)_3$	1	H	CH_3	157-159	base
67.	5-(4-Cl-phenyl)isoxazol-3-yl	bond	$(CH_2)_3$	1	H	CH_3	125-127	base
68.	3-(4-Cl-phenyl)isoxazol-5-yl	bond	$(CH_2)_3$	1	H	H	132-134	base
69.	3-(4-Cl-phenyl)isoxazol-5-yl	bond	$(CH_2)_3$	1	H	CH_3	108-110	base
70.	3-(naphthalen-2-yl)isoxazol-5-yl	bond	$(CH_2)_3$	1	H	CH_3	71-73	base
71.	1,1-di-(4-F-phenyl)methyl	bond	$(CH_2)_3$	1	H	CH_3	(446)	base
72.	3-Cl-phenyl	bond	$(CH_2)_4$	1	H	CH_3	103-105	base
73.	4-Cl-phenyl	bond	$(CH_2)_4$	1	H	CH_3	120-122	base

Cpd	R_1	G	$[A]_p$	n	R_2	R_3	m.p. (°C) (or M+H)	base or salt
74.	3-CN-phenyl	bond	$(CH_2)_4$	1	H	CH_3	127-129	base
75.	3-CF_3-phenyl	bond	$(CH_2)_4$	1	H	CH_3	98-100	base
76.	4-CF_3-phenyl	bond	$(CH_2)_4$	1	H	CH_3	129-131	base
77.	pyrimidin-2-yl	bond	$(CH_2)_4$	1	H	CH_3	141-143	base
78.	pyrimidin-5-yl	bond	$(CH_2)_4$	1	H	CH_3	114-116	base
79.	thiazol-2-yl	bond	$(CH_2)_4$	1	H	CH_3	93-95	base
80.	naphthalen-1-yl	bond	$(CH_2)_4$	1	H	CH_3	90-92	base
81.	naphthalen-2-yl	bond	$(CH_2)_4$	1	H	CH_3	109-111	base
82.	2-phenyl-phenyl	bond	$(CH_2)_4$	1	H	CH_3	92-94	base
83.	3-phenyl-phenyl	bond	$(CH_2)_4$	1	H	CH_3	97-99	base
84.	phenyl	bond	$CH=CHCH_2$ *(E)*	1	H	H	115-117	base
85.	phenyl	bond	$CH=CHCH_2$ *(E)*	1	H	CH_3	109-111	base
86.	3-Cl-phenyl	bond	$C\equiv CCH_2$	1	H	CH_3	114-116	base
87.	4-Cl-phenyl	bond	$C\equiv CCH_2$	1	H	CH_3	127-129	base
88.	3-CF_3-phenyl	bond	$C\equiv CCH_2$	1	H	CH_3	131-133	base
89.	4-CF_3-phenyl	bond	$C\equiv CCH_2$	1	H	CH_3	125-127	base
90.	3-CN-phenyl	bond	$C\equiv CCH_2$	1	H	CH_3	134-140	base
91.	pyrimidin-2-yl	bond	$C\equiv CCH_2$	1	H	CH_3	137-139	base
92.	pyrimidin-5-yl	bond	$C\equiv CCH_2$	1	H	CH_3	151-153	base
93.	thiazol-2-yl	bond	$C\equiv CCH_2$	1	H	CH_3	111-113	base
94.	naphthalen-1-yl	bond	$C\equiv CCH_2$	1	H	CH_3	131-134	base
95.	naphthalen-2-yl	bond	$C\equiv CCH_2$	1	H	CH_3	(366)	base
96.	2-phenyl-phenyl	bond	$C\equiv CCH_2$	1	H	CH_3	(392)	base
97.	3-phenyl-phenyl	bond	$C\equiv CCH_2$	1	H	CH_3	125-127	base
98.	4-phenyl-phenyl	bond	$C\equiv CC(CH_3)_2$	1	H	CH_3	137-139	base
99.	3-CF_3-phenyl	bond	$C\equiv CCH_2$	2	H	H	102-104	base
100.	3-CF_3-phenyl	bond	$C\equiv CCH_2$	2	H	CH_3	92-94	base

