

New pyrrolidine and thiazolidine compounds, a process for their preparation and pharmaceutical compositions containing them

The present invention relates to new pyrrolidine and thiazolidine compounds, to a process for their preparation, to pharmaceutical compositions containing them and to their use as inhibitors of dipeptidyl-peptidase IV (DPP IV).

5 Dipeptidyl-peptidase IV is a membrane serine protease present in numerous human tissues and involved in numerous pathologies :

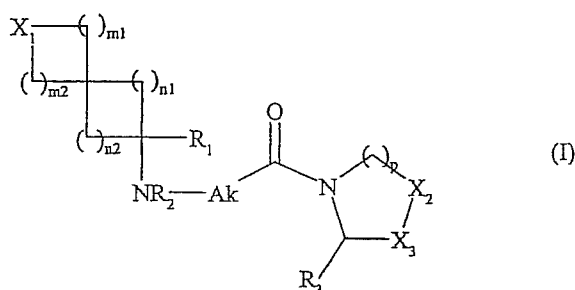
In particular, DPP IV has been shown to be responsible for inactivation of GLP-1 (glucagon-like peptide-1). GLP-1, being an important stimulator of the secretion of insulin in the pancreas, has a direct beneficial effect on the level of glucose in the blood.

10 Inhibition of DPP IV accordingly represents an extremely promising approach in the treatment of glucose intolerance and of disorders associated with hyperglycaemia such as, for example, non-insulin-dependent diabetes (type II diabetes) or obesity.

DPP IV-inhibitors have already been described in the literature, in particular amide compounds in Patent Application EP 0 490 379 and in the journal Adv. Exp. Med. Biol. 15 1997, 421, 157-160, carbamate compounds in Patent Application DE 19826972, α -amino acid compounds in Patent Application EP 1 258 476 and sulphone compounds in Patent Application EP 1 245 568.

20 The compounds of the invention have dipeptidyl-peptidase IV-inhibiting properties, making them particularly useful for the treatment of glucose intolerance and of disorders associated with hyperglycaemia.

More specifically, the present invention relates to the compounds of formula (I) :



wherein :

- ♦ X_1 represents an atom or group selected from $CR_{4a}R_{4b}$, O, $S(O)_{q1}$ and NR_5 ,
 wherein R_{4a} and R_{4b} , which may be identical or different, each represent a hydrogen
 atom or a linear or branched C_1 - C_6 alkyl group,
 5 or R_{4a} and R_{4b} together form, with the carbon atom carrying them, a C_3 - C_7 cycloalkyl
 group,
 q_1 represents zero, 1 or 2,
 and R_5 represents a hydrogen atom or a linear or branched C_1 - C_6 alkyl group optionally
 substituted by a hydroxy group,
- 10 ♦ m_1 represents zero or an integer of from 1 to 4 inclusive,
 ♦ m_2 represents an integer of from 1 to 4 inclusive,
 ♦ n_1 and n_2 , which may be identical or different, each represent an integer of from 1 to 3
 inclusive,
- 15 ♦ R_1 represents a hydrogen atom or a group selected from carboxy, linear or branched
 C_1 - C_6 alkoxycarbonyl, carbamoyl optionally substituted by 1 or 2 linear or branched
 C_1 - C_6 alkyl groups, and linear or branched C_1 - C_6 alkyl optionally substituted by a
 hydroxy group or by an amino group optionally substituted by 1 or 2 linear or branched
 C_1 - C_6 alkyl groups,
- 20 ♦ R_2 represents a hydrogen atom or a linear or branched C_1 - C_6 alkyl group,
 ♦ A_k represents a linear or branched C_1 - C_4 alkylene chain optionally substituted by one or
 more halogen, preferably fluorine, atoms,
 ♦ p represents zero, 1 or 2,
 ♦ R_3 represents a hydrogen atom or a cyano group,
- 25 ♦ X_2 and X_3 , which may be identical or different, each represent either a $S(O)_{q2}$ group,
 wherein q_2 represents zero, 1 or 2, or a $CR_{6a}R_{6b}$ group, wherein R_{6a} and R_{6b} , which may
 be identical or different, each represent a hydrogen atom or a halogen, preferably
 fluorine, atom, or R_{6a} represents a hydrogen atom and R_{6b} represents a hydroxy group,

to their optical isomers, where they exist, and to addition salts thereof with a
 pharmaceutically acceptable acid.

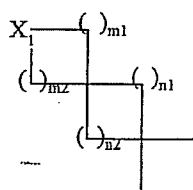
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Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, methanesulphonic acid, camphoric acid, oxalic acid.

X_1 preferably represents an oxygen atom or a $-\text{CH}_2-$ group.

m_1 and m_2 preferably each represent 1 or 2.

n_1 and n_2 preferably each represent 1 or 2, and are preferably identical.



preferably represents a group selected from



and



10 R_2 preferably represents a hydrogen atom.

A_k preferably represents a $-\text{CH}_2-$ group.

p preferably represents 1.

R_3 preferably represents a cyano group. In that case, the configuration of the carbon carrying it is preferably (S) when X_2 and X_3 each represent a $\text{CR}_{6a}\text{R}_{6b}$ group, and (R) when

15 X_2 or X_3 represents a $\text{S}(\text{O})_{q2}$ group.

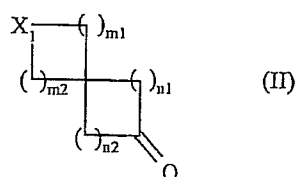
X_2 and X_3 preferably each represent a $\text{CR}_{6a}\text{R}_{6b}$ group.

Preferred compounds of formula (I) are :

- (2S)-1-({[9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino}acetyl)-2-pyrrolidinecarbonitrile, and its addition salts with a pharmaceutically acceptable acid;
- 5 - (2S)-1-({[3-(hydroxymethyl)spiro[5.5]undec-3-yl]amino}acetyl)-2-pyrrolidinecarbonitrile, and its addition salts with a pharmaceutically acceptable acid;
- (2S)-1-({[2-(hydroxymethyl)spiro[3.4]oct-2-yl]amino}acetyl)-2-pyrrolidinecarbonitrile, and its addition salts with a pharmaceutically acceptable acid;
- 10 - (4R)-3-[(spiro[5.5]undec-3-ylamino)acetyl]-1,3-thiazolidine-4-carbonitrile, and its addition salts with a pharmaceutically acceptable acid;
- 2-({2-[(2S)-2-cyanopyrrolidinyl]-2-oxoethyl}amino)spiro[3.3]heptane-2-carboxamide, and its addition salts with a pharmaceutically acceptable acid;
- (2S)-1-({[2-(2-hydroxymethyl)-7-oxaspiro[3.5]non-2-yl]amino}acetyl)-2-pyrrolidinecarbonitrile, and its addition salts with a pharmaceutically acceptable acid;
- 15 - (2S,4S)-4-fluoro-1-({[9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino}acetyl)-2-pyrrolidinecarbonitrile, its (2S,4R) isomer, its (2R, 4R) isomer and addition salts thereof with a pharmaceutically acceptable acid;
- (2S)-4,4-difluoro-1-({[9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino}acetyl)-2-pyrrolidinecarbonitrile, and its addition salts with a pharmaceutically acceptable acid;
- 20 - and (4R)-3-({[9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino}acetyl)-1,3-thiazolidine-4-carbonitrile, and its addition salts with a pharmaceutically acceptable acid.

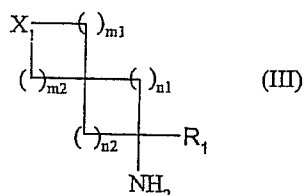
25 The invention relates also to a process for the preparation of compounds of formula (I) starting from a compound of formula (II) :

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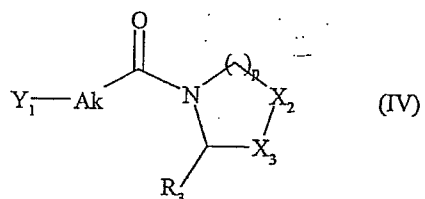
wherein X_1 , m_1 , m_2 , n_1 and n_2 are as defined for formula (I),

which is converted to a compound of formula (III) :



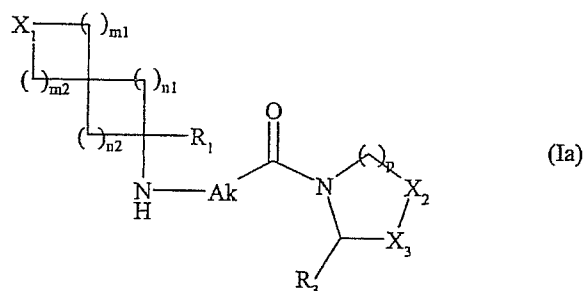
5 wherein X_1 , m_1 , m_2 , n_1 , n_2 and R_1 are as defined for formula (I),

which is reacted with a compound of formula (IV) :



wherein Ak , p , R_3 , X_2 and X_3 are as defined for formula (I) and Y_1 represents a leaving group,

