

(I)

- ◆ Het represents a heteroaryl group,
- ◆ T represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group optionally substituted by one to three halogen atoms, an alkyl(C₁-C₄)-NR₁R₂ group or an alkyl(C₁-C₄)-OR₆ group,
- ◆ R₁ and R₂ independently of one another represent a hydrogen atom or a linear or branched (C₁-C₆)alkyl group, or R₁ and R₂ form with the nitrogen atom carrying them a heterocycloalkyl group,
- ◆ R₃ represents a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₂-C₆)alkenyl group, a linear or branched (C₂-C₆)alkynyl group, a cycloalkyl group, a (C₃-C₁₀)cycloalkyl-(C₁-C₆)alkyl group wherein the alkyl group may be linear or branched, a heterocycloalkyl group, an aryl group or a heteroaryl group, it being understood that one or more carbon atoms of the groups defined hereinbefore, or carbon atoms of their possible substituents, may be deuterated,
- ◆ R₄ represents an aryl, heteroaryl, cycloalkyl or linear or branched (C₁-C₆)alkyl group, it being understood that one or more carbon atoms of the groups defined

hereinbefore, or carbon atoms of their possible substituents, may be deuterated,

- ◆ R_5 represents a hydrogen atom or a halogen atom, a linear or branched (C_1-C_6) alkyl group, or a linear or branched (C_1-C_6) alkoxy group,
- ◆ R_6 represents a hydrogen atom or a linear or branched (C_1-C_6) alkyl group,
- ◆ R_7 represents a group selected from R'_7 , R'_7-CO- , $R'_7-O-CO-$, $NR'_7R''_7-CO-$, R'_7-SO_2- , $R'_7-NR''_7-SO_2-$ wherein R'_7 et R''_7 independently of one another represent a hydrogen atom, a linear or branched (C_1-C_6) alkyl group, a linear or branched (C_2-C_6) alkenyl group, a linear or branched (C_2-C_6) alkynyl group, a cycloalkyl, a heterocycloalkyl, an aryl group, or a heteroaryl,
- ◆ R_8 and R_9 represent, independently of one another, an oxo group or a halogen atom,
- ◆ p and p' are, independently of one another, integers equal to 0, 1, 2, 3 or 4,
- ◆ q and q' are, independently of one another, integers equal to 1, 2 or 3,

it being understood that when compound of formula (I) contains a hydroxy group, this latter group may be optionally substituted by one of the following groups: $-PO(OM)(OM')$, $-PO(OM)(O^-M_1^+)$, $-PO(O^-M_1^+)(O^-M_2^+)$, $-PO(O^-)(O^-)M_3^{2+}$, $-PO(OM)(O[CH_2CH_2O]_nCH_3)$, or $-PO(O^-M_1^+)(O[CH_2CH_2O]_nCH_3)$, wherein M and M' independently of one another represent a hydrogen atom, a linear or branched (C_1-C_6) alkyl group, a linear or branched (C_2-C_6) alkenyl group, a linear or branched (C_2-C_6) alkynyl group, a cycloalkyl or a heterocycloalkyl, both of them being composed of from 5 to 6 ring members, while M_1^+ and M_2^+ independently of one another represent a pharmaceutically acceptable monovalent cation, M_3^{2+} represents a pharmaceutically acceptable divalent cation and n is an integer comprised between 1 to 5,

it also being understood that:

- "aryl" means a phenyl, naphthyl, biphenyl or indenyl group,
- "heteroaryl" means any mono- or bi-cyclic group composed of from 5 to 10 ring members, having at least one aromatic moiety and containing from 1 to 4 hetero atoms selected from oxygen, sulphur and nitrogen (including quaternary nitrogens),
- "cycloalkyl" means any mono- or bi-cyclic non-aromatic carbocyclic group containing from 3 to 10 ring members, which may include fused, bridged or spiro ring systems,

- "heterocycloalkyl" means any mono- or bi-cyclic non-aromatic carbocyclic group, composed of from 3 to 10 ring members, and containing from one to 3 hetero atoms selected from oxygen, sulphur, SO, SO₂ and nitrogen, it being understood that bicyclic group may be fused or spiro type,

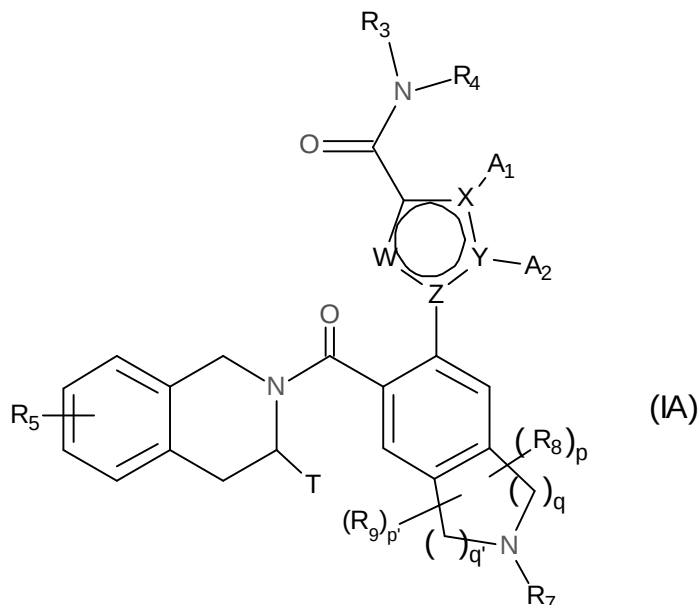
it being possible for the aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups so defined and the alkyl, alkenyl, alkynyl, alkoxy, to be substituted by from 1 to 3 groups selected from: linear or branched (C₁-C₆)alkyl ; linear or branched (C₂-C₆)alkenyl group; linear or branched (C₂-C₆)alkynyl group; (C₃-C₆)spiro; linear or branched (C₁-C₆)alkoxy; (C₁-C₆)alkyl-S-; hydroxyl; oxo (or *N*-oxide where appropriate); nitro; cyano; -COOR'; -OCOR'; -NR'R"; R'CONR''-; NR'R''CO-; linear or branched (C₁-C₆)polyhaloalkyl; trifluoromethoxy; (C₁-C₆)alkylsulphonyl; halogen; aryl; heteroaryl; aryloxy; arylthio; cycloalkyl or heterocycloalkyl, it being understood that R' and R" independently of one another represent a hydrogen atom, a linear or branched (C₁-C₆)alkyl group or an unsubstituted aryl group,

