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**PORTER J ET AL: "Tetrahydroisoquinoline amide substituted phenyl pyrazoles as selective Bcl-2 inhibitors",**

Fortsættes ...

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 19, no. 1, 1  
janvier 2009 (2009-01-01), pages 230-233, XP025816913, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2008.10.113  
[extrait le 2008-10-31]

PORTER J ET AL: "Atropisomeric small molecule Bcl-2 ligands: Determination of bioactive conformation",  
BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 19, no. 6, 15  
mars 2009 (2009-03-15), pages 1767-1772, XP026005876, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2009.01.071  
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**Description**

The present invention relates to new indolizine compounds, to a process for their preparation and to pharmaceutical compositions containing them.

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The compounds of the present invention are new and have very valuable pharmacological characteristics in the field of apoptosis and cancerology.

Apoptosis, or programmed cell death, is a physiological process that is crucial for embryonic development and maintenance of tissue homeostasis.

Apoptotic-type cell death involves morphological changes such as condensation of the nucleus, DNA fragmentation and also biochemical phenomena such as the activation of caspases which cause damage to key structural components of the cell, so inducing its disassembly and death. Regulation of the process of apoptosis is complex and involves the activation or repression of several intracellular signalling pathways (Cory S. *et al.*, Nature Review Cancer, 2002, 2, 647-656).

Deregulation of apoptosis is involved in certain pathologies. Increased apoptosis is associated with neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and ischaemia. Conversely, deficits in the implementation of apoptosis play a significant role in the development of cancers and their chemoresistance, in auto-immune diseases, inflammatory diseases and viral infections. Accordingly, absence of apoptosis is one of the phenotypic signatures of cancer (Hanahan D. *et al.*, Cell 2000, 100, 57-70).

25

The anti-apoptotic proteins of the Bcl-2 family are associated with numerous pathologies. The involvement of proteins of the Bcl-2 family is described in numerous types of cancer, such as colorectal cancer, breast cancer, small-cell lung cancer, non-small-cell lung cancer, bladder cancer, ovarian cancer, prostate cancer, chronic lymphoid leukaemia, follicular lymphoma, myeloma, prostate cancer, etc. Overexpression of the anti-apoptotic proteins of the Bcl-2 family is involved in tumorigenesis, in resistance to chemotherapy and in the clinical prognosis of patients affected by cancer. There is, therefore, a

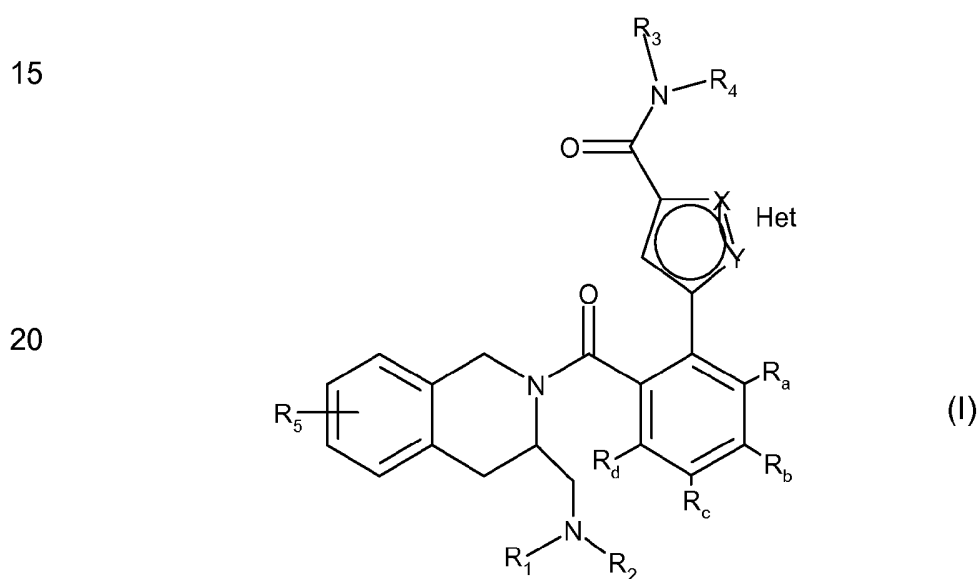
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therapeutic need for compounds that inhibit the anti-apoptotic activity of the proteins of the Bcl-2 family.

J. Porter *et al.* describe tetrahydroisoquinoline compounds as Bcl-2 inhibitors  
5 (Bio. Med. Chem. Lett. 19 (2009) 230-233 and 1767-1772).

In addition to being new, the compounds of the present invention have pro-apoptotic properties making it possible to use them in pathologies involving a defect in apoptosis, such as, for example, in the treatment of cancer and of  
10 immune and auto-immune diseases.

The present invention relates more especially to compounds of formula (I):



wherein:

♦ X and Y represent a carbon atom or a nitrogen atom, it being understood that they may not simultaneously represent two carbons atoms or two  
30 nitrogen atoms,

♦ the Het moiety of the group  represents an optionally substituted, aromatic or non-aromatic ring composed of 5, 6 or 7 ring

- members, which may contain, in addition to the nitrogen represented by X or by Y, from one to 3 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 (C<sub>1</sub>-C<sub>6</sub>)alkyl group or a group -C(O)-O-Alk wherein Alk is a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- 5 is a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- ◆ R<sub>1</sub> and R<sub>2</sub> independently of one another represent a hydrogen atom or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- or R<sub>1</sub> and R<sub>2</sub> form with the nitrogen atom carrying them a heterocycloalkyl composed of from 4 to 7 ring members, which may contain, in addition to the nitrogen atom, another hetero atom selected from oxygen, sulphur, SO<sub>2</sub> and NR wherein R represents a hydrogen atom, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group, a (C<sub>1</sub>-C<sub>6</sub>)alkylsulphonyl group, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)polyhaloalkyl group or a group -C(O)-
- 10 O-Alk wherein Alk is a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- ◆ R<sub>3</sub> represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group, a (C<sub>2</sub>-C<sub>6</sub>)alkenyl group, a (C<sub>2</sub>-C<sub>6</sub>)alkynyl group, a cycloalkyl group, a linear or branched (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)alkyl group, an aryl group or a heteroaryl group,
  - ◆ R<sub>4</sub> represents an aryl group, a heteroaryl group, a cycloalkyl group or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- 20
- ◆ R<sub>5</sub> represents a hydrogen atom or a halogen atom,
  - ◆ R<sub>a</sub>, R<sub>b</sub>, R<sub>c</sub> and R<sub>d</sub> independently of one another represent a hydrogen atom, a halogen atom, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy group, a hydroxy group, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)polyhaloalkyl group or a trifluoromethoxy group, or the substituents of one of the pairs (R<sub>a</sub>,R<sub>b</sub>), (R<sub>b</sub>,R<sub>c</sub>) or (R<sub>c</sub>,R<sub>d</sub>) form together with the carbon atoms carrying them a ring composed of from 5 to 7 ring members, which may contain from one to 3 hetero atoms selected 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 (C<sub>1</sub>-C<sub>6</sub>)alkyl group or a group -C(O)-O-Alk wherein Alk is a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group, it also being understood that one or more carbon atoms of the ring defined hereinbefore may be
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- 30

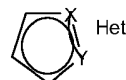
deuterated,

it being understood that:

- "aryl" means a phenyl, naphthyl, biphenyl or indenyl group,
- 5 - "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 3 hetero atoms selected from oxygen, sulphur and nitrogen,
- "cycloalkyl" means any mono- or bi-cyclic non-aromatic carbocyclic group containing from 4 to 10 ring members,

10

it being possible for the alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups so defined to be substituted by from 1 to 3 groups selected from linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)spiro, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl-S-, hydroxy, oxo (or *N*-oxide where appropriate), nitro, cyano, -COOR',  
 15 NR'R'', linear or branched (C<sub>1</sub>-C<sub>6</sub>)polyhaloalkyl, trifluoromethoxy, (C<sub>1</sub>-C<sub>6</sub>)alkylsulphonyl or halogen, it being understood that R' and R'' independently of one another represent a hydrogen atom or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,



- 20 it being possible for the Het moiety of the group defined hereinbefore to be substituted by a group selected from linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxy, NR<sub>1</sub>'R<sub>1</sub>' and halogen, it being understood that R<sub>1</sub>' and R<sub>1</sub>' have the same definitions as the groups R' and R'' mentioned hereinbefore,

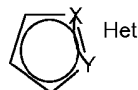
- 25 to their enantiomers and diastereoisomers, and to addition salts thereof with a pharmaceutically acceptable acid or base.

- Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid,  
 30 phosphonic 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, camphoric acid etc.

Among the pharmaceutically acceptable bases there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, triethylamine, *tert*-butylamine etc.

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The group:



advantageously represents one of the following groups: 5,6,7,8-  
 10 tetrahydroindolizine optionally substituted by a hydroxy, indolizine, 1,2,3,4-  
 tetrahydropyrrolo[1,2-*a*]pyrazine, *tert*-butyl 3,4-dihydropyrrolo[1,2-*a*]pyrazine-  
 2(1*H*)-carboxylate, 3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine, 2,3-dihydro-1*H*-  
 pyrrolizine optionally substituted by a hydroxy, 6,7,8,9-tetrahydro-5*H*-  
 pyrrolo[1,2-*a*]azepine or pyrrolo[1,2-*a*]pyrazine.

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In the preferred compounds of the invention,  $R_1$  and  $R_2$  each represents an alkyl  
 group optionally substituted by a methoxy, or  $R_1$  and  $R_2$  form with the nitrogen  
 atom carrying them a heterocycloalkyl selected from the following groups:  
 morpholine optionally substituted by one or more linear or branched ( $C_1$ -  
 20  $C_6$ )alkyl(s), oxidomorpholine, thiomorpholine 1,1-dioxide, 1,4-oxazepan, 3-  
 methoxypyrrolidine, 3,3-difluoropyrrolidine, 3-methoxyazetidine, 3-  
 fluoroazetidine, oxopiperazine or piperazine, the last two groups being  
 substituted by a linear or branched ( $C_1$ - $C_6$ )alkyl group, a linear or branched ( $C_1$ -  
 $C_6$ )polyhaloalkyl group or a methylsulphonyl group.

25

Preferably,  $R_a$  and  $R_d$  each represents a hydrogen atom and ( $R_b, R_c$ ) form  
 together with the carbon atoms carrying them a 1,3-dioxolane group in which  
 one of the carbon atoms is optionally deuterated, a 1,4-dioxane group, a 1,4-  
 dioxepan group, or  $R_a$ ,  $R_c$  and  $R_d$  each represents a hydrogen atom and  $R_b$   
 30 represents a halogen, a methyl, a methoxy, an ethoxy, a trifluoromethyl or a  
 trifluoromethoxy.

The preferred group  $R_4$  is a 4-hydroxyphenyl, 3-fluoro-4-hydroxyphenyl or 5-

hydroxypyrimidine.

In the preferred compounds, R<sub>3</sub> represents a group selected from phenyl, indole, indoline, 1,2,3,4-tetrahydroquinoline, 3,4-dihydro-2*H*-1,4-benzoxazine, indane, 1*H*-indazole, 1*H*-pyrrolo[2,3-*b*]pyridine, pyrimidine, cyclobutylmethyl, cyclopropylmethyl, 1*H*-pyrazole, pyridine, pyridazine, those groups optionally having one or more substituents selected from halogen, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, cyano and linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy.

10 The preferred compounds of the invention are listed below:

- *N*-(4-hydroxyphenyl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl]-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide,
- 3-{5-chloro-2-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide,
- *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-3-{2,2-dideuterio-6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizine carboxamide,
- *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-3-(6-[[((3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide,
- *N*-(4-hydroxyphenyl)-3-{7-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-2,3-dihydro-1,4-benzodioxin-6-yl]-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide,
- *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[((3*S*)-3-(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-1-indolizine carboxamide,
- *N*-[4-(hydroxy)phenyl]-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizine carboxamide,
- *N*-(4-hydroxyphenyl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl]-*N*-phenyl-1-indolizine



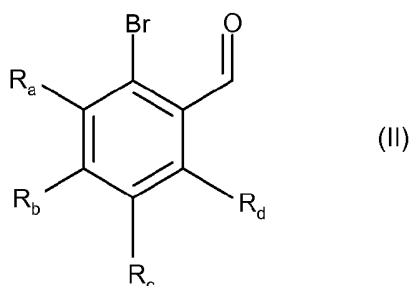
carboxamide,

- 3-{5-chloro-2-[[[(3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinoliny]carbonyl]phenyl]-N-(4-hydroxyphenyl)-N-(1-methyl-1H-indol-5-yl)-1-indolizine carboxamide,
- 5 - 6-{5-chloro-2-[[[(3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinoliny]carbonyl]phenyl]-N-(3-fluoro-4-methylphenyl)-N-(4-hydroxyphenyl)-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazine-8-carboxamide,
- 3-(5-chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-N-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide,
- 10 - N-(3-fluoro-4-methylphenyl)-N-(4-hydroxyphenyl)-3-{6-[[[(3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl]-5,6,7,8-tetrahydro-1-indolizine carboxamide,
- 15 - N-[4-(hydroxy)phenyl]-N-(1-methyl-2,3-dihydro-1H-indol-5-yl)-3-{6-[[[(3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl]-5,6,7,8-tetrahydro-1-indolizine carboxamide,
- 3-{5-chloro-2-[[[(3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinoliny]carbonyl]phenyl]-N-(4-hydroxyphenyl)-N-(1-methyl-2,3-dihydro-1H-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide,
- 20 - N-(4-hydroxyphenyl)-N-(1-methyl-1H-indol-5-yl)-3-{6-[[[(3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl]-1-indolizine carboxamide,
- 3-{5-chloro-2-[[[(3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinoliny]carbonyl]phenyl]-N-(4-hydroxyphenyl)-N-(1-methyl-2,3-dihydro-1H-indol-5-yl)-1-indolizine carboxamide,
- 25 - 6-{5-chloro-2-[[[(3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinoliny]carbonyl]phenyl]-N-(4-hydroxyphenyl)-N-phenyl-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazine-8-carboxamide,
- 30 - N-(3-fluorophenyl)-N-(4-hydroxyphenyl)-3-(6-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide,

their enantiomers and diastereoisomers, and addition salts thereof with a

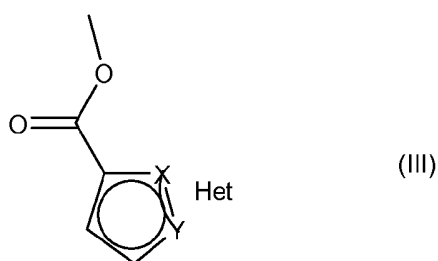
pharmaceutically acceptable acid or base.

The invention relates also to a process for the preparation of compounds of formula (I), which process is characterised in that there is used as starting  
5 material the compound of formula (II):



wherein  $R_a$ ,  $R_b$ ,  $R_c$  and  $R_d$  are as defined for formula (I),

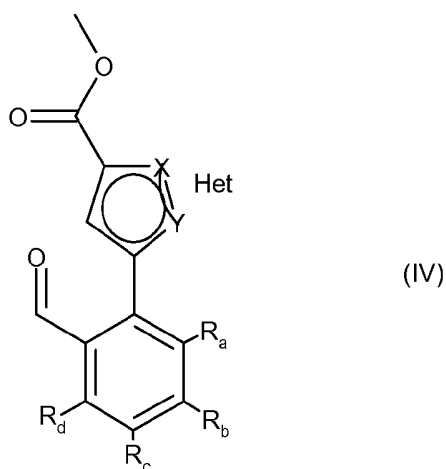
10 which compound of formula (II) is subjected to a Heck reaction, in an aqueous or organic medium, in the presence of a palladium catalyst, of a base, of a phosphine and of the compound of formula (III):



wherein the groups X, Y and Het are as defined for formula (I),

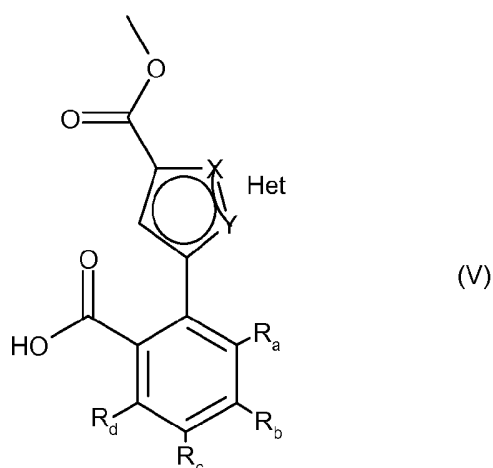
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to obtain the compound of formula (IV):



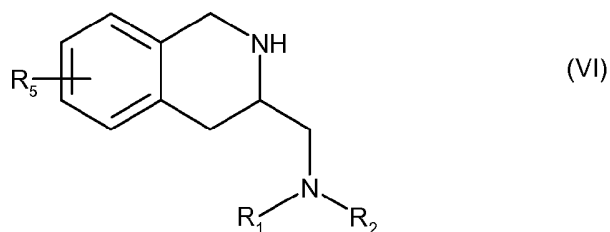
wherein  $R_a$ ,  $R_b$ ,  $R_c$ ,  $R_d$ ,  $X$ ,  $Y$  and  $Het$  are as defined for formula (I),

the aldehyde function of which compound of formula (IV) is oxidised to the  
5 carboxylic acid to form the compound of formula (V):



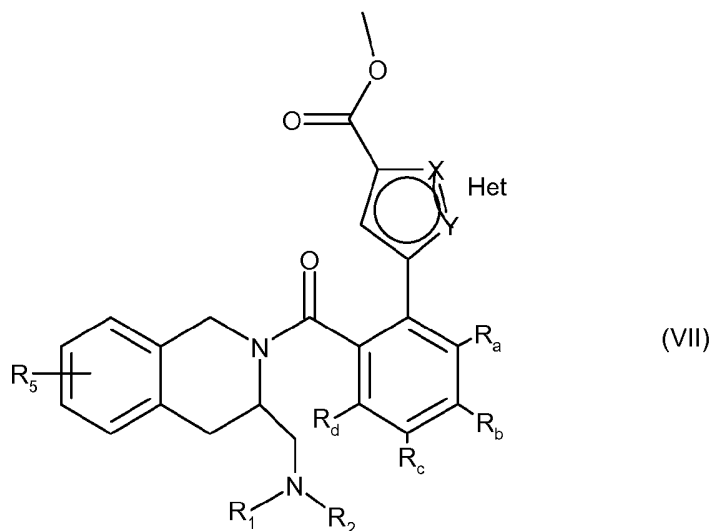
wherein  $R_a$ ,  $R_b$ ,  $R_c$ ,  $R_d$ ,  $X$ ,  $Y$  and  $Het$  are as defined for formula (I),

which compound of formula (V) is then subjected to peptide coupling with a  
10 compound of formula (VI):



wherein  $R_1$ ,  $R_2$  and  $R_5$  are as defined for formula (I),

to yield the compound of formula (VII):



wherein  $R_a$ ,  $R_b$ ,  $R_c$ ,  $R_d$ ,  $R_1$ ,  $R_2$ ,  $R_5$ ,  $X$ ,  $Y$  and  $Het$  are as defined for formula (I),

5

the ester function of which compound of formula (VII) 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  $NHR_3R_4$  wherein  $R_3$  and  $R_4$  have the same meanings as for formula (I), to yield the compound of formula (I),

10

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,

15

it being understood that, at any time considered appropriate in the course of the above-described process, certain groups (hydroxy, amino...) of the reagents or intermediates of synthesis may be protected and then deprotected according to the requirements of synthesis.

20

More especially, when one of the groups  $R_3$  or  $R_4$  of the amine  $NHR_3R_4$  is substituted by a hydroxy function, the latter may be subjected beforehand to a protection reaction prior to coupling with the carboxylic acid formed from the compound of formula (VII), or with a corresponding acid derivative thereof, the

resulting protected compound of formula (I) subsequently undergoes a deprotection reaction and is then optionally converted into one of its addition salts with a pharmaceutically acceptable acid or base.

- 5 The compounds of formulae (II), (III), (VI) and the amine  $\text{NHR}_3\text{R}_4$  are either commercially available or can be obtained by the person skilled in the art using conventional chemical reactions described in the literature.

Pharmacological study of the compounds of the invention has shown that they  
10 have pro-apoptotic properties. The ability to reactivate the apoptotic process in cancerous cells is of major therapeutic interest in the treatment of cancers and of immune and auto-immune diseases.

More especially, the compounds according to the invention will be useful in the  
15 treatment of chemo- or radio-resistant cancers, and in malignant haemopathies and small-cell lung cancer.

Among the cancer treatments envisaged there may be mentioned, without implying any limitation, cancers of the bladder, brain, breast and uterus, chronic lymphoid leukaemias, colorectal cancer, cancers of the oesophagus and liver,  
20 lymphoblastic leukaemias, follicular lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer and small-cell lung cancer.

The present invention relates also to pharmaceutical compositions comprising  
25 at least one compound of formula (I) in combination with one or more pharmaceutically acceptable excipients.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral, nasal,  
30 per- or trans-cutaneous, rectal, perlingual, ocular or respiratory administration, especially tablets or dragées, sublingual tablets, sachets, paquets, capsules, glossettes, lozenges, suppositories, creams, ointments, dermal gels, and drinkable or injectable ampoules.

The dosage varies according to the sex, age and weight of the patient, the administration route, the nature of the therapeutic indication, or of any associated treatments, and ranges from 0.01 mg to 1 g per 24 hours in one or  
5 more administrations.

Furthermore, the present invention relates also to the association of a compound of formula (I) with an anticancer agent selected from genotoxic agents, mitotic poisons, anti-metabolites, proteasome inhibitors, kinase  
10 inhibitors and antibodies, and also to pharmaceutical compositions comprising that type of association and their use in the manufacture of medicaments for use in the treatment of cancer.

The compounds of the invention may also be used in association with  
15 radiotherapy in the treatment of cancer.

The following Preparations and Examples illustrate the invention but do not limit it in any way.

20

**Preparation 1: 6-[1-(Methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]-1,3-benzodioxole-5-carboxylic acid**

**Step A: 1-Formyl-2-piperidinecarboxylic acid**

25 To a solution of 40 g of a racemic mixture of 2-piperidinecarboxylic acid (0.310 mmol) in 300 mL of formic acid at 0°C there are added dropwise 200 mL (2.15 mmol) of acetic anhydride. The whole is then stirred at ambient temperature overnight. The reaction mixture is then cooled to 0°C, hydrolysed by the addition of 250 mL of water and stirred for half an hour at 0°C before being  
30 concentrated to dryness. The oil so obtained is taken up in 200 mL of methanol and then concentrated to dryness. The title product is obtained in the form of an oil with a yield of 98%. It is used directly, without further purification, for the following step.

**<sup>1</sup>H-NMR:**  $\delta$  (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300°K): 13.0 (m, 1H OH); 8.0-8.05 (2s, 1H aldehyde); 4.9-4.5 (2d, 1H  $\alpha$  of N and COOH); 4.1-2.6 (m, 2H to  $\alpha$  of N); 2.2-1.2 (m, 6H piperidine).

5 **IR:**  $\nu$ : -OH: 2000-3000 cm<sup>-1</sup> acid;  $\nu$ : >C=O 1703 cm<sup>-1</sup> broad band.

**Step B: Methyl 5,6,7,8-tetrahydro-1-indolizinecarboxylate**

To a solution of 10 g of carboxylic acid obtained in Step A (63.6 mmol) in 65 mL of dichloroethane there are added in succession 13.4 g of tosyl chloride (70.4  
10 mmol), 11.5 mL of methyl 2-chloroacrylate (113.5 mmol) and then, dropwise, 17.8 mL of *N,N,N*-triethylamine (127.2 mmol). The reaction mixture is then refluxed for 1.5 hours. It is then brought to ambient temperature, and then 5 mL of methyl 2-chloroacrylate (48.9 mmol) and, dropwise, 9 mL of *N,N,N*-triethylamine (64 mmol) are added. The whole is heated at reflux overnight.

15 The reaction mixture is subsequently diluted with methylene chloride, washed in succession with a 1N HCl solution, a saturated NaHCO<sub>3</sub> solution and then a saturated NaCl solution until a neutral pH is obtained. The organic phase is then dried over MgSO<sub>4</sub>, filtered, concentrated to dryness, and purified by chromatography over silica gel (heptane/AcOEt gradient). The title product is  
20 obtained in the form of an oil.

**<sup>1</sup>H-NMR:**  $\delta$  (400 MHz; CDCl<sub>3</sub>; 300°K): 6.55-6.40 (d, 2H, tetrahydroindolizine); 3.91 (t, 3H methyl ester); 3.78 (s, 3H tetrahydroindolizine); 3.08 (t, 2H, tetrahydroindolizine); 1.95-1.85 (m, 4H, tetrahydroindolizine)

25 **IR:**  $\nu$ :>C=O 1692 cm<sup>-1</sup> ester

**Step C: Methyl 3-(6-formyl-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydro-1-indolizinecarboxylate**

To a solution of 6.4 g of the ester obtained in Step B (35.7 mmol) in 12 mL of  
30 *N,N*-dimethylacetamide there are added in succession 12.3 g of 6-bromo-1,3-benzodioxole-5-carbaldehyde (53.6 mmol) and 7 g of potassium acetate (71.4 mmol), and the whole is then stirred under argon for 20 minutes. 1.3 g of

palladium catalyst  $\text{PdCl}_2(\text{PPh}_3)_2$  (1.8 mmol) are then added. The reaction mixture is subsequently heated at  $130^\circ\text{C}$  for one hour before  $139\ \mu\text{L}$  of  $\text{H}_2\text{O}$  are added thereto. Heating is maintained at that same temperature overnight. The mixture is allowed to return to ambient temperature and is then diluted with  
 5 AcOEt. Animal charcoal is added (2 g per g of product) and the whole is stirred at ambient temperature for one hour and then filtered. The organic phase is then washed with water, dried over magnesium sulphate and concentrated to dryness. The crude product so obtained is purified on silica gel (heptane/AcOEt gradient). The title product is obtained in the form of an oil.

