

NOVEL AMINO ACID DERIVATIVES, METHOD FOR PRODUCTION THEREOF AND
PHARMACEUTICAL COMPOSITIONS COMPRISING SAID DERIVATIVE

The present invention relates to new amino acid compounds, to a process for their preparation, to pharmaceutical compositions containing them and to the use thereof as inhibitors of trypsin-related serine proteases.

One of those serine proteases, activated protein C, is the key enzyme in a powerful physiological anticoagulation process, as its natural substrates, activated factor V and activated factor VIII, are potent promoters of blood coagulation (Dahlbäck B, Thrombosis Research 1995, 77, 1-43).

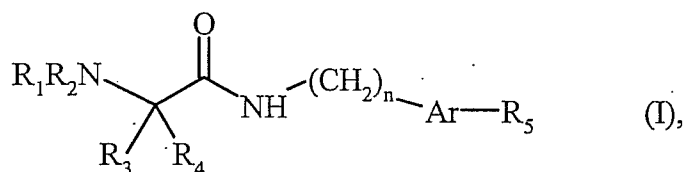
Direct and specific inhibition of activated protein C is an effective means of inhibiting that natural anticoagulant process and of promoting blood coagulation in haemorrhagic clinical situations and accordingly represents an extremely promising approach in the treatment of disorders involving a dysfunction of haemostasis requiring procoagulant treatment, such as von Willebrand's disease or haemophilia A or B.

Peptidomimetic compounds having inhibitory activity with respect to activated protein C have already been described in the patent specification WO98/22125.

It has been especially valuable to synthesise new serine protease inhibitors in order to increase the potency and selectivity of the compounds already described in the literature.

Moreover, in the presence of traces of tissue factor and thrombomodulin, these new compounds increase the generation of thrombin in human plasma and they are active *via* the oral route.

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



wherein :

5 ➤ R_1 represents an aryl group, a heteroaryl group or a linear or branched (C_1 - C_6)alkyl group optionally substituted by one or more identical or different groups selected from aryl and heteroaryl, or R_1 represents a group of formula $-(CO)-CR_6R_7NR_8R_9$ wherein :

- R_6 represents a hydrogen atom or a group selected from aryl, heteroaryl, heterocycloalkyl, (C_3 - C_8)cycloalkyl and linear or branched (C_1 - C_6)alkyl optionally substituted by one or more identical or different groups selected from aryl, heteroaryl, heterocycloalkyl, (C_3 - C_8)cycloalkyl and carboxy,
- R_7 represents a hydrogen atom or a linear or branched (C_1 - C_6)alkyl group,
- or R_6 and R_7 together form a (C_3 - C_8)cycloalkyl group,
- R_8 represents a hydrogen atom or a linear or branched (C_1 - C_6)alkyl group,
- and R_9 represents a hydrogen atom or a group R'_9 wherein R'_9 represents a group selected from :

- linear or branched (C_1 - C_6)alkyl optionally substituted by an aryl, carboxy, linear or branched (C_1 - C_6)alkoxy-carbonyl or carbamoyl group,
- aryl,
- heteroaryl,
- and sulphonyl substituted by a group selected from (C_3 - C_8)cycloalkyl, heterocycloalkyl, aryl (optionally substituted by an aryloxy or heteroaryloxy group), and linear or branched (C_1 - C_6)alkyl optionally substituted by an aryl, heteroaryl, (C_3 - C_8)cycloalkyl or heterocycloalkyl group,

15 ➤ R_2 represents a hydrogen atom or a linear or branched (C_1 - C_6)alkyl group,

20 ➤ R_3 represents a hydrogen atom or a linear or branched (C_1 - C_6)alkyl group optionally substituted by one or more aryl groups,

25 ➤ R_4 represents a saturated or unsaturated, 7- to 15-membered bicyclic system or a linear or branched (C_1 - C_6)alkyl group optionally substituted by one or more aryl groups, or R_3 and R_4 , together with the carbon atom carrying them, form a saturated or unsaturated, 3- to 18-membered, mono-, bi- or tri-cyclic system optionally containing

one or more hetero atoms selected from O, S and N and optionally substituted by one or more identical or different groups selected from halogen, linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)alkoxy, hydroxy, linear or branched (C₁-C₆)trihaloalkyl, amino (optionally substituted by one or more linear or branched (C₁-C₆)alkyl groups) and carboxy,

➤ n represents zero, 1 or 2,

➤ Ar represents an aryl or heteroaryl group,

➤ R₅ represents a group selected from amino, guanidino, cyano and amidino optionally substituted by a hydroxy or linear or branched (C₁-C₆)alkoxy-carbonyl group,

to their optical isomers, and also to addition salts thereof with a pharmaceutically acceptable acid.

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, oxalic acid, methanesulphonic acid, benzenesulphonic acid, camphoric acid.

A heterocycloalkyl group is understood to mean a 3- to 8-membered, saturated monocyclic group containing one, two or three hetero atoms selected from oxygen, nitrogen and sulphur, it being understood that the heterocycle may optionally be substituted by one or more identical or different groups selected from halogen, linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)alkoxy, oxo, hydroxy, linear or branched (C₁-C₆)trihaloalkyl and amino (optionally substituted by one or more linear or branched (C₁-C₆)alkyl groups). Preferred heterocycloalkyl groups are morpholinyl, piperazinyl or piperidyl groups.

An aryl group is understood to mean phenyl, biphenyl or naphthyl, each of those groups being optionally substituted by one or more identical or different groups selected from

halogen, linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)alkoxy, hydroxy, linear or branched (C₁-C₆)trihaloalkyl, amino (optionally substituted by one or more linear or branched (C₁-C₆)alkyl groups) and carboxy.

A heteroaryl group is understood to mean a monocyclic aromatic group or a bicyclic group in which at least one of the rings is aromatic, comprising from 5 to 12 members and containing one, two or three identical or different hetero atoms selected from oxygen, nitrogen and sulphur, it being understood that the heteroaryl may optionally be substituted by one or more identical or different groups selected from halogen, linear or branched (C₁-C₆)alkyl, hydroxy, linear or branched (C₁-C₆)alkoxy, trihalomethyl and amino (optionally substituted by one or more linear or branched (C₁-C₆)alkyl groups). Among the heteroaryl groups there may be mentioned, without implying any limitation, thienyl, pyridyl, furyl, pyrrolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl and quinolyl groups.

Preferred heteroaryl groups are pyridyl (optionally substituted), benzisoxazolyl and indazolyl groups.

An advantageous aspect of the invention relates to compounds of formula (I) wherein R₁ represents a group of formula -(CO)-CHR₆NHR₉ wherein R₆ represents a (C₃-C₈)cycloalkyl group, or linear or branched (C₁-C₆)alkyl optionally substituted by a (C₃-C₈)cycloalkyl group, and R₉ represents a group selected from linear or branched (C₁-C₆)alkyl optionally substituted by a carboxy, linear or branched (C₁-C₆)alkoxy-carbonyl or carbamoyl group, and linear or branched (C₁-C₆)alkylsulphonyl substituted by a (C₃-C₈)cycloalkyl group.

Another advantageous aspect of the invention relates to compounds of formula (I) wherein R₃ and R₄, which may be the same or different, each represent a linear or branched (C₁-C₆)alkyl group.

Another advantageous aspect of the invention relates to compounds of formula (I) wherein R₃ and R₄ together form an optionally substituted indanyl group or a cyclopentapyridyl group.

Another advantageous aspect of the invention relates to compounds of formula (I) wherein n represents 1.

Another advantageous aspect of the invention relates to compounds of formula (I) wherein Ar represents a phenyl group and R₅ represents an amidino group optionally substituted by a hydroxy group.

Another advantageous aspect of the invention relates to compounds of formula (I) wherein Ar represents a pyridyl group substituted by a methyl group and R₅ represents an amino group.

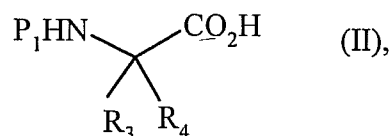
When R₁ represents a group of formula $-(CO)-CHR_6NR_8R_9$ wherein R₆, R₈ and R₉ are as defined for formula (I), the carbon atom carrying the substituents R₆ and NR₈R₉ constitutes a centre of asymmetry, the configuration of which is preferably R.

Among the preferred compounds of the invention there may be mentioned more especially :

- {[(1R)-2-({2-[(4-amidinobenzyl)-amino]-carbonyl]-indan-2-yl}-amino)-1-cyclohexyl-2-oxoethyl]-amino}acetic acid, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- ethyl {[(1R)-2-({2-[(4-[amino-(hydroxyimino)-methyl]-benzyl)-amino]-carbonyl]-indan-2-yl}-amino)-1-cyclohexyl-2-oxoethyl]-amino}acetate, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- {[(1R)-2-({2-[(4-amidinobenzyl)-amino]-carbonyl]-indan-2-yl}-amino)-1-cyclohexylmethyl-2-oxoethyl]-amino}acetic acid, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- {[(1R)-2-({2-[(4-amidinobenzyl)-amino]-carbonyl]-indan-2-yl}-amino)-1-isopropyl-2-oxoethyl]-amino}acetic acid, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,

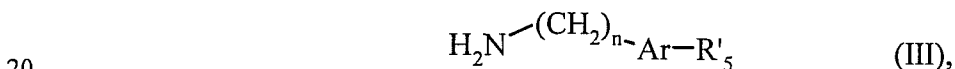
- N-(4-amidinobenzyl)-2-(((2R)-2-cyclohexyl-2-[(cyclohexylmethyl)-sulphonyl]-amino}-ethanoyl)-amino]-2-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- 5 - N-(4-amidinobenzyl)-2-(((2R)-2-[(cyclohexylmethyl)-sulphonyl]-amino}-3-méthylbutanoyl)-amino]-2-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- N-(4-amidinobenzyl)-2-(((2R)-2-[(isobutylsulphonyl]-amino}-3-methylbutanoyl)-amino]-2-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- 10 - and N-(4-amidinobenzyl)-6-(((2R)-2-[(cyclohexylmethyl)-sulphonyl]-amino}-3-methylbutanoyl)-amino]-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid.