Cpd	R_1	G	$[A]_p$	n	R_2	R_3	m.p. (°C) (or M+H)	base or salt
101.	3-Cl-phenyl	bond	$C\equiv C(CH_2)_2$	1	H	CH_3	115-117	base
102.	4-Cl-phenyl	bond	$C\equiv C(CH_2)_2$	1	H	CH_3	141-143	base
103.	3-CF_3-phenyl	bond	$C\equiv C(CH_2)_2$	1	H	CH_3	93-95	base
104.	4-CF_3-phenyl	bond	$C\equiv C(CH_2)_2$	1	H	CH_3	142-144	base
105.	3-CN-phenyl	bond	$C\equiv C(CH_2)_2$	1	H	CH_3	144-146	base
106.	pyrimidin-2-yl	bond	$C\equiv C(CH_2)_2$	1	H	CH_3	120-122	base
107.	pyrimidin-5-yl	bond	$C\equiv C(CH_2)_2$	1	H	CH_3	159-161	base
108.	thiazol-2-yl	bond	$C\equiv C(CH_2)_2$	1	H	CH_3	103-105	base
109.	naphthalen-1-yl	bond	$C\equiv C(CH_2)_2$	1	H	CH_3	99-101	base
110.	naphthalen-2-yl	bond	$C\equiv C(CH_2)_2$	1	H	CH_3	140-142	base
111.	2-phenyl-phenyl	bond	$C\equiv C(CH_2)_2$	1	H	CH_3	(406)	base
112.	3-phenyl-phenyl	bond	$C\equiv C(CH_2)_2$	1	H	CH_3	102-104	base
113.	3-Cl-phenyl	bond	$C\equiv C(CH_2)_3$	1	H	CH_3	79-81	base
114.	4-Cl-phenyl	bond	$C\equiv C(CH_2)_3$	1	H	CH_3	126-128	base
115.	2-F,4-Cl-phenyl	bond	$C\equiv C(CH_2)_3$	1	H	CH_3	131-133	base
116.	2-Cl,4-F-phenyl	bond	$C\equiv C(CH_2)_3$	1	H	CH_3	133-135	base
117.	2-Cl,4-Cl-phenyl	bond	$C\equiv C(CH_2)_3$	1	H	CH_3	133-135	base
118.	2-Cl,5-Cl-phenyl	bond	$C\equiv C(CH_2)_3$	1	H	CH_3	110-112	base
119.	3-Cl,4-Cl-phenyl	bond	$C\equiv C(CH_2)_3$	1	H	CH_3	119-121	base
120.	3-Cl,4-F-phenyl	bond	$C\equiv C(CH_2)_3$	1	H	CH_3	98-100	base
121.	phenyl	O	$(CH_2)_2$	1	H	CH_3	233-235	base
122.	2-Cl-phenyl	O	$(CH_2)_2$	1	H	H	90-92	base
123.	2-Cl-phenyl	O	$(CH_2)_2$	1	H	CH_3	184-186	HCl
124.	2-CN-phenyl	O	$(CH_2)_2$	1	H	CH_3	109-111	base
125.	3-Cl-phenyl	O	$(CH_2)_2$	1	H	H	> 300	HCl
126.	3-Cl-phenyl	O	$(CH_2)_2$	1	H	CH_3	105-107	base
127.	3-CN-phenyl	O	$(CH_2)_2$	1	H	CH_3	141-143	base
128.	4-F-phenyl	O	$(CH_2)_2$	1	H	CH_3	134-136	base
129.	4-Cl-phenyl	O	$(CH_2)_2$	1	H	H	115-117	base
130.	4-Cl-phenyl	O	$(CH_2)_2$	1	H	CH_3	159-161	base
131.	4-CN-phenyl	O	$(CH_2)_2$	1	H	H	145-147	base
132.	4-CN-phenyl	O	$(CH_2)_2$	1	H	CH_3	138-140	base
133.	4-$(CH_3)_3C$-phenyl	O	$(CH_2)_2$	1	H	CH_3	111-113	HCl
134.	4-CF_3-phenyl	O	$(CH_2)_2$	1	H	H	104-106	base
135.	4-CF_3O-phenyl	O	$(CH_2)_2$	1	H	H	96-98	base
136.	4-CF_3O-phenyl	O	$(CH_2)_2$	1	H	CH_3	93-96	base
137.	2-Cl,3-Cl-phenyl	O	$(CH_2)_2$	1	H	H	136-138	base

