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(54) Benævnelse: **NYE INDOLIZINDERIVATIVER, FREMGANGSMÅDE TIL DERES FREMSTILLING OG FARMACEUTISKE SAMMENSÆTNINGER SOM INDEHOLDER DEM**

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WO-A2-2006/023778

Description

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

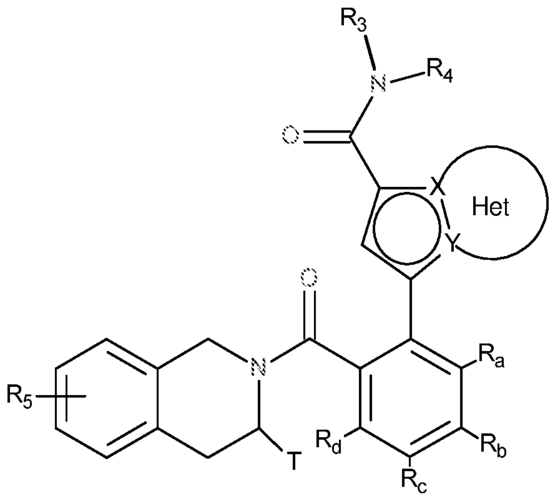
The compounds of the present invention are new and have very valuable pharmacological characteristics in the field of apoptosis and cancerology.

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).

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, lymphoma a therapeutic need for compounds that inhibit the anti-apoptotic activity of the proteins of the Bcl-2 family. Among the Bcl-2 inhibitors already known in the literature there may be singled out the compounds 2-(1,2,3,4-tetrahydroisoquinolin-2-carbonyl)-4-(sulphonyl-carbamoyl)phenyl described in WO 2012/162365, the compounds 1-(1,2,3,4-tetrahydroiso-quinolin-2-carbonyl)-2,3,4-trihydroxyphenyl described in WO 2006/023778 and the compounds 3-[2-(1,2,3,4-tetrahydroisoquinolin-2-carbonyl)phenyl]indolizine described in WO 2013/110890. They are all potentially of interest in the treatment of cancer.

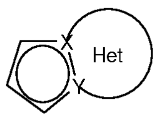
In addition to being new, the compounds of the present invention have pro-apoptotic properties making it possible to use them in pathologies involving a defect in apoptosis, such as, for example, in the treatment of cancer, auto-immune diseases and diseases of the immune system.

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



(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 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 $(C_1\text{-}C_6)$alkyl group or a group -C(O)-O-Alk wherein Alk is a linear or branched $(C_1\text{-}C_6)$alkyl group,

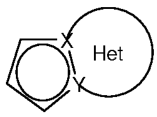
- ♦ T represents a hydrogen atom, a linear or branched (C_1-C_6)alkyl group optionally substituted by from one to three halogen atoms, a group (C_2-C_4)alkyl-NR_1R_2, or a group (C_1-C_4)alkyl-OR_6,
- ♦ R_1 and R_2 independently of one another represent a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,
  or R_1 and R_2 form with the nitrogen atom carrying them a heterocycloalkyl,
- ♦ R_3 represents a linear (C_1-C_6)alkyl group, an aryl group or a heteroaryl group, it being possible for the last two groups to be substituted by from one to three groups selected from halogen, linear or branched (C_1-C_6)alkyl, linear or branched (C_1-C_6)alkoxy, cyano and linear or branched heterocycloalkyl-(C_1-C_6)alkyl, it being understood that one or more of the carbon atoms of the preceding groups, or of their possible substituents, may be deuterated,
- ♦ R_4 represents a 4-hydroxyphenyl group, it being understood that one or more of the carbon atoms of the preceding group, or of its possible substituents, may be deuterated,
- ♦ R_5 represents a hydrogen or halogen atom, a linear or branched (C_1-C_6)alkyl group, or a linear or branched (C_1-C_6)alkoxy group,
- ♦ R_6 represents a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,
- ♦ R_a and R_d each represent a hydrogen atom and (R_b,R_c) form together with the carbon atoms carrying them a 1,3-dioxolane group or a 1,4-dioxane group, or R_a, R_c and R_d each represent a hydrogen atom and R_b represents a hydrogen, a halogen, a methyl or a methoxy, or R_a, R_b and R_d each represent a hydrogen atom and R_c represents a hydroxy group or a methoxy group,

it being understood that:

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

group composed of 3 to 10 ring members and containing from 1 to 3 hetero atoms selected from oxygen, sulphur, SO, SO_2 and nitrogen,

it being possible for the aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups so defined and the groups alkyl, alkenyl, alkynyl and alkoxy to be substituted by from 1 to 3 groups selected from linear or branched (C_1-C_6)alkyl, (C_3-C_6)spiro, linear or branched (C_1-C_6)alkoxy, (C_1-C_6)alkyl-S-, hydroxy, oxo (or *N*-oxide where appropriate), nitro, cyano, -COOR', -OCOR', NR'R", linear or branched (C_1-C_6)polyhaloalkyl, trifluoromethoxy, (C_1-C_6)alkylsulphonyl, halogen, aryl, heteroaryl, aryloxy, arylthio, cycloalkyl, heterocycloalkyl optionally substituted by one or more halogen atoms or alkyl groups, it being understood that R' and R", each independently of the other, represent a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

it being possible for the Het moiety of the group 

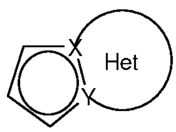
defined in formula (I) to be substituted by from one to three groups selected from linear or branched (C_1-C_6)alkyl, hydroxy, linear or branched (C_1-C_6)alkoxy, $NR_1'R_1''$ and halogen, it being understood that R_1' and R_1'' are as defined for the groups R' and R" mentioned hereinbefore,

their enantiomers and diastereoisomers, and 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, 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.

Advantageously, the group:



represents one of the following groups: 5,6,7,8-tetrahydroindolizine optionally substituted by an amino group; indolizine; 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine optionally substituted by a methyl; pyrrolo[1,2-*a*]pyrimidine. The groups 5,6,7,8-tetrahydroindolizine and indolizine are more especially preferred.

In preferred compounds of the invention, T represents a hydrogen atom, a methyl group (and more especially an *(R)*-methyl), a group 2-(morpholin-4-yl)ethyl, 3-(morpholin-4-yl)propyl, $-CH_2-OH$, 2-aminoethyl, 2-(3,3-difluoropiperidin-1-yl)ethyl, 2-[(2,2-difluoroethyl)amino]ethyl or 2-(3-methoxyazetidin-1-yl)ethyl.

Preferably, R_a and R_d each represent a hydrogen atom and (R_b,R_c), together with the carbon atoms carrying them, form a 1,3-dioxolane group; or R_a, R_c and R_d each represent a hydrogen atom and R_b represents a halogen.

In preferred compounds of the invention, R_3 represents a heteroaryl group selected from the following group: 1*H*-indole, 2,3-dihydro-1*H*-indole, 1*H*-indazole, pyridine, 1*H*-pyrrolo[2,3-*b*]pyridine, 1*H*-pyrazole, imidazo[1,2-*a*]pyridine, pyrazolo[1,5-*a*]pyrimidine, [1,2,4]triazolo[1,5-*a*]pyrimidine, and 1*H*-pyrazolo[3,4-*b*]pyridine, all of which may be substituted by a linear or branched (C_1-C_6)alkyl group.

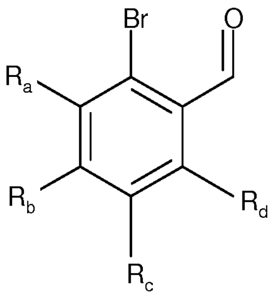
Preferred compounds according to the invention are included in the following group:

- *N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-{1-[2-(morpholin-4-yl)ethyl]-1*H*-indol-5-yl}-5,6,7,8-tetrahydroindolizine-1-carboxamide,
- *N*-(4-hydroxyphenyl)-3-(6-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide,
- *N*-{3-fluoro-4-[2-(morpholin-4-yl)ethoxy]phenyl}-*N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxamide,

- *N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-4-yl)indolizine-1-carboxamide,
- *N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(2-methylpyridin-4-yl)indolizine-1-carboxamide,
- *N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)indolizine-1-carboxamide,
- *N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide,
- *N*-(2,6-dimethylpyridin-4-yl)-*N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxamide,
- *N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-4-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide,
- 3-(5-chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)indolizine-1-carboxamide,
- *N*-(4-hydroxyphenyl)-*N*-(2-methoxypyridin-4-yl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxamide,

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

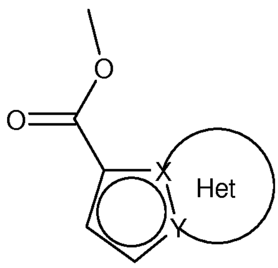
The invention relates also to a process for the preparation of compounds of formula (I), which process is characterised in that there is used as starting material the compound of formula (II):



(II)

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

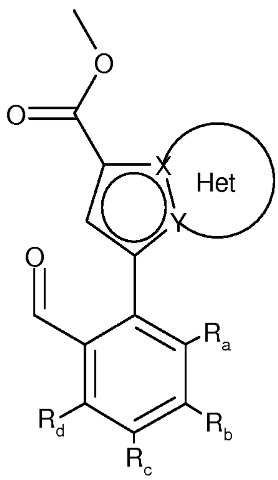
which compound of formula (II) is subjected to a Heck reaction, in an aqueous or organic medium, in the presence of a palladium catalyst, of a base, of a phosphine and of the compound of formula (III):



(III)

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

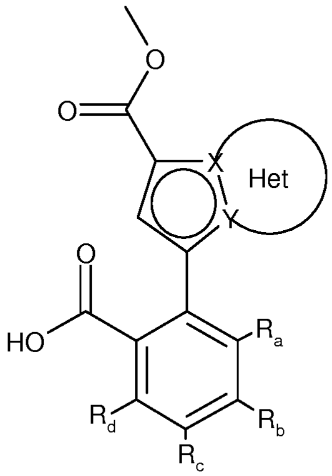
to obtain the compound of formula (IV):



(IV)

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

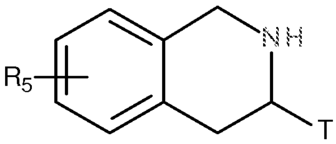
the aldehyde function of which compound of formula (IV) is oxidised to a carboxylic acid to form the compound of formula (V):



(V)

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

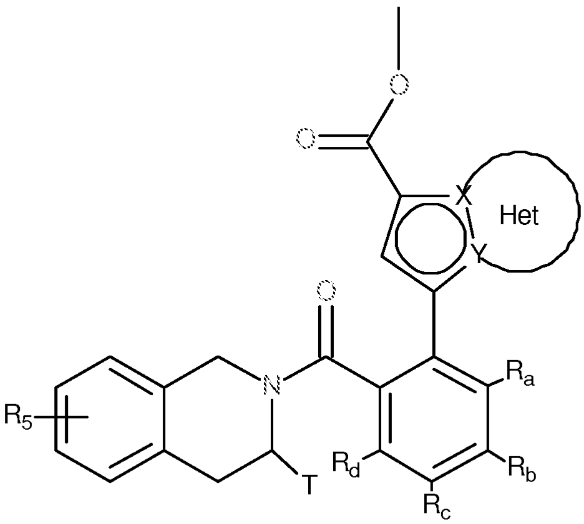
which compound of formula (V) is then subjected to peptide coupling with a compound of formula (VI):



(VI)

wherein T and R_5 are as defined for formula (I),

to yield the compound of formula (VII):



(VII)

wherein R_a, R_b, R_c, R_d, T, R_5, X, Y and Het are as defined for formula (I), the ester function of which compound of formula (VII) is hydrolysed to yield the corresponding carboxylic acid or carboxylate, which may be converted into an acid derivative such as the corresponding acyl chloride or 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),

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

it being understood that, at any 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.

More particularly, 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 any 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.

The compounds of formulae (II), (III), (VI) and the amine NHR_3R_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 have pro-apoptotic properties. The ability to reactivate the apoptotic process in cancerous cells is of major therapeutic interest in the treatment of cancers, auto-immune diseases and diseases of the immune system.

More especially, the compounds according to the invention will be useful in the 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, the treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukaemias, colorectal cancer, cancers of the œsophagus and liver, lymphoblastic leukaemias, non-Hodgkin lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer and small-cell lung cancer. Among non-Hodgkin lymphomas, there may be mentioned more preferably follicular lymphomas, mantle cell lymphomas, diffuse large B-cell lymphomas, small lymphocytic lymphomas and marginal zone B-cell lymphomas.

The present invention relates also to pharmaceutical compositions comprising 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, 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 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 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 radiotherapy in the treatment of cancer.

Finally, the compounds of the invention may be linked to monoclonal antibodies or fragments thereof or linked to scaffold proteins that can be related or not to monoclonal antibodies.

Antibody fragments must be understood as fragments of Fv, scFv, Fab, F(ab')2, F(ab'), scFv-Fc type or diabodies, which generally have the same specificity of binding as the antibody from which they are descended. According to the present invention, antibody fragments of the invention can be obtained starting from antibodies by methods such as digestion by enzymes, such as pepsin or papain, and/or by cleavage of the disulfide bridges by chemical reduction. In another manner, the antibody fragments comprised in the present invention can be obtained by techniques of genetic recombination likewise well known to the person skilled in the art or else by peptide synthesis by means of, for example, automatic peptide synthesizers such as those supplied by the company Applied Biosystems, etc.

Scaffold proteins that can be related or not to monoclonal antibodies are understood to mean a protein that contains or not an immunoglobulin fold and that yields a binding capacity similar to a monoclonal antibody. The man skilled in the art knows how to select the protein scaffold. More particularly, it is known that, to be selected, such a scaffold should display several features as follow (Skerra A., J. Mol. Recogn., 13, 2000, 167-187): phylogenetically good conservation, robust architecture with a well-known three-dimensional molecular organization (such as, for example, crystallography or NMR), small size, no or only a low degree of post-translational modifications, easy to produce, express and purify. Such a protein scaffold can be, but without limitation, a structure selected from the group consisting in fibronectin and preferentially the tenth fibronectin type III domain (FNfn10), lipocalin, anticalin (Skerra A., J. Biotechnol., 2001, 74(4):257-75), the protein Z derivative from the domain B of staphylococcal protein A, thioredoxin A or any protein with a repeated domain such as an "ankyrin repeat" (Kohl et al., PNAS, 2003, vol.100, No.4, 1700-1705), "armadillo repeat", "leucine-rich repeat" or "tetratricopeptide repeat". There could also be mentioned a scaffold derivative from toxins (such as, for example, scorpion, insect, plant or mollusc toxins) or protein inhibitors of neuronal nitric oxide synthase (PIN).

The following Preparations and Examples illustrate the invention without limiting it in any way.

General procedures

All reagents and anhydrous solvents are obtained from commercial sources and were used without further purification or drying. Flash chromatography is performed on an ISCO CombiFlash Rf 200i apparatus with pre-packed silica-gel cartridges (SiliaSep™ F60 (40-63µm, 60Å). Thin layer chromatography was conducted with 5 x 10 cm plates coated with Merck Type 60 F_{254} silica gel. Microwave heating was performed with a CEM Discover® SP apparatus.

Analytical LC-MS

The compounds of the invention were characterized by high-performance liquid chromatography coupled with mass spectroscopy (HPLC-MS) on either an Agilent HP1200 rapid-resolution apparatus coupled to a 6140 mass detector with a multi-mode source (m/z range 150 to 1000 atomic mass units or amu) or an Agilent HP1100 apparatus coupled to a 1946D mass detector with an electrospray ionisation source (m/z range 150 to 1000 amu). The conditions and methods listed below are identical for both machines.

Detection:	UV detection at 230, 254 and 270 nm.
Injection Volume:	2 µL
Mobile Phases:	A - Water + 10 mMol / ammonium formate + 0.08% (v/v) formic acid at pH ca 3.5.
	B - 95% Acetonitrile + 5% A + 0.08% (v/v) formic acid

Method A ***(3.75 min; either positive (pos) or positive and negative (pos / neg) ionisation)***

Column: Gemini 5µm, C18, 30 mm x 4.6mm (Phenomenex).

Temperature: 35°C.

Gradient:

Time (min)	**Solvent A (%)**	**Solvent B (%)**	**Flow (mL/min)**
0	95	5	2
0.25	95	5	2
2.50	95	5	2
2.55	5	95	3
3.60	5	95	3
3.65	5	95	2
3.70	95	5	2
3.75	95	5	2

Method B ***(1.9 min; either positive (pos) or positive and negative (pos / neg) ionisation)***

Column: Gemini 5µm, C18, 30 mm x 4.6mm (Phenomenex).

Temperature: 35°C.

Gradient:

Time (min)	Solvent A (%)	Solvent B (%)	Flow (mL/min)
0	95	5	1.1
0.12	95	5	1.1
1.30	5	95	1.1
1.35	5	95	1.7
1.85	5	95	1.7
1.90	5	95	1.1
1.95	95	5	1.1

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

Step A*: *1-Formyl-2-piperidine-carboxylic acid

To a solution of 40 g of a racemic mixture of 2-piperidine-carboxylic acid (0.310 mmol) in 300 mL of formic acid placed at 0°C there are added, dropwise, 200 mL (2.15 mmol) of acetic anhydride. The batch is then stirred at ambient temperature overnight. Then, the reaction mixture is cooled to 0°C, hydrolysed by adding 250 mL of water, and stirred for half an hour at 0°C before being concentrated to dryness. The oil thereby 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 in a yield of 98 %. It is used directly, without being otherwise purified, in the next Step.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 13.0 (m, 1H OH); 8.0-8.05 (2s, 1H aldehyde); 4.9-4.5 (2d, 1H α to the N and COOH) ; 4.1-2.6 (m, 2H α to the N); 2.2-1.2 (m, 6H piperidine)

IR: ν: -OH: 2000-3000 cm^{-1} acid; ν: >C=O 1703 cm^{-1} wide band

<u>Step B</u>: Methyl 5,6,7,8-tetrahydro-1-indolizine-carboxylate

To a solution of 10 g of the carboxylic acid obtained in Step A (63.6 mmol) in 65 mL of dichloromethane there are successively added 13.4 g of tosyl chloride (70.4 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 hour 30 minutes. It is then placed at ambient temperature, and there are then added 5 mL of methyl 2-chloroacrylate (48.9 mmol) and, dropwise, 9 mL of *N,N,N*-triethylamine (64 mmol). The batch is refluxed overnight.

The reaction mixture is then diluted with methylene chloride, washed successively with 1N HCl solution, saturated $NaHCO_3$ solution and then saturated NaCl solution until a neutral pH is obtained. The organic phase is then dried over $MgSO_4$, filtered, concentrated to dryness and purified by chromatography over silica gel (heptane/AcOEt gradient). The title product is obtained in the form of an oil.

^{1}H NMR: δ (400 MHz; $CDCl_3$; 300K): 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)

IR: ν:>C=O 1692 cm^{-1} ester

<u>Step C</u>: Methyl 3-(6-formyl-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydro-1-indolizine-carboxylate

To a solution of 6.4 g of the ester obtained in Step B (35.7 mmol) in 12 mL of *N,N*-dimethylacetamide there are successively added 12.3 g of 6-bromo-1,3-benzodioxole-5-carbaldehyde (53.6 mmol) and 7 g of potassium acetate (71.4 mmol), and then the batch is stirred under argon for 20 minutes. There are then added 1.3 g of palladium catalyst $PdCl_2(PPh_3)_2$ (1.8 mmol). The reaction mixture is then heated at 130°C for one hour before adding 139 μL of H_2O thereto. Heating is maintained at that same temperature overnight. The mixture is allowed to return to ambient temperature and it is then diluted with AcOEt. Animal charcoal (2 g per g of product) is added and the batch is stirred at ambient temperature for 1 hour and then filtered. The organic phase is then washed with water, dried over magnesium sulphate and concentrated to dryness. The crude product thereby obtained is purified over silica gel (heptane/ACOEt gradient). The title product is obtained in the form of an oil.