10

**$^1\text{H-NMR}$ :**  $\delta$ : (400 MHz;  $\text{dms}\text{-d}_6$ ;  $353^\circ\text{K}$ ): 9.65 (s, 1H, H aldehyde); 7.3-7.15 (2s, 2H, H aromatic); 6.45 (s, 1H tetrahydroindolizine); 6.20 (s, 2H methylenedioxy); 3.70 (s, 3H methyl ester); 3.5-4.0 (m, 2H tetrahydroindolizine); 3.05 (m, 2H tetrahydroindolizine); 1.85 (m, 4H tetrahydroindolizine)

15 **IR:**  $\nu$ :  $>\text{C}=\text{O}$   $1695\ \text{cm}^{-1}$  ester;  $\nu$ :  $>\text{C}=\text{O}$   $1674\ \text{cm}^{-1}$

**Step D: 6-[1-(Methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]-1,3-benzodioxole-5-carboxylic acid**

There is prepared a solution containing 3.37 g of the compound obtained in  
 20 Step C (10.3 mmol) in 9.3 mL of acetone and 8.8 mL (80.24 mmol) of 2-methyl-2-butene, which solution is placed at  $0^\circ\text{C}$ . There are added, dropwise, 9.3 mL of an aqueous solution containing a mixture of 3.3 g of  $\text{NaClO}_2$  (36.05 mmol) and 3.6 g of  $\text{Na}_2\text{PO}_4$  (25.75 mmol). The whole is subsequently stirred at ambient temperature for 7 hours. The reaction mixture is then concentrated in order to  
 25 remove the acetone. The solid then obtained is filtered, washed with water and then dried *in vacuo* at  $40^\circ\text{C}$  overnight. The title product is obtained in the form of a solid, which is used subsequently without being purified further.

**$^1\text{H-NMR}$ :**  $\delta$  (400 MHz;  $\text{dms}\text{-d}_6$ ;  $300^\circ\text{K}$ ): 12.10 (m, 1H, H carboxylic acid); 7.40-  
 30 6.88 (2s, 2H, H aromatic); 6.20 (s, 1H, H tetrahydroindolizine); 6.18 (s, 2H, H methylenedioxy); 3.70 (s, 3H, methyl ester); 3.55 (t, 2H tetrahydroindolizine); 3.00 (t, 2H tetrahydroindolizine); 1.80 (m, 4H, H tetrahydroindolizine)



IR:  $\nu$ : -OH: 3000-2000  $\text{cm}^{-1}$  acid;  $\nu$ :  $\text{>C=O}$  1686-1676  $\text{cm}^{-1}$  ester+acid;  $\nu$ :  $\text{>C=C<}$  1608  $\text{cm}^{-1}$

**Preparation 2: 4-Bromo-2-[1-(methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]benzoic acid**

The procedure is as in the process of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 2,4-dibromobenzaldehyde. There is obtained a mixture of two regioisomers, which are separated by chromatography.

10

**Preparation 3: 4-Chloro-2-[1-(methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]benzoic acid**

The procedure is as in the process of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 2-bromo-4-chlorobenzaldehyde.

15

**Preparation 4: 4-Fluoro-2-[1-(methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]benzoic acid**

The procedure is as in the process of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 2-bromo-4-fluorobenzaldehyde.

20

**Preparation 5: 8-[1-(Methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]-3,4-dihydro-2H-1,5-benzodioxepine-7-carboxylic acid**

The procedure is as in the process of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 8-bromo-3,4-dihydro-2H-1,5-benzodioxepine-7-carbaldehyde.

25

**Preparation 6: 4-Methoxy-2-[1-(methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]benzoic acid**

The procedure is as in the process of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 2-bromo-4-methoxybenzaldehyde.

30

**Preparation 7: 7-[1-(Methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid**

The procedure is as in the process of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 7-bromo-2,3-dihydro-1,4-benzodioxine-6-carbaldehyde.

**Preparation 8: 4-Ethoxy-2-[1-(methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]benzoic acid**

The procedure is as in the process of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 2-bromo-4-ethoxybenzaldehyde.

**Preparation 9: 2,2-Dideuterio-6-[1-(methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]-1,3-benzodioxole-5-carboxylic acid****Step A: 2,2-Dideuterio-1,3-benzodioxole-5-carbaldehyde**

To a solution of 30 g of 3,4-dihydroxybenzaldehyde (217 mmol) in 110 mL of anhydrous DMF there are added in succession 114 g of caesium carbonate (347 mmol) and 22 mL of dideuterated methylene chloride (347 mmol). The reaction mixture is subsequently stirred at ambient temperature overnight. After filtering off the insoluble portion over Celite, the residual filtrate is subsequently hydrolysed by addition of 200 mL of water and then extracted with ethyl acetate. The organic phases are then combined, washed with a saturated LiCl solution and then dried over MgSO<sub>4</sub>. After concentration to dryness, the residue is purified by chromatography over silica gel (petroleum ether/AcOEt gradient). The title product is obtained in the form of a solid.

**<sup>1</sup>H-NMR:** δ: (400 MHz; dmsd-d<sub>6</sub>; 300°K): 9.8 (s, 1H, H aldehyde); 7.4-6.95 (m, 3H, H aromatic)

**IR:** ν: C=O aldehyde: 1670 cm<sup>-1</sup>

**Step B: 6-Bromo-2,2-dideuterio-1,3-benzodioxole-5-carbaldehyde**

To a solution of 10 g of the compound obtained in Step A (65.7 mmol) in 100 mL of methanol cooled to 0°C there are added dropwise 3.7 mL of a solution of bromine (1.1 molar equivalents) in 10 mL of methanol. The whole is subsequently stirred at ambient temperature overnight. The reaction mixture is concentrated to dryness and then taken up in water. After stirring, the resulting solid is subsequently filtered and then dried.

**<sup>1</sup>H-NMR:**  $\delta$  (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300°K): 10.2 (s, 1H, H aldehyde); 7.4 (s, 1H, H aromatic); 7.05 (s, 1H, H aromatic)

**IR:**  $\nu$ : C=O aldehyde: 1670 cm<sup>-1</sup>; C=C aromatic: 1611 cm<sup>-1</sup>

**Step C: 2,2-Dideuterio-6-[1-(methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]-1,3-benzodioxole-5-carboxylic acid**

The procedure is as in the protocol described in Steps C and D of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 6-bromo-2,2-dideuterio-1,3-benzodioxole-5-carbaldehyde.

**Preparation 10: 2-[1-(Methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]-4-(trifluoromethyl)benzoic acid**

The procedure is as in the protocol described in Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 2-bromo-4-(trifluoromethyl)benzaldehyde.

**Preparation 11: 2-[1-(Methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]-4-(trifluoromethoxy)benzoic acid**

The procedure is as in the protocol described in Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 2-bromo-4-(trifluoromethoxy)benzaldehyde.

**Preparation 12: 2-[1-(Methoxycarbonyl)-5,6,7,8-tetrahydro-3-indoliziny]benzoic acid**

The procedure is as in the protocol described in Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 2-

bromobenzaldehyde.

**Preparation 13: 6-[1-(Methoxycarbonyl)-3-indoliziny]-1,3-benzodioxole-5-carboxylic acid**

5

**Step A: 1-(Carboxymethyl)-1,2-dihydropyridinium bromide**

To a solution of 16.2 mL of pyridine (200 mmol) in 120 mL of ethyl acetate there are added in portions 27.8 g (200 mmol) of bromoacetic acid. The whole is subsequently stirred at ambient temperature overnight. The precipitate so  
10 obtained is filtered off and then washed with cold ethyl acetate. After drying, the title product is obtained in the form of a powder, which is used directly for the following step.

**<sup>1</sup>H-NMR:**  $\delta$  (400 MHz; dmso-d<sub>6</sub>; 300°K): 9.15 (d, 2H, H aromatic pyridine)); 8.7  
15 (t, 1H, H aromatic); 8.25 (t, 2H, H aromatic); 5.65 (s, 2H, H CH<sub>2</sub>COOH)  
**IR:**  $\nu$ : C=O: 1732 cm<sup>-1</sup>; -OH acid: 2800 cm<sup>-1</sup>

**Step B: Methyl 1-indolizinecarboxylate**

To a suspension of 6.55 g of the pyridinium salt obtained in Step A (30 mmol) in  
20 240 mL of toluene there are added in succession 16.7 mL of methyl acrylate (150 mmol), 4.2 mL of triethylamine (30 mmol) and then, in portions, 20.9 g of MnO<sub>2</sub> (240 mmol). The whole is subsequently heated at 90°C for 3 hours. After cooling, the reaction mixture is filtered over a Celite cake and concentrated to dryness. The title product is then isolated by purification on silica gel  
25 (heptane/AcOEt gradient: 0-10%) in the form of an oil, which crystallises when cold.

**<sup>1</sup>H-NMR:**  $\delta$  (300 MHz; dmso-d<sub>6</sub>; 300°K): 8.5 (d, 1H, H indolizine); 8.05 (d, 1H, H indolizine); 7.6 (s, 1H, H indolizine); 7.15 (m, 2H, H indolizine); 6.85 (m, 1H, H  
30 indolizine); 4.25 (q, 2H, -C(O)CH<sub>2</sub>CH<sub>3</sub>); 1.35 (t, 3H, -C(O)CH<sub>2</sub>CH<sub>3</sub>)  
**IR:**  $\nu$ : C=O ester: 1675 cm<sup>-1</sup>; C=C aromatic: 1634 cm<sup>-1</sup>

**Step C: 6-[1-(Methoxycarbonyl)-3-indoliziny]-1,3-benzodioxole-5-carboxylic acid**

The procedure is as in the protocol described in Steps C and D of Preparation 1.

5

**Preparation 14: 4-Chloro-2-[1-(methoxycarbonyl)-3-indoliziny]benzoic acid**

Methyl 1-indolizinecarboxylate is formed according to the process described in Steps A and B of Preparation 13. The title product is subsequently obtained according to the protocol described in Steps C and D of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 2-bromo-4-chlorobenzaldehyde.

10

**Preparation 15: 7-[1-(Methoxycarbonyl)-3-indoliziny]-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid**

15

Methyl 1-indolizinecarboxylate is formed according to the process described in Steps A and B of Preparation 13. The title product is subsequently obtained according to the protocol described in Steps C and D of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 7-bromo-2,3-dihydro-1,4-benzodioxine-6-carbaldehyde.

20

**Preparation 16: 4-Methoxy-2-[1-(methoxycarbonyl)-3-indoliziny]benzoic acid**

Methyl 1-indolizinecarboxylate is formed according to the process described in Steps A and B of Preparation 13. The title product is subsequently obtained according to the protocol described in Steps C and D of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 2-bromo-4-methoxybenzaldehyde.

25

**Preparation 17: 6-[2-(*tert*-Butoxycarbonyl)-8-(methoxycarbonyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-6-yl]-1,3-benzodioxole-5-carboxylic acid**

30

**Step A: 1-*tert*-Butyl 3-methyl 4-formyl-1,3-piperazinedicarboxylate**

To a solution of pentafluorophenol in 520 mL of anhydrous ether at 0°C there are added in succession 49 g of 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (286 mmol) in portions and 12 mL of formic acid (312 mmol). The whole is stirred at ambient temperature for 2 hours. There is subsequently  
 5 added a mixture of 32 g of 1-*tert*-butyl 3-methyl 1,3-piperazinedicarboxylate (130 mmol) and 18 mL of triethylamine (130 mmol) in solution in 520 mL of CH<sub>2</sub>Cl<sub>2</sub>. The whole is stirred overnight at ambient temperature. The reaction mixture is hydrolysed with an 1N aqueous HCl solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phases are subsequently combined and then washed with  
 10 a saturated aqueous NaHCO<sub>3</sub> solution and then with a saturated aqueous NaCl solution until neutral. After drying over MgSO<sub>4</sub>, filtration and concentration to dryness, the product is isolated by chromatography over silica gel (petroleum ether/AcOEt gradient: 0-30%). The title product is obtained in the form of an oil.

15 **IR:**  $\nu$ : C=O: 1674-1745 cm<sup>-1</sup>

**m/z** (C<sub>12</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>): 272.1(M<sup>+</sup>); 295.121 (M+Na)<sup>+</sup>; 567.253 (2M+Na)<sup>+</sup>

**Step B: Lithium 4-(*tert*-butoxycarbonyl)-1-formyl-2-piperazinecarboxylate**

To a solution of 28 g of the compound obtained in Step A (103 mmol) in 515 mL  
 20 of dioxane there are added 4.8 g of LiOH (113 mmol) in solution in 100 mL of H<sub>2</sub>O. The whole is stirred at ambient temperature for 4 hours. The reaction mixture is subsequently concentrated to dryness and then co-evaporated several times with ethyl acetate. The title product is obtained in the form of a solid and is used directly for the following cyclisation step.

25

**<sup>13</sup>C-NMR:**  $\delta$  (500 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300°K): 46 (s, C piperazine); 42-38 (m, C piperazine); 58-53 (s, C piperazine); 28.5 (s, C <sup>t</sup>Bu).

**IR:**  $\nu$ : C=O: 1650 cm<sup>-1</sup>; 2800 cm<sup>-1</sup>

30 **Step C: 2-*tert*-Butyl 8-methyl 3,4-dihydropyrrolo[1,2-*a*]pyrazine-2,8(1H)-dicarboxylate**

To a suspension of 29 g of the compound obtained in Step B (103 mmoles) in 800 mL of dichloroethane there are added in succession 24 g of tosyl chloride

(124 mmol), 12.6 mL of methyl 2-chloroacrylate (124 mmol) and then 35 mL of triethylamine (247 mmoles). The whole is stirred at reflux for 2 hours. After cooling, the reaction mixture is diluted with ethyl acetate, and the organic phase is washed with a saturated NaCl solution until neutral. After drying over MgSO<sub>4</sub>,  
 5 filtration and concentration to dryness, the title product is isolated by chromatography over silica gel (petroleum ether/AcOEt gradient: 0-20%) in the form of a solid.

**<sup>1</sup>H-NMR:** δ (400 MHz; dms<sup>o</sup>-d<sub>6</sub>; 300°K): 6.8-6.43 (m, 2H, H pyrrole); 4.75-3.75  
 10 (m, 6H, H piperazine)); 3.73 (s, 3H, H COOCH<sub>3</sub>); 1.48 (s, 9H, H <sup>t</sup>Bu).

**IR:** ν: C=O (conjugated ester): 1712 cm<sup>-1</sup>; C=O (carbamate): 1677cm<sup>-1</sup>

**Step D: 6-[2-(tert-Butoxycarbonyl)-8-(methoxycarbonyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-6-yl]-1,3-benzodioxole-5-carboxylic acid**

15 The procedure is as in the protocol described in Steps C and D of Preparation 1.

**Preparation 18: 6-[7-(Methoxycarbonyl)-2,3-dihydro-1H-pyrrolizin-5-yl]-1,3-benzodioxole-5-carboxylic acid**

20 The procedure is as in the protocol described in Preparation 1, replacing the 2-piperidinecarboxylic acid used in Step A by proline.

**Preparation 19: 4-Chloro-2-[7-(methoxycarbonyl)-2,3-dihydro-1H-pyrrolizin-5-yl]benzoic acid**

25 The procedure is as in the protocol described in Preparation 1, replacing the 2-piperidinecarboxylic acid used in Step A by proline, while the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C is replaced by 2-bromo-4-chlorobenzaldehyde.

30 **Preparation 20: 4-Chloro-2-[8-(methoxycarbonyl)-3,4-dihydro-1H-pyrrolo-[2,1-c][1,4]oxazin-6-yl]benzoic acid**

The procedure is as in the protocol described in Preparation 1, replacing 2-piperidinecarboxylic acid by 3-morpholinecarboxylic acid, while the 6-bromo-

1,3-benzodioxole-5-carbaldehyde used in Step C is replaced by 2-bromo-4-chlorobenzaldehyde.

**Preparation 21:** 6-[8-(Methoxycarbonyl)-3,4-dihydro-1*H*-pyrrolo[2,1-  
5 c][1,4]oxazin-6-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is as in the protocol described in Preparation 1, replacing 2-piperidinecarboxylic acid by 3-morpholinecarboxylic acid.

**Preparation 22:** 4-Chloro-2-[1-(methoxycarbonyl)-6,7,8,9-tetrahydro-5*H*-  
10 pyrrolo[1,2-*a*]azepin-3-yl]benzoic acid

The procedure is as in the protocol described in Preparation 1, replacing 2-piperidinecarboxylic acid by 2-azepanecarboxylic acid, while the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C is replaced by 2-bromo-4-chlorobenzaldehyde.

15

**Preparation 23:** 6-[1-(Methoxycarbonyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-  
a]azepin-3-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is as in the protocol described in Preparation 1, replacing 2-piperidinecarboxylic acid by 2-azepanecarboxylic acid.

20

**Preparation 24:** 4-Chloro-2-[3-(methoxycarbonyl)-5,6,7,8-tetrahydro-1-  
indoliziny]benzoic acid

**Step A: Methyl 1-(4-bromobutyl)-1*H*-pyrrole-2-carboxylate**

- 25 To a suspension of 6.7 g (241.7 mmol) of NaH (60%) in 400 mL of anhydrous THF at 0°C there are added 20 g (161.13 mmol) of methyl 1*H*-pyrrole-2-carboxylate (see *Tetrahedron* **2008**, 64, 7745). The whole is stirred at ambient temperature for one hour. Then, 95 mL of 1,4-dibromobutane are added. After the addition, the reaction mixture is heated at reflux for 12 hours. The
- 30 precipitate obtained is filtered off and then washed with THF. The filtrate is subsequently concentrated to dryness. The compound is then isolated by chromatography over silica gel (cyclohexane/ethyl acetate gradient: 0 to 20%) in the form of an oil.



**Elemental microanalysis:**

	%C	%H	%N	%Br
Calculated	46.17	5.42	5.38	30.72
5 Found	46.76	5.56	5.29	30.77

IR:  $\nu$ : -C=O: 1700  $\text{cm}^{-1}$ ;  $\nu$ : C-O-C: 1238  $\text{cm}^{-1}$

**Step B: Methyl 5,6,7,8-tetrahydro-3-indolizinecarboxylate**

A solution of 8 g (30.8 mmol) of the brominated derivative obtained in Step A in  
 10 700 mL of acetonitrile is brought to reflux. There is added thereto a solution of a  
 mixture of 25 g of azobisisobutyronitrile (151 mmol) and of 30 g of  $\text{Bu}_3\text{SnH}$  (100  
 mmol) in 500 mL of toluene. The whole is refluxed for 120 hours. The reaction  
 mixture is subsequently concentrated to dryness. The compound is then  
 isolated by chromatography over silica gel (cyclohexane/ethyl acetate gradient  
 15 5 to 10%) in the form of an oil.

**$^1\text{H-NMR}$ :**  $\delta$  (400 MHz;  $\text{CDCl}_3$ ; 300°K): 6.90 (d, 1H, H pyrrole); 5.85 (d, 1H, H  
 pyrrole); 4.30 (t, 2H,  $\text{CH}_2$  indolizine); 3.80 (s 3H, Me); 2.80 (t, 2H,  $\text{CH}_2$   
 indolizine); 1.95 (m, 2H,  $\text{CH}_2$  indolizine); 1.80 (m, 2H,  $\text{CH}_2$  indolizine)

20 IR:  $\nu$ : -C=O: 1695  $\text{cm}^{-1}$

**Step C: 4-Chloro-2-[3-(methoxycarbonyl)-5,6,7,8-tetrahydro-1-indoliziny]benzoic acid**

The procedure is as in the protocol described in Steps C and D of Preparation  
 25 1.

**Preparation 25: 2-[1-(Methoxycarbonyl)-5,6,7,8-tetrahydroindolizin-3-yl]-4-methylbenzoic acid**

The procedure is as in the process of Preparation 1, replacing the 6-bromo-1,3-  
 30 benzodioxole-5-carbaldehyde used in Step C by 2-bromo-4-methylbenzaldehyde.

**Preparation 26: 4-Fluoro-2-[8-(methoxycarbonyl)-3,4-dihydro-1H-pyrrolo-**

**[2,1-c][1,4]oxazin-6-yl]benzoic acid**

The procedure is as in the protocol described in Preparation 1, replacing 2-piperidinecarboxylic acid by 3-morpholinecarboxylic acid, while the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C is replaced by 2-bromo-4-fluorobenzaldehyde.

**Preparation 27: 4-Fluoro-2-[1'-(methoxycarbonyl)-5',6'-dihydro-8'H-spiro[1,3-dioxolane-2,7'-indolizin]-3'-yl]benzoic acid****10 Step A: Methyl 8-formyl-1,4-dioxa-8-azaspiro[4.5]decane-7-carboxylate**

24 g of methyl 1,4-dioxa-8-azaspiro[4.5]decane-9-carboxylate (111 mmol) are dissolved in 80 mL of ethyl acetate and 80 mL of dichloromethane. There are added 26 g of (4-nitrophenyl) formate (155 mmol), and the whole is stirred at ambient temperature for one hour. The reaction mixture is evaporated to dryness and taken up in ethyl acetate. The organic phase is subsequently washed in succession with a 1 N NaOH solution, water, and then with a saturated NH<sub>4</sub>Cl solution until a neutral pH is reached. It is subsequently dried over magnesium sulphate, filtered and concentrated to dryness. The oil so obtained is purified by flash chromatography (heptane/ethyl acetate gradient).

20 The title product is obtained in the form of an oil.

**<sup>1</sup>H-NMR:**  $\delta$  (400 MHz; dmsO-d<sub>6</sub>; 300°K): 8.15 (s, 1H, CHO); 5.0-4.75 (m, 1H, H tertiary); 4.3-3.7 (m, 5H, 4H ethylenedioxy + 1H aliphatic piperidine); 3.70 (s, 3H, Me); 3.4-2.9 (2m, 1H, H aliphatic piperidine); 2.3-1.75 (m, 2H, H aliphatic piperidine); 1.7-1.5 (m, 2H, H aliphatic piperidine)

**Step B: 8-Formyl-1,4-dioxa-8-azaspiro[4.5]decane-7-carboxylic acid**

15.25 g of the compound obtained in Step A (62.7 mmol) are dissolved in 160 ml of dioxane. A solution of 125 mL of 1M KOH is added dropwise, and the whole is stirred at ambient temperature for one hour. There are subsequently added 125 mL of 1M HCl, and the compound is extracted with dichloromethane. The organic phase is dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. The title product is obtained in the form of a powder.

**<sup>1</sup>H-NMR:**  $\delta$  (400 MHz; dmso-d<sub>6</sub>; 300°K) 13.5-12 (m, 1H, OH); 8.1 + 8.0 (2s, 1H, CHO); 4.9 + 4.6 (2m, 1H, H tertiary); 4.0-3.8 (m, 4H, ethylenedioxy); 4.2 + 3.7 (2ms, 1H, H aliphatic piperidine); 3.4 + 2.9 (2m, 1H, H aliphatic piperidine); 2.4-1.5 (m, 4H, H aliphatic piperidine)  
**IR:**  $\nu$ : OH: 3500-2000 cm<sup>-1</sup>; -C=O (acid + aldehyde): 1731 + 1655 cm<sup>-1</sup>

**Step C: Methyl 5',6'-dihydro-8'H-spiro[1,3-dioxolane-2,7'-indolizine]-1'-carboxylate**

To a solution of 13.5 g (62.7 mmol) of the acid obtained in Step B in 380 mL of dichloroethane there are added in succession 39.5 mL (238.4 mmol) of triethylamine and then, by spatula, 12.5 g (65.6 mmol) of *para*-toluenesulphonyl chloride and 23.7 mL (238.4 mmol) of methyl chloroacrylate. The whole is stirred at 80°C for 18 hours. The reaction mixture is subsequently filtered over Celite. The filtrate is subsequently washed with a saturated NaHCO<sub>3</sub> solution and then with a saturated NH<sub>4</sub>Cl solution. The organic phase is dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. The oil so obtained is purified by flash chromatography (heptane/ethyl acetate gradient). The product is obtained in the form of a solid.

20

**<sup>1</sup>H-NMR:**  $\delta$  (400 MHz; dmso-d<sub>6</sub>; 300°K) 6.70 (d, 1H, pyrrole); 6.40 (d, 1H, pyrrole); 4.05 (t, 2H, H aliphatic, piperidine); 4.00 (m, 4H, ethylenedioxy); 3.70 (s, 3H, methyl); 3.15 (s, 2H, H aliphatic piperidine); 2.05 (t, 2H, H aliphatic piperidine)

25 **IR:**  $\nu$ : -C=O (ester): 1689 cm<sup>-1</sup>

**Step D: Methyl 3'-(5-fluoro-2-formylphenyl)-5',6'-dihydro-8'H-spiro[1,3-dioxolane-2,7'-indolizine]-1'-carboxylate**

The procedure is as in the process of Step C of Preparation 1, replacing 6-bromo-1,3-benzodioxole-5-carbaldehyde by 2-bromo-4-fluorobenzaldehyde.

30

**Step E: 4-Fluoro-2-[1'-(methoxycarbonyl)-5',6'-dihydro-8'H-spiro[1,3-dioxolane-2,7'-indolizin]-3'-yl]benzoic acid**

The procedure is as in the process of Step D of Preparation 1.