Cpd	R_1	G	$[A]_p$	n	R_2	R_3	m.p. (°C) (or M+H)	base or salt
138.	2-Cl,3-Cl-phenyl	O	$(CH_2)_2$	1	H	CH_3	132-134	base
139.	2-Cl,4-Cl-phenyl	O	$(CH_2)_2$	1	H	H	178-180	base
140.	2-Cl,4-Cl-phenyl	O	$(CH_2)_2$	1	H	CH_3	102-104	base
141.	3-Cl,4-Cl-phenyl	O	$(CH_2)_2$	1	H	CH_3	128-130	base
142.	3-Cl,4-Cl-phenyl	O	$(CH_2)_2$	1	H	H	126-128	base
143.	3-Cl,5-Cl-phenyl	O	$(CH_2)_2$	1	H	CH_3	111-113	base
144.	3-CF_3,5-CF_3-phenyl	O	$(CH_2)_2$	1	H	CH_3	137-139	base
145.	3,4-(OCH_2O)-phenyl	O	$(CH_2)_2$	1	H	CH_3	139-141	base
146.	3-phenyl-phenyl	O	$(CH_2)_2$	1	H	H	120-122	HCl
147.	3-phenyl-phenyl	O	$(CH_2)_2$	1	H	CH_3	143-145	HCl
148.	4-phenyl-phenyl	O	$(CH_2)_2$	1	H	H	238-240	base
149.	4-phenyl-phenyl	O	$(CH_2)_2$	1	H	CH_3	130-132	base
150.	naphthalen-1-yl	O	$(CH_2)_2$	1	H	H	116-118	base
151.	naphthalen-1-yl	O	$(CH_2)_2$	1	H	CH_3	135-137	base
152.	naphthalen-2-yl	O	$(CH_2)_2$	1	H	H	88-90	base
153.	naphthalen-2-yl	O	$(CH_2)_2$	1	H	CH_3	118-120	base
154.	quinolin-6-yl	O	$(CH_2)_2$	1	H	H	203-205	base
155.	quinolin-6-yl	O	$(CH_2)_2$	1	H	CH_3	126-128	base
156.	quinolin-8-yl	O	$(CH_2)_2$	1	H	CH_3	99-101	base
157.	phenyl	O	$(CH_2)_3$	1	H	CH_3	103-105	base
158.	2-Cl-phenyl	O	$(CH_2)_3$	1	H	CH_3	119-121	base
159.	3-Cl-phenyl	O	$(CH_2)_3$	1	H	CH_3	95-97	base
160.	4-Cl-phenyl	O	$(CH_2)_3$	1	H	CH_3	116-118	base
161.	2-Cl,3-Cl-phenyl	O	$(CH_2)_3$	1	H	CH_3	110-112	base
162.	2-Cl,4-Cl-phenyl	O	$(CH_2)_3$	1	H	CH_3	115-117	base
163.	2-Cl,5-Cl-phenyl	O	$(CH_2)_3$	1	H	CH_3	134-136	base
164.	2-Cl,6-Cl-phenyl	O	$(CH_2)_3$	1	H	CH_3	100-102	base
165.	3-Cl,5-Cl-	O	$(CH_2)_3$	1	H	CH_3	121-123	base