^{1}H NMR: δ:(400 MHz; dmso-d6; 353°K): 9.65 (s, 1H, H aldehyde); 7.3-7.15 (2s, 2H, aromatic Hs); 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)

IR: ν: >C=O 1695 cm^{-1} ester; ν: >C=O 1674 cm^{-1}

<u>Step D</u>: ***6-[1-(Methoxycarbonyl)-5,6,7,8-tetrahydro-3-indolizinyl]-1,3-benzodioxole-5-carboxylic acid***

A solution containing 3.37 g of the compound obtained in Step C (10.3 mmol) in 9.3 mL of acetone and 8.8 mL (80.24 mmol) of 2-methyl-2-butene is prepared and placed at 0°C. There are added, dropwise, 9.3 mL of an aqueous solution containing a mixture of 3.3 g of $NaClO_2$ (36.05 mmol) and 3.6 g of Na_2PO_4 (25.75 mmol). The batch is then stirred at ambient temperature for 7 hours. The reaction mixture is then concentrated in order to remove the acetone. The solid then obtained is filtered off, washed with water and then dried at 40°C *in vacuo* overnight. The title product is obtained in the form of a solid, which is subsequently used without being otherwise purified.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 12.10 (m, 1H, H carboxylic acid); 7.40-6.88 (2s, 2H, aromatic Hs); 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: ν: -OH: 3000-2000 cm^{-1} acid; ν: >C=O 1686-1676 cm^{-1} ester+acid; ν: >C=C< 1608 cm^{-1}

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

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

To a solution of pentafluorophenol in 520 mL of anhydrous ether placed at 0°C there are successively added 49 g of 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (286 mmol) in portions and 12 mL of formic acid (312 mmol). The batch is stirred at ambient temperature for 2 hours. There is then added a mixture of 32 g of 1-*tert*-butyl 3-methyl 1,3-piperazinedicarboxylate (130 mmol) and 18 mL of triethylamine (130 mmol) dissolved in 520 mL of CH_2Cl_2. The batch is stirred overnight at ambient temperature. The reaction mixture is hydrolysed with 1N aqueous HCl solution and extracted with CH_2Cl_2. The organic phases are then combined and then washed with saturated aqueous $NaHCO_3$ solution and then with saturated aqueous NaCl solution until neutral. After drying over $MgSO_4$, filtering and concentrating 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.

IR: ν: C=O: 1674-1745 cm^{-1}

m/z ($C_{12}H_{20}N_2O_5$): 272.1(M+); 295.121 $(M+Na)^+$; 567.253 $(2M+Na)^+$

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 of dioxane there are added 4.8 g of LiOH (113 mmol) dissolved in 100 mL of H_2O. The batch is stirred at ambient temperature for 4 hours. The reaction mixture is then 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 in the following cyclisation step.

^{13}C NMR: δ (500 MHz; dmso-d6; 300K): 46 (s, C piperazine); 42-38 (m, C piperazine); 58-53 (s, C piperazine); 28.5 (s, C ^tBu)

IR: ν: C=O: 1650 cm^{-1} ; 2800 cm^{-1}

***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 mmol) in 800 mL of dichloromethane there are successively added 24 g of tosyl chloride (124 mmol), 12.6 mL of methyl 2-chloroacrylate (124 mmol) and then 35 mL of triethylamine (247 mmol). The batch is stirred at reflux for 2 hours. After cooling, the reaction mixture is diluted with ethyl acetate and the organic phase is washed with saturated NaCl solution until neutral. After drying over $MgSO_4$, filtering and concentrating to dryness, the title product is isolated by chromatography over silica gel (petroleum ether / AcOEt gradient: 0-20%) in the form of a solid.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 6.8-6.43 (m, 2H, H pyrrole); 4.75-3.75 (m, 6H, H piperazine); 3.73 (s, 3H, H COOCH3); 1.48 (s, 9H, H ^{t}Bu)

IR: ν: C=O (conjugated ester): 1712 cm^{-1}; C=O (carbamate): 1677 cm^{-1}

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

The procedure is in accordance with the protocol described in Steps C and D of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C with 2-bromo-4-chlorobenzaldehyde.

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

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

Preparation 4: 7-[2-(*tert*-Butoxycarbonyl)-8-(methoxycarbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]pyrazin-6-yl]-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid

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

The procedure is in accordance with the process described in Steps A-C of Preparation 2.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 6.8-6.43 (m, 2H, H pyrrole); 4.75-3.75 (m, 6H, H piperazine); 3.73 (s, 3H, H COOCH3); 1.48 (s, 9H, H ^{t}Bu)
IR: ν: C=O (conjugated ester): 1712 cm^{-1}; C=O (carbamate): 1677 cm^{-1}

***Step B**: 7-[2-(tert-Butoxycarbonyl)-8-(methoxycarbonyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-6-yl]-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid*

The procedure is in accordance with the protocol described in Steps C and D of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C with 7-bromo-2,3-dihydro-1,4-benzodioxine-6-carbaldehyde.

Preparation 5: 4-Chloro-2-[1-(methoxycarbonyl)-3-indolizinyl]benzoic acid

***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 batch is then stirred at ambient temperature overnight. The precipitate thereby 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 in the next Step.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 9.15 (d, 2H, aromatic Hs pyridine); 8.7 (t, 1H, aromatic H); 8.25 (t, 2H, aromatic H); 5.65 (s, 2H, H CH_2COOH)
IR: ν: C=O: 1732 cm^{-1}; -OH acid: 2800 cm^{-1}

***Step B**: Methyl 1-indolizinecarboxylate*

To a suspension of 6.55 g of the pyridinium salt obtained in Step A (30 mmol) in 240 mL of toluene there are successively added 16.7 mL of methyl acrylate (150 mmol), 4.2 mL of triethylamine (30 mmol) and then, in portions, 20.9 g of MnO_2 (240 mmol). The batch is then heated at 90°C for 3 hours. After cooling, the reaction mixture is filtered over a cake of Celite and concentrated to dryness. The title product is then isolated by purification over silica gel (heptane / AcOEt gradient: 0-10%) in the form of an oil which crystallises in the cold state.

^{1}H NMR: δ (300 MHz; dmso-d6; 300K): 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 indolizine); 4.25 (q, 2H, -C(O)CH_2CH_3); 1.35 (t, 3H, -C(O)CH_2CH_3)

IR: ν: C=O ester: 1675 cm^{-1}; aromatic C=C moieties: 1634 cm^{-1}

__Step C__: 4-Chloro-2-[1-(methoxycarbonyl)-3-indolizinyl]benzoic acid

The procedure is in accordance with the protocol described in Steps C and D of Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C with 2-bromo-4-chlorobenzaldehyde.

__Preparation 6:__ 2-[2-(*tert*-Butoxycarbonyl)-8-(methoxycarbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]pyrazin-6-yl]-4-fluorobenzoic acid

The procedure is in accordance with the protocol described in Preparation 2, replacing the 2-bromo-4-chlorobenzaldehyde used in Step D with 2-bromo-4-fluorobenzaldehyde.

__Preparation 7:__ 6-[2-(*tert*-Butoxycarbonyl)-8-(methoxycarbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]pyrazin-6-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the protocol described in Preparation 2, replacing the 2-bromo-4-chlorobenzaldehyde used in Step D with 6-bromo-1,3-benzodioxole-5-carbaldehyde.

__Preparation 8:__ 6-[1'-(Methoxycarbonyl)-5',6'-dihydro-8'*H*-spiro[1,3-dioxolane-2,7'-indolizin]-3'-yl]-1,3-benzodioxole-5-carboxylic acid

__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 batch is stirred at ambient temperature for 1 hour. The reaction mixture is evaporated to dryness and taken up in ethyl acetate. The organic phase is then successively washed with 1N NaOH solution, water and then with saturated NH_4Cl solution until a neutral pH is obtained. It is then dried over magnesium sulphate, filtered and concentrated to dryness. The oil thereby obtained is purified by flash

chromatography (heptane/ethyl acetate gradient). The title product is obtained in the form of an oil.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 8.15 (s, 1H, CHO); 5.0-4.75 (m, 1H, tertiary H); 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)

<u>Step B</u>: 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) is dissolved in 160 mL of dioxane. A solution of 125 mL of 1M KOH is added dropwise and the batch is stirred at ambient temperature for 1 hour. There are then added 125 mL of 1M HCl and the compound is extracted with dichloromethane. The organic phase is dried over $MgSO_4$, filtered and concentrated to dryness. The title product is obtained in the form of a powder.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K) 13.5-12 (m, 1H, OH); 8.1 + 8.0 (2s, 1H, CHO); 4.9 + 4.6 (2m, 1H, tertiary H); 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: ν: OH: 3500-2000 cm^{-1}; -C=O (acid + aldehyde): 1731 + 1655 cm^{-1}

<u>Step C</u>: 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 dichloromethane there are successively added 39.5 mL (238.4 mmol) of triethylamine and then, in portions, 12.5 g (65.6 mmol) of *para*-toluenesulphonyl chloride and 23.7 mL (238.4 mmol) of methyl chloroacrylate. The batch is stirred at 80°C for 18 hours. The reaction mixture is then filtered over Celite. The filtrate is then washed with saturated $NaHCO_3$ solution and then with saturated NH_4Cl solution. The organic phase is dried over $MgSO_4$, filtered and concentrated to dryness. The oil thereby obtained is purified by flash chromatography (heptane/ethyl acetate gradient). The product is obtained in the form of a solid.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K) 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)

IR: ν:-C=O (ester):1689 cm^{-1}

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

The procedure is in accordance with the process of Step C of Preparation 1.

***Step E:* 6-[1'-(Methoxycarbonyl)-5',6'-dihydro-8'H-spiro[1,3-dioxolane-2,7'-indolizin]-3'-yl]-1,3-benzodioxole-5-carboxylic acid**

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

Preparation 9: 6-[1-(Methoxycarbonyl)-3-indolizinyl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the protocol described in Preparation 5, replacing the 2-bromo-4-chlorobenzaldehyde used in Step C with 6-bromo-1,3-benzodioxole-5-carbaldehyde.

Preparation 10: 4-Methyl-2-[1-(methoxycarbonyl)-5,6,7,8-tetrahydro-3-indolizinyl]-benzoic acid

The procedure is in accordance with the protocol described in Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C with 2-bromo-4-methylbenz-aldehyde.

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

The procedure is in accordance with the protocol described in Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C with 2-bromo-benzaldehyde.

<u>Preparation 12:</u> 6-[8-(Methoxycarbonyl)pyrrolo[1,2-*a*]pyrimidin-6-yl]-1,3-benzo-dioxole-5-carboxylic acid

<u>Step A</u>: Methyl pyrrolo[1,2-a]pyrimidine-8-carboxylate

To a solution of 6.2 g of methyl 2-pyrimidin-2-ylacetate (40.75 mmol) in 250 mL of acetone there are successively added 14.04 g (167 mmol) of $NaHCO_3$ in the form of a powder, 13.2 mL (203.75 mmol) of chloroacetaldehyde and then 3.54 g (40.75 mmol) of lithium bromide. The batch is heated at 60°C for 24 hours. The reaction mixture is then concentrated to dryness, taken up in ethyl acetate, washed with water, dried over $MgSO_4$, filtered and then concentrated to dryness. The solid thereby obtained is then purified by chromatography over silica gel (AcOEt). The expected product is obtained in the form of an oil.

Mass spectrum:

Empirical formula: $C_8H_8N_2O_2$

LC/MS: m/z = $[M+H]^+$ = 177

<u>Step B</u>: Methyl 6-(6-formyl-1,3-benzodioxol-5-yl)pyrrolo[1,2-a]pyrimidine-8-carboxylate

To a solution of 3.93 g of the compound obtained in Step A (22.3 mmol) in 80 mL of anhydrous dimethylacetamide there are added 7.66 g (33.45 mmol) of 6-bromo-1,3-benzodioxole-5-carbaldehyde and 4.4 g (44.6 mmol) of potassium acetate. The batch is degassed under nitrogen for 15 minutes. There are then added 1.56 g (2.23 mmol) of $PdCl_2(PPh_3)_4$ catalyst. The reaction mixture is heated at 130°C for 16 hours under an inert atmosphere. After drying, the residue is taken up in dichloromethane; the batch is filtered over a cake of Celite and then the filtrate is washed with water, dried over $MgSO_4$ and concentrated to dryness. The black solid is then chromatographed over silica gel (CH_2Cl_2/MeOH 5 %). The expected product is obtained in the form of a solid.

Mass spectrum:

Empirical formula: $C_{17}H_{12}N_2O_3$

LC/MS: m/z = $[M+H]^+$ = 325

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

To a solution of 2.91 g (8.97 mmol) of the aldehyde obtained in Step B in 140 mL of acetone cooled to 0°C there are added 2-methylbutene and then, dropwise, a mixture of 2.8 g (17.94 mmol) of $NaH_2PO_4.2H_2O$ and 2.84 g (31.4 mmol) of $NaClO_2$ dissolved in 30 mL of water. The batch is stirred at ambient temperature for 4 hours. The reaction mixture is then concentrated *in vacuo* to remove the acetone, placed at 0°C and then acidified to pH = 2-3 by adding 5N HCl solution dropwise. The formation of a precipitate is observed, which is filtered off, washed with water and then with diethyl ether and dried *in vacuo*.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 12.7 (m, 1H, CO**OH**); 8.45 (d, 1H, aromatic H, H pyrrolo [1,2-a]pyrimidine); 8.19 (d, 1H, aromatic H, H pyrrolo [1,2-a]pyrimidine); 6.9 (dd, 1H, aromatic H, H pyrrolo [1,2-a]pyrimidine); 7.51 (s, 1H, aromatic H); 7.21 (s, 1H, aromatic H); 7.07 (s, 1H, aromatic H); 6.2 (s, 2H, aliphatic Hs, O-**CH_2**-O); 3.8 (s, 3H, aliphatic Hs, COO**CH_3**)

IR: ν -OH-: 3300 to 1800 cm^{-1}; ν -CO-: 1705 cm^{-1}, ν >C=C<: 1616 cm^{-1}

<u>Preparation 13:</u> 4-Methoxy-2-[1-(methoxycarbonyl)-5,6,7,8-tetrahydro-3-indolizinyl]-benzoic acid

The procedure is in accordance with the protocol described in Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C with 2-bromo-4-methoxy-benzaldehyde.

<u>Preparation 14:</u> 5-Methoxy-2-[1-(methoxycarbonyl)-5,6,7,8-tetrahydro-3-indolizinyl]-benzoic acid

The procedure is in accordance with the protocol described in Preparation 1, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step C with 2-bromo-5-methoxy-benzaldehyde.

Preparation 15: 7-[1-(Methoxycarbonyl)-5,6,7,8-tetrahydro-3-indolizinyl]-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid

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

Preparation 16: 2-[1-(Methoxycarbonyl)-3-indolizinyl]benzoic acid

The procedure is in accordance with the process of Preparation 5, replacing the 2-bromo-4-chlorobenzaldehyde used in Step C with 2-bromo-benzaldehyde.

Preparation 17: 4-Fluoro-2-[1-(methoxycarbonyl)-3-indolizinyl]benzoic acid

The procedure is in accordance with the process of Preparation 5, replacing the 2-bromo-4-chlorobenzaldehyde used in Step C with 2-bromo-4-fluorobenzaldehyde.

Preparation 18: 4-Fluoro-2-[1-(methoxycarbonyl)-5,6,7,8-tetrahydro-3-indolizinyl]-benzoic acid

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

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

Step A: {(3S)-2-[(4-Methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}methyl 4-methylbenzenesulphonate

To a solution of 30.2 g of [(3*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (185 mmol) in 750 mL of dichloromethane there are successively added 91.71 g of tosyl chloride (481 mmol) and then, dropwise, 122.3 mL of *N,N,N*-triethylamine (740 mmol). The reaction mixture is then stirred at ambient temperature for 20 hours. It is then diluted with dichloromethane, washed successively with 1M HCl solution, saturated $NaHCO_3$ solution and then saturated NaCl solution until neutral. The organic phase is then dried over $MgSO_4$, filtered and concentrated to dryness. The solid obtained is then dissolved in a minimum volume of dichloromethane and then cyclohexane is added until a precipitate is formed. This precipitate is then filtered off and washed with cyclohexane. After drying, the title product is obtained in the form of crystals.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.75 (d, 2H, aromatic Hs, *ortho* O-tosyl); 7.6 (d, 2H, aromatic Hs, *ortho* *N*-tosyl); 7.5 (d, 2H, aromatic Hs, *meta* O-tosyl); 7.3 (d, 2H, aromatic Hs, *meta* *N*-tosyl); 7.15-6.9 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.4-4.15 (dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 4.25 (m, 1H, aliphatic H, tetrahydroisoquinoline); 4.0-3.8 (2dd, 2H, aliphatic Hs, **CH_2**-O-tosyl); 2.7 (2dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 2.45 (s, 3H, O-SO_2-Ph- **CH_3**); 2.35 (s, 3H, *N*-SO_2-Ph- **CH_3**)

IR: ν: -SO_2: 1339-1165 cm^{-1}

***Step B*: (3R)-3-Methyl-2-[(4-methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinoline**

To a suspension of 8.15 g (214.8 mmol) of $LiAlH_4$ in 800 mL of methyl *tert*-butyl ether (MTBE) there are added 101.2 g of the ditosyl compound obtained in Step A (214.8 mmol) dissolved in 200 mL of MTBE. The batch is then heated at 50°C for 2 hours. It is allowed to cool and placed at 0°C, and there are then added, dropwise, 12 mL of 5N NaOH solution. The batch is stirred at ambient temperature for 45 minutes. The solid thereby obtained is then filtered off and washed with MTBE and then with dichloromethane. The filtrate is then concentrated to dryness. The title product is then obtained in the form of a solid.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.70 (d, 2H, aromatic Hs, *ortho* *N*-tosyl); 7.38 (d, 2H, aromatic Hs, *meta* *N*-tosyl); 7.2-7.0 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.4 (m, 2H, aliphatic Hs, tetrahydroisoquinoline); 4.3 (m, 1H, aliphatic H, tetrahydroisoquinoline); 2.85-2.51 (2dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 2.35 (s, 3H, *N*-SO_2-Ph- **CH_3**); 0.90 (d, 3H, tetrahydroisoquinoline-**CH_3**)

IR : ν: -SO_2: 1332-1154 cm^{-1}

***Step C:* (3R)-3-Methyl-1,2,3,4-tetrahydroisoquinoline**

To a solution of 31.15 g (103.15 mmol) of the monotosyl compound obtained in Step B in 500 mL of anhydrous methanol there are added, in portions, 3.92 g (161 mmol) of magnesium turnings. The batch is stirred in the presence of ultrasound for 96 hours. The reaction mixture is then filtered and the solid is washed several times with methanol. The filtrate is then concentrated to dryness. After purification by column chromatography over silica gel (dichloromethane /EtOH /NH_4OH), the title product is obtained in the form of an oil.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.05 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 3.90 (m, 2H, aliphatic Hs, tetrahydroisoquinoline); 2.85 (m, 1H, aliphatic H, tetrahydroisoquinoline); 2.68-2.4 (2dd, 2H, aliphatic Hs, tetrahydro-isoquinoline); 1.12 (d, 3H, tetrahydroisoquinoline-**CH_3**); 2.9-2.3 (m, broad, 1H, **HN** (tetrahydroisoquinoline))

IR: ν: -NH: 3248 cm^{-1}

<u>Step D</u>: (3R)-3-Methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

To a solution of 14.3 g (97.20 mmol) of the compound obtained in Step C in 20 mL of anhydrous ethanol there are added, dropwise, 100 mL of a 1M solution of HCl in ether. The batch is stirred at ambient temperature for 1 hour and then filtered. The crystals thereby obtained are washed with ethyl ether. After drying, the title product is obtained in the form of crystals.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 9.57 (m, broad, 2H, **NH_2^+** (tetrahydro-isoquinoline); 7.22 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.27 (s, 2H, aliphatic Hs, tetrahydroisoquinoline); 3.52 (m, 1H, aliphatic H, tetrahydroisoquinoline); 3.03--2.85 (2dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 1.39 (d, 3H, tetrahydroisoquinoline-**CH_3**)

IR: ν: -NH_2^+: 3000-2300 cm^{-1} ; ν: aromatic -CH: 766 cm^{-1}

<u>Preparation 2':</u> (3*S*)-3-[2-(Morpholin-4-yl)ethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride

<u>Step A:</u> tert-Butyl (3S)-3-(2-morpholino-2-oxo-ethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate

To a solution of 3 g (10.30 mmol) of [(3*S*)-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-3-yl]acetic acid in 100 mL of dichloromethane there are added, dropwise, 1.10 mL (11.32 mmol) of morpholine and, still dropwise, 4.3 mL (30.9 mmol) of triethylamine, 2.20 g (12.40 mmol) of 1,2-dichloromethane and 1.70 g (1.68 mmol) of hydroxybenzotriazole. The batch is stirred at ambient temperature for 15 hours. The reaction mixture is then diluted with dichloromethane and washed successively with 1M HCl solution, saturated $NaHCO_3$ solution and then saturated NaCl solution until neutral. The organic phase is then dried over $MgSO_4$, filtered and concentrated to dryness. After purification by column chromatography over silica gel (dichloromethane/MeOH), the title product is obtained in the form of an oil.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.20-7.10 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.70 (m, 1H, aliphatic Hs, CH tetrahydroisoquinoline); 4.75-4.20 (2m, 2H, aliphatic Hs, CH_2 alpha to N tetrahydroisoquinoline); 3.60 (m, 8H, aliphatic Hs, morpholine); 3.00 and 2.70 (2dd, 2H, aliphatic H, tetrahydroisoquinoline); 2.50-2.20 (2d, 2H, aliphatic Hs, CH_2CO); 1.40 (s, 9H, ^{t}Bu)