10 to yield compounds of formula (Ia), a particular case of the compounds of formula (I) wherein R_2 represents a hydrogen atom :



wherein X_1 , m_1 , m_2 , n_1 , n_2 , R_1 , Ak , p , R_3 , X_2 and X_3 are as defined for formula (I),

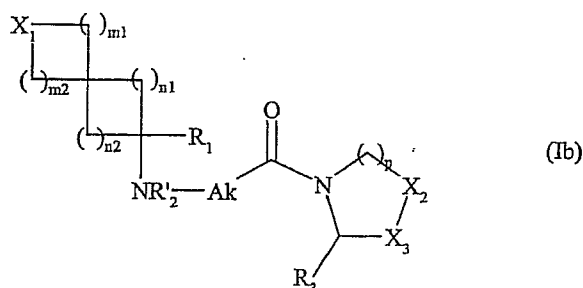
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which, when it is desired to obtain compounds of formula (I) wherein R_2 is other than a hydrogen atom, is reacted with a compound of formula (V) :



wherein Y_2 represents a leaving group and R'_2 represents a linear or branched C_1 - C_6 -alkyl group,

to yield compounds of formula (Ib), a particular case of the compounds of formula (I) wherein R_2 represents a linear or branched C_1 - C_6 alkyl group :



wherein X_1 , m_1 , m_2 , n_1 , n_2 , R_1 , Ak , p , R_3 , X_2 and X_3 are as defined for formula (I) and R'_2 is as defined hereinbefore,

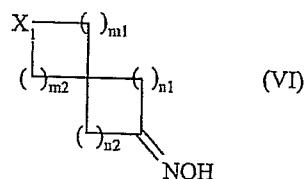
which compounds of formulae (Ia) and (Ib), which constitute the totality of the compounds of formula (I),

are purified according to a conventional purification technique, are optionally separated into their optical isomers according to a conventional separation technique and, if desired, are converted into addition salts with a pharmaceutically acceptable acid.

The compounds of formula (IV) can be prepared according to the process described in *J. Med. Chem.* **2002**, Vol. 45(12), 2362-2365.

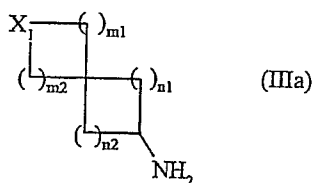
When it is desired to obtain compounds of formula (I) wherein R_1 represents a hydrogen atom, the compound of formula (II) is reacted with hydroxylamine to yield a compound of formula (VI) :

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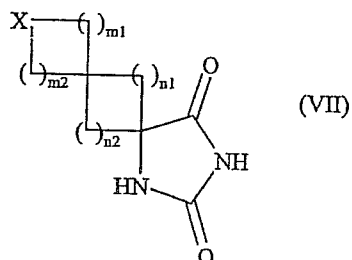
wherein X_1 , m_1 , m_2 , n_1 and n_2 are as defined for formula (I),

which is then hydrogenated to a compound of formula (IIIa), a particular case of the compounds of formula (III) wherein R_1 represents a hydrogen atom :



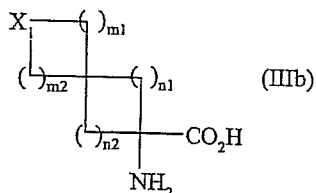
wherein X_1 , m_1 , m_2 , n_1 and n_2 are as defined for formula (I).

When it is desired to obtain compounds of formula (I) wherein R_1 represents a hydroxymethyl, carboxy or alkoxy carbonyl group, the compound of formula (II) is reacted with ammonium carbonate and potassium cyanide to yield a compound of formula (VII) :



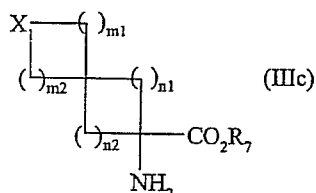
wherein X_1 , m_1 , m_2 , n_1 and n_2 are as defined for formula (I),

which is heated with barium sulphate to yield a compound of formula (IIIb), a particular case of the compounds of formula (III) wherein R_1 represents a carboxy group :



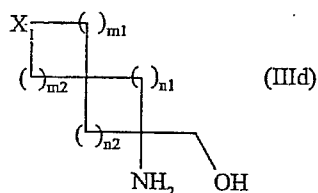
wherein X_1 , m_1 , m_2 , n_1 and n_2 are as defined for formula (I),

which is esterified to a compound of formula (IIIc), a particular case of the compounds of formula (III) wherein R_1 represents an alkoxy-carbonyl group :



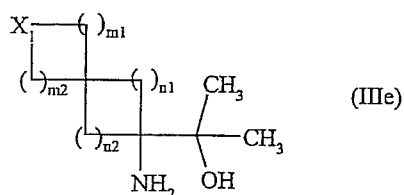
wherein X_1 , m_1 , m_2 , n_1 and n_2 are as defined for formula (I) and R_7 represents a linear or branched C_1 - C_6 alkyl group,

the reduction of which yields a compound of formula (IIIId), a particular case of the compounds of formula (III) wherein R_1 represents a hydroxymethyl group :



wherein X_1 , m_1 , m_2 , n_1 and n_2 are as defined for formula (I).

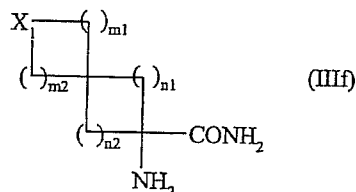
When it is desired to obtain compounds of formula (I) wherein R_1 represents a 1-hydroxy-1-methylethyl group, the compound of formula (IIIc) is, after protection of the amine function, reacted with methylmagnesium iodide to yield, after deprotection of the amine function, a compound of formula (IIIe), a particular case of the compounds of formula (III) wherein R_1 represents a 1-hydroxy-1-methylethyl group :



wherein X_1 , m_1 , m_2 , n_1 and n_2 are as defined for formula (I).

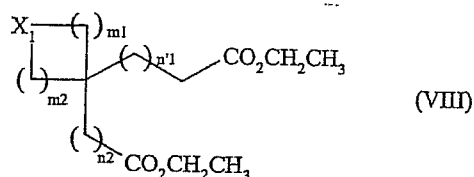
When it is desired to obtain compounds of formula (I) wherein R_1 represents a carbamoyl group, the compound of formula (IIIb) is, after protection of the amine function, reacted with ammonia in the presence of a coupling agent to yield, after deprotection of the amine function, a compound of formula (IIIf), a particular case of the compounds of formula (III)

5 wherein R_1 represents a carbamoyl group :



wherein X_1 , m_1 , m_2 , n_1 and n_2 are as defined for formula (I).

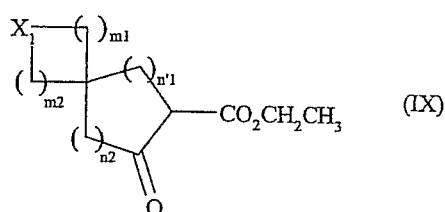
The compounds of formula (II) can be obtained starting from a compound of formula (VIII) :



10

wherein X_1 , m_1 , m_2 and n_2 are as defined hereinbefore and n'_1 represents zero, 1 or 2,

which is placed in the presence of a base, such as sodium hydride, to yield a compound of formula (IX) :

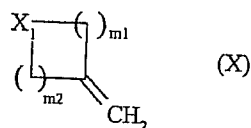


15

wherein X_1 , m_1 , m_2 , n'_1 and n_2 are as defined hereinbefore,

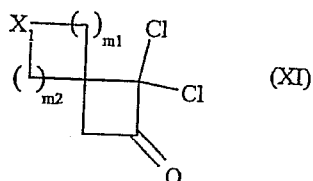
the reaction of which with potassium hydroxide yields a compound of formula (II).

The compounds of formula (IIa), a particular case of the compounds of formula (II) wherein n_1 and n_2 are identical and each represent 1, can also be obtained starting from a compound of formula (X) :



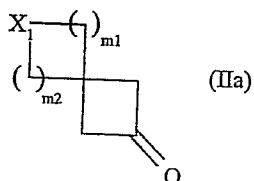
5 wherein X_1 , m_1 and m_2 are as defined for formula (I),

which is reacted with trichloroacetic acid chloride and zinc to yield a compound of formula (XI) :



wherein X_1 , m_1 and m_2 are as defined for formula (I),

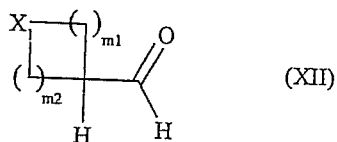
10 the reduction of which yields a compound of formula (IIa) :



wherein X_1 , m_1 and m_2 are as defined for formula (I).

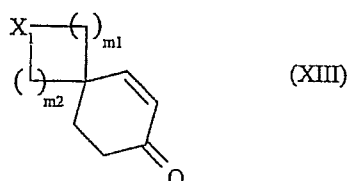
The compounds of formula (IIb), a particular case of the compounds of formula (II) wherein n_1 and n_2 are identical and each represent 2,

15 can also be obtained starting from a compound of formula (XII) :



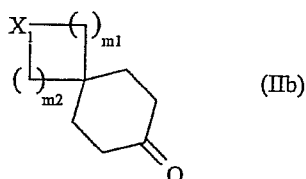
wherein X_1 , m_1 and m_2 are as defined for formula (I),

which is reacted with methyl vinyl ketone to yield a compound of formula (XIII) :



wherein X_1 , m_1 and m_2 are as defined for formula (I),

the catalytic hydrogenation of which yields a compound of formula (IIb) :



5 wherein X_1 , m_1 and m_2 are as defined for formula (I).