wherein said linear or branched (C₁-C₆)alkyl groups, said linear or branched (C₂-C₆)alkenyl group, said linear or branched (C₂-C₆)alkynyl group, said linear or branched (C₁-C₆)alkoxy, said aryl, said heteroaryl, said aryloxy, said arylthio, said cycloalkyl, and said heterocycloalkyl are optionally substituted by from 1 to 3 groups selected from the substituents of the aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups and the alkyl, alkenyl, alkynyl, alkoxy defined above, namely:

linear or branched (C₁-C₆)alkyl; linear or branched (C₂-C₆)alkenyl group; linear or branched (C₂-C₆)alkynyl group; (C₃-C₆)spiro; linear or branched (C₁-C₆)alkoxy; (C₁-C₆)alkyl-S-; hydroxyl; oxo (or *N*-oxide where appropriate); nitro; cyano; -COOR'; -OCOR'; -NR'R"; R'CONR''-; NR'R''CO-; linear or branched (C₁-C₆)polyhaloalkyl; trifluoromethoxy; (C₁-C₆)alkylsulphonyl; halogen; aryl; heteroaryl; aryloxy; arylthio; cycloalkyl or heterocycloalkyl, it being understood that R' and R" independently of one another represent a hydrogen atom, a linear or branched (C₁-C₆)alkyl group or an unsubstituted aryl group,

its enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

2. Compound of formula (IA) according to claim 1:



wherein:

- ◆ W represents a C-A₃ group or a nitrogen atom,
- ◆ X, Y and Z represent a carbon atom or a nitrogen atom, it being understood that only one of them represent a nitrogen atom, while the two others represent carbon atoms,
- ◆ A₁, A₂ and A₃ independently of one another represent a hydrogen atom or a halogen atom, a linear or branched (C₁-C₆)polyhaloalkyl group, a linear or branched (C₁-C₆)alkyl group or a cycloalkyl group,
or A₃ represents a hydrogen atom (when W represents a C-A₃ group) while A₁ and A₂ form together with the atoms carrying them an optionally substituted aromatic or non-aromatic ring Cy, composed of 5, 6 or 7 ring members, which may contain from one to 4 hetero atoms selected independently from oxygen, sulphur and nitrogen, it being understood that the nitrogen in question may be substituted by a group representing a hydrogen atom, a linear or branched (C₁-C₆)alkyl group or a group -C(O)-O-Alk wherein Alk is a linear or branched (C₁-C₆)alkyl group,
or W represents a nitrogen atom while A₁ and A₂ form together with the atoms carrying them an optionally substituted aromatic or non-aromatic ring Cy,

composed of 5, 6 or 7 ring members, which may contain from one to 4 hetero atoms selected independently from oxygen, sulphur and nitrogen, it being understood that the nitrogen in question may be substituted by a group representing a hydrogen atom, a linear or branched (C₁-C₆)alkyl group or a group -C(O)-O-Alk wherein Alk is a linear or branched (C₁-C₆)alkyl group,

- ◆ T represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group optionally substituted by one to three halogen atoms, an alkyl(C₁-C₄)-NR₁R₂ group or an alkyl(C₁-C₄)-OR₆ group,
- ◆ R₁ and R₂ independently of one another represent a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,
or R₁ and R₂ form with the nitrogen atom carrying them a heterocycloalkyl,
- ◆ R₃ represents a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₂-C₆)alkenyl group, a linear or branched (C₂-C₆)alkynyl group, a cycloalkyl group, a (C₃-C₁₀)cycloalkyl-(C₁-C₆)alkyl group wherein the alkyl group may be linear or branched, a heterocycloalkyl group, an aryl group or a heteroaryl group, it being understood that one or more carbon atoms of the groups defined hereinbefore, or carbon atoms of their possible substituents, may be deuterated,
- ◆ R₄ represents an aryl, heteroaryl, cycloalkyl or linear or branched (C₁-C₆)alkyl group, it being understood that one or more carbon atoms of the groups defined hereinbefore, or carbon atoms of their possible substituents, may be deuterated,
- ◆ R₅ represents a hydrogen atom or a halogen atom, a linear or branched (C₁-C₆)alkyl group, or a linear or branched (C₁-C₆)alkoxy group,
- ◆ R₆ represents a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,
- ◆ R₇ represents a group selected from R'₇, R'₇-CO-, R'₇-O-CO-, NR'₇R''₇-CO-, R'₇-SO₂-, R'₇-NR''₇-SO₂- wherein R'₇ et R''₇ independently of one another represent a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₂-C₆)alkenyl group, a linear or branched (C₂-C₆)alkynyl group, a cycloalkyl, a heterocycloalkyl, an aryl group, or a heteroaryl,
- ◆ R₈ and R₉ represent, independently of one another, an oxo group or a halogen atom,
- ◆ p and p' are, independently of one another, integers equal to 0, 1, 2, 3 or 4,
- ◆ q and q' are, independently of one another, integers equal to 1, 2 or 3,