The invention relates also to a process for the preparation of compounds of formula (I),
 15 which process is characterised in that a compound of formula (II) :



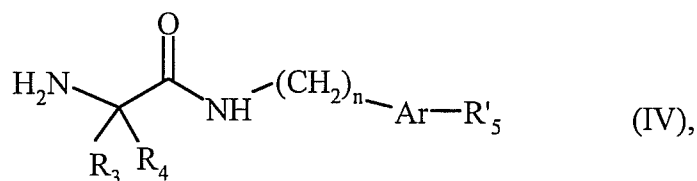
wherein R₃ and R₄ are as defined for formula (I) and P₁ represents a protecting group for the amino function,

is reacted, under peptide coupling conditions, with a compound of formula (III) :



20 wherein n and Ar are as defined for formula (I) and R'₅ represents a group selected from amino, guanidino and amidino optionally substituted by a hydroxy or linear or branched (C₁-C₆)alkoxy-carbonyl group, each of those groups being optionally substituted by a protecting group,

25 to yield, after deprotection, the compound of formula (IV) :



wherein R_3 , R_4 , n , Ar and R'_5 are as defined hereinbefore,

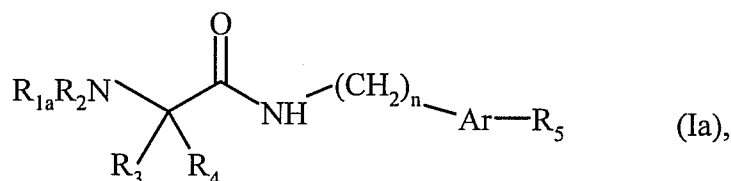
which is reacted :

- either, when it is desired to obtain compounds of formula (I) wherein R_1 represents an aryl group, a heteroaryl group or a linear or branched (C_1 - C_6)alkyl group which is optionally substituted, with a compound of formula (V):



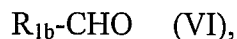
wherein R_{1a} represents an aryl group, a heteroaryl group or a linear or branched (C_1 - C_6)alkyl group optionally substituted by one or more groups selected from aryl and heteroaryl, and Z represents a leaving group such as, for example, a halogen atom or a tosylate, mesylate or triflate group,

to yield, after optional deprotection, the compounds of formula (Ia), a particular case of the compounds of formula (I) :

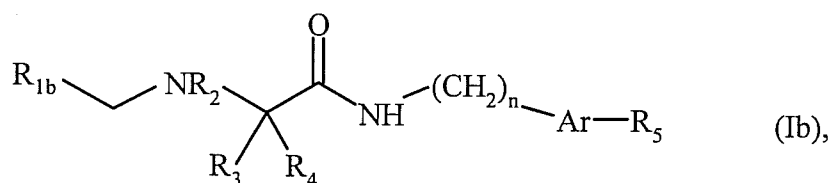


wherein R_{1a} , R_2 , R_3 , R_4 , n , Ar and R_5 are as defined hereinbefore,

- or, when it is desired to obtain compounds of formula (I) wherein R_1 represents an optionally substituted, linear or branched (C_2 - C_6)alkyl group, with a compound of formula (VI), under reductive amination conditions :

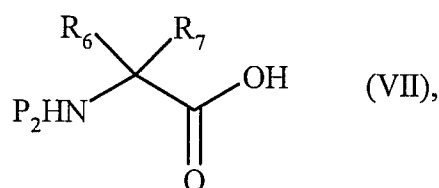


wherein R_{1b} represents a linear or branched (C_1 - C_5)alkyl group optionally substituted by one or more groups selected from aryl and heteroaryl, to yield, after optional deprotection, the compounds of formula (Ib), a particular case of the compounds of formula (I) :

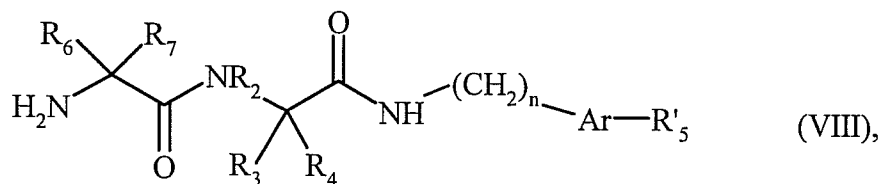


wherein R_{1b} , R_2 , R_3 , R_4 , n , Ar and R_5 are as defined hereinbefore,

- or, when it is desired to obtain compounds of formula (I) wherein R_1 represents a group of formula $\text{---(CO)---CR}_6\text{R}_7\text{NR}_8\text{R}_9$, wherein R_6 , R_7 , R_8 and R_9 are as defined for formula (I), with a compound of formula (VII), under peptide coupling conditions :

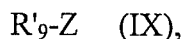


wherein R_6 and R_7 are as defined for formula (I) and P_2 represents a protecting group for the amino function, to yield, after deprotection, the compound of formula (VIII) :



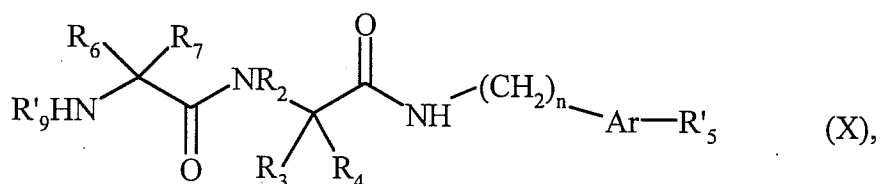
wherein R_6 , R_7 , R_2 , R_3 , R_4 , n , Ar and R'_5 are as defined hereinbefore,

which is reacted, if desired, with a compound of formula (IX) :



wherein R'_9 is as defined for formula (I) and Z represents a leaving group such as, for example, a halogen atom or a tosylate, mesylate or triflate group,

to yield the compound of formula (X) :



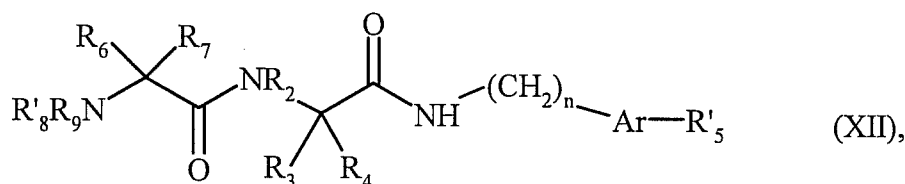
wherein R'_9 , R_6 , R_7 , R_2 , R_3 , R_4 , n , Ar and R'_5 are as defined hereinbefore,

which compounds of formula (VIII) or (X) are reacted, if desired, with a compound of formula (XI) :



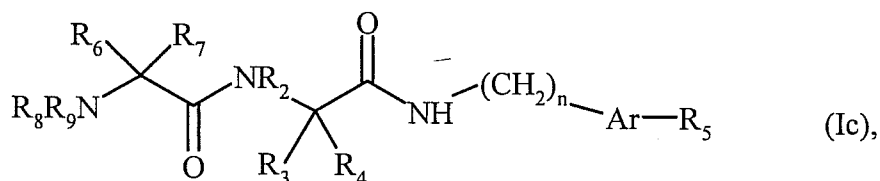
wherein R'_8 represents a linear or branched (C_1 - C_6)alkyl group and Z represents a leaving group such as, for example, a halogen atom or a tosylate, mesylate or triflate group,

to yield the compound of formula (XII) :



wherein R'_8 , R_6 , R_7 , R_2 , R_3 , R_4 , n , Ar and R'_5 are as defined hereinbefore and R_9 is as defined for formula (I),

which compounds of formula (VIII), (X) or (XII) are optionally deprotected to yield the compound of formula (Ic), a particular case of the compounds of formula (I) :



wherein R_8 , R_9 , R_6 , R_7 , R_2 , R_3 , R_4 , n , Ar and R_5 are as defined hereinbefore,

the compounds of formulae (Ia), (Ib) and (Ic) constituting the totality of the compounds of formula (I), which are purified, if necessary, according to a conventional purification technique, are separated, if desired, into their isomers according to a conventional separation technique and are converted, if desired, into their addition salts with a pharmaceutically acceptable acid.

Besides the fact that the compounds of the present invention are new, they possess especially valuable pharmacological properties.

They are powerful inhibitors of activated protein C, making them useful in the treatment of any pathological condition involving activated protein C and especially in the treatment of

disorders involving a dysfunction of haemostasis requiring procoagulant treatment, including all haemorrhagic clinical situations such as von Willebrand's disease or haemophilia A or B.

5 They may also be used as antidote medicaments in antithrombotic treatments such as anticoagulant, antiplatelet and fibrinolytic treatments.

The invention relates also to pharmaceutical compositions comprising, as active ingredient, a compound of formula (I) with one or more appropriate, inert, non-toxic excipients. Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral (intravenous or
10 subcutaneous) or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions etc.

The useful dosage can be varied according to the nature and severity of the disorder, the administration route and the age and weight of the patient and ranges from 1 to 500 mg per
15 day in one or more administrations.

The Examples that follow illustrate the invention but do not limit it in any way.

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

Preparations A to F yield synthesis intermediates that are useful in preparing compounds of
20 the invention.

The structures of the compounds described in the Examples were determined according to the usual spectrophotometric techniques (infrared, NMR, mass spectrometry).

PREPARATION A : Benzyl [4-aminomethyl-phenyl]-(imino)-methyl-carbamate

The expected product is obtained according to the procedure described by G. De Nanteuil *et al.* (Synth. Comm. 1998, Vol. 28 N° 23, pp. 4419-4429).

PREPARATION B : Benzyl [4-aminomethyl-phenyl]-(hydroxyimino)-methyl-carbamate

The expected product is obtained according to the procedure described by G. De Nanteuil *et al.* (Synth. Comm. 1998, Vol. 28 N° 23, pp. 4419-4429).

PREPARATION C : 6-Amino-3-aminomethyl-2-methylpyridine**Step A : 6-Amino-3-cyano-2-methylpyridine**

10 Copper(I) cyanide (12 mmol) is added to 10 mmol of 6-amino-3-bromo-2-methylpyridine dissolved in dimethylformamide. The mixture is refluxed for 10 hours, then cooled to 80°C and poured into a solution of sodium cyanide (40 mmol) in water. After stirring for 1 hour at ambient temperature, the mixture is extracted with ethyl acetate. The organic phase is washed and then dried and evaporated to yield the expected product in the form of an ochre
15 solid.

Step B : 6-Amino-3-aminomethyl-2-methylpyridine

A solution of the compound described in the Step above (10 mmol) in ethanol is placed under hydrogen overnight in the presence of Raney nickel. After filtering off the catalyst, the solvent is evaporated off to yield the expected product.

PREPARATION D : Methyl [4-aminomethyl-phenyl]-(imino)-methyl-carbamate

The expected product is obtained according to the procedure described by G. De Nanteuil *et al.* (Synth. Comm. 1998, Vol. 28 N° 23, pp. 4419-4429), starting from 4-bromomethyl-benzonitrile and methyl chloroformate.

PREPARATION E : Hexyl [4-aminomethyl-phenyl]-(imino)-methyl-carbamate

The expected product is obtained according to the procedure described by G. De Nanteuil *et al.* (Synth. Comm. 1998, Vol. 28 N° 23, pp. 4419-4429), starting from 4-bromomethyl-benzonitrile and hexyl chloroformate.

PREPARATION F : 4-Aminomethyl-N-hydroxybenzenecarboximidamide

The expected product is obtained according to the procedure described by G. De Nanteuil *et al.* (Synth. Comm. 1998, Vol. 28 N° 23, pp. 4419-4429).