In addition to the fact that they are new, the compounds of the present invention have valuable pharmacological properties. They have dipeptidyl-peptidase IV-inhibiting properties, making them useful in the treatment of glucose intolerance and disorders associated with hyperglycaemia, such as type II diabetes or obesity.

10

The invention extends also to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I) with one or more appropriate, inert, non-toxic excipients. Amongst the pharmaceutical compositions according to the invention there may be mentioned more especially those which are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous) or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, injectable preparations, drinkable suspensions.

15

The useful dosage is adaptable in accordance with the nature and severity of the disorder, the administration route and also the age and weight of the patient and any associated treatments. The dosage ranges from 0.5 mg to 2 g per 24 hours in one or more administrations.

20

The Examples which follow illustrate the invention.

The starting materials used are known products or products prepared according to known procedures.

The structures of the compounds described in the Examples were determined according to customary spectrometric techniques (infra-red, NMR, mass spectrometry).

5

A compound having a (2RS) configuration is understood as being a racemic mixture of compounds of configurations (2R) and (2S).

EXAMPLE 1 : (2S)-1-([9-(Hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino)-acetyl)-2-pyrrolidinecarbonitrile :

10 Step A : 3-Oxaspiro[5.5]undec-7-en-9-one

0.5 ml of sulphuric acid is added to 317 mmol of tetrahydro-2H-pyran-4-carboxaldehyde and 317 mmol of methyl vinyl ketone in 500 ml of benzene. The reaction mixture is then refluxed for 3 hours, water being removed using a Dean-Stark apparatus, and then a further 317 mmol of methyl vinyl ketone are added and reflux is continued for 3 hours.

15 The mixture is subsequently washed, dried and then concentrated, and the residue obtained is distilled to yield the expected product.

Step B : 3-Oxaspiro[5.5]undecan-9-one

147.4 mmol of the compound obtained in the above Step are hydrogenated for 15 hours, at ambient temperature and 4.6 bar, in 100 ml of ethyl acetate in the presence of a catalytic amount of 10% Pd/C.

20

The catalyst is then filtered off, and rinsing with ethyl acetate and concentration are carried out to yield the expected product.

Step C : 11-Oxa-1,3-diazadispiro[4.2.5.2]pentadecane-2,4-dione

165 ml of aqueous 60% ethanol and 480 mmol of ammonium carbonate are added to 300 mmol of the compound obtained in the above Step. The reaction mixture is then heated to 55°C, 5.3 g of potassium cyanide in 40 ml of water are subsequently added in the course of 5 min., and the mixture is stirred for 2 hours at 55°C. The ethanol is then evaporated off
5 and the mixture is subsequently filtered; the cake is rinsed with water and with acetone and then dried to yield the expected product in the form of a flaky white solid.

Step D: *9-Amino-3-oxaspiro[5.5]undecane-9-carboxylic acid hydrochloride*

In a 1-litre autoclave, 177.8 mmol of barium sulphate are added to 88.9 mmol of the compound obtained in the above Step in 335 ml of water. The mixture is then heated
10 overnight at 160°C and subsequently cooled in an ice bath. The barium carbonate formed is filtered off and rinsed with water, and carbon dioxide is bubbled into the aqueous phase. The aqueous phase is then filtered again, and the filtrate is subsequently concentrated to dryness to yield the expected product in the form of a powder.

Step E: *Methyl 9-amino-3-oxaspiro[5.5]undecane-9-carboxylate hydrochloride*

15 100 ml of methanol are added to 61.3 mmol of the compound obtained in the above Step. The resulting suspension is cooled to 5°C and then 184 mmol of thionyl chloride are added dropwise. The reaction mixture is subsequently stirred for 1 hour at 20°C and then for 2 hours at reflux, before being evaporated to dryness to yield the expected product in the form of a powder.

20 Step F: *(9-Amino-3-oxaspiro[5.5]undec-9-yl)methanol*

6.8 g of lithium aluminium hydride, and then 59.7 mmol of the compound obtained in the above Step in the form of a base in solution in 75 ml of tetrahydrofuran, are added at 0°C to 50 ml of tetrahydrofuran. The reaction mixture is subsequently stirred for 30 min. at 0°C and then overnight at 20°C.
25 It is subsequently cooled to 5°C and there are then added 6.8 ml of water, 6.8 ml of 15% sodium hydroxide solution and 3 x 6.8 ml of water. The mixture is stirred vigorously for

20 min. and then filtered over Celite. The precipitate is rinsed with ether and the filtrate is dried and then evaporated to yield the expected product in the form of a solid.

Step G: (2S)-1-([9-(Hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino)acetyl)-2-pyrrolidinecarbonitrile

- 5 90 ml of dichloromethane, 6 mmol of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile and then 24 mmol of potassium carbonate are added to 12 mmol of the compound obtained in the above Step. After stirring for 6 days at 20°C, the precipitate formed is filtered off and rinsed with dichloromethane, and the filtrates are concentrated to dryness. The residue obtained is purified by chromatography on silica (eluant : dichloromethane/methanol 97/3)
- 10 to yield the expected product in the form of a yellow oil which solidifies in the cold to yield a white powder.

Elemental microanalysis :

	% C	% H	% N
<i>Calculated</i>	64.45	8.71	12.53
<i>Found</i>	64.50	8.78	12.28

EXAMPLE 2 : (2S)-1-[(Spiro[5.5]undec-3-ylamino)acetyl]-2-pyrrolidinecarbonitrile hydrochloride :

- 15 Step A : Spiro[5.5]undecan-3-one

The expected product is obtained according to the procedure described in Steps A and B of Example 1, with the replacement of tetrahydro-2H-pyran-4-carboxaldehyde with cyclohexanecarboxaldehyde in Step A.

- 20 Step B : Spiro[5.5]undecan-3-one oxime :

70 ml of pyridine and 3.45 g of hydroxylamine hydrochloride are added to 39 mmol of the compound obtained in the above Step in solution in dioxane. The reaction mixture is then

heated at reflux overnight and subsequently concentrated to dryness to yield an oil, which crystallises and which is washed with water to yield the expected product in the form of a powder after filtration and drying.

Step C: *Spiro[5.5]undec-3-ylamine*

- 5 3 ml of concentrated ammonium hydroxide and a catalytic amount of Raney nickel are added to 15.8 mmol of the compound obtained in the above Step in solution in dioxane. The reaction mixture is then hydrogenated overnight at ambient temperature and pressure. The catalyst is subsequently filtered off and rinsed and the solution is concentrated to yield the expected product in the form of an oil.

10 Step D: *(2S)-1-[(Spiro[5.5]undec-3-ylamino)acetyl]-2-pyrrolidinecarbonitrile*

The expected product is obtained according to the procedure described in Step G of Example 1, starting from the compound obtained in the above Step and (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile.

15 Step E: *(2S)-1-[(Spiro[5.5]undec-3-ylamino)acetyl]-2-pyrrolidinecarbonitrile hydrochloride*

The expected product is obtained by converting the compound obtained in the above Step into a salt using hydrochloric acid.

Elemental microanalysis:

	% C	% H	% N	% Cl
<i>Calculated</i>	63.60	8.90	12.36	10.43
<i>Found</i>	63.66	8.92	12.18	10.23

20 EXAMPLE 3: *(2S)-1-[(Spiro[4.5]dec-8-ylamino)acetyl]-2-pyrrolidinecarbonitrile hydrochloride*:

The expected product is obtained according to the procedure of Example 2, with the replacement of cyclohexanecarboxaldehyde with cyclopentanecarboxaldehyde in Step A.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	62.66	8.66	12.89	10.88
<i>Found</i>	62.58	8.76	12.92	10.97

5 **EXAMPLE 4** : N-[2-Oxo-2-(1-pyrrolidinyl)ethyl]spiro[5.5]undec-3-ylamine
hydrochloride :

10 The expected product is obtained according to the procedure of Example 2, with the replacement of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile with 1-(chloroacetyl)-pyrrolidine in Step D.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	64.84	9.92	8.90	11.26
<i>Found</i>	65.54	9.89	8.98	11.28

EXAMPLE 5 : (2S)-1-([3-(Hydroxymethyl)spiro[5.5]undec-3-yl]amino}acetyl)-2-pyrrolidinecarbonitrile :

15 The expected product is obtained according to the procedure of Example 1, with the replacement of tetrahydro-2H-pyran-4-carboxaldehyde with cyclohexanecarboxaldehyde in Step A.

Elemental microanalysis :

	% C	% H	% N
<i>Calculated</i>	68.43	9.37	12.60
<i>Found</i>	68.78	9.32	12.45

EXAMPLE 6 : (2S)-1-[(Spiro[5.7]tridec-3-ylamino)acetyl]-2-pyrrolidinecarbonitrile hydrochloride :

The expected product is obtained according to the procedure of Example 2, with the replacement of cyclohexanecarboxaldehyde with cyclooctanecarboxaldehyde in Step A.