IR: ν: C=O: 1687 ;1625 cm^{-1}

<u>Step B:</u> 1-(Morpholin-4-yl)-2-[(3S)-1,2,3,4-tetrahydroisoquinolin-3-yl]ethanone hydrochloride

To a solution of 2.88 g (7.18 mmol) of the compound obtained in Step A in 16 mL of dichloromethane there are added, dropwise, 80 mL (80 mmol) of a 1M solution of HCl in ether. The batch is stirred at ambient temperature for 15 hours and then the suspension is filtered and the precipitate is washed with ether. After drying, the title product is obtained in the form of a solid.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 9.80-9.50 (m, 2H, NH_2^+); 7.30-7.10 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.30 (m, 2H, aliphatic Hs, CH_2 alpha to N tetrahydroisoquinoline); 3.80 (m, 1H, aliphatic Hs, CH tetrahydroisoquinoline); 3.70-3.40 (2m, 8H, aliphatic Hs, morpholine); 3.15 and 2.8 (m, 4H, aliphatic H, CH_2 tetrahydroisoquinoline and CH_2CO)

IR: ν: -NH_2^+: 2800-1900 cm^{-1}; ν: C=O: 1620 cm^{-1}

***Step C**: (3S)-3-[2-(Morpholin-4-yl)ethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride*

A solution of 2.2 g (7.44 mmol) of the compound obtained in Step B in 22 mL of MTBE and 5 mL of dichloromethane is prepared. After cooling in an ice bath at 0°C, there are added thereto, dropwise, 15 mL (15 mmol) of 1M $LiAlH_4$ solution in tetrahydrofuran. The batch is then stirred at ambient temperature for 6 hours. It is placed at 0°C, and there is then added, dropwise, 1 mL of 5N NaOH solution. The batch is stirred at ambient temperature for 45 minutes. The solid is then filtered off and washed with MTBE and then with dichloromethane and the filtrate is concentrated to dryness. The oil thereby obtained is diluted with dichloromethane and there are added, dropwise, 6.3 mL of a 1M solution of HCl in ether. The batch is stirred at ambient temperature for 1 hour and then filtered. The crystals thereby obtained are washed with ethyl ether. After drying, the title product is obtained in the form of a solid.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 11.35 + 9.80 (2m, 2H, NH_2^+); 10.00 (m, H, NH^+); 7.20 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.30 (s, 2H, aliphatic Hs, CH_2 alpha to N tetrahydroisoquinoline); 4.00 + 3.85 (2m, 4H, aliphatic Hs, CH_2 alpha to N morpholine); 3.70 (m, 1H, aliphatic Hs, CH tetrahydroisoquinoline); 3.55-3.30 (m, 4H, aliphatic Hs, CH alpha to O morpholine and CH_2-morpholine); 3.15 (dd, 1H, aliphatic H, CH_2 tetrahydroisoquinoline); 3.10 (m, 2H, aliphatic H, CH alpha to O morpholine); 2.90 (dd, 1H, aliphatic H, CH_2 tetrahydroisoquinoline); 2.30 + 2.15 (2m, 2H, aliphatic H, CH_2-tetrahydroisoquinoline)

IR: ν: NH^+ / -NH_2^+: between 3500 and 2250 cm^{-1} ; ν: C=C: weak 1593 cm^{-1} ; ν: aromatic C-H: 765 cm^{-1}

<u>Preparation 3':</u> tert-Butyl {2-[(3*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl]ethyl}-carbamate

<u>Step A:</u> Benzyl (3S)-3-(2-hydroxyethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

The title compound is obtained starting from (3*S*)-2-[(benzyloxy)carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid based on a protocol from the literature (Jinlong Jiang *et al. Bioorganic & Medicinal Chemistry Letters*, 14, 1795, **2004**).

<u>Step B:</u> Benzyl (3S)-3-{2-[(methylsulphonyl)oxy]ethyl}-3,4-dihydroisoquinoline-2(1H)-carboxylate

To a solution of 10.6 g of the compound of Step A (35.6 mmol) in 350 mL of anhydrous CH_2Cl_2 placed at 0°C there are successively added 10.1 mL of triethylamine (71.2 mmol) and then, dropwise, 3.1 mL of methanesulphonyl chloride (39 mmol). The reaction mixture is then stirred at ambient temperature for 2 hours. Hydrolysis is then carried out by slowly adding water. The product is extracted several times with CH_2Cl_2. The organic phases are then combined and successively washed with 1N HCl solution, saturated NaCl solution, saturated $NaHCO_3$ solution and saturated NaCl solution until neutral. They are then dried over $MgSO_4$ and concentrated to dryness. After purification by chromatography over silica gel (petroleum ether/AcOEt gradient), the expected product is obtained in the form of a foam.

LC/MS: m/z = $(M + H)^+$ = 375

<u>Step C:</u> Benzyl (3S)-3-(cyanomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

To a solution of 15.4 g of the compound obtained in Step B (41.02 mmol) in 250 mL of anhydrous DMSO there are added 22 g (449 mmol) of sodium cyanide. The batch is then heated at 60°C for 12 hours. It is allowed to cool and then the reaction mixture is diluted by adding ethyl acetate. Hydrolysis is then carried out with saturated $NaHCO_3$ solution. After extracting two more times with ethyl acetate, the organic phases are combined, washed with H_2O, dried over $MgSO_4$ and concentrated to dryness. After purification by chromatography over silica gel (hexane/AcOEt 7/3), the expected product is obtained in the form of an oil.

LC/MS: m/z = $[M+H]^+$ = 307.1

***Step D:* Benzyl (3S)-3-(2-aminoethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate**

To a solution of 15.4 g of the compound obtained in Step C (50.3 mmol) in 300 mL of anhydrous THF placed at 0°C there are added, dropwise, a 1N solution of BH_3-THF. The reaction mixture is allowed to come back to ambient temperature gradually and then the batch is stirred for 14 hours. The reaction mixture is then hydrolysed by slowly adding saturated NH_4Cl solution. After extracting twice with ethyl acetate, the organic phases are combined and dried over $MgSO_4$. After concentrating to dryness, the expected product is obtained in the form of a foam which is used directly without purification in the next protection step.

***Step E:* Benzyl (3S)-3-{2-[(tert-butoxycarbonyl)amino]ethyl}-3,4-dihydroisoquinoline-2(1H)-carboxylate**

To a solution of 15.6 g of the compound obtained in Step D (50.3 mmol) in 670 mL of CH_2Cl_2 there are successively added 13.2 g (60.36 mmol) of Boc_2O in portions, 14 mL of triethylamine (100.6 mmol) and DMAP in a catalytic amount. The batch is stirred at ambient temperature for 5 hours. The reaction mixture is then hydrolysed with water and extracted twice with CH_2Cl_2. The organic phases are combined, washed with water and dried over $MgSO_4$. After concentration to dryness and purification by chromatography over silica gel (heptane/AcOEt gradient), the expected product is obtained in the form of an oil.

LC/MS: m/z = $(M + H)^+$ = 411

***Step F:* tert-Butyl {2-[(3S)-1,2,3,4-tetrahydroisoquinolin-3-yl]ethyl}carbamate**

To a solution of 10.4 g of the compound obtained in Step E (25.5 mmol) in 210 mL of anhydrous MeOH there are added 2.71 g (2.55 mmol) of Pd/C 10%. The batch is degassed for 30 minutes and is then stirred under a hydrogen atmosphere for 16 hours. The reaction mixture is then filtered and concentrated to dryness. The expected product is obtained in the form of a solid which is taken up in a mixture of pentane/Et_2O (90/10), triturated and filtered. After drying, the product is obtained in the form of a solid.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.1-6.98 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 6.83 (m, 1H, CH_2**NH**Boc); 3.85 (s, 2H, aliphatic Hs, tetrahydroisoquinoline); 3.09 (q, 2H, **CH_2**NHBoc); 2.73 (m, 1H, aliphatic Hs, tetrahydroisoquinoline); 2.70 and 2.39 (2m, 2H, aliphatic Hs, tetrahydroisoquinoline); 1.63 (m, 2H, aliphatic Hs); 1.38 (s, 9H, NHCOO**tBu**)

IR: ν: >NH: 3378, -3201 cm^{-1} (amine, amide); ν: >C=O: 1683 cm^{-1} (amide); ν: >NH: 1524 cm^{-1} (amide); ν: >C=O: 1168 cm^{-1}

LC/MS: m/z = $[M+H]^+$ = 277

<u>Preparation 4':</u> (3*R*)-3-[3-(Morpholin-4-yl)propyl]-1,2,3,4-tetrahydroisoquinoline

<u>Step A:</u> {(3S)-2-[(4-Methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}methyl 4-methylbenzenesulphonate

The procedure is the same as that of Step A of Preparation 1'.

<u>Step B:</u> tert-Butyl 2-({(3R)-2-[(4-methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}methyl)-3-(morpholin-4-yl)-3-oxopropanoate

To a suspension of 1 g of NaH (60 %) (25.08 mmol) in 30 mL of MTBE there are added, dropwise, a solution of 5 g of *tert*-butyl 3-morpholino-3-oxopropanoate (21.81 mmol) in 20 mL of anhydrous MTBE. This suspension stirred at ambient temperature for 1 hour and then the compound obtained in Step A is added in the form of a powder. The batch is stirred at 60°C for 30 hours. 100 mL of saturated ammonium chloride solution are added. The resulting solution is extracted with dichloromethane. The organic phase is then dried over $MgSO_4$, filtered and concentrated to dryness. After purification by column chromatography over silica gel (dichloromethane/MeOH), the expected product is obtained in the form of an oil.

^{1}H NMR (500 MHz, dmso-d6) δ ppm: 7.63/7.59 (2d, 2 H), 7.3/7.26 (2d, 2 H), 7.13 (m, 2 H), 7.09/6.97 (2t, 2 H), 4.64/4.55/4.36/4.28 (2AB, 2 H), 4.25/4.11 (2m, 1 H), 3.81 (m, 1 H), 3.73-3.48 (m, 4H), 3.57-3.32 (m, 4 H), 2.51 (m, 2 H), 2.32/2.31 (2s, 3 H), 1.88/1.79 (2m, 2 H), 1.39/1.38 (2s, 9 H)

IR (ATR) cm^{-1}: ν: >C=O: 1731 (ester); ν: >C=O: 1644 (amide); ν: -SO2: 1334-1156; ν: >C-O-C<: 1115; γ: >CH-Ar: 815-746-709

Step C: ***2-({(3R)-2-[(4-Methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}methyl)-3-(morpholin-4-yl)-3-oxopropanoic acid***

To a solution of 9.5 g (17.97 mmol) of the compound obtained in Step B in 40 mL of dioxane there are added, dropwise, 20 mL of a 4M solution of HCl in dioxane. The batch is stirred at ambient temperature for 48 hours and then the solution is concentrated to dryness. After drying, the expected product is obtained in the form of an oil.

^{1}H NMR (400 MHz, dmso-d6) δ ppm: 12.75 (m, 1 H), 7.6 (2*d, 2 H), 7.3 (2*d, 2 H), 7.1/6.95 (2*m, 4 H), 4.7-4.2 (d, 2 H), 4.25/4.12 (2*m, 1 H), 3.9-3.3 (m, 9 H), 2.55 (d, 2 H), 2.3 (2*s, 3 H), 1.8 (t, 2 H)

IR (ATR) cm^{-1}: ν: -OH: 3500 to 2000; ν: >C=O: 1727 (acid); ν: >C=O: 1634 (amide); ν: -SO2: 1330-1155

Step D: ***3-{(3R)-2-[(4-Methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}-1-(morpholin-4-yl)propan-1-one***

To a solution of 7.80 g (16.51 mmol) of the compound obtained in Step C in 100 mL of DMSO there are added 1.16 g (19.83 mmol) of solid sodium chloride and then, dropwise, 5 mL of water. The batch is stirred at 130°C for 1 hour and then the solution is concentrated to ¾. The reaction mixture is then diluted with dichloromethane and washed successively with saturated lithium chloride solution and then with saturated NaCl solution. Thghe organic phase is then dried over $MgSO_4$, filtered and concentrated to dryness. After purification by column chromatography over silica gel (cyclohexane/ethyl acetate), the expected product is obtained in the form of an oil.

^{1}H NMR (400 MHz, dmso-d6) δ ppm: 7.65 (d, 2 H), 7.3 (d, 2 H), 7.15/7 (2 m, 4 H), 4.6 (d, 1 H), 4.25 (d, 1 H), 4.2 (m, 1 H), 3.5 (m, 4 H), 3.4 (2 m, 4 H), 2.6 (2 dd, 2 H), 2.35 (s, 3 H), 2.3 (m, 2 H), 1.5 (quad., 2 H)
IR (ATR) cm^{-1}: ν: >C=O: 1639; ν: -SO2: 1331-1156; γ: >CH-Ar: 815-675

Step E: ***(3R)-2-[(4-Methylphenyl)sulphonyl]-3-[3-(morpholin-4-yl)propyl]-1,2,3,4-tetrahydroisoquinoline***

To a solution of 6.0 g (14.0 mmol) of the compound obtained in Step D in 60 mL of MTBE and 14 mL of dichloromethane there are added 1.06 g (28 mmol) of LAH in portions over 5 minutes. The batch is stirred at ambient temperature for 15 hours. There are added, dropwise, 1.5 mL of water and stirring is carried out for 15 minutes. There are then added, dropwise, 1.5 mL of 5M sodium hydroxide solution and stirring is carried out for 15 minutes. The reaction mixture is then diluted with MTBE and dichloromethane. The suspension is then filtered and the precipitate is washed with MTBE and dichloromethane. The organic phase is then dried over $MgSO_4$, filtered and concentrated to dryness. After purification by column chromatography over silica gel (dichloromethane/EtOH/NH_4OH), the expected product is obtained in the form of an oil.

^{1}H NMR (400 MHz, dmso-d6) δ ppm: 7.68 (d, 2 H), 7.32 (d, 2 H), 7.1 (unresolved peak, 4 H), 4.65/4.23 (AB, 2 H), 4.2 (m, 1 H), 3.55 (t, 4 H), 2.7/2.6 (ABx, 2 H), 2.35 (s, 3 H), 2.25 (t, 4 H), 2.2 (t, 2 H), 1.4/1.3 (2m, 4 H)
IR (ATR) cm^{-1}: ν: -SO2: 1333-1158

Step F: ***(3R)-3-[3-(Morpholin-4-yl)propyl]-1,2,3,4-tetrahydroisoquinoline***

To a solution of 1.50 g (3.62 mmol) of the compound obtained in Step E in 20 mL of anhydrous methanol there are added 2.0 g (82.3 mmol), in portions, of magnesium turnings. The batch is stirred in the presence of ultrasound for 96 hours. The reaction mixture is then filtered, the solid is washed several times with methanol, and the filtrate is concentrated to dryness. After purification by column chromatography over silica gel (dichloromethane/EtOH/NH_4OH), the expected product is obtained in the form of an oil.

^{1}H NMR (400 MHz, dmso-d6) δ ppm: 7.3 (d, 2 H), 7.1 (t, 2 H), 7.1 (d+t, 3 H), 7 (d, 2 H), 3.9 (s, 2 H), 3.55 (t, 4 H), 2.75 (m, 1 H), 2.72/2.45 (dd, 2 H), 2.35 (t, 4 H), 2.25 (t, 2 H), 1.6 (m, 2 H), 1.45 (m, 2 H)

IR (ATR) cm^{-1}: ν: >NH2+/NH+: 3500-2300; ν: >C-O-C<: 1115

High-resolution mass spectroscopy (*ESI*+-/FIA/HR*):*

Empirical formula: $C_{16}H_{24}N_2O$

$[M+H]^+$, calculated: 261.1961

$[M+H]^+$, measured: 261.1959

<u>Preparation 5'</u>: (3*S*)-3-[2-(3,3-Difluoropiperidin-1-yl)ethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride

The procedure is in accordance with the process of Preparation 2', replacing the morpholine used in Step A with 3,3-difluoro-1-piperidine.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 11.3 (m, 1H, **NH^+**); 10.2-9.8 (m, 2H, **NH_2^+**); 7.25 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.3 (broad s, 2H, aliphatic Hs, CH tetrahydroisoquinoline); 4.0-3.3 (m, 7H, aliphatic Hs); 3.15-2.95 (dd, 2H, aliphatic Hs, CH tetrahydroisoquinoline); 2.4-1.9 (m, 6H, aliphatic Hs, H 3,3-difluoro-1-piperidine)

IR: ν: NH^+ /NH_2^+: between 300 and 2500 cm^{-1} ; ν: C-F: 1204 cm^{-1}

<u>Preparation 6'</u>: (3*S*)-3-[2-(3-Methoxyazetidin-1-yl)ethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride

The procedure is in accordance with the process of Preparation 2', replacing the morpholine used in Step A with 3-methoxyazetidine.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 11.3 (m, 1H, NH^+); 10.00 (m, 2H, NH_2^+); 7.20 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.4 (m, 1H, aliphatic H, 3-methoxy azetidine); 4.30 (s, 2H, aliphatic Hs, tetrahydroisoquinoline); 4.2-3.45 (m, 4H , 3-methoxyazetidine); 4.2-3.6 (m, 3H, aliphatic Hs); 3.1 and 2.95 (dd, 2H, aliphatic Hs); 3.25 (s, 3H, **OCH_3**)

Preparation 7': **(3*S*)-3-Methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride**

The procedure is in accordance with the process of Preparation 1', replacing the [(3*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol used in Step A with [(3*R*)-1,2,3,4-tetrahydro-isoquinolin-3-yl]methanol.

Preparation 1'': **N-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-pyrazol-4-amine**

Step A: ***4-{[tert-Butyl(dimethyl)silyl]oxy}aniline***

The title compound is obtained starting from 4-aminophenol in THF in the presence of imidazole and *tert*-butyl(dimethyl)silyl chloride in accordance with the protocol described in the literature (S. Knaggs *et al.*, *Organic & Biomolecular Chemistry*, 3(21), 4002-4010; **2005).**

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 6.45-6.55 (dd, 4H, aromatic Hs); 4.60 (m, 2H, $\mathbf{NH_2}$-Ph); 0.90 (s, 9H, Si $(CH_2)_2CH(\mathbf{CH_3})_2$); 0.10 (s, 6H, Si $(\mathbf{CH_2})_2CH(CH_3)_2$)

IR: ν: $-NH_2^+$: 3300-3400 cm^{-1}

Step B: ***N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-1-methyl-pyrazol-4-amine***

To a solution of 30.8 g (0.137 mol) of the compound of Step A in 525 mL of anhydrous toluene there are successively added 29.8 g of sodium *tert*-butylate (0.310 mol), 4.55 g of $Pd_2(dba)_3$ (also referred to as tris(dibenzylideneacetone)dipalladium(0)) (4.96 mmol), 4.81 g of 2-di-*tert*-butylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl (9.91 mmol) and 12.8 mL of 4-bromo-1-methyl-1*H*-pyrazole (0.124 mol). The batch is degassed under argon for 30 minutes and then refluxed for 3 hours. It is allowed to cool. The reaction mixture is concentrated to dryness and then taken up in dichloromethane, filtered over Celite and then concentrated to dryness again. The residue is then purified by chromatography over silica gel (CH_2Cl_2/AcOEt gradient) to provide the expected product in the form of a solid.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.55 (s, 1H, pyrazole); 7.23 (s, 1H, pyrazole); 7.18 (broad s, 1H, **NH_2**-Ph); 6.64 (m, 4H, aromatic Hs); 3.77 (s, 3H, **CH_3**-pyrazole); 0.90 (s, 9H, Si $(CH_2)_2CH(\mathbf{CH_3})_2$); 0.12 (s, 6H, Si $(\mathbf{CH_2})_2CH(CH_3)_2$)

IR: ν -NH^+: 3275 cm^{-1}; ν Ar and C=N: 1577 and 1502 cm^{-1}; ν -Si-C-: 1236 cm^{-1}; ν -Si-O-: 898 cm^{-1}; ν -Si-C-: 828, 774 cm^{-1}

<u>Preparation 2":</u> *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indol-5-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 5-bromo-1-methyl-1*H*-indole.

<u>Preparation 3":</u> *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-indol-5-amine

<u>Step A:</u> 5-Bromo-1-[2-(morpholin-4-yl)ethyl]-1H-indole

To a suspension of NaH (4.5 g; 112 mmol) in anhydrous THF (300 mL) placed at 0°C there are added, in portions, 5-bromo-1*H*-indole (10.4 g; 51 mmol). After stirring for 20 minutes at 0°C, 4-(2-chloroethyl)morpholine hydrochloride (10.4 g; 56 mmol) is added in portions over 1 hour. After stirring overnight at ambient temperature, the reaction mixture is placed at 80°C for 5 hours. It is then poured over a mixture of aqueous sodium bicarbonate and dichloromethane. The aqueous phase is extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and concentrated to dryness, and the residue is purified by chromatography over silica gel (CH_2Cl_2/MeOH gradient) to provide the expected product in the form of an oil.