it being understood that when compound of formula (I) contains a hydroxy group, this latter group may be optionally substituted by one of the following groups: $-\text{PO}(\text{OM})(\text{OM}')$, $-\text{PO}(\text{OM})(\text{O}^-\text{M}_1^+)$, $-\text{PO}(\text{O}^-\text{M}_1^+)(\text{O}^-\text{M}_2^+)$, $-\text{PO}(\text{O}^-)(\text{O}^-)\text{M}_3^{2+}$, $-\text{PO}(\text{OM})(\text{O}[\text{CH}_2\text{CH}_2\text{O}]_n\text{CH}_3)$, or $-\text{PO}(\text{O}^-\text{M}_1^+)(\text{O}[\text{CH}_2\text{CH}_2\text{O}]_n\text{CH}_3)$, wherein M and M' independently of one another represent a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₂-C₆)alkenyl group, a linear or branched (C₂-C₆)alkynyl group, a cycloalkyl or a heterocycloalkyl, both of them being composed of from 5 to 6 ring members, while M₁⁺ and M₂⁺ independently of one another represent a pharmaceutically acceptable monovalent cation, M₃²⁺ represents a pharmaceutically acceptable divalent cation and n is an integer comprised between 1 to 5,

it also being understood that:

- "aryl" means a phenyl, naphthyl, biphenyl or indenyl group,
- "heteroaryl" means any mono- or bi-cyclic group composed of from 5 to 10 ring members, having at least one aromatic moiety and containing from 1 to 4 hetero atoms selected from oxygen, sulphur and nitrogen (including quaternary nitrogens),
- "cycloalkyl" means any mono- or bi-cyclic non-aromatic carbocyclic group containing from 3 to 10 ring members, which may include fused, bridged or spiro ring systems,
- "heterocycloalkyl" means any mono- or bi-cyclic non-aromatic carbocyclic group, composed of from 3 to 10 ring members, and containing from one to 3 hetero atoms selected from oxygen, sulphur, SO, SO₂ and nitrogen, it being understood that bicyclic group may be fused or spiro type,

it being possible for the aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups so defined and the alkyl, alkenyl, alkynyl, alkoxy, to be substituted by from 1 to 3 groups selected from: linear or branched (C₁-C₆)alkyl; linear or branched (C₂-C₆)alkenyl group; linear or branched (C₂-C₆)alkynyl group; (C₃-C₆)spiro; optionally substituted linear or branched (C₁-C₆)alkoxy;

(C₁-C₆)alkyl-S-; hydroxyl; oxo (or N-oxide where appropriate); nitro; cyano; -COOR'; -OCOR'; -NR'R''; R'CONR''-; NR'R''CO-; linear or branched (C₁-C₆)polyhaloalkyl; trifluoromethoxy; (C₁-C₆)alkylsulphonyl; halogen; aryl; heteroaryl; aryloxy; arylthio;

cycloalkyl or heterocycloalkyl, it being understood that R' and R" independently of one another represent a hydrogen atom, a linear or branched (C₁-C₆)alkyl group or an unsubstituted aryl group,

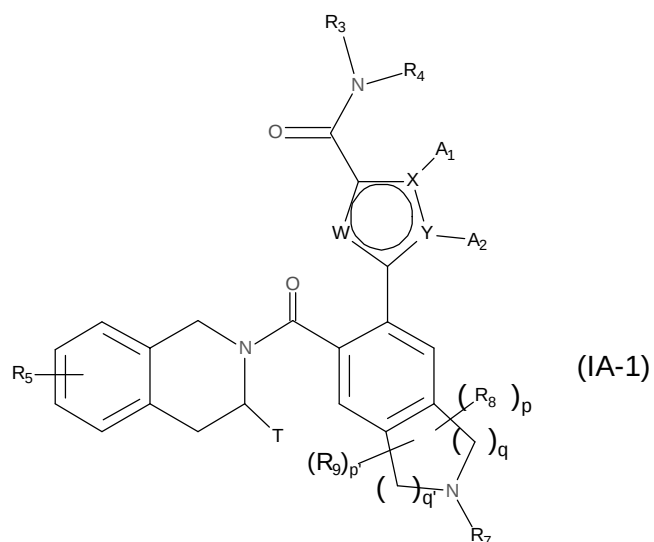
wherein said linear or branched (C₁-C₆)alkyl groups, said linear or branched (C₂-C₆)alkenyl group, said linear or branched (C₂-C₆)alkynyl group, said linear or branched (C₁-C₆)alkoxy, said aryl, said heteroaryl, said aryloxy, said arylthio, said cycloalkyl, and said heterocycloalkyl are optionally substituted by from 1 to 3 groups selected from the substituents of the aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups and the alkyl, alkenyl, alkynyl, alkoxy defined above, namely:

linear or branched (C₁-C₆)alkyl; linear or branched (C₂-C₆)alkenyl group; linear or branched (C₂-C₆)alkynyl group; (C₃-C₆)spiro; linear or branched (C₁-C₆)alkoxy; (C₁-C₆)alkyl-S-; hydroxyl; oxo (or *N*-oxide where appropriate); nitro; cyano; -COOR'; -OCOR'; -NR'R"; R'CONR''-; NR'R''CO-; linear or branched (C₁-C₆)polyhaloalkyl; trifluoromethoxy; (C₁-C₆)alkylsulphonyl; halogen; aryl; heteroaryl; aryloxy; arylthio; cycloalkyl or heterocycloalkyl, it being understood that R' and R" independently of one another represent a hydrogen atom, a linear or branched (C₁-C₆)alkyl group or an unsubstituted aryl group,

it being possible for the Cy moiety defined in formula (I) to be substituted by from 1 to 3 groups selected from linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)polyhaloalkyl, hydroxy, linear or branched (C₁-C₆)alkoxy, COOH, NR₁'R₁" and halogen, it being understood that R₁' and R₁" have the same definitions than the groups R' and R" mentioned hereinbefore,