**Preparation 28: 4-Fluoro-2-[(2R)-2-hydroxy-7-(methoxycarbonyl)-2,3-dihydro-1H-pyrrolizin-5-yl]benzoic acid**

5

**Step A: Methyl (4R)-4-[[tert-butyl(dimethyl)silyl]oxy]-L-prolinate**

The protection of the alcohol function of methyl (4R)-4-hydroxy-L-prolinate by a *tert*-butyldimethylsilyl group is carried out according to the protocol described in document WO 2012040242.

10

**Step B: Methyl (4R)-4-[[tert-butyl(dimethyl)silyl]oxy]-1-formyl-L-prolinate**

13.7 g (52.8 mmol) of compound of Step A are dissolved in 100 mL of acetonitrile. There are added thereto 13.2 g (79.3 mmol) of (4-nitrophenyl) formate and 39 mL (238 mmol) of diisopropylethylamine. The whole is stirred at ambient temperature for 6 hours. The reaction mixture is evaporated to dryness and taken up in ethyl acetate. The organic phase is subsequently washed in succession with a 1 N NaOH solution, with water, and then with a saturated NH<sub>4</sub>Cl solution until neutral. It is subsequently dried over magnesium sulphate, filtered and concentrated to dryness. The oil so obtained is purified by flash chromatography (gradient: dichloromethane/ammoniacal methanol). The title product is obtained in the form of an oil.

**<sup>1</sup>H-NMR:**  $\delta$  (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300°K): 8.15 and 8.12 (s, 1H, formyl); 4.62 and 4.25 (t, 1H, H alpha ester); 4.40 (m, 1H, SiOCH<sub>3</sub>); 3.65 and 3.6 (s, 3H, OMe); 3.5 and 3.3 (m, 2H, 2H proline); 2.12 and 1.95 (m, 2H, 2H proline); 0.8 (s, 9H, Si<sup>t</sup>Bu); 0.05 (s, 6H, SiMe<sub>2</sub>).

**IR:**  $\nu$ : C=O ester: 1749 cm<sup>-1</sup>; C=O formyl: 1659 cm<sup>-1</sup>

**Step C: Lithium (2S,4R)-4-[[tert-butyl(dimethyl)silyl]oxy]-1-formylpyrrolidine-2-carboxylate**

30

The compound of Step B (26.2 g; 91.1 mmol) is dissolved in 450 mL of dioxane. A solution of lithium hydroxide (4.2 g; 100 mmol) in water (90 mL) is added. The whole is stirred at ambient temperature for 7 hours. The reaction mixture is

evaporated to dryness and used as such for the following step.

**Step D: Methyl (2R)-2-[[tert-butyl(dimethyl)silyl]oxy]-2,3-dihydro-1H-pyrrolizine-7-carboxylate**

- 5 To a solution of 22.4 g (80.2 mmol) of the lithium carboxylate obtained in Step D in 640 mL of dichloroethane there are added in succession 27 mL (192 mmol) of triethylamine and then, in portions, 18 g (96 mmol) of *para*-toluenesulphonic chloride and 9.7 mL (96.2 mmol) of methyl chloroacrylate. The reaction mixture is heated at reflux for 18 hours and then cooled and diluted in ethyl acetate. The
- 10 organic phase is washed with water and then with brine, before being dried over MgSO<sub>4</sub>. After filtration and concentration of the mixture, the oil obtained is purified by flash chromatography (gradient: heptane/ethyl acetate). The title product is obtained in the form of an oil.

- 15 **<sup>1</sup>H-NMR:** δ (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300°K): 6.7 (d, 1H, H pyrrole); 6.4 (d, 1H, H pyrrole); 5.0 (m, 1H, SiOCH<sub>3</sub>); 4.2-3.75 (ABx, 2H, 2H dihydropyrrolizine); 3.3+2.8 (ABx, 2H, 2H dihydropyrrolizine); 3.70 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>); 0.9 (s, 9H, <sup>t</sup>Bu); 0.10 (ABx, 6H, SiMe<sub>2</sub>)

- IR:** ν: -C=O (ester): 1701 cm<sup>-1</sup>; SiCH<sub>3</sub>: 1249 cm<sup>-1</sup>; Si-O: 1118-1090 cm<sup>-1</sup>; Si-C: 835-777 cm<sup>-1</sup>
- 20

**Step E: Methyl (2R)-2-[[tert-butyl(dimethyl)silyl]oxy]-5-(5-fluoro-2-formylphenyl)-2,3-dihydro-1H-pyrrolizine-7-carboxylate**

- The procedure is as in the process of Step C of Preparation 1, replacing 6-bromo-1,3-benzodioxole-5-carbaldehyde by 2-bromo-4-fluorobenzaldehyde.
- 25

**Step F: 2-[(2R)-2-[[tert-Butyl(dimethyl)silyl]oxy]-7-(methoxycarbonyl)-2,3-dihydro-1H-pyrrolizin-5-yl]-4-fluorobenzoic acid**

The procedure is as in the process of Step D of Preparation 1.

30

**Preparation 29: 4-Fluoro-2-[(2S)-2-hydroxy-7-(methoxycarbonyl)-2,3-dihydro-1H-pyrrolizin-5-yl]benzoic acid**

The procedure is as in the process of Preparation 28, replacing the methyl (4R)-

4-hydroxy-*L*-prolinate used in Step A by methyl (4*S*)-4-hydroxy-*L*-prolinate.

**Preparation 30: 4-Fluoro-2-[7-hydroxy-1-(methoxycarbonyl)-5,6,7,8-tetrahydroindolizin-3-yl]benzoic acid**

- 5 The procedure is as in the process of Preparation 27, replacing the 2-bromo-4-fluorobenzaldehyde used in Step D by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

**Preparation 31: 6-[8-(Methoxycarbonyl)pyrrolo[1,2-*a*]pyrazin-6-yl]-1,3-benzodioxole-5-carboxylic acid**

**Step A: Methyl pyrrolo[1,2-*a*]pyrazine-8-carboxylate**

- To a solution of 10 g (65.7 mmol) of methyl pyrazin-2-ylacetate in 263 mL of anhydrous acetone (4 mL/mmol) there are added in succession 5.7 g of lithium bromide (65.7 mmol), 22.1 g of sodium bicarbonate (263 mmol) and then 9.4 mL of chloroacetaldehyde (50% solution in water) (72.6 mmoles). The whole is subsequently heated at reflux overnight. The reaction mixture is subsequently concentrated to dryness and then taken up in ethyl acetate. The organic phase is washed with a saturated sodium chloride solution, dried over magnesium sulphate, filtered and then concentrated to dryness. There is obtained an oil, which is purified by chromatography over silica gel (CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate gradient). After concentration, the title product is obtained in the form of a solid.

- <sup>1</sup>H-NMR:** δ (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300°K): 9.36 (m, 1H, H pyrazine); 8.50 (dd, 1H, H pyrazine); 7.8 (m, 2H, 1H pyrazine, 1H pyrrole); 7.31 (m, 1H, H pyrrole). 3.88 (s, 3H, OCH<sub>3</sub>)

**IR:** ν: -C=O (conjugated ester): 1686 cm<sup>-1</sup>

**Step B: 6-[8-(Methoxycarbonyl)pyrrolo[1,2-*a*]pyrazin-6-yl]-1,3-benzodioxole-5-carboxylic acid**

The procedure is as in the processes of Steps C and D of Preparation 1.

**Preparation 32: 4-Fluoro-2-[1-(methoxycarbonyl)-3-indoliziny]benzoic**

**acid**

Methyl 1-indolizinecarboxylate is formed according to the process described in Steps A and B of Preparation 13. The title product is subsequently obtained according to the protocol described in Steps C and D of Preparation 1, replacing  
 5 the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C by 2-bromo-4-fluorobenzaldehyde.

**Preparation 1': (3S)-3-(4-Morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline**

10

**Step A: Benzyl (3S)-3-(4-morpholinylcarbonyl)-3,4-dihydro-2(1H)-isoquinoline carboxylate**

To a solution of 5 g of (3S)-2-[(benzyloxy)carbonyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (16 mmol) in 160 mL of dichloromethane there are  
 15 added 1.5 mL of morpholine (17.6 mmol) and then 9 mL of *N,N,N*-triethylamine (64 mmol), 3.3 g of 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (EDC) (19.2 mmol) and 2.6 g of hydroxybenzotriazole (HOBT) (19.2 mmol). The reaction mixture is stirred at ambient temperature overnight and is then poured onto a solution of ammonium chloride and extracted with ethyl acetate. The organic  
 20 phase is subsequently dried over magnesium sulphate and then filtered and evaporated to dryness. The crude product so obtained is then purified by chromatography over silica gel (dichloromethane/methanol gradient). The product is obtained in the form of a foam.

25 **<sup>1</sup>H-NMR:**  $\delta$  (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 353°K): 7.30 (m, 5H benzyl); 7.15 (m, 4H aromatic); 5.2-5.0 (m, 3H, 2H benzyl, 1H dihydroisoquinoline); 4.75-4.5 (2d, 2H dihydroisoquinoline); 3.55-3.3 (m, 8H morpholine); 3.15-2.9 (2dd, 2H dihydroisoquinoline)

**IR:**  $\nu$ : >C=O: 1694; 1650 cm<sup>-1</sup>

30

**Step B: Benzyl (3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinoline carboxylate**

To a solution of 5.3 g of the product obtained in Step A (13.9 mmol) in 278 mL

of tetrahydrofuran there are added 14 mL of  $\text{BH}_3\text{Me}_2\text{S}$  (27.8 mmol) at ambient temperature. The whole is heated for 4 hours at  $80^\circ\text{C}$ . It is allowed to return to ambient temperature, and then there are added 7 mL (14 mmol) of  $\text{BH}_3\text{Me}_2\text{S}$ . The reaction mixture is again heated at  $80^\circ\text{C}$  for 2 hours. The tetrahydrofuran is subsequently evaporated off, and there are then added slowly methanol and then 5.6 mL of 5N hydrochloric acid (27.8 mmol). The mixture is stirred at ambient temperature overnight and then at  $80^\circ\text{C}$  for one hour. There is subsequently added a saturated  $\text{NaHCO}_3$  solution to the reaction mixture at  $0^\circ\text{C}$  until a pH of 8 is reached, and then extraction with ethyl acetate is carried out.

The organic phase is subsequently dried over magnesium sulphate and then filtered and evaporated to dryness. The title product is obtained in the form of an oil.

**$^1\text{H-NMR}$ :**  $\delta$  (400 MHz;  $\text{dmsO-d}_6$ ;  $353^\circ\text{K}$ ): 7.43-7.30 (unresolved peak, 5H benzyl); 7.19 (m, 4H aromatic); 5.16 (m, 2H, 2H benzyl); 4.79-4.29 (d, 2H dihydroisoquinoline); 4.58 (m, 1H dihydroisoquinoline); 3.50 (m, 4H morpholine); 3.02-2.80 (dd, 2H dihydroisoquinoline); 2.42-2.28 (unresolved peak, 5H, 4H morpholine, 1H morpholine); 2.15 (dd, 1H morpholine)

**IR:**  $\nu$ :  $>\text{CH}$ :  $2810\text{ cm}^{-1}$ ;  $\nu$ :  $>\text{C}=\text{O}$ :  $1694\text{ cm}^{-1}$ ;  $\nu$ :  $>\text{C}-\text{O}-\text{C}<$ :  $1114\text{ cm}^{-1}$ ;  $\nu$ :  $>\text{CH}-\text{Ar}$ :  $751$ ;  $697\text{ cm}^{-1}$

**Step C: (3S)-3-(4-Morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline**

To a solution of 4.9 g of the compound of Step B (13.4 mmol) in 67 mL of ethanol there is added 0.980 g of palladium dihydroxide (20% by mass) at ambient temperature. The reaction mixture is placed under 1.2 bar of hydrogen at ambient temperature for 4 hours. It is subsequently passed over a Whatman filter, and then the palladium is rinsed several times with ethanol. The filtrate is evaporated to dryness. The title product is obtained in the form of an oil.

**$^1\text{H-NMR}$ :**  $\delta$  (400 MHz;  $\text{dmsO-d}_6$ ;  $300^\circ\text{K}$ ): 7.12-7.0 (unresolved peak, 4H aromatic); 3.92 (s, 2H tetrahydroisoquinoline); 3.60 (t, 4H morpholine); 2.98 (m, 1H tetrahydroisoquinoline); 2.68 (dd, 1H tetrahydroisoquinoline); 2.5-2.3 (unresolved peak, 8H, 1H tetrahydroisoquinoline, 6H morpholine, 1H NH)



IR:  $\nu$ : >NH: 3322  $\text{cm}^{-1}$ ;  $\nu$ : >C-O-C<: 1115  $\text{cm}^{-1}$ ;  $\nu$ : >CH-Ar: 742  $\text{cm}^{-1}$

**Preparation 2': (3*R*)-3-(4-Morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline**

- 5 The procedure is as in the process of Preparation 1', replacing the (3*S*)-2-[(benzyloxy)carbonyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid used in Step A by (3*R*)-2-[(benzyloxy)carbonyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid.

10 **Preparation 3': (3*S*)-3-[(4-Methyl-1-piperazinyl)methyl]-1,2,3,4-tetrahydro-isoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine used in Step A by 1-methyl-piperazine.

15 **Preparation 4': (3*S*)-3-(1,4-Oxazepan-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine used in Step A by 1,4-oxazepan.

20 **Preparation 5': (3*S*)-3-[(3*R*)-3-Methylmorpholinyl]methyl}-1,2,3,4-tetrahydroisoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine used in Step A by (3*R*)-3-methylmorpholine.

25 **Preparation 6': (3*S*)-3-[(3*S*)-3-Methylmorpholinyl]methyl}-1,2,3,4-tetrahydroisoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine used in Step A by (3*S*)-3-methylmorpholine.

30 **Preparation 7': (3*S*)-3-[(3*S*,5*S*)-3,5-Dimethylmorpholinyl]methyl}-1,2,3,4-tetrahydroisoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine used in Step A by (3*S*,5*S*)-3,5-dimethylmorpholine.

**Preparation 8':                    *N,N*-Dimethyl[(3*S*)-1,2,3,4-tetrahydro-3-isoquinoliny]methanamine**

The procedure is as in the process of Preparation 1', replacing the morpholine  
5 used in Step A by *N,N*-dimethylamine.

**Preparation 9': (3*S*)-3-{[4-(2-Methoxyethyl)piperazin-1-yl]methyl}-1,2,3,4-tetrahydroisoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine  
10 used in Step A by 1-(2-methoxyethyl)piperazine.

**Preparation 10': 1-Methyl-4-[(3*S*)-1,2,3,4-tetrahydroisoquinolin-3-ylmethyl]-piperazin-2-one**

The procedure is as in the process of Preparation 1', replacing the morpholine  
15 used in Step A by 1-methylpiperazin-2-one.

**Preparation 11': 2-Methoxy-*N*-methyl-*N*-[(3*S*)-1,2,3,4-tetrahydroisoquinolin-3-ylmethyl]ethanamine**

The procedure is as in the process of Preparation 1', replacing the morpholine  
20 used in Step A by 2-methoxy-*N*-methylethanamine.

**Preparation 12': *N*-Ethyl-2-methoxy-*N*-[(3*S*)-1,2,3,4-tetrahydroisoquinolin-3-ylmethyl]ethanamine**

The procedure is as in the process of Preparation 1', replacing the morpholine  
25 used in Step A by *N*-ethyl-2-methoxyethanamine.

**Preparation 13': (3*S*)-3-{[4-(Methylsulphonyl)piperazin-1-yl]methyl}-1,2,3,4-tetrahydroisoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine  
30 used in Step A by 1-(methylsulphonyl)piperazine.

**Preparation 14': (3*S*)-3-{[4-(2,2,2-Trifluoroethyl)piperazin-1-yl]methyl}-1,2,3,4-tetrahydroisoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine used in Step A by 1-(2,2,2-trifluoroethyl)piperazine.

**Preparation 15': (3S)-3-[(1,1-Dioxidothiomorpholin-4-yl)methyl]-1,2,3,4-tetrahydroisoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine used in Step A by thiomorpholine 1,1-dioxide.

**Preparation 16': (3S)-3-[(3-Methoxypyrrolidin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine used in Step A by 3-methoxypyrrolidine.

**Preparation 17': (3S)-3-[(3,3-Difluoropyrrolidin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine used in Step A by 3,3-difluoropyrrolidine.

**Preparation 18': (3S)-3-[(3-Methoxyazetidin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine used in Step A by 3-methoxyazetidine.

**Preparation 19': (3S)-3-[(3-Fluoroazetidin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinoline**

The procedure is as in the process of Preparation 1', replacing the morpholine used in Step A by 3-fluoroazetidine.

**Preparation 1'': 4-[[*tert*-Butyl(dimethyl)silyl]oxy]-*N*-phenylaniline**

- 30 To a solution of 12 g of 4-anilinophenol (64.7 mmol) in 200 mL of acetonitrile there are added at ambient temperature 6.7 g of imidazole (97.05 mmol) and 11.7 g of *tert*-butyl(chloro)dimethylsilane (77.64 mmol). The whole is stirred at 70°C for 4 hours. Then the reaction mixture is poured onto water and extracted

with ether. The organic phase is subsequently dried over magnesium sulphate and then filtered and evaporated to dryness. The crude product so obtained is then purified by chromatography over silica gel (petroleum ether/dichloromethane gradient). The title product is obtained in the form of a powder.

**<sup>1</sup>H-NMR:**  $\delta$  (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300°K): 7.84 (s, 1H NH); 7.17 (t, 2H aniline); 6.98 (d, 2H phenoxy); 6.94 (d, 2H aniline); 6.76 (d, 2H phenoxy); 6.72 (t, 1H aniline); 0.95 (s, 9H *tert*-butyl); 0.15 (s, 6H dimethyl)

**IR:**  $\nu$ : >NH: 3403 cm<sup>-1</sup>; >Ar: 1597 cm<sup>-1</sup>

The amines NHR<sub>3</sub>R<sub>4</sub> wherein R<sub>3</sub> and R<sub>4</sub> independently of one another represent an aryl or heteroaryl group are obtained according to the processes described in the literature (Slurry D.S. *et al.*, Chemical Science, 2011, 2, 27-50, Charles M.D. *et al.*, Organic Letters, 2005, 7, 3965-3968). The reaction of protection of the hydroxy function of the 4-anilinophenol described in Preparation 1" can be applied to various secondary amines NHR<sub>3</sub>R<sub>4</sub> (as defined hereinbefore) having one or more hydroxy functions, when they are available commercially. Alternatively, the secondary amines having at least one hydroxy substituent may be synthesised directly in a protected form, i.e. starting from reagents whose hydroxy function has been protected beforehand. Among the protecting groups, *tert*-butylsilyloxy and benzyloxy are especially preferred.

Among the amines NHR<sub>3</sub>R<sub>4</sub> having a hydroxy substituent that are used for synthesising the compounds of the invention there may be mentioned: 4-(4-toluidino)phenol, 4-(4-chloroanilino)phenol, 4-(3-fluoro-4-methylanilino)phenol, 4-[4-(trifluoromethoxy)anilino]phenol, 4-[4-hydroxyanilino]phenol, {4-[(1-methyl-1*H*-indol-6-yl)amino]phenyl}methanol, 4-(2,3-dihydro-1*H*-indol-6-ylamino)phenol, 4-[(1-methyl-2,3-dihydro-1*H*-indol-6-yl)amino]phenol, 4-[(1-methyl-1*H*-indol-6-yl)amino]phenol, 4-[(1-methyl-1*H*-indol-6-yl)amino]cyclohexanol, 4-[(1-methyl-1,2,3,4-tetrahydro-6-quinolinyl)amino]phenol, 4-[(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl)amino]phenol, 4-[4-(diethylamino)anilino]phenol, 4-(2,3-dihydro-1*H*-inden-5-ylamino)phenol, 4-[(1-methyl-1*H*-indazol-5-yl)amino]phenol, 4-[(1'-methyl-1',2'-

- dihydrospiro[cyclopropane-1,3'-indol]-5'-yl)amino]phenol, 4-[(1,3,3-trimethyl-2,3-dihydro-1*H*-indol-5-yl)amino]phenol, 4-[4-methoxy-3-(trifluoromethyl)-anilino]phenol, 4-[4-(methylsulphanyl)-3-(trifluoromethyl)anilino]phenol, 2-fluoro-4-[(1-methyl-1*H*-indol-5-yl)amino]phenol, 4-[(1-ethyl-1*H*-indol-5-yl)amino]phenol, 4-[(1-ethyl-2,3-dihydro-1*H*-indol-5-yl)amino]phenol, 4-[(1-isopropyl-2,3-dihydro-1*H*-indol-5-yl)amino]phenol, 4-(butylamino)phenol, 3-[(1-methyl-1*H*-indol-5-yl)amino]-1-propanol, 4-[(1-methyl-1*H*-indol-5-yl)amino]-1-butanol, 4-[(3-fluoro-4-methylphenyl)amino]phenol, 4-[(3-chloro-4-methylphenyl)amino]phenol, 4-[(4-fluorophenyl)amino]phenol, 4-[(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)amino]phenol, 4-[(4-fluorophenyl)amino]phenol, 4-[(2-fluorophenyl)amino]phenol, 4-[(3-fluorophenyl)amino]phenol, 4-[(2,4-difluorophenyl)amino]phenol, 4-[(3,4-difluorophenyl)amino]phenol, 3-[(4-hydroxyphenyl)amino]benzonitrile, 4-[(3-methoxyphenyl)amino]phenol, 4-[(3,5-difluorophenyl)amino]phenol, 4-[(3-methylphenyl)amino]phenol, 4-[(4-hydroxyphenyl)amino]benzonitrile, 4-[(3-chlorophenyl)amino]phenol, 4-(pyrimidin-2-ylamino)phenol, 4-[(cyclobutylmethyl)amino]phenol, 2-[(4-hydroxyphenyl)amino]benzonitrile, 4-[(1-methyl-1*H*-pyrazol-4-yl)-methyl]amino]phenol, 4-[(cyclopropylmethyl)amino]phenol, 4-[(1-methyl-1*H*-pyrazol-3-yl)methyl]amino]phenol, 4-(but-2-yn-1-ylamino)phenol, 4-(pyrazin-2-ylamino)phenol, 4-(pyridin-2-ylamino)phenol, 4-(pyridazin-3-ylamino)phenol, 4-(pyrimidin-5-ylamino)phenol, 4-(pyridin-3-ylamino)phenol, 4-[(3,5-difluoro-4-methoxyphenyl)amino]phenol, 4-(pyridin-4-ylamino)phenol, 4-[(3-fluoro-4-methoxyphenyl)amino]phenol, 2-(phenylamino)pyrimidin-5-ol, 5-[(4-hydroxyphenyl)amino]-2-methoxybenzonitrile, 4-[(3-(trifluoromethyl)phenyl)amino]phenol.

The hydroxy function(s) of the secondary amines listed above is (are) protected beforehand by a suitable protecting group prior to coupling to an acid derivative of the compound of formula (VII) as defined in the preceding general process.

- Example 1:** *N*-(4-Hydroxyphenyl)-3-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl]carbonyl]-1,3-benzodioxol-5-yl]-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

**Step A: Methyl      3-[6-[(3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl]-5,6,7,8-tetrahydro-1-indolizinecarboxylate**

To a solution of 2 g of the compound of Preparation 1 in 20 mL of dichloromethane there are added at ambient temperature 5.5 mL of *N,N,N*-triethylamine (6.96 mmol), 2.12 g of the compound of Preparation 1' (6.96 mmol), and then 0.94 g of hydroxybenzotriazole (HOBT) and 1.34 g of 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (EDC) (6.96 mmol). The reaction mixture is subsequently stirred at ambient temperature overnight, and is then poured onto an ammonium chloride solution and extracted with ethyl acetate. The organic phase is subsequently dried over magnesium sulphate and then filtered and evaporated to dryness. The crude product so obtained is then purified by chromatography over silica gel (heptane/AcOEt gradient). The title product is obtained in the form of an oil.

15

**<sup>1</sup>H-NMR:**  $\delta$  (500 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300°K): 7.2-6.9 (m, 4H, H aromatic); 7.04-7.03-7.00 (m, 1H, H aromatic); 6.85 (m, 1H, H aromatic); 6.35-6.26-6.06 (m, 1H, H tetrahydroindolizine); 6.15-6.12 (m, 2H, H methylenedioxy); 5.06-4.84 (m, 1H, H dihydroisoquinoline); 4.86-4.17 (m, 2H, H dihydroisoquinoline); 3.65-3.6-3.55 (m, 3H, H methyl ester); 3.43-4.26 (m, 2H, H tetrahydroindolizine); 3.58-3.5 (m, 4H, H morpholine); 2.37-3.05 (m, 4H, 2H dihydroisoquinoline, 2H tetrahydroindolizine); 1.68-2.56 (m, 4H, H morpholine); 1.4-2.0 (m, 4H, H tetrahydroindolizine)

**IR:**  $\nu$ : >C=O 1695 cm<sup>-1</sup> ester;  $\nu$ : >C=O 1625 cm<sup>-1</sup> amide;  $\nu$ : >C-O-C< 1214-1176-1115 cm<sup>-1</sup>; >CH-Ar 772-744 cm<sup>-1</sup>

25

**Step B:      Lithium      3-[6-[(3S)-3-(morpholinomethyl)-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-5,6,7,8-tetrahydro-1-indolizinecarboxylate**

To a solution of 4.6 g of the compound of Step A (8.26 mmol) in 24 mL of dioxane there is added a solution of lithium hydroxide (675 mg, 16.1 mmol). The whole is placed in a 140 W microwave oven at 100°C for a period of 2.5 hours. The reaction mixture is subsequently filtered and dried. The solid so obtained is

30

dried at 40°C in a hot cabinet in the presence of P<sub>2</sub>O<sub>5</sub>.