EXAMPLE 1 : {[(1R)-2-({2-[(4-Amidinobenzyl)-amino]-carbonyl}-indan-2-yl)-amino}-1-cyclohexyl-2-oxoethyl)-amino}acetic acid hydrochloride

Step A : Benzyl (4-{[(2-[(tert-butyloxycarbonyl)-amino]-indan-2-yl)-carbonyl]-amino}-methyl)-phenyl)-(imino)-methyl-carbamate

To a solution of 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid (10 mmol) and the compound described in Preparation A (10 mmol) in dimethylformamide there are added O-(1*H*-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (11 mmol) and diisopropylethylamine (11 mmol). After stirring overnight at ambient temperature, the solvent is evaporated off. The residue obtained is taken up in ethyl acetate. The organic phase is washed, dried and then evaporated. The expected product is

obtained after purification of the residue by chromatography on silica gel, using a mixture of dichloromethane/ethyl acetate (1/1) as eluant.

Step B : Benzyl (4-[(2-amino-indan-2-yl)-carbonyl]-amino)-methyl-phenyl)-(imino)-methyl-carbamate dihydrochloride

For 30 minutes, a current of HCl gas is passed, with stirring, at 0°C, into a solution of the compound described in the Step above (10 mmol) in ethyl acetate. After stirring overnight at ambient temperature, the precipitate formed is filtered off, rinsed with ethyl acetate and then dried *in vacuo* using a desiccator.

Step C : Benzyl {4-[(2-[(2R)-2-[(tert-butyloxycarbonyl)-amino]-2-cyclohexylethano-yl)-amino]-indan-2-yl)-carbonyl]-amino)-methyl-phenyl}-(imino)-methylcarbamate

To a solution of the compound described in the Step above (10 mmol) and (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine (10 mmol) in dimethylformamide there are added O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (11 mmol), 1-hydroxybenzotriazole hydrate (11 mmol) and diisopropylethylamine (11 mmol). After stirring overnight at ambient temperature, the solvent is evaporated off. The residue obtained is taken up in ethyl acetate. The organic phase is washed, dried and then evaporated. The expected product is obtained after purification of the residue by chromatography on silica gel, using a mixture of dichloromethane/ethyl acetate (1/1) as eluant.

Step D : Benzyl {4-[(2-[(2R)-2-amino-2-cyclohexylethano-yl)-amino]-indan-2-yl)-carbonyl]-amino)-methyl-phenyl}-(imino)-methylcarbamate dihydrochloride

For 30 minutes, a current of HCl gas is passed, with stirring, at 0°C, into a solution of the compound described in the Step above (10 mmol) in ethyl acetate. After stirring overnight

at ambient temperature, the precipitate formed is filtered off, rinsed with ethyl acetate and then dried *in vacuo* using a desiccator.

Step E : Benzyl {[(1R)-2-({2-[(4-{(benzyloxycarbonyl)-amino}-(imino)-methyl)-benzyl]-amino)-carbonyl]-indan-2-yl}-amino)-1-cyclohexyl-2-oxoethyl]-amino}-acetate

To a solution of the compound described in the Step above (10 mmol) in acetonitrile there are added potassium carbonate (30 mmol) and then benzyl 2-bromoacetate (11 mmol). After stirring overnight, the solution is filtered and evaporated; the residue is taken up in ethyl acetate, and the organic phase is washed, dried and evaporated.

Step F : {[(1R)-2-({2-[(4-Amidinobenzyl)-amino)-carbonyl]-indan-2-yl}-amino)-1-cyclohexyl-2-oxoethyl]-amino}acetic acid hydrochloride

A solution of the compound described in the Step above (10 mmol) in ethanol is placed under hydrogen overnight in the presence of 10 % Pd/C (0.5 g). After filtering off the catalyst, the solvent is evaporated off to yield, after conversion into a salt using hydrochloric acid, the expected product.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	62.04	6.69	12.92	6.54
Found :	61.61	6.35	12.74	7.86

EXAMPLE 2 : {[(1R)-2-({1-[(4-Amidinobenzyl)-amino)-carbonyl]-cyclohexyl}-amino)-1-cyclohexyl-2-oxoethyl]-amino}acetic acid hydrochloride

The expected product is obtained according to the procedure described in Example 1, replacing the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid by 1-[(tert-butyloxycarbonyl)-amino]-cyclohexanecarboxylic acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	59.10	7.54	13.78	6.98
Found :	59.20	7.30	13.52	8.09

5 **EXAMPLE 3 :** [((1R)-2-{[2-({4-Amidinobenzyl}-amino)-1,1-dimethyl-2-oxoethyl]-amino}-1-cyclohexyl-2-oxoethyl)-amino]acetic acid hydrochloride

The expected product is obtained according to the procedure described in Example 1, replacing the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid by N-(tert-butyloxy-carbonyl)-2-methylalanine.

10 **EXAMPLE 4 :** N-(4-Amidinobenzyl)-2-((2R)-2-[(benzylsulphonyl)-amino]-2-cyclohexylethanoyl)-amino)-2-methylpropionamide hydrochloride

15 The expected product is obtained according to the procedure described in Example 1, starting from N-(tert-butyloxycarbonyl)-2-methylalanine, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and phenylmethane-sulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% Cl	% S
Calculated :	57.48	6.79	12.41	6.28	5.68
Found :	57.75	6.97	12.35	5.94	5.59

20 **EXAMPLE 5 :** N-(4-Amidinobenzyl)-1-((2R)-2-[(benzylsulphonyl)-amino]-2-cyclohexylethanoyl)-amino)-cyclopentanecarboxamide hydrochloride

25 The expected product is obtained according to the procedure described in Example 1, starting from 1-[(tert-butyloxycarbonyl)-amino]-cyclopentanecarboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and phenylmethanesulphonyl chloride.

EXAMPLE 6 : N-(4-Amidinobenzyl)-2-((2R)-2-([1,1'-biphenyl]-4-yl-sulphonyl)-amino)-2-cyclohexylethanoyl}-amino)-2-methylpropionamide hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from N-(tert-butyloxycarbonyl)-2-methylalanine, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and [1,1'-biphenyl]-4-sulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% Cl	% S
Calculated :	61.38	6.44	11.18	5.66	5.12
Found :	60.47	6.51	11.00	6.00	4.86

EXAMPLE 7 : N-(4-Amidinobenzyl)-2-((2R)-2-(phenylsulphonyl)-amino)-2-cyclohexylethanoyl}-amino)-2-methylpropionamide hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from N-(tert-butyloxycarbonyl)-2-methylalanine, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and benzenesulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% Cl	% S
Calculated :	55.30	6.51	12.40	8.79	5.68
Found :	54.67	6.58	12.74	8.89	5.06

EXAMPLE 8 : N-(4-Amidinobenzyl)-2-((2R)-2-[(2-naphthylsulphonyl)-amino]-2-cyclohexylethanoyl)-amino)-2-methylpropionamide hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from N-(tert-butyloxycarbonyl)-2-methylalanine, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and 2-naphthalene-sulphonyl chloride.

Elemental microanalysis :

		% C	% H	% N	% Cl	% S
10	Calculated :	60.04	6.38	11.67	5.91	5.34
	Found :	60.03	6.47	11.37	5.79	5.25

EXAMPLE 9 : N-(4-Amidinobenzyl)-2-((2R)-2-[[4-(4-pyridyloxy)-phenylsulphonyl]-amino]-2-cyclohexylethanoyl)-amino)-2-methylpropionamide dihydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from N-(tert-butyloxycarbonyl)-2-methylalanine, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and 4-(4-pyridyloxy)-benzenesulphonyl chloride.

Elemental microanalysis :

		% C	% H	% N	% Cl	% S
20	Calculated :	54.78	5.93	12.36	10.43	4.72
	Found	55.16	6.02	12.24	10.37	4.41

EXAMPLE 10 : N-(4-Amidinobenzyl)-2-((2R)-2-[(benzylsulphonyl)-amino]-2-phenylethanoyl)-amino)-2-methylpropionamide hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from N-(tert-butyloxycarbonyl)-2-methylalanine, the compound described in

Preparation A, (R)-N-(tert-butyloxycarbonyl)-phenylglycine and phenylmethanesulphonyl chloride.

Elemental microanalysis :

		% C	% H	% N	% Cl	% S
5	Calculated :	58.11	5.78	12.55	6.35	5.75
	Found	58.05	5.84	12.45	6.34	5.76

EXAMPLE 11 : N-(4-Amidinobenzyl)-2-((2R)-2-[[4-pyridyl]-methyl-sulphonyl]-amino)-2-cyclohexylethanoyl}-amino)-2-methylpropionamide dihydrochloride

- 10 The expected product is obtained according to the procedure described in Example 1, starting from N-(tert-butyloxycarbonyl)-2-methylalanine, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and (4-pyridyl)-methanesulphonyl chloride.

Elemental microanalysis :

		% C	% H	% N	% Cl	% S
15	Calculated :	51.91	6.37	13.97	11.79	5.33
	Found	52.53	6.22	14.21	10.93	5.07

EXAMPLE 12 : {[1(R)-2-({1-[[4-Amidinobenzyl]-amino]-carbonyl}-cyclopentyl)-amino)-1-(dicyclohexylmethyl)-2-oxoethyl]-amino}acetic acid hydrochloride

20

The expected product is obtained according to the procedure described in Example 1, starting from 1-[(tert-butyloxycarbonyl)-amino]-cyclopentanecarboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-dicyclohexylalanine and benzyl 2-bromoacetate.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	61.57	8.07	11.58	8.21
Found	61.58	8.00	11.25	7.75

5 **EXAMPLE 13 : N-(4-Amidinobenzyl)-2-((2R)-2-[(cyclohexylmethylsulphonyl)-amino]-2-cyclohexylethanoyl)-amino)-2-methylpropionamide hydrochloride**

10 The expected product is obtained according to the procedure described in Example 1, starting from N-(tert-butyloxycarbonyl)-2-methylalanine, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and cyclohexylmethane-sulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% Cl	% S
Calculated :	56.88	7.78	12.28	6.22	5.62
15 Found :	56.95	7.74	12.16	6.49	5.35

EXAMPLE 14 : N-(4-Amidinobenzyl)-2-((2R)-2-[(4-morpholinylsulphonyl)-amino]-2-cyclohexylethanoyl)-amino)-2-methylpropionamide hydrochloride

20 The expected product is obtained according to the procedure described in Example 1, starting from N-(tert-butyloxycarbonyl)-2-methylalanine, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and 4-morpholine-sulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% Cl	% S
Calculated :	51.56	7.03	15.03	6.34	5.73
25 Found :	51.67	6.69	15.10	7.12	5.37

EXAMPLE 15 : N-(4-Amidinobenzyl)-2-((2R)-2-[[3-(4-morpholinyl)-propylsulphonyl]-amino]-2-cyclohexylethanoyl)-amino)-2-methylpropionamide dihydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from N-(tert-butyloxycarbonyl)-2-methylalanine, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and 3-(4-morpholinyl)propanesulphonyl chloride.

