

**NEW PYRROLE COMPOUNDS, A PROCESS FOR THEIR PREPARATION  
AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

The present invention relates to new pyrrole 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.

5 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  
10 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).

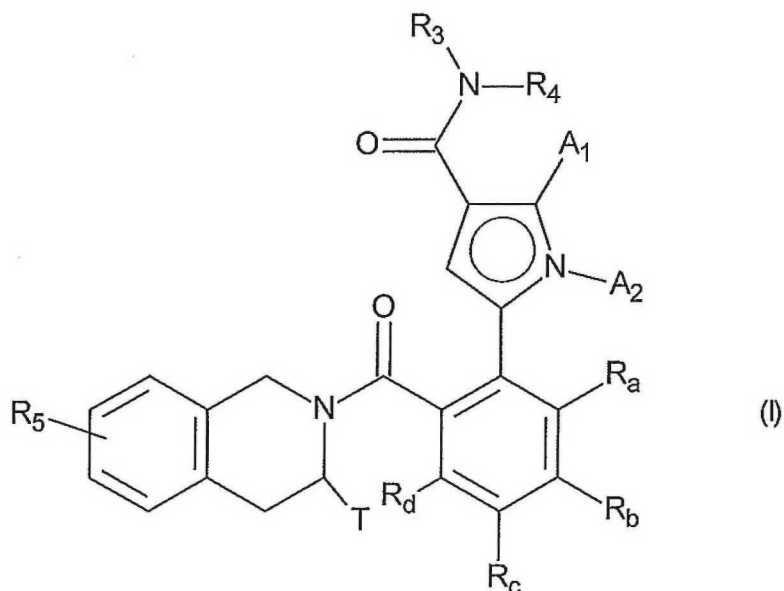
Deregulation of apoptosis is involved in certain pathologies. Increased apoptosis is associated with neurodegenerative diseases such as Parkinson's disease, Alzheimer's  
15 disease and ischaemia. Conversely, deficits in the implementation of apoptosis play a significant role in the development of cancers 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.  
20 The involvement of proteins of the Bcl-2 family is described in numerous types of cancer, such as colorectal cancer, breast cancer, small-cell lung cancer, non-small-cell lung cancer, bladder cancer, ovarian cancer, prostate cancer, chronic lymphoid leukaemia, follicular lymphoma, myeloma, etc. Overexpression of the anti-apoptotic proteins of the Bcl-2 family is involved in tumorigenesis, in resistance to chemotherapy and in the clinical  
25 prognosis of patients affected by cancer. There is, therefore, a therapeutic need for compounds that inhibit the anti-apoptotic activity of the proteins of the Bcl-2 family.

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):



wherein:

- 5        ♦ A<sub>1</sub> and A<sub>2</sub>, each independently of the other, represent a hydrogen or halogen atom, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)polyhaloalkyl group, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group or a cycloalkyl group,
- ♦ T represents a hydrogen atom, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group optionally substituted by from one to three halogen atoms, a group (C<sub>1</sub>-C<sub>4</sub>)alkyl-NR<sub>1</sub>R<sub>2</sub>, or a  
10       group (C<sub>1</sub>-C<sub>4</sub>)alkyl-OR<sub>6</sub>,
- ♦ R<sub>1</sub> and R<sub>2</sub>, each independently of the other, represent a hydrogen atom or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group, or R<sub>1</sub> and R<sub>2</sub> form with the nitrogen atom carrying them a heterocycloalkyl,
- 15       ♦ R<sub>3</sub> represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group, a linear or branched (C<sub>2</sub>-C<sub>6</sub>)alkenyl group, a linear or branched (C<sub>2</sub>-C<sub>6</sub>)alkynyl group, a cycloalkyl group, a (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)alkyl group wherein the alkyl moiety is linear or branched, a heterocycloalkyl group, an aryl group or a heteroaryl group, 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 an aryl group, a heteroaryl group, a cycloalkyl group or a linear or branched  $(C_1-C_6)$ alkyl group, it being understood that one or more of the carbon atoms of the preceding groups, or of their 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,
- ♦  $R_a, R_b, R_c$  and  $R_d$ , each independently of the others, represent  $R_7$ , a halogen atom, a linear or branched  $(C_1-C_6)$ alkoxy group, a hydroxy group, a linear or branched  $(C_1-C_6)$ polyhaloalkyl group, a trifluoromethoxy group,  $-NR_7R_7'$ , nitro,  $R_7-CO-(C_0-C_6)alkyl-$ ,  $R_7-CO-NH-(C_0-C_6)alkyl-$ ,  $NR_7R_7'-CO-(C_0-C_6)alkyl-$ ,  $NR_7R_7'-CO-(C_0-C_6)alkyl-O-$ ,  $R_7-SO_2-NH-(C_0-C_6)alkyl-$ ,  $R_7-NH-CO-NH-(C_0-C_6)alkyl-$ ,  $R_7-O-CO-NH-(C_0-C_6)alkyl-$ , a heterocycloalkyl group, or the substituents of one of the pairs  $(R_a, R_b)$ ,  $(R_b, R_c)$  or  $(R_c, R_d)$  form together with the carbon atoms carrying them a ring composed of from 5 to 7 ring members, which may contain from one to 2 hetero atoms selected from oxygen and sulphur, it also being understood that one or more carbon atoms of the ring defined hereinbefore may be deuterated or substituted by from one to 3 groups selected from halogen and linear or branched  $(C_1-C_6)alkyl$ ,
- ♦  $R_7$  and  $R_7'$ , each independently of the other, represent a hydrogen, a linear or branched  $(C_1-C_6)alkyl$ , a linear or branched  $(C_2-C_6)alkenyl$ , a linear or branched  $(C_2-C_6)alkynyl$ , an aryl or a heteroaryl, or  $R_7$  and  $R_7'$ , together with the nitrogen atom carrying them, form a heterocycle composed of from 5 to 7 ring members,

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 from 3 to 10 ring members and containing from 1 to 3 hetero atoms selected from oxygen, sulphur, SO, SO<sub>2</sub> 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 optionally substituted, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)spiro, optionally substituted, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl-S-, hydroxy, oxo (or *N*-oxide where appropriate), nitro, cyano, -COOR', -OCOR', NR'R'', linear or branched (C<sub>1</sub>-C<sub>6</sub>)polyhaloalkyl, trifluoromethoxy, (C<sub>1</sub>-C<sub>6</sub>)alkylsulphonyl, halogen, optionally substituted 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 an optionally substituted, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

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

Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, 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, A<sub>1</sub> represents a hydrogen atom or a methyl group.

Furthermore, A<sub>2</sub> preferably represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group optionally substituted by a group selected from halogen, hydroxy, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, NR'R'' and morpholine.



In another embodiment of the invention, A<sub>2</sub> represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)polyhaloalkyl group or a cyclopropyl group.

Even more preferably, A<sub>1</sub> and A<sub>2</sub> both represent a methyl group.

In a preferred embodiment of the invention, T represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl. In another preferred embodiment, T represents a group alkyl(C<sub>1</sub>-C<sub>4</sub>)-NR<sub>1</sub>R<sub>2</sub>, and more particularly a group alkyl(C<sub>1</sub>-C<sub>4</sub>)-NR<sub>1</sub>R<sub>2</sub> wherein R<sub>1</sub> and R<sub>2</sub> form with the nitrogen atom carrying them a heterocycloalkyl.

In preferred compounds of the invention, T represents a methyl, aminomethyl, (morpholin-4-yl)methyl, (4-methylpipérazin-1-yl)methyl, 2-(morpholin-4-yl)ethyl, [2-(morpholin-4-yl)ethoxy]methyl, hydroxymethyl, [2-(dimethylamino)ethoxy]methyl, hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl, 1-oxa-6-azaspiro[3.3]hept-6-ylmethyl, 3-(morpholin-4-yl)propyl or trifluoromethyl group. Even more preferably, T represents a (morpholin-4-yl)methyl, methyl or 3-(morpholin-4-yl)propyl group.