**<sup>1</sup>H-NMR:** δ (400 MHz; dms<sub>2</sub>-d<sub>6</sub>; 353°K): 6.7-7.15 (unresolved peak, 6H, H aromatic); 6.21 (s, 1H, H aromatic); 6.03 (s, 2H, H methylenedioxy); 4.0-5.0  
5 (unresolved peak, 3H dihydroisoquinoline); 3.4-3.6 (unresolved peak, 3H tetrahydroindolizine, 3H morpholine); 2.5-3.1 (unresolved peak, 4H, 2H tetrahydroindolizine, 2H morpholine); 1.5-2.4 (unresolved peak, 10H morpholine)

**IR:** ν: >C=O 1567 broad cm<sup>-1</sup> acetate; ν: 1236 cm<sup>-1</sup>

10

**Step C:**        ***N-(4-[[tert-Butyl(dimethyl)silyl]oxy}phenyl)-3-{6-[[((3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-N-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide***

To a solution of 2.6 g of the compound of Step B (4.73 mmol) in 47 mL of  
15 dichloromethane there are added, dropwise, 1.2 mL of oxalyl chloride at 0°C. The reaction mixture is stirred at ambient temperature for 11 hours, and then co-evaporated several times with dichloromethane. The product so obtained is suspended in 37 mL of dichloromethane and is then added to a solution of 2.1 g  
20 of the compound obtained in Preparation 1" (7.1 mmol) in 10 mL of dichloromethane in the presence of 0.6 mL of pyridine (7.1 mmol). The whole is stirred at ambient temperature overnight. The reaction mixture is concentrated and purified by chromatography over silica gel (dichloromethane/methanol gradient). The title product is obtained in the form of a foam.

25 **<sup>1</sup>H-NMR:** δ (500MHz; dms<sub>2</sub>-d<sub>6</sub>; 300°K): 6.9-7.3 (9H aromatic); 6.88 (2H aromatic); 6.72-6.87 (2H aromatic); 6.64 (2H aromatic); 6.13 (2H methylenedioxy); 5.05-4.74(1H dihydroisoquinoline); 4.25-4.13 (2H dihydroisoquinoline); 3.44-3.7 (4H morpholine); 3.62-3.52 (2H tetrahydroindolizine); 3.0-2.6 (4H, 2H tetrahydroindolizine, 2H  
30 dihydroisoquinoline); 2.54-1.94 (6H morpholine); 1.91-1.53 (4H tetrahydroindolizine); 0.92 (9H *tert*-butyl); 0.17 (6H dimethyl)

**IR:** ν: >C=O: 1632 cm<sup>-1</sup>; ν: >C-O-C<: 1237 cm<sup>-1</sup>; ν: -Si-O-C-: 1035 cm<sup>-1</sup>; -Si-C-:

910 cm<sup>-1</sup>; >CH-Ar: 806 cm<sup>-1</sup>

**Step D:** *N*-(4-Hydroxyphenyl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl]-*N*-phenyl-

**5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride**

To a solution of 1.9 g of the compound obtained in Step C (2.3 mmol) in 4 mL of methanol there is added 0.646 g (11.5 mmol) of potassium hydroxide dissolved in 8 mL of methanol. The whole is stirred at ambient temperature for 30 minutes. The reaction mixture is subsequently diluted in dichloromethane and washed in succession with a 1N HCl solution, a saturated NaHCO<sub>3</sub> solution and then a saturated NaCl solution until a neutral pH is reached. The organic phase is subsequently dried over magnesium sulphate, filtered and evaporated. The crude product so obtained is purified on silica gel (dichloromethane/methanol gradient). The solid is subsequently dissolved in dichloromethane, and 2 mL of 1N ethereal hydrogen chloride are added. The whole is stirred for one hour and then evaporated to dryness. The hydrochloride so obtained is dissolved in a water/acetonitrile mixture until completely dissolved and is then lyophilised.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	69.11	5.8	7.5	4.74
<i>Found</i>	68.95	5.46	7.51	4.48

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 50.8° (c = 9 mg/mL, MeOH)

**Example 2:** *N*-(4-Hydroxyphenyl)-*N*-(4-methylphenyl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl]-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by 4-[[*tert*-butyl(dimethyl)silyl]oxy]-*N*-(4-methylphenyl)aniline.



**Elemental microanalysis:**

	%C	%H	%N	%Cl	%Cl <sup>-</sup>
Calculated	69.42	5.96	7.36	4.66	4.66
5 Found	69.19	5.76	7.19	4.62	4.48

**Example 3:** *N*-(4-Chlorophenyl)-*N*-(4-hydroxyphenyl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizine carboxamide  
10 hydrochloride

The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by 4-[[*tert*-butyl(dimethyl)silyl]oxy]-*N*-(4-chlorophenyl)aniline.

15

**Elemental microanalysis:**

	%C	%H	%N	%Cl	%Cl <sup>-</sup>
Calculated	66.07	5.42	7.17	9.07	4.54
Found	65.74	5.14	7.08	9.02	4.48

20

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 80.9° (c = 2.5 mg/mL, MeOH)

**Example 4:** *N*-(3-Fluoro-4-methylphenyl)-*N*-(4-hydroxyphenyl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizine carboxamide  
25 hydrochloride

The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by 4-[[*tert*-butyl(dimethyl)silyl]oxy]-*N*-(3-fluoro-4-methylphenyl)aniline.

30

**High-resolution mass (ESI+):**

Empirical formula: C<sub>44</sub>H<sub>43</sub>FN<sub>4</sub>O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 743.3245

[M+H]<sup>+</sup> measured: 743.3250

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 40.7° (c = 2.5 mg/mL, MeOH)

5

**Example 5:** *N*-(4-Hydroxyphenyl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl]-*N*-[4-(trifluoromethoxy)phenyl]-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

10

The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by 4-[[*tert*-butyl(dimethyl)silyl]oxy]-*N*-(4-trifluoromethoxyphenyl)aniline.

15 **Elemental microanalysis:**

	%C	%H	%N	%Cl-
<i>Calculated</i>	63.57	5.09	6.74	4.26
<i>Found</i>	63.38	4.95	6.88	4.23

20

**Example 6:** *N,N*-bis(4-Hydroxyphenyl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl]-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

25

The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by 4-[[*tert*-butyl(dimethyl)silyl]oxy]-*N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)aniline.

30 **Elemental microanalysis:**

	%C	%H	%N	%Cl-
<i>Calculated</i>	67.66	5.68	7.34	4.64

<i>Found</i>	67.11	5.49	7.31	4.74
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**Rotatory power:**  $(\alpha)_D^{20} = + 50.8^\circ$  (c = 6 mg/mL, MeOH)

- 5 **Example 7:** *N*-[4-(Hydroxymethyl)phenyl]-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl]-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

- 10 The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by *N*-[4-([*tert*-butyl(dimethyl)silyl]oxy)methyl]phenyl]-1-methyl-1*H*-indol-5-amine.

**Elemental microanalysis:**

15		%C	%H	%N	%Cl
	<i>Calculated</i>	69.32	5.94	8.6	4.35
	<i>Found</i>	69.63	5.75	8.59	4.13

- 20 **Example 8:** *N*-(2,3-Dihydro-1*H*-indol-5-yl)-*N*-[4-(hydroxy)phenyl]-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl]-5,6,7,8-tetrahydro-1-indolizine carboxamide bis(hydrochloride)}

- 25 The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by *N*-(4-([*tert*-butyl(dimethyl)silyl]oxy)phenyl)-5-indolinamine.

**Elemental microanalysis:**

30		%C	%H	%N	%Cl
	<i>Calculated</i>	65.53	5.74	8.49	8.60
	<i>Found</i>	65.47	5.69	8.43	7.82

**Rotatory power:**  $(\alpha)_D^{20} = + 40.9^\circ$  (c = 3.5 mg/mL, MeOH)

**Example 9:** *N*-[4-(Hydroxy)phenyl]-*N*-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-3-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl]carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-

5 indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-5-indolinamine.

10

**High-resolution mass (ESI+):**

Empirical formula: C<sub>46</sub>H<sub>47</sub>N<sub>5</sub>O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 766.3605

[M+H]<sup>+</sup> measured: 766.3601

15

**Example 10:** *N*-[4-(Hydroxy)phenyl]-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl]carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

20

The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

25 **Elemental microanalysis:** (theory for 1.1 HCl)

	%C	%H	%N	%Cl
<i>Calculated</i>	68.72	5.78	8.71	4.85
<i>Found</i>	68.39	5.55	8.66	4.33

30 **Rotatory power:** (α)<sub>D</sub><sup>20</sup> = + 37.6° (c = 7 mg/mL, MeOH)

**Example 11:** *N*-(4-Hydroxyphenyl)-3-{6-[[[(3*R*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl]carbonyl]-1,3-benzodioxol-5-yl]-*N*-phenyl-

**5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride**

The procedure is as in the process of Example 1, replacing the compound of Preparation 1' used in Step A by the compound of Preparation 2'.

5

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	69.11	5.80	7.50	4.74
<i>Found</i>	68.89	5.23	7.41	4.62

10

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = - 45.1° (c = 9 mg/mL, MeOH)

**Example 12:** *N*-(4-Hydroxycyclohexyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-

15 *1,3-benzodioxol-5-yl*}-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy}cyclohexyl)-1-methyl-1*H*-indol-5-amine.

20

**High-resolution mass (ESI+):**

Empirical formula: C<sub>46</sub>H<sub>51</sub>N<sub>5</sub>O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 770.3918

25 [M+H]<sup>+</sup> measured: 770.3928

**Example 13:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[((3*S*)-3-[(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizine carboxamide bis(hydrochloride)

30

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1' used in Step A by the compound of Preparation 3',

and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 {[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

**Elemental microanalysis:**

5		%C	%H	%N	%Cl	%Cl <sup>-</sup>
	<i>Calculated</i>	66.43	5.93	9.89	8.34	8.34
	<i>Found</i>	66.36	5.79	9.83	8.11	7.67

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 60.1° (c = 6 mg/mL, MeOH)

10

**Example 14:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[[(3*S*)-  
 3-(1,4-oxazepan-4-yl)methyl]-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-  
 benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizine carboxamide  
 hydrochloride

15

The procedure is as in the process of Example 1, replacing on the one hand the  
 compound of Preparation 1' used in Step A by the compound of Preparation 4',  
 and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 {[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

20

**Elemental microanalysis:**

	%C	%H	%N	%Cl	%Cl <sup>-</sup>
<i>Calculated</i>	69.32	5.94	8.60	4.35	4.35
<i>Found</i>	69.24	5.56	8.52	4.47	4.44

25

**Example 15:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[[(3*S*)-  
 3-[(3*R*)-3-methylmorpholinyl]methyl]-3,4-dihydro-2(1*H*)-  
 isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-  
 indolizine carboxamide hydrochloride

30

The procedure is as in the process of Example 1, replacing on the one hand the  
 compound of Preparation 1' used in Step A by the compound of Preparation 5',  
 and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-

{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

**Elemental microanalysis:**

		%C	%H	%N	%Cl
5	<i>Calculated</i>	69.32	5.94	8.60	4.35
	<i>Found</i>	69.10	5.68	8.52	4.29

**Example 16:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[[(3*S*)-3-[(3*S*)-3-methylmorpholinyl]methyl]-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1' used in Step A by the compound of Preparation 6', and on the other hand the compound of Preparation 1'' used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

**Elemental microanalysis:**

		%C	%H	%N	%Cl
20	<i>Calculated</i>	69.32	5.94	8.60	4.35
	<i>Found</i>	68.97	5.55	8.44	3.73

**Example 17:** 3-{6-[[[(3*S*)-3-[(3*S*,5*S*)-3,5-Dimethylmorpholinyl]methyl]-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1' used in Step A by the compound of Preparation 7', and on the other hand the compound of Preparation 1'' used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	69.59	6.08	8.45	4.28
<i>Found</i>	69.29	5.52	8.46	4.09

5 **Example 18:** 3-{5-Bromo-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the  
 10 compound of Preparation 1 used in Step A by the compound of Preparation 2, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.

**High-resolution mass (ESI+):**

15 Empirical formula: C<sub>45</sub>H<sub>44</sub><sup>79</sup>BrN<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 798.2655

[M+H]<sup>+</sup> measured: 798.2626

20 **Example 19:** 3-{5-Bromo-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the  
 25 compound of Preparation 1 used in Step A by the compound of Preparation 2, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-5-indolinamine.

**High-resolution mass (ESI+):**

30 Empirical formula: C<sub>45</sub>H<sub>46</sub><sup>79</sup>BrN<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 800.2811

[M+H]<sup>+</sup> measured: 800.2791



**Example 20:** 3-{5-Chloro-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

- 5 The procedure is as in the process of Example 1, replacing the compound of Preparation 1 used in Step A by the compound of Preparation 3.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
10 <i>Calculated</i>	68.38	5.74	7.59	4.81
<i>Found</i>	67.89	5.71	7.72	4.68

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 53.7° (c = 6 mg/mL, MeOH)

- 15 **Example 21:** 3-{5-Chloro-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(2,3-dihydro-1*H*-indol-5-yl)-*N*-(4-hydroxyphenyl)-5,6,7,8-tetrahydro-1-indolizine carboxamide bis(hydrochloride)

- 20 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-5-indolinamine.

- 25 **High-resolution mass (ESI+):**

Empirical formula: C<sub>44</sub>H<sub>44</sub><sup>35</sup>ClN<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 742.3160

[M+H]<sup>+</sup> measured: 742.3120

- 30 **Example 22:** 3-{5-Chloro-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

5

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	68.04	5.72	8.82	4.91
<i>Found</i>	67.84	5.46	8.64	5.21

10

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 55.9° (c = 7 mg/mL, MeOH)

**Example 23:** 3-{5-Chloro-2-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(*1H*)-isoquinolinyl)carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide bis(hydrochloride)

15

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-5-indolinamine.

20

**Elemental microanalysis:**

	%C	%H	%N	%Cl	%Cl
25 <i>Calculated</i>	65.18	5.83	8.45	12.83	8.55
<i>Found</i>	65.75	5.45	8.39	11.71	7.54

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 56.6° (c = 6 mg/mL, MeOH)

**Example 24:** 3-{5-Fluoro-2-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(*1H*)-isoquinolinyl)carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

30

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 4, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

5

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	69.80	5.86	9.04	4.58
<i>Found</i>	69.57	5.62	8.76	4.47

10

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 55.0° (c = 5 mg/mL, MeOH)

**Example 25:** 3-{5-Fluoro-2-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(*1H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

15

The procedure is as in the process of Example 1, replacing the compound of Preparation 1 used in Step A by the compound of Preparation 4.

20 **Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	69.94	5.87	7.77	4.92
<i>Found</i>	69.70	5.32	7.72	4.80

25 **Example 26:** 3-{5-Chloro-2-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(*1H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1,2,3,4-tetrahydro-6-quinoliny)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

30 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1,2,3,4-tetrahydro-6-

quinolinamine.

**Elemental microanalysis:** (theory for 1.5 HCl)

	%C	%H	%N	%Cl
5 <i>Calculated</i>	66.97	6.05	8.49	6.45
<i>Found</i>	66.80	5.55	8.32	6.23

**Example 27:** 3-{5-Chloro-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-7-amine.

**Elemental microanalysis:** (theory for 1.1 HCl)

	%C	%H	%N	%Cl
20 <i>Calculated</i>	66.53	5.84	8.62	4.80
<i>Found</i>	66.59	5.39	8.47	4.80

**Example 28:** 3-{5-Chloro-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-[4-(diethylamino)phenyl]-*N*-(4-hydroxyphenyl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*<sup>1</sup>-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-*N*<sup>4</sup>,*N*<sup>4</sup>-diethyl-1,4-benzenediamine.

**Elemental microanalysis:** (theory for 1.6 HCl)

	%C	%H	%N	%Cl
<i>Calculated</i>	66.51	6.26	8.43	6.83
<i>Found</i>	66.71	5.58	8.39	7.08

- 5 **Example 29:** 3-{5-Chloro-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(2,3-dihydro-1*H*-inden-5-yl)-*N*-(4-hydroxyphenyl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

10 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-5-indanamine.

**Elemental microanalysis:**

15

	%C	%H	%N	%Cl
<i>Calculated</i>	69.49	5.96	7.20	4.56
<i>Found</i>	69.47	5.43	7.21	4.21

- 20 **Example 30:** 3-{5-Chloro-2-[(3*S*)-3-[(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide bis(hydrochloride)

25 The procedure is as in the process of Example 1, replacing on the one hand the compounds of Preparations 1 and 1' used in Step A by the respective compounds of Preparations 3 and 3', and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.

- 30 **High-resolution mass (ESI+):**

Empirical formula: C<sub>46</sub>H<sub>47</sub><sup>35</sup>ClN<sub>6</sub>O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 767.3476

[M+H]<sup>+</sup> measured: 767.3476

**Example 31:** *N*-(4-Hydroxyphenyl)-3-{8-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-3,4-dihydro-2*H*-1,5-benzodioxepin-7-yl]}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

5

The procedure is as in the process of Example 1, replacing the compound of Preparation 1 used in Step A by the compound of Preparation 5.

**High-resolution mass (ESI+):**

10 Empirical formula: C<sub>45</sub>H<sub>46</sub>N<sub>4</sub>O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 739.3496

[M+H]<sup>+</sup> measured: 739.3479

**Example 32:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{8-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-3,4-dihydro-2*H*-1,5-benzodioxepin-7-yl]}-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

15

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 5, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

20

**Elemental microanalysis:**

25		%C	%H	%N	%Cl <sup>-</sup>
	<i>Calculated</i>	69.59	6.08	8.45	4.78
	<i>Found</i>	69.23	5.46	8.41	4.16

**Example 33:** *N*-(4-Hydroxyphenyl)-3-{5-methoxy-2-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl]}-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

30

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 6, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

5

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	70.26	6.15	8.91	4.51
<i>Found</i>	69.78	5.36	8.90	4.29

10

**Rotatory power:**  $(\alpha)_D^{20} = + 42.1^\circ$  (c = 6 mg/mL, MeOH)

**Example 34:** *N*-(4-Hydroxyphenyl)-3-{7-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-2,3-dihydro-1,4-benzodioxin-6-yl]-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

15

The procedure is as in the process of Example 1, replacing the compound of Preparation 1 used in Step A by the compound of Preparation 7.

20 **Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	69.42	5.96	7.36	4.66
<i>Found</i>	69.39	5.56	7.30	4.49

25 **Rotatory power:**  $(\alpha)_D^{20} = + 34.5^\circ$  (c = 6 mg/mL, MeOH)

**Example 35:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{7-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-2,3-dihydro-1,4-benzodioxin-6-yl]-5,6,7,8-tetrahydro-1-indolizine carboxamide

30

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 7, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-

{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine, it being understood that the product so obtained is not subjected to a step of salt formation in the presence of ethereal hydrogen chloride.

5 **Elemental microanalysis:**

	%C	%H	%N
<i>Calculated</i>	72.57	6.09	9.00
<i>Found</i>	73.11	5.70	8.95

10 **Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 88.2° (c = 7 mg/mL, MeOH)

**Example 36:** 3-{5-Ethoxy-2-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

15

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 8, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

20

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	70.53	6.30	8.75	4.43
<i>Found</i>	70.77	5.59	8.66	4.22

25

**Example 37:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{2,2-dideuterio-6-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

30

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 9, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-



{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>46</sub>H<sub>43</sub>N<sub>5</sub>O<sub>6</sub>D<sub>2</sub>

5 [M+H]<sup>+</sup> calculated: 766.3573

[M+H]<sup>+</sup> measured: 766.3533

**Rotatory power:** (α)<sub>D</sub><sup>20</sup> = + 35.5° (c = 3.5 mg/mL, MeOH)

10 **Example 38:** *N*-(4-Hydroxyphenyl)-3-{2,2-dideuterio-6-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

15 **Step A:** *N*-(4-Hydroxyphenyl)-3-{2,2-dideuterio-6-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide

The procedure is as in the process of Example 1, replacing the compound of Preparation 1 used in Step A by the compound of Preparation 9, it being understood that the step of salt formation in the presence of ethereal hydrogen chloride is carried out only in the following Step B.

20

**Step B:** *N*-(4-Hydroxyphenyl)-3-{2,2-dideuterio-6-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

25

The product obtained in Step A is dissolved in dichloromethane, and 2 mL of 1*N* ethereal hydrogen chloride are added. The whole is stirred for one hour and then evaporated to dryness. The hydrochloride so obtained is dissolved in a water/acetonitrile mixture until completely dissolved, and is then lyophilised.

30

**Elemental microanalysis:**

%C	%H	%N	%Cl	%Cl <sup>-</sup>
----	----	----	-----	------------------

<i>Calculated</i>	68.93	5.80	7.48	4.73	4.73
<i>Found</i>	68.45	5.49	7.57	4.63	4.54

**Example 39:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-3-{7-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-2,3-dihydro-1,4-benzodioxin-6-yl]-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 7, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indazol-5-amine.

**Elemental microanalysis:**

	%C	%H	%N	%Cl <sup>-</sup>
<i>Calculated</i>	67.76	5.81	10.31	4.35
<i>Found</i>	67.82	5.25	9.87	4.18

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 42.6° (c = 5 mg/mL, MeOH)

**Example 40:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1,2,3,4-tetrahydro-6-quinolinyl)-3-{7-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-2,3-dihydro-1,4-benzodioxin-6-yl]-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 7, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1,2,3,4-tetrahydro-6-quinolinamine.

**Elemental microanalysis:**

%C	%H	%N	%Cl	%Cl <sup>-</sup>
----	----	----	-----	------------------

<i>Calculated</i>	66.51	6.16	8.08	8.18	8.18
<i>Found</i>	66.85	5.88	8.04	6.47	6.25

**Example 41:** *N*-(4-Hydroxyphenyl)-*N*-(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl)-3-{7-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-2,3-dihydro-1,4-benzodioxin-6-yl}-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 7, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-7-amine.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>47</sub>H<sub>49</sub>N<sub>5</sub>O<sub>7</sub>

[M+H]<sup>+</sup> calculated: 796.3710

[M+H]<sup>+</sup> measured: 796.3687

**Example 42:** 3-{5-Chloro-2-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indazol-5-amine.

**Elemental microanalysis:**

	%C	%H	%N	%Cl	%Cl <sup>-</sup>
<i>Calculated</i>	66.75	5.60	10.61	8.96	4.48
<i>Found</i>	66.63	5.06	10.42	8.83	4.46

**Example 43:** 1-{5-Chloro-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-3-indolizine carboxamide hydrochloride

5

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 24, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{*tert*-butyl(dimethyl)silyl}oxy)phenyl)-1-methyl-1*H*-indol-5-amine.

10

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	68.35	5.74	8.86	8.97
<i>Found</i>	68.29	5.21	8.76	9.04

15

**Example 44:** 3-{5-Fluoro-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

20

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 4, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{*tert*-butyl(dimethyl)silyl}oxy)phenyl)-1-methyl-1*H*-indazol-5-amine.

25

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	68.16	5.72	10.84	4.57
<i>Found</i>	67.93	5.01	10.89	4.24

30

**Example 45:** 3-{5-Chloro-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-

**2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1'-methyl-1',2'-dihydrospiro[cyclopropane-1,3'-indol]-5'-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide**

- 5 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-(1'-methyl-1',2'-dihydrospiro[cyclopropane-1,3'-indol]-5'-yl)amine.

10

**Elemental microanalysis:**

	%C	%H	%N
<i>Calculated</i>	72.15	6.18	8.95
<i>Found</i>	71.86	5.76	8.85

15

**Example 46: 3-{5-Chloro-2-[(*(3S)*-3-(1,4-oxazepan-4-ylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride**

- 20 The procedure is as in the process of Example 1, replacing on the one hand the compounds of Preparations 1 and 1' used in Step A by the respective compounds of Preparations 3 and 4', and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.

25

**Elemental microanalysis:**

	%C	%H	%N
<i>Calculated</i>	68.65	5.89	8.70
<i>Found</i>	68.33	5.45	8.54

30

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 13.6° (c = 4 mg/mL, MeOH)

**Example 47: *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-[2-[(*(3S)*-3-**

**(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinoliny]carbonyl]-5-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride**

- 5 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 10, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.

10 **Elemental microanalysis:**

	%C	%H	%N	%Cl <sup>-</sup>
<i>Calculated</i>	67.02	5.50	8.50	4.30
<i>Found</i>	67.01	5.11	8.47	4.21

- 15 **Example 48:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-[2-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-5-(trifluoromethoxy)phenyl]-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

- 20 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 11, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.

25 **Elemental microanalysis:**

	%C	%H	%N	%Cl	%Cl <sup>-</sup>
<i>Calculated</i>	65.75	5.40	8.33	4.22	4.22
<i>Found</i>	65.78	5.00	8.35	4.33	4.50

- 30 **Example 49:** 3-{5-Chloro-2-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1,3,3-trimethyl-2,3-dihydro-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 5 {{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1,3,3-trimethyl-5-indolinamine, it being understood that the product so obtained is not subjected to a step of salt formation in the presence of ethereal hydrogen chloride.

**Elemental microanalysis:**

10		%C	%H	%N
	<i>Calculated</i>	71.97	6.42	8.93
	<i>Found</i>	71.87	6.22	8.94

**Example 50:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-3-{2,2-  
 15 dideuterio-6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-  
 isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-  
 indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the  
 20 compound of Preparation 1 used in Step A by the compound of Preparation 9,  
 and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 {{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indazol-5-amine.