Elemental microanalysis :

		% C	% H	% N	% Cl	% S
10	Calculated :	50.85	7.29	13.18	11.12	4.70
	Found :	50.92	7.07	13.41	11.56	4.70

EXAMPLE 16 : N-(4-Amidinobenzyl)-2-((2R)-2-[(benzylsulphonyl)-amino]-2-cyclohexylethanoyl)-amino)-2-indancarboxamide hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and phenylmethanesulphonyl chloride.

Elemental microanalysis :

		% C	% H	% N	% Cl	% S
20	Calculated :	62.10	6.32	10.97	5.55	5.02
	Found :	62.61	6.36	10.88	5.61	4.99

EXAMPLE 17 : N-(4-Amidinobenzyl)-1-((2R)-2-[(benzylsulphonyl)-amino]-2-cyclohexylethanoyl)-amino)-cyclohexanecarboxamide hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from 1-[(tert-butyloxycarbonyl)-amino]-cyclohexanecarboxylic acid, the

compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and phenylmethanesulphonyl chloride.

Elemental microanalysis :

		% C	% H	% N	% Cl	% S
5	Calculated :	59.64	7.01	11.59	5.87	5.31
	Found :	59.38	7.11	11.40	6.16	5.07

EXAMPLE 18 : {[(1R)-2-({1-[(4-Amidinobenzyl)-amino]-carbonyl}-cyclopentyl)-amino)-1-cyclohexyl-2-oxoethyl}-amino}-acetic acid hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from 1-[(tert-butyloxycarbonyl)-amino]-cyclopentanecarboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and benzyl 2-bromoacetate.

Elemental microanalysis :

		% C	% H	% N	% Cl
15	Calculated :	57.08	7.26	13.87	9.13
	Found :	57.03	7.17	13.40	9.31

EXAMPLE 19 : N-(4-Amidinobenzyl)-2-({ (2R)-2-[(benzylsulphonyl)-amino]-2-benzylethanoyl}-amino)-2-methylpropionamide hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from N-(tert-butyloxycarbonyl)-2-methylalanine, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-phenylalanine and phenylmethanesulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% Cl	% S
Calculated :	58.78	5.99	12.24	6.20	5.60
Found :	59.28	6.10	11.99	6.21	5.57

5 **EXAMPLE 20 : Ethyl {[(1R)-2-({2-[(4-[amino-(hydroxyimino)-methyl]-benzyl)-amino]-carbonyl]-indan-2-yl}-amino)-1-cyclohexyl-2-oxoethyl}-amino}-acetate**

10 The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid, the compound described in Preparation B, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and ethyl 2-bromoacetate.

Elemental microanalysis :

15

	% C	% H	% N
Calculated :	65.55	7.15	12.74
Found :	65.47	6.91	12.59

EXAMPLE 21 : 2-{{(2R)-2-Amino-2-cyclohexylethanoyl}-amino}-N-[(6-amino-2-methyl-3-pyridyl)-methyl]-2-indancarboxamide dihydrochloride

Step A : 2-Amino-N-[(6-amino-2-methyl-3-pyridyl)-methyl]-2-indancarboxamide dihydrochloride

20 The expected product is obtained according to the procedure described in Steps A and B of Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid and the compound described in Preparation C.

Step B : 2-{{[(2R)-2-Amino-2-cyclohexylethanoyl]-amino}-N-[(6-amino-2-methyl-3-pyridyl)-methyl]-2-indancarboxamide dihydrochloride

The expected product is obtained according to the procedure described in Steps C and D of Example 1, starting from the compound obtained in the Step above and (R)-N-(tert-butylloxycarbonyl)-cyclohexylglycine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	59.05	6.94	13.77	13.94
Found :	59.35	6.55	13.60	14.27

EXAMPLE 22 : {[[(1R)-2-({2-[(6-Amino-2-methyl-3-pyridyl)-methyl]-amino)-carbonyl]-indan-2-yl}-amino)-1-cyclohexyl-2-oxoethyl]-amino}acetic acid dihydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butylloxycarbonyl)-amino]-2-indancarboxylic acid, the compound described in Preparation C, (R)-N-(tert-butylloxycarbonyl)-cyclohexylglycine and benzyl 2-bromoacetate.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	57.24	6.58	12.36	12.52
Found :	57.53	6.58	12.31	12.08

EXAMPLE 23 : N-{{(6-Amino-2-methyl-3-pyridyl)-methyl}-2-((2R)-2-[(benzylsulphonyl)-amino]-2-cyclohexylethanoyl)-amino-2-indancarboxamide hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butylloxycarbonyl)-amino]-2-indancarboxylic acid, the compound

described in Preparation C, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and phenylmethanesulphonyl chloride.

Elemental microanalysis :

		% C	% H	% N	% Cl	% S
5	Calculated :	61.38	6.44	11.18	5.66	5.12
	Found :	61.30	6.54	10.94	5.74	4.83

EXAMPLE 24 : [((1R)-2-{[2-({[4-Amidinobenzyl]-amino)-1,1-dimethyl-2-oxoethyl]-amino}-1-phenyl-2-oxoethyl)-amino]acetic acid hydrochloride

10 The expected product is obtained according to the procedure described in Example 1, starting from N-(tert-butyloxycarbonyl)-2-methylalanine, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-phenylglycine and benzyl 2-bromoacetate.

EXAMPLE 25 : [((1R)-2-{[2-({[(3-Amino-1*H*-indazol-6-yl)-methyl]-amino}-carbonyl)-indan-2-yl]-amino}-1-cyclohexyl-2-oxoethyl)-amino]acetic acid hydrochloride

15 The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid, 6-(aminomethyl)-1*H*-indazol-3-amine (the preparation of which is described in Patent Application WO 00/26211), (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and benzyl 2-bromoacetate.

20

EXAMPLE 26 : [((1R)-2-{[2-({[(3-Amino-1,2-benzisoxazol-6-yl)-methyl]-amino}-carbonyl)-indan-2-yl]-amino}-1-cyclohexyl-2-oxoethyl)-amino]acetic acid trifluoroacetate

Step A : *[((1R)-2-{[2-({[(3-Amino-1,2-benzisoxazol-6-yl)-methyl]-amino}-carbonyl)-indan-2-yl]-amino}-1-cyclohexyl-2-oxoethyl)-amino]acetic acid*

The expected product is obtained according to the procedure described in Steps A to C of Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid, 6-(aminomethyl)-1,2-benzisoxazol-3-amine (the preparation of which is described in Patent Application WO 00/26210), (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and benzyl 2-bromoacetate.

Step B : *[((1R)-2-{[2-({[(3-Amino-1,2-benzisoxazol-6-yl)-methyl]-amino}-carbonyl)-indan-2-yl]-amino}-1-cyclohexyl-2-oxoethyl)-amino]acetic acid trifluoroacetate*

The expected product is obtained according to the procedure described in Step D of Example 1, replacing the HCl gas by trifluoroacetic acid.

Elemental microanalysis :

		% C	% H	% N	% Cl
15	Calculated :	59.81	6.42	13.95	7.06
	Found	59.75	6.35	13.60	6.76

EXAMPLE 27 : {[(1R)-2-({2-[(4-Amidinophenyl)-amino]-carbonyl)-indan-2-yl]-amino}-1-cyclohexyl-2-oxoethyl]-amino}acetic acid hydrochloride

The expected product is obtained according to the procedure described in Example 1, replacing the compound of Preparation A by benzyl (4-aminophenyl)-(imino)-methyl-carbamate.

EXAMPLE 28 : {[(1R)-2-({2-[(4-Amidinobenzyl)-amino]-carbonyl}-indan-2-yl)-amino)-1-phenyl-2-oxoethyl]-amino}acetic acid dihydrochloride

The expected product is obtained according to the procedure described in Example 1, replacing the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-phenylglycine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	58.74	5.46	12.23	12.39
Found	59.06	5.49	12.14	12.13

EXAMPLE 29 : {[(1R)-2-({2-[(4-Amidinobenzyl)-amino]-carbonyl}-indan-2-yl)-amino)-1-benzyl-2-oxoethyl]-amino}acetic acid dihydrochloride

The expected product is obtained according to the procedure described in Example 1, replacing the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-phenylalanine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	59.39	5.67	11.94	12.09
Found	59.70	5.65	11.84	11.68

EXAMPLE 30 : {[(1R)-2-({2-[(4-Amidinobenzyl)-amino]-carbonyl}-indan-2-yl)-amino)-1-cyclohexylmethyl-2-oxoethyl]-amino}acetic acid dihydrochloride

The expected product is obtained according to the procedure described in Example 1, replacing the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-cyclohexylalanine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	58.78	6.63	11.82	11.97
Found	59.55	6.55	11.92	11.92

5 **EXAMPLE 31 : N-[(6-Amino-2-methyl-3-pyridyl)-methyl]-2-[(2-phenethyl)-amino]-2-indancarboxamide dihydrochloride**

To 10 mmol of the compound described in Step A of Example 21 dissolved in 1,2-dichloroethane there are added 10 mmol of phenylacetaldehyde and then 14 mmol of sodium triacetoxyborohydride. After stirring for 4 hours, water is added and the reaction mixture is then separated and extracted with dichloromethane. The combined organic phases are dried and then filtered and evaporated. The residue thereby obtained is purified by chromatography on silica (eluant : dichloromethane/methanol 95/5) to yield, after conversion into a salt using hydrochloric acid, the expected product.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated :	63.42	6.39	11.83	14.98
Found	63.92	6.33	11.89	15.36

EXAMPLE 32 : {[(1S)-2-({2-[(4-Amidinobenzyl)-amino]-carbonyl}-indan-2-yl)-amino)-1-cyclohexyl-2-oxoethyl]-amino}acetic acid dihydrochloride

20 The expected product is obtained according to the procedure described in Steps C to F of Example 1, starting from the compound described in Step B of Example 1 and (S)-N-(tert-butyloxycarbonyl)-cyclohexylglycine.

Elemental microanalysis :

25

	% C	% H	% N	% Cl
Calculated :	58.13	6.45	12.11	12.26
Found :	58.46	6.59	12.02	11.99

EXAMPLE 33 : N-[(6-Amino-2-methyl-3-pyridyl)-methyl]-2-[(2,2-diphenylethyl)-amino]-2-indancarboxamide hydrochloride

The expected product is obtained according to the procedure described in Example 31, replacing the phenylacetaldehyde by diphenylacetaldehyde.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	67.75	6.24	10.20	12.90
Found :	68.15	6.18	10.19	12.96

10 **EXAMPLE 34 : N-[(6-Amino-2-methyl-3-pyridyl)-methyl]-2-[(3-phenylpropyl)-amino]-2-indancarboxamide hydrochloride**

The expected product is obtained according to the procedure described in Example 31, replacing the phenylacetaldehyde by 3-phenylpropanal.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 Calculated :	64.06	6.62	11.49	14.55
Found :	64.74	6.51	11.59	14.68

EXAMPLE 35 : N-(4-Amidinobenzyl)-2-[(2,2-diphenylethyl)-amino]-2-indancarboxamide hydrochloride

20 Step A : Benzyl (4-[[[(2-[(2,2-diphenylethyl)-amino]-indan-2-yl)-carbonyl]-amino]-methyl]-phenyl)-(imino)-methylcarbamate hydrochloride

The expected product is obtained according to the procedure described in Example 31, starting from the compound obtained in Step B of Example 1 and diphenylacetaldehyde.