^{1}H NMR: δ (400 MHz; CDCl3; 300K): 7.75 (d, 1H); 7.30 (dd, 1H); 7.20 (d, 1H); 7.15 (d, 1H); 6.40 (d, 1H); 4.20 (t, 2H); 3.70 (m, 4H); 2.75 (t, 2H); 2.45 (m, 4H)

<u>Step B:</u> 5-Bromo-1-[2-(morpholin-4-yl)ethyl]-1H-indole

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with the compound obtained in Step A.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.35 (d, 1H); 7.15 (s, 1H); 6.85 (d, 3H); 6.70 (d, 2H); 7.30 (d, 1H); 6.25 (d, 1H), 4.20 (t, 2H); 3.55 (m, 4H); 2.65 (t, 2H); 2.45 (m, 4H); 1.45 (s, 9H), 0.15 (s, 6H)

<u>Preparation 4''</u>: *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-1-[2-(morpholin-4-yl)ethyl]-2,3-dihydro-1*H*-indol-5-amine

The procedure is in accordance with the process of Preparation 2'', replacing the 5-bromoindole used in Step A with 5-bromo-2,3-dihydro-1*H*-indole.

<u>Preparation 5''</u>: *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-4-fluoroaniline

The procedure is in accordance with the process of Preparation 1'', replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 1-bromo-4-fluorobenzene.

<u>Preparation 6''</u>: *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-3-fluoro-4-methylaniline

The procedure is in accordance with the process of Preparation 1'', replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 4-bromo-2-fluoro-1-methylbenzene.

<u>Preparation 7''</u>: *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indazol-5-amine

The procedure is in accordance with the process of Preparation 1'', replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 5-bromo-1-methyl-1*H*-indazole.

<u>Preparation 8''</u>: 4-{[*tert*-Butyl(dimethyl)silyl]oxy}-*N*-phenylaniline

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 batch is stirred at 70°C for 4 hours. The reaction mixture is then poured into water and extracted with ether. The organic phase is then dried over magnesium sulphate, then filtered and evaporated to dryness. The crude product thereby obtained is then purified by chromatography over silica gel (petroleum ether/dichloromethane gradient). The title product is obtained in the form of a powder.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 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: ν: >NH: 3403 cm^{-1}; >Ar: 1597 cm^{-1}

Preparation 9'': 4-Benzyloxy-*N*-phenyl-aniline

To a solution of 4-hydroxy-*N*-phenyl-aniline (30 g; 162 mmol) in acetonitrile (400 mL) there are added 58 g of Cs_2CO_3 (178 mmol) and stirring is carried out for 15 minutes at ambient temperature. Benzyl bromide (22.5 mL; 178 mmol) is then added dropwise and then the reaction mixture is refluxed for 4 hours. After filtering and rinsing with acetonitrile, the filtrate is concentrated and chromatographed over silica gel (petroleum ether/AcOEt gradient). The title product is then obtained in the form of a colourless solid.

Preparation 10'': *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-3-fluoro-4-[2-(morpholin-4-yl)ethoxy]aniline

The procedure is in accordance with the process of Preparation 3'', replacing the 5-bromo-1*H*-indole used in Step A by 4-bromo-2-fluorophenol.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.75 (d, 1H); 7 (dd, 1H); 6.9 (d, 2H); 6.75 (m, 3H); 6.7 (ddd, 1H); 4.05 (t, 2H); 3.6 (t, 4H); 2.65 (t, 2H); 2.45 (t, 4H); 0.95 (s, 9H); 0.2 (s, 6H)

Preparation 11'': *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)pyridin-4-amine

The procedure is in accordance with the process of Preparation 1'', replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 4-bromopyridine.

IR: ν -NH-: 3200 and 2500 cm^{-1}; ν -Si-O-: 902 cm^{-1}; ν -Si-C-: 820 cm^{-1}

Preparation 12'': 3-[(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)amino]benzonitrile

The procedure is in accordance with the process of Preparation 1'', replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 3-bromobenzonitrile.

Preparation 13'': *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-3-fluoroaniline

The procedure is in accordance with the process of Preparation 1'', replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 1-bromo-3-fluorobenzene.

Preparation 14'': *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-3,4-difluoroaniline

The procedure is in accordance with the process of Preparation 1'', replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 4-bromo-1,2-difluorobenzene.

Preparation 15'': 4-{[*tert*-Butyl(dimethyl)silyl]oxy}-*N*-{4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl}aniline

Step A:* *1-(4-Bromobenzyl)-3,3-difluoropiperidine

To a solution of 4-bromobenzaldehyde (500 mg; 2.7 mmol) in 12 mL of dichloromethane there are added, in the order stated, 3,3-difluoropiperidine hydrochloride (470 mg; 3 mmol), sodium triacetoxyborohydride (860 mg; 4 mmol) and acetic acid (0.17 mL; 3 mmol). After stirring for 1 hour at ambient temperature, the reaction mixture is poured over a mixture of aqueous sodium bicarbonate and dichloromethane. The aqueous phase is extracted with dichloromethane. The organic phase is dried over $MgSO_4$, concentrated to dryness and the residue is purified by chromatography over silica gel (CH_2Cl_2/MeOH gradient) to provide the expected product in the form of an oil.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K):7.55 (dd, 2H); 7.25 (dd, 2H); 3.55 (s, 2H); 2.7 (t, 2H); 2.35 (t, 2H); 1.85 (m, 2H); 1.65 (m, 2H)

Step B:* *4-{[tert-Butyl(dimethyl)silyl]oxy}-N-{4-[(3,3-difluoropiperidin-1-yl)methyl]-phenyl}aniline

The procedure is in accordance with the process of Preparation 1'', replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 1-[(4-bromophenyl)methyl]-3,3-difluoro-piperidine.

<u>Preparation 16"</u>: *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)quinolin-6-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 6-bromo-quinoline.

IR: ν -NH-: 3300 cm^{-1}

<u>Preparation 17"</u>: *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-2-methylpyridin-4-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 4-bromo-2-methyl-pyridine.

IR: ν -NH-: 3200 and 3100 cm^{-1}

<u>Preparation 18"</u>: *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 5-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (obtained in accordance with a protocol from the literature: *Heterocycles*, 60(4), 865, **2003**).

IR: ν:-NH-: 3278 cm^{-1}; ν: aromatic -C=C- moieties: 1605 cm^{-1}

<u>Preparation 19"</u>: *N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)pyridin-3-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 3-bromo-pyridine.

<u>Preparation 20"</u>: 4-{[*tert*-Butyl(dimethyl)silyl]oxy}-*N*-{4-[(3,3-difluoropiperidin-1-yl)-ethyl]phenyl}aniline

<u>Step A:</u> 2-(4-Bromophenyl)-1-(3,3-difluoropiperidin-1-yl)ethanone

To a solution of 4-bromophenylacetic acid (4 g; 18.6 mmol) and 3,3-difluoropiperidine hydrochloride (2.5 g; 20.4 mmol) in dichloromethane (190 mL) there are added EDC

(3.8 g; 22.3 mmol), HOBt (3 g; 22.3 mmol) and triethylamine (1.3 mL; 593 mmol). The reaction mixture is stirred for 17 hours at ambient temperature and is then poured over a mixture of aqueous sodium bicarbonate and ethyl acetate. The aqueous phase is extracted with ethyl acetate. The organic phase is washed with 0.1N hydrochloric acid, with water and with brine before being dried over $MgSO_4$ and concentrated to dryness. The residue is purified by chromatography over silica gel (petroleum ether/ethyl acetate gradient) to provide the expected product in the form of a solid.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K):7.5 (d, 2H); 7.2 (d, 2H); 3.8 (t, 2H); 3.7 (s, 3H); 3.5 (t, 2H); 2 (m, 2H); 1.6 (m, 2H)

***Step B:** 1-[2-(4-Bromophenyl)ethyl]-3,3-difluoropiperidine*

To a solution of the compound of Step A (4.6 g; 14.5 mmol) in anhydrous THF (145 mL) there is added a 1M solution of borane dimethyl sulphide in THF (14.5 mL; 14.5 mmol). The reaction mixture is heated at 80°C for 3 hours and then the solvent is evaporated off under reduced pressure. The residue is treated with methanol (50 mL) and then with 5N HCl (5.8 mL). After stirring overnight at ambient temperature and refluxing for 3 hours, the pH of the reaction mixture is adjusted to 8 with saturated sodium bicarbonate solution; the aqueous phase is then extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and concentrated to dryness, and the residue is purified by chromatography over silica gel (CH_2Cl_2/MeOH gradient) to provide the expected product in the form of an oil.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K):7.45 (d, 2H); 7.20 (d, 2H); 2.71 (m, 2H); 2.69 (t, 2H); 2.58 (dd, 2H); 2.45 (dd, 2H); 1.86 (m, 2H); 1.63 (m, 2H)

***Step C:** 4-{[tert-Butyl(dimethyl)silyl]oxy}-N-{4-[(3,3-difluoropiperidin-1-yl)ethyl]-phenyl}aniline*

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B by the compound of Step B.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.7 (s, 1H); 7.45 (d, 2H); 7.39 (t, 2H); 7.31 (t, 1H); 7.0 (m, 4H); 6.9 (d, 2H); 6.81 (d, 2H); 5.05 (s, 2H); 2.7 (t, 2H); 2.6 (t, 2H); 2.5 (t, 2H); 2.45 (t, 2H); 1.89 (m, 2H); 1.68 (m, 2H)

Preparation 21": **4-{[*tert*-Butyl(dimethyl)silyl]oxy}-*N*-{4-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]phenyl}aniline**

The procedure is in accordance with the process of Preparation 19", replacing the 3,3-difluoropiperidine hydrochloride in Step A with 3,3-difluoropyrrolidine hydrochloride.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.7 (s, 1H); 7.45 (d, 2H); 7.35 (t, 2H); 7.34 (t, 1H); 7.05-6.85 (m, 8H); 5.05 (s, 2H); 2.9 (t, 2H); 2.75-2.25 (m, 8H)

Preparation 22": ***N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-2,6-dimethylpyridin-4-amine**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 4-bromo-2,6-dimethylpyridine.

IR: ν: -NH-: 3300 and 2700 cm^{-1}; ν:-Si-O-: 900 cm^{-1}; ν: -Si-C-: 823 cm^{-1}

Preparation 23": ***N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-1-[2-(morpholin-4-yl)-ethyl]-1*H*-pyrazol-4-amine**

The procedure is in accordance with the process of Preparation 2", replacing the 5-bromoindole used in Step A with 4-bromo-1*H*-pyrazole.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.61 (s, 1H); 7.25 (s, 1H); 7.18 (s, 1H); 6.65 (m, 4H); 4.15 (t, 2H); 3.55 (t, 4H); 2.7 (t, 2H); 2.4 (t, 4H); 0.95 (s, 9H); 0.15 (s, 6h)

Preparation 24": ***N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-3-fluoropyridin-4-amine**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 4-bromo-3-fluoro-pyridine.

IR: ν -NH-: 3200 and 3000 cm^{-1}; ν -Si-O-: 900 cm^{-1}; ν -Si-C-: 820 cm^{-1}

Preparation 25'': ***N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)imidazo[1,2-*a*]-pyridin-7-amine**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 7-bromoimidazo[1,2-*a*]pyridine (prepared starting from 4-bromopyridin-2-amine in accordance with a protocol in the literature: WO 2008124323 A1).

IR: ν -NH-: 3300-3000 cm^{-1}; ν -C=N-: 1652 cm^{-1}; ν -C=C-: 1610 cm^{-1}; ν -Si-C-: 1236 cm^{-1}; ν -Si-O-: 898 cm^{-1}; ν -Si-C-: 828, 774 cm^{-1}

Preparation 26'': ***N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-2-methyl-imidazo[1,2-*a*]pyridin-7-amine**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 7-bromo-2-methyl-imidazo[1,2-*a*]pyridine (prepared starting from 4-bromopyridin-2-amine in accordance with a protocol in the literature: A. J. Helliot *et al. J. Heterocyclic Chemistry* 19, 1437, **1982**).

IR: ν -NH-: 3300-3000 cm^{-1}; ν -C=N-: 1652 cm^{-1}; ν -C=C-: 1610 cm^{-1}; ν -Si-C-: 1236 cm^{-1}; ν -Si-O-: 898 cm^{-1}; ν -Si-C-: 828, 774 cm^{-1}

Preparation 27'': ***N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-6-methylpyridin-3-amine**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 3-bromo-6-methyl-pyridine.

IR: ν -NH-: 3251 cm^{-1}; ν aromatic -C=C- moieties: 1605 cm^{-1}

Preparation 28": ***N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-5-fluoropyridin-3-amine**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 3-bromo-5-fluoro-pyridine.

IR: ν -NH-: 3400-3000 cm^{-1}; ν -C-F-: 1245 cm^{-1}

Preparation 29": ***N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-2-methoxypyridin-4-amine**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 4-bromo-2-methoxy-pyridine.

IR: ν -NH-: 3200 and 3000 cm^{-1}; ν aromatic -C=C- moieties: 1618, 1601 cm^{-1}

Preparation 30": ***N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-2-(propan-2-yl)pyridin-4-amine**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 4-bromo-2-(propan-2-yl)pyridine.

IR: ν -NH-: 3300 and 3100 cm^{-1}

Preparation 31": ***N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)pyrazolo[1,5-*a*]-pyrimidin-6-amine**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 6-bromopyrazolo[1,5-*a*]pyrimidine.

IR: ν -NH-: 3272 cm^{-1}; ν -C=N-: 1634 cm^{-1}; ν -C=C-: 1616 cm^{-1}

Preparation 32": ***N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-3,3a-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidin-6-amine**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 6-bromo-3,3a-dihydro[1,2,4]triazolo[1,5-*a*]-

pyrimidine prepared in accordance with the literature (WO 2011015343) starting from 4*H*-1,2,4-triazol-3-amine and 2-bromopropanedial.

IR: ν -NH-: 3244 cm^{-1}

Preparation 33": ***N*-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)pyridin-4-amine 1-oxide**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 4-bromopyridine 1-oxide prepared in accordance with the literature (WO 2009117269) starting from 4-bromopyridine.

IR: ν -NH-: 3246 cm^{-1}; ν aromatic -C=C- moieties: 1618 cm^{-1}

Mass spectrum:

Empirical formula: $C_{17}H_{24}N_2O_2Si$

$[M]^{+}$. measured m/z: 316

$[M-O]^{+}$. measured m/z: 300

$[M-C_4H_9]^{+}$. measured m/z: 259

Preparation 34": ***N*-[4-[*tert*-Butyl(dimethyl)silyl]oxyphenyl]-1-methyl-pyridin-1-ium-4-amine chloride**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 4-bromo-1-methyl-pyridin-1-ium chloride prepared in accordance with the literature starting from 4-bromopyridine.

Preparation 35": ***N*-[4-[*tert*-Butyl(dimethyl)silyl]oxyphenyl]-1-methyl-pyrazolo[3,4-*b*]pyridin-5-amine**

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 5-bromo-1-methyl-pyrazolo[3,4-*b*]pyridine prepared in accordance with the literature (WO 2006052568).

^{1}H NMR (400 MHz, dmso-d6) δ ppm: 8.33 (d, 1 H), 7.94 (bs, 1 H), 7.92 (s, 1 H), 7.71 (d, 1 H), 6.95 (d, 2 H), 6.76 (d, 2 H), 4.01 (s, 3 H), 0.95 (s, 9 H), 0.17 (s, 6 H)

IR (ATR) cm^{-1}: 3290 ν >OH; 1503 ν Ar; 1249 γ -Si-CH_3

Preparation 36'': ***N*-[4-[*tert*-Butyl(dimethyl)silyl]oxyphenyl]-3-methyl-pyrazolo[1,5-*a*]pyrimidin-6-amine**

The procedure is in accordance with the process of Preparation 1'', replacing the 4-bromo-1-methyl-1*H*-pyrazole used in Step B with 6-bromo-3-methyl-pyrazolo[1,5-*a*]pyrimidine prepared in accordance with the literature (WO 2011015343 and WO2011049917).

^{1}H NMR (400 MHz, dmso-d6) δ ppm: 8.49 (d, 1 H), 8.4 (d, 1 H), 7.98 (m, 1 H), 7.87 (s, 1 H), 7 (d, 2 H), 6.81 (d, 2 H), 2.29 (s, 3 H), 0.98 (s, 9 H), 0.2 (s, 6 H)

IR (ATR) cm^{-1}: 3257 ν >NH

The amines NHR_3R_4 wherein R_3 and R_4, each independently of the other, represent an aryl or heteroaryl group are obtained in accordance with processes described in the literature (Surry D.S. *et al.*, *Chemical Science*, 2011, 2, 27-50, Charles M.D. *et al.*, *Organic Letters*, 2005, 7, 3965-3968). The reaction protecting the hydroxy function of the 4-anilinophenol described in Preparation 8'' can be applied to various secondary amines NHR_3R_4 (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*-butyl(dimethyl)silyloxy and benzyloxy are especially preferred.

Among the amines NHR_3R_4 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-(trifluoro-methyl)anilino]phenol, 4-[4-(methylsulphanyl)-3-(trifluoromethyl)anilino]phenol, 2-fluoro-4-[(1-methyl-1H-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-hydroxy-phenyl)amino]benzonitrile, 4-[(3-methoxyphenyl)amino]phenol, 4-[(3,5-difluorophenyl)-amino]phenol, 4-[(3-methylphenyl)amino]phenol, 4-[(4-hydroxyphenyl)amino]benzo-nitrile, 4-[(3-chlorophenyl)amino]phenol, 4-(pyrimidin-2-ylamino)phenol, 4-[(cyclobutyl-methyl)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-yl-amino)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, 4-(methylamino)phenol, 4-(ethylamino)phenol and 4-(propan-2-ylamino)phenol.

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

<u>Example 1.</u> **N-(4-Hydroxyphenyl)-3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-indol-5-yl)-5,6,7,8-tetrahydro-indolizine-1-carboxamide**

<u>Step A</u>: Methyl 3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxylate

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), 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 then stirred at ambient temperature overnight; it is then poured onto a solution of ammonium chloride and extracted with ethyl acetate. The organic phase is then dried over magnesium sulphate, and then filtered and evaporated to dryness. The crude product thereby obtained is then purified by chromatography over silica gel (heptane/AcOEt gradient) to yield the expected product.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.2-6.8 (m, 4H, aromatic Hs, H tetrahydroisoquinoline); 7.10 (s, 1H, aromatic H, benzodioxole); 6.92 (s, 1H, aromatic H, benzodioxole); 6.25 (m, 1H, H tetrahydroindolizine); 6.10 (s, 2H, aliphatic Hs, O**CH_2**O); 4.80 (m, 1H, aliphatic H, H tetrahydroisoquinoline); 4.20 (m, 1H, aliphatic H, H tetrahydroisoquinoline); 4.1-3.5 (m, 3H); 3.60 (s, 3H, COO**CH_3**); 2.90 (m, 2H, aliphatic Hs, H tetrahydroindolizine); 2.45 (m, 2H, aliphatic Hs, H tetrahydroisoquinoline); 1.70 (m, 4H, aliphatic Hs, H tetrahydroindolizine); 0.80 (m, 3H, aliphatic Hs, **CH_3**-THIQ).

IR: ν: >C=O 1694 cm^{-1} (conjugated ester); ν: >C=O 1624 cm^{-1} (amide);
ν: >C-Ar 772-742 cm^{-1}

<u>Step B</u>: Lithium 3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxylate

To a solution containing 8.26 mmol of the compound of Step A in 24 mL of dioxane there is added a solution of lithium hydroxide (675 mg, 16.1 mmol). The batch is placed in a microwave oven at 140 W, 100°C for a period of 2 hours 30 minutes. The reaction mixture is then filtered and evaporated. The solid thereby obtained is dried at 40°C in an oven in the presence of P_2O_5.

<u>Step C:</u> ***N-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)-3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-indol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide***

To a solution containing 4.73 mmol of the compound of Step B in 47 mL of 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 is then co-evaporated several times with dichloromethane. The product thereby obtained is suspended in 37 mL of dichloromethane and is then added to a solution containing 7.1 mmol of the compound obtained in Preparation 2" in 10 mL of dichloromethane in the presence of 0.6 mL of pyridine (7.1 mmol). The batch is stirred at ambient temperature overnight. The reaction mixture is concentrated, purified by chromatography over silica gel (dichloromethane/methanol gradient) to yield the expected product.