Preferably, R<sub>a</sub> and R<sub>d</sub> each represent a hydrogen atom and (R<sub>b</sub>,R<sub>c</sub>), together with the carbon atoms carrying them, form a 1,3-dioxolane group or a 1,4-dioxane group; or R<sub>a</sub>, R<sub>c</sub> and R<sub>d</sub> each represent a hydrogen atom and R<sub>b</sub> represents a hydrogen or halogen atom or a methoxy group. Even more preferably, R<sub>a</sub> and R<sub>d</sub> each represent a hydrogen atom and (R<sub>b</sub>,R<sub>c</sub>), together with the carbon atoms carrying them, form a 1,3-dioxolane group; or R<sub>a</sub>, R<sub>c</sub> and R<sub>d</sub> each represent a hydrogen atom and R<sub>b</sub> represents a halogen, preferably a chlorine or fluorine atom.

In another embodiment of the invention, R<sub>a</sub> and R<sub>d</sub> each represent a hydrogen atom, R<sub>b</sub> represents a hydrogen or halogen atom and R<sub>c</sub> a hydroxy or methoxy group, or: R<sub>a</sub> and R<sub>d</sub> each represent a hydrogen atom, R<sub>b</sub> represents a hydroxy or methoxy group and R<sub>c</sub> a halogen atom.

Alternatively, R<sub>a</sub>, R<sub>b</sub> and R<sub>d</sub> advantageously each represent a hydrogen atom and R<sub>c</sub> represents a group selected from R<sub>7</sub>-CO-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl-, R<sub>7</sub>-SO<sub>2</sub>-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl-, R<sub>7</sub>-

NH-CO-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl- and R<sub>7</sub>-O-CO-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl-. For those specific compounds, R<sub>3</sub> preferably represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl or a heteroaryl optionally substituted by a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, and R<sub>4</sub> represents a 4-hydroxyphenyl group. Even more preferably, R<sub>3</sub> represents a methyl.

- 5 Preferred R<sub>4</sub> groups are as follows: phenyl; 4-hydroxyphenyl; 3-fluoro-4-hydroxyphenyl; 2-hydroxypyrimidine; 3-hydroxypyridine. Even more preferably, R<sub>4</sub> represents a 4-hydroxyphenyl group.

In preferred compounds of the invention, R<sub>3</sub> represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group (preferably methyl), aryl or heteroaryl, all being optionally substituted. The groups  
10 aryl and heteroaryl are more especially preferred. Finally, R<sub>3</sub> preferably represents a group selected from phenyl, 1*H*-pyrazole, 1*H*-indole, 1*H*-indazole, pyridine, pyrimidine, 1*H*-pyrrolo[2,3-*b*]pyridine, 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine, 1*H*-benzimidazole, 1*H*-pyrrole, 1*H*-pyrrolo[2,3-*c*]pyridine, 1*H*-pyrrolo[3,2-*b*]pyridine, 5*H*-pyrrolo[3,2-*d*]pyrimidine, thiophene, pyrazine, 1*H*-pyrazolo[3,4-*b*]pyridine, 1,2-oxazole, and 1*H*-  
15 pyrazolo[1,5-*a*]pyrimidine, those groups optionally having one or more substituents selected from halogen, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, cyano, cyclopropyl, oxetane, tetrahydrofuran, -CO-O-CH<sub>3</sub>, trideuteriomethyl, 2-(morpholin-4-yl)ethyl and 2-(morpholin-4-yl)ethoxy. More preferably, R<sub>3</sub> represents a group 1-methyl-1*H*-pyrazol-4-yl, pyridin-4-yl, 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl, 5-  
20 cyano-1-methyl-1*H*-pyrrol-3-yl, 5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl, 1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl, 5-cyano-2-methyl-1-(trideuteriomethyl)-1*H*-pyrrol-3-yl.

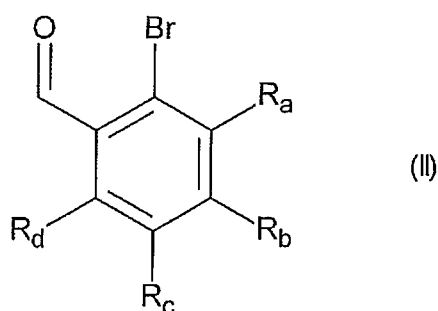
Preferred compounds according to the invention are included in the following group:

- 25 - 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide,  
- 5-(5-chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide,

- *N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide,
- 5      - *N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide,
- 5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide,
- 10      - 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide,
- 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide,
- 15      - 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1-methyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide,
- *N*-(5-cyano-1-methyl-1*H*-pyrrol-3-yl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide,
- 20      - 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide,
- 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide,
- 25      - *N*-(5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide,
- 30      - 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-[5-cyano-2-methyl-1-(trideuteriomethyl)-1*H*-pyrrol-3-yl]-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide,

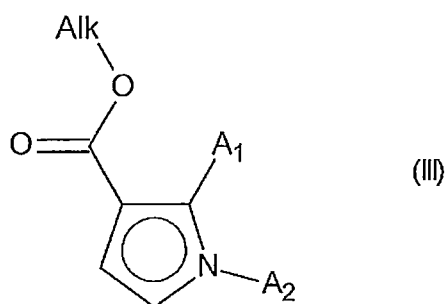
their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

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  
5 formula (II):



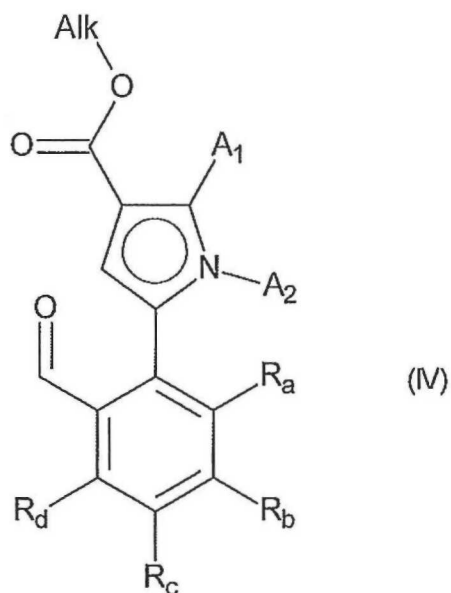
wherein R<sub>a</sub>, R<sub>b</sub>, R<sub>c</sub> and R<sub>d</sub> are as defined for formula (I),

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  
10 compound of formula (III):



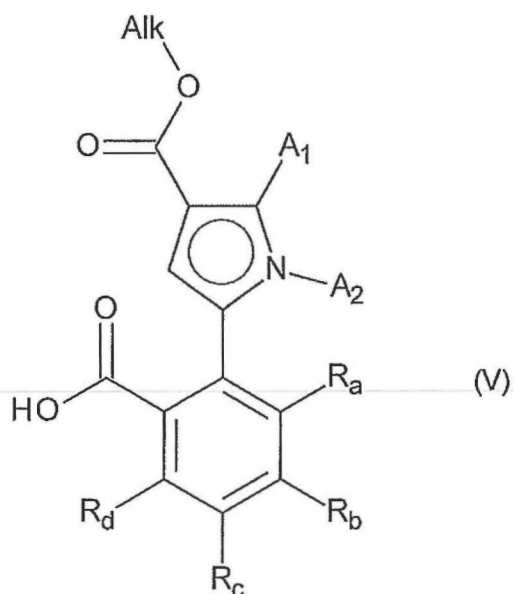
wherein the groups A<sub>1</sub> and A<sub>2</sub> are as defined for formula (I) and Alk represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl,

to obtain the compound of formula (IV):



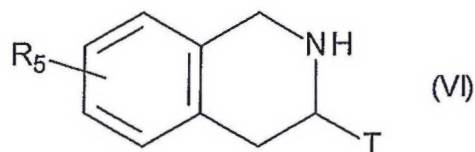
wherein  $A_1$ ,  $A_2$ ,  $R_a$ ,  $R_b$ ,  $R_c$  and  $R_d$  are as defined for formula (I) and Alk is as defined hereinbefore,