Step B : *N*-(4-Amidinobenzyl)-2-[(2,2-diphenylethyl)-amino]-2-indan-carboxamide hydrochloride

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

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	73.20	6.33	10.67	6.75
Found :	72.55	5.96	10.15	7.42

10 **EXAMPLE 36 : Ethyl ((1R)-1-cyclohexyl-2-[(2-[(4-{imino-[(methoxycarbonyl)-amino]-methyl}-benzyl)-amino]-carbonyl]-indan-2-yl)-amino]-2-oxoethyl)-amino)-acetate :**

The expected product is obtained according to the procedure described in Steps A to E of Example 1, replacing, in Step A, Preparation A by Preparation D and, in Step E, the benzyl 2-bromoacetate by ethyl 2-bromoacetate.

15 Elemental microanalysis :

	% C	% H	% N
Calculated :	64.96	6.98	11.84
Found :	64.29	6.91	11.45

20 **EXAMPLE 37 : Ethyl ((1R)-1-cyclohexyl-2-[(2-[(4-{imino-[(hexyloxy}-carbonyl)-amino]-methyl}-benzyl)-amino]-carbonyl]-indan-2-yl)-amino]-2-oxoethyl)-amino)-acetate :**

25 The expected product is obtained according to the procedure described in Steps A to E of Example 1, replacing, in Step A, Preparation A by Preparation E and, in Step E, the benzyl 2-bromoacetate by ethyl 2-bromoacetate.

Elemental microanalysis :

	% C	% H	% N
Calculated :	67.15	7.77	10.58
Found :	67.21	7.85	10.57

5 **EXAMPLE 38 : N-(4-Amidinobenzyl)-2-((2R)-2-[(2-amino-2-oxoethyl)-amino]-2-cyclohexylethanoyl)-amino)-2-indancarboxamide hydrochloride**

The expected product is obtained according to the procedure of Example 1, replacing the benzyl 2-bromoacetate in Step E by 2-bromoacetamide.

Elemental microanalysis :

10

	% C	% H	% N	% Cl
Calculated :	62.15	6.89	15.53	6.55
Found :	62.77	6.70	15.33	6.75

EXAMPLE 39 A : {[(1R)-2-({2-[(4-Amidinobenzyl)-amino]-carbonyl}-indan-2-yl)-amino)-1-isopropyl-2-oxoethyl]-amino}acetic acid hydrochloride

15 The expected product is obtained according to the procedure of Example 1, replacing the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine in Step C by (R)-N-(tert-butyloxycarbonyl)-valine.

Elemental microanalysis :

20

	% C	% H	% N	% Cl
Calculated :	59.81	6.42	13.95	7.06
Found :	59.75	6.35	13.60	6.76

EXAMPLE 39 B : {[(1R)-2-({2-[(4-Amidinobenzyl)-amino]-carbonyl]-indan-2-yl}-amino)-1-isopropyl-2-oxoethyl]-amino}acetic acid dihydrochloride

Elemental microanalysis :

		% C	% H	% N	% Cl
5	Calculated :	55.76	6.18	13.01	13.17
	Found :	55.62	6.27	12.75	13.45

EXAMPLE 40 : N-(4-Amidinobenzyl)-2-[(2R)-2-cyclohexyl-2-[(cyclohexylmethyl)-sulphonyl]-amino]-ethanoyl]-amino]-2-indancarboxamide hydrochloride

10 The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and cyclohexylmethanesulphonyl chloride.

Elemental microanalysis :

		% C	% H	% N	% Cl	% S
15	Calculated :	61.52	7.20	10.87	5.50	4.98
	Found :	61.22	7.22	10.67	5.49	4.91

EXAMPLE 41 : N-(4-Amidinobenzyl)-2-[(2R)-2-cyclohexyl-2-[(cyclohexylmethyl)-sulphonyl]-amino]-ethanoyl]-amino]-2,3-dihydro-1H-cyclopenta[b]-naphthalene-2-carboxamide hydrochloride

20

The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2,3-dihydro-1H-cyclopenta[b]-naphthalene-2-carboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and cyclohexylmethanesulphonyl chloride.

EXAMPLE 42 : N-(4-Amidinobenzyl)-2-(((2R)-2-cyclohexyl-2-((cyclohexylmethyl)-sulphonyl)-amino)-ethanoyl)-amino]-2,3-dihydro-1H-cyclopenta[a]-naphthalene-2-carboxamide hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2,3-dihydro-1H-cyclopenta[a]-naphthalene-2-carboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine and cyclohexylmethanesulphonyl chloride.

EXAMPLE 43 : N-(4-Amidinobenzyl)-2-(((2R)-2-((cyclohexylmethyl)-sulphonyl)-amino)-3-methylbutanoyl)-amino]-2,3-dihydro-1H-cyclopenta[a]-naphthalene-2-carboxamide hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2,3-dihydro-1H-cyclopenta[a]-naphthalene-2-carboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-valine and cyclohexylmethanesulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% Cl	% S
Calculated :	62.42	6.78	10.70	4.90	5.42
Found :	62.95	7.02	10.65	4.71	5.39

EXAMPLE 44 : N-(4-Amidinobenzyl)-2-(((2R)-2-((cyclohexylmethyl)-sulphonyl)-amino)-3-methylbutanoyl)-amino]-2,3-dihydro-1H-cyclopenta[b]-naphthalene-2-carboxamide hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2,3-dihydro-1H-cyclopenta[b]-naphthalene-2-carboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-valine and cyclohexylmethanesulphonyl chloride.

EXAMPLE 45 : $\{[(1R)-2-((2-((4\text{-Amidinobenzyl})\text{-amino})\text{-carbonyl})-2,3\text{-dihydro-}1H\text{-cyclopenta}[b]\text{naphth-2-yl})\text{-amino})-1\text{-cyclohexyl-2-oxoethyl})\text{-amino}\}\text{-acetic acid hydrochloride}$

The expected product is obtained according to the procedure described in Example 1, replacing the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid in Step A by 2-[(tert-butyloxycarbonyl)-amino]-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene-2-carboxylic acid.

EXAMPLE 46 : $\{[(1R)-2-((2-((4\text{-Amidinobenzyl})\text{-amino})\text{-carbonyl})-2,3\text{-dihydro-}1H\text{-cyclopenta}[a]\text{naphth-2-yl})\text{-amino})-1\text{-cyclohexyl-2-oxoethyl})\text{-amino}\}\text{-acetic acid hydrochloride}$

The expected product is obtained according to the procedure described in Example 1, replacing the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid in Step A by 2-[(tert-butyloxycarbonyl)-amino]-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene-2-carboxylic acid.

EXAMPLE 47 : $\{[(1R)-1-((2-((4\text{-Amidinobenzyl})\text{-amino})\text{-carbonyl})-2,3\text{-dihydro-}1H\text{-cyclopenta}[a]\text{naphth-2-yl})\text{-amino})\text{-carbonyl})-2\text{-methylpropyl})\text{-amino}\}\text{-acetic acid hydrochloride}$

The expected product is obtained according to the procedure described in Example 1, replacing, in Step A, the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid by 2-[(tert-butyloxycarbonyl)-amino]-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene-2-carboxylic acid and, in Step C, the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-valine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	63.09	6.21	12.69	6.42
Found :	63.46	6.08	12.60	6.57

5 **EXAMPLE 48 : ((1R)-1-[(2-[(4-Amidinobenzyl)-amino)-carbonyl]-2,3-dihydro-1H-cyclopenta[b]naphth-2-yl)-amino)-carbonyl]-2-methylpropyl)-amino)-acetic acid hydrochloride**

The expected product is obtained according to the procedure described in Example 1, replacing, in Step A, the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid by
 10 2-[(tert-butyloxycarbonyl)-amino]-2,3-dihydro-1H-cyclopenta[b]naphthalene-2-carboxylic acid and, in Step C, the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-valine.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 Calculated :	63.09	6.21	12.69	6.42
Found :	63.17	5.91	12.39	6.49

EXAMPLE 49 : N-(4-Amidinobenzyl)-2-[(2R)-2-[(cyclohexylmethyl)-sulphonyl]-amino]-3-methylbutanoyl)-amino]-2-indancarboxamide hydrochloride

20 The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-valine and cyclohexylmethane-sulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% S	% Cl
Calculated :	59.64	7.01	11.59	5.31	5.87
Found :	59.75	7.07	11.43	5.22	5.92

5 **EXAMPLE 50 : N-(4-Amidinobenzyl)-2-(((2R)-2-((cyclohexylmethyl)-sulphonyl)-amino)-3-methylbutanoyl)-amino]-2,3-dihydro-1H-phenalene-2-carboxamide hydrochloride**

10 The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2,3-dihydro-1H-phenalene-2-carboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-valine and cyclohexylmethanesulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% S	% Cl
Calculated :	62.42	6.78	10.70	4.90	5.42
15 Found :	62.79	7.58	10.63	4.49	5.31

EXAMPLE 51 : (((1R)-1-[(2-[(4-Amidinobenzyl)-amino)-carbonyl]-2,3-dihydro-1H-phenalen-2-yl)-amino)-carbonyl]-2-methylpropyl)-amino)-acetic acid dihydrochloride

20 The expected product is obtained according to the procedure described in Example 1, replacing, in Step A, the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid by 2-[(tert-butyloxycarbonyl)-amino]-2,3-dihydro-1H-phenalene-2-carboxylic acid and, in Step C, the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-valine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	59.18	5.99	11.90	12.05
Found :	59.56	5.59	11.85	11.25

5 **EXAMPLE 52 : N-(4-Amidinobenzyl)-2-[(2R)-2-{[isobutylsulphonyl]-amino}-3-methylbutanoyl)-amino]-2-indancarboxamide hydrochloride**

The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-valine and isobutanesulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% S	% Cl
Calculated :	57.48	6.79	12.41	5.68	6.28
Found :	57.77	6.93	12.28	5.41	6.38

15 **EXAMPLE 53 : ((1R)-1-[(6-[(4-Amidinobenzyl)-amino)-carbonyl]-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-6-yl)-amino)-carbonyl]-2-methylpropyl)-amino)-acetic acid dihydrochloride**