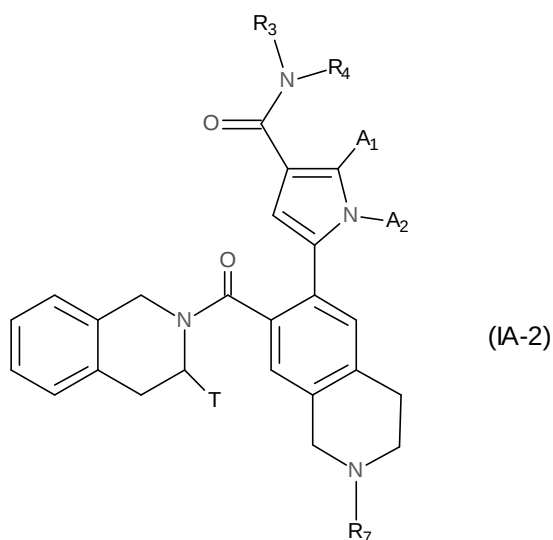
its enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

3. Compound of formula (IA-1) according to claim 1 or 2:



wherein X, Y, W, A₁, A₂, R₃, R₄, R₅, R₇, R₈, R₉, T, p, p', q and q' are as defined in claim 2, its enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

4. Compound of formula (IA-2) according to claim 1 to 3:



wherein A₁, A₂, R₃, R₄, R₇ and T are as defined in claim 2,

its enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

5. Compound of formula (I) according to any one of claims 1 to 4 wherein R₄ represents a phenyl substituted at the *para* position by a group of formula -OPO(OM)(OM'), -OPO(OM)(O⁻M₁⁺), -OPO(O⁻M₁⁺)(O⁻M₂⁺), -OPO(O⁻)(O⁻)M₃²⁺, -OPO(OM)(O[CH₂CH₂O]_nCH₃), or -OPO(O⁻M₁⁺)(O[CH₂CH₂O]_nCH₃), wherein M and M' independently of one another represent a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₂-C₆)alkenyl group, a linear or branched (C₂-C₆)alkynyl group, a cycloalkyl or a heterocycloalkyl, both of them being composed of from 5 to 6 ring members, while M₁⁺ and M₂⁺ independently of one another represent a pharmaceutically acceptable monovalent cation, M₃²⁺ represents a pharmaceutically acceptable divalent cation and n is an integer comprised between 1 to 5, it being understood that the phenyl group may be optionally substituted by one or more halogen atoms.

6. Compound of formula (I) according to any one of claims 1 to 5 wherein Het represents one of the following groups: 5,6,7,8-tetrahydroindolizine, indolizine or 1,2-dimethyl-1*H*-pyrrole.

7. Compound of formula (I) according to any one of claims 1 to 6 wherein q=1 and q'=1.

8. Compound of formula (I) according to any one of claims 1 to 6 wherein q=2 and q'=1.

9. Compound of formula (I) according to any one of claims 1 to 8 wherein T represents a hydrogen atom, a methyl group, a (morpholin-4-yl)methyl group, a 3-(morpholin-4-yl)propyl group, a dimethylaminomethyl group, or a (4-methylpiperazin-1-yl)methyl group.

10. Compound of formula (I) according to any one of claims 1 to 9 wherein R₃ represents a linear or branched (C₁-C₆)alkyl group, an aryl group or a heteroaryl group.

11. Compound of formula (I) according to claim 1 to 10 wherein R₃ represents a group

selected from phenyl, methyl, ethyl, propyl, butyl, 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine or 5-cyano-1,2-dimethyl-1*H*-pyrrole.

12. Compound of formula (I) according to any one of claims 1 to 11 wherein R₄ represents a linear or branched (C₁-C₆)alkyl group or an aryl group.

13. Compound of formula (I) according to claim 1 to 12 wherein R₄ represents a phenyl or 4-hydroxyphenyl group.

14. Compound of formula (I) according to any one of claims 1 to 13 wherein R₇ represents a group R'₇-CO- or R'₇-O-CO-.

15. Compound of formula (I) according to any one of claims 1 to 14 wherein R'₇ represents an aryl, a cycloalkyl or an alkyl.

16. Compound of formula (I) according to claim 15 wherein R'₇ represents an naphthalene, phenyl or indole group.

17. Compound of formula (I) according to claim 16 wherein the phenyl group is substituted by a group selected from: an alkyl, cyano, alkynyl, halogen, alkoxy, or -NR'R''.

18. Compound of formula (I) according to claim 16 wherein the phenyl group is substituted by a group selected from : methyl, ethyl, methoxy, chloro, bromo, cyano, 2-dimethylaminoethylamino, ethynyl, 2-dimethylaminoethoxy, 2-(dimethylamino)ethyl(methyl)amino, or dimethylcarbamoylethyl.