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



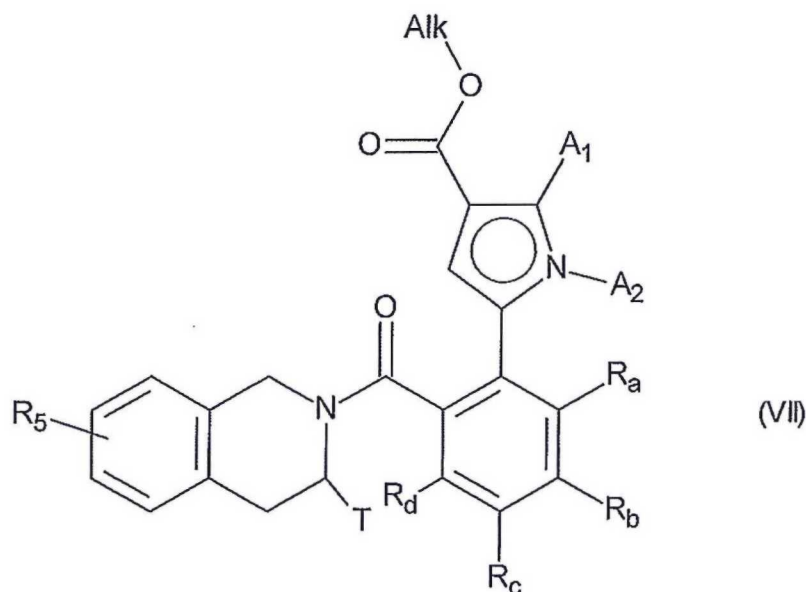
wherein  $A_1$ ,  $A_2$ ,  $R_a$ ,  $R_b$ ,  $R_c$  and  $R_d$  are as defined for formula (I) and Alk is as defined hereinbefore,

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



wherein T and R<sub>5</sub> are as defined for formula (I),

5 to yield the compound of formula (VII):



wherein A<sub>1</sub>, A<sub>2</sub>, R<sub>a</sub>, R<sub>b</sub>, R<sub>c</sub>, R<sub>d</sub>, T and R<sub>5</sub> are as defined for formula (I) and Alk is as defined hereinbefore,

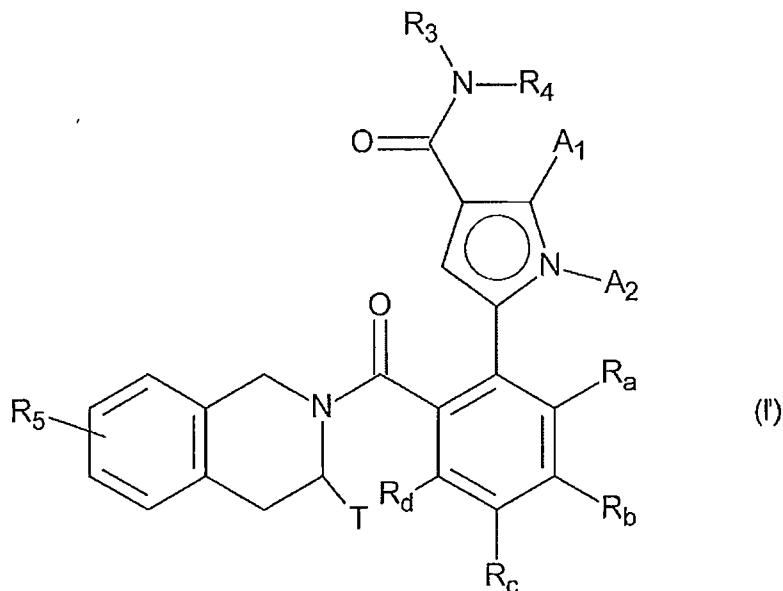
the ester function of which compound of formula (VII) is hydrolysed to yield the  
 10 corresponding carboxylic acid or carboxylate, which may be converted into an acid derivative such as the corresponding acyl chloride or anhydride before being coupled with an amine NHR<sub>3</sub>R<sub>4</sub> wherein R<sub>3</sub> and R<sub>4</sub> 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  
 15 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.

- 5 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  
10 of its addition salts with a pharmaceutically acceptable acid or base.

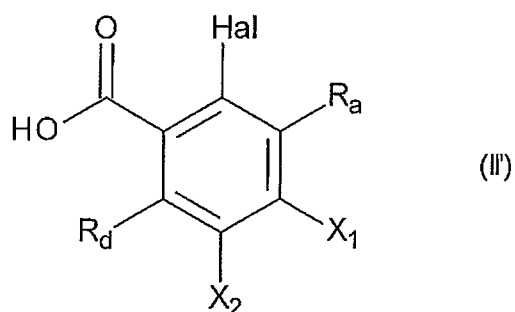
The present invention relates also to an alternative process for the preparation of compounds of formula (I'), which are particular cases of the compounds of formula (I) as defined hereinbefore:



15 wherein:

- $A_1$ ,  $A_2$ ,  $R_a$ ,  $R_d$ ,  $R_3$ ,  $R_4$ ,  $T$  and  $R_5$  are as defined for formula (I),
- $R_b$  and  $R_c$  are such that one represents a hydrogen and the other a group selected from  $R_7$ -CO-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl-,  $R_7$ -SO<sub>2</sub>-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl-,  $R_7$ -NH-CO-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl- and  $R_7$ -O-CO-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl-,

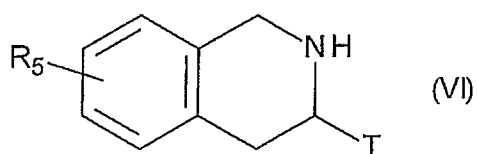
which preparation process uses as starting material a compound of formula (II'):



wherein:

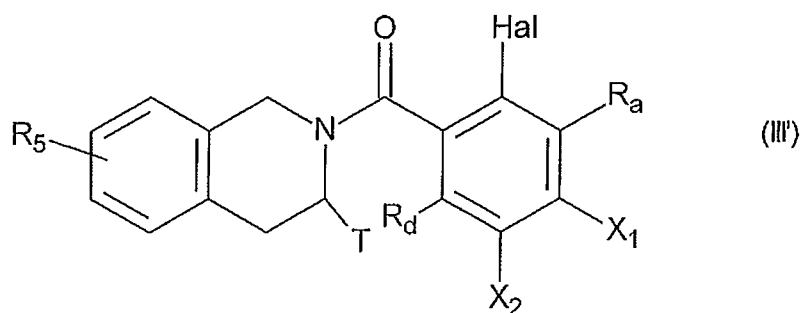
- R<sub>a</sub> and R<sub>d</sub> are as defined for formula (I),
- Hal represents a halogen atom,
- X<sub>1</sub> and X<sub>2</sub> are such that one represents a (C<sub>0</sub>-C<sub>6</sub>)alkyl-NH<sub>2</sub> group while the other represents a hydrogen atom,

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



wherein T and R<sub>5</sub> are as defined for formula (I),

to yield the compound of formula (III'):

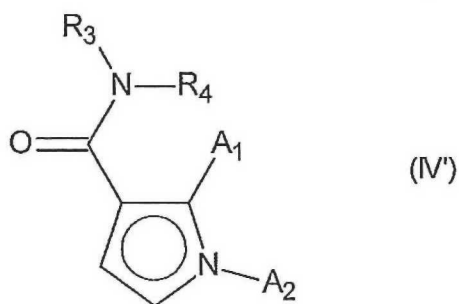




wherein:

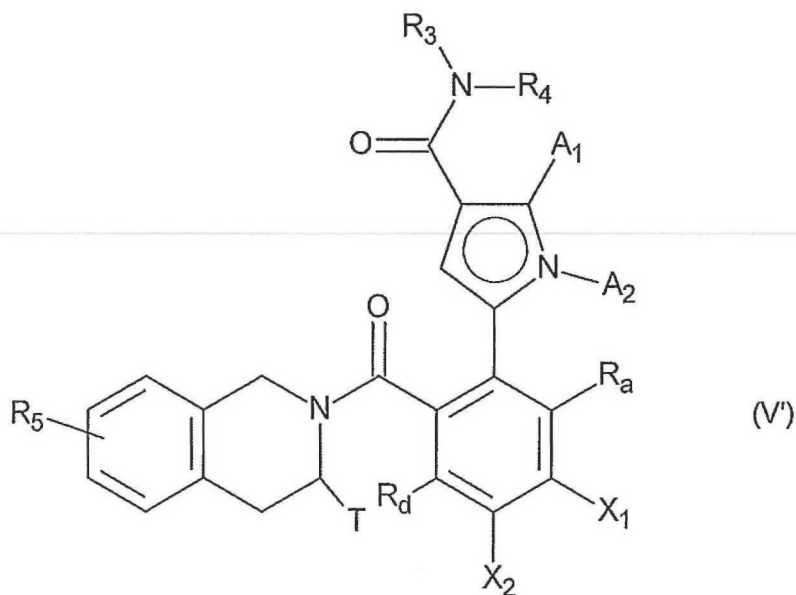
- $R_a$ ,  $R_d$ ,  $T$  and  $R_5$  are as defined for formula (I),
- Hal represents a halogen atom,
- $X_1$  and  $X_2$  are such that one represents a  $(C_0-C_6)alkyl-NH_2$  group while the other represents a hydrogen atom,

which compound of formula (III') 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 a compound of formula (IV'):



wherein  $A_1$ ,  $A_2$ ,  $R_3$  and  $R_4$  are as defined for formula (I),

to form the compound of formula (V'):



wherein:

- $A_1$ ,  $A_2$ ,  $R_a$ ,  $R_d$ ,  $R_3$ ,  $R_4$ ,  $T$  and  $R_5$  are as defined for formula (I),
- $X_1$  and  $X_2$  are such that one represents a  $(C_0-C_6)$ alkyl- $NH_2$  group while the other represents a hydrogen atom,

5      which compound of formula (V') is then subjected to an acylation or sulphonylation reaction to yield the compound of formula (I'),

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

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.

15      The compounds of formulae (II), (III), (II'), (IV'), (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.

20      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.

25      Among the cancer treatments envisaged there may be mentioned, without implying any limitation, cancers of the bladder, brain, breast and uterus, chronic lymphoid leukaemias, colorectal cancer, cancers of the oesophagus and liver, 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')<sub>2</sub>, 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.

**Preparation 1:**      **4-Chloro-2-[4-(ethoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]benzoic acid**

***Step A: Ethyl 1,2-dimethyl-1H-pyrrole-3-carboxylate***

To a solution of 10 g of ethyl 2-methyl-1H-pyrrole-3-carboxylate (65.3 mmol) and 8.95 mL (130.6 mmol) of methyl iodide in 70 mL of dimethylformamide placed at 0°C there are added, in three portions, 2.61 g (65.3 mmol) of sodium hydride (NaH) 60 %. The batch is then stirred at 0°C for 1 hour. Then, the reaction mixture is hydrolysed by the addition of 420 mL of ice-cold water. The reaction mixture is then diluted with ethyl acetate, successively washed with 0.1M aqueous hydrochloric acid (HCl) solution, saturated aqueous LiCl solution and then brine. The organic phase is then dried over MgSO<sub>4</sub>, filtered, concentrated to dryness and purified by chromatography over silica gel (petroleum ether/AcOEt gradient).

<sup>1</sup>H NMR: δ (400 MHz; dmso-d<sub>6</sub>; 300K): 6.65 (d, 1H pyrrole); 6.3 (1d, 1H pyrrole); 4.1 (1q, 2H, OCH<sub>2</sub>CH<sub>3</sub>); 3.5 (s, 3H N-pyrrole); 2.4 (s, 3H pyrrole); 1.5 (1t, 3H OCH<sub>2</sub>CH<sub>3</sub>)

IR: ν: >C=O: 1688 cm<sup>-1</sup>; ν: C-O-C: 1172 cm<sup>-1</sup>

***Step B: Ethyl 5-(5-chloro-2-formylphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxylate***

To a solution of 10.5 g of the compound obtained in Step A (62,8 mmol) in 65 mL of *N,N*-dimethylacetamide there are successively added 15.2 g of 2-bromo-4-chlorobenzaldehyde (69 mmol), 12.3 g of potassium acetate (125.6 mmol) and then the batch is stirred under argon for 20 minutes. There are then added 2.2 g of palladium catalyst PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (3.14 mmol). The reaction mixture is then heated at 130°C overnight. The mixture is allowed to return to ambient temperature and it is then diluted with dichloromethane. Animal charcoal is added (2 g per g of product) and the batch is stirred at ambient temperature for 1 hour and then filtered. The organic phase is then washed with water, dried over MgSO<sub>4</sub> and concentrated to dryness. The crude product thereby obtained is purified by chromatography over silica gel (petroleum ether/AcOEt gradient). The title product is obtained in the form of a solid.

<sup>1</sup>H NMR:  $\delta$  (400 MHz; dmso-d<sub>6</sub>; 300K): 9.8 (s, 1H, formyl); 7.91-7.69-7.61 (d, 3H, aromatic Hs); 6.5 (s, 1H pyrrole); 4.2 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>); 3.4 (s, 3H, CH<sub>3</sub>-N-pyrrole); 2.55 (s, 3H pyrrole); 1.28 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>)

**Step C: 4-Chloro-2-[4-(ethoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]benzoic acid**

5 A solution is prepared containing 12.85 g of the compound obtained in Step B (42 mmol) and 35.7 mL (336 mmol) of 2-methyl-2-butene in a mixture containing 20 mL of acetone and 20 mL of tetrahydrofuran. There are added, dropwise, 200 mL of an aqueous solution containing a mixture of 13.3 g of sodium chlorite (NaClO<sub>2</sub>) (147 mmol) and 14.5 g of sodium hydrogen phosphate (NaHPO<sub>4</sub>) (105 mmol). The batch is then vigorously stirred at  
10 ambient temperature for 7 hours. The reaction mixture is then concentrated to remove the acetone. Ethyl acetate is added, and the organic phase is washed with water, dried over MgSO<sub>4</sub> and then concentrated to dryness. The residue is then taken up in a minimum of ethyl ether. The solid then obtained is filtered off, washed with ether and then dried *in vacuo* at 40°C overnight. The title product is obtained in the form of a solid, which is  
15 subsequently used without being otherwise purified.

<sup>1</sup>H NMR:  $\delta$  (400 MHz; dmso-d<sub>6</sub>; 300K): 13 (m, 1H COOH); 7.85-7.6-7.41(d,dd, wd, 3H, aromatic Hs); 6.3 (s, 1H, H pyrrole); 4.15 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>); 3.25 (s, 3H, CH<sub>3</sub>-N-pyrrole); 2.5 (s, 3H, CH<sub>3</sub>-pyrrole); 1.25 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>)

IR:  $\nu$ : -OH: 3100-2500 cm<sup>-1</sup> acid;  $\nu$ : >C=O: 1681 cm<sup>-1</sup> ester + acid

20 **Preparation 2:**      **2-[4-(Ethoxycarbonyl)-1-methyl-1H-pyrrol-2-yl]benzoic acid**

The procedure is in accordance with the process of Preparation 1, replacing, on the one hand, the ethyl 2-methyl-1H-pyrrole-3-carboxylate used in Step A by ethyl 1H-pyrrole-3-carboxylate and, on the other hand, the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-benzaldehyde.

25 **Preparation 3:**      **4-Chloro-2-[4-(ethoxycarbonyl)-1-methyl-1H-pyrrol-2-yl]benzoic acid**

The procedure is in accordance with the process of Preparation 1, replacing the ethyl 2-methyl-1H-pyrrole-3-carboxylate used in Step A by ethyl 1H-pyrrole-3-carboxylate.

**Preparation 4:** 6-[4-(Ethoxycarbonyl)-1-methyl-1*H*-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the process of Preparation 1, replacing, on the one hand, the ethyl 2-methyl-1*H*-pyrrole-3-carboxylate used in Step A by ethyl 1*H*-pyrrole-3-carboxylate and, on the other hand, the 2-bromo-4-chlorobenzaldehyde used in Step B by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

**IR:**  $\nu$ : -OH: 3500-2300  $\text{cm}^{-1}$  acid;  $\nu$ :  $\text{>C=O}$ : 1688-1670  $\text{cm}^{-1}$  ester + acid

**Preparation 5:** 4-Chloro-2-[4-(ethoxycarbonyl)-1-ethyl-1*H*-pyrrol-2-yl]benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A, on the one hand, the ethyl 2-methyl-1*H*-pyrrole-3-carboxylate by ethyl 1*H*-pyrrole-3-carboxylate and, on the other hand, the methyl iodide by ethyl iodide (see the protocol described in US 6,258,805 B1).