**Elemental microanalysis:**

25		%C	%H	%N	%Cl <sup>-</sup>
	<i>Calculated</i>	67.28	5.66	10.46	4.41
	<i>Found</i>	66.77	5.07	10.25	3.92

**Example 51:** *N*-(3-Fluoro-4-methylphenyl)-*N*-(4-hydroxyphenyl)-3-{2,2-  
 30 dideuterio-6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-  
 isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-  
 indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 9, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{*tert*-butyl(dimethyl)silyl}oxy)phenyl)-3-fluoro-4-methylaniline.

5

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	67.64	5.69	7.17	4.54
<i>Found</i>	67.08	5.18	7.04	4.28

10

**Example 52:** 3-{5-Chloro-2-[(*(3S)*-3-[(dimethylamino)methyl]-3,4-dihydro-2(*1H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

15 The procedure is as in the process of Example 1, replacing on the one hand the compounds of Preparations 1 and 1' used in Step A by the respective compounds of Preparations 3 and 8', and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{*tert*-butyl(dimethyl)silyl}oxy)phenyl)-1-methyl-1*H*-indol-5-amine.

20

**High-resolution mass (ESI+):**

Empirical formula: C<sub>43</sub>H<sub>42</sub><sup>35</sup>ClN<sub>5</sub>O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 712.3054

[M+H]<sup>+</sup> measured: 712.3060

25

**Rotatory power:** (α)<sub>D</sub><sup>20</sup> = + 35.8° (c = 6 mg/mL, MeOH)

**Example 53:** 3-{5-Chloro-2-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(*1H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-[4-methoxy-3-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

30

The procedure is as in the process of Example 1, replacing on the one hand the



compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-4-methoxy-3-(trifluoromethyl)aniline.

5 **Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	63.23	5.19	6.70	4.24
<i>Found</i>	63.08	4.68	6.79	3.92

10 **Example 54:** 3-{5-Chloro-2-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-[4-(methylsulphanyl)-3-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

15 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-4-(methylsulphanyl)-3-(trifluoromethyl)aniline.

20

**Elemental microanalysis:**

	%C	%H	%N	%S	%Cl
<i>Calculated</i>	62.04	5.09	6.58	3.76	4.16
<i>Found</i>	62.10	4.90	6.61	3.37	3.99

25

**Example 55:** 3-{5-Chloro-2-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(3-fluoro-4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

30

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-

{{*tert*-butyl(dimethyl)silyl}oxy}-3-fluorophenyl)-1-methyl-1*H*-indol-5-amine.

**Elemental microanalysis:**

		%C	%H	%N	%Cl
5	<i>Calculated</i>	66.83	5.48	8.66	4.38
	<i>Found</i>	66.84	4.92	8.68	3.63

**Example 56:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{2-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 12, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

**Elemental microanalysis:**

		%C	%H	%N	%Cl
	<i>Calculated</i>	71.84	5.63	9.31	4.71
20	<i>Found</i>	71.74	5.25	9.24	4.38

**Example 57:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[((3*S*)-3-[(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-1-indolizine carboxamide bis(hydrochloride)

25

The procedure is as in the process of Example 1, replacing on the one hand the compounds of Preparations 1 and 1' used in Step A by the respective compounds of Preparations 13 and 3', and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

30

**Elemental microanalysis:**

	%C	%H	%N	%Cl
--	----	----	----	-----

65

<i>Calculated</i>	66.74	5.48	9.94	8.38
<i>Found</i>	66.69	5.25	9.80	8.03

**Rotatory power:**  $(\alpha)_D^{20} = + 113.2^\circ$  (c = 6 mg/mL, MeOH)

5

**Example 58:** *N*-(4-Hydroxyphenyl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl]-*N*-phenyl-1-indolizine carboxamide hydrochloride

- 10 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 13.

**Elemental microanalysis:**

	%C	%H	%N	%Cl <sup>-</sup>
15 <i>Calculated</i>	69.49	5.29	7.54	4.77
<i>Found</i>	69.41	5.00	7.61	4.45

**Rotatory power:**  $(\alpha)_D^{20} = + 111.4^\circ$  (c = 6 mg/mL, MeOH)

- 20 **Example 59:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl]-1-indolizine carboxamide hydrochloride

- 25 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 13, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.

**Elemental microanalysis:**

	%C	%H	%N	%Cl <sup>-</sup>
30 <i>Calculated</i>	69.38	5.32	8.79	4.45
<i>Found</i>	68.95	5.12	8.57	3.92

**Rotatory power:**  $(\alpha)_D^{20} = + 116.8^\circ$  ( $c = 5$  mg/mL, MeOH)

**Example 60:** *N*-(1-Ethyl-1*H*-indol-5-yl)-*N*-(4-hydroxyphenyl)-3-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-

5 *benzodioxol-5-yl*}-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 13, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
10 {[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-ethyl-1*H*-indol-5-amine.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
Calculated	69.66	5.47	8.64	4.38
15 Found	69.81	5.13	8.64	4.30

**Example 61:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-3-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-

20 *isoquinoliny]carbonyl*]-1,3-benzodioxol-5-yl}-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 13, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
25 {[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-5-indolinamine.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>46</sub>H<sub>43</sub>N<sub>5</sub>O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 762.3292

30 [M+H]<sup>+</sup> measured: 762.3284

**Example 62:** *N*-(4-Hydroxyphenyl)-*N*-(1-isopropyl-1*H*-indol-5-yl)-3-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-

**benzodioxol-5-yl}-1-indolizine carboxamide hydrochloride**

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 13,  
 5 and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 {[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-isopropyl-1*H*-indol-5-amine.

**Elemental microanalysis:** (theory for 1.3 HCl)

		%C	%H	%N	%Cl <sup>-</sup>
10	<i>Calculated</i>	69.94	5.62	8.50	4.30
	<i>Found</i>	69.66	5.50	8.42	4.28

**Example 63:** *N*-(1-Ethyl-2,3-dihydro-1*H*-indol-5-yl)-*N*-(4-hydroxyphenyl)-3-  
 {6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-  
 15 isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-1-indolizine carboxamide  
 hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 13,  
 20 and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 {[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-ethyl-5-indolinamine.

**Elemental microanalysis:** (theory for 1.3 HCl)

		%C	%H	%N	%Cl <sup>-</sup>
25	<i>Calculated</i>	68.57	5.67	8.51	5.60
	<i>Found</i>	68.11	5.23	8.36	5.65

**Example 64:** *N*-(4-Hydroxyphenyl)-*N*-(1-isopropyl-2,3-dihydro-1*H*-indol-5-  
 yl)-3-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-  
 30 isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-1-indolizine carboxamide  
 hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the

compound of Preparation 1 used in Step A by the compound of Preparation 13, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-isopropyl-5-indolinamine.

5 **Elemental microanalysis:** (theory for 1.3 HCl)

	%C	%H	%N	%Cl <sup>-</sup>
<i>Calculated</i>	68.85	5.81	8.36	5.50
<i>Found</i>	68.58	5.68	8.49	5.10

10 **Example 65:** 3-{5-Chloro-2-(((3*S*)-3-[(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-1-indolizine carboxamide bis(hydrochloride)

The procedure is as in the process of Example 1, replacing on the one hand the compounds of Preparations 1 and 1' used in Step A by the respective compounds of Preparations 14 and 3', and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

20 **Elemental microanalysis:** (theory for 1.9 HCl)

	%C	%H	%N	%Cl <sup>-</sup>
<i>Calculated</i>	66.36	5.44	10.09	8.09
<i>Found</i>	66.35	5.38	9.86	7.70

25 **Example 66:** 3-{5-Chloro-2-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-1-indolizine carboxamide bis(hydrochloride)

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 14, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-5-indolinamine.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
Calculated	65.50	5.37	8.49	12.89
Found	66.02	4.91	8.50	12.11

5

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 142.2° (c = 3.5 mg/mL, MeOH)

**Example 67:** 3-{5-Chloro-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 14, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
Calculated	68.70	5.25	8.90	4.51
Found	68.43	4.88	8.83	4.13

20

**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 133.3° (c = 3.5 mg/mL, MeOH)

**Example 68:** 3-{5-Chloro-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-fluorophenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-1-indolizine carboxamide hydrochloride

25

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 14, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-fluorophenyl)-1-methyl-1*H*-indol-5-amine, it being understood that step D is then limited to a step of formation of the hydrochloride.

30

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	68.53	5.11	8.88	4.49
<i>Found</i>	68.48	4.71	9.09	4.28

5

**Example 69:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1,2,3,4-tetrahydro-6-quinolinyl)-3-{7-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(*1H*)-isoquinolinyl)carbonyl]-2,3-dihydro-1,4-benzodioxin-6-yl}-1-indolizine carboxamide hydrochloride

10

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 15, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1,2,3,4-tetrahydro-6-quinolinamine.

15

**High-resolution mass (ESI+):**Empirical formula: C<sub>48</sub>H<sub>47</sub>N<sub>5</sub>O<sub>6</sub>[M+H]<sup>+</sup> calculated: 790.360520 [M+H]<sup>+</sup> measured: 790.3591

**Example 70:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{7-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(*1H*)-isoquinolinyl)carbonyl]-2,3-dihydro-1,4-benzodioxin-6-yl}-1-indolizine carboxamide hydrochloride

25

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 15, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.

30

**Elemental microanalysis:**

	%C	%H	%N	%Cl	%Cl
<i>Calculated</i>	69.66	5.47	8.64	4.38	4.38



71

<i>Found</i>	69.45	4.68	8.56	4.64	4.21
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**Example 71:** *N*-(4-Hydroxyphenyl)-3-{5-methoxy-2-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(1-methyl-1*H*-indol-5-yl)-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 16, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>46</sub>H<sub>43</sub>N<sub>5</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 746.3342

[M+H]<sup>+</sup> measured: 746.3348

**Example 72:** *Tert*-butyl 8-[[4-hydroxy(1-methyl-1*H*-indol-5-yl)anilino]carbonyl]-6-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 17, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine, it being understood that the product so obtained is not subjected to a step of salt formation in the presence of ethereal hydrogen chloride.

**Elemental microanalysis:**

	%C	%H	%N
<i>Calculated</i>	69.43	6.06	9.72
<i>Found</i>	69.41	5.84	9.68

**Example 73:** *Tert*-butyl 8-[[4-hydroxy(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-anilino]carbonyl]-6-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl]-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate

5

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 17, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-5-indolinamine, it being understood that the product so obtained is not subjected to a step of salt formation in the presence of ethereal hydrogen chloride.

10

**Elemental microanalysis:**

	%C	%H	%N
15 <i>Calculated</i>	69.27	6.28	9.69
<i>Found</i>	69.20	6.11	9.77

**Example 74:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-6-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl]-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide bis(hydrochloride)

20

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 17, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine, it being understood that the product so obtained is not subjected to a step of salt formation in the presence of ethereal hydrogen chloride as described in Step D of Example 1. The compound so obtained is deprotected in the presence of 10 equivalents of trifluoroacetic acid in dichloromethane (10 mL/mmol) at ambient temperature overnight. Then, the product is subsequently isolated by concentrating the reaction mixture to dryness. It is finally subjected to a step of salt formation in the presence of ethereal hydrogen chloride.

25

30

**Elemental microanalysis:** (theory for 1.9 HCl)

	%C	%H	%N	%Cl <sup>-</sup>
Calculated	64.80	5.55	10.08	8.08
5 Found	64.48	5.41	9.85	7.84

**Example 75:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-6-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide tris(hydrochloride)

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 17, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 15 {[(*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-5-indolinamine, it being understood that the product so obtained is not subjected to a step of salt formation in the presence of ethereal hydrogen chloride as described in Step D of Example 1. The compound so obtained is deprotected in the presence of  
 20 equivalents of trifluoroacetic acid in dichloromethane (10 mL/mmol) at ambient temperature overnight. Then, the product is subsequently isolated by concentrating the reaction mixture to dryness. It is finally subjected to a step of salt formation in the presence of ethereal hydrogen chloride.

**Elemental microanalysis:**

25	%C	%H	%N	%Cl <sup>-</sup>
Calculated	61.68	5.64	9.59	12.14
Found	61.65	5.35	9.45	11.72

**Example 76:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5-{6-[[[(3*S*)-3-  
 30 [(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-2,3-dihydro-1*H*-pyrrolizine-7-carboxamide bis(hydrochloride)

The procedure is as in the process of Example 1, replacing on the one hand the compounds of Preparations 1 and 1' used in Step A by the respective compounds of Preparations 18 and 3', and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>46</sub>H<sub>46</sub>N<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 763.3608

10 [M+H]<sup>+</sup> measured: 763.3594

**Example 77:** 5-{5-Chloro-2-[[[(3*S*)-3-[(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2(1*H*)-isoquinolinyl]carbonyl]phenyl]-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-2,3-dihydro-1*H*-pyrrolizine-7-carboxamide  
15 bis(hydrochloride)

The procedure is as in the process of Example 1, replacing on the one hand the compounds of Preparations 1 and 1' used in Step A by the respective compounds of Preparations 19 and 3', and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.

**Elemental microanalysis:** (theory for 1.9 HCl)

	%C	%H	%N	%Cl
25 Calculated	65.70	5.75	10.22	8.19
Found	65.46	5.55	10.68	7.65

**Example 78:** 6-{5-Chloro-2-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl]carbonyl]phenyl]-*N*-(4-hydroxyphenyl)-*N*-phenyl-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxamide hydrochloride  
30

The procedure is as in the process of Example 1, replacing the compound of Preparation 1 used in Step A by the compound of Preparation 20.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
Calculated	66.57	5.45	7.57	4.79
5 Found	66.22	5.23	7.53	4.57

**Example 79:** 6-{5-Chloro-2-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(2,3-dihydro-1*H*-indol-5-yl)-*N*-(4-hydroxyphenyl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxamide  
10 bis(hydrochloride)

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 20, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
15 [[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-5-indolinamine.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
Calculated	63.20	5.43	8.57	8.68
20 Found	62.64	5.19	8.39	8.03

**Example 80:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-6-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-  
25 carboxamide

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 21, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
30 [[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine, it being understood that the product so obtained is not subjected to a step of salt formation in the presence of ethereal hydrogen chloride.

**Elemental microanalysis:**

	%C	%H	%N
<i>Calculated</i>	70.57	5.66	9.14
<i>Found</i>	69.99	5.53	9.04

5

**Example 81:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-6-{6-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxamide hydrochloride

10

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 21, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-5-indolinamine.

15

**Elemental microanalysis:**

	%C	%H	%N	%Cl <sup>-</sup>
<i>Calculated</i>	67.20	5.76	8.71	4.41
<i>Found</i>	66.67	5.60	8.66	5.10

20

**Example 82:** 6-{5-Chloro-2-[[[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(3-fluoro-4-methylphenyl)-*N*-(4-hydroxyphenyl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxamide hydrochloride

25

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 20, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-3-fluoro-4-methylaniline.

30

**Elemental microanalysis:**

	%C	%H	%N	%Cl	%Cl <sup>-</sup>
<i>Calculated</i>	65.37	5.35	7.26	9.19	4.59

77

Found	65.49	4.67	7.45	9.18	4.40
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**Rotatory power:** ( $\alpha$ )<sub>D</sub><sup>20</sup> = + 35.0° (c = 6 mg/mL, MeOH)

- 5 **Example 83:** 3-{5-Chloro-2-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-6-yl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carboxamide hydrochloride
- 10 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 22, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.
- 15 **High-resolution mass (ESI+):**  
 Empirical formula: C<sub>46</sub>H<sub>46</sub><sup>35</sup>ClN<sub>5</sub>O<sub>4</sub>  
 [M+H]<sup>+</sup> calculated: 768.3317  
 [M+H]<sup>+</sup> measured: 768.3254
- 20 **Example 84:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-6-yl)-3-{6-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl]carbonyl]-1,3-benzodioxol-5-yl}-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carboxamide hydrochloride
- 25 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 23, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.
- 30 **Elemental microanalysis:**

	%C	%H	%N	%Cl
Calculated	69.32	5.94	8.60	4.35
Found	69.42	5.52	8.74	4.05

**Rotatory power:**  $(\alpha)_D^{20} = + 86.6^\circ$  ( $c = 8$  mg/mL, MeOH)

**Example 85:** 3-{5-Chloro-2-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(*1H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(3-thienyl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-3-thiophenamine.

**Elemental microanalysis:**

		%C	%H	%N	%S	%Cl
15	Calculated	64.60	5.42	7.53	4.31	4.77
	Found	64.67	5.05	7.37	3.90	4.19

**Example 86:** 6-{5-Chloro-2-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(*1H*)-isoquinoliny]carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 20, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1*H*-indol-5-amine.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>44</sub>H<sub>42</sub><sup>35</sup>ClN<sub>5</sub>O<sub>5</sub>

30 [M+H]<sup>+</sup> calculated: 756.2953  
[M+H]<sup>+</sup> measured: 756.2936

**Example 87:** *N*-Butyl-*N*-(4-hydroxyphenyl)-3-{6-[(*(3S)*-3-(4-



**morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride**

- 5 The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by *N*-butyl-4-[[*tert*-butyl(dimethyl)silyl]oxy]aniline.

***Elemental microanalysis:***

	%C	%H	%N	%Cl <sup>-</sup>
10 <i>Calculated</i>	67.71	6.51	7.70	4.87
<i>Found</i>	67.48	6.30	7.74	5.01

- Example 88: *N*-Butyl-*N*-[(3-{6-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indoliziny]methyl]-1-butanamine hydrochloride**
- 15

The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by *N,N*-dibutylamine, it being understood that Step D is then limited to a step of formation of the hydrochloride.

20

***High-resolution mass (ESI<sup>+</sup>):***

Empirical formula: C<sub>39</sub>H<sub>50</sub>N<sub>4</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 655.3859

[M+H]<sup>+</sup> measured: 655.3826

25

**Example 89: 3-{5-Chloro-2-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]carbonyl]phenyl}-*N*-(3-hydroxypropyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride**

- 30 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(3-[[*tert*-butyl(dimethyl)silyl]oxy]propyl)-1-methyl-1*H*-indol-5-amine.

**Elemental microanalysis:**

	%C	%H	%N	%Cl	%Cl <sup>-</sup>
Calculated	66.66	6.26	9.25	9.37	4.68
5 Found	66.51	5.87	9.25	9.12	4.21

**Example 90:** 3-{5-Chloro-2-[[[(3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinolinyl]carbonyl]phenyl]-N-(4-hydroxybutyl)-N-(1-methyl-1H-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride

10

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by N-(3-[[tert-butyl(dimethyl)silyl]oxy]butyl)-1-methyl-1H-indol-5-amine.

15

**Elemental microanalysis:**

	%C	%H	%N	%Cl <sup>-</sup>
Calculated	67.01	6.41	9.09	4.60
Found	66.93	5.88	9.23	4.30

20

**Example 91:** N-(3-Fluoro-4-methylphenyl)-3-(5-fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

25 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 4, and on the other hand the compound of Preparation 1" used in Step C by N-(4-[[tert-butyl(dimethyl)silyl]oxy]phenyl)-3-fluoro-4-methylaniline.

30 **Elemental microanalysis:**

	%C	%H	%N	%Cl <sup>-</sup>
Calculated	68.56	5.75	7.44	4.71
Found	68.57	5.23	7.53	4.74

**Example 92:** *N*-(3-Fluoro-4-methylphenyl)-*N*-(4-hydroxyphenyl)-6-(6-([(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)-1,3-benzodioxol-5-yl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxamide  
5 hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 21, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
10 {[(*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3-fluoro-4-methylaniline.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	66.11	5.42	7.17	4.54
15 <i>Found</i>	66.02	4.92	7.13	4.26

**Example 93:** 3-(5-Chloro-2-([(3*R*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide  
20 hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compounds of Preparations 1 and 1' used in Step A by the compounds of Preparations 3 and 2', and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[(*tert*-butyl(dimethyl)silyl]oxy)phenyl)-1-methyl-1*H*-indol-  
25 5-amine.

**Elemental microanalysis:**

	%C	%H	%N	%Cl	%Cl
30 <i>Calculated</i>	68.35	5.74	8.86	8.97	4.48
<i>Found</i>	68.27	5.14	8.92	8.70	4.08

**Example 94:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-3-(6-([(3*S*)-

**3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride**

- 5 The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indazol-5-amine.

***Elemental microanalysis:***

10		%C	%H	%N	%Cl
	<i>Calculated</i>	67.45	5.66	10.49	4.42
	<i>Found</i>	67.40	5.19	10.40	4.11

- Example 95:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-(5-methyl-2-  
15 {[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

- The procedure is as in the process of Example 1, replacing on the one hand the  
20 compound of Preparation 1 used in Step A by the compound of Preparation 25, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-[[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

***Elemental microanalysis:***

25		%C	%H	%N	%Cl
	<i>Calculated</i>	71.72	6.28	9.09	4.60
	<i>Found</i>	71.17	5.66	8.85	4.47

- Example 96:** *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5-(6-{[(3*S*)-3-  
30 (morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-2,3-dihydro-1*H*-pyrrolizine-7-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the

compound of Preparation 1 used in Step A by the compound of Preparation 18, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

5 **Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	68.74	5.64	8.91	4.51
<i>Found</i>	68.41	4.96	8.84	4.31

- 10 **Example 97:** *N*-(3-Chloro-4-methylphenyl)-3-(5-chloro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

- 15 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-3-chloro-4-methylaniline.

20 **Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	65.69	5.51	7.13	4.51
<i>Found</i>	65.58	5.03	7.05	4.25

- 25 **Example 98:** *N*-(3-Fluoro-4-methylphenyl)-6-(5-fluoro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxamide hydrochloride

- 30 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 26, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-3-fluoro-4-methylaniline.

**High-resolution mass (ESI+):**Empirical formula: C<sub>42</sub>H<sub>40</sub>F<sub>2</sub>N<sub>4</sub>O<sub>5</sub>[M+H]<sup>+</sup> calculated: 719.30455 [M+H]<sup>+</sup> measured: 719.3030

**Example 99:** 6-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-fluorophenyl)-N-(4-hydroxyphenyl)-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazine-8-carboxamide  
 10 hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 26, and on the other hand the compound of Preparation 1" used in Step C by 4-  
 15 {[*tert*-butyl(dimethyl)silyl]oxy}-N-(4-fluorophenyl)aniline.

**High-resolution mass (ESI+):**Empirical formula: C<sub>41</sub>H<sub>38</sub>F<sub>2</sub>N<sub>4</sub>O<sub>5</sub>[M+H]<sup>+</sup> calculated: 705.288920 [M+H]<sup>+</sup> measured: 705.2882

**Example 100:** 3-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-7-hydroxy-N-(4-hydroxyphenyl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide  
 25 hydrochloride

**Step A: Methyl** 3'-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-5',6'-dihydro-8'H-spiro[1,3-dioxolane-2,7'-indolizine]-1'-carboxylate

30 The procedure is as in the process of Step A of Example 1, replacing the compound of Preparation 1 by the compound of Preparation 27.

**Step B: Methyl** 3-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroiso-

***quinolin-2(1H)-yl]carbonyl}phenyl)-7-(prop-2-en-1-yloxy)-5,6,7,8-tetrahydroindolizine-1-carboxylate***

The procedure is as in the process of Steps B, C and D of Example 113.

- 5 ***Step C: N-(4-{{tert-Butyl(dimethyl)silyl}oxy}phenyl)-3-(5-fluoro-2-{{(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-phenyl-7-(prop-2-en-1-yloxy)-5,6,7,8-tetrahydroindolizine-1-carboxamide***

The procedure is as in the processes of Steps B and C of Example 1.

- 10 ***Step D: N-(4-{{tert-Butyl(dimethyl)silyl}oxy}phenyl)-3-(5-fluoro-2-{{(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-phenyl-7-hydroxy-5,6,7,8-tetrahydroindolizine-1-carboxamide***

There is subsequently carried out a reaction of deprotection of the allyl group in the presence of 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (also called  
15 dimethyl barbiturate) and of tetrakis(triphenylphosphine)palladium in a mixture of methanol and dichloromethane.

- Step E: 3-(5-Fluoro-2-{{(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-7-hydroxy-N-(4-hydroxyphenyl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride***
- 20

Deprotection of the *tert*-butylsilyloxy group is carried out according to the process of Step D of Example 1.

25 ***Elemental microanalysis:***

	%C	%H	%N
<i>Calculated</i>	71.98	5.90	7.99
<i>Found</i>	71.18	5.98	7.18

30 ***High-resolution mass (ESI+):***

Empirical formula: C<sub>42</sub>H<sub>42</sub>FN<sub>4</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 701.3139

[M+H]<sup>+</sup> measured: 701.3134

**Example 101:** 6-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N-(1-methyl-1H-indazol-5-yl)-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazine-8-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 20, and on the other hand the compound of Preparation 1" used in Step C by N-(4-  
 10 [[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1H-indazol-5-amine.

**Elemental microanalysis:**

	%C	%H	%N
Calculated	65.07	5.33	10.59
15 Found	65.54	4.86	10.57

**Example 102:** (2R)-5-(5-Fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-2-hydroxy-N-(4-hydroxyphenyl)-N-phenyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide  
 20 hydrochloride

**Step A: Methyl** (2R)-2-[[*tert*-butyl(dimethyl)silyl]oxy}-5-(5-fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-2,3-dihydro-1H-pyrrolizine-7-carboxylate

25 The procedure is as in the process of Step A of Example 1, replacing the compound of Preparation 1 by the compound of Preparation 28.