<u>Step D:</u> ***N-(4-Hydroxyphenyl)-3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-indol-5-yl)-5,6,7,8-tetrahydro-indolizine-1-carboxamide***

To a solution containing 2.3 mmol of the compound obtained in Step C in 4 mL of methanol there is added 0.646 g (11.5 mmol) of potassium hydroxide dissolved in 8 mL of methanol. The batch is stirred at ambient temperature for 30 minutes. The reaction mixture is then diluted with dichloromethane and washed successively with 1N HCl solution, saturated $NaHCO_3$ solution and then saturated NaCl solution until a neutral pH is obtained. The organic phase is then dried over magnesium sulphate, filtered and evaporated. The crude product thereby obtained is purified over silica gel (dichloromethane/methanol gradient) and then lyophilised to provide the expected product.

High-resolution mass spectroscopy (ESI+):

Empirical formula: $C_{42}H_{38}CN_4O_5$

$[M+H]^+$, calculated: 679.2920

$[M+H]^+$, measured: 679.2908

<u>Example 2.</u> *N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-{1-[2-(morpholin-4-yl)ethyl]-1*H*-indol-5-yl}-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

The procedure is in accordance with the processes described in Steps A-D of Example 1 using the appropriate reagents. After the step of purification over silica gel (*cf.* Step D), the solid is then dissolved in dichloromethane and 2 mL of 1N HCl in ether are added. The entire batch is stirred for 1 hour and then evaporated to dryness. The hydrochloride thereby obtained is dissolved in a mixture of water/acetonitrile until dissolution is complete and is then lyophilised.

Elemental microanalysis: (%, theoretical:measured)

%C=69.32:68.93; %H=5.94:5.74; %N=8.6:8.51; %Cl-=4.35:4.6

Unless otherwise mentioned, the compounds of the following Examples are synthesised in accordance with the process of Example 1 using, in Step A: (i) the appropriate acid obtained according to one of Preparations 1 to 18 and (ii) the appropriate tetrahydroisoquinoline compound obtained according to one of Preparations 1' to 7' and, in Step C: (iii) the suitable NHR_3R_4 amine (a non-exhaustive list is proposed in Preparations 1" to 36").

<u>Example 3.</u> 6-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide hydrochloride

The procedure is in accordance with the process of Example 1, replacing, on the one hand, the compound of Preparation 1 used in Step A with the compound of Preparation 2 and, on the other hand, the compound of Preparation 1" used in Step C with *N*-(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indol-5-amine, it being understood that the product thereby obtained is not subjected to a step of conversion into a salt in the presence of HCl in ether as is described in Step D of Example 1. The compound thereby obtained is deprotected in the presence of 10 equivalents of trifluoroacetic acid in dichloromethane (10 mL/mmol) at ambient temperature overnight. The product is then isolated by concentrating the reaction mixture to dryness. Finally, it is subjected to a step of conversion into a salt in the presence of HCl in ether.

Elemental microanalysis: (%, theoretical:measured)

%C=67.99:65.52; %H=5.28:4.49; %N=9.91:9.24; %Cl=10.03:9.95; %Cl-=5.02:5.45

High-resolution mass spectroscopy (ESI+):

Empirical formula: $C_{40}H_{36}ClN_5O_3$

$[M+H]^+$, calculated: 670.2585

$[M+H]^+$, measured: 670.2587

Example 4. 3-[5-Chloro-2-(3,4-dihydroisoquinolin-2(1*H*)-ylcarbonyl)phenyl]-*N*-(4-hydroxyphenyl)-*N*-{1-[2-(morpholin-4-yl)ethyl]-1*H*-indol-5-yl}-5,6,7,8-tetrahydro-indolizine-1-carboxamide

Elemental microanalysis: % measured (theoretical)

%C=70.85(71.65);%H=5.39(5.88);%N=9.11(9.28);%Cl=4.48(4.7)

Example 5. 3-[5-Chloro-2-(3,4-dihydroisoquinolin-2(1*H*)-ylcarbonyl)phenyl]-*N*-(4-hydroxyphenyl)-*N*-{1-[2-(morpholin-4-yl)ethyl]-2,3-dihydro-1*H*-indol-5-yl}-5,6,7,8-tetrahydroindolizine-1-carboxamide

Step A: N-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)-3-[5-chloro-2-(3,4-dihydro-isoquinolin-2(1H)-ylcarbonyl)phenyl]-N-{1-[2-(morpholin-4-yl)ethyl]-2,3-dihydro-1H-indol-5-yl}-5,6,7,8-tetrahydroindolizine-1-carboxamide

The procedure is in accordance with the protocols described in Steps A-C of Example 1 using the compound of Preparation 3 and 1,2,3,4-tetrahydroisoquinoline in Step A, and the compound of Preparation 4" in Step C.

<u>*Step B:*</u> ***3-[5-Chloro-2-(3,4-dihydroisoquinolin-2(1H)-ylcarbonyl)phenyl]-N-(4-hydroxy-phenyl)-N-{1-[2-(morpholin-4-yl)ethyl]-2,3-dihydro-1H-indol-5-yl}-5,6,7,8-tetrahydro-indolizine-1-carboxamide***

To a solution of 1.3 g (1.45 mmol) of the compound of Step A in 13 mL of acetic acid there is added, at ambient temperature, sodium cyanoborohydride (900 mg; 15 mmol). After stirring for 2 hours, the reaction mixture is concentrated to dryness, and then diluted with methanol (8 mL) and treated with a 1M solution of potassium hydroxide in methanol (6.3 mL; 6.3 mmol). After 1 hour at ambient temperature, the reaction mixture is concentrated to dryness, and then chromatographed over silica gel (dichloromethane/methanol gradient) and then lyophilised to provide the expected product in the form of a powder.

Elemental microanalysis: % measured (theoretical)

%C=70.74(71.46);%H=5.74(6.13);%N=9(9.26);%Cl=4.46(4.69)

<u>Example 6.</u> *N*-(4-Hydroxyphenyl)-2-methyl-6-(7-{[(3*R*)-3-methyl-3,4-dihydroiso-quinolin-2(1*H*)-yl]carbonyl}-2,3-dihydro-1,4-benzodioxin-6-yl)-*N*-(1-methyl-1*H*-indol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide hydrochloride

The procedure is analogous to that described for Example 7, in Step A substituting the compound of Preparation 2 with the compound of Preparation 4.

Elemental microanalysis: (%, theoretical:measured)

%C=69.39:69.13; %H=5.69:4.98; %N=9.41:9.37; %Cl-=4.76:4.65

Example 7. 6-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-indol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide

Step A:* *tert-Butyl 8-[(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)(1-methyl-1H-indol-5-yl)-carbamoyl]-6-(5-chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-phenyl)-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate

The procedure is in accordance with the protocols described in Steps A-C of Example 1 using the compounds of Preparations 2 and 1' in Step A, and the compound of Preparation 2" in Step C.

Step B:* *tert-Butyl 6-(5-chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl)-8-[(4-hydroxyphenyl)(1-methyl-1H-indol-5-yl)carbamoyl]-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate

To a solution of the compound of Step A (1.1 g; 1.25 mmol) in methanol (6 mL) there is added a 1M solution of potassium hydroxide in methanol (6.2 mL; 6.2 mmol). After 2 hours at ambient temperature, the methanol is evaporated off *in vacuo* and the residue is taken up in a mixture composed of dichloromethane and saturated sodium bicarbonate solution. The combined organic phases are dried over $MgSO_4$ and concentrated to dryness. The residue obtained is purified by chromatography over silica gel (CH_2Cl_2/MeOH gradient) to provide the expected product in the form of a solid.

IR : ν: NH: 3450 cm^{-1}; ν: CO: 1745-1620 cm^{-1}

Step C:* *tert-Butyl 6-(5-chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl)-8-[{4-[(2,2-dimethylpropanoyl)oxy]phenyl}(1-methyl-1H-indol-5-yl)carbamoyl]-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate

To a solution of the compound of Step B (0.7 g; 0.93 mmol) in dichloromethane (7 mL) there are added, at ambient temperature, triethylamine (0.2 mL; 1.39 mmol) and then pivaloyl chloride (0.11 mL; 0.93 mmol). After stirring for 2 hours at ambient temperature, the reaction mixture is washed with water and with brine, dried over $MgSO_4$ and concentrated to dryness. The residue obtained is used as is in the next Step without being analysed.

Step D: ***2,2-Dimethyl 4-[{[6-(5-chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-8-yl]carbonyl}(1-methyl-1H-indol-5-yl)amino]phenyl propanoate***

To a solution of the compound of the preceding Step (0.82 g; 0.93 mmol) in dichloromethane (9 mL) there is added, at 0°C, trifluoroacetic acid (0.7 mL; 13.9 mmol) dropwise. After stirring for 15 hours at ambient temperature, saturated sodium bicarbonate solution is slowly added to the reaction mixture and then the phases are separated. The aqueous phase is extracted with dichloromethane. The combined organic phases are dried over $MgSO_4$ and concentrated to dryness. The residue obtained is purified by chromatography over silica gel (CH_2Cl_2/MeOH gradient) to provide the expected product in the form of a solid.

LC/MS: m/z = $[M+H]^+$= 754.30

Step E: ***2,2-Dimethyl 4-[{[6-(5-chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-8-yl]carbonyl}(1-methyl-1H-indol-5-yl)amino]phenyl propanoate***

To a solution of the compound of the preceding Step (0.41 g; 0.54 mmol) in dichloromethane (2 mL) there are added, at ambient temperature, formaldehyde (48 µL; 1.74 mmol) and then sodium triacetoxyborohydride (161 mg; 0.76 mmol). After stirring for 2 hours at ambient temperature, the reaction mixture is diluted with dichloromethane and then washed with saturated sodium bicarbonate solution. The organic phase is dried over $MgSO_4$ and concentrated to dryness. The residue obtained is purified by chromatography over silica gel (CH_2Cl_2/MeOH gradient). The expected product is obtained in the form of a solid.

LC/MS: m/z = $[M+H]^+$= 768.32

__Step F:__ 6-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-indol-5-yl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-8-carboxamide

To a solution of the compound of the preceding Step (0.25 g; 0.32 mmol) in dioxane (1 mL) there is added a solution of lithium hydroxide (27 mg; 0.65 mmol) in water (1 mL). After stirring for 5 hours at ambient temperature, the reaction mixture is concentrated and diluted with saturated sodium bicarbonate solution. The aqueous phase is extracted with CH_2Cl_2. The organic phase is dried over $MgSO_4$ and concentrated to dryness. The residue obtained is purified by chromatography over silica gel (CH_2Cl_2/MeOH gradient). The expected product is then obtained in the form of a solid.

Elemental microanalysis: (%, theoretical:measured)

%C=71.97:71.51; %H=5.6:5.25; %N=10.24:10.12

__Example 8.__ 3-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-{1-[2-(morpholin-4-yl)ethyl]-1*H*-indol-5-yl}indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=69:69.16; %H=5.41:4.82; %N=8.75:8.69; %Cl-=4.43:4.13

__Example 9.__ 6-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-phenyl)-*N*-(4-fluorophenyl)-*N*-(4-hydroxyphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazine-8-carboxamide hydrochloride

The procedure is in accordance with the process of Example 1, replacing, on the one hand, the compound of Preparation 1 used in Step A with the compound of Preparation 6 and, on the other hand, the compound of Preparation 1" used in Step C with the compound of Preparation 5", it being understood that the product thereby obtained is not subjected to a step of conversion into a salt in the presence of HCl in ether as is described in Step D of Example 1. The compound thereby obtained is deprotected in the presence of 10 equivalents of trifluoroacetic acid in dichloromethane (10 mL/mmol) at ambient temperature overnight. The product is then isolated by concentrating the reaction mixture to dryness. Finally, it is subjected to a step of conversion into a salt in the presence of HCl in ether.

Elemental microanalysis: (%, theoretical:measured)

%C=67.83:67.41; %H=5.08:4.61; %N=8.55:8.39; %Cl-=5.41:5.28

Example 10. 6-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(3-fluoro-4-methylphenyl)-*N*-(4-hydroxyphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide hydrochloride

The procedure is in accordance with the process of Example 1, replacing, on the one hand, the compound of Preparation 1 used in Step A with the compound of Preparation 6 and, on the other hand, the compound of Preparation 1" used in Step C with the compound of Preparation 6", it being understood that the product thereby obtained is not subjected to a step of conversion into a salt in the presence of HCl in ether as is described in Step D of Example 1. The compound thereby obtained is deprotected in the presence of 10 equivalents of trifluoroacetic acid in dichloromethane (10 mL/mmol) at ambient temperature overnight. The product is then isolated by concentrating the reaction mixture to dryness. Finally, it is subjected to a step of conversion into a salt in the presence of HCl in ether.

Elemental microanalysis: (%, theoretical:measured)

%C=68.21:68.29; %H=5.27:4.91; %N=8.37:8.34; %Cl-=5.3:5.17

Example 11. *N*-(4-Hydroxyphenyl)-6-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-1*H*-indazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide hydrochloride

The procedure is in accordance with the process of Example 1, replacing, on the one hand, the compound of Preparation 1 used in Step A with the compound of Preparation 7 and, on the other hand, the compound of Preparation 1" used in Step C with *N*-(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indazol-5-amine, it being understood that the product thereby obtained is not subjected to a step of conversion into a salt in the presence of HCl in ether as is described in Step D of Example 1. The compound thereby obtained is deprotected in the presence of 10 equivalents of trifluoroacetic acid in dichloromethane (10 mL/mmol) at ambient temperature overnight. The product is then isolated by concentrating the reaction mixture to dryness. Finally, it is subjected to a step of conversion into a salt in the presence of HCl in ether.

Elemental microanalysis: (%, theoretical:measured)
%H=5.2:4.83; %N=11.72:11.64; %Cl-=4.94:5.34; %C=66.99:66.19

<u>Example 12.</u> 6-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide hydrochloride

The procedure is in accordance with the process of Example 1, replacing, on the one hand, the compound of Preparation 1 used in Step A with the compound of Preparation 2 and, on the other hand, the compound of Preparation 1" used in Step C with *N*-(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1*H*-indazol-5-amine, it being understood that the product thereby obtained is not subjected to a step of conversion into a salt in the presence of HCl in ether as is described in Step D of Example 1. The compound thereby obtained is deprotected in the presence of 10 equivalents of trifluoroacetic acid in dichloromethane (10 mL/mmol) at ambient temperature overnight. The product is then isolated by concentrating the reaction mixture to dryness. Finally, it is subjected to a step of conversion into a salt in the presence of HCl in ether.

Elemental microanalysis: (%, theoretical:measured)
%C=66.19:65.83; %H=5.13:4.99; %N=11.88:11.85; %Cl-=5.01:5.36

<u>Example 13.</u> *N*-(4-Hydroxyphenyl)-3-(6-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)
%C=69.42:69.47; %H=5.96:5.58; %N=7.36:7.36; %Cl-=4.66:4.42

Example 14. ***N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-3-(6-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride**

Elemental microanalysis: (%, theoretical:measured)

%C=67.76:67.81; %H=5.81:5.63; %N=10.31:10.13; %Cl-=4.35:4.22

Example 15. **7-Amino-*N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-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-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5',6'-dihydro-8'H-spiro[1,3-dioxolane-2,7'-indolizine]-1'-carboxylate

The procedure is in accordance with the protocol of Step A of Example 1, replacing the compound of Preparation 1 with the compound of Preparation 8.

Step B: Methyl 3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-7-oxo-5,6,7,8-tetrahydroindolizine-1-carboxylate

4.47 mmol of the compound of Step A dissolved in 75 mL of THF are stirred in the presence of 37 mL of 1M HCl at reflux for 15 hours. 100 mL of water and 100 mL of ethyl acetate are added to the reaction mixture. There are then added 4 g of $NaHCO_3$ (4.7 mmol) in the form of a powder until a basic pH is obtained. The compound is extracted with ethyl acetate; the organic phase is dried over $MgSO_4$, filtered and concentrated to dryness.

Step C: Methyl 7-hydroxy-3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxylate

To a solution of 4.47 mmol of the compound obtained in Step B in 30 mL of methanol there are added, in portions, 558 mg (14.75 mmol) of sodium borohydride. The reaction mixture is stirred for 1 hour at ambient temperature. 50 mL of 1M HCl are then added and the methanol is evaporated off. The aqueous phase is then neutralised using $NaHCO_3$ and then extracted with dichloromethane. The organic phase is successively washed with H_2O, dried over $MgSO_4$, filtered and concentrated to dryness. The oil thereby obtained is purified by flash chromatography (dichloromethane/ethanol-ammonia gradient) to yield the expected product.

Step D: ***Methyl 3-(6-{[(3R)-3-methyl-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 4.13 mmol of the compound obtained in Step C. The resulting 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 slowly added (over 15 minutes). The reaction mixture is stirred for 1 hour at 0°C, and then for 15 hours at ambient temperature. The resulting solution is hydrolysed with saturated aqueous NH_4Cl solution. The compound is extracted with ethyl acetate; the organic phase is dried over $MgSO_4$, filtered and concentrated to dryness. The oil thereby obtained is purified by flash chromatography (cyclohexane/ethyl acetate gradient) to yield the expected product.

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

The procedure is in accordance with the processes described in Steps B and C of Example 1 using the appropriate reagents.

Step F: ***N-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)-7-hydroxy-3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide***

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

Step G: ***7-Azido-N-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide***

To a solution of the compound of Step F (550 mg; 0.72 mmol) in methylene chloride (6 mL) there are added, at ambient temperature, triethylamine (300 µL; 1.8 mmol) and mesyl chloride (0.14 mL; 1.8 mmol). After stirring for 20 minutes, the reaction mixture is concentrated to dryness and then diluted with 10 mL of DMSO. 470 mg of NaN_3 in powder form (7.2 mmol) are added thereto. The reaction mixture is left for 20 hours at ambient temperature and then for 20 hours at 50°C. It is then poured onto a mixture of dichloromethane and water. The organic phase is washed 3 times with water and then with brine, dried over $MgSO_4$, and then concentrated to dryness to yield the expected product which is used as is in the next Step.

Step H: ***7-Amino-N-(4-hydroxyphenyl)-3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride***

To a solution of 550 mg of the compound of Step G (0.7 mmol) in ethanol (10 mL) there are added, at ambient temperature, 20 mg of Pd/C 10%. After stirring for 15 hours under 1 bar of hydrogen, the reaction mixture is passed through a Whatman filter and concentrated to dryness. After purification by column chromatography over silica gel (dichloromethane/methanol gradient), the solid is then dissolved in dichloromethane, and 2 mL of 1N HCl in ether are added. The entire batch is stirred for 1 hour and then evaporated to dryness. The hydrochloride thereby obtained is dissolved in a mixture of water/acetonitrile until dissolution is complete and then lyophilised to yield the expected compound in the form of a powder.

Elemental microanalysis: (%, theoretical:measured)

%C=69.17:68.68; %H=5.51:5.09; %N=8.27:8.41; %Cl-=5.24:5.28

Example 16. 3-(6-{[(3*S*)-3-(Hydroxymethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-*N*-phenyl-5,6,7,8-tetrahydro-indolizine-1-carboxamide

Step A: ***Methyl 3-(6-{[(3S)-3-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxylate***

The procedure is in accordance with the process in Step A of Example 1 using (3*S*)-1,2,3,4-tetrahydroisoquinolin-3-ylmethanol.

Step B: ***Methyl 3-(6-{[(3S)-3-[(prop-2-en-1-yloxy)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxylate***

To a suspension of NaH (703 mg; 17.6 mmol) in THF (20 mL) there is added a solution of 7.8 g of the compound of Step A (16 mmol) dissolved in a mixture of THF (50 mL) and DMF (30 mL). After stirring for 1 hour there is added allyl bromide (1.7 mL; 19 mmol). The reaction mixture is stirred for 48 hours at ambient temperature and is then poured onto a mixture of ethyl acetate and water. The organic phase is washed 3 times with water, and with saturated LiOH solution, dried over $MgSO_4$ and concentrated to dryness. After purification by chromatography over silica gel (dichloromethane/methanol gradient), the expected product is obtained in the form of a solid.

^{1}H NMR: δ: (500MHz; dmso-d6; 300K): 7.2-6.9 (m, 4H); 7.05 (m, 1H); 6.9 (m, 1H); 6.45-6.1 (m, 1H); 6.15 (m, 2H); 5.9-5.65 (m, 1H); 5.2-5.0 (m, 2H); 5.05-3.8 (m, 1H); 4.85-4.25 (m, 2H); 4.3-3.45 (m, 7H); 3.4-2.4 (m, 6H); 1.95-1.45 (m, 4H)

Step C: ***N-[4-(Benzyloxy)phenyl]-N-phenyl-3-(6-{[(3S)-3-[(prop-2-en-1-yloxy)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydro-indolizine-1-carboxamide***

The procedure is in accordance with the processes of Steps B and C of Example 1 using 4-(benzyloxy)-*N*-phenylaniline (*cf.* Preparation 9").