**Preparation 6:** 4-Chloro-2-[1-cyclopropyl-4-(ethoxycarbonyl)-1*H*-pyrrol-2-yl]benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A, on the one hand, the ethyl 2-methyl-1*H*-pyrrole-3-carboxylate by ethyl 1*H*-pyrrole-3-carboxylate and, on the other hand, the methyl iodide by cyclopropylboronic acid (see the protocol described in Bénard S. *et al*, Journal of Organic Chemistry 73(16), 6441-6444, 2008).

**Preparation 7:** 4-Chloro-2-[4-(ethoxycarbonyl)-1-(propan-2-yl)-1*H*-pyrrol-2-yl]-benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A, on the one hand, the ethyl 2-methyl-1*H*-pyrrole-3-carboxylate by ethyl 1*H*-pyrrole-3-carboxylate and, on the other hand, the methyl iodide by isopropyl iodide (see the protocol described in Okada E. *et al*, Heterocycles 34(7), 1435-1441, 1992).

**Preparation 8: 4-Fluoro-2-[4-(methoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]benzoic acid**

The procedure is in accordance with the process of Preparation 1, replacing, in Step A, the ethyl 2-methyl-1H-pyrrole-3-carboxylate by methyl 2-methyl-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-4-fluorobenzaldehyde.

IR:  $\nu$ : -OH: 2727-2379  $\text{cm}^{-1}$  acid;  $\nu$ :  $\text{>C=O}$ : 1687  $\text{cm}^{-1}$

**Preparation 9: 6-{1-[2-(Benzyloxy)ethyl]-4-(ethoxycarbonyl)-5-methyl-1H-pyrrol-2-yl}-1,3-benzodioxole-5-carboxylic acid**

**Step A: Ethyl 1-[2-(benzyloxy)ethyl]-2-methyl-1H-pyrrole-3-carboxylate**

The procedure is in accordance with the process of Step A of Preparation 1, replacing the methyl iodide used as alkylating agent by benzyl 2-bromoethyl ether.

$^1\text{H}$  NMR:  $\delta$  (400 MHz;  $\text{dmso-d}_6$ ; 300K): 7.32 (t, 2H, aromatic Hs, H *meta* benzyl ether); 7.3 (t, 1H, aromatic H, H *para* benzyl ether); 7.23 (d, 2H, aromatic Hs, H *ortho* benzyl ether); 6.72 (d, 1H, H- pyrrole); 6.35 (d, 1H, H- pyrrole); 4.48 (s, 2H, aliphatic Hs, O- $\text{CH}_2$ -Ph); 4.15 (q, 2H, aliphatic Hs, O- $\text{CH}_2$ - $\text{CH}_3$ ); 4.1 (t, 2H, aliphatic Hs,  $\text{CH}_2$ -O- $\text{CH}_2$ -Ph); 3.7 (t, 2H, aliphatic Hs,  $\text{CH}_2$ - $\text{CH}_2$ -O- $\text{CH}_2$ -Ph); 2.45 (s, 3H,  $\text{CH}_3$ - pyrrole); 1.25 (t, 3H, aliphatic Hs, O- $\text{CH}_2$ - $\text{CH}_3$ )

IR:  $\nu$ :  $\text{>C=O}$ : 1689  $\text{cm}^{-1}$

**Step B: 6-{1-[2-(Benzyloxy)ethyl]-4-(ethoxycarbonyl)-5-methyl-1H-pyrrol-2-yl}-1,3-benzodioxole-5-carboxylic acid**

The procedure is in accordance with the processes of Steps B and C of Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

$^1\text{H}$  NMR:  $\delta$  (400 MHz;  $\text{dmso-d}_6$ ; 300K): 7.35 (s, 1H, aromatic H, H benzodioxole); 7.30 (m, 3H, aromatic Hs, H benzyl ether); 7.25 (s, 1H, aromatic H, H benzodioxole); 7.10 (d,



2H, aromatic Hs, H *ortho* benzyl ether); 12.55 (broad s, 1H, COOH); 6.75 (s, 1H, H-pyrrole); 6.15 (broad s, 2H, aliphatic Hs, O-CH<sub>2</sub>-O); 4.30 (s, 2H, aliphatic Hs, O-CH<sub>2</sub>-Ph); 4.15 (q, 2H, aliphatic Hs, O-CH<sub>2</sub>-CH<sub>3</sub>); 3.9 (m, 2H, aliphatic Hs, CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-Ph); 3.40 (t, 2H, aliphatic Hs, CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-Ph); 2.50 (s, 3H, CH<sub>3</sub>-pyrrole); 1.25 (t, 3H, aliphatic Hs, O-CH<sub>2</sub>-CH<sub>3</sub>)

IR:  $\nu$ : -OH: 3200-2300 cm<sup>-1</sup> acid;  $\nu$ : >C=O: 1687 cm<sup>-1</sup> acid

**Preparation 10:** 2-{1-[3-(Benzyloxy)propyl]-4-(ethoxycarbonyl)-5-methyl-1H-pyrrol-2-yl}-4-fluorobenzoic acid

The procedure is in accordance with the process of Preparation 9, replacing the benzyl 2-bromoethyl ether used in Step A by benzyl 3-bromopropyl ether and also the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step B by 2-bromo-4-fluorobenzaldehyde.

IR:  $\nu$ : -OH: 3200-2305 cm<sup>-1</sup> acid;  $\nu$ : >C=O: 1690 cm<sup>-1</sup> acid

**Preparation 11:** 6-[4-(Ethoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

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

**Preparation 12:** 4-Methoxy-2-[4-(methoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]-benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing the ethyl 2-methyl-1H-pyrrole-3-carboxylate used in Step A by methyl 2-methyl-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-4-methoxybenzaldehyde.

IR:  $\nu$ : -OH: 3000-2500 cm<sup>-1</sup> acid;  $\nu$ : >C=O: 1693 + 1670 cm<sup>-1</sup> acid + ester

**Preparation 13: 7-[4-(Methoxycarbonyl)-1,5-dimethyl-1*H*-pyrrol-2-yl]-2,3-dihydro-1,4-benzodioxin-6-carboxylic acid**

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1*H*-pyrrole-3-carboxylate by methyl 2-methyl-1*H*-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 7-bromo-2,3-dihydro-1,4-benzodioxin-6-carbaldehyde.

IR:  $\nu$ : -OH: 3100-2500  $\text{cm}^{-1}$  acid;  $\nu$ :  $>\text{C}=\text{O}$ : 1690 + 1674  $\text{cm}^{-1}$  acid + ester

**Preparation 14: 4-Fluoro-5-methoxy-2-[4-(methoxycarbonyl)-1,5-dimethyl-1*H*-pyrrol-2-yl]benzoic acid**

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1*H*-pyrrole-3-carboxylate by methyl 2-methyl-1*H*-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-4-fluoro-5-methoxybenzaldehyde.

**Preparation 15: 4-Fluoro-5-hydroxy-2-[4-(methoxycarbonyl)-1,5-dimethyl-1*H*-pyrrol-2-yl]benzoic acid**

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1*H*-pyrrole-3-carboxylate by methyl 2-methyl-1*H*-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-4-fluoro-5-hydroxy-benzaldehyde.

**Preparation 16: 6-[4-(Ethoxycarbonyl)-1-methyl-5-trifluoromethyl-1*H*-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid**

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1*H*-pyrrole-3-carboxylate by ethyl 2-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

**Preparation 17: 6-[4-(Ethoxycarbonyl)-1-ethyl-5-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid**

The procedure is in accordance with the process of Preparation 11, replacing the methyl iodide by ethyl iodide (see the protocol described in US 6,258,805 B1).