19. Compound of formula (I) according to any one of claims 1 to 15 wherein p=p'=0.

20. Compound of formula (I) according to any one of claims 1 to 15 which is

- *N*-(4-Hydroxyphenyl)-*N*-methyl-3-{7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-2-(2-phenylacetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl}-5,6,7,8-tetrahydroindolizine-1-carboxamide;
- Phenyl 6-{1-[(4-hydroxyphenyl)(methyl)carbamoyl]-5,6,7,8-tetrahydroindolizin-3-

- yl}-7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
- Phenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
 - Phenyl 6-{1-[(4-hydroxyphenyl)(methyl)carbamoyl]-5,6,7,8-tetrahydroindolizin-3-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate hydrochloride;
 - Phenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate hydrochloride;
 - 4-Methylphenyl 6-{1-[(4-hydroxyphenyl)(methyl)carbamoyl]-5,6,7,8-tetrahydroindolizin-3-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate hydrochloride;
 - 2-Methylphenyl 6-{1-[(4-hydroxyphenyl)(methyl)carbamoyl]-5,6,7,8-tetrahydroindolizin-3-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
 - 4-Methoxyphenyl 6-{1-[(4-hydroxyphenyl)(methyl)carbamoyl]-5,6,7,8-tetrahydroindolizin-3-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
 - 4-Chlorophenyl 6-{1-[(4-hydroxyphenyl)(methyl)carbamoyl]-5,6,7,8-tetrahydroindolizin-3-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
 - 4-Ethylphenyl 6-{1-[(4-hydroxyphenyl)(methyl)carbamoyl]-5,6,7,8-tetrahydroindolizin-3-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
 - 4-Cyanophenyl 6-{1-[(4-hydroxyphenyl)(methyl)carbamoyl]-5,6,7,8-tetrahydroindolizin-3-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
 - 2-Methoxyphenyl 6-{1-[(4-hydroxyphenyl)(methyl)carbamoyl]-5,6,7,8-tetrahydroindolizin-3-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;

- 4-Methylphenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
- 4-Chlorophenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
- 4-Cyanophenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
- 4-Cyanophenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
- 4-{[2-(Dimethylamino)ethyl]amino}phenyl 6-{1-[(4-hydroxyphenyl)(methyl)carbamoyl]-5,6,7,8-tetrahydroindolizin-3-yl}-7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
- Phenyl 6-{4-[(4-hydroxyphenyl)(propyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
- Phenyl 6-{4-[butyl(4-hydroxyphenyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
- Phenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*S*)-3-[(4-methylpiperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
- *N*-Butyl-*N*-(4-hydroxyphenyl)-1,2-dimethyl-5-{7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-2-(2-phenylacetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl}-1*H*-pyrrole-3-carboxamide;
- 3-[2-(Dimethylamino)ethoxy]phenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
- 4-{[2-(Dimethylamino)ethyl](methyl)amino}phenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*R*)-3-methyl-1,2,3,4-

- tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
- 4-Ethynylphenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
 - Naphthalen-2-yl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
 - 1*H*-Indol-5-yl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
 - 3-[2-(Dimethylcarbamoyl)ethyl]phenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
 - 4-Bromophenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*S*)-3-(morpholin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
 - (1*r*,4*r*)-4-[[*tert*-Butoxy)carbonyl]amino}cyclohexyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
 - 4-[2-(Dimethylcarbamoyl)ethyl]phenyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate; or
 - Cyclohexyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*R*)-3-[3-(morpholin-4-yl)propyl]-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.

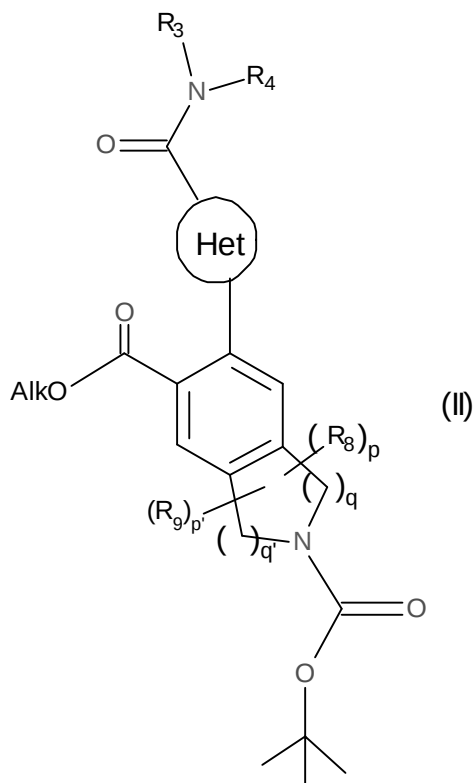
21. Compound which is selected from the following list:

- *N*-(4-Hydroxyphenyl)-*N*-methyl-3-{7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-2-{2-[4-(4-methylpiperazin-1-yl)phenyl]acetyl}-1,2,3,4-tetrahydroisoquinolin-6-yl}-5,6,7,8-tetrahydroindolizine-1-carboxamide,
- *N*-(4-Hydroxyphenyl)-*N*-methyl-3-{7-[(3*R*)-3-methyl-1,2,3,4-

tetrahydroisoquinoline-2-carbonyl]-2-(2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl}-5,6,7,8-tetrahydroindolizine-1-carboxamide,