Cpd	R_1	G	$[A]_p$	n	R_2	R_3	m.p. (°C) (or M+H)	base or salt
	phenyl							
166.	phenyl	C=O	$(CH_2)_2$	1	H	CH_3	141-143	base
167.	4-Cl-phenyl	C=O	$(CH_2)_2$	1	H	CH_3	172-174	base
168.	phenyl	C=O	$(CH_2)_3$	1	H	CH_3	110-112	base

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 ([1-^{3}H] ethanolamine) of anandamide [1-^{3}H ethanolamine] by FAAH (*Life Sciences (1995), 56, 1999-2005* and *Journal of Pharmacology and Experimental Therapeutics (1997), 283, 729-34*). 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) 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 [1-^{3}H ethanolamine] (specific activity: 15-20 Ci/mmol) diluted to 10 µM with cold anandamide, and the membrane preparation (400 µg of frozen tissue per assay) are added. After 15 minutes at 25°C the 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 1-^{3}H ethanolamine 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.

Table 2 below shows the IC_{50} of some compounds according to the invention

Table 2

Compound	IC_{50}
21	0.072 µM
48	0.050 µM
49	0.032 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 (p.o.) or intraperitoneally (i.p.) in suspension in Tween 80 at 0.5%, 60 minutes or 120 minutes before the administration of PBQ. Under these conditions the most potent compounds of the invention reduce by 35 to 70% the number of stretches induced by PBQ, within a dose range of between 1 and 30 mg/kg. For example, compounds 49 and 69 of the table reduce by 43% and 47% respectively, the number of stretches induced by PBQ, at a dose of 10 mg/kg at 120 minutes.

The FAAH enzyme (*Chemistry and Physics of Lipids*, (2000), 108, 107-21) catalyses the hydrolysis of endogenous derivatives of amides and of esters of various fatty acids such as *N*-arachidonylethanolamine (anandamide), *N*-palmitoylethanolamine, *N*-oleoylethanolamine, 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 disease, irritable bowel syndrome; acute or chronic peripheral pain; dizziness, vomiting, nausea, especially that 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 according to the invention 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 an acid addition 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 according to the invention. These pharmaceutical compositions include an effective dose of a compound according to the invention, or an acid addition salt or a hydrate or pharmaceutically acceptable solvate of the said compound, and optionally one or more pharmaceutically acceptable excipients.

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

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, local, intrathecal, intranasal, transdermal, pulmonary, ocular or rectal administration the active principle of formula (I) above, or its acid addition 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.

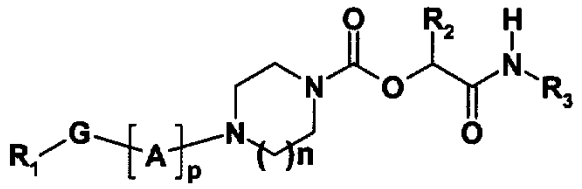
There may be particular cases in which higher or lower dosages are appropriate; such dosages also belong to the invention. In accordance with common practice the dosage appropriate to each patient is determined by the doctor according to the method of administration, the weight and

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 addition salts with a pharmaceutically acceptable acid, or a solvate or a hydrate of the said compound.

Claims

1. Compound of the formula (I)



(I)

in which

n represents an integer 1 or 2;

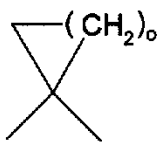
p represents an integer ranging from 1 to 7;

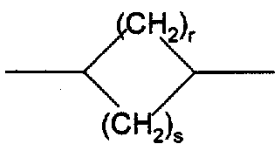
A is selected from one or more groups X, Y and/or Z;

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

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

Z represents a group of formula:





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;

G represents a single bond, an oxygen or sulphur atom or an SO, SO_2, C=O or CH(OH) group;

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

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

R_5 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 or C_1-C_6-fluorothioalkyl group, a group NR_7R_8, NR_7COR_8, $NR_7CO_2R_8$, $NR_7SO_2R_8$, COR_7, CO_2R_7, $CONR_7R_8$, SO_2R_7 or $SO_2NR_7R_8$, or an -O-(C_{1-3}-alkylene)-O group;