**Preparation 18: 6-[4-(Ethoxycarbonyl)-1-methyl-5-(trifluoromethyl)-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid**

**Step A: Ethyl 1-methyl-2-(trifluoromethyl)pyrrole-3-carboxylate**

Ethyl 4,4,4-trifluoro-3-oxo-butanoate (29 ml, 0.219 mmol) is added to methylamine (40 % solution in water) (50 ml, 0.580 mmol) cooled to 10°C; a white precipitate forms. 1,2-Dibromoethyl acetate (prepared according to *Molecules*, 16, 9368-9385; 2011) is added dropwise. The reactor is then sealed and heated at 70°C for 45 minutes. The reaction mixture is cooled, then extracted with ethyl acetate, dried over sodium sulphate (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness. The crude reaction product obtained is purified by chromatography over silica gel using heptane and ethyl acetate as eluants. The expected compound is obtained in the form of crystals.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 7.11 (d, 1 H), 6.52 (d, 1 H), 4.21 (quad, 2 H), 3.8 (s, 3 H), 1.27 (t, 3 H)

<sup>19</sup>F NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: -53.9

IR (ATR) cm<sup>-1</sup>: 3145 + 3128 ν -CH, 1711 ν >C=O, 1183 + 1117 + 1078 ν -CF<sub>3</sub>

**Step B: 6-[4-(Ethoxycarbonyl)-1-methyl-5-(trifluoromethyl)-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid**

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

**Preparation 19: 6-[1-(2-Benzyloxyethyl)-4-ethoxycarbonyl-5-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid**

***Step A: Ethyl 1-(2-benzyloxyethyl)-2-methyl-pyrrole-3-carboxylate***

Ethyl 2-methyl-1H-pyrrole-3-carboxylate (10 g, 65.3 mmol) is dissolved in 100 mL of dimethylformamide under argon cooled to 0°C, and then 2-bromoethoxymethylbenzene (28.1 g, 130.6 mmol) is added all at once. The reaction mixture is placed under stirring. There is then added thereto, at 0°C, in three portions, NaH (1.72 g, 71.83 mmol) over a period of 15 minutes. The reaction mixture is stirred for 15 minutes at 0°C, and then for 15 hours at ambient temperature. It is then poured into an ice bath and then extracted 3 times with ethyl acetate. The organic phase is washed 3 times with saturated aqueous lithium chloride solution, dried over MgSO<sub>4</sub>, filtered and then evaporated to dryness. The residue thereby obtained is purified by chromatography over silica gel using petroleum ether and ethyl acetate as eluants. The expected compound is obtained in the form of an oil.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 7.32 (t, 2 H), 7.3 (t, 1 H), 7.23 (d, 2 H), 6.72 (d, 1 H), 6.35 (d, 1 H), 4.48 (s, 2 H), 4.15 (quad., 2 H), 4.1 (t, 2 H), 3.7 (t, 2 H), 2.45 (s, 3 H), 1.25 (t, 3 H)

IR (ATR) cm<sup>-1</sup>: 1689 ν -C=O

***Step B: Ethyl 1-(2-benzyloxyethyl)-5-(6-formyl-1,3-benzodioxol-5-yl)-2-methyl-pyrrole-3-carboxylate***

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

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 9.5 (s, 1 H), 7.3 (s, 1 H), 7.25 (m, 3 H), 7.05 (m, 2 H), 7 (s, 1 H), 6.4 (s, 1 H), 6.2 (bs, 2 H), 4.25 (s, 2 H), 4.2 (quad., 2 H), 4.05 (m, 2 H), 3.4 (m, 2 H), 2.55 (s, 3 H), 1.25 (t, 3 H)

***Step C: 6-[1-(2-Benzyloxyethyl)-4-ethoxycarbonyl-5-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid***

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

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 12.55 (bs, 1 H), 7.35 (s, 1 H), 7.3 (m, 3 H), 7.2 (m, 3 H), 6.75 (s, 1 H), 6.15 (s, 2 H), 4.3 (s, 2 H), 4.15 (quad., 2 H), 3.9 (m, 2 H), 3.4 (t, 2 H), 2.5 (s, 3 H), 1.25 (t, 3 H)

IR (ATR) cm<sup>-1</sup>: 3200-2300 ν -OH, 1687 (+ shoulder) ν-C=O carboxylic acid + conjugated ester

**Preparation 20:** 6-[4-(Ethoxycarbonyl)-1-ethyl-5-methyl-1*H*-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the protocol described in Preparation 11, replacing the methyl iodide by ethyl iodide.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 12.49 (bs, 1 H), 7.33 (s, 1 H), 6.89 (s, 1 H), 6.17 (s, 2 H), 6.13 (s, 1 H), 4.15 (quad, 2 H), 3.69 (quad, 2 H), 2.51 (s, 3 H), 1.24 (t, 3 H), 1.01 (t, 3 H)

**Preparation 21:** 6-[4-(Ethoxycarbonyl)-1-(2-fluoroethyl)-5-methyl-1*H*-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the process of Preparation 11, replacing the methyl iodide by 1-bromo-2-fluoroethane.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>, 300K) δ ppm: 12.53 (bs, 1 H), 7.34 (s, 1 H), 6.9 (s, 1 H), 6.16 (s, 1 H), 6.16 (s, 2 H), 4.4 (dt, 2 H), 4.15 (quad, 2 H), 4.01 (m, 2 H), 2.51 (s, 3 H), 1.24 (t, 3 H)

<sup>19</sup>F NMR (400 MHz, dmso-d<sub>6</sub>, 300 K) δ ppm: -222

IR: ν: -OH: 3700-2400 cm<sup>-1</sup> acid; ν: >C=O: 1689 cm<sup>-1</sup> acid; ν: >CF: 1213 cm<sup>-1</sup>

**Preparation 22:** 6-{4-(Ethoxycarbonyl)-1-methyl-5-[2-(morpholin-4-yl)ethyl]-1H-pyrrol-2-yl}-1,3-benzodioxole-5-carboxylic acid

***Step A: 3,3-Diethoxypropanoic acid***

To a solution of 25 g of ethyl 3,3-diethoxypropionate (131 mmol) in 79 mL of methanol there are added 13.1 mL of aqueous 35 % sodium hydroxide solution (452 mmol). The reaction mixture is stirred at ambient temperature for 3 hours. The reaction mixture is then concentrated to remove the methanol. After dissolving the undissolved material by adding water, aqueous 5N HCl solution is added to obtain a pH of 5. Dichloromethane is added and then the organic phase is washed with brine. After drying over  $\text{MgSO}_4$  and concentrating to dryness, the title product is obtained in the form of an oil which is used in the next Step without being otherwise purified.

$^1\text{H}$  NMR (400 MHz,  $\text{dmsO-d}_6$ )  $\delta$  ppm: 12.2 (s, 1 H), 4.8 (t, 1 H), 3.58/3.47 (2m, 4 H), 2.5 (d, 2 H), 1.09 (t, 6 H)

***Step B: Ethyl 5,5-diethoxy-3-oxo-pentanoate***

To a solution of 16 mL of 3-ethoxy-3-oxomalonic acid (135 mmol) in 40 mL of tetrahydrofuran there are added, under argon, 21.9 g of powdered magnesium (90.4 mmol). The mixture obtained is then heated at 80°C for 7 hours. After returning to ambient temperature, this mixture is transferred by cannula to a solution of 10 g of the compound obtained in Step A (61.7 mmol) in 64 mL of tetrahydrofuran to which there has previously been added, in portions, 11 g of carbonyldiimidazole (66 mmol). The reaction mixture is stirred for 3 days at ambient temperature. After concentration, the residue is taken up in a mixture of ethyl acetate and aqueous sodium hydrogen sulphate ( $\text{NaHSO}_4$ ) solution. The mixture is stirred vigorously until no more gas is evolved. After separation of the phases, the organic phase is washed successively with water, saturated aqueous  $\text{NaHCO}_3$  solution and finally brine. After drying over  $\text{MgSO}_4$  and concentrating to dryness, the title product is obtained in the form of an oil which is used in the next Step without being otherwise purified.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 4.84 (t, 1 H), 4.08 (q, 2 H), 3.59 (s, 2 H), 3.56/3.46 (2m, 4 H), 2.8 (d, 2 H), 1.18 (t, 3 H), 1.09 (t, 6 H)

**Step C: Ethyl 2-(2,2-diethoxyethyl)-1-methyl-pyrrole-3-carboxylate**

To a solution of 11.8 g of the compound obtained in Step B (50.8 mmol) in 76 mL of water there are added, dropwise at 0°C, 6.6 ml of aqueous 40 % methylamine solution (76.2 mmol). The reaction mixture is stirred and gently reheated to ambient temperature over 5 hours. After returning to 0°C, 8.8 mL of aqueous 40 % methylamine solution (102 mmol) and then 16.6 mL of aqueous 50 % chloroacetaldehyde solution (127 mmol) are each added dropwise at a temperature of less than 10°C. The reaction mixture is stirred at ambient temperature for 16 hours and then diluted with ethyl acetate. The organic phase is washed with brine, dried over MgSO<sub>4</sub> and concentrated to dryness. The crude product thereby obtained is purified by chromatography over silica gel using petroleum ether and ethyl acetate as eluants. The title product is obtained in the form of an oil.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 6.7 (d, 1 H), 6.33 (d, 1 H), 4.55 (t, 1 H), 4.15 (q, 2 H), 3.6 (m, 2 H), 3.6 (s, 3 H), 3.3 (m, 2 H), 3.15 (d, 2 H), 1.25 (t, 3 H), 1.05 (t, 6 H)