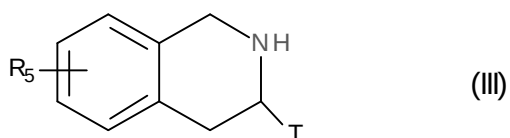
- *N*-(4-Hydroxyphenyl)-*N*-methyl-3-{7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-2-{2-[4-(morpholin-4-ylmethyl)phenyl]acetyl}-1,2,3,4-tetrahydroisoquinolin-6-yl}-5,6,7,8-tetrahydroindolizine-1-carboxamide,
- 3-[2-(2-{4-[(Dimethylamino)methyl]phenyl}acetyl)-7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinolin-6-yl]-*N*-(4-hydroxyphenyl)-*N*-methyl-5,6,7,8-tetrahydroindolizine-1-carboxamide,
- 3-[2-(2-{4-[2-(Dimethylamino)ethoxy]phenyl}acetyl)-7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinolin-6-yl]-*N*-(4-hydroxyphenyl)-*N*-methyl-5,6,7,8-tetrahydroindolizine-1-carboxamide,
- *N*-(4-Hydroxyphenyl)-*N*-methyl-3-{7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-2-{2-[3-(4-methylpiperazin-1-yl)phenyl]acetyl}-1,2,3,4-tetrahydroisoquinolin-6-yl}-5,6,7,8-tetrahydroindolizine-1-carboxamide,
- (1*r*,4*r*)-4-[[(*tert*-Butoxy)carbonyl]amino}cyclohexyl 6-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-7-[(3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.

22. Process for the preparation of a compound of formula (I) according to claim 1 characterised in that there is used as starting material the compound of formula (II):



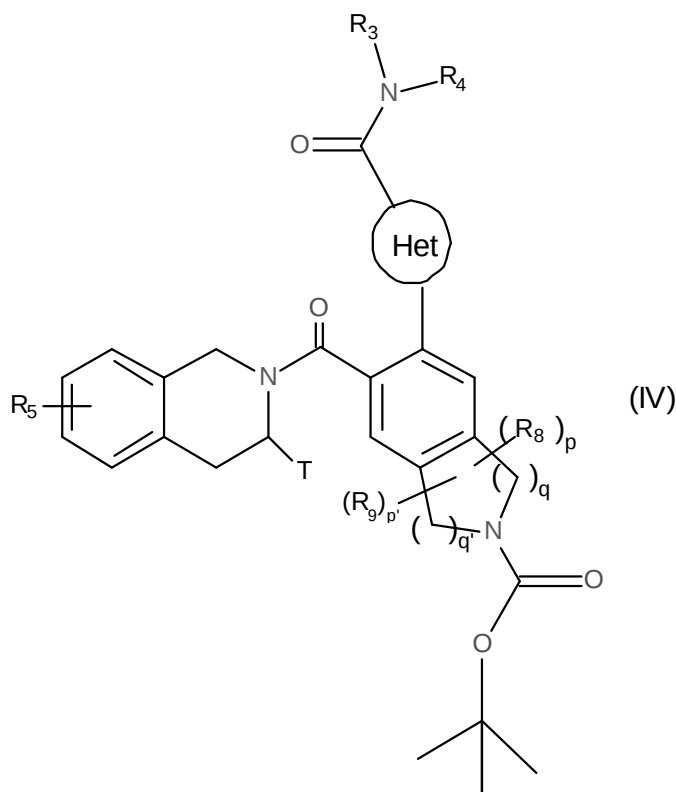
wherein Het, R₃, R₄, R₈, R₉, p, p', q and q' are as defined for formula (I) and Alk represents a linear or branched (C₁-C₆) alkyl group,

the ester function of which compound of formula (II) is hydrolysed to yield the corresponding carboxylic acid which is then subjected to peptide coupling with a compound of formula (III) :



wherein R₅ and T are as defined for formula (I),

to yield the compound of formula (IV) :



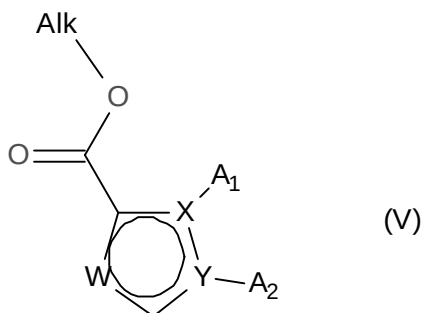
wherein Het, R₃, R₄, R₅, R₈, R₉, T, p, p', q and q' are as defined for formula (I),

compound of formula (IV) which is deprotected and subjected to an acylation or a sulfonylation reaction, and which can optionally be subjected to the action of a pyrophosphate or a phosphonate derivative in basic conditions, to yield the compound of formula (I),

which compound of formula (I) may be purified according to a conventional separation technique, which is converted, if desired, into its addition salts with a pharmaceutically acceptable acid or base and which is optionally separated into its isomers according to a conventional separation technique,

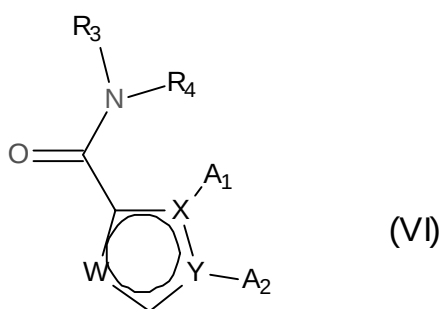
it being understood that at any moment considered appropriate during the course of the process described above, some groups of the starting reagents or of the synthesis intermediates, can be protected and subsequently deprotected, as required by the synthesis.