<u>Step D:</u> 3-(6-{[(3S)-3-(Hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide

To a suspension of 5.1 g (6.65 mmol) of the compound of Step C in a mixture of dichloromethane (7 mL) and methanol (2 mL) there are added dimethylbarbituric acid (2.1 g; 13.3 mmol) and tetrakis(triphenylphosphine)palladium(0) (300 mg; 0.3 mmol). After stirring for 15 hours at 45°C, the reaction mixture is poured onto a mixture of ethyl acetate and water. The organic phase is washed twice with water, dried over $MgSO_4$, concentrated to dryness and diluted with methanol (5 mL). The batch is then stirred for 24 hours under a hydrogen atmosphere in the presence of Pd/C (100 mg). The reaction mixture is then passed through a Whatman filter, concentrated to dryness, then chromatographed over silica gel (dichloromethane/methanol gradient) and finally lyophilised to yield the expected product in the form of a powder.

Elemental microanalysis: %, measured (theoretical)

%C=72.38(73);%H=5.22(5.5);%N=6.59(6.55)

<u>Example 17.</u> *N*-{3-Fluoro-4-[2-(morpholin-4-yl)ethoxy]phenyl}-*N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=67.12:66.79; %H=5.26:4.98; %N=6.96:7.17; %Cl-=4.4:4.77

<u>Example 18.</u> 3-[6-(3,4-Dihydroisoquinolin-2(1*H*)-ylcarbonyl)-1,3-benzodioxol-5-yl]-*N*-{3-fluoro-4-[2-(morpholin-4-yl)ethoxy]phenyl}-*N*-(4-hydroxyphenyl)indolizine-1-carboxamide hydrochloride

Elemental microanalysis: %, measured (theoretical)

%C=66.99(66.79);%H=4.93(5.1);%N=7.11(7.08);%Cl-=4.46(4.48)

<u>Example 19.</u> *N*-(4-Hydroxyphenyl)-3-(5-methyl-2-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-phenyl-5,6,7,8-tetrahydro-indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)
%C=72.26:72.51; %H=6.48:6.13; %N=7.66:7.71; %Cl=4.85:4.95; %Cl-=4.85:4.64

<u>Example 20.</u> *N*-(4-Hydroxyphenyl)-3-(2-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)
%C=72:71.11; %H=6.32:5.94; %N=7.81:7.65; %Cl-=4.94:5.08

<u>Example 21.</u> *N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-4-yl)indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)
%C=69.24:69.12; %H=4.74:4.23; %N=8.5:8.45; %Cl-=5.38:5.2

<u>Example 22.</u> *N*-(4-Hydroxyphenyl)-6-(6-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenylpyrrolo[1,2-*a*]-pyrimidine-8-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)
%C=68.11:66.66; %H=5.32:4.93; %N=9.24:8.84; %Cl-=4.68:5.78

High-resolution mass spectroscopy (ESI+):
Empirical formula: $C_{43}H_{39}N_5O_6$
$[M+H]^+$, calculated: 655.2915
$[M+H]^+$, measured: 655.2915

<u>Example 23.</u> *N*-(3-Cyanophenyl)-*N*-(4-hydroxyphenyl)-3-(6-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)
%C=68.74:68.59; %H=5.64:5.5; %N=8.91:8.98; %Cl-=4.51:4.48

<u>Example 24.</u> *N*-(3-Fluorophenyl)-*N*-(4-hydroxyphenyl)-3-(6-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)
%C=67.81:67.45; %H=5.69:5.61; %N=7.19:7.42; %Cl-=4.55:4.84

<u>Example 25.</u> *N*-(3,4-Difluorophenyl)-*N*-(4-hydroxyphenyl)-3-(6-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)
%C=66.28:66.56; %H=5.44:5.25; %N=7.03:7.21; %Cl-=4.45:4.32

<u>Example 26.</u> *N*-(3-Fluorophenyl)-3-(6-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydro-isoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydro-indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)
%C=69.24:70.16; %H=5.81:5.79; %N=7.34:7.47; %Cl-=4.64:4.58

<u>Example 27.</u> 3-(5-Chloro-2-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(3-fluorophenyl)-*N*-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=67.1:67.68; %H=5.63:5.4; %N=7.28:7.34; %Cl-=4.61:4.59

<u>Example 28.</u> *N*-(4-Hydroxyphenyl)-3-(5-methoxy-2-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-phenyl-5,6,7,8-tetrahydro-indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=70.72:70.05; %H=6.34:5.95; %N=7.5:7.33; %Cl-=4.74:4.74

<u>Example 29.</u> *N*-(4-Hydroxyphenyl)-3-(4-methoxy-2-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-phenyl-5,6,7,8-tetrahydro-indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=70.72:68.96; %H=6.34:5.78; %N=7.5:7.24; %Cl-=4.74:4.62

High-resolution mass spectroscopy (ESI+):

Empirical formula: C_{44} H_{46} N_4 O_5

$[M+H]^+$, calculated: 711.3546

$[M+H]^+$, measured: 711.3540

<u>Example 30.</u> *N*-{4-[(3,3-Difluoropiperidin-1-yl)methyl]phenyl}-*N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=68.31:69.12; %H=5.22:4.93; %N=7.08:6.96; %Cl-=4.48:4.07

<u>Example 31.</u> *N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(quinolin-6-yl)indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=71.13:71.29; %H=4.69:4.39; %N=7.9:8.14; %Cl-=5:4.5

<u>Example 32.</u> *N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(2-methylpyridin-4-yl)indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=69.59:69.81; %H=4.94:4.53; %N=8.32:8.59; %Cl-=5.27:5.01

<u>Example 33.</u> *N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=69.14:70.09; %H=4.81:4.55; %N=9.83:10.09; %Cl-=4.98:3.26

<u>Example 34.</u> *N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-3-yl)indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=69.24:70.21; %H=4.74:4.42; %N=8.5:8.51; %Cl-=5.38:3.33

<u>Example 35.</u> *N*-{4-[2-(3,3-Difluoropiperidin-1-yl)ethyl]phenyl}-*N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=68.61:67.96; %H=5.38:5.14; %N=6.96:6.76; %Cl-=4.4:4.36

<u>Example 36.</u> *N*-{4-[2-(3,3-Difluoropyrrolidin-1-yl)ethyl]phenyl}-*N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)
%C=68.31:68.51; %H=5.22:4.85; %N=7.08:6.83; %Cl-=4.48:4.48

<u>Example 37.</u> 3-(6-{[(3*S*)-3-(2-Aminoethyl)-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

<u>Step A</u>: Methyl 3-(6-{[(3S)-3-{2-[(tert-butoxycarbonyl)amino]ethyl}-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxylate

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), the compound of Preparation 3' (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 then stirred at ambient temperature overnight, and it is then poured onto ammonium chloride solution and extracted with ethyl acetate. The organic phase is then dried over magnesium sulphate, and then filtered and evaporated to dryness. The crude product thereby obtained is then purified by chromatography over silica gel (heptane/AcOEt gradient) to yield the expected product.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.2-6.8 (m, 4H, aromatic Hs, H tetrahydroisoquinoline); 7.15-6.90 (m, 4H, aromatic H, tetrahydroisoquinoline); 7.00-6.80 (m, 2H, aromatic H, benzodioxole); 6.68+6.55+6.25 (m, 1H, **NH**); 6.50-6.05 (m, 1H, aromatic H, tetrahydroindolizine); 6.12 (m, 2H, aliphatic Hs, O**CH$_2$**O); 4.95+4.20+4.10 (m, 2H, aliphatic H, **CH$_2$**N tetrahydroisoquinoline); 4.85+4.78+3.80 (m, 1H, aliphatic H, **CH** tetrahydroisoquinoline); 4.00-3.40 (m, 2H, aliphatic Hs, **CH$_2$**N tetrahydroindolizine); 3.70-3.50 (m, 3H, COO**CH$_3$**); 2.95-2.45 (m, 2H, aliphatic Hs, **CH$_2$**NHBoc); 2.98-2.30 (m, 2H, aliphatic Hs, **CH$_2$**C tetrahydroindolizine); 3.00+2.60+2.42 (m, 2H, aliphatic Hs, **CH$_2$**CH tetrahydroindolizine); 1.95-1.40 (m, 4H, aliphatic Hs, **CH$_2$CH$_2$**

tetrahydroindolizine); 1.35-1.25 (m, 9H, aliphatic Hs, **tBu**); 1.50-1.15 (m, 2H, aliphatic Hs, **CH$_2$**CH$_2$NHBoc)

Step B: ***Lithium 3-(6-{[(3S)-3-{2-[(tert-butoxycarbonyl)amino]ethyl}-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxylate***

To a solution containing 8.26 mmol of the compound of Step A in 24 mL of dioxane there is added a solution of lithium hydroxide (675 mg, 16.1 mmol). The batch is placed in a microwave oven at 140 W, 100°C for a period of 2 hours 30 minutes. The reaction mixture is then filtered and evaporated. The solid thereby obtained is dried at 40°C in an oven in the presence of P_2O_5.

Step C: ***tert-Butyl (2-{(3S)-2-[(6-{1-[(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-(phenyl)carbamoyl]-5,6,7,8-tetrahydroindolizin-3-yl}-1,3-benzodioxol-5-yl)carbonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}ethyl)carbamate***

To a solution containing 4.73 mmol of the compound of Step B in 47 mL of 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 is then co-evaporated several times with dichloromethane. The product thereby obtained is suspended in 37 mL of dichloromethane, and is then added to a solution containing 7.1 mmol of the compound obtained in Preparation 8" in 10 mL of dichloromethane in the presence of 0.6 mL of pyridine (7.1 mmol). The batch is stirred at ambient temperature overnight.

The reaction mixture is concentrated and purified by chromatography over silica gel (dichloromethane/methanol gradient) to yield the expected product.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.0 (m, 11H, aromatic Hs, Ph + 4H, tetrahydroisoquinoline + 2H, PhO); 6.80-6.65 (m, 2H, aromatic Hs, PhO); 6.95-6.85 (m, 2H, aromatic H, benzodioxole); 6.70+6.40 (3tl, 1H, **NH**); 6.10 (m, 2H, aliphatic Hs, O**CH$_2$**O); 5.25-4.85 (m, 1H, aromatic H, tetrahydroindolizine); 5.00+4.00 (m, 2H, aliphatic H, **CH$_2$**N tetrahydroisoquinoline); 4.90-3.60 (m, 1H, aliphatic H, **CH** tetrahydroisoquinoline); 4.10-3.40 (m, 2H, aliphatic Hs, **CH$_2$**N tetrahydroindolizine); 3.00-2.50 (m, 2H, aliphatic Hs, **CH$_2$**C tetrahydroindolizine); 3.00+2.40 (m, 2H, aliphatic Hs, **CH$_2$**CH tetrahydroindolizine); 3.00-2.50 (m, 2H, aliphatic Hs, **CH_2**NHBoc); 1.80-1.50 (m, 4H, aliphatic Hs, **CH_2CH_2** tetrahydroindolizine); 1.50-1.30 (m, 2H, aliphatic Hs, **CH_2**CH_2NHBoc); 1.35 (2s, 9H, aliphatic Hs, **tBu**); 0.90 (s, 9H, aliphatic Hs, **tBu**-Si); 0.10 (m, 6H, aliphatic Hs, **Me**-Si)

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

To a solution of 800 mg (0.92 mmol) of the compound of Step C in 10 mL of methanol there are added 258 mg (4.60 mmol) of KOH. After stirring for 3 hours at ambient temperature, the reaction mixture is treated with 4M HCl solution in 6 mL of dioxane. After stirring for 2 hours at ambient temperature, the reaction mixture is concentrated and treated with saturated aqueous $NaHCO_3$ solution and extracted with methylene chloride. The organic phase is then dried over magnesium sulphate, and then filtered and evaporated to dryness. The crude product thereby obtained is then purified by chromatography over silica gel (dichloromethane/methanol gradient). The compound is then dissolved in 5 mL of dichloromethane, and 2.5 mL of 1M HCl in ether are added. The compound is filtered off and dried *in vacuo*. The expected product is obtained in the form of a foam.

Elemental microanalysis: (%, theoretical:measured)

%C=69.51:69.53; %H=5.69:5.27; %N=8.11:8.04; %Cl-=5.13:5.2

High-resolution mass spectroscopy (ESI+):

Empirical formula: $C_{40}H_{38}N_4O_5$

$[M+H]^+$, calculated: 655.2915

$[M+H]^+$, measured: 655.2915

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 9.55+9.45 (2s, 1H, OH); 7.80+7.75 (2s, 3H, **NH_3^+**); 7.46-6.55 (m, 11H, aromatic Hs, Ph + 4H, tetrahydroisoquinoline + 2H, PhO); 6.90-6.55 (m, 2H, aromatic Hs, PhO); 7.00-6.70 (several s, 2H, aromatic H, benzodioxole); 5.35-5.00 (several s, 1H, aromatic H, tetrahydroindolizine); 6.10 (several s, 2H, aliphatic Hs, O**CH_2**O); 5.00-3.35 (several m, 4H, aliphatic H, **CH_2**N tetrahydroisoquinoline + **CH_2**N tetrahydroindolizine); 4.85+4.75+3.60 (several m, 1H, aliphatic H, **CH**

tetrahydroisoquinoline); 2.85-2.45 (several m, 2H, aliphatic Hs, **CH_2**NH_2); 3.00-2.45 (several m, 2H, aliphatic Hs, **CH_2**C tetrahydroindolizine); 3.05+2.30 (several m, 2H, aliphatic Hs, **CH_2**CH tetrahydroisoquinoline); 1.85-1.40 (several m, 2H, aliphatic Hs, **CH_2** tetrahydroisoquinoline); 1.95-1.35 (several m, 2H, aliphatic Hs, **CH_2** tetrahydroisoquinoline); 1.75-1.40 (several m, 2H, aliphatic Hs, **CH_2**CH_2NH_2)

IR: ν: -OH: 3375 cm^{-1} (phenol); ν: -NH3$^+$: 3500-2300 cm^{-1} (salt of primary amine); ν: >C=O 1612 cm^{-1} + shoulder (amide)

Example 38. ***N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride**

Elemental microanalysis: (%, theoretical:measured)

%C=69.71:69.62; %H=6.11:5.67; %N=7.23:7.12; %Cl-=4.57:4.81

Example 39. ***N*-(2,6-Dimethylpyridin-4-yl)-*N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxamide hydrochloride**

Elemental microanalysis: (%, theoretical:measured)

%C=69.91:69.68; %H=5.13:4.78; %N=8.15:8.03; %Cl-=5.16:5.16

Example 40. ***N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide**

Elemental microanalysis: (%, theoretical:measured)

%C=74.86:74.88; %H=5.64:5.31; %N=6.72:6.78

Example 41. **3-(6-{[(3*S*)-3-[2-(3,3-Difluoropiperidin-1-yl)ethyl]-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**

Elemental microanalysis: (%, theoretical:measured)

%C=67.96:68.34; %H=5.7:5.4; %N=7.04:6.97; %Cl-=4.46:4.27

__Example 42.__ *N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-4-yl)-5,6,7,8-tetrahydro-indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=68.82:69.46; %H=5.32:4.95; %N=8.45:8.48; %Cl-=5.35:4.6

__Example 43.__ 3-(6-{[(3*S*)-3-{2-[(2,2-Difluoroethyl)amino]ethyl}-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

__Step A__: Ethyl 3-(6-{[(3S)-3-{2-[(tert-butoxycarbonyl)amino]ethyl}-3,4-dihydroiso-quinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxylate

The process is analogous to that described in Step A of Example 37.

__Step B__: Ethyl 3-(6-{[(3S)-3-{2-[(tert-butoxycarbonyl)(2,2-difluoroethyl)amino]-ethyl}-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxylate

To a suspension of 337 mg of NaH (60 %) (8.41 mmol) in 13 mL of dimethylformamide there is added, dropwise, a solution of 1.01 g (1.68 mmol) of the compound of Step A in 13 mL of dimethylformamide. The resulting suspension is stirred at ambient temperature for 15 minutes and there are then added 1.08 g (5.04 mmol) of 2,2-difluoroethyl trifluoromethanesulphonate in 13 mL of dimethylformamide. The batch is stirred at ambient temperature for 2 hours. A solution of 20 mL of saturated ammonium chloride is added. The solution is extracted with ethyl acetate. The organic phase is then dried over $MgSO_4$, filtered and concentrated to dryness. After purification by column chromatography over silica gel (cyclohexane/ethyl acetate), the expected product is obtained in the form of an oil.

High-resolution mass spectroscopy (ESI+):

Empirical formula: $C_{37}H_{43}CN_3O_7$

$[M+H]^+$, calculated: 680.3142

$[M+H]^+$, measured: 680.3145

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.25-6.90 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 7.10-6.75 (m, 2H, aromatic H, benzodioxole); 6.40-6.05 (m, 1H, aromatic H, tetrahydroindolizine); 6.10 (m, 2H, aliphatic Hs, O**CH_2**O); 6.25-5.90 (m, 1H, aliphatic Hs, **CHF_2**); 4.95-4.10 (m, 2H, aliphatic H, **CH_2**N tetrahydroisoquinoline); 4.80+3.80 (2m, 1H, aliphatic H, **CH** tetrahydroisoquinoline); 4.10-4.00 (m, 2H, **CH_2** Et); 4.05-3.40 (m, 2H, aliphatic H, **CH_2**N tetrahydroindolizine); 3.60-2.60 (m, 4H, aliphatic H, **CH_2**CHF_2 +**CH_2**NBoc); 3.00-2.35 (m, 2H, aliphatic Hs, **CH_2**C tetrahydroindolizine); 3.00+2.45 (m, 2H, aliphatic Hs, **CH_2**CH tetrahydroisoquinoline); 1.95+1.40 (m, 4H, aliphatic Hs, **CH_2CH_2** tetrahydroindolizine); 1.40 (m, 9H, aliphatic Hs, **^{t}Bu**); 1.65-1.20 (m, 2H, aliphatic Hs, **CH_2**CH_2NBoc); 1.18+1.10 (2t, 3H, aliphatic Hs **CH_3** Et)

Step C*: *tert-Butyl (2-{(3S)-2-[(6-{1-[(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)(phenyl)-carbamoyl]-5,6,7,8-tetrahydroindolizin-3-yl}-1,3-benzodioxol-5-yl)carbonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}ethyl)(2,2-difluoroethyl)carbamate

The process is analogous to that described in Steps B and C of Example 37.

^{1}H NMR: δ (400 MHz; dmso-d6; 300K): 7.30-6.60 (m, 9H, aromatic Hs, 4H tetrahydroisoquinoline + Ph); 6.90-6.70 (m, 2H, aromatic H, benzodioxole); 6.80-6.60 (m, 4H, PhO); 6.10 (m, 2H, aliphatic Hs, O**CH_2**O); 6.20-5.90 (m, 1H, aliphatic Hs, **CHF_2**); 5.50-4.80 (4s, 1H, aromatic H, tetrahydroindolizine); 5.20-4.00 (m, 2H, aliphatic H, **CH_2**N tetrahydroisoquinoline); 4.80+4.70+3.50 (3m, 1H, aliphatic H, **CH** tetrahydroisoquinoline); 4.20-3.40 (m, 2H, aliphatic H, **CH_2**N tetrahydroindolizine); 3.60-3.10 (m, 4H, aliphatic H, **CH_2**CHF_2 +**CH_2**NBoc); 3.00+2.60 (m, 2H, aliphatic Hs, **CH_2**CH tetrahydroisoquinoline); 3.00-2.50 (m, 2H, aliphatic Hs, **CH_2**C tetrahydroindolizine); 1.80+1.50 (m, 4H, aliphatic Hs, **CH_2CH_2** tetrahydroindolizine); 1.60-1.30 (m, 2H, aliphatic Hs, **CH**$_2$CH$_2$NBoc); 1.40-1.30 (m, 9H, aliphatic Hs, **tBu**); 0.90 (4s, 9H, aliphatic Hs, **tBu**-Si); 0.10 (4s, 6H, aliphatic Hs, **Me**-Si)

***Step D**: 3-(6-{[(3S)-3-{2-[(2,2-Difluoroethyl)amino]ethyl}-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide*

To a solution of 933 mg (1.00 mmol) of the compound of Step C in 10 mL of methanol there are added 280 mg (5.00 mmol) of KOH. After stirring for 3 hours at ambient temperature, the reaction mixture is treated with 4M HCl solution in 6 mL of dioxane. After stirring for 2 hours at ambient temperature, the reaction mixture is concentrated and treated with aqueous saturated $NaHCO_3$ solution and then extracted with methylene chloride. The organic phase is then dried over magnesium sulphate, and then filtered and evaporated to dryness. The crude product thereby obtained is then purified by chromatography over silica gel (dichloromethane/methanol gradient) to yield the expected product in the form of a foam.