The expected product is obtained according to the procedure described in Example 1, replacing, in Step A, the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid by 6-[(tert-butyloxycarbonyl)-amino]-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-6-carboxylic acid and, in Step C, the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-valine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	60.59	6.07	11.40	11.54
Found :	61.11	6.11	11.34	11.68

EXAMPLE 54 : N-(4-Cyanobenzyl)-2-(((2R)-2-((cyclohexylmethyl)-sulphonyl)-amino)-3-methylbutanoyl)-amino]-2-indancarboxamide

The expected product is obtained according to the procedure described in Steps A to E of Example 1, replacing, in Step A, the compound of Preparation A by 4-(aminomethyl)benzonitrile and, in Step E, the benzyl 2-bromoacetate by cyclohexylmethanesulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% S
Calculated :	65.43	6.95	10.17	5.82
Found :	65.28	6.93	10.17	5.73

EXAMPLE 55 : N-{4-[(Hydroxyamino)-(imino)-methyl]-benzyl}-2-(((2R)-2-((cyclohexylmethyl)-sulphonyl)-amino)-3-methylbutanoyl)-amino]-2-indancarboxamide

The expected product is obtained according to the procedure described in Steps A to E of Example 1, replacing, in Step A, the compound of Preparation A by the compound of Preparation F and, in Step E, the benzyl 2-bromoacetate by cyclohexylmethanesulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% S
Calculated :	61.73	7.08	12.00	5.49
Found :	61.52	7.06	11.99	5.16

EXAMPLE 56 : {[2-({2-[(4-Amidinobenzyl)-amino]-carbonyl}-indan-2-yl)-amino)-1,1-dimethyl-2-oxoethyl}-amino}acetic acid dihydrochloride

The expected product is obtained according to the procedure described in Example 1, replacing the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine in Step C by N-(tert-butyloxycarbonyl)-2-methylalanine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	54.97	5.96	13.35	13.52
Found :	54.97	5.84	13.13	12.69

EXAMPLE 57 : ({1-[(2-[(4-Amidinobenzyl)-amino]-carbonyl}-indan-2-yl)-amino)-carbonyl}-cyclopentyl}-amino)-acetic acid dihydrochloride

The expected product is obtained according to the procedure described in Example 1, replacing the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine in Step C by 1-[(tert-butyloxycarbonyl)-amino]-cyclopentanecarboxylic acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	56.73	6.04	12.72	12.88
Found :	56.57	5.92	12.61	12.23

EXAMPLE 58 : ((1R)-1-[(2-[(4-Amidinobenzyl)-amino]-carbonyl}-indan-2-yl)-amino)-carbonyl]-propyl}-amino)-acetic acid dihydrochloride

The expected product is obtained according to the procedure described in Example 1, replacing the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine in Step C by (2R)-2-[(tert-butyloxycarbonyl)-amino]-butanoic acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	54.97	5.96	13.35	13.52
Found :	54.68	5.85	13.14	12.87

5 **EXAMPLE 59 : ((1R,2R)-1-[(2-[(4-Amidinobenzyl)-amino)-carbonyl]-indan-2-yl)-amino)-carbonyl]-2-methylbutyl)-amino)-acetic acid dihydrochloride**

The expected product is obtained according to the procedure described in Example 1, replacing the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine in Step C by (2R,3R)-N-(tert-butyloxycarbonyl)-isoleucine.

10 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	56.52	6.39	12.68	12.83
Found :	57.26	6.43	12.69	12.61

15 **EXAMPLE 60 : ((1R)-1-[(2-[(4-Amidinobenzyl)-amino)-carbonyl]-indan-2-yl)-amino)-carbonyl]-2,2-dimethylpropyl)-amino)-acetic acid dihydrochloride**

The expected product is obtained according to the procedure described in Example 1, replacing the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine in step C by (2R)-2-[(tert-butyloxycarbonyl)-amino]-3,3-dimethylbutanoic acid.

20 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	56.52	6.39	12.68	12.83
Found :	56.98	6.36	12.61	12.34

EXAMPLE 61 : Diastereoisomer 1 of ((1R)-1-[(6-[(4-amidinobenzyl)-amino)-carbonyl]-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-amino)-carbonyl]-2-methylpropyl)-amino)-acetic acid trihydrochloride

Step A: Diastereoisomer 1 of benzyl ((1R)-1-[(6-[(4-[(benzyloxy)-carbonyl]-amino)-(imino)-methyl]-benzyl)-amino)-carbonyl]-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-amino)-carbonyl]-2-methylpropyl)-amino)-acetate

The expected product is obtained according to the procedure described in Steps A to E of Example 1, replacing, in Step A, the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid by 6-[(tert-butyloxycarbonyl)-amino]-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid and, in Step C, the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-valine, and then separating the mixture of diastereoisomers thereby obtained by chromatography on silica.

The expected product is the first of the diastereoisomers separated in that manner.

Step B: Diastereoisomer 1 of ((1R)-1-[(6-[(4-amidinobenzyl)-amino)-carbonyl]-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-amino)-carbonyl]-2-methylpropyl)-amino)-acetic acid trihydrochloride

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

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	50.05	5.78	14.59	18.47
Found :	50.39	5.71	14.54	18.37

EXAMPLE 62 : Diastereoisomer 2 of ((1R)-1-[(6-[(4-amidinobenzyl)-amino)-carbonyl]-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-amino)-carbonyl]-2-methylpropyl)-amino)-acetic acid trihydrochloride

Step A: Diastereoisomer 2 of benzyl ((1R)-1-[(6-[(4-[(benzyloxy)-carbonyl]-amino)-(imino)-methyl]-benzyl)-amino)-carbonyl]-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-amino)-carbonyl]-2-methylpropyl)-amino)-acetate

The expected product is the second of the diastereoisomers separated in Step A of Example 61.

Step B: Diastereoisomer 2 of ((1R)-1-[(6-[(4-amidinobenzyl)-amino)carbonyl]-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-amino)-carbonyl]-2-methylpropyl)-amino)-acetic acid trihydrochloride

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

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	50.05	5.78	14.59	18.47
Found :	50.14	5.56	14.45	19.00

EXAMPLE 63 : Hexyl (4-{[(2-[(2R)-2-{[(cyclohexylmethyl)-sulphonyl]-amino}-3-methylbutanoyl)-amino]-indan-2-yl)-carbonyl]-amino}-methyl)-phenyl)-(imino)-methylcarbamate

The expected product is obtained according to the procedure described in Steps A to E of Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid, the compound described in Preparation E, (R)-N-(tert-butyloxycarbonyl)-valine and cyclohexylmethanesulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% S
Calculated :	63.86	7.68	10.06	4.61
Found :	64.10	7.93	9.89	4.30

5 **EXAMPLE 64 : N-(4-Amidinobenzyl)-6-(((2R)-2-((cyclohexylmethyl)-sulphonyl)-amino)-3-methylbutanoyl)-amino]-6,7-dihydro-5H-cyclopenta[b]-pyridine-6-carboxamide dihydrochloride**

The expected product is obtained according to the procedure described in Example 1, starting from 6-[(tert-butyloxycarbonyl)-amino]-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-valine and cyclohexylmethanesulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% S	% Cl
Calculated :	54.28	6.60	13.10	5.00	11.05
Found :	54.57	6.57	13.05	4.99	10.85

15 **EXAMPLE 65 : (((1R)-1-[(6-[(4-Amidinobenzyl)-amino)carbonyl]-6,7-dihydro-5H-cyclopenta[c]pyridin-6-yl)-amino)-carbonyl]-2-methylpropyl)-amino)-acetic acid trihydrochloride**

The expected product is obtained according to the procedure described in Example 1, replacing, in Step A, the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid by 6-[(tert-butyloxycarbonyl)-amino]-6,7-dihydro-5H-cyclopenta[c]pyridine-6-carboxylic acid and, in Step C, the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-valine.

EXAMPLE 66 : N-(4-Amidinobenzyl)-2-[(2R)-2-(isobutylamino)-3-methylbutanoyl]-amino}-2-indancarboxamide dihydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid, the compound described in Preparation A, N-(tert-butyloxycarbonyl)-glycine and isobutyl chloride.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	58.30	6.73	14.16	14.34
Found :	57.97	6.86	14.19	14.92

EXAMPLE 67 : N-[(6-Amino-2-methyl-3-pyridyl)-methyl]-2-[(2R)-2-(isobutylamino)-3-methylbutanoyl]-amino}-2-indancarboxamide dihydrochloride

The expected product is obtained in the form of the base according to the procedure described in Steps C to E of Example 1, starting from the compound obtained in Step A of Example 21, N-(tert-butyloxycarbonyl)-glycine and isobutyl chloride, and is then converted into a salt using hydrochloric acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	57.26	6.89	14.52	14.70
Found :	57.17	7.02	14.49	14.95

EXAMPLE 68 : {[2-({2-[(4-Amidinobenzyl)-amino]-carbonyl}-indan-2-yl)-amino}-2-oxoethyl]-amino}acetic acid dihydrochloride

The expected product is obtained according to the procedure described in Example 1, replacing the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine in Step C by N-(tert-butyloxycarbonyl)-glycine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	53.23	5.48	14.11	14.28
Found :	53.40	5.56	14.00	14.32

5 **EXAMPLE 69 : {[(1R)-2-({2-[(4-Amidinobenzyl)-amino]-carbonyl}-5,6-dimethoxy-indan-2-yl)-amino)-1-isopropyl-2-oxoethyl}-amino}-acetic acid hydrochloride**

The expected product is obtained according to the procedure of Example 1, replacing, in Step A, the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid by 2-[(tert-butyloxycarbonyl)-amino]-5,6-dimethoxy-2-indancarboxylic acid and, in Step C, the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-valine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	57.70	6.46	12.46	6.31
Found :	58.06	6.32	12.50	6.78

15 **EXAMPLE 70 : ((1R)-1-[(2-[(4-Amidinobenzyl)-amino]-carbonyl]-indan-2-yl)-amino)-carbonyl]-3-methylbutyl)-amino)-acetic acid hydrochloride**

The expected product is obtained according to the procedure described in Example 1, replacing the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine in Step C by (R)-N-(tert-butyloxycarbonyl)-leucine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	60.52	6.64	13.57	6.87
Found :	60.39	6.53	13.40	7.56

EXAMPLE 71 : {[(1R)-2-({2-[(4-Amidinobenzyl)-amino]-carbonyl}-indan-2-yl)-amino}-1-methyl-2-oxoethyl)-amino}acetic acid dihydrochloride

The expected product is obtained according to the procedure described in Example 1, replacing the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine in Step C by (R)-N-(tert-butyloxycarbonyl)-alanine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	54.12	5.73	13.72	13.89
Found :	54.34	5.87	13.53	14.35

EXAMPLE 72 : N-(4-Amidinobenzyl)-2-[(2R)-2-{[isobutylsulphonyl]-amino}-3-methylbutanoyl]-amino]-5,6-dimethoxy-2-indancarboxamide hydrochloride

The expected product is obtained according to the procedure described in Example 1, starting from 2-[(tert-butyloxycarbonyl)-amino]-5,6-dimethoxy-2-indancarboxylic acid, the compound described in Preparation A, (R)-N-(tert-butyloxycarbonyl)-valine and isobutanesulphonyl chloride.