**Step D: Ethyl 1-methyl-2-(2-morpholinoethyl)pyrrole-3-carboxylate**

To a solution of 3.8 g of the compound obtained in Step C (14.05 mmol) in 28 mL of tetrahydrofuran there are added 58 mL of aqueous 10 % sulphuric acid solution. The reaction mixture is stirred at ambient temperature for 2 hours and then diluted with a mixture of ethyl acetate and water. After separation, the organic phase is washed with brine, dried over MgSO<sub>4</sub> and concentrated to dryness. To a solution of the residue thereby obtained in 70 mL of dichloroethane there are added a solution of 13.5 mL of morpholine (14.5 mmol) in a mixture composed of 30 mL of dichloroethane and 3.6 mL of 4N aqueous HCL solution in dioxane (14.5 mmol), and then 7.4 g of sodium triacetoxyborohydride (NaBH(OAc)<sub>3</sub>) (35.13 mmol). The reaction mixture is stirred at ambient temperature for 3 hours and then diluted with a mixture of dichloromethane and saturated aqueous NaHCO<sub>3</sub> solution. After separation of the phases and extraction of the aqueous phase with dichloromethane, the organic phases are dried over MgSO<sub>4</sub> and concentrated to dryness.

The crude product thereby obtained is purified by chromatography over silica gel using dichloromethane and methanol as eluants. The title product is isolated in the form of an oil.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 6.66 (d, 1 H), 6.31 (d, 1 H), 4.14 (q, 2 H), 3.58 (s, 3 H), 3.57 (m, 4 H), 3.05 (m, 2 H), 2.45-2.38 (m, 6 H), 1.24 (t, 3 H)

5     **Step E: 6-{4-(Ethoxycarbonyl)-1-methyl-5-[2-(morpholin-4-yl)ethyl]-1H-pyrrol-2-yl}-1,3-benzodioxole-5-carboxylic acid**

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

10    **Preparation 23: 6-[4-(Ethoxycarbonyl)-1-methyl-5-(morpholin-4-ylmethyl)-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid**

**Step A: Ethyl 4,4-diethoxy-3-oxo-butanoate**

To a solution of 40 g of ethyl diethoxyacetate (227 mmol) in 67 mL of ethyl acetate there are added under argon, in portions, 6 g of sodium (261 mmol). The reaction mixture is then stirred at ambient temperature for 48 hours. There are added 10 mL of methanol, and then the mixture is hydrolysed with 65 mL of water. The pH of the reaction mixture is adjusted to pH 6 by adding 1N aqueous HCl solution. The mixture is separated and then extracted with ethyl acetate. The organic phases are combined, washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. The title product is obtained in the form of an oil which is used in the next Step without being otherwise purified.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 3.6 (s, 2 H), 1.28 (t, 9 H), 3.7-3.6 (2m, 4 H), 4.7 (s, 1 H), 4.2 (quad, 2 H)

**Step B: Ethyl 2-(2,2-diethoxymethyl)-1-methyl-pyrrole-3-carboxylate**

The title compound is obtained in accordance with the process described in Step C of Preparation 22, starting from the ethyl 4,4-diethoxy-3-oxo-butanoate obtained in the preceding Step.



<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 6.73 (d, 1 H), 6.32 (d, 1 H), 6.23 (s, 1 H), 4.17 (q, 2 H), 3.7 (s, 3 H), 3.68/3.43 (2m, 4 H), 1.26 (t, 3 H), 1.13 (t, 6 H)

**Step C: Ethyl 1-methyl-2-(2-morpholinomethyl)pyrrole-3-carboxylate**

The title compound is obtained in accordance with the process described in Step D of Preparation 22, starting from the ethyl 2-(2,2-diethoxymethyl)-1-methyl-pyrrole-3-carboxylate obtained in the preceding Step.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 6.74 (d, 1 H), 6.32 (d, 1 H), 4.15 (q, 2 H), 3.8 (s, 2 H), 3.65 (s, 3 H), 3.5 (m, 4 H), 2.32 (m, 4 H), 1.22 (t, 3 H)

**Step D: 6-[4-(Ethoxycarbonyl)-1-methyl-5-(morpholin-4-ylmethyl)-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid**

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

**Preparation 24: 6-[4-(Methoxycarbonyl)-5-(2-methoxyethyl)-1-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid**

**Step A: Methyl 2-(2-methoxyethyl)-1-methyl-pyrrole-3-carboxylate**

The title compound is obtained in accordance with the protocol of Step C of Preparation 22, using methyl 5-methoxy-3-oxovalerate.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 6.69 (wd, 1 H), 6.31 (wd, 1 H), 3.69 (s, 3 H), 3.59 (s, 3 H), 3.49 (t, 2 H), 3.2 (s, 3 H), 3.11 (t, 2 H)

**Step B: 6-[4-(Methoxycarbonyl)-5-(2-methoxyethyl)-1-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid**

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

**Preparation 25: 2-[4-(Ethoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]benzoic acid**

The procedure is in accordance with the process of Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromobenzaldehyde.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 12.81 (m, 1 H), 7.84 (m, 1 H), 7.59 (m, 1 H), 7.51 (m, 1 H), 7.35 (m, 1 H), 6.23 (s, 1 H), 4.16 (q, 2 H), 3.24 (s, 3 H), 2.5 (s, 3 H), 1.25 (t, 3 H)

**Preparation 26: 5-Fluoro-2-[4-(methoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]benzoic acid**

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1H-pyrrole-3-carboxylate by methyl 2-methyl-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-5-fluorobenzaldehyde.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 7.6 (dd, 1 H), 7.42 (m, 2 H), 6.22 (s, 1 H), 4.15 (q, 2 H), 3.21 (s, 3 H), 2.5 (s, 3 H), 1.23 (t, 3 H)

<sup>19</sup>F NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: -113

**Preparation 27: 2-[4-(Ethoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]-5-fluoro-4-methoxybenzoic acid**

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1H-pyrrole-3-carboxylate by methyl 2-methyl-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-4-methoxy-5-fluorobenzaldehyde.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 9.65 (d, 1 H), 7.67 (d, 1 H), 7.24 (d, 1 H), 6.48 (s, 1 H), 4.19 (q, 2 H), 3.97 (s, 3 H), 3.38 (s, 3 H), 2.56 (s, 3 H), 1.26 (t, 3 H).

**Preparation 28: 2-(4-Ethoxycarbonyl-1,5-dimethyl-1*H*-pyrrol-2-yl)-4-fluoro-5-methoxybenzoic acid**

5 The procedure is in accordance with Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde used in Step B by 4-fluoro-5-methoxybenzaldehyde.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 12.9 (m, 1 H), 7.6 (d, 1 H), 7.22 (d, 1 H), 6.23 (s, 1 H), 4.2 (quad, 2 H), 3.95 (s, 3 H), 3.25 (s, 3 H), 2.5 (s, 3 H), 1.25 (t, 3 H)

**Preparation 29: 5-Chloro-2-[4-(ethoxycarbonyl)-1,5-dimethyl-1*H*-pyrrol-2-yl]benzoic acid**

10 The procedure is in accordance with the process of Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-5-chlorobenzaldehyde.

**Preparation 30: 2-{1-[2-(Benzyloxy)ethyl]-4-(ethoxycarbonyl)-5-methyl-1*H*-pyrrol-2-yl}-4-chlorobenzoic acid**

15 The procedure is in accordance with the process of Preparation 19, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde by 2-bromo-4-chlorobenzaldehyde.