***Elemental microanalysis:** (%, theoretical:measured)*

%C=70.18:69.79; %H=5.61:5.67; %N=7.79:7.7

High-resolution mass spectroscopy (ESI+):

Empirical formula: $C_{42}H_{40}F_2N_4O_5$

$[M+H]^+$, calculated: 655.2915

$[M+H]^+$, measured: 655.2915

Example 44. ***N*-(4-Hydroxyphenyl)-3-(6-{[(3*S*)-3-[2-(3-methoxyazetidin-1-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide**

***Elemental microanalysis:** (%, theoretical:measured)*

%C=72.91:72.73; %H=6.12:5.67; %N=7.73:7.74

<u>Example 45.</u> *N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-{1-[2-(morpholin-4-yl)ethyl]-1*H*-pyrazol-4-yl}indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)
%C=66.27:66.05; %H=5.43:5.27; %N=11.04:11.07; %Cl-=4.66:4.61

<u>Example 46.</u> *N*-(3-Fluoropyridin-4-yl)-*N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxamide hydrochloride

High-resolution mass spectroscopy (ESI+):
Empirical formula: $C_{38}H_{29}FN_4O_5$
$[M+H]^+$, calculated: 641.2195
$[M+H]^+$, measured: 641.2195

<u>Example 47.</u> 3-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide

Elemental microanalysis: (%, theoretical:measured)
%C=69.72:69.53; %H=5.53:5.6; %N=11.29:10.85

<u>Example 48.</u> *N*-(4-Hydroxyphenyl)-3-(7-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-2,3-dihydro-1,4-benzodioxin-6-yl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide

Elemental microanalysis: (%, theoretical:measured)
%C=70.9:70.89; %H=5.79:5.56; %N=10.88:10.8

<u>Example 49.</u> 3-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(pyridin-4-yl)indolizine-1-carboxamide hydrochloride

Elemental microanalysis: (%, theoretical:measured)

%C=68.42:68.17; %H=4.65:4.48; %N=8.63:8.48; %Cl-=5.46:5.13

Example 50. **3-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)indolizine-1-carboxamide**

Elemental microanalysis: (%, theoretical:measured)

%C=72.12:71.58; %H=4.84:4.84; %N=10.51:10.48

Example 51. ***N*-(4-Hydroxyphenyl)-*N*-(imidazo[1,2-*a*]pyridin-7-yl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxamide hydrochloride**

Elemental microanalysis: (%, theoretical:measured)

%C=68.81:68.28; %H=4.62:4.59; %N=10.03:9.66; %Cl-=5.08:4.81

Example 52. ***N*-(4-Hydroxyphenyl)-3-(2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)indolizine-1-carboxamide**

Elemental microanalysis: (%, theoretical:measured)

%C=76.05:75.88; %H=5.26:5.24; %N=11.09:11.09

Example 53. ***N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(2-methylimidazo[1,2-*a*]pyridin-7-yl)indolizine-1-carboxamide hydrochloride**

Elemental microanalysis: (%, theoretical:measured)

%C=69.14:69.65; %H=4.81:4.75; %N=9.83:9.79; %Cl-=4.98:4.7

Example 54. ***N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(6-methylpyridin-3-yl)indolizine-1-carboxamide hydrochloride**

Elemental microanalysis: (%, theoretical:measured)
%C=69.59:68.78; %H=4.94:5; %N=8.32:8.33; %Cl-=5.27:5.18

Example 55. ***N*-(5-Fluoropyridin-3-yl)-*N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxamide**

Elemental microanalysis: (%, theoretical:measured)
%C=71.24:70.77; %H=4.56:4.36; %N=8.75:8.82

Example 56. ***N*-(4-Hydroxyphenyl)-*N*-(2-methoxypyridin-4-yl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxamide**

High-resolution mass spectroscopy (ESI+):
Empirical formula: $C_{39}H_{32}N_4O_6$
$[M+H]^+$, calculated: 653.2395
$[M+H]^+$, measured: 653.2385

Example 57. **3-[6-(3,4-Dihydroisoquinolin-2(1H)-ylcarbonyl)-1,3-benzodioxol-5-yl]-N-(4-hydroxyphenyl)-N-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide**

Elemental microanalysis: %, measured (theoretical)
%C=74.17(74.62);%H=5.43(5.44);%N=6.87(6.87)

Example 58. ***N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-[2-(propan-2-yl)pyridin-4-yl]indolizine-1-carboxamide hydrochloride**

Elemental microanalysis: (%, theoretical:measured)

%C=70.23:69.95; %H=5.32:5.4; %N=7.99:7.99; %Cl-=5.06:4.92

<u>Example 59.</u> *N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyrazolo[1,5-*a*]pyrimidin-6-yl)indolizine-1-carboxamide

Elemental microanalysis: (%, theoretical:measured)

%C=70.68:70.47; %H=4.56:4.61; %N=12.68:12.45

<u>Example 60.</u> 3-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)indolizine-1-carboxamide

Elemental microanalysis: %, measured (theoretical)

%C=71.85(72.11);%H=4.78(5.04);%N=10.79(11.68)

<u>Example 61.</u> 3-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide

Elemental microanalysis: %, measured (theoretical)

%C=72.31(71.62);%H=5.6(5.68);%N=10.94(11.6)

<u>Example 62.</u> 3-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(pyridin-4-yl)indolizine-1-carboxamide

Elemental microanalysis: %, measured (theoretical)

%C=74.08(74.48);%H=4.82(4.9);%N=8.59(9.39)

<u>Example 63.</u> 3-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)indolizine-1-carboxamide

Elemental microanalysis: %, measured (theoretical)

%C=73.14(73.95);%H=4.83(4.96);%N=10.29(10.78)

<u>Example 64.</u> 3-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(pyridin-4-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide

Elemental microanalysis: %, measured (theoretical)

%C=74.61(73.98);%H=5.26(5.54);%N=8.94(9.33)

<u>Example 65.</u> 3-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide

Elemental microanalysis: %, measured (theoretical)

%C=73.59(73.49);%H=5.22(5.55);%N=9.93(10.71)

<u>Example 66.</u> *N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-([1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)-indolizine-1-carboxamide

Elemental microanalysis: %, measured (theoretical)

%C=68.57(68.77);%H=3.92(4.4);%N=14.21(14.77)

High-resolution mass spectroscopy (ESI+):

Empirical formula: $C_{38}H_{29}N_7O_5$

$[M+H]^+$, calculated: 664.2303

$[M+H]^+$, measured: 664.2310

<u>Example 67.</u> *N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-oxidopyridin-4-yl)indolizine-1-carboxamide

Elemental microanalysis: %, measured (theoretical)

%C=69.7(71.46);%H=4.43(4.73);%N=8.54(8.77)

High-resolution mass spectroscopy (ESI+):

Empirical formula: $C_{38}H_{30}N_4O_6$

$[M+H]^+$, calculated: 639.2238

$[M+H]^+$, measured: 639.2234

<u>Example 68.</u> *N*-(4-Hydroxyphenyl)-3-(2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(pyridin-4-yl)indolizine-1-carboxamide hydrochloride

Elemental microanalysis: %, measured (theoretical)

%C=71.97(72.25);%H=5.21(5.08);%N=8.99(9.11);%Cl-=5.32(5.76)

High-resolution mass spectroscopy (ESI+):

Empirical formula: $C_{37}H_{30}N_4O_3$

$[M+H]^+$, calculated: 579.2391

$[M+H]^+$, measured: 579.2403

<u>Example 69.</u> *N*-(4-Hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-3-(6-{[(3*R*)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide hydrochloride

Elemental microanalysis: %, measured (theoretical)

%C=67.63(68.06);%H=5.27(5.95);%N=10.08(10.13);%Cl-=4.53(4.27)

High-resolution mass spectroscopy (ESI+):

Empirical formula: $C_{47}H_{48}N_6O_6$

$[M+H]^+$, calculated: 793.3708

$[M+H]^+$, measured: 793.3704

<u>Example 70.</u> *N*-(4-Hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)indolizine-1-carboxamide

<u>Step A:</u> N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-3-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)indolizine-1-carboxamide

The title product is obtained in accordance with the process of Step A of Example 86, replacing the compound of Preparation 36" with that of Preparation 35".

LCMS: $[M+H]^+$ = 791.4 vs. 791.3 calculated

<u>Step B</u>: N-(4-Hydroxyphenyl)-3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)indolizine-1-carboxamide

The procedure is in accordance with a protocol analogous to that described in Step D of Example 1. The product thereby obtained is subjected to a step of conversion into a salt in the presence of HCl in ether.

IR (ATR) cm^{-1}: 2500 to 3000 ν -OH, 1614 ν >C=O amides, 1236 ν >C-O-C<,
740 γ >CH-Ar

Elemental microanalysis: %, measured (theoretical)

%C=71.07(70.99);%H=4.45(4.77);%N=12.37(12.42)

High-resolution mass spectroscopy (ESI+):

Empirical formula: $C_{40}H_{32}N_6O_5$

$[M+H]^+$, calculated: 677.2507

$[M+H]^+$, measured: 677.2510

Example 71. 4-[(4-Hydroxyphenyl){[3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizin-1-yl]carbonyl}amino]-1-methyl-pyridinium chloride

Step A: 4-[(4-Hydroxyphenyl){[3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}-1,3-benzodioxol-5-yl)indolizin-1-yl]carbonyl}amino]-1-methyl pyridinium iodide

The compound of Example 21 (311 mg, 0.5 mmol) is dissolved in dichloromethane and washed with saturated aqueous sodium hydrogen carbonate solution. After drying the organic phase over magnesium sulphate and evaporating to dryness, the residue is dissolved in ethanol (30 mL). Methyl iodide (45 µL, 0.7 mmol) is then added and the reaction mixture is heated to 40°C. The solution thereby obtained is evaporated to dryness. The crude reaction product is purified over a silica gel column using dichloromethane and methanol as solvents. The compound is obtained in the form of a white powder which is used directly in the next Step.

^{1}H NMR (500 MHz, dmso-d6) δ ppm: 9.95 (bs, 1 H), 8.6-8.45 (m, 2 H), 8.35-8.05 (several m, 1 H), 8.3-8 (several m, 1 H), 7.45-6.7 (several m, 8 H), 7.4-6.9 (several m, 4 H), 6.45-6.3 (several s, 1 H), 6.45-6.3 (m, 2 H), 6.15 (s, 2 H), 5.05-3.55 (several d, 2 H), 4.75/3.8 (m+m, 1 H), 4.15 (2*s, 3 H), 2.95-2.1 (several m, 2 H), 1-0.15 (several m, 3 H)

Step B: 4-[(4-Hydroxyphenyl){[3-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}-1,3-benzodioxol-5-yl)indolizin-1-yl]carbonyl}amino]-1-methyl pyridinium chloride

The compound of the preceding Step (320 mg, 0.42 mmol) is dissolved in methanol (20 mL), and then silver carbonate (173 mg, 0.628 mmol) is added, in portions, over 10 minutes. The resulting suspension is stirred for 1 hour at ambient temperature; the precipitate is filtered off and washed with methanol. The filtrate is concentrated to dryness, and then treated with 50 mL of 2N hydrochloric acid solution, heated at 60°C for 30 minutes and then evaporated to dryness. The final product is obtained after purification over a silica C18 column using a 0.1 % hydrochloric acid solution and acetonitrile as solvents. The title compound is obtained in the form of a white powder which is lyophilised in a mixture of water/acetonitrile.

IR (ATR) cm^{-1}: 3388 ν -OH phenol, 1650 + 1627 ν >C=O amides

High-resolution mass spectroscopy (ESI+):
Empirical formula: $C_{39}H_{33}N_4O_5$
$[M]^+$, calculated = 637.2445.
$[M]^+$, measured = 637.2431

The compounds of Examples 72, 73, 77, 78-80, 84 and 85 are synthesised in accordance with the process of Example 3 using the acid of Preparation 7, the appropriate 1,2,3,4-tetrahydroisoquinoline or the appropriate compound obtained in accordance with one of Preparations 1' to 7', and the suitable NHR_3R_4 amine.

Example 72. ***N*-(4-Hydroxyphenyl)-*N*-methyl-6-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazine-8-carboxamide**

LC/MS ($C_{33}H_{32}N_4O_5$) 565 $[M+H]^+$; RT 1.47 (Method B), it being understood that RT denotes retention time

Example 73. ***N*-Ethyl-*N*-(4-hydroxyphenyl)-6-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazine-8-carboxamide**

LC/MS ($C_{34}H_{34}N_4O_5$) 579 $[M+H]^+$; RT 1.55 (Method B)

Example 74. **3-[6-(3,4-Dihydroisoquinolin-2(1*H*)-ylcarbonyl)-1,3-benzodioxol-5-yl]-*N*-(4-hydroxyphenyl)-*N*-methyl-5,6,7,8-tetrahydroindolizine-1-carboxamide**

LC/MS ($C_{33}H_{31}N_3O_5$) 550 $[M+H]^+$; RT 1.24 (Method B)

Example 75. **3-[6-(3,4-Dihydroisoquinolin-2(1*H*)-ylcarbonyl)-1,3-benzodioxol-5-yl]-*N*-ethyl-*N*-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide**

LC/MS ($C_{34}H_{33}N_3O_5$) 564 $[M+H]^+$; RT 1.30 (Method B)

<u>Example 76.</u> *N*-Butyl-3-[6-(3,4-dihydroisoquinolin-2(1*H*)-ylcarbonyl)-1,3-benzodioxol-5-yl]-*N*-(4-hydroxyphenyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide

LC/MS ($C_{36}H_{37}N_3O_5$) 592 $[M+H]^+$; RT 1.39 (Method B)

<u>Example 77.</u> *N*-Ethyl-*N*-(4-hydroxyphenyl)-6-(6-{[(3*S*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide

LC/MS ($C_{34}H_{34}N_4O_5$) 579 $[M+H]^+$; RT 1.50 (Method B)

<u>Example 78.</u> *N*,*N*-Dibutyl-6-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide

LC/MS ($C_{34}H_{42}N_4O_4$) 571 $[M+H]^+$; RT 1.79 (Method B)

<u>Example 79.</u> *N*-Butyl-*N*-(4-hydroxyphenyl)-6-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide

LC/MS ($C_{36}H_{38}N_4O_5$) 607 $[M+H]^+$; RT 1.65 (Method B)

<u>Example 80.</u> *N*-(4-Hydroxyphenyl)-6-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(propan-2-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide

LC/MS ($C_{35}H_{36}N_4O_5$) 593 $[M+H]^+$; RT 1.58 (Method B)

<u>Example 81.</u> *N*-(4-Hydroxyphenyl)-*N*-methyl-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide

LC/MS ($C_{34}H_{33}N_3O_5$) 564 $[M+H]^+$; RT 2.48 (Method A)

<u>Example 82.</u> *N*-(4-Hydroxyphenyl)-*N*-methyl-3-(6-{[(3*S*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide

LC/MS ($C_{34}H_{33}N_3O_5$) 564 $[M+H]^+$; RT 2.55 (Method A)

<u>Example 83.</u> 3-[6-(3,4-Dihydroisoquinolin-2(1*H*)-ylcarbonyl)-1,3-benzodioxol-5-yl]-*N*-(4-hydroxyphenyl)-*N*-methylindolizine-1-carboxamide

LC/MS ($C_{33}H_{27}N_3O_5$) 546 $[M+H]^+$; RT 2.40 (Method A)

<u>Example 84.</u> 6-[6-(3,4-Dihydroisoquinolin-2(1*H*)-ylcarbonyl)-1,3-benzodioxol-5-yl]-*N*-(4-hydroxyphenyl)-*N*-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide

LC/MS ($C_{32}H_{30}N_4O_5$) 551 $[M+H]^+$; RT 1.45 (Method B)

<u>Example 85.</u> 6-[6-(3,4-Dihydroisoquinolin-2(1*H*)-ylcarbonyl)-1,3-benzodioxol-5-yl]-*N*-ethyl-*N*-(4-hydroxyphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxamide

LC/MS ($C_{33}H_{32}N_4O_5$) 565 $[M+H]^+$; RT 1.49 (Method B)

<u>Example 86.</u> *N*-(4-Hydroxyphenyl)-3-[6-[(3*R*)-3-methyl-3,4-dihydro-1*H*-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-*N*-(3-methylpyrazolo[1,5-*a*]pyrimidin-6-yl)-indolizine-1-carboxamide hydrochloride

<u>Step A:</u> N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-3-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(3-methylpyrazolo[1,5-a]pyrimidin-6-yl)indolizine-1-carboxamide

To a solution of 0.6 g of 3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizine-1-carboxylic acid (1.3 mmol) in 6 mL of dichloroethane there is added 0.18 mL of 1-chloro-*N,N*,2-trimethyl-prop-1-en-1-amine (2 mmol). The reaction mixture is stirred at ambient temperature for 2 hours and there is then added 0.8 g of the compound of Preparation 36" (2.2 mmol). The batch is refluxed for 20 hours and is then cooled and diluted with a mixture of dichloromethane and saturated $NaHCO_3$

solution. After separation of the phases, the organic phase is dried over $MgSO_4$ and concentrated to dryness. The crude product thereby obtained is purified by chromatography over silica gel (dichloromethane/methanol gradient).

LC/MS: $[M+H]^+$ = 791.4 vs. 791.3 calculated

Step B: N-(4-Hydroxyphenyl)-3-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(3-methylpyrazolo[1,5-a]pyrimidin-6-yl)indolizine-1-carboxamide hydrochloride

The procedure is in accordance with a protocol analogous to that described in Step D of Example 1. The product thereby obtained is subjected to a step of conversion into a salt in the presence of HCl in ether.

IR (ATR) cm^{-1}: 2500 to 3000 ν -OH, 1614 ν >C=O amides, 1236 ν >C-O-C<, 740 γ >CH-Ar

High-resolution mass spectroscopy (ESI+):

Empirical formula: $C_{40}H_{32}N_6O_5$

$[M+H]^+$, calculated: 677.2507

$[M+H]^+$, measured: 677.2506

PHARMACOLOGICAL STUDY

EXAMPLE A: Inhibition of Bcl-2 by the fluorescence polarisation technique

The fluorescence polarisation tests were carried out on microplates (384 wells). The Bcl-2 protein, labelled (histag-Bcl-2 such that Bcl-2 corresponds to the UniProtKB® primary accession number: P10415), at a final concentration of 2.50×10^{-8} M, is mixed with a fluorescent peptide (Fluorescein-REIGAQLRRMADDLNAQY), at a final concentration of 1.00×10^{-8} M in a buffer solution (Hepes 10 mM, NaCl 150 mM, Tween20 0.05%, pH 7.4), in the presence or absence of increasing concentrations of test compounds. After incubation for 2 hours, the fluorescence polarisation is measured.
The results are expressed in IC_{50} (the concentration of compound that inhibits fluorescence polarisation by 50 %) and are presented in Table 1 below.

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 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.

The results show that the compounds of the invention are cytotoxic.