**Step B: Methyl** (2R)-5-(5-fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-2-hydroxy-2,3-dihydro-1H-pyrrolizine-7-carboxylate

To a solution of the compound of Step A (1 g; 1.54 mmol) in THF (8 mL) there is added a 1 M tetrabutylammonium fluoride solution (1.7 mL; 1.7 mmol). The reaction mixture is stirred for 3 hours at ambient temperature, and then the THF



is evaporated off and replaced by ethyl acetate. The organic phase is washed with water and then with brine, before being dried over  $\text{MgSO}_4$ , filtered and concentrated to dryness. The crude product obtained (830 mg) is used as such in the following step.

5

**$^1\text{H-NMR}$ :**  $\delta$  (500 MHz;  $\text{dmsO-d}_6$ ; 300°K) 7.55-6.9 (m, 7H, H aromatic); 6.55-6.35 (m, 1H, H aromatic dihydropyrrolizine); 5.5-5.3 (m, 1H, alcohol); 5.25-4.6 (m, 1H, H tertiary tetrahydroisoquinoline); 5.0-4.2 (m, 2H, H aliphatic tetrahydroisoquinoline); 4.95-4.62 (m, 1H, HCOH); 3.7-3.6 (sl, 3H, OMe); 3.6-10 3.2. (m, 2H, 2H, H aliphatic dihydropyrrolizine); 3.7-3.5 (m, 4H, H morpholine); 3.0-2.4 (m, 2H, H aliphatic tetrahydroisoquinoline); 2.6-1.96 (m, 4H, H morpholine); 2.6-1.96 (m, 2H, H aliphatic dihydropyrrolizine)

**Step C: Methyl**      ***(2R)-5-(5-fluoro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-2-(prop-2-en-1-yloxy)-2,3-dihydro-1H-pyrrolizine-7-carboxylate***

To a suspension of 62 mg (1.54 mmol) of sodium hydride in 8 mL of anhydrous THF cooled to 0°C there is added a solution of the compound of Step B (820 mg; 1.54 mmol) in THF (6 mL). The suspension is stirred for 15 minutes at 0°C. 20 There is subsequently added 0.15 mL (1.69 mmol) of allyl bromide, dropwise. The reaction mixture is stirred for 5 hours at ambient temperature, and then hydrolysed with a saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The organic phase is dried over  $\text{MgSO}_4$ , filtered and concentrated to dryness. The oil so obtained is purified by flash 25 chromatography (gradient: dichloromethane/ammoniacal methanol) to yield the title product in solid form.

**$^1\text{H-NMR}$ :**  $\delta$  (500 MHz;  $\text{dmsO-d}_6$ ; 300°K): 7.5-6.8 (m, 7H, H aromatic); 6.55-6.3 (m, 1H, H aromatic dihydropyrrolizine); 5.9 (s, 1H, H allyl); 5.3-5.2 (m, 2H, H allyl); 5.2-5.0 (m, 1H, H tertiary tetrahydroisoquinoline); 5.0-4.2 (m, 2H, H aliphatic tetrahydroindolizine); 4.7-4.42 (m, 1H, HCOallyl); 4.6-3.85 (m, 2H, H aliphatic dihydropyrrolizine); 4.6-3.85 (m, 2H,  $\text{CH}_2$  allylic); 3.7-3.5 (m, 3H, OMe); 3.65-3.5 (m, 4H, morpholine); 3.3-2.4 (m, 4H, morpholine and H aliphatic

30

dihydropyrrolidine); 2.4-1.7 (m, 6H, morpholine and CH<sub>2</sub>N)

**Step D: (2R)-N-(4-{{tert-Butyl(dimethyl)silyl}oxy}phenyl)-5-(5-fluoro-2-  
 5 {[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-  
 yl]carbonyl}phenyl)-N-phenyl-2-(prop-2-en-1-yloxy)-2,3-dihydro-1H-  
 pyrrolizine-7-carboxamide**

The procedure is as in the processes of Steps B and C of Example 1.

**Step E: (2R)-N-(4-{{tert-Butyl(dimethyl)silyl}oxy}phenyl)-5-(5-fluoro-2-  
 10 {[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-  
 yl]carbonyl}phenyl)-2-hydroxy-N-phenyl-2,3-dihydro-1H-pyrrolizine-7-  
 carboxamide**

There is then carried out a reaction of deprotection of the allyl group in the presence of 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (also called dimethyl  
 15 barbiturate) and of tetrakis(triphenylphosphine)palladium (Synlett, 2007, 21, p. 3136).

**Step F: (2R)-5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydro-  
 20 isoquinolin-2(1H)-yl]carbonyl}phenyl)-2-hydroxy-N-(4-hydroxyphenyl)-N-  
 phenyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide hydrochloride**

Deprotection of the *tert*-butylsilyloxy group is carried out according to the process of Step D of Example 1.

***Elemental microanalysis:***

25		%C	%H	%N	%Cl <sup>-</sup>
	<i>Calculated</i>	68.09	5.57	7.75	4.90
	<i>Found</i>	67.73	5.10	7.54	4.84

***High-resolution mass (ESI<sup>+</sup>):***

30 Empirical formula: C<sub>41</sub>H<sub>39</sub>N<sub>4</sub>O<sub>5</sub>  
 [M+H]<sup>+</sup> calculated: 687.2983  
 [M+H]<sup>+</sup> measured: 687.2958

**Example 103:** 3-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide

5

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by N-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-5-amine.

10

**High-resolution mass (ESI+):**

Empirical formula: C<sub>44</sub>ClH<sub>44</sub>N<sub>6</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 755.3113

[M+H]<sup>+</sup> measured: 755.3088

15

**Example 104:** N-(4-Hydroxyphenyl)-3-(5-methoxy-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(1-methyl-1H-indazol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

20 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 6, and on the other hand the compound of Preparation 1" used in Step C by N-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1H-indazol-5-amine.

25 **Elemental microanalysis:**

	%C	%H	%N	%Cl
Calculated	68.65	6.02	10.67	4.50
Found	67.91	5.52	10.53	4.08

30 **Example 105:** N-(4-Hydroxyphenyl)-3-(6-{[(3S)-3-{[4-(2-methoxyethyl)piperazin-1-yl]methyl}-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide bis(hydrochloride)

The procedure is as in the process of Example 1, replacing the compound of Preparation 1' used in Step A by the compound of Preparation 9'.

5 **Elemental microanalysis:**

	%C	%H	%N
<i>Calculated</i>	65.71	6.11	8.33
<i>Found</i>	66.57	6.16	8.44

10 **Example 106:** (2*S*)-5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-2-hydroxy-*N*-(4-hydroxyphenyl)-*N*-phenyl-2,3-dihydro-1*H*-pyrrolizine-7-carboxamide hydrochloride

15 The procedure is as in the process of Example 102, replacing the compound of Preparation 28 used in Step A by the compound of Preparation 29.

**Elemental microanalysis:**

	%C	%H	%N	%Cl <sup>-</sup>
20 <i>Calculated</i>	68.09	5.57	7.75	4.90
<i>Found</i>	68.16	5.13	7.74	4.97

**Example 107:** 3-(5-Chloro-2-{[(3*S*)-3-[(4-methyl-3-oxopiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

25

The procedure is as in the process of Example 1, replacing on the one hand the compounds of Preparations 1 and 1' used in Step A by the respective compounds of Preparations 3 and 10', and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indol-5-amine.

30

**Elemental microanalysis:**

	%C	%H	%N	%Cl	%Cl <sup>-</sup>
<i>Calculated</i>	67.56	5.67	10.28	8.67	4.34
<i>Found</i>	67.31	5.14	10.18	8.27	3.76

5

**Example 108:** 3-(5-Chloro-2-[[[(3S)-3-[[[2-methoxyethyl](methyl)amino]methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-N-(1-methyl-1H-indol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

10

The procedure is as in the process of Example 1, replacing on the one hand the compounds of Preparations 1 and 1' used in Step A by the respective compounds of Preparations 3 and 11', and on the other hand the compound of Preparation 1" used in Step C by N-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1H-indol-5-amine.

15

**Elemental microanalysis:**

	%C	%H	%N	%Cl <sup>-</sup>
<i>Calculated</i>	68.18	5.98	8.83	4.47
<i>Found</i>	68.30	5.61	8.78	4.46

20

**Example 109:** N-(4-Hydroxyphenyl)-3-(6-[[[(3S)-3-[[[4-oxidomorpholin-4-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl])-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide

25

To a solution of the compound of Example 1, taken in the form of the free base, in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> there is added in portions *meta*-chloroperbenzoic acid (0.242 mg; 1.4 mmol). The whole is subsequently stirred at ambient temperature overnight. The reaction mixture is subsequently concentrated to dryness, and then the residue is purified by reverse-phase flash chromatography (gradient: acetonitrile/water/trifluoroacetic acid). There is obtained, after concentration, the title product in the form of a solid.

30

**Elemental microanalysis:**

	%C	%H	%N
<i>Calculated</i>	71.06	5.82	7.71
<i>Found</i>	70.59	5.36	7.69

5

**High-resolution mass (ESI+):**Empirical formula: C<sub>43</sub>H<sub>42</sub>N<sub>4</sub>O<sub>7</sub>[M+H]<sup>+</sup> calculated: 727.3132[M+H]<sup>+</sup> measured: 727.3110

10

**Example 110:** 3-(5-Chloro-2-{[(3S)-3-{ethyl(2-methoxyethyl)amino}methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N-(1-methyl-1H-indol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

15

The procedure is as in the process of Example 1, replacing on the one hand the compounds of Preparations 1 and 1' used in Step A by the respective compounds of Preparations 3 and 12', and on the other hand the compound of Preparation 1" used in Step C by N-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1H-indol-5-amine.

20

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	68.48	6.12	8.68	4.39
<i>Found</i>	68.40	5.78	8.61	4.23

25

**Example 111:** 3-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-fluorophenyl)-N-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

30

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by 4-

{{*tert*-butyl(dimethyl)silyl}oxy}-*N*-(4-fluorophenyl)aniline.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>42</sub>H<sub>40</sub>ClN<sub>4</sub>O<sub>4</sub>

5 [M+H]<sup>+</sup> calculated: 719.2722

[M+H]<sup>+</sup> measured: 719.2806

**Example 112:** *N*-(4-Hydroxyphenyl)-3-(5-methoxy-2-(((3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-phenyl-

10 5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing the compound of Preparation 1 used in Step A by the compound of Preparation 6.

15 **Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	70.43	6.19	7.64	4.83
<i>Found</i>	70.17	5.79	7.60	4.69

20 **Example 113:** 7-Hydroxy-*N*-(4-hydroxyphenyl)-3-(6-(((3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

**Step A:** Methyl 3'-(6-(((3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)-1,3-benzodioxol-5-yl)-5',6'-dihydro-8'*H*-spiro[1,3-dioxolane-2,7'-indolizine] -1'-carboxylate

25

The procedure is as in the process of Step A of Example 1, replacing the compound of Preparation 1 by the compound of Preparation 30.

30 **Step B:** Methyl 3-(6-(((3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)-1,3-benzodioxol-5-yl)-7-oxo-5,6,7,8-tetrahydroindolizine-1-carboxylate

2.75 g of the compound of Step A (4.47 mmol) in solution in 75 mL of THF are

stirred in the presence of 37 mL of 1 M HCl at reflux for 15 hours. 100 mL of water and 100 mL of ethyl acetate are added to the reaction mixture. There are subsequently added 4 g of NaHCO<sub>3</sub> (4.7 mmol) in powder form until a basic pH is reached. The compound is extracted with ethyl acetate, and the organic  
 5 phase is dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. The title product is obtained in the form of an oil.

**<sup>1</sup>H-NMR:** δ (500MHz; dms<sub>o</sub>-d<sub>6</sub>; 300°K): 7.9-7.2 (m, 4H, H aromatic); 7.02 (m, 1H, H aromatic); 6.88 (m, 1H, H aromatic); 6.44-5.87 (m, 1H, H aromatic  
 10 tetrahydroindolizine); 6.17 (d, 2H, CH<sub>2</sub> methylenedioxy); 5.07/4.85/3.79 (m, 1H, H tertiary tetrahydroisoquinoline); 4.88/4.27/4.24 (m, 2H, H aliphatic tetrahydroisoquinoline); 4.22-3.43 (m, 4H, H aliphatic tetrahydroindolizine); 3.59-3.49 (m, 4H, H aliphatic morpholine); 3.75-3.52 (s, 3H, Me); 2.93-2.49 (m, 2H, H aliphatic tetrahydroindolizine); 2.75-2.28 (m, 2H, H aliphatic  
 15 tetrahydroindolizine); 2.68-1.68 (m, 6H, H aliphatic morpholine + CH<sub>2</sub>)

**Step C: Methyl 7-hydroxy-3-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydro-isoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-5,6,7,8-tetrahydroindolizine-1-carboxylate**

20 To a solution of 2.55 g of the compound obtained in Step B (4.47 mmol) in 30 mL of methanol there are added in portions 558 mg (14.75 mmol) of sodium borohydride. The reaction mixture is stirred for one hour at ambient temperature. 50 mL of 1M HCl are subsequently added, and the methanol is evaporated off. The aqueous phase is subsequently neutralised with NaHCO<sub>3</sub>  
 25 and then extracted with dichloromethane. The organic phase is washed in succession with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. The oil so obtained is purified by flash chromatography (dichloromethane/ethanol-ammonia gradient). The title product is obtained in the form of a solid.

30

**<sup>1</sup>H-NMR:** δ (500MHz; dms<sub>o</sub>-d<sub>6</sub>; 300°K): 7.22-6.97 (m, 4H, H aromatic tetrahydroisoquinoline); 7.05 (s, 1H, H aromatic); 6.89 (s, 1H, H aromatic); 6.37/6.3/6.07 (m, 1H, H aromatic tetrahydroindolizine); 6.16 (d, 2H, CH<sub>2</sub>



methylenedioxy); 5.09 (m, 1H, H tertiary tetrahydroisoquinoline); 4.87-4.21 (m, 2H, H aliphatic tetrahydroindolizine); 4.20-3.67 (m, 2H, H aliphatic tetrahydroindolizine); 4.10-3.86 (m, 1H, H tertiary tetrahydroindolizine); 3.69-3.58 (s, 3H, Me); 3.69-3.52 (m, 4H, H aliphatic morpholine); 2.96 + 2.43 (m, 2H, H aliphatic tetrahydroisoquinoline); 2.55-2.0 (m, 6H, H aliphatic morpholine + CH<sub>2</sub>); 2.4-1.5 (m, 4H, H aliphatic tetrahydroindolizine)

IR: OH: 3239 cm<sup>-1</sup>; -C=O (ester): 1696 cm<sup>-1</sup>; -C=O (amide): 1624 cm<sup>-1</sup>; C-C-OH (secondary alcohol): 1034 cm<sup>-1</sup>

10 ***Step D: Methyl 3-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-7-(prop-2-en-1-yloxy)-5,6,7,8-tetrahydroindolizine-1-carboxylate***

To a suspension of 331 mg (8.26 mmol) of sodium hydride in 15 mL of anhydrous THF cooled to 0°C there are added 2.37 g (4.13 mmol) of the compound obtained in Step C. The suspension is stirred for 15 minutes at 0°C, and then a solution of 790 µL (9.1 mmol) of allyl bromide in 10 mL of THF is added slowly (over a period of 15 minutes). The reaction mixture is stirred for one hour at 0°C and then for 15 hours at ambient temperature. The solution is hydrolysed with a saturated aqueous NH<sub>4</sub>Cl solution. The compound is extracted with ethyl acetate; the organic phase is dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. The oil so obtained is purified by flash chromatography (cyclohexane/ethyl acetate gradient). The title product is obtained in the form of a solid.

25 **<sup>1</sup>H-NMR:** δ (500 MHz; dmsO-d<sub>6</sub>; 300°K): 7.2-6.9 (m, 4H, H aromatic tetrahydroisoquinoline); 7.2-6.8 (m, 2H, H aromatic); 6.4-6.0 (m, 1H, H aromatic tetrahydroindolizine); 6.10 (d, 2H, CH<sub>2</sub> methylenedioxy); 5.9 (m, 1H, allyl); 5.35-5.10 (m, 2H, allyl); 5.1+4.75 (m, 1H, H tertiary tetrahydroisoquinoline); 4.15-3.9 (m, 2H, CH<sub>2</sub> allyl); 3.9-3.6 (m, 1H, H tertiary tetrahydroindolizine); 4.1-3.4 (m, 4H, H aliphatic morpholine); 4.9-3.4 (m, 4H, 2H aliphatic tetrahydroindolizine + 2H aliphatic tetrahydroisoquinoline); 3.8-3.6 (s, 3H, Me); 2.55-1.6 (m, 6H, H aliphatic morpholine + CH<sub>2</sub>); 3.3-1.5 (m, 6H, 4H aliphatic tetrahydroindolizine + 2H aliphatic tetrahydroisoquinoline)

**Step E: N-(4-{{tert-Butyl(dimethyl)silyl}oxy}phenyl)-3-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-7-(prop-2-en-1-yloxy)-5,6,7,8-**

**5 tetrahydroindolizine-1-carboxamide**

The procedure is as in the processes of Steps B and C of Example 1.

**Step F: N-(4-{{tert-Butyl(dimethyl)silyl}oxy}phenyl)-7-hydroxy-3-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-**

**10 benzodioxol-5-yl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide**

There is then carried out a reaction of deprotection of the allyl group in the presence of 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (also called dimethyl barbiturate) and of tetrakis(triphenylphosphine)palladium in a mixture of methanol and dichloromethane.

15

**Step G: 7-Hydroxy-N-(4-hydroxyphenyl)-3-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride**

Deprotection of the silyloxy group is carried out according to the process of Step

20 D of Example 1.

**Elemental microanalysis:**

	%C	%H	%N	%Cl <sup>-</sup>
Calculated	67.66	5.68	7.34	4.64
25 Found	67.02	5.27	7.36	4.61

**High-resolution mass (ESI<sup>+</sup>):**

Empirical formula: C<sub>43</sub>H<sub>43</sub>N<sub>4</sub>O<sub>7</sub>

[M+H]<sup>+</sup> calculated: 727.3132

30 [M+H]<sup>+</sup> measured: 727.3121

**Example 114: N-(3-Fluoro-4-methylphenyl)-N-(4-hydroxyphenyl)-3-(5-methoxy-2-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-**

**yl]carbonyl}phenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide  
hydrochloride**

The procedure is as in the process of Example 1, replacing on the one hand the  
5 compound of Preparation 1 used in Step A by the compound of Preparation 6,  
and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3-fluoro-4-methylaniline.

**Elemental microanalysis:**

10		%C	%H	%N	%Cl
	<i>Calculated</i>	69.05	6.06	7.32	4.63
	<i>Found</i>	68.90	5.56	7.33	4.41

**Example 115:** 3-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-  
15 dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(2-fluorophenyl)-*N*-(4-  
hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the  
compound of Preparation 1 used in Step A by the compound of Preparation 3,  
20 and on the other hand the compound of Preparation 1" used in Step C by 4-  
{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-(2-fluorophenyl)aniline.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>42</sub>H<sub>40</sub>ClN<sub>4</sub>O<sub>4</sub>

25 [M+H]<sup>+</sup> calculated: 719.2722

[M+H]<sup>+</sup> measured: 719.2802

**Example 116:** 3-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-  
dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(3-fluorophenyl)-*N*-(4-  
30 hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the  
compound of Preparation 1 used in Step A by the compound of Preparation 3,

and on the other hand the compound of Preparation 1" used in Step C by 4-  
 {[*tert*-butyl(dimethyl)silyl]oxy}-*N*-(3-fluorophenyl)aniline.

**High-resolution mass (ESI+):**

5 Empirical formula: C<sub>42</sub>H<sub>40</sub>ClN<sub>4</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 719.2722

[M+H]<sup>+</sup> measured: 719.2819

**Example 117:** 3-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-  
 10 dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(2,4-difluorophenyl)-*N*-(4-  
 hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the  
 compound of Preparation 1 used in Step A by the compound of Preparation 3,  
 15 and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 {[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-2,4-difluoroaniline.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>42</sub>H<sub>39</sub>ClF<sub>2</sub>N<sub>4</sub>O<sub>4</sub>

20 [M+H]<sup>+</sup> calculated: 737.2628

[M+H]<sup>+</sup> measured: 737.2660

**Example 118:** 3-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-  
 dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(3,4-difluorophenyl)-*N*-(4-  
 25 hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the  
 compound of Preparation 1 used in Step A by the compound of Preparation 3,  
 and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 30 {[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3,4-difluoroaniline.

**Elemental microanalysis:**

%C

%H

%N

%Cl<sup>-</sup>

<i>Calculated</i>	65.20	5.21	7.24	4.58
<i>Found</i>	65.26	5.01	6.90	4.57

**Example 119:** 3-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(3-cyanophenyl)-N-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by 3-[(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)amino]benzonitrile.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
15 <i>Calculated</i>	67.71	5.42	9.18	4.65
<i>Found</i>	67.00	5.20	8.89	4.54

**Example 120:** N-(4-Hydroxyphenyl)-6-(6-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenylpyrrolo[1,2-a]pyrazine-8-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing the compound of Preparation 1 used in Step A by the compound of Preparation 31.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>42</sub>H<sub>37</sub>N<sub>5</sub>O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 708.2822

[M+H]<sup>+</sup> measured: 708.2788

**Example 121:** N-(3-Fluorophenyl)-N-(4-hydroxyphenyl)-6-(6-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)pyrrolo[1,2-a]pyrazine-8-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 31, and on the other hand the compound of Preparation 1" used in Step C by 4-[[*tert*-butyl(dimethyl)silyl]oxy]-*N*-(3-fluorophenyl)aniline.

5

**High-resolution mass (ESI+):**

Empirical formula: C<sub>42</sub>H<sub>36</sub>FN<sub>5</sub>O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 726.2728

[M+H]<sup>+</sup> measured: 726.2723

10

**Example 122:** *N*-(3-Fluorophenyl)-*N*-(4-hydroxyphenyl)-3-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

15

The procedure is as in the process of Example 1, replacing the compound of Preparation 1" used in Step C by 4-[[*tert*-butyl(dimethyl)silyl]oxy]-*N*-(3-fluorophenyl)aniline.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>43</sub>H<sub>41</sub>FN<sub>4</sub>O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 729.3088

[M+H]<sup>+</sup> measured: 729.3068

25

**Example 123:** *N*-(4-Hydroxyphenyl)-3-(6-{[(3*S*)-3-{[4-(methylsulphonyl)piperazin-1-yl]methyl}-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

30

The procedure is as in the process of Example 1, replacing the compound of Preparation 1' used in Step A by the compound of Preparation 13'.

**Elemental microanalysis:**

	%C	%H	%N	%S	%Cl
<i>Calculated</i>	64.11	5.62	8.50	3.89	4.30
<i>Found</i>	64.19	5.07	8.52	3.87	4.02

5

**Example 124:** 3-(5-Chloro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)phenyl)-N-(4-hydroxyphenyl)-N-(3-methoxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

- 10 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by N-(4-[[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3-methoxyaniline.

15 **Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	67.27	5.78	7.30	4.62
<i>Found</i>	67.54	5.35	7.32	4.62

- 20 **Example 125:** 3-(5-Chloro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)phenyl)-N-(3,5-difluorophenyl)-N-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

- 25 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by N-(4-[[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3,5-difluoroaniline.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	65.20	5.21	7.24	4.58
<i>Found</i>	65.85	4.93	7.04	4.76

30

**Example 126:** 3-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N-(3-methylphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

- 5 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by N-(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3-methylaniline.

10 **Elemental microanalysis:**

	%C	%H	%N	%Cl
Calculated	68.70	5.90	7.45	4.72
Found	68.94	5.72	7.21	4.84

- 15 **Example 127:** N-(4-Hydroxyphenyl)-N-phenyl-3-(6-{[(3S)-3-{[4-(2,2,2-trifluoroethyl)piperazin-1-yl]methyl}-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

- 20 The procedure is as in the process of Example 1, replacing the compound of Preparation 1' used in Step A by the compound of Preparation 14'.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
25 Calculated	65.25	5.48	8.45	4.28
Found	64.91	5.23	8.37	4.96

- 30 **Example 128:** N-(4-Hydroxyphenyl)-3-(6-{[(3S)-3-{[4-methyl-3-oxopiperazin-1-yl]methyl}-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing the compound of Preparation 1' used in Step A by the compound of Preparation 10'.



**Elemental microanalysis:**

	%C	%H	%N	%Cl
Calculated	68.25	5.73	9.04	4.58
5 Found	68.04	5.09	8.82	4.64

**Example 129:** 3-(5-Chloro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)phenyl)-N-(4-cyanophenyl)-N-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

10

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by 4-[(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)amino]benzonitrile.

15

**Elemental microanalysis:**

	%C	%H	%N
Calculated	67.71	5.42	9.18
Found	68.17	5.15	8.71

20

**Example 130:** 3-(5-Chloro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)phenyl)-N,N-diphenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

25 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-phenylaniline.

30 **High-resolution mass (ESI+):**

Empirical formula: C<sub>42</sub>H<sub>40</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 735.2427

[M+H]<sup>+</sup> measured: 735.2524

**Example 131:** 3-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(3-chlorophenyl)-N-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

5

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by N-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-3-chloroaniline.

10

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	65.33	5.35	7.26	4.59
<i>Found</i>	64.08	5.29	6.92	4.59

15

**Example 132:** 3-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-N-(pyrimidin-2-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

20 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by N-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)pyrimidin-2-amine.