Elemental microanalysis :

	% C	% H	% N	% S	% Cl
Calculated :	55.80	6.78	11.22	5.14	5.68
Found :	55.58	6.94	11.21	4.90	6.01

EXAMPLE 73 : {[(1R)-1-({[(1S)-2-({4-Amidinobenzyl)-amino}-1-benzyl-2-oxoethyl)-amino]-carbonyl)-2-methylpropyl]amino}-acetic acid dihydrochloride

The expected product is obtained according to the procedure of Example 1, replacing, in Step A, the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid by (S)-N-(tert-

butyloxycarbonyl)-phenylalanine and, in Step C, the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-valine.

Elemental microanalysis :

		% C	% H	% N	% Cl
5	Calculated :	54.75	6.32	13.30	13.47
	Found :	54.90	6.40	13.27	13.08

EXAMPLE 74 : ((1R)-1-[(1S)-2-[4-Amidinobenzyl]-amino)-1-benzhydryl-2-oxoethyl]-amino}-carbonyl)-2-methylpropyl]amino}-acetic acid dihydrochloride

10 The expected product is obtained according to the procedure of Example 1, replacing, in Step A, the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid by (2S)-2-[(tert-butyloxycarbonyl)-amino]-3,3-diphenylpropanoic acid and, in Step C, the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-valine.

Elemental microanalysis :

		% C	% H	% N	% Cl
15	Calculated :	59.80	6.19	11.62	11.77
	Found :	60.35	6.15	11.88	11.62

EXAMPLE 75 : ((1R)-1-[(1S)-2-[4-Amidinobenzyl]-amino)-1-(2,3-dihydro-1H-inden-2-yl)-2-oxoethyl]-amino}-carbonyl)-2-methylpropyl]amino}-acetic acid dihydrochloride

20

The expected product is obtained according to the procedure of Example 1, replacing, in Step A, the 2-[(tert-butyloxycarbonyl)-amino]-2-indancarboxylic acid by (2S)-2-[(tert-butyloxycarbonyl)-amino]-(2,3-dihydro-1H-inden-2-yl)ethanoic acid and, in Step C, the (R)-N-(tert-butyloxycarbonyl)-cyclohexylglycine by (R)-N-(tert-butyloxycarbonyl)-valine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated :	56.52	6.39	12.68	12.83
Found :	56.63	6.57	12.80	12.62

5 **PHARMACOLOGICAL STUDY OF COMPOUNDS OF THE INVENTION****EXAMPLE 76 : Inhibition of activated protein C and of coagulation and fibrinolysis
serine proteases**

In order to assess *in vitro* the inhibitory activity of products of the invention on purified human activated protein C (Diagnostica Stago), the chromogenic substrate pyroGlu-Pro-Arg-pNA (0.39mM, S2366, Chromogenix) was added to a given amount of activated
10 protein C (2nM) previously incubated with or without the inhibitor under test (20°C, 30 minutes).

In order to assess *in vitro* the selectivity with respect to thrombin and plasmin, the same protocol was applied to purified human thrombin (0.7nM, Sigma) and to purified human
15 plasmin (2nM, Stago), using as substrates purified human fibrinogen (6μM, Enzyme Research Laboratories) and the paranitroanilide peptide <Glu-Phe-Lys-pNA (0.37mM, S2403, Chromogenix), respectively.

The inhibitors, enzymes and substrates are diluted in the same buffer (0.01mM phosphate buffer pH 7.4 containing 0.12M sodium chloride and 0.05 % bovine serum albumin in the
20 case of thrombin and 50mM TRIS-HCl buffer pH 7.4 containing 0.12M sodium chloride, 3mM calcium chloride and 0.05 % bovine serum albumin in the case of activated protein C and plasmin) and then dispensed in a volume of 50 μl onto a polystyrene microplate.

The paranitroanilide liberated or the fibrin formed by the action of the serine protease is measured spectrophotometrically at 405 nm after reacting for from 10 to 30 minutes at 20°C.

In this test the compounds of the invention are powerful inhibitors of activated protein C (the concentration of compounds inhibiting 50 % (IC_{50}) of the enzymatic activity being of the order of from 20 to 1000nM).

The compounds moreover possess very marked selectivity with respect to a fibrinolysis serine protease, plasmin, and a coagulation serine protease, thrombin.

By way of example, the compound of Example 1 has an IC_{50} of 820nM with respect to activated protein C, of 1100nM with respect to plasmin and of >33,000nM with respect to thrombin.

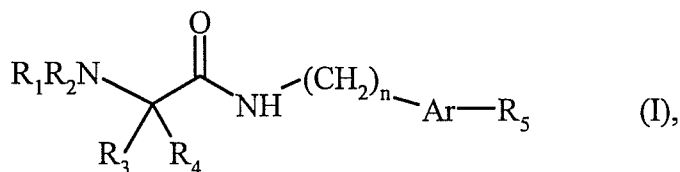
EXAMPLE 77 : Pharmaceutical composition

Formula for the preparation of 1000 tablets each containing 10 mg of active ingredient :

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

CLAIMS

1. Compound of formula (I) :



wherein :

- 5 **▮** R₁ represents an aryl group, a heteroaryl group or a linear or branched (C₁-C₆)alkyl group optionally substituted by one or more identical or different groups selected from aryl and heteroaryl, or R₁ represents a group of formula -(CO)-CR₆R₇NR₈R₉ wherein :
- 10 - R₆ represents a hydrogen atom or a group selected from aryl, heteroaryl, heterocycloalkyl, (C₃-C₈)cycloalkyl and linear or branched (C₁-C₆)alkyl optionally substituted by one or more identical or different groups selected from aryl, heteroaryl, heterocycloalkyl, (C₃-C₈)cycloalkyl and carboxy,
- 15 - R₇ represents a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,
- or R₆ and R₇ together form a (C₃-C₈)cycloalkyl group,
- R₈ represents a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,
- and R₉ represents a hydrogen atom or a group R'₉ wherein R'₉ represents a group selected from :
- 20 • linear or branched (C₁-C₆)alkyl optionally substituted by an aryl, carboxy, linear or branched (C₁-C₆)alkoxy-carbonyl or carbamoyl group,
- aryl,
- heteroaryl,
- 25 • and sulphonyl substituted by a group selected from (C₃-C₈)cycloalkyl, heterocycloalkyl, aryl (optionally substituted by an aryloxy or heteroaryloxy group), and linear or branched (C₁-C₆)alkyl optionally substituted by an aryl, heteroaryl, (C₃-C₈)cycloalkyl or heterocycloalkyl group,

- R₂ represents a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,
- R₃ represents a hydrogen atom or a linear or branched (C₁-C₆)alkyl group optionally substituted by one or more aryl groups,
- R₄ represents a saturated or unsaturated, 7- to 15-membered bicyclic system or a linear
5 or branched (C₁-C₆)alkyl group optionally substituted by one or more aryl groups,
or R₃ and R₄, together with the carbon atom carrying them, form a saturated or
unsaturated, 3- to 18-membered, mono-, bi- or tri-cyclic system optionally containing
one or more hetero atoms selected from O, S and N and optionally substituted by one
or more identical or different groups selected from halogen, linear or branched
10 (C₁-C₆)alkyl, linear or branched (C₁-C₆)alkoxy, hydroxy, linear or branched
(C₁-C₆)trihaloalkyl, amino (optionally substituted by one or more linear or branched
(C₁-C₆)alkyl groups) and carboxy,
- n represents zero, 1 or 2,
- Ar represents an aryl or heteroaryl group,
- 15 ➤ R₅ represents a group selected from amino, guanidino, cyano and amidino optionally
substituted by a hydroxy or linear or branched (C₁-C₆)alkoxy-carbonyl group,

its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,

a heterocycloalkyl group being understood to mean a 3- to 8-membered, saturated
monocyclic group containing one, two or three hetero atoms selected from oxygen,
20 nitrogen and sulphur, it being understood that the heterocycle may optionally be
substituted by one or more identical or different groups selected from halogen, linear or
branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)alkoxy, oxo, hydroxy, linear or branched
(C₁-C₆)trihaloalkyl and amino (optionally substituted by one or more linear or branched
(C₁-C₆)alkyl groups),

an aryl group being understood to mean phenyl, biphenyl or naphthyl, each of those groups being optionally substituted by one or more identical or different groups selected from halogen, linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)alkoxy, hydroxy, linear or branched (C₁-C₆)trihaloalkyl, amino (optionally substituted by one or more linear or branched (C₁-C₆)alkyl groups) and carboxy,

and a heteroaryl group being understood to mean a mono- or bi-cyclic, 5- to 12-membered, aromatic group containing one, two or three hetero atoms selected from oxygen, nitrogen and sulphur, it being understood that the heteroaryl may optionally be substituted by one or more identical or different groups selected from halogen, linear or branched (C₁-C₆)alkyl, hydroxy, linear or branched (C₁-C₆)alkoxy, trihalomethyl and amino (optionally substituted by one or more linear or branched (C₁-C₆)alkyl groups).

2. Compound of formula (I) according to claim 1, wherein R₁ represents a group of formula -(CO)-CHR₆NHR₉ wherein R₆ represents a (C₃-C₈)cycloalkyl group, or linear or branched (C₁-C₆)alkyl optionally substituted by a (C₃-C₈)cycloalkyl group, and R₉ represents a group selected from linear or branched (C₁-C₆)alkyl optionally substituted by a carboxy, linear or branched (C₁-C₆)alkoxy-carbonyl or carbamoyl group, and linear or branched (C₁-C₆)alkylsulphonyl substituted by a (C₃-C₈)cycloalkyl group.
3. Compound of formula (I) according to either claim 1 or claim 2, wherein R₃ and R₄, which may be the same or different, each represent a linear or branched (C₁-C₆)alkyl group.
4. Compound of formula (I) according to either claim 1 or claim 2, wherein R₃ and R₄ together form an optionally substituted indanyl group or a cyclopentapyridyl group.
5. Compound of formula (I) according to any one of claims 1 to 4, wherein n represents 1.