5

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	65.28	9.31	11.42	9.63
<i>Found</i>	65.56	9.01	11.21	9.63

EXAMPLE 7 : (2S)-1-[(3-Oxaspiro[5.5]undec-9-ylamino)acetyl]-2-pyrrolidine-carbonitrile hydrochloride :

The expected product is obtained according to the procedure described in Steps B to E of Example 2, starting from the compound obtained in Step B of Example 1.

10

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	59.72	8.26	12.29	10.37
<i>Found</i>	59.79	7.96	12.16	10.96

EXAMPLE 8 : (2S)-1-[(Dispiro[5.2.5.2]hexadec-3-ylamino)acetyl]-2-pyrrolidine-carbonitrile :

The expected product is obtained according to the procedure described in Steps A to D of Example 2, with the replacement of cyclohexanecarboxaldehyde with spiro[5.5]undecane-3-carboxaldehyde in Step A.

15

Elemental microanalysis :

	% C	% H	% N
Calculated	74.35	10.04	11.31
Found	74.40	9.94	11.07

EXAMPLE 9 : (2S)-1-[(Spiro[3.3]hept-2-ylamino)acetyl]-2-pyrrolidinecarbonitrile hydrochloride :Step A : 1,1-Dichlorospiro[3.3]heptan-2-one

- 5 6.25 g of powdered zinc and then 11 ml of trichloroacetic acid chloride in solution in 170 ml of ether are added to 5 g of methylenecyclobutane in solution in ether. The solution is subjected to sonication for 3 hours while maintaining the temperature at 20°C, and then the black solution is filtered through Whatman filter. The filtrate is washed, dried, filtered and concentrated to yield the expected product in the form of a brown oil.

10 Step B : Spiro[3.3]heptan-2-one

28 g of the compound obtained in the above Step and then 620 ml of water are added to 420 ml of glacial acetic acid. The reaction mixture is cooled using a cold water bath, and then 28.1 g of powdered zinc are added. After stirring for 20 min., the bath is removed and the reaction mixture is stirred overnight at 20°C.

- 15 The solution is filtered, extracted with pentane and evaporated. The residue is taken up in pentane and the solution is washed, dried, filtered and concentrated to yield the expected product in the form of a clear yellow liquid.

Step C : (2S)-1-[(Spiro[3.3]hept-2-ylamino)acetyl]-2-pyrrolidinecarbonitrile

- 20 The expected product is obtained according to the procedure described in Steps B to D of Example 2, starting from the compound obtained in the above Step.

- 19 -

Step D: (2S)-1-[(Spiro[3.3]hept-2-ylamino)acetyl]-2-pyrrolidinecarbonitrile
hydrochloride

The expected product is obtained by converting the compound obtained in the above Step into a salt using hydrochloric acid.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	59.25	7.81	14.81	12.49
Found	59.27	7.78	14.51	12.93

EXAMPLE 10 : (2S)-1-[(Spiro[5.9]pentadec-3-ylamino)acetyl]-2-pyrrolidine-carbonitrile :

The expected product is obtained according to the procedure described in Steps A to D of
10 Example 2, with the replacement of cyclohexanecarboxaldehyde with cyclodecane-carboxaldehyde in Step A.

Melting point : 83°C

Elemental microanalysis :

	% C	% H	% N
Calculated	73.49	10.37	11.69
Found	73.46	10.44	11.64

15 **EXAMPLE 11 : (2S)-1-[(Spiro[3.5]non-7-ylamino)acetyl]-2-pyrrolidinecarbonitrile
hydrochloride :**

Step A: Ethyl 7-oxospiro[3.5]nonane-6-carboxylate

20.6 mmol of 3-[1-(ethoxycarbonyl)ethyl]cyclobutyl]propionic acid ethyl ester in solution
in tetrahydrofuran are added at 0°C to 22.7 mmol of 95% sodium hydride in suspension in
20 15 ml of tetrahydrofuran. The reaction mixture is refluxed for 4 hours and then 49 ml of

- 20 -

acetic acid are added. The tetrahydrofuran is evaporated off and the residue obtained is extracted with ethyl acetate. The combined organic phases are washed, filtered, dried and evaporated to yield an oil, which is subjected to chromatography on silica (eluant : dichloromethane/ethyl acetate 95/5) to yield the expected product.

5 Step B : *Spiro[3.5]nonan-7-one*

11.1 g of potassium hydroxide in 100 ml of water are added to 39.7 mmol of the compound obtained in the above Step in solution in dioxane. The reaction mixture is refluxed overnight and then, after returning to ambient temperature, is extracted with ether. The combined organic phases are washed, dried, filtered and evaporated to yield the expected product in the form of a volatile oil.

Step C : *(2S)-1-[(Spiro[3.5]non-7-ylamino)acetyl]-2-pyrrolidinecarbonitrile hydrochloride*

The expected product is obtained according to the procedure described in Steps B to E of Example 2, starting from the compound obtained in the above Step.

15 Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	61.62	8.40	13.47	11.37
<i>Found</i>	61.39	8.32	13.22	11.91

EXAMPLE 12 : *(2S)-1-[(Spiro[3.5]non-2-ylamino)acetyl]-2-pyrrolidinecarbonitrile trifluoroacetate* :

Step A : *(2S)-1-[(Spiro[3.5]non-2-ylamino)acetyl]-2-pyrrolidinecarbonitrile*

20 The expected product is obtained according to the procedure described in Steps A to C of Example 9, with the replacement of methylenecyclobutane with methylenecyclohexane in Step A.

Step B : (2*S*)-1-[(Spiro[3.5]non-2-ylamino)acetyl]-2-pyrrolidinecarbonitrile trifluoroacetate

The expected product is obtained by converting the compound obtained in the above Step into a salt using trifluoroacetic acid.

5 Mass spectrometry : $[M + H]^+ = 276$

EXAMPLE 13 : (2*S*)-1-[(Spiro[5.6]dodec-3-ylamino)acetyl]-2-pyrrolidine-carbonitrile :

10 The expected product is obtained according to the procedure described in Steps A to D of Example 2, with the replacement of cyclohexanecarboxaldehyde with cycloheptanecarboxaldehyde in Step A.

Elemental microanalysis :

	% C	% H	% N
Calculated	71.88	9.84	13.24
Found	71.52	9.95	13.14

EXAMPLE 14 : (2*S*)-1-[(Spiro[3.4]oct-2-ylamino)acetyl]-2-pyrrolidinecarbonitrile hydrochloride :

15 Step A : Spiro[3.4]octan-2-one

The expected product is obtained according to the procedure described in Steps A and B of Example 9, with the replacement of methylenecyclobutane with methylenecyclopentane in Step A.

Step B: (2S)-1-[(Spiro[3.4]oct-2-ylamino)acetyl]-2-pyrrolidinecarbonitrile hydrochloride

The expected product is obtained according to the procedure described in Steps B to E of Example 2, starting from the compound obtained in the above Step.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	60.49	8.12	14.11	11.90
Found	61.08	8.00	14.18	11.37

EXAMPLE 15 : (2S)-1-[(3,3-Dioxo-3-thiaspiro[5.5]undec-9-ylamino)acetyl]-2-pyrrolidinecarbonitrile :

The expected product is obtained according to the procedure described in Steps A to D of Example 2, with the replacement of cyclohexanecarboxaldehyde with tetrahydro-2H-thiopyran-4-carboxaldehyde 1,1-dioxide in Step A.

Elemental microanalysis :

	% C	% H	% N	% S
Calculated	57.76	7.70	11.89	9.07
Found	57.42	7.54	11.48	8.83

EXAMPLE 16 : (2S)-1-([2-(Hydroxymethyl)spiro[3.3]hept-2-yl]amino)acetyl)-2-pyrrolidinecarbonitrile hydrochloride :

15 Step A: (2S)-1-([2-(Hydroxymethyl)spiro[3.3]hept-2-yl]amino)acetyl)-2-pyrrolidinecarbonitrile

The expected product is obtained according to the procedure described in Steps C to G of Example 1, with the replacement of 3-oxaspiro[5.5]undecan-9-one in Step C with the compound obtained in Step B of Example 9.

Step B: (2S)-1-([2-(Hydroxymethyl)spiro[3.3]hept-2-yl]amino)acetyl)-2-pyrrolidinecarbonitrile hydrochloride

The expected product is obtained by converting the compound obtained in the above Step into a salt using hydrochloric acid.

5 Elemental microanalysis:

	% C	% H	% N	% Cl
Calculated	57.41	7.71	13.39	11.30
Found	57.32	8.02	13.33	11.91

EXAMPLE 17: (2S)-1-([2-(Hydroxymethyl)spiro[3.4]oct-2-yl]amino)acetyl)-2-pyrrolidinecarbonitrile hydrochloride:

10 Step A: (2S)-1-([2-(Hydroxymethyl)spiro[3.4]oct-2-yl]amino)acetyl)-2-pyrrolidinecarbonitrile

The expected product is obtained according to the procedure described in Steps C to G of Example 1, with the replacement of 3-oxaspiro[5.5]undecan-9-one in Step C with the compound obtained in Step A of Example 14.