Table 1: IC_{50} of Bcl-2 inhibition (fluorescence polarisation test) and of cytotoxicity for RS4;11 cells

	IC_{50} (nM) Bcl-2 FP	IC_{50} (nM) MTT RS4;11		IC_{50} (nM) Bcl-2 FP	IC_{50} (nM) MTT RS4;11
Example 1	17.9	11.3	**Example 29**	19.0	163
Example 2	17.0	36	**Example 30**	10.4	52.3
Example 3	33.6	66.5	**Example 31**	5.4	13.7
Example 4	56.4	251	**Example 32**	5.0	32.7
Example 5	55.9	416	**Example 33**	4.6	6.33
Example 6	60.3	161	**Example 34**	5.6	27.3
Example 7	46.4	108	**Example 35**	15.1	62.2
Example 8	24.5	20.5	**Example 36**	12.6	49.7
Example 9	40.6	780	**Example 37**	2.9	24.7
Example 10	24.7	439	**Example 38**	4.6	9.52
Example 11	10.9	83.7	**Example 39**	4.6	26.3
Example 12	10.4	116	**Example 40**	6.0	49
Example 13	5.8	33.65	**Example 41**	41.5	294
Example 14	3.7	7.6	**Example 42**	5.1	57.6
Example 15	5.7	166	**Example 43**	4.8	26
Example 16	7.5	252	**Example 44**	2.9	8.56
Example 17	3.4	11.8	**Example 45**	3.8	63.8
Example 18	7.5	47.7	**Example 46**	4.1	27.9
Example 19	8.0	235	**Example 47**	4.3	90.1
Example 20	11.1	205	**Example 48**	3.6	24.7
Example 21	4.6	25.3	**Example 49**	3.7	84.7
Example 22	12.9	263	**Example 50**	2.2	28.2
Example 23	3.8	9.99	**Example 51**	4.8	68.8
Example 24	6.2	28.4	**Example 52**	7.9	20.9
Example 25	7.9	30	**Example 53**	5.4	70.9
Example 26	16.6	300	**Example 54**	6.6	45
Example 27	7.7	44.1	**Example 55**	5.5	22.8
Example 28	8.8	112	**Example 56**	4.7	36.7

	IC_{50} (nM) Bcl-2 FP	IC_{50} (nM) MTT RS4;11		IC_{50} (nM) Bcl-2 FP	IC_{50} (nM) MTT RS4;11
Example 57	21.2	282	**Example 72**	90.2	1520
Example 58	6.4	68.5	**Example 73**	83.6	1320
Example 59	4.0	21.2	**Example 74**	68.7	1340
Example 60	5.4	60.3	**Example 75**	67.7	1360
Example 61	7.0	61.3	**Example 76**	77.6	1630
Example 62	5.6	96.6	**Example 77**	25.1% @10 µM	1880
Example 63	6.2	25.4	**Example 78**	823.3	1880
Example 64	7.8	282	**Example 79**	99.1	1010
Example 65	5.3	62.8	**Example 80**	299.3	1880
Example 66	4.7	42	**Example 81**	12.1	778
Example 67	ND	ND	**Example 82**	42% @10 µM	1880
Example 68	8.3	82.4	**Example 83**	35.8	1500
Example 69	4.6	1.38	**Example 84**	524.9	ND
Example 70	5.2	6.17	**Example 85**	242.7	ND
Example 71	49	ND	**Example 86**	5	20.1

ND: not determined

For partial inhibitors, the percentage fluorescence polarisation inhibition for a given concentration of the test compound is indicated. Accordingly, 25.1% @10 µM means that 25.1 % fluorescence polarisation inhibition is observed for a concentration of test compound equal to 10 µM.

EXAMPLE C: Induction of caspase activity *in vivo*.

The ability of the compounds of the invention to activate caspase 3 is evaluated in a xenograft model of RS4;11 leukaemia cells.

$1x10^7$ 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 lysates.

This enzymatic measurement is carried out by assaying the appearance of a fluorigenic 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 control mice.

The results obtained show that the compounds of the invention are capable of inducing apoptosis in RS4;11 tumour cells *in vivo*.

EXAMPLE D: Quantification of the cleaved form of caspase 3 *in vivo*.

The ability of the compounds of the invention to activate caspase 3 is evaluated in a xenograft model of RS4;11 leukaemia cells.
$1x10^7$ 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 (after a time period T) and lysed, and the cleaved (activated) form of caspase 3 is quantified in the tumour 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.

The results show that the compounds of the invention are capable of inducing apoptosis in RS4;11 tumour cells *in vivo*.

Table 2: Caspase activation factors (cleaved caspase 3 MSD test in the tumours of treated mice versus control mice) *in vivo*, after treatment by the oral route (exact doses in brackets)

Compound tested	Time period after which the tumour is removed (T)	Activation factor ± SEM (versus control)
Example 2	6 hours	14.6 (50 mg/kg)
Example 13	2 hours	23.1 (50 mg/kg)
Example 17	2 hours	15.3 (50 mg/kg)
Example 21	2 hours	24.8 ± 1.4 (50 mg/kg)
Example 32	2 hours	54.4 ± 2.8 (25 mg/kg)
Example 33	2 hours	31.1 ± 10.8 (25 mg/kg)
Example 38	2 hours	27.5 ± 2.6 (25 mg/kg)
Example 39	2 hours	34.1 ± 2.4 (25 mg/kg)
Example 42	2 hours	77.5 ± 4.8 (25 mg/kg)
Example 50	2 hours	45.2 ± 3.9 (25 mg/kg)
Example 56	2 hours	10.3 ± 4.2 (25 mg/kg)

EXAMPLE E: Anti-tumour activity *in vivo*

The anti-tumour activity of the compounds of the invention is evaluated in a xenograft model of RS4;11 leukaemia cells.

1×10^7 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^3, the mice are treated orally with the various compounds in two 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.

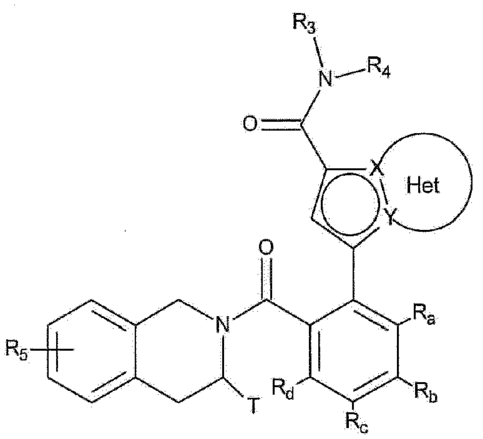
The results obtained accordingly show that the compounds of the invention are capable of inducing significant tumour regression during the treatment period.

EXAMPLE F: Pharmaceutical composition: Tablets

1000 tablets containing a dose of 5 mg of a compound selected from Examples 1 to 86	5 g
Wheat starch	20 g
Maize starch	20 g
Lactose	30 g
Magnesium stearate	2 g
Silica	1 g
Hydroxypropylcellulose	2 g

Patentkrav

1. Forbindelse med formel (I):

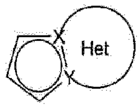


(I)

hvor:

X og Y repræsenterer et carbonatom eller et nitrogenatom, idet det forstås, at de ikke samtidigt repræsenterer to carbonatomer eller to nitrogenatomer,

◆ gruppens Het-gruppe



repræsenterer en eventuelt substitueret, aromatisk eller ikke-aromatisk ring, som er sammensat af 5, 6 eller 7 ringmedlemmer, der, udover nitrogenet, som er repræsenteret ved X eller Y, kan indeholde fra et til 3 heteroatomer, der er udvalgt uafhængigt af oxygen, svovl og nitrogen, idet det forstås, 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, hvori alk er en lineær eller forgrenet (C_1-C_6)-alkylgruppe,

◆ T repræsenterer et hydrogenatom, en lineær eller forgrenet (C_1-C_6)-alkylgruppe, der eventuelt er substitueret med fra et til tre halogenatomer, en gruppe (C_2-C_4)-alkyl-NR_1R_2, eller en gruppe (C_1-C_4)-alkyl-OR_6,

◆ R_1 og R_2 repræsenterer uafhængigt af hinanden et hydrogenatom eller en lineær eller forgrenet (C_1-C_6)-alkylgruppe, eller R_1 og R_2 danner med nitrogenatomet, der bærer dem, en heterocycloalkyl,

◆ R_3 repræsenterer en lineær (C_1-C_6)-alkylgruppe, en arylgruppe eller en heteroarylgruppe, idet er det muligt for de to sidste grupper at være substitueret med fra en til tre grupper, der er valgt blandt halogen, lineær eller forgrenet (C_1-C_6)-alkyl, lineær eller forgrenet (C_1-C_6)-alkoxy og cyano, idet det forstås, at et eller flere af carbonatomerne i de foregående grupper eller af deres mulige substituenter kan være deutereret,

◆ R_4 repræsenterer en 4-hydroxyphenylgruppe, idet det forstås, at et eller flere af carbonatomerne i den foregående gruppe eller af dets mulige substituenter kan være deutereret,

◆ R_5 repræsenterer et hydrogen eller halogenatom, en lineær eller forgrenet (C_1-C_6)-alkylgruppe, eller en lineær eller forgrenet (C_1-C_6)-alkoxygruppe,

◆ R_6 repræsenterer et hydrogenatom eller en lineær eller forgrenet (C_1-C_6)-alkylgruppe,

◆ R_a og R_d repræsenterer hver et hydrogenatom og (R_b, R_c) danner sammen med carbonatomerne, der bærer dem, en 1,3-dioxolangruppe eller en 1,4-dioxangruppe, eller R_a, R_c og R_d repræsenterer hver et hydrogenatom og R_b repræsenterer et hydrogen, et halogen, en methyl eller en methoxy eller R_a, R_b og R_d repræsenterer hver et hydrogenatom og R_c repræsenterer en hydroxygruppe eller en methoxygruppe,

det forstås at:

"aryl" betyder en phenyl-, naphthyl-, biphenyl- eller indenylgruppe,

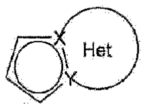
- "heteroaryl" betyder enhver mono- eller bicyklisk gruppe, der er sammensat af fra 5 til 10 ringmedlemmer, som har mindst en aromatisk del og som indeholder fra 1 til 4 heteroatomer, der er udvalgt blandt oxygen, svovl og nitrogen (herunder kvaternære nitrogener)

- "cycloalkyl" betyder enhver mono- eller bicyklisk, ikke-aromatisk, carbocyklisk gruppe, der indeholder fra 3 til 10 ringmedlemmer,

- "heterocycloalkyl" betyder en hvilken som helst mono- eller bicyklisk, ikke-aromatisk, kondenseret eller spirogruppe, der er sammensat af 3 til 10 ringmedlemmer og som indeholder fra 1 til 3 heteroatomer, der er valgt blandt oxygen, svovl, SO, SO_2 og nitrogen,

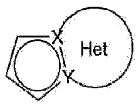
det er muligt for aryl-, heteroaryl-, cycloalkyl- og heterocycloalkylgrupperne, der er defineret således, og grupperne alkyl, alkenyl, alkynyl og alkoxy at være substitueret med fra 1 til 3 grupper, som er valgt blandt lineære eller forgrenede

(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 *N*-oxid, hvor det er hensigtsmæssigt), nitro, cyano, -COOR', -OCOR', NR'R", lineær eller forgrenet (C_1-C_6)-polyhalogenalkyl, trifluormethoxy, (C_1-C_6)-alkylsulfonyl, halogen, aryl, heteroaryl, aryloxy, arylthio, cycloalkyl, heterocycloalkyl, der eventuelt er substitueret med et eller flere halogenatomer eller alkylgrupper, idet det forstås, at R' og R" hver uafhængigt af hinanden repræsenterer et hydrogenatom eller en lineær eller forgrenet (C_1-C_6)-alkylgruppe, det er muligt for gruppens Het-gruppe



der er defineret i formel (I), at være substitueret med fra en til tre grupper, som er valgt blandt lineært eller forgrenet (C_1-C_6)-alkyl, hydroxy, lineært eller forgrenet (C_1-C_6)-alkoxy, $NR_1'R_1''$og halogen, idet det forstås, at R_1' og R_1'' er som defineret for grupperne R' og R" nævnt ovenfor,
deres enantiomerer og diastereoisomerer og additionssalte deraf med en farmaceutisk acceptabel syre eller base.

2. Forbindelse med formel (I) ifølge krav 1, hvor gruppen



repræsenterer en af følgende grupper: 5,6,7,8-tetrahydroindolizin, der eventuelt er substitueret med en aminogruppe; indolizin; 1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazin, der eventuelt er substitueret med en methyl; pyrrolo[1,2-*a*]-pyrimidin.

3. Forbindelse med formel (I) ifølge krav 1 eller 2, hvor T repræsenterer et hydrogenatom, en methylgruppe, en gruppe 2-(morpholin-4-yl)-ethyl, 3-(morpholin-4-yl) propyl, $-CH_2-OH$, 2-aminoethyl, 2-(3,3-difluoropiperidin-1-yl)-ethyl, 2-[(2,2-difluorethyl)-amino]-ethyl eller 2-(3-methoxyazetidin-1-yl)-ethyl.

4. Forbindelse med formel (I) ifølge et af kravene 1 til 3, hvor R_3 repræsenterer en heteroarylgruppe, der er valgt blandt følgende gruppe: 1*H*-indol, 2,3-dihydro-1*H*-indol, 1*H*-indazol, pyridin, 1*H*-pyrrolo[2,3-*b*]-pyridin, 1*H*-pyrazol, imidazo[l, 2-

a] pyridin, pyrazolo[1,5-*a*]-pyrimidin, [1,2,4]triazolo[1,5-*a*]-pyrimidin og 1*H*-pyrazolo-[3,4-*b*]-pyridin, som alle kan være substitueret med en lineær eller forgrenet (C_1-C_6)-alkylgruppe.

5. Forbindelser med formlen (I) ifølge krav 1, der er valgt blandt følgende gruppe:

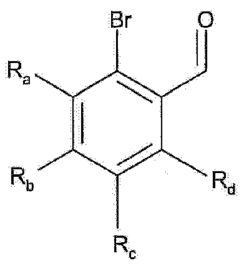
- *N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}-1,3-benzodioxol-5-yl)-*N*-{1-[2-(morpholin-4-yl)ethyl]-1*H*-indol-5-yl}-5,6,7,8-tetrahydroindolizin-1-carboxamid,
- *N*-(4-hydroxyphenyl)-3-(6-{[(3*S*)-3-[2-(moipholin-4-yl)ethyl]-3,4-dihydro-isoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizin-1-carboxamid,
- *N*-{3-fluor-4-[2-(morpholin-4-yl)ethoxy]phenyl}-*N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizin-1-carboxamid,
- *N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-4-yl)indolizin-1-carboxamid,
- *N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*) -yl]-carbonyl} -1,3-benzodioxol-5-yl) -*N*-(2-methylpyridin-4-yl)indolizin-1-carboxamid,
- *N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-1*H*-pynolo[2,3-*b*]pyridin-5-yl)-indolizin-1-carboxamid,
- *N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizin-1-carboxamid,
- *N*-(2,6-dimethylpyridin-4-yl)-*N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizin-1-carboxamid,
- *N*-(4-hydroxyphenyl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-4-yl)-5,6,7,8-tetrahydroindolizin-1-carboxamid,

3- (5-chlor-2-{[(3*R*}-3-methyl-3,4-dihydroisoquinolin-2(1*H)*-yl]carbonyl} phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)indolizin-1-carboxamid,

- *N*-(4-hydroxyphenyl)-*N*-(2-methoxypyridin-4-yl)-3-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)indolizin-1-carboxamid,

deres enantiomerer og diastereoisomerer og additionssalte deraf med en farmaceutisk acceptabel syre eller base.

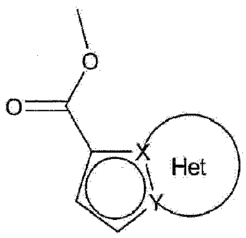
6. Fremgangsmåde til fremstilling af forbindelser med formlen (I) ifølge krav 1, kendetegnet ved, at der som udgangsmateriale anvendes forbindelsen med formel (II):



(II)

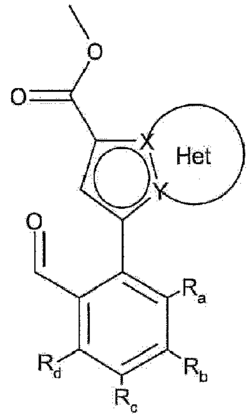
hvor R_a, R_b, R_c og R_d er som defineret for formel (I),

hvilken forbindelse med formel (II) udsættes for en Heck-reaktion i et vandigt eller organisk medium i nærvær af en palladiumkatalysator, af en base, af en phosphin og af forbindelsen med formel (III):



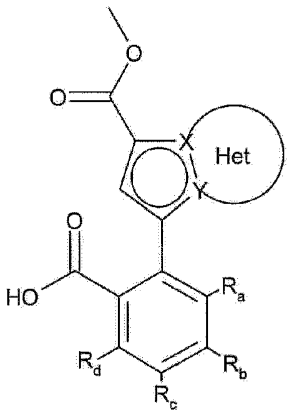
(III)

hvor grupperne X, Y og Het er som defineret for formel (I), for at opnå forbindelsen med formel (IV):



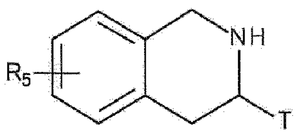
(IV)

hvor R_a, R_b, R_c, R_d, X, Y og Het er som defineret for formel (I), hvilken aldehydfunktion af forbindelse med formlen (IV) oxideres til en carboxylsyre for at danne forbindelsen med formel (V):



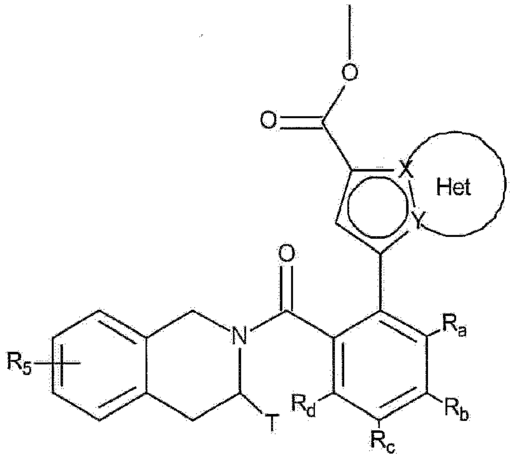
(V)

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 peptidkobling med en forbindelse med formel (VI):



(VI)

hvor T og R_5 er som defineret for formel (I), for at give forbindelsen med formel (VII):



(VII)

hvor R_a, R_b, R_c, R_d, T, R_5, X, Y og Het er som defineret for formel (I), hvilken esterfunktion af forbindelsen med formlen (VII) hydrolyseres for at opnå den tilsvarende carboxylsyre eller carboxylat, som kan omdannes til et syrederivat, såsom det tilsvarende acylchlorid eller anhydrid, inden det kobles med en amin NHR_3R_4 hvor R_3 og R_4 har de samme betydninger som for formel (I), for at give forbindelsen med formel (I), hvilken forbindelse med formel (I) kan oprenses ifølge en konventionel separationsteknik, som om ønsket omdannes til dens additionssalte med en farmaceutisk acceptabel syre eller base, og som eventuelt er separeret i dets isomerer ifølge en konventionel separationsteknik, idet det forstås, at visse grupper (hydroxy, amino ...) af reagenserne eller mellemprodukter kan beskyttes, når det anses for passende i løbet af den ovenfor beskrevne fremgangsmåde, og derefter afbeskyttes ifølge syntesens behov.

7. Fremgangsmåde ifølge krav 6 til fremstilling af en forbindelse med formlen (I), hvor en af grupperne R_3 eller R_4 er substitueret med en hydroxyfunktion, kendetegnet ved, at aminen NHR_3R_4 på forhånd underkastes en reaktion, der beskytter hydroxyfunktionen, forud for enhver kobling med carboxylsyren, der er dannet ud fra forbindelsen med formlen (VII), eller med et tilsvarende syrederivat deraf, hvorefter den resulterende beskyttede forbindelse med formlen (I) underkastes en afbeskyttelsesreaktion og omdannes derefter eventuelt til et af dets additionssalte med en farmaceutisk acceptabel syre eller base.

8. Farmaceutisk sammensætning, der omfatter en forbindelse med formlen (I) ifølge et hvilket som helst af kravene 1 til 5 eller et additionssalt deraf med en farmaceutisk acceptabel syre eller base i kombination med et eller flere farmaceutisk acceptable excipienser.

9. Farmaceutisk sammensætning ifølge krav 8 til anvendelse som et pro-apoptotisk middel.

10. Farmaceutisk sammensætning ifølge krav 8 til anvendelse ved behandling af cancer, autoimmune sygdomme og immunsystemet.

11. Farmaceutisk sammensætning ifølge krav 8 til anvendelse til behandling af kræft i blære, hjerne, bryst og livmoder, kroniske lymfoide leukæmier, kolorektal cancer, esophagus og lever, lymfoblast leukæmier, ikke-Hodgkin lymfomer, melanomer, maligne hæmopatier, myelomer, ovariecancer, ikke-småcellet lungekræft, prostatacancer og småcellet lungekræft.

12. Forbindelse med formel (I) ifølge et af kravene 1 til 5, eller et additionssalt deraf med en farmaceutisk acceptabel syre eller base, til anvendelse ved behandling af kræft i blære, hjerne, bryst og livmoder, kroniske lymfoide leukæmier, kolorektal kræft i esophagus og lever, lymfoblast leukæmier, non-Hodgkin lymfomer, melanomer, maligne hæmopati, myelomer, ovariecancer, ikke-småcellet lungekræft, prostatacancer og småcellet lungekræft.

13. Forbindelse af en forbindelse med formlen (I) ifølge et hvilket som helst af kravene 1 til 5 med et anti-cancer middel, der er valgt blandt genotoksiske midler, mitotiske forgiftninger, antimetabolitter, proteasominhibitorer, kinaseinhibitorer og antistoffer.

14. Farmaceutisk sammensætning, der omfatter en forbindelse ifølge krav 13 i kombination med et eller flere farmaceutisk acceptable excipienser.

15. Forbindelse ifølge krav 13 til anvendelse ved behandling af cancer.

16. Forbindelse med formel (I) ifølge et hvilket som helst af kravene 1 til 5 til anvendelse i forbindelse med strålebehandling ved behandling af cancer.