6. Compound of formula (I) according to any one of claims 1 to 5, wherein Ar represents a phenyl group and R₅ represents an amidino group optionally substituted by a hydroxy group.
7. Compound of formula (I) according to any one of claims 1 to 5, wherein Ar represents a pyridyl group substituted by a methyl group and R₅ represents an amino group.
8. Compound of formula according to claim 1, wherein R₁ represents a group of formula $-(CO)-CHR_6NR_8R_9$ wherein R₆, R₈ and R₉ are as defined for formula (I) and the centre of asymmetry composed of the carbon atom carrying the substituents R₆ and NR₈R₉ is of the R configuration.
9. Compound of formula (I) according to claim 1, which is {[(1R)-2-({2-[(4-amidinobenzyl)-amino)-carbonyl]-indan-2-yl}-amino)-1-cyclohexyl-2-oxoethyl]-amino}acetic acid, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid.
10. Compound of formula (I) according to claim 1, which is ethyl {[(1R)-2-({2-[(4-amino-(hydroxyimino)-methyl)-benzyl]-amino)-carbonyl]-indan-2-yl}-amino)-1-cyclohexyl-2-oxoethyl]-amino}-acetate, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid.
11. Compound of formula (I) according to claim 1, which is {[(1R)-2-({2-[(4-amidinobenzyl)-amino)-carbonyl]-indan-2-yl}-amino)-1-cyclohexylmethyl-2-oxoethyl]-amino}acetic acid, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid.
12. Compound of formula (I) according to claim 1, which is {[(1R)-2-({2-[(4-amidinobenzyl)-amino)-carbonyl]-indan-2-yl}-amino)-1-isopropyl-2-oxoethyl]-amino}acetic acid, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid.

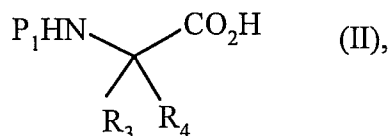
13. Compound of formula (I) according to claim 1, which is N-(4-amidinobenzyl)-2-
 [((2R)-2-cyclohexyl-2-{{(cyclohexylmethyl)-sulphonyl}-amino}-ethanoyl)-amino]-2-
 indancarboxamide, its optical isomers, and also addition salts thereof with a
 pharmaceutically acceptable acid.

14. Compound of formula (I) according to claim 1, which is N-(4-amidinobenzyl)-2-
 [((2R)-2-{{(cyclohexylmethyl)-sulphonyl}-amino}-3-methylbutanoyl)-amino]-2-indan-
 carboxamide, its optical isomers, and also addition salts thereof with a
 pharmaceutically acceptable acid.

15. Compound of formula (I) according to claim 1, which is N-(4-amidinobenzyl)-2-
 [((2R)-2-{{(isobutylsulphonyl)-amino}-3-methylbutanoyl)-amino]-2-indancarboxamide,
 its optical isomers, and also addition salts thereof with a pharmaceutically acceptable
 acid.

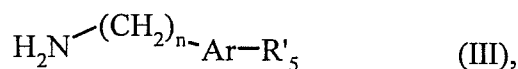
16. Compound of formula (I) according to claim 1, which is N-(4-amidinobenzyl)-6-
 [((2R)-2-{{(cyclohexylmethyl)-sulphonyl}-amino}-3-methylbutanoyl)-amino]-6,7-
 dihydro-5H-cyclopenta[b]pyridine-6-carboxamide, its optical isomers, and also
 addition salts thereof with a pharmaceutically acceptable acid.

17. Process for the preparation of compounds of formula (I) according to claim 1,
 characterised in that a compound of formula (II) :



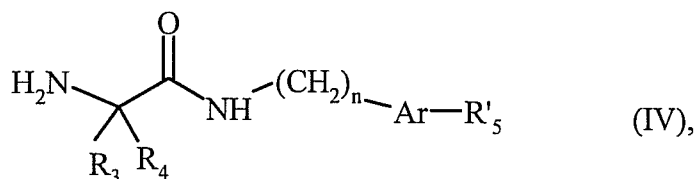
wherein R₃ and R₄ are as defined for formula (I) and P₁ represents a protecting group for
 the amino function,

is reacted, under peptide coupling conditions, with a compound of formula (III) :



wherein n and Ar are as defined for formula (I) and R'_5 represents a group selected from amino, guanidino and amidino optionally substituted by a hydroxy or linear or branched (C_1-C_6) alkoxy-carbonyl group,

to yield, after deprotection, the compound of formula (IV) :



wherein R_3 , R_4 , n , Ar and R'_5 are as defined hereinbefore,

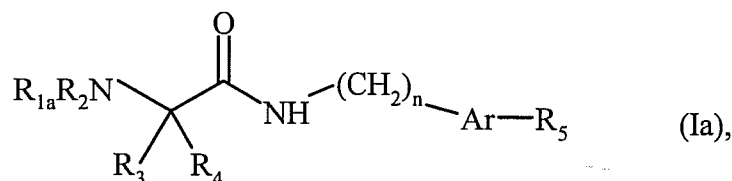
which is reacted :

- either, when it is desired to obtain compounds of formula (I) wherein R_1 represents an aryl group, a heteroaryl group or a linear or branched (C_1-C_6) alkyl group which is optionally substituted, with a compound of formula (V):



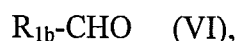
wherein R_{1a} represents an aryl group, a heteroaryl group or a linear or branched (C_1-C_6) alkyl group optionally substituted by one or more groups selected from aryl and heteroaryl, and Z represents a leaving group such as, for example, a halogen atom or a tosylate, mesylate or triflate group,

to yield, after optional deprotection, the compounds of formula (Ia), a particular case of the compounds of formula (I) :

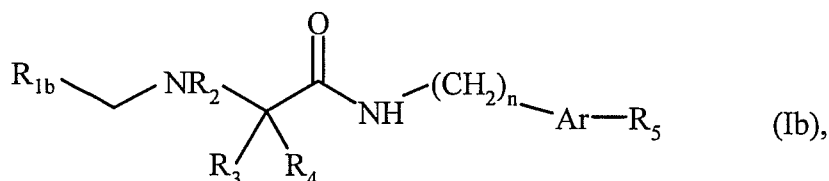


wherein R_{1a} , R_2 , R_3 , R_4 , n , Ar and R_5 are as defined hereinbefore,

- or, when it is desired to obtain compounds of formula (I) wherein R_1 represents an optionally substituted, linear or branched (C_2-C_6) alkyl group, with a compound of formula (VI), under reductive amination conditions :

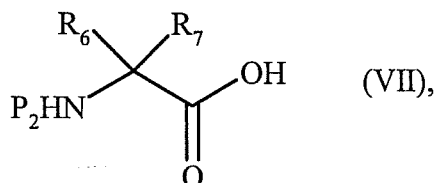


wherein R_{1b} represents a linear or branched (C_1 - C_5)alkyl group optionally substituted by one or more groups selected from aryl and heteroaryl, to yield, after optional deprotection, the compounds of formula (Ib), a particular case of the compounds of formula (I) :

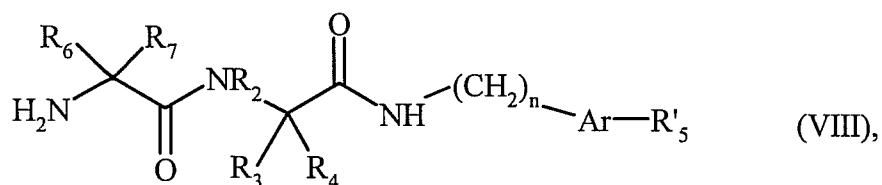


wherein R_{1b} , R_2 , R_3 , R_4 , n , Ar and R_5 are as defined hereinbefore,

- or, when it is desired to obtain compounds of formula (I) wherein R_1 represents a group of formula $-(CO)-CR_6R_7NR_8R_9$, wherein R_6 , R_7 , R_8 and R_9 are as defined for formula (I), with a compound of formula (VII), under peptide coupling conditions :



wherein R_6 and R_7 are as defined for formula (I) and P_2 represents a protecting group for the amino function, to yield, after deprotection, the compound of formula (VIII) :



wherein R_6 , R_7 , R_2 , R_3 , R_4 , n , Ar and R'_5 are as defined hereinbefore,

which is reacted, if desired, with a compound of formula (IX) :



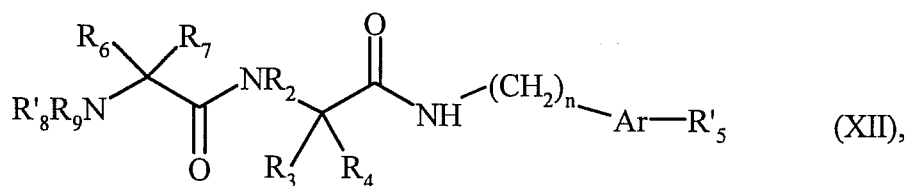
wherein R'_9 is as defined for formula (I) and Z represents a leaving group such as, for example, a halogen atom or a tosylate, mesylate or triflate group, to yield the compound of formula (X) :

which compounds of formula (VIII) or (X) are reacted, if desired, with a compound of formula (XI) :



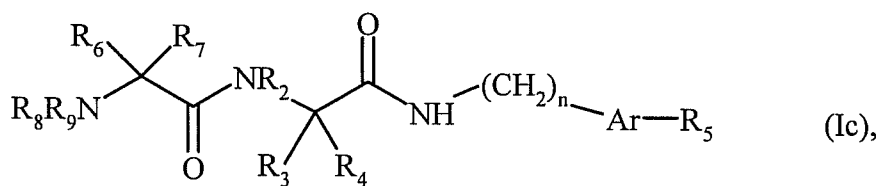
wherein R₈ represents a linear or branched (C₁-C₆)alkyl group and Z represents a leaving group such as, for example, a halogen atom or a tosylate, mesylate or triflate group,

to yield the compound of formula (XII) :



wherein R'_8 , R_6 , R_7 , R_2 , R_3 , R_4 , n , Ar and R'_5 are as defined hereinbefore and R_9 is as defined for formula (I),

which compounds of formula (VIII), (X) or (XII) are optionally deprotected to yield the compound of formula (Ic), a particular case of the compounds of formula (I) :



wherein R₈, R₉, R₆, R₇, R₂, R₃, R₄, n, Ar and R₅ are as defined hereinbefore,

the compounds of formulae (Ia), (Ib) and (Ic) constituting the totality of the compounds of formula (I), which are purified, if necessary, according to a conventional purification technique, are separated, if desired, into their isomers according to a conventional separation technique and are converted, if desired, into their addition salts with a pharmaceutically acceptable acid.

18. Pharmaceutical composition comprising as active ingredient a compound according to any one of claims 1 to 16, in combination with one or more inert, non-toxic and pharmaceutically acceptable carriers.
- 5 19. Pharmaceutical composition according to claim 18, for use as a medicament in the treatment of any pathological condition involving activated protein C.
20. Pharmaceutical composition according to claim 19, for use as a medicament in the treatment of disorders involving a dysfunction of haemostasis requiring procoagulant treatment, including all haemorrhagic clinical situations such as von Willebrand's disease or haemophilia A or B.
- 10 21. Pharmaceutical composition according to claim 19, for use as an antidote medicament in antithrombotic treatments such as anticoagulant, antiplatelet and fibrinolytic treatments.