15 Step B: (2S)-1-([2-(Hydroxymethyl)spiro[3.4]oct-2-yl]amino)acetyl)-2-pyrrolidinecarbonitrile hydrochloride

The expected product is obtained by converting the compound obtained in the above Step into a salt using hydrochloric acid.

Elemental microanalysis:

	% C	% H	% N	% Cl
Calculated	58.62	7.99	12.82	10.81
Found	58.53	7.90	12.65	10.81

EXAMPLE 18 : (4R)-3-[(Spiro[5.5]undec-3-yl-amino)acetyl]-1,3-thiazolidine-4-carbonitrile trifluoroacetate :

Step A : (4R)-3-[(Spiro[5.5]undec-3-yl-amino)acetyl]-1,3-thiazolidine-4-carbonitrile

- 5 The expected product is obtained according to the procedure described in Step G of Example 1, starting from the compound obtained in Step C of Example 2 and (4R)-3-(chloroacetyl)-1,3-thiazolidine-4-carbonitrile.

Step B : (4R)-3-[(Spiro[5.5]undec-3-yl-amino)acetyl]-1,3-thiazolidine-4-carbonitrile trifluoroacetate

- 10 The expected product is obtained by converting the compound obtained in the above Step into a salt using trifluoroacetic acid.

Elemental microanalysis :

	% C	% H	% N	% S
<i>Calculated</i>	52.40	6.48	9.65	7.36
<i>Found</i>	52.10	6.54	9.42	7.19

EXAMPLE 19 : 2-({2-[(2S)-2-Cyanopyrrolidinyl]-2-oxoethyl}amino)spiro[3.3]-heptane-2-carboxamide :

15

Step A : 2-Aminospiro[3.3]heptane-2-carboxylic acid

The expected product is obtained according to the procedure described in Steps C and D of Example 1, starting from the compound obtained in Step B of Example 9.

Step B: 2-(tert-Butyloxycarbonylamino)spiro[3.3]heptane-2-carboxylic acid

40 ml of dioxane and then, at 0°C, 6.71 g of di(tert-butyl) dicarbonate in dioxane are added to 4.35 g of the compound obtained in the above Step in solution in 11 ml of sodium hydroxide solution. After one night at 20°C, the dioxane is evaporated off and the residue
5 obtained is taken up in water. Extraction is carried out with ether, and then the aqueous phase is acidified to pH 3 using an aqueous 10% citric acid solution. The aqueous phase is extracted with ethyl acetate. The organic phases are combined and washed with brine, dried and concentrated to dryness to yield the expected product in the form of a white paste.

10 Step C: 2-(tert-Butyloxycarbonylamino)spiro[3.3]heptane-2-carboxamide

811 mg of N-hydroxysuccinimide and 1.45 g of dicyclohexylcarbodiimide are added to 1.8 g of the compound obtained in the above Step in solution in tetrahydrofuran. After one night at 20°C, the reaction mixture is filtered, and gaseous ammonia is bubbled into the filtrate. After one night at 20°C, the reaction mixture is filtered again and concentrated to
15 dryness to yield the expected product in the form of a white powder.

Step D: 2-Aminospiro[3.3]heptane-2-carboxamide hydrochloride

1.84 g of the compound obtained in the above Step are dissolved in ethyl acetate and then gaseous HCl is bubbled through at 0°C for 10 min.. A precipitate appears. After 30 min. at 0°C, the precipitate is filtered off and rinsed with ethyl acetate, and then dried to yield the
20 expected product in the form of a white powder.

Step E: 2-({2-[(2S)-2-Cyanopyrrolidinyl]-2-oxoethyl}amino)spiro[3.3]heptane-2-carboxamide

The expected product is obtained according to the procedure described in Step G of Example 1, starting from the compound obtained in the above Step and (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile.
25

Elemental microanalysis :

	% C	% H	% N
Calculated	62.05	7.64	19.30
Found	62.05	7.48	19.20

EXAMPLE 20 : (2S)-1-[(3-Azaspiro[5.5]undec-9-ylamino)acetyl]-2-pyrrolidine-carbonitrile bis(trifluoroacetate) :Step A : 3-Azaspiro[5.5]undecan-9-one

- 5 The expected product is obtained according to the procedure described in Steps A and B of Example 1, with the replacement of tetrahydro-2H-pyran-4-carboxaldehyde with benzyl 4-formyl-1-piperidinecarboxylate in Step A.

Step B : tert-Butyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate:

- 10 The expected product is obtained by reaction of the compound obtained in the above Step with di-tert-butyl dicarbonate in accordance with the procedure described in Step B of Example 19.

Step C : tert-Butyl 9-({2-[(2S)-2-cyanopyrrolidinyl]-2-oxoethyl}amino)-3-azaspiro-[5.5]undecane-3-carboxylate

- 15 The expected product is obtained according to the procedure described in Steps B to D of Example 2, starting from the compound obtained in the above Step.

Step D: (2S)-1-[(3-Azaspiro[5.5]undec-9-ylamino)acetyl]-2-pyrrolidinecarbonitrile bis(trifluoroacetate)

The expected product is obtained by reaction of the compound obtained in the above Step with 30 equivalents of trifluoroacetic acid in dichloromethane at 0-5°C for 1 hour. The mixture is concentrated to dryness. The compound is purified by preparative HPLC.

Mass spectrometry: $[M + H]^+ = 305$

EXAMPLE 21: (2S)-1-([3-(Hydroxymethyl)-9,9-dimethylspiro[5.5]undec-3-yl]-amino)acetyl)-2-pyrrolidinecarbonitrile:

The expected product is obtained according to the procedure of Example 1, with the replacement of tetrahydro-2H-pyran-4-carboxaldehyde with 4,4-dimethylcyclohexane-carboxaldehyde in Step A.

Elemental microanalysis:

	% C	% H	% N
Calculated	69.77	9.76	11.62
Found	69.54	9.72	11.43

EXAMPLE 22: (2S)-1-([2-(1-Hydroxy-1-methylethyl)spiro[3.3]hept-2-yl]amino)-acetyl)-2-pyrrolidinecarbonitrile hydrochloride:

15

Step A: Methyl 2-aminospiro[3.3]heptane-2-carboxylate

The expected product is obtained according to the procedure described in Step E of Example 1, starting from the compound obtained in Step A of Example 19.

Step B: *Methyl 2-(tert-butyloxycarbonylamino)spiro[3.3]heptane-2-carboxylate*

5.8 ml of triethylamine and then, at 0°C, 9.02 g of di(tert-butyl) dicarbonate in dichloromethane, are added to 8.5 g of the compound obtained in the above Step in solution in dichloromethane. After stirring overnight at 20°C, the reaction mixture is washed with an aqueous 10% citric acid solution and then with water. The organic phase is dried, filtered and concentrated to yield the expected product in the form of an orange oil.

Step C: *2-(2-tert-Butyloxycarbonylamino)spiro[3.3]hept-2-yl)-2-propanol*

There are added to 50 ml of ether 42 ml of a 3M solution of methylmagnesium iodide in ether and then, at 0°C and dropwise, 5 g of the compound obtained in the above Step in solution in ether. After stirring for 1 hour at 0°C, ammonium chloride is added and then the reaction mixture is stirred for 1 hour at 20°C. The aqueous phase is extracted with ethyl acetate and then the combined organic phases are washed, dried and concentrated to dryness to yield the expected product in the form of an oil which crystallises.

Step D: *2-(2-Aminospiro[3.3]hept-2-yl)-2-propanol trifluoroacetate*

40 ml of trifluoroacetic acid are added at 0°C to 4.8 g of the compound obtained in the above Step in solution in dichloromethane. After stirring for 30 min. at 0°C, the reaction mixture is evaporated to dryness and the residue is taken up several times with toluene; the toluene is then evaporated off to yield the expected product in the form of a colourless oil.

Step E: *(2S)-1-({[2-(1-Hydroxy-1-methylethyl)spiro[3.3]hept-2-yl]amino}acetyl)-2-pyrrolidinecarbonitrile*

The expected product is obtained according to the procedure described in Step G of Example 1, starting from the compound obtained in the above Step and (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile.

Step F: (2S)-1-({[2-(1-Hydroxy-1-methylethyl)spiro[3.3]hept-2-yl]amino}acetyl)-2-pyrrolidinecarbonitrile hydrochloride

The expected product is obtained by converting the compound obtained in the above Step into a salt using hydrochloric acid.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	59.72	8.26	12.29	10.37
Found	58.96	8.48	11.95	10.99

EXAMPLE 23 : (2S)-1-[(3-Thiaspiro[5.5]undec-9-ylamino)acetyl]-2-pyrrolidine-carbonitrile hydrochloride :

Step A : 3-Thiaspiro[5.5]undecan-9-one oxime 3,3-dioxide

10 The expected product is obtained according to the procedure described in Steps A and B of Example 2, with the replacement of cyclohexanecarboxaldehyde with tetrahydro-2H-thiopyran-4-carboxaldehyde 1,1-dioxide in Step A.