23. Process according for the preparation of a compound of formula (IA-1) according to claim 3 characterised in that there is used as starting material the compound of formula (V):



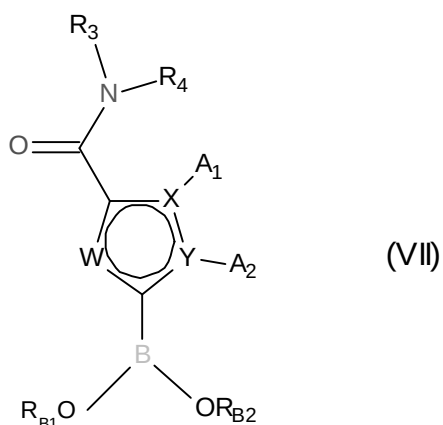
wherein X, Y, W, A₁ and A₂ are as defined for formula (IA) and Alk represents a linear or branched (C₁-C₆) alkyl group,

the ester function of which compound of formula (V) is hydrolysed to yield the carboxylic acid or the corresponding carboxylate, which may be converted into an acid derivative such as acyl chloride or the corresponding anhydride before being coupled with an amine NHR₃R₄ wherein R₃ and R₄ have the same meanings as for formula (IA), to yield the compound of formula (VI):



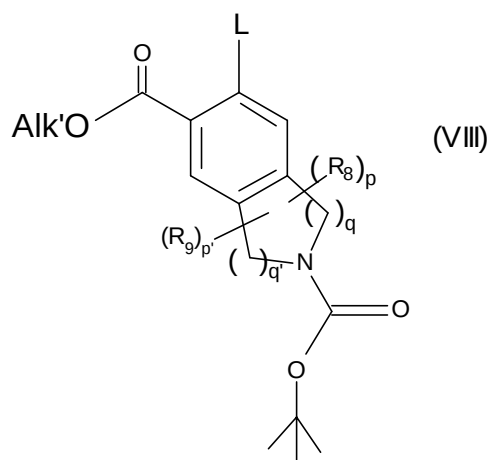
wherein X, Y, W, A₁, A₂, R₃ and R₄ are as defined for formula (IA),

compound of formula (VI) which is then halogenated and further converted into the corresponding borohydride derivative of formula (VII) :



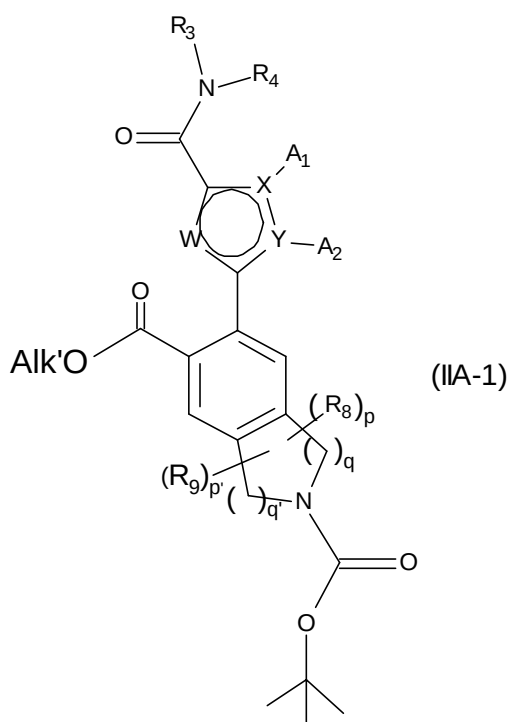
wherein X, Y, W, A₁, A₂, R₃ and R₄ are as defined for formula (IA), and R_{B1} and R_{B2} represent a hydrogen, a linear or branched (C₁-C₆) alkyl group, or R_{B1} and R_{B2} form with the oxygen atoms carrying them an optionally methylated ring,

which compound of formula (VII) is further subjected to coupling with a compound of formula (VIII):



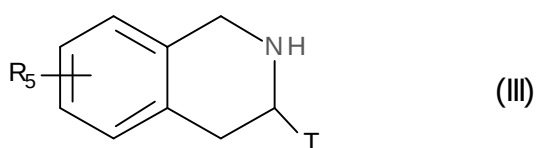
wherein R₈, R₉, p, p', q and q' are as defined for formula (IA), and Alk' represents a linear or branched (C₁-C₆) alkyl group, and L represents a leaving group selected from halogen or sulfonate,

to yield the compound of formula (IIA-1) :



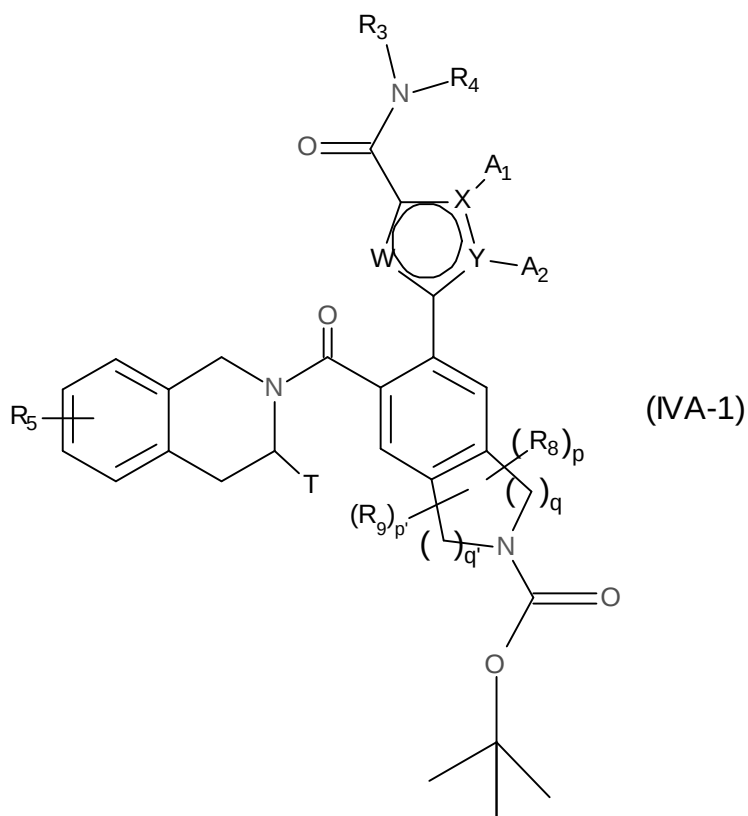
wherein X, Y, W, A₁, A₂, R₃, R₄, R₈, R₉, p, p', q, and q' are as defined for formula (IA) and Alk' is as defined previously,

the ester function of which compound of formula (IIA-1) is hydrolysed to yield the corresponding carboxylic acid which is then subjected to peptide coupling with a compound of formula (III) :