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

R_7 and R_8 represent independently of one another a hydrogen

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

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

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

n represents an integer 1 or 2;

p represents an integer ranging from 1 to 7;

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

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

Y represents either a C_2-alkenylene group or a C_2-alkynylene group;

G represents a single bond, an oxygen atom or a C=O group;

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

R_4 represents a group selected from a phenyl, naphthalenyl, diphenylmethyl, quinolinyl, indolyl, pyrazolyl, isoxazolyl, pyrimidinyl and thiazolyl;

R_5 represents a halogen atom or a cyano group, a C_{1-6}-alkyl group, a C_{1-6}-alkoxy group, a C_{1-6}-fluoroalkyl group, a C_1-C_6-fluoroalkoxy group, or an -O-(C_{1-3}-alkylene)-O group;

R_6 represents a phenyl, naphthalenyl or benzyloxy group;

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

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

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

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

n represents an integer;

p represents an integer ranging from 1 to 4;

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

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

Y represents a C_2-alkynylene group;

G represents a single bond or an oxygen atom;

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

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

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

R_6 represents a phenyl group;

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

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

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

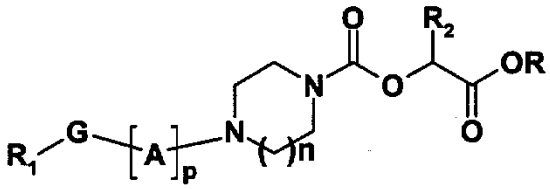
4. Compound of formula (I) according to any one

of Claims 1 to 3, characterized in that

R_2 represents a hydrogen atom;

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

5. Process for preparing a compound of formula (I) according to any one of Claims 1 to 4, comprising the step consisting in converting the carbamate ester of general formula (II)

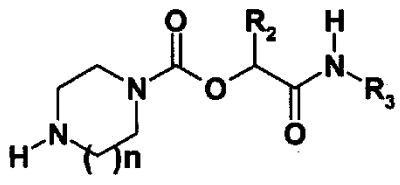


(II)

in which R_1, R_2, G, A, p and n are as defined in the general formula (I) according to Claim 1 and R represents a methyl or ethyl group,

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

6. Process for preparing a compound of formula (I) according to any one of Claims 1 to 4, comprising the step consisting in converting the carbamate-amide of general formula (V)

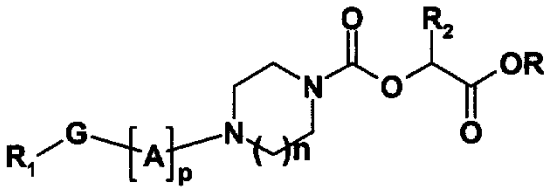


(V)

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

by reaction with a derivative of general formula R_1-G-$[A]_p$-W (VI), in which R_1, G, p and A are as defined in the general formula (I) and W represents a chlorine, bromine or iodine atom, or a mesylate or tosylate group.

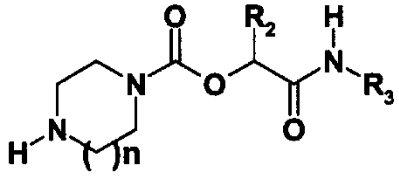
7. Compound of the general formula (II),



(II)

in which R_1, R_2, G, A, p and n are as defined in the general formula (I) according to Claim 1 and R represents a methyl or ethyl group.

8. Compound of the general formula (V),



(V)

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

9. Compound of formula (I) according to any one of Claims 1 to 4, in the form of a base, addition salt with an acid, hydrate or pharmaceutically acceptable solvate, for its use as a medicinal product.

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

11. Use of a compound of formula (I) according to any one of Claims 1 to 4, in the form of a base, addition salt with an acid, hydrate or pharmaceutically acceptable solvate, 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 4, in the form of a base, salt, hydrate or pharmaceutically acceptable solvate, 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.