Step B : 3-Thiaspiro[5.5]undecan-9-amine

15 4 g of the compound obtained in the above Step are added in portions to 7.9 g of lithium aluminium hydride in suspension in 200 ml of tetrahydrofuran. The reaction mixture is then refluxed for 12 hours and subsequently hydrolysed by the addition of 8 ml of water, 8 ml of a 15% sodium hydroxide solution and 16 ml of water.

The salts obtained are then filtered off and the filtrate is subsequently concentrated to dryness to yield the title product.

Step C: (2S)-1-[(3-Thiaspiro[5.5]undec-9-ylamino)acetyl]-2-pyrrolidinecarbonitrile

The expected product is obtained according to the procedure described in Step G of Example 1, starting from the compound obtained in the above Step and (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile.

5 Step D: (2S)-1-[(3-Thiaspiro[5.5]undec-9-ylamino)acetyl]-2-pyrrolidinecarbonitrile hydrochloride

The expected product is obtained by converting the compound obtained in the above Step into a salt using hydrochloric acid.

Elemental microanalysis:

	% C	% H	% N	% S	% Cl
Calculated	57.04	7.88	11.74	8.96	9.90
Found	59.67	7.96	11.56	9.14	10.52

10 **EXAMPLE 24**: (2S)-1-({[3-(2-Hydroxyethyl)-3-azaspiro[5.5]undec-9-yl]amino}-acetyl)-2-pyrrolidinecarbonitrile bis(trifluoroacetate):

Step A: 3-Azaspiro[5.5]undecan-9-one

15 The expected product is obtained according to the procedure described in Steps A and B of Example 1, with the replacement of tetrahydro-2H-pyran-4-carboxaldehyde with benzyl 4-formyl-1-piperidinecarboxylate in Step A.

Step B: 3-(2-Hydroxyethyl)-3-azaspiro[5.5]undecan-9-one

The expected product is obtained by alkylation of the compound obtained in the above Step with 2-bromoethanol in the presence of potassium carbonate.

Step C: (2S)-1-({[3-(2-Hydroxyethyl)-3-azaspiro[5.5]undec-9-yl]amino}acetyl)-2-pyrrolidinecarbonitrile

The expected product is obtained according to the procedure described in Steps B to D of Example 2, starting from the compound obtained in the above Step.

5 Step D: (2S)-1-({[3-(2-Hydroxyethyl)-3-azaspiro[5.5]undec-9-yl]amino}acetyl)-2-pyrrolidinecarbonitrile bis(trifluoroacetate)

The expected product is obtained by converting the compound obtained in the above Step into a salt using trifluoroacetic acid.

Elemental microanalysis:

	% C	% H	% N
Calculated	47.92	5.94	9.72
Found	47.28	5.94	9.38

10 **EXAMPLE 25**: (2S)-1-({[2-(2-Hydroxymethyl)-7-oxaspiro[3.5]non-2-yl]amino}acetyl)-2-pyrrolidinecarbonitrile:

Step A: 7-Oxaspiro[3.5]nonan-2-one

15 The expected product is obtained according to the procedure described in Steps A and B of Example 9, with the replacement of methylenecyclobutane with 4-methylenetetrahydro-2H-pyran in Step A.

Step B: (2S)-1-({[2-(2-Hydroxymethyl)-7-oxaspiro[3.5]non-2-yl]amino}acetyl)-2-pyrrolidinecarbonitrile

20 The expected product is obtained according to the procedure described in Steps C to G of Example 1, starting from the compound obtained in the above Step.

Melting point : 103°C

Elemental microanalysis :

	% C	% H	% N
<i>Calculated</i>	62.52	8.20	13.67
<i>Found</i>	62.56	8.25	13.32

EXAMPLE 26 : (2S)-1-([2-(2-Hydroxymethyl)spiro[3.5]non-2-yl]amino)acetyl)-2-pyrrolidinecarbonitrile :

5

Step A : Spiro[3.5]nonan-2-one

The expected product is obtained according to the procedure described in Steps A and B of Example 9, with the replacement of methylenecyclobutane with methylenecyclohexane in Step A.

Step B : (2S)-1-([2-(2-Hydroxymethyl)spiro[3.5]non-2-yl]amino)acetyl)-2-pyrrolidinecarbonitrile

10 The expected product is obtained according to the procedure described in Steps C to G of Example 1, starting from the compound obtained in the above Step.

Elemental microanalysis :

	% C	% H	% N
<i>Calculated</i>	66.85	8.91	13.76
<i>Found</i>	66.66	8.55	13.65

EXAMPLE 27 : (2S)-1-[(7-Oxaspiro[3.5]non-2-ylamino)acetyl]-2-pyrrolidine-carbonitrile trifluoroacetate :

Step A : (2S)-1-[(7-Oxaspiro[3.5]non-2-ylamino)acetyl]-2-pyrrolidinecarbonitrile

- 5 The expected product is obtained according to the procedure described in Steps A to C of Example 9, with the replacement of methylenecyclobutane with 4-methylenetetrahydro-2H-pyran in Step A.

Step B : (2S)-1-[(7-Oxaspiro[3.5]non-2-ylamino)acetyl]-2-pyrrolidinecarbonitrile trifluoroacetate

- 10 The expected product is obtained by converting the compound obtained in the above Step into a salt using trifluoroacetic acid.

Elemental microanalysis :

	% C	% H	% N
Calculated	52.17	6.18	10.74
Found	52.15	6.35	10.73

EXAMPLE 28 : (2S)-1-[(Spiro[2.5]oct-6-ylamino)acetyl]-2-pyrrolidinecarbonitrile :

Step A : Spiro[2.5]octan-6-one

- 15 The expected product is obtained according to the procedure described in Steps A and B of Example 11, with the replacement of 3-[1-(ethoxycarbonyl)ethyl]cyclobutyl]propionic acid with 3-[1-(ethoxycarbonyl)ethyl]cyclopropyl]propionic acid in Step A.

Step B : (2S)-1-[(Spiro[2.5]oct-6-ylamino)acetyl]-2-pyrrolidinecarbonitrile

- 20 The expected product is obtained according to the procedure described in Steps A to D of Example 2, starting from the compound obtained in the above Step.

Elemental microanalysis :

	% C	% H	% N
<i>Calculated</i>	68.93	8.87	16.08
<i>Found</i>	68.90	8.76	16.06

EXAMPLE 29 : (2S,4S)-4-Fluoro-1-([9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]-amino}acetyl)-2-pyrrolidinecarbonitrile :

- 5 The expected product is obtained according to the procedure described in Example 1, with the replacement of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile with (2S,4S)-1-(chloroacetyl)-4-fluoro-2-pyrrolidinecarbonitrile in Step G.

Elemental microanalysis :

	% C	% H	% N
<i>Calculated</i>	61.17	7.99	11.89
<i>Found</i>	61.63	7.87	11.47

EXAMPLE 30 : (2S)-4,4-Difluoro-1-([9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino}acetyl)-2-pyrrolidinecarbonitrile :

10

The expected product is obtained according to the procedure described in Example 1, with the replacement of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile with (2S)-1-(chloroacetyl)-4,4-difluoro-2-pyrrolidinecarbonitrile in Step G.

Elemental microanalysis :

	% C	% H	% N
<i>Calculated</i>	58.21	7.33	11.31
<i>Found</i>	58.30	7.62	11.21

15

EXAMPLE 31 : (9-{[2-Oxo-2-(1-pyrrolidinyl)ethyl]amino}-3-oxaspiro[5.5]undec-9-yl)methanol :

The expected product is obtained according to the procedure described in Example 1, with the replacement of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile with 1-(chloroacetyl)-pyrrolidine in Step G.

Elemental microanalysis :

	% C	% H	% N
Calculated	65.77	9.74	9.02
Found	65.75	9.62	8.85

EXAMPLE 32 : (4R)-3-([9-(Hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino)-acetyl)-1,3-thiazolidine-4-carbonitrile :

The expected product is obtained according to the procedure described in Example 1, with the replacement of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile with (4R)-3-(chloroacetyl)-1,3-thiazolidine-4-carbonitrile in Step G.

Elemental microanalysis :

	% C	% H	% N	% S
Calculated	57.76	7.70	11.89	9.07
Found	57.44	7.88	11.51	8.02

EXAMPLE 33 : (2S,4S)-4-Hydroxy-1-([9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino)acetyl)-2-pyrrolidinecarbonitrile:

The expected product is obtained according to the procedure described in Example 1, with the replacement of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile with (2S,4S)-1-(chloroacetyl)-4-hydroxy-2-pyrrolidinecarbonitrile in Step G.

EXAMPLE 34 : (2S,4R)-4-Fluoro-1-([9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino)acetyl-2-pyrrolidinecarbonitrile trifluoroacetate :

The expected product is obtained according to the procedure described in Example 1, with the replacement of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile with (2S,4R)-1-(chloro-
5 acetyl)-4-fluoro-2-pyrrolidinecarbonitrile in Step G.