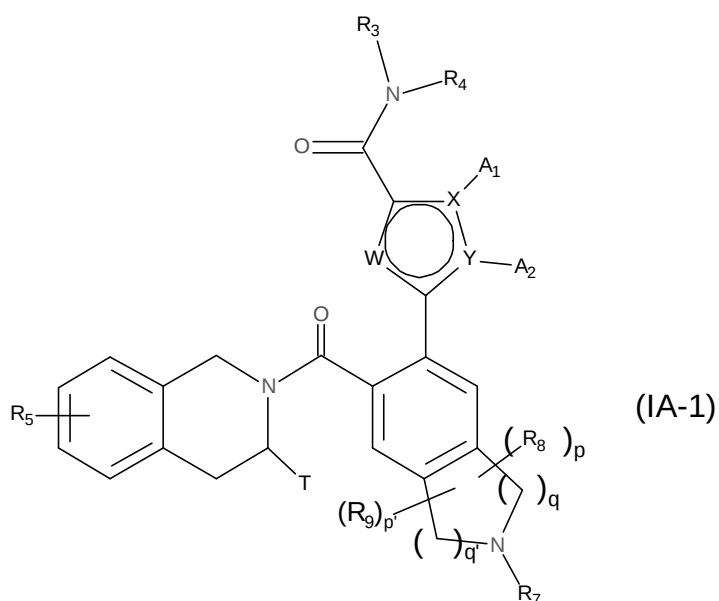
wherein R₅ and T are as defined for formula (IA),

to yield the compound of formula (IVA-1) :



wherein X, Y, W, A₁, A₂, R₃, R₄, R₅, R₈, R₉, T, p, p', q, q' are as defined for formula (IA),

compound of formula (IVA-1) which is deprotected and subjected to an acylation or a sulfonylation reaction, and which can optionally be subjected to the action of a pyrophosphate or a phosphonate derivative in basic conditions, to yield the compound of formula (IA-1):



wherein X, Y, W, A₁, A₂, R₃, R₄, R₅, R₇, R₈, R₉, T, p, p', q and q' are as defined for formula (IA),

which compound of formula (IA-1) may be purified according to a conventional separation technique, which is converted, if desired, into its addition salts with a pharmaceutically acceptable acid or base and which is optionally separated into its isomers according to a conventional separation technique,

it being understood that at any moment considered appropriate during the course of the process described above, some groups of the starting reagents or of the synthesis intermediates, can be protected and subsequently deprotected, as required by the synthesis.

24. Process according to claim 22 or 23 for the preparation of a compound of formula (I) wherein one of the groups R₃ and R₄ is substituted by a hydroxy function, characterised in that the amine NHR₃R₄ is subjected beforehand to a protection reaction of the hydroxy function prior to coupling with the carboxylic acid formed from the compound of formula (V), or with a corresponding acid derivative thereof, the resulting protected function subsequently undergoes a deprotection reaction at the last stage of the process.

25. Pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 21 or an addition salt thereof with a pharmaceutically acceptable

acid or base in combination with one or more pharmaceutically acceptable excipients.

26. Pharmaceutical composition according to claim 25 for use as pro-apoptotic agents.

27. Pharmaceutical composition according to claim 25 for use in the treatment of cancers and of auto-immune and immune system diseases.

28. Pharmaceutical composition according to claim 25 for use in the treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukaemias, cancer of the colon, oesophagus and liver, lymphoblastic leukaemias, non-Hodgkin lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer and small-cell lung cancer.

29. Use of a pharmaceutical composition according to claim 25 in the manufacture of medicaments for use as pro-apoptotic agents.

30. Use of a pharmaceutical composition according to claim 25 in the manufacture of medicaments for use in the treatment of cancers and of auto-immune and immune system diseases.

31. Use of a pharmaceutical composition according to claim 25 in the manufacture of medicaments for use in the treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukaemias, cancer of the colon, oesophagus and liver, lymphoblastic leukaemias, non-Hodgkin lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer and small-cell lung cancer.

32. Compound of formula (I) according to any one of claims 1 to 21, or an addition salt thereof with a pharmaceutically acceptable acid or base, for use in the treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukaemias, cancer of the colon, oesophagus and liver, lymphoblastic leukaemias, non-Hodgkin lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer and small-cell lung cancer.

33. Use of a compound of formula (I) according to any one of claims 1 to 21, or an addition salt thereof with a pharmaceutically acceptable acid or base, in the manufacture of medicaments for use in the treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukaemias, cancer of the colon, oesophagus and liver, lymphoblastic leukaemias, non-Hodgkin lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer and small-cell lung cancer.

34. Combination of a compound of formula (I) according to any one of claims 1 to 21 with an anti-cancer agent selected from genotoxic agents, mitotic poisons, anti-metabolites, proteasome inhibitors, kinase inhibitors and antibodies.

35. Pharmaceutical composition comprising a combination according to claim 34 in combination with one or more pharmaceutically acceptable excipients.

36. Combination according to claim 34 for use in the treatment of cancers.

37. Use of a combination according to claim 34 in the manufacture of medicaments for use in the treatment of cancers.

38. Compound of formula (I) according to any one of claims 1 to 21 for use in combination with radiotherapy in the treatment of cancers.