25 **Elemental microanalysis:**

	%C	%H	%N
<i>Calculated</i>	64.95	5.45	11.36
<i>Found</i>	64.62	5.07	10.92

30 **Example 133:** 3-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(cyclobutylmethyl)-N-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by 4-{{tert-butyl(dimethyl)silyl}oxy}-N-(cyclobutylmethyl)aniline.

5

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	68.16	6.39	7.76	3.93
<i>Found</i>	68.69	5.93	7.45	3.81

10

**Example 134:** 3-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(2-cyanophenyl)-N-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

15 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by 2-[(4-{{tert-butyl(dimethyl)silyl}oxy}phenyl)amino]benzonitrile.

20 **Elemental microanalysis:**

	%C	%H	%N
<i>Calculated</i>	67.71	5.42	9.18
<i>Found</i>	67.34	4.95	8.73

25 **Example 135:** 3-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-N-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

30 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by N-(4-{{tert-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1H-pyrazol-4-amine.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
Calculated	64.77	5.71	11.33	4.78
5 Found	64.62	5.33	10.71	4.10

**Example 136:** 3-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(cyclopropylmethyl)-N-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

10

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by 4-[[*tert*-butyl(dimethyl)silyl]oxy]-N-(cyclopropylmethyl)aniline.

15

**Elemental microanalysis:**

	%C	%H	%N	%Cl
Calculated	67.13	6.20	7.83	4.95
Found	67.58	5.79	7.36	4.16

20

**Example 137:** 3-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-N-(1-methyl-1H-pyrazol-3-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

25

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by N-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1H-pyrazol-3-amine.

30

**Elemental microanalysis:**

	%C	%H	%N	%Cl
Calculated	64.77	5.71	11.33	4.78

<i>Found</i>	64.20	5.47	10.78	5.27
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**Example 138:** *N*-(But-2-yn-1-yl)-3-(5-chloro-2-([(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)phenyl)-*N*-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by 4-  
10 {[(*tert*-butyl(dimethyl)silyl]oxy)-*N*-(but-2-yn-1-yl)aniline.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	64.95	5.45	11.36	4.79
15 <i>Found</i>	65.53	5.19	10.88	5.38

**Example 139:** 3-(5-Chloro-2-([(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)phenyl)-*N*-(4-hydroxyphenyl)-*N*-(pyridin-2-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
20 {[(*tert*-butyl(dimethyl)silyl]oxy)phenyl)pyridin-2-amine.

**Elemental microanalysis:**

	%C	%H	%N
<i>Calculated</i>	66.66	5.59	9.48
25 <i>Found</i>	67.12	5.37	9.11

**Example 140:** 3-(5-Chloro-2-([(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)phenyl)-*N*-(4-hydroxyphenyl)-*N*-(pyridazin-3-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

30

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 5 {*tert*-butyl(dimethyl)silyl}oxy}phenyl)pyridazin-3-amine.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>42</sub>H<sub>39</sub>ClN<sub>6</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 703.2721

10 [M+H]<sup>+</sup> measured: 703.2783

**Example 141:** 3-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(pyrimidin-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

15

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 {*tert*-butyl(dimethyl)silyl}oxy}phenyl)pyrimidin-5-amine.

20

**Elemental microanalysis:**

	%C	%H	%N	%Cl
<i>Calculated</i>	68.32	5.59	11.95	5.04
<i>Found</i>	68.05	5.52	11.83	5.50

25

**Example 142:** 3-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(pyridin-3-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide bis(hydrochloride)

30

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-

{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)pyridin-3-amine.

**High-resolution mass (ESI+):**

Empirical formula: C<sub>41</sub>H<sub>40</sub>ClN<sub>5</sub>O<sub>4</sub>

5 [M+H]<sup>+</sup> calculated: 702.2769

[M+H]<sup>+</sup> measured: 702.2858

**Example 143:** 3-(5-Chloro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(3,5-difluoro-4-methoxyphenyl)-*N*-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

10

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-3,5-difluoro-4-methoxyaniline.

15

**High-resolution mass (ESI+):**

Empirical formula: C<sub>43</sub>H<sub>41</sub>ClF<sub>2</sub>N<sub>4</sub>O<sub>5</sub>

20 [M+H]<sup>+</sup> calculated: 767.2734

[M+H]<sup>+</sup> measured: 767.2804

**Example 144:** 3-(5-Chloro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(pyridin-4-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide bis(hydrochloride)

25

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)pyridin-4-amine.

30

**High-resolution mass (ESI+):**

Empirical formula: C<sub>41</sub>H<sub>40</sub>ClN<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 702.2842

[M+H]<sup>+</sup> measured: 702.2842

- 5 **Example 145:** 3-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(3-fluoro-4-methoxyphenyl)-N-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

- 10 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by N-(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)-3-fluoro-4-methoxyaniline.

- 15 **High-resolution mass (ESI<sup>+</sup>):**

Empirical formula: C<sub>43</sub>H<sub>42</sub>ClFN<sub>4</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 749.2828

[M+H]<sup>+</sup> measured: 749.2878

- 20 **Example 146:** N-(4-Hydroxyphenyl)-3-(6-[[[(3S)-3-[(2-methoxyethyl)-(methyl)amino]methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

- 25 The procedure is as in the process of Example 1, replacing the compound of Preparation 1' used in Step A by the compound of Preparation 11'.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
30 <i>Calculated</i>	68.93	6.05	7.48	4.73
<i>Found</i>	68.84	5.85	7.56	4.60

- Example 147:** 3-(6-[[[(3S)-3-[(1,1-Dioxidothiomorpholin-4-yl)methyl]-3,4-



**dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride**

- 5 The procedure is as in the process of Example 1, replacing the compound of Preparation 1' used in Step A by the compound of Preparation 15'.

***Elemental microanalysis:***

		%C	%H	%N	%S	%Cl
10	<i>Calculated</i>	64.94	5.45	7.04	4.03	4.46
	<i>Found</i>	65.27	5.13	7.14	3.90	4.30

- Example 148: *N*-(5-Hydroxypyrimidin-2-yl)-3-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide trifluoroacetate**
- 15

**Step A: *N*-[5-(Benzyloxy)pyrimidin-2-yl]-3-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide**

- 20 The procedure is as in Steps A, B and C of the process of Example 1, replacing the compound of Preparation 1" used in Step C by 5-(benzyloxy)-*N*-phenylpyrimidin-2-amine.

- Step B: *N*-(5-Hydroxypyrimidin-2-yl)-3-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide trifluoroacetate**
- 25

- The compound of Step A (150 mg; 0.2 mmol) is dissolved in 8 mL of methanol, and 30 mg of Pd/C (10% by mass palladium) are added. The reaction mixture is stirred under a hydrogen atmosphere (1.2 bar) for 15 hours and is then filtered
- 30 over a Whatman filter, concentrated *in vacuo* and purified by reverse-phase chromatography (gradient: acetonitrile/water in the presence of trifluoroacetic acid). The desired product is obtained in the form of a trifluoroacetate salt.

**High-resolution mass (ESI+):**Empirical formula: C<sub>41</sub>H<sub>40</sub>N<sub>6</sub>O<sub>6</sub>[M+H]<sup>+</sup> calculated: 713.3082[M+H]<sup>+</sup> measured: 713.3080

5

**Example 149:** *N*-(4-Hydroxyphenyl)-3-(6-([(3*S*)-3-[(3-methoxypyrrolidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

- 10 The procedure is as in the process of Example 1, replacing the compound of Preparation 1' used in Step A by the compound of Preparation 16'.

**Elemental microanalysis:**

	%C	%H	%N	%Cl
15 <i>Calculated</i>	69.42	5.96	7.36	4.66
<i>Found</i>	70.19	5.48	7.22	4.53

**Example 150:** 3-(5-Chloro-2-([(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)phenyl)-*N*-(3-cyano-4-methoxyphenyl)-*N*-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

20

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 3, and on the other hand the compound of Preparation 1" used in Step C by 5-[(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)amino]-2-methoxybenzonitrile.

25

**High-resolution mass (ESI+):**Empirical formula: C<sub>44</sub>H<sub>42</sub>ClN<sub>5</sub>O<sub>5</sub>30 [M+H]<sup>+</sup> calculated: 756.2874[M+H]<sup>+</sup> measured: 756.2917

**Example 151:** *N*-(4-Hydroxyphenyl)-3-(5-methoxy-2-([(3*S*)-3-(morpholin-4-

**ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride**

The procedure is as in the process of Example 1, replacing on the one hand the  
 5 compound of Preparation 1 used in Step A by the compound of Preparation 6,  
 and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 {[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-pyrazol-4-amine.

***High-resolution mass (ESI+):***

10 Empirical formula: C<sub>41</sub>H<sub>44</sub>N<sub>6</sub>O<sub>5</sub>  
 [M+H]<sup>+</sup> calculated: 701.3446  
 [M+H]<sup>+</sup> measured: 701.3446

**Example 152: 3-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-  
 15 dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-[3-  
 (trifluoromethyl)phenyl]-5,6,7,8-tetrahydroindolizine-1-carboxamide  
 hydrochloride**

The procedure is as in the process of Example 1, replacing on the one hand the  
 20 compound of Preparation 1 used in Step A by the compound of Preparation 3,  
 and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
 {[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3-(trifluoromethyl)aniline.

***High-resolution mass (ESI+):***

25 Empirical formula: C<sub>43</sub>H<sub>40</sub>ClF<sub>3</sub>N<sub>4</sub>O<sub>4</sub>  
 [M+H]<sup>+</sup> calculated: 769.2690  
 [M+H]<sup>+</sup> measured: 769.2718

**Example 153: 3-(6-{[(3*S*)-3-[(3,3-difluoropyrrolidin-1-yl)methyl]-3,4-dihydro-  
 30 isoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-  
*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride**

The procedure is as in the process of Example 1, replacing the compound of

Preparation 1' used in Step A by the compound of Preparation 17'.

**Elemental microanalysis:**

	%C	%H	%N
5 <i>Calculated</i>	67.31	5.39	7.30
<i>Found</i>	68.07	5.60	7.23

**Example 154:**    *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-3-(7-  
 10    {[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-  
       2,3-dihydro-1,4-benzodioxin-6-yl)-5,6,7,8-tetrahydroindolizine-1-  
       carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the  
 compound of Preparation 1 used in Step A by the compound of Preparation 7,  
 15    and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
       {[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-pyrazol-4-amine.

**Example 155:**    *N*-(4-Hydroxyphenyl)-3-(7-{[(3*S*)-3-(morpholin-4-ylmethyl)-  
 3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-2,3-dihydro-1,4-benzodioxin-6-  
 20    yl)-*N*-(pyrimidin-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide  
       hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the  
 compound of Preparation 1 used in Step A by the compound of Preparation 7,  
 25    and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-  
       {[*tert*-butyl(dimethyl)silyl]oxy}phenyl)pyrimidin-5-amine.

**Example 156:**    *N*-(4-Hydroxyphenyl)-3-(6-{[(3*S*)-3-[(3-methoxyazetidin-1-  
 yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-  
 30    *N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide

The procedure is as in the process of Example 1, replacing the compound of  
 Preparation 1' used in Step A by the compound of Preparation 18'.

**Elemental microanalysis:**

	%C	%H	%N
Calculated	72.66	5.96	7.88
5 Found	72.32	5.51	7.96

**High-resolution mass (ESI+):**Empirical formula: C<sub>43</sub>H<sub>42</sub>N<sub>4</sub>O<sub>6</sub>[M+H]<sup>+</sup> calculated: 711.317710 [M+H]<sup>+</sup> measured: 711.3178

**Example 157:** 3-(6-{[(3S)-3-[(3-fluoroazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide  
 15 hydrochloride

The procedure is as in the process of Example 1, replacing the compound of Preparation 1' used in Step A by the compound of Preparation 19'.

20 **Example 158:** 3-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide  
 hydrochloride

25 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 4, and on the other hand the compound of Preparation 1" used in Step C by N-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1H-pyrazol-4-amine.

30 **Example 159:** 3-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N-(1-methyl-1H-pyrazol-4-yl)indolizine-1-carboxamide hydrochloride

The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 32, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-pyrazol-4-amine.

5

**Example 160:** 3-(5-Chloro-2-[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)indolizine-1-carboxamide hydrochloride

10 The procedure is as in the process of Example 1, replacing on the one hand the compound of Preparation 1 used in Step A by the compound of Preparation 14, and on the other hand the compound of Preparation 1" used in Step C by *N*-(4-{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-pyrazol-4-amine.

15

### PHARMACOLOGICAL STUDY

#### EXAMPLE A: Inhibition of Bcl-2 by the fluorescence polarisation technique

20

The fluorescence polarisation tests were carried out on microplates (384 wells). The Bcl-2 protein, at a final concentration of  $2.50 \times 10^{-8}$  M, is mixed with a fluorescent peptide (Fluorescein-REIGAQLRRMADDLNAQY), at a final concentration of  $1.00 \times 10^{-8}$  M in a buffer solution (Hepes 10 mM, NaCl 150 mM, Tween20 0.05%, pH 7.4), in the presence or in the absence of increasing concentrations of test compounds. After incubation for 2 hours, the fluorescence polarisation is measured.

25

The results are expressed in  $IC_{50}$  (the concentration of compound that inhibits fluorescence polarisation by 50%) and are presented in Table 1 below.

30

The results show that the compounds of the invention inhibit interaction between the Bcl-2 protein and the fluorescent peptide described hereinbefore.

**EXAMPLE B: *In vitro* cytotoxicity**

The cytotoxicity studies were carried out on the RS4;11 leukaemia tumour line.

The cells are distributed onto microplates and exposed to the test compounds  
5 for 48 hours. The cell viability is then quantified by a colorimetric assay, the  
Microculture Tetrazolium Assay (Cancer Res., 1987, 47, 939-942).

The results are expressed in  $IC_{50}$  (the concentration of compound that inhibits  
cell viability by 50%) and are presented in Table 1 below.

10 The results show that the compounds of the invention are cytotoxic.

**Table 1: IC<sub>50</sub> of Bcl-2 inhibition (fluorescence polarisation test)**  
**and of cytotoxicity for RS4;11 cells**

	IC <sub>50</sub> (nM) Bcl-2 FP	IC <sub>50</sub> (nM) MTT RS4;11		IC <sub>50</sub> (nM) Bcl-2 FP	IC <sub>50</sub> (nM) MTT RS4;11
<b>Example 1</b>	18	60.1	<b>Example 32</b>	34	71.3
<b>Example 2</b>	20	49.8	<b>Example 33</b>	23	12.2
<b>Example 3</b>	20	44.7	<b>Example 34</b>	27	65.8
<b>Example 4</b>	19	27.1	<b>Example 35</b>	15	11.7
<b>Example 5</b>	51	98	<b>Example 36</b>	43	135
<b>Example 6</b>	15	30	<b>Example 37</b>	19	11.6
<b>Example 8</b>	15	25.6	<b>Example 38</b>	21	61.8
<b>Example 9</b>	13	16.1	<b>Example 39</b>	16	14.1
<b>Example 10</b>	18	11	<b>Example 40</b>	15	32.2
<b>Example 13</b>	12	8.63	<b>Example 41</b>	26	44
<b>Example 14</b>	16	10.7	<b>Example 42</b>	13	53.6
<b>Example 15</b>	17	20.4	<b>Example 43</b>	110	142
<b>Example 16</b>	18	23.4	<b>Example 44</b>	14	45
<b>Example 17</b>	81	120	<b>Example 45</b>	47	76.8
<b>Example 18</b>	32	24.9	<b>Example 46</b>	21	56.8
<b>Example 19</b>	27	42.3	<b>Example 47</b>	58	194
<b>Example 20</b>	35	105	<b>Example 48</b>	130	229
<b>Example 21</b>	22	34.6	<b>Example 49</b>	45	169
<b>Example 22</b>	27	19.1	<b>Example 50</b>	13	4.01
<b>Example 23</b>	14	23	<b>Example 51</b>	32	26
<b>Example 24</b>	17	29.8	<b>Example 52</b>	16	19.8
<b>Example 25</b>	29	143	<b>Example 53</b>	180	138
<b>Example 26</b>	17	40	<b>Example 54</b>	180	106
<b>Example 27</b>	17	35.4	<b>Example 55</b>	34	19.4
<b>Example 28</b>	25	76.1	<b>Example 56</b>	20	25.9
<b>Example 29</b>	35	85.5	<b>Example 57</b>	12	8.62



<b>Example 30</b>	13	8.59	<b>Example 58</b>	22	40.1
<b>Example 31</b>	33	340	<b>Example 59</b>	13	8.13
	IC <sub>50</sub> (nM) Bcl-2 FP	IC <sub>50</sub> (nM) MTT RS4;11		IC <sub>50</sub> (nM) Bcl-2 FP	IC <sub>50</sub> (nM) MTT RS4;11
<b>Example 60</b>	19	11.7	<b>Example 98</b>	12	73.5
<b>Example 61</b>	22	14.5	<b>Example 99</b>	25	213
<b>Example 62</b>	22	19.3	<b>Example 100</b>	22	856
<b>Example 63</b>	21	18.8	<b>Example 101</b>	5	22.1
<b>Example 64</b>	31	23.3	<b>Example 103</b>	6	16.8
<b>Example 65</b>	14	9.19	<b>Example 104</b>	7	21.6
<b>Example 66</b>	16	21.7	<b>Example 105</b>	10	28.9
<b>Example 67</b>	24	17.7	<b>Example 107</b>	7	8.29
<b>Example 69</b>	26	16.7	<b>Example 108</b>	9	36.4
<b>Example 70</b>	19	14	<b>Example 109</b>	30	483
<b>Example 71</b>	21	24.4	<b>Example 110</b>	29	129
<b>Example 72</b>	220	270	<b>Example 111</b>	15	81.5
<b>Example 74</b>	24	241	<b>Example 112</b>	9	139
<b>Example 76</b>	17	49	<b>Example 113</b>	16	190
<b>Example 77</b>	23	70.4	<b>Example 114</b>	9	43.1
<b>Example 78</b>	31	101	<b>Example 115</b>	8	58.1
<b>Example 79</b>	31	67.5	<b>Example 116</b>	10	43.6
<b>Example 80</b>	18	18.8	<b>Example 117</b>	15	194
<b>Example 81</b>	28	39.3	<b>Example 118</b>	15	71
<b>Example 82</b>	33	21.9	<b>Example 119</b>	9	31.6
<b>Example 83</b>	18	41.2	<b>Example 121</b>	34	445
<b>Example 84</b>	18	20.6	<b>Example 122</b>	16	43.5
<b>Example 85</b>	41	246	<b>Example 123</b>	22	92.1
<b>Example 86</b>	22	29.5	<b>Example 124</b>	28	101
<b>Example 87</b>	27	121	<b>Example 125</b>	38	81.8
<b>Example 91</b>	8	65.5	<b>Example 126</b>	26	115
<b>Example 92</b>	5	40.2	<b>Example 127</b>	26	129

<b>Example 94</b>	3	8.16	<b>Example 128</b>	10	63.4
<b>Example 95</b>	6	13.5	<b>Example 129</b>	9	46.7
<b>Example 96</b>	11	58.8	<b>Example 131</b>	30	88.4
<b>Example 97</b>	20	45.4	<b>Example 134</b>	37	305
	IC <sub>50</sub> (nM) Bcl-2 FP	IC <sub>50</sub> (nM) MTT RS4;11		IC <sub>50</sub> (nM) Bcl-2 FP	IC <sub>50</sub> (nM) MTT RS4;11
<b>Example 135</b>	6	37.4	<b>Example 144</b>	n.d.	59.9
<b>Example 141</b>	n.d.	72.5	<b>Example 145</b>	n.d.	28.9
<b>Example 142</b>	n.d.	66.1	<b>Example 146</b>	n.d.	153
<b>Example 143</b>	n.d.	43.8	<b>Example 147</b>	n.d.	74.2

### **EXAMPLE C: Induction of caspase activity *in vivo***

The ability of the compounds of the invention to activate caspase 3 is evaluated  
5 in a xenograft model of RS4;11 leukaemia cells.

1x10<sup>7</sup> RS4;11 cells are grafted sub-cutaneously into immunosuppressed mice (SCID strain). 25 to 30 days after the graft, the animals are treated orally with the various compounds. Sixteen hours after treatment, the tumour masses are recovered and lysed, and the caspase 3 activity is measured in the tumour  
10 lysates.

This enzymatic measurement is carried out by assaying the appearance of a fluorogenic cleavage product (DEVDase activity, Promega). It is expressed in the form of an activation factor corresponding to the ratio between the two caspase activities: the activity for the treated mice divided by the activity for the  
15 control mice.

The results obtained are presented in Table 2 and show that the compounds of the invention are capable of inducing apoptosis in RS4;11 tumour cells *in vivo*.

**Table 2: Caspase activation factors (DEVDase activity in the tumours of treated mice versus control mice) *in vivo*, after oral treatment (exact doses in brackets)**

5

Compound tested	Activation factor (versus control)
<b>Example 1</b>	29.3 (100 mg/kg)
<b>Example 2</b>	27.8 (100 mg/kg)
<b>Example 3</b>	5.7 (50 mg/kg)
<b>Example 4</b>	29.2 (50 mg/kg)
<b>Example 8</b>	9.8 (50 mg/kg)
<b>Example 9</b>	20.6 (50 mg/kg)
<b>Example 10</b>	13.8 (50 mg/kg)
<b>Example 22</b>	11.3 (50 mg/kg)
<b>Example 23</b>	22.7 (50 mg/kg)
<b>Example 58</b>	23.3 (50 mg/kg)
<b>Example 59</b>	23 (50 mg/kg)
<b>Example 66</b>	24.7 (50 mg/kg)
<b>Example 67</b>	18.9 (50 mg/kg)

**EXAMPLE D: Quantification of the cleaved form of caspase 3 *in vivo***

10 The ability of the compounds of the invention to activate caspase 3 is evaluated in a xenograft model of RS4;11 leukaemia cells.

1x10<sup>7</sup> RS4;11 cells are grafted sub-cutaneously into immunosuppressed mice (SCID strain). 25 to 30 days after the graft, the animals are treated orally with the various compounds. After treatment, the tumour masses are recovered and lysed, and the cleaved (activated) form of caspase 3 is quantified in the tumour  
15 lysates.

The quantification is carried out using the "Meso Scale Discovery (MSD) ELISA platform" test, which specifically assays the cleaved form of caspase 3. It is

expressed in the form of an activation factor corresponding to the ratio between the quantity of cleaved caspase 3 in the treated mice divided by the quantity of cleaved caspase 3 in the control mice.

- 5 The results obtained are presented in Table 3 and show that the compounds of the invention are capable of inducing apoptosis in RS4;11 tumour cells *in vivo*.

**Table 3: Caspase activation factors (cleaved caspase 3 MSD test in the tumours of treated mice versus control mice) *in vivo*, after oral treatment (exact doses in brackets)**

Compound tested	Activation factor (versus control)
<b>Example 78</b>	10.4 (25 mg/kg)
<b>Example 87</b>	18.3 (50 mg/kg)
<b>Example 122</b>	17.4 (25 mg/kg)
<b>Example 135</b>	60 (50 mg/kg)

**EXAMPLE E: Anti-tumour activity *in vivo***

- 15 The anti-tumour activity of the compounds of the invention is evaluated in a xenograft model of RS4;11 leukaemia cells.
- 1x10<sup>7</sup> RS4;11 cells are grafted sub-cutaneously into immunosuppressed mice (SCID strain). 25 to 30 days after the graft, when the tumour mass has reached about 150 mm<sup>3</sup>, the mice are treated orally with the various compounds in two
- 20 different regimes (daily treatment for five days per week for two weeks, or two treatments weekly for two weeks). The tumour mass is measured twice weekly from the start of treatment.

- The compounds of the invention have anti-tumour activities, by the oral route, in
- 25 the RS4;11 leukaemia model (acute lymphoblastic leukaemia) with  $\Delta T/C$  (qualification parameter of the activity of a product, which is defined as the ratio

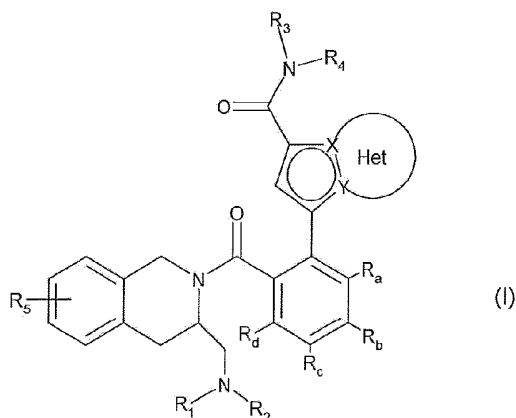
tumour volume of the treated group/tumour volume of the untreated control group) ranging from -15 to -56% related to tumour regression. The results obtained therefore show that the compounds of the invention are capable of inducing significant tumour regression during the treatment period.