Elemental microanalysis :

	% C	% H	% N
<i>Calculated</i>	50.67	6.13	8.77
<i>Found</i>	50.47	6.05	8.47

EXAMPLE 35 : [9-([2-[(3S)-3-Fluoropyrrolidinyl]-2-oxoethyl]amino)-3-oxaspiro[5.5]undec-9-yl]methanol :

The expected product is obtained according to the procedure described in Example 1, with
10 the replacement of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile with (3S)-1-(chloro-
acetyl)-3-fluoropyrrolidine in Step G.

EXAMPLE 36 : (9-([2-Oxo-2-(3,3,4,4-tetrafluoro-1-pyrrolidinyl)ethyl]amino)-3-oxaspiro[5.5]undec-9-yl)methanol:

The expected product is obtained according to the procedure described in Example 1, with
15 the replacement of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile with 1-(chloroacetyl)-
3,3,4,4-tetrafluoropyrrolidine in Step G.

Elemental microanalysis :

	% C	% H	% N
<i>Calculated</i>	53.40	6.85	7.33
<i>Found</i>	53.83	6.67	7.18

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EXAMPLE 37 : (2S)-1-([7-(Hydroxymethyl)spiro[3.5]non-7-yl]amino)acetyl)-2-pyrrolidinecarbonitrile :

The expected product is obtained according to the procedure described in Example 1, with the replacement of 3-oxaspiro[5.5]undecan-9-one in Step C with the compound obtained in
5 Step B of Example 11.

EXAMPLE 38 : (2S)-1-([8-(Hydroxymethyl)spiro[4.5]dec-8-yl]amino)acetyl)-2-pyrrolidinecarbonitrile :

The expected product is obtained according to the procedure of Example 1, with the replacement of tetrahydro-2H-pyran-4-carboxaldehyde with cyclopentanecarboxaldehyde in Step A.

10

EXAMPLE 39 : (2S)-1-([(2,2-Dioxo-2-thiaspiro[3.5]non-7-yl)amino]acetyl)-2-pyrrolidinecarbonitrile :

The expected product is obtained according to the procedure described in Steps A to D of Example 2, with the replacement of cyclohexanecarboxaldehyde with 3-thietane-carboxaldehyde 1,1-dioxide in Step A.
15

EXAMPLE 40 : (2S)-1-[3-(Spiro[5.5]undec-3-ylamino)propanoyl]-2-pyrrolidine-carbonitrile hydrochloride :

Step A : (2S)-1-[3-(Spiro[5.5]undec-3-ylamino)propanoyl]-2-pyrrolidinecarbonitrile

The expected product is obtained according to the procedure described in Step G of
20 Example 1, starting from the compound obtained in Step C of Example 2 and (2S)-1-(3-chloropropionyl)-2-pyrrolidinecarbonitrile.

Step B : (2S)-1-[3-(Spiro[5.5]undec-3-ylamino)propanoyl]-2-pyrrolidinecarbonitrile hydrochloride

The expected product is obtained by converting the compound obtained in the above Step
5 into a salt using hydrochloric acid.

Mass spectrometry : $[M + H]^+ = 318$.

EXAMPLE 41 : (2S)-1-((2RS)-2-([9-(Hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]-amino)propanoyl)-2-pyrrolidinecarbonitrile trifluoroacetate

10

The expected product is obtained according to the procedure of Example 1, with the replacement of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile with (2S)-1-[(2RS)-2-bromopropanoyl]-2-pyrrolidinecarbonitrile in Step G.

15 Mass spectrometry : $[M + H]^+ = 350$.

EXAMPLE 42 : (2R)-1-([9-(Hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino)-acetyl)-2-pyrrolidinecarbonitrile :

20 The expected product is obtained according to the procedure of Example 1, with the replacement of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile with (2R)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile in Step G.

Elemental microanalysis :

	% C	% H	% N
Calculated	64.45	8.71	12.53
Found	64.04	8.75	12.21

EXAMPLE 43 : (2RS)-4,4-Difluoro-1-([9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino)acetyl)-2-pyrrolidinecarbonitrile

The expected product is obtained according to the procedure of Example 1, with the replacement of (2S)-1-(chloroacetyl)-2-pyrrolidinecarbonitrile with (2RS)-1-(chloro-
5 acetyl)-4,4-difluoro-2-pyrrolidinecarbonitrile in Step G.

Elemental microanalysis :

	% C	% H	% N
Calculated	58.21	7.33	11.31
Found	57.46	7.41	10.94

EXAMPLE 44 : (2R)-4,4-Difluoro-1-([9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino)acetyl)-2-pyrrolidinecarbonitrile

10 The expected product is obtained by separation by preparative chiral HPLC chromatography of the racemic compound of Example 43.

Melting point : 128°C.

PHARMACOLOGICAL STUDY OF THE COMPOUNDS OF THE INVENTION

EXAMPLE 45 : Inhibition of dipeptidyl-peptidase IV in pig kidney

15 Preparation of the membrane fraction of pig kidney

Pig kidney tissue (large white pig, 2 to 3 months' old) was homogenised (5 g of tissue in 15 ml of Tris buffer (114mM, pH 7.8-8)) and then centrifuged at 150000 x g for 30 min. at 4°C. The pellet was taken up in 15 ml of buffer and re-centrifuged at 150000 x g for 30 min. at 4°C. With stirring, the resulting pellet was dissolved in 15 ml of buffer with
20 60mM n-octyl-β-glucopyranoside for 30 min. at ambient temperature. After centrifugation at 150000 x g for 30 min. at 4°C, the supernatant was dialysed (MWCO 12-14000) against 114mM Tris pH 7.8-8, and then divided into aliquots at -80°C.

Measurement of dipeptidyl peptidase IV (DPP IV) activity :

The enzymatic activity is measured by cleavage of a chromogenic substrate, glycyl-prolyl-*p*-nitroanilide (Gly-Pro-pNA), giving Gly-Pro and pNA (*p*-nitroaniline); the latter is
 5 detected by absorbance at 405nm. The activity is measured in the absence (control) or in the presence of 10 μ l of the inhibitors, using 10 μ l of the pig kidney preparation (0.81 mU, 1U = 1 μ mol of pNA product/min. at 37°C). Incubation is started by adding the substrate (250 μ l), dissolved in Tris buffer (114mM) pH 7.8-8, over a period of 60 min. at 37°C. For the products dissolved in dimethyl sulphoxide, the final concentration of the latter did not
 10 exceed 0.37%. The results were expressed as a percentage of the control, and the IC₅₀ values (effective dose for 50% inhibition of the control activity) were determined using non-linear analysis between 0 and 100%, (GraphPad Prism version 4.01 for Windows). Each measurement was carried out in quadruplicate and each IC₅₀ determination was carried out from 1 to 5 times.

15

The results obtained (geometric mean of the IC₅₀s) for the compounds representing the invention are compiled in the following Table:

Compound	IC ₅₀ DPP IV (nM)
Example 1	76.1
Example 5	68.5
Example 6	27.2
Example 8	23.0
Example 17	43.6
Example 18	3.5
Example 20	73.1
Example 23	27.0
Example 28	171
Example 29	31.6
Example 30	20.5

The above results show that the compounds of the invention are potent inhibitors of DPP IV.

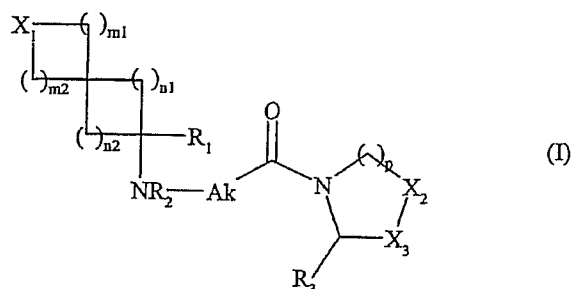
EXAMPLE 46 : Pharmaceutical composition

Formulation for the preparation of 1000 tablets each containing a dose of 10 mg

5	compound of Example 1	10 g
	hydroxypropyl cellulose	2 g
	wheat starch	10 g
	lactose	100 g
	magnesium stearate.....	3 g
10	talc	3 g

WHAT WE CLAIM IS:

1. Compound of formula (I) :



wherein :

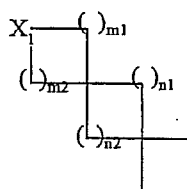
- 5 ♦ X_1 represents an atom or group selected from $\text{CR}_{4a}\text{R}_{4b}$, O , $\text{S}(\text{O})_{q_1}$ and NR_5 ,
 wherein R_{4a} and R_{4b} , which may be identical or different, each represent a hydrogen
 atom or a linear or branched C_1 - C_6 alkyl group,
 or R_{4a} and R_{4b} together form, with the carbon atom carrying them, a C_3 - C_7 cycloalkyl
 group,
- 10 q_1 represents zero, 1 or 2,
 and R_5 represents a hydrogen atom or a linear or branched C_1 - C_6 alkyl group optionally
 substituted by a hydroxy group,
- ♦ m_1 represents zero or an integer of from 1 to 4 inclusive,
- ♦ m_2 represents an integer of from 1 to 4 inclusive,
- 15 ♦ n_1 and n_2 , which may be identical or different, each represent an integer of from 1 to 3
 inclusive,
- ♦ R_1 represents a hydrogen atom or a group selected from carboxy, linear or branched
 C_1 - C_6 alkoxycarbonyl, carbamoyl optionally substituted by 1 or 2 linear or branched
 C_1 - C_6 alkyl groups, and linear or branched C_1 - C_6 alkyl optionally substituted by a
 hydroxy group or by an amino group optionally substituted by 1 or 2 linear or branched
 C_1 - C_6 alkyl groups,
- 20 ♦ R_2 represents a hydrogen atom or a linear or branched C_1 - C_6 alkyl group,

- ♦ Ak represents a linear or branched C₁-C₄alkylene chain optionally substituted by one or more halogen atoms,
- ♦ p represents zero, 1 or 2,
- ♦ R₃ represents a hydrogen atom or a cyano group,
- 5 ♦ X₂ and X₃, which may be identical or different, each represent either a S(O)_{q2} group, wherein q₂ represents zero, 1 or 2, or a CR_{6a}R_{6b} group, wherein R_{6a} and R_{6b}, which may be identical or different, each represent a hydrogen atom or a halogen atom, or R_{6a} represents a hydrogen atom and R_{6b} represents a hydroxy group,

its isomers, where they exist, and its addition salts with a pharmaceutically acceptable acid.

- 10 2. Compound of formula (I) according to claim 1, wherein X₁ represents an oxygen atom or a -CH₂- group.
3. Compound of formula (I) according to claim 1 or 2, wherein m₁ and m₂ each represent 1 or 2.
- 15 4. Compound of formula (I) according to any one of claims 1 to 3, wherein n₁ and n₂ each represent 1 or 2 and are identical.

5. Compound of formula (I) according to claim 1, wherein



group selected from



and

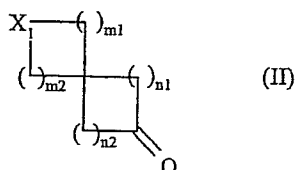


6. Compound of formula (I) according to any one of claims 1 to 5, wherein R₂ represents a hydrogen atom.

7. Compound of formula (I) according to any one of claims 1 to 6, wherein Ak represents a $-\text{CH}_2-$ group.
8. Compound of formula (I) according to any one of claims 1 to 7, wherein p represents 1.
9. Compound of formula (I) according to any one of claims 1 to 8, wherein R_3 represents a cyano group.
10. Compound of formula (I) according to any one of claims 1 to 9, wherein X_2 represents a $\text{CR}_{6a}\text{R}_{6b}$ group.
11. Compound of formula (I) according to any one of claims 1 to 10, wherein X_3 represents a $\text{CR}_{6a}\text{R}_{6b}$ group.
12. Compound of formula (I) according to claims 9, 10 and 11, in which the configuration of the carbon carrying the R_3 group is (S).
13. Compound of formula (I) according to claim 9, wherein X_2 or X_3 represents a $\text{S}(\text{O})_{q2}$ group and the configuration of the carbon carrying the R_3 group is (R).
14. Compound of formula (I) according to claim 1 which is selected from the following compounds :
 - (2S)-1-([9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino}acetyl)-2-pyrrolidinecarbonitrile, and its addition salts with a pharmaceutically acceptable acid;
 - (2S)-1-([3-(hydroxymethyl)spiro[5.5]undec-3-yl]amino}acetyl)-2-pyrrolidinecarbonitrile, and its addition salts with a pharmaceutically acceptable acid;
 - (2S)-1-([2-(hydroxymethyl)spiro[3.4]oct-2-yl]amino}acetyl)-2-pyrrolidinecarbonitrile, and its addition salts with a pharmaceutically acceptable acid;
 - (4R)-3-[(spiro[5.5]undec-3-ylamino)acetyl]-1,3-thiazolidine-4-carbonitrile, and its addition salts with a pharmaceutically acceptable acid;

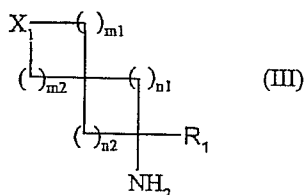
- 2-({2-[(2S)-2-cyanopyrrolidinyl]-2-oxoethyl}amino)spiro[3.3]heptane-2-carboxamide, and its addition salts with a pharmaceutically acceptable acid;
- (2S)-1-({[(2-(2-hydroxymethyl)-7-oxaspiro[3.5]non-2-yl]amino}acetyl)-2-pyrrolidinecarbonitrile, and its addition salts with a pharmaceutically acceptable acid;
- (2S,4S)-4-fluoro-1-({[9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino}-acetyl)-2-pyrrolidinecarbonitrile, its (2S,4R) isomer, its (2R, 4R) isomer and addition salts thereof with a pharmaceutically acceptable acid;
- (2S)-4,4-difluoro-1-({[9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino}-acetyl)-2-pyrrolidinecarbonitrile, and its addition salts with a pharmaceutically acceptable acid;
- and (4R)-3-({[9-(hydroxymethyl)-3-oxaspiro[5.5]undec-9-yl]amino}acetyl)-1,3-thiazolidine-4-carbonitrile, and its addition salts with a pharmaceutically acceptable acid.

- 15 15. Process for the synthesis of compounds of formula (I) according to claim 1 starting from a compound of formula (II) :



wherein X_1 , m_1 , m_2 , n_1 and n_2 are as defined in claim 1,

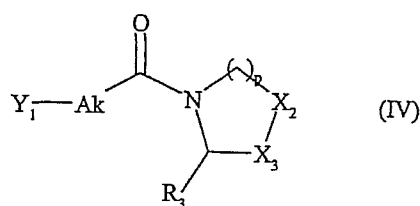
- 20 which is converted to a compound of formula (III) :



wherein X_1 , m_1 , m_2 , n_1 , n_2 and R_1 are as defined in claim 1,

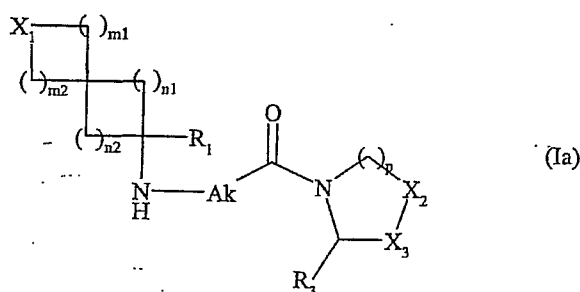
which is reacted with a compound of formula (IV) :

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wherein Ak, p, R₃, X₂ and X₃ are as defined in claim 1 and Y₁ represents a leaving group,

to yield compounds of formula (Ia), a particular case of the compounds of formula (I) wherein R₂ represents a hydrogen atom :



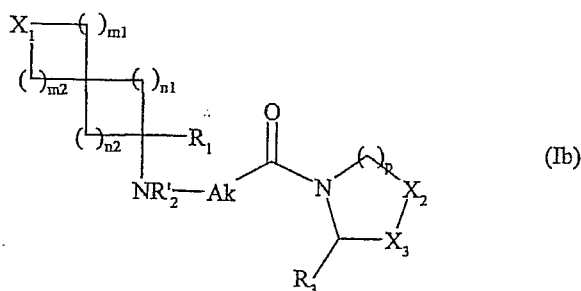
wherein X₁, m₁, m₂, n₁, n₂, R₁, Ak, p, R₃, X₂ and X₃ are as defined in claim 1,

which, when it is desired to obtain compounds of formula (I) wherein R₂ is other than a hydrogen atom, is reacted with a compound of formula (V) :



wherein Y₂ represents a leaving group and R'₂ represents a linear or branched C₁-C₆-alkyl group,

to yield compounds of formula (Ib), a particular case of the compounds of formula (I) wherein R₂ represents a linear or branched C₁-C₆alkyl group :



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wherein X_1 , m_1 , m_2 , n_1 , n_2 , R_1 , A_k , p , R_3 , X_2 and X_3 are as defined in claim 1 and R'_2 is as defined hereinbefore,

5 which compounds of formula (Ia) and (Ib), which constitute the totality of the compounds of formula (I),

are purified according to a conventional purification technique, are optionally separated into their optical isomers according to a conventional separation technique and, if desired, are converted into addition salts with a pharmaceutically acceptable acid.

10 16. Pharmaceutical composition comprising as active ingredient a compound according to any one of claims 1 to 14 in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

17. Use of a compound according to any one of claims 1 to 14 for the manufacture of medicaments for use as dipeptidyl-peptidase IV inhibitors.

15 18. Use of a compound according to any one of claims 1 to 14 for the manufacture of medicaments for use in the treatment of glucose intolerance and of disorders associated with hyperglycaemia.

19. Use of a compound according to any one of claims 1 to 14 for the manufacture of medicaments for use in the treatment of type II diabetes.

20 20. A compound as claimed in claim 1 substantially as herein described with reference to any example thereof.

21. A process as claimed in claim 15 substantially as herein described with reference to any example thereof.

22. A pharmaceutical composition as claimed in claim 16 substantially as herein described with reference to any example thereof.

23. A use as claimed in any one of claims 17-19 substantially as herein described with reference to any example thereof.

END OF CLAIMS