5

**EXAMPLE F: Pharmaceutical composition: Tablets**

1000 tablets containing a dose of 5 mg of a compound selected from Examples

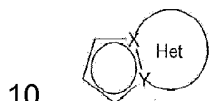
	1 to 160	5 g
10	Wheat starch	20 g
	Maize starch	20 g
	Lactose	30 g
	Magnesium stearate	2 g
	Silica	1 g
15	Hydroxypropylcellulose	2 g

**Patentkrav****1. Forbindelse med formelen (I):**

5 hvor:

◆ X og Y betegner et carbonatom eller et nitrogenatom, idet det er underforstået, at de kan ikke samtidig repræsenterer to carbonatomer eller to nitrogenatomer,

◆ Het-delen af gruppen



betegner en eventuelt substitueret, aromatisk eller ikke-aromatisk ring, der er sammensat af 5, 6 eller 7 led, som kan indeholde, ud over nitrogenatomet, der er repræsenteret af X eller af Y, fra en til 3 heteroatomer, der er udvalgt uafhængigt blandt oxygen, svovl og nitrogen, idet det er underforstået, at det pågældende nitrogen kan være substitueret med en gruppe, der repræsenterer et hydrogenatom, en lineær eller forgrenet (C<sub>1</sub>-C<sub>6</sub>)-alkylgruppe eller en gruppe - C(O)-O-Alk, hvor Alk er en lineær eller forgrenet (C<sub>1</sub>-C<sub>6</sub>)-alkylgruppe,

◆ R<sub>1</sub> og R<sub>2</sub> betegner uafhængigt af hinanden et hydrogenatom eller en lineær eller forgrenet (C<sub>1</sub>-C<sub>6</sub>)-alkylgruppe,

20 eller R<sub>1</sub> og R<sub>2</sub> danne med nitrogenatomet, der bærer dem, en heterocycloalkyl, der er sammensat af fra 4 til 7 led, som kan indeholde, ud over nitrogenatomet, et andet heteroatom, der er valgt blandt oxygen, svovl, SO<sub>2</sub> og NR, hvor R betegner et hydrogenatom, en lineær eller forgrenet (C<sub>1</sub>-C<sub>6</sub>)-alkylgruppe, en (C<sub>1</sub>-C<sub>6</sub>)-alkylsulfonylgruppe, en lineær eller forgrenet (C<sub>1</sub>-C<sub>6</sub>)-poly-halogen-

alkylgruppe eller en gruppe  $-C(O)-O-Alk$ , hvor Alk er en lineær eller forgrenet ( $C_1-C_6$ )-alkylgruppe,

◆  $R_3$  betegner en lineær eller forgrenet ( $C_1-C_6$ )-alkylgruppe, en ( $C_2-C_6$ )-alkenylgruppe, en ( $C_2-C_6$ )-alkynylgruppe, en cycloalkylgruppe, en lineær eller  
5 forgrenet ( $C_4-C_{10}$ )-cycloalkyl-( $C_1-C_6$ )-alkylgruppe, en arylgruppe eller en heteroarylgruppe,

◆  $R_4$  betegner en aryl-, heteroaryl-, cycloalkyl- eller lineær eller forgrenet ( $C_1-C_6$ )-alkylgruppe,

◆  $R_5$  betegner et hydrogenatom eller et halogenatom,

10 ◆  $R_a$ ,  $R_b$ ,  $R_c$  og  $R_d$  betegner uafhængigt af hinanden et hydrogenatom, et halogenatom, en lineær eller forgrenet ( $C_1-C_6$ )-alkylgruppe, en lineær eller forgrenet ( $C_1-C_6$ )-alkoxygruppe, en hydroxygruppe, en lineær eller forgrenet ( $C_1-C_6$ )-polyhalogenalkylgruppe, eller en trifluormethoxygruppe, eller substituenterne i et af parrene ( $R_a, R_b$ ), ( $R_b, R_c$ ) eller ( $R_c, R_d$ ) danner sammen  
15 med de carbonatomer, der bærer dem, en ring sammensat af fra 5 til 7 led, som kan indeholde fra et til 3 heteroatomer, der er valgt blandt oxygen, svovl og nitrogen, idet det er underforstået, at det pågældende nitrogen kan være substitueret med en gruppe, der repræsenterer et hydrogenatom, en lineær eller forgrenet ( $C_1-C_6$ )-alkylgruppe eller en gruppe  $-C(O)-O-Alk$ , hvor Alk er en  
20 lineær eller forgrenet ( $C_1-C_6$ )-alkylgruppe, idet det også er underforstået, at et eller flere carbonatomer i ringen, der er defineret ovenfor kan deuteret, idet:

- "aryl" betyder en phenyl-, naphthyl-, biphenyl- eller indenylgruppe,

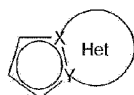
- "heteroaryl" betyder enhver mono- eller bicyklisk gruppe sammensat af fra 5 til  
25 10 led, der har mindst en aromatisk del og indeholder fra 1 til 3 heteroatomer valgt blandt oxygen, svovl og nitrogen,

- "cycloalkyl" betyder enhver mono- eller bicyklisk ikke-aromatisk carbocyklisk gruppe indeholdende fra 4 til 10 led,

det er muligt for således definerede alkyl-, aryl-, heteroaryl-, cycloalkyl- og  
30 heterocycloalkylgrupper at være substitueret med fra 1 til 3 grupper valgt blandt eventuelt substitueret lineær eller forgrenet ( $C_1-C_6$ )-alkyl, ( $C_3-C_6$ )-spiro, lineær eller forgrenet ( $C_1-C_6$ )-alkoxy, ( $C_1-C_6$ )-alkyl-S-, hydroxy, oxo (eller eventuelt *N*-

oxid), nitro, cyan,  $-\text{COOR}'$ ,  $\text{NR}'\text{R}''$ , lineær eller forgrenet  $(\text{C}_1\text{-C}_6)$ -polyhalogenalkyl, trifluormethoxy,  $(\text{C}_1\text{-C}_6)$ -alkylsulfonyl eller halogen, dog således at  $\text{R}'$  og  $\text{R}''$  uafhængigt af hinanden betegner et hydrogenatom eller en lineær eller forgrenet  $(\text{C}_1\text{-C}_6)$ -alkylgruppe,

- 5 idet det er muligt for Het-delen af gruppen

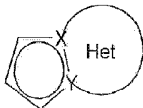


der er defineret ovenfor til være substitueret med en gruppe, der er valgt blandt lineær eller forgrenet  $(\text{C}_1\text{-C}_6)$ -alkyl, hydroxy,  $\text{NR}_1'\text{R}_1''$  og halogen, idet det forudsættes, at  $\text{R}_1'$  og  $\text{R}_1''$  har de samme definitioner som grupperne  $\text{R}'$  og  $\text{R}''$ ,

- 10 der er nævnt ovenfor,

deres enantiomerer og diastereoisomerer samt additionssalte med en farmaceutisk acceptabel syre eller base.

## 2. Forbindelse med formlen (I) ifølge krav 1, hvor gruppen



15

repræsenterer en af følgende grupper: 5,6,7,8-tetrahydroindolizin, der eventuelt er substitueret med en hydroxy-, indolizin, 1,2,3,4-tetrahydropyrrolo[1,2- $\alpha$ ]pyrazin, tert-butyl-3,4-dihydro-pyrrolo[1,2- $\alpha$ ]pyrazin-2(1*H*)-carboxylat, 3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4] oxazin, 2,3-dihydro-1*H*-pyrrolizin eventuelt  
20 substitueret med en hydroxy-, 6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2- $\alpha$ ]azepin eller pyrrolo[1,2- $\alpha$ ]pyrazin.

3. Forbindelse med formlen (I) ifølge krav 1, hvor  $\text{R}_1$  og  $\text{R}_2$  hver betegner en alkylgruppe, der eventuelt er substitueret med en methoxy eller  $\text{R}_1$  og  $\text{R}_2$  danner  
25 med nitrogenatomet, der bærer dem, en heterocycloalkylgruppe, der er valgt blandt følgende grupper: morpholin eventuelt substitueret med en eller flere lineære eller forgrenede  $(\text{C}_1\text{-C}_6)$ -alkyl eller -alkyler, oxidomorpholin, thiomorpholin-1,1-dioxid, 1,4-oxazepan, 3-methoxypyrrolidin, 3,3-difluoropyrrolidin, 3-methoxyazetidin, 3-fluoroazetidin, oxopiperazin eller



piperazin, de sidste to grupper er substitueret med en lineær eller forgrenet (C<sub>1</sub>-C<sub>6</sub>)-alkylgruppe, lineær eller forgrenet (C<sub>1</sub>-C<sub>6</sub>)-polyhaloalkylgruppe eller methylsulfonylgruppe.

- 5    4. Forbindelse med formlen (I) ifølge krav 1, hvor R<sub>a</sub> og R<sub>d</sub> hver betegner et hydrogenatom, og (R<sub>b</sub>, R<sub>c</sub>) danner sammen med de carbonatomer, der bærer dem, en 1,3-dioxolan-gruppe, en af carbonatomerne er eventuelt deutereret, en 1,4-dioxan-gruppe, en 1,4-dioxepan-gruppe, eller R<sub>a</sub>, R<sub>c</sub> og R<sub>d</sub> betegner hver et hydrogenatom, og R<sub>b</sub> betegner et halogen, en methyl, en methoxy, en ethoxy,  
10 en trifluormethyl eller en trifluormethoxy.

5. Forbindelse med formlen (I) ifølge krav 1, hvor R<sub>4</sub> betegner en 4-hydroxyphenylgruppe, en 3-fluor-4-hydroxyphenylgruppe eller en 5-hydroxypyrimidingruppe.

15

6. Forbindelse med formlen (I) ifølge krav 1, hvor R<sub>3</sub> betegner en gruppe, der er valgt blandt phenyl, indol, indolin, 1,2,3,4-tetrahydroquinolin, 3,4-dihydro-2*H*-1,4-benzoxazin, indan, 1*H*-indazol, 1*H*-pyrrolo[2,3-*bo*]pyridin, pyrimidin, cyclobutylmethyl, cyclopropylmethyl, 1*H*pyrazol, pyridin, pyridazin, de grupper,  
20 som eventuelt har én eller flere substituenten valgt blandt halogen, lineær eller forgrenet (C<sub>1</sub>-C<sub>6</sub>)-alkyl, cyano og lineær eller forgrenet (C<sub>1</sub>-C<sub>6</sub>)-alkoxy.

7. Forbindelse med formlen (I) ifølge krav 1, valgt fra følgende gruppe:

- *N*-(4-hydroxyphenyl)-3-{6-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(*1H*)-isoquinoliny)-carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizin-carboxamid,
- 3-{5-chlor-2-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(*1H*)-isoquinoliny)-carbonylo]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizin-carboxamid,
- 30 - *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-3-{2,2-dideuterio-6-[(*(3S)*-3-(4-morpholinylmethyl)-3,4-dihydro-2(*1H*)-isoquinoliny)-carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizin-carboxamid,

- *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-3-(6-(((3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizin-1-carboxamid,
- *N*-(4-hydroxyphenyl)-3-{7-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*-isoquinolinyl)-carbonyl)-2,3-dihydro-1,4-benzodioxin-6-yl)}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizin-carboxamid,
- *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-(((3*S*)-3-[(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2(1*H*)-isoquinolinyl)-carbonyl)-1,3-benzodioxol-5-yl}-1-indolizin-carboxamid,
- 10 - *N*-[4-(hydroxy)phenyl]-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(*H*)-isoquinolinyl)-carbonyl)-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizin-carboxamid,
- *N*-(4-hydroxyphenyl)-3-{6-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)-carbonyl)-1,3-benzodioxol-5-yl}-*N*-phenyl-1-indolizin-carboxamid,
- 15 - 3-{5-chlor-2-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)-carbonylo]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-1-indolizin-carboxamid,
- 6-{5-chlor-2-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)-carbonylo]phenyl}-*N*-(3-fluoro-4-methylphenyl)-*N*-(4-hydroxyphenyl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*] [1,4] oxazin-8-carboxamid,
- 20 - 3-(5-chlor-2-(((3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl)-phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5,6,7,8-tetrahydroindolizin-1-carboxamid,
- *N*-(3-fluoro-4-methylphenyl)-*N*-(4-hydroxyphenyl)-3-{6-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)-carbonyl)-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizin-carboxamid,
- 25 - *N*-[4-(hydroxy)phenyl]-*N*-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-3-{6-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)-carbonyl)-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizin-carboxamid,
- 30 - 3-{5-chlor-2-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)-carbonylo]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizin-carboxamid,

- *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)]-carbonyl]-1,3-benzodioxol-5-yl}-1-indolizin-carboxamid,
  - 3-{5-chlor-2-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)]-carbonylo]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-1-indolizin-carboxamid,
  - 6-{5-chlor-2-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)]-carbonylo]phenyl}-*N*-(4-hydroxyphenyl)-*N*-phenyl-3,4-dihydro-1*H*-pyrrolo[2,1-*c*]-[1,4]oxazin-8-carboxamid,
  - 10 - *N*-(3-fluorophenyl)-*N*-(4-hydroxyphenyl)-3-(6-[[((3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)]-carbonyl]-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizin-1-carboxamid,
- deres enantiomerer og diastereoisomerer samt additionssalte med en farmaceutisk acceptabel syre eller base.
- 15
- 8.** Forbindelse med formlen (I) ifølge krav 1, valgt fra følgende gruppe:
- *N*-(4-hydroxyphenyl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)]-carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizin-carboxamid,
  - 20 - 3-{5-chlor-2-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)]-carbonyl]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizin-carboxamid,
  - *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-3-{2,2-dideuterio-6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)]-carbonyl]-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydro-1-indolizin-carboxamid,
  - 25 - *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-3-(6-[[((3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)]carbonyl]-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizin-1-carboxamid,
  - *N*-(4-hydroxyphenyl)-3-{7-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)]-carbonyl]-2,3-dihydro-1,4-benzodioxin-6-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizin-carboxamid,
  - 30

- *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[((3*S*)-3-(4-methyl-1-piperazinyl)methyl)-3,4-dihydro-2(1*H*)-isoquinoliny]-carbonyl]-1,3-benzodioxol-5-yl}-1-indolizin-carboxamid,
  - *N*-[4-(hydroxy)phenyl]-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]-carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizin-carboxamid,
  - *N*-(4-hydroxyphenyl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]-carbonyl]-1,3-benzodioxol-5-yl]-*N*-phenyl-1-indolizin-carboxamid,
  - 3-{5-chlor-2-[[((3*S*)-3-(4-morpho]dihylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]-carbonylo]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-1-indolizin-carboxamid,
  - 6-{5-chlor-2-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]-carbonylo]phenyl}-*N*-(3-fluoro-4-methylphenyl)-*N*-(4-hydroxyphenyl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-8-carboxamid,
  - 3-(5-chlor-2-[[((3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl)-phenyl]-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5,6,7,8-tetrahydroindolizin-1-carboxamid,
- deres enantiomerer og diastereoisomerer samt additionssalte med en farmaceutisk acceptabel syre eller base.

20

**9.** Forbindelse med formlen (I) ifølge krav 8, hvilket er *N*-(4-hydroxyphenyl)-3-{6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]-carbonyl]-1,3-benzodioxol-5-yl]-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizin-carboxamid.

25 **10.** Forbindelse med formlen (I) ifølge krav 8, som er 3-{5-chlor-2-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]-carbonylo]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-5,6,7,8-tetrahydro-1-indolizin-carboxamid.

30 **11.** Forbindelse med formlen (I) ifølge krav 8, hvilket er *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-3-{2,2-dideuterio-6-[[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny]-carbonyl]-1,3-benzodioxol-5-yl}-5,6,7,8-

tetrahydro-1-indolizin-carboxamid.

**12.** Forbindelse med formlen (I) ifølge krav 8, hvilket er *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-3-(6-(((3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizin-1-carboxamid.

**13.** Forbindelse med formlen (I) ifølge krav 8, hvilket er *N*-(4-hydroxyphenyl)-3-{7-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)-carbonyl)-2,3-dihydro-1,4-benzodioxin-6-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizin-carboxamid.

**14.** Forbindelse med formlen (I) ifølge krav 8, hvilket er *N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-(((3*S*)-3-[(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2(1*H*)-isoquinoliny)-carbonyl)-1,3-benzodioxol-5-yl}-1-indolizin-carboxamid.

**15.** Forbindelse med formlen (I) ifølge krav 8, hvilket er *N*-[4-(hydroxy)phenyl]-*N*-(1-methyl-1*H*-indol-5-yl)-3-{6-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)-carbonyl)-1,3-benzodioxol-5-yl}-5,6,7,8-tetrahydro-1-indolizin-carboxamid.

**16.** Forbindelse med formlen (I) ifølge krav 8, hvilket er *N*-(4-hydroxyphenyl)-3-{6-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)-carbonyl)-1,3-benzodioxol-5-yl}-*N*-phenyl-1-indolizin-carboxamid.

**17.** Forbindelse med formlen (I) ifølge krav 8, hvilket er 3-{5-chlor-2-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)-carbonylo]phenyl}-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-1-indolizin-carboxamid.

30

**18.** Forbindelse med formlen (I) ifølge krav 8, hvilket er 6-{5-chlor-2-(((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinoliny)-carbonylo]phenyl}-*N*-(3-fluoro-4-methylphenyl)-*N*-(4-hydroxyphenyl)-3,4-dihydro-1*H*-pyrrolo[2,1-

c][1,4]oxazin-8-carboxamid.

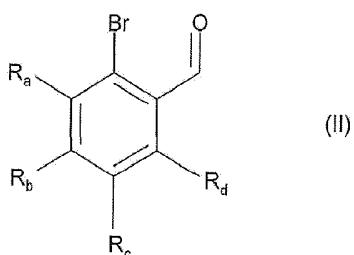
19. Forbindelse med formel (I) ifølge krav 8, hvilket er 3-(5-chlor-2-[[*(3S)*-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(*1H*)-yl]-carbonyl]-phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5,6,7,8-tetrahydroindolizin-1-carboxamid.

20. Hydrochloridsaltet af en forbindelse med formel (I) ifølge et hvilket som helst af kravene 9 til 13 og 15 til 19.

10

21. Dihydrochloridsalt af forbindelsen med formel (I) ifølge krav 14.

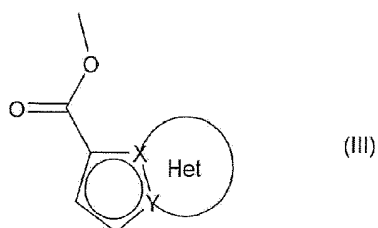
22. Fremgangsmåde til fremstilling af en forbindelse med formel (I) ifølge krav 1, **kendetegnet ved, at** der som udgangsmateriale anvendes forbindelsen med formel (II):



hvor  $R_a$ ,  $R_b$ ,  $R_c$  og  $R_d$  er som defineret for formel (I),

hvilken forbindelse med formel (II) underkastes en Heck-reaktion, i et vandigt eller organisk medium, i nærvær af en palladiumkatalysator, en base, en

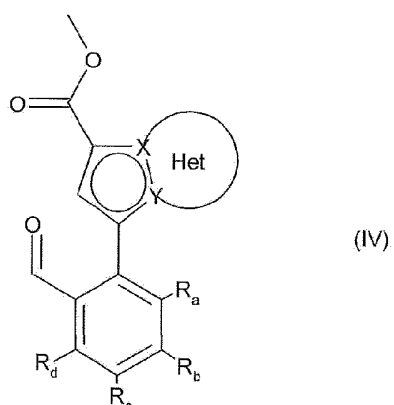
20 phosphin og forbindelsen med formel (III):



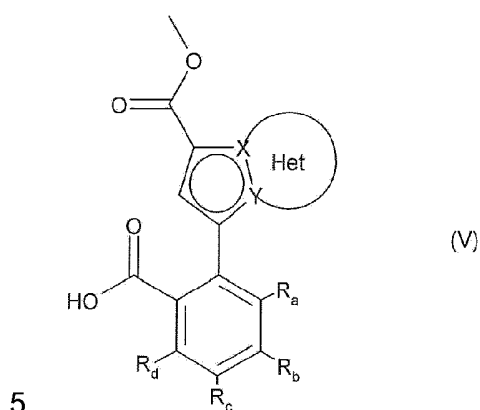
hvor grupperne X, Y og Het er som defineret for formel (I),

til opnåelse af forbindelsen med formel (IV):

10

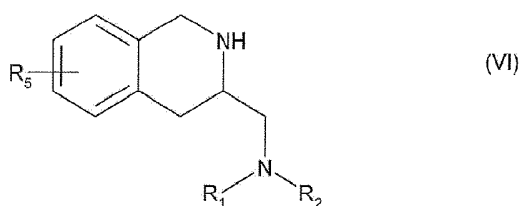


hvor  $R_a$ ,  $R_b$ ,  $R_c$ ,  $R_d$ , X, Y og Het er som defineret for formel (I),  
 aldehydfunktionen af forbindelsen med formlen (IV) oxideres til carboxylsyren til  
 dannelse af forbindelsen med formlen (V):

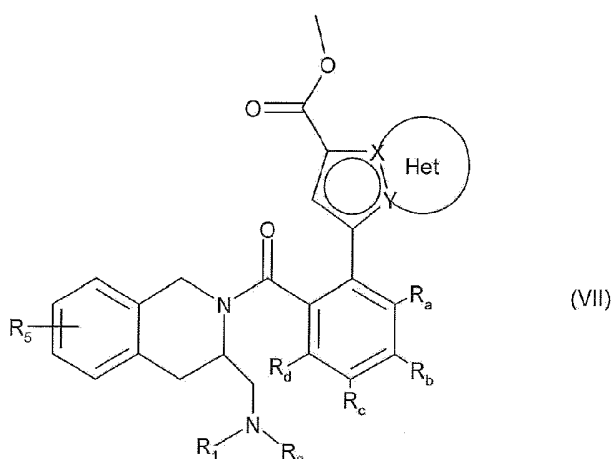


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hvor  $R_a$ ,  $R_b$ ,  $R_c$ ,  $R_d$ , X, Y og Het er som defineret for formel (I),  
 hvilken forbindelse med formel (V) derefter underkastes en peptidkobling med  
 en forbindelse med formlen (VI):



10 hvor  $R_1$ ,  $R_2$  og  $R_5$  er som defineret for formel (I),  
 til opnåelse af forbindelsen med formlen (VII):



hvor  $R_a$ ,  $R_b$ ,  $R_c$ ,  $R_d$ ,  $R_1$ ,  $R_2$ ,  $R_5$ ,  $X$ ,  $Y$  og  $Het$  er som defineret for formel (I),

esterfunktionen af forbindelsen med formlen (VII) hydrolyseres til opnåelse af den tilsvarende carboxylsyre eller det tilsvarende carboxylat, som kan  
 5 omdannes til et syrederivat, såsom det tilsvarende acylchlorid eller det tilsvarende anhydrid, inden det kobles med en amin  $NHR_3R_4$  hvor  $R_3$  og  $R_4$  har de samme betydninger som for formel (I), hvilket fører til forbindelsen med formel (I),

hvilken forbindelse med formel (I) kan oprenses ifølge en klassisk  
 10 adskillesesteknik, som omdannes, om ønsket, til additionssalte heraf med en farmaceutisk acceptabel syre eller base, og som eventuelt er adskilt i dens isomerer ifølge en klassisk adskillesesteknik,  
 idet det forstås, at visse grupper (hydroxy, amino ...) af reagenserne eller mellemprodukterne af syntesen på ethvert tidspunkt af forløbet af den ovenfor  
 15 beskrevne fremgangsmåde, der anses for passende, kan beskyttes og derefter afbeskyttes ifølge kravene til syntesen.

**23.** Fremgangsmåde ifølge krav 22 til fremstilling af en forbindelse med formlen (I), hvori en af grupperne  $R_3$  og  $R_4$  er substitueret med en hydroxygruppe,  
 20 **kendetegnet ved, at** aminen  $NHR_3R_4$  på forhånd er underkastet en reaktion til beskyttelse af hydroxyfunktionen før kobling med carboxylsyren af forbindelsen med formlen (VII), eller med et tilsvarende syrederivat deraf, idet den resulterende beskyttede forbindelse med formlen (I) efterfølgende underkastes en reaktion til fraspaltning af beskyttelsesgruppen og eventuelt derefter  
 25 omdannes til et af sine additionssalte med en farmaceutisk acceptabel syre eller



base.

**24.** Farmaceutisk sammensætning omfattende en forbindelse med formlen (I) ifølge et hvilket som helst af kravene 1 til 19 eller et additionssalt heraf med en farmaceutisk acceptabel syre eller base i kombination med en eller flere farmaceutisk acceptable excipients.

**25.** Farmaceutisk sammensætning ifølge krav 24 til anvendelse som et pro-apoptotisk middel.

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**26.** Farmaceutisk sammensætning ifølge krav 24 til anvendelse i behandlingen af cancer og immune og autoimmune sygdomme.

**27.** Farmaceutisk sammensætning ifølge krav 24 til anvendelse ved behandling af cancer i blæren, hjerne, bryst og livmoder, kroniske lymfoide leukæmier, colorektal cancer, esophagus og lever, lymfoblastiske leukæmier, follikulære lymfomer, melanomer, maligne hæmopatier, myelomer, ovariecancer, ikke-småcellet lungecancer, prostatacancer og småcellet lungecancer.

**28.** Forbindelse med formlen (I) ifølge et hvilket som helst af kravene 1 til 19, eller et additionssalt deraf med en farmaceutisk acceptabel syre eller base, til anvendelse ved behandling af cancer i blæren, hjerne, bryst og uterus, kroniske lymfoide leukæmier, colorektal cancer, esophagus og lever, lymfoblastiske leukæmier, follikulære lymfomer, melanomer, maligne hæmopatier, myelomer, ovariecancer, ikke-små-cellet lungecancer, prostatacancer og småcellet lungecancer.

**29.** Kombination af en forbindelse med formlen (I) ifølge et hvilket som helst af kravene 1 til 21 med et anticancermiddel, der er valgt blandt genotoksiske midler, mitotiske gifte, antimetabolitter, proteasominhibitorer, kinaseinhibitorer og antistoffer.

**30.** Farmaceutisk sammensætning omfattende en kombination ifølge krav 29 i kombination med en eller flere farmaceutisk acceptable excipienser.

**31.** Kombination ifølge krav 29 til anvendelse ved behandling af cancere.

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**32.** Forbindelse med formlen (I) ifølge et hvilket som helst af kravene 1 til 21 til anvendelse i kombination med strålebehandling til behandling af cancere.