**Preparation 31: 5-Methoxy-2-[4-(methoxycarbonyl)-1,5-dimethyl-1*H*-pyrrol-2-yl]-benzoic acid**

20 The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1*H*-pyrrole-3-carboxylate by methyl 2-methyl-1*H*-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-5-methoxybenzaldehyde.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 12.8 (bs, 1 H), 7.34 (wd, 1 H), 7.26 (d, 1 H), 7.15 (dd, 1 H), 6.19 (s, 1 H), 3.84 (s, 3 H), 3.69 (s, 3 H), 3.22 (s, 3 H), 2.5 (s, 3 H)

**Preparation 32:** 6-[1-(2,2-Difluoroethyl)-4-(ethoxycarbonyl)-5-methyl-1*H*-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the protocol of Preparation 19, replacing the 2-bromoethoxymethylbenzene used in Step A by 2-bromo-1,1-difluoro-ethane.

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

**Step A:** {(3*S*)-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  
10 reaction mixture is then stirred at ambient temperature for 20 hours. It is then diluted with dichloromethane, washed successively with 1M HCl solution, saturated aqueous NaHCO<sub>3</sub> solution and then brine until neutral. The organic phase is then dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. The solid obtained is then dissolved in a minimum volume of  
15 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.

<sup>1</sup>H NMR: δ (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 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<sub>2</sub>-O-tosyl); 2.7 (2dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 2.45 (s, 3H, O-SO<sub>2</sub>-Ph- CH<sub>3</sub>); 2.35 (s, 3H, N-SO<sub>2</sub>-Ph- CH<sub>3</sub>)  
20

25 IR: ν: -SO<sub>2</sub>: 1339-1165 cm<sup>-1</sup>

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

To a suspension of 8.15 g (214.8 mmol) of lithium aluminium hydride (LiAlH<sub>4</sub>) 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.

**<sup>1</sup>H NMR:**  $\delta$  (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 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<sub>2</sub>-Ph-CH<sub>3</sub>); 0.90 (d, 3H, tetrahydroisoquinoline-CH<sub>3</sub>)

**IR :**  $\nu$ : -SO<sub>2</sub>: 1332-1154 cm<sup>-1</sup>

**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 chromatography over silica gel using dichloromethane and ammonia-in-ethanol as eluants, the title product is obtained in the form of an oil.

**<sup>1</sup>H NMR:**  $\delta$  (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 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, tetrahydroisoquinoline); 1.12 (d, 3H, tetrahydroisoquinoline-CH<sub>3</sub>); 2.9-2.3 (m, broad, 1H, HN (tetrahydroisoquinoline))

**IR:**  $\nu$ : -NH: 3248 cm<sup>-1</sup>

**Step D: (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.

**<sup>1</sup>H NMR:**  $\delta$  (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300K): 9.57 (m, broad, 2H,  $\text{NH}_2^+$  (tetrahydroisoquinoline)); 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<sub>3</sub>)

**IR:**  $\nu$ :  $\text{-NH}_2^+$ : 3000-2300  $\text{cm}^{-1}$ ;  $\nu$ : aromatic -CH: 766  $\text{cm}^{-1}$

**Preparation 2':      *tert*-Butyl      [(3*S*)-1,2,3,4-tetrahydroisoquinolin-3-ylmethyl]-carbamate**

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

This compound is obtained using a protocol from the literature (R. B. Kawthekar *et al* *South Africa Journal of Chemistry* 63, 195, 2009) starting from 15 g of (3*S*)-1,2,3,4-tetrahydroisoquinolin-3-ylmethanol (91,9 mmol) in the presence of benzyl chloroformate and triethylamine in solution in dichloromethane. After purification by chromatography over silica gel using petroleum ether and ethyl acetate as eluants, the title product is obtained in the form of an oil.

**<sup>1</sup>H NMR:**  $\delta$  (300 MHz; DMSO-d<sub>6</sub>; 300K): 7.33 (m, 5H, aromatic Hs, O-benzyl); 7.15 (s, 4H, aromatic Hs, H tetrahydroisoquinoline); 5.13 (s, 2H, CH<sub>2</sub>-Ph); 4.73 (d, 1H, H tetrahydroisoquinoline); 4.47 (m, H, CH<sub>2</sub>OH); 4.36 (m, 1H, H tetrahydroisoquinoline); 4.28 (d, 1H, H tetrahydroisoquinoline); 3.39 (dd, 1H, CH<sub>2</sub>OH); 3.23 (dd, 1H, , CH<sub>2</sub>OH); 2.93 (dd, 1H, H tetrahydroisoquinoline); 2.86 (dd, 1H, H tetrahydroisoquinoline)

**IR:**  $\nu$ : OH: 3416  $\text{cm}^{-1}$ ;  $\nu$ : <C=O 1694  $\text{cm}^{-1}$ ;  $\nu$ :aromatic >C-H: 754  $\text{cm}^{-1}$

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

This compound is obtained using a protocol from the literature (D. Pagé *et al J. Med. Chem*, 44, 2387, 2001) starting from 23 g of the compound obtained in Step A (77.3 mmol) in the presence of diphenylphosphoryl azide and triphenylphosphine in solution in THF.  
5 After purification by chromatography over silica gel using petroleum ether and ethyl acetate as eluants, the title product is obtained in the form of an oil.

**<sup>1</sup>H NMR:**  $\delta$  (400 MHz; DMSO-d<sub>6</sub>; 300K): 7.36 (m, 5H, aromatic Hs, O-benzyl); 7.19 (m, 4H, aromatic Hs, H tetrahydroisoquinoline); 5.16 (s, 2H, CH<sub>2</sub>-Ph); 4.76 (d, 1H, H tetrahydroisoquinoline); 4.53 (m, 1H, H tetrahydroisoquinoline); 4.30 (m, 1H, H  
10 tetrahydroisoquinoline); 3.28 (m, 2H, , CH<sub>2</sub>N<sub>3</sub>); 3.06 (dd, 1H, H tetrahydroisoquinoline); 2.78 (dd, 1H, H tetrahydroisoquinoline)

**IR:**  $\nu$ : N<sub>3</sub>: 2095 cm<sup>-1</sup>;  $\nu$ : <C=O: 1694 cm<sup>-1</sup>;  $\nu$ : aromatic >C-H: 754 cm<sup>-1</sup>

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

To a solution of 20.9 g (64.5 mmol) of the azido compound obtained in Step B in 650 mL  
15 of THF, there are successively added 25.5 g (97.2 mmol) of triphenylphosphine and 157 mL of water. The batch is refluxed for 2 hours 30 minutes. The reaction mixture is then concentrated to dryness and the residue oil is then taken up in isopropyl ether. A white precipitate appears; it is filtered off and washed with isopropyl ether. The filtrate is then concentrated to dryness and then purified by chromatography over silica gel using  
20 dichloromethane and methanol as eluants. The title product is obtained in the form of an oil.

**<sup>1</sup>H NMR:**  $\delta$  (400 MHz; DMSO-d<sub>6</sub>; 300K): 7.40 (m, 5H, aromatic Hs, O-benzyl); 7.20 (m, 4H, aromatic Hs, H tetrahydroisoquinoline); 5.15 (s, 2H, CH<sub>2</sub>-Ph); 4.75-4.3 (m, 2H, H tetrahydroisoquinoline); 4.30 (d, 1H, H tetrahydroisoquinoline); 2.90 (m, 2H, , CH<sub>2</sub>NH<sub>2</sub>);  
25 2.45 (m, 2H, H tetrahydroisoquinoline); 1.40 (m, 2H, NH<sub>2</sub>)

**IR:**  $\nu$ : NH<sub>2</sub>: 3400-3300 cm<sup>-1</sup>;  $\nu$ : <C=O: 1688 cm<sup>-1</sup>

**Step D:** *Benzyl (3S)-3-(((tert-butoxycarbonyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate*

To a solution of 18.4 g (62.1 mmol) of the compound obtained in Step C in 630 mL of dichloromethane there are successively added 17.5 mL (124 mmol) of triethylamine and, in portions, 14.9 g (68.3 mmol) of di-*tert*-butyl dicarbonate. The batch is stirred at ambient temperature for 2 h. The reaction mixture is then concentrated and ethyl acetate is then added. The organic phase is successively washed with 1M HCl solution, brine, saturated aqueous NaHCO<sub>3</sub> solution and then brine. After drying, concentrating to dryness and purifying by chromatography over silica gel using petroleum ether and ethyl acetate as eluants, the title product is obtained in the form of an oil.

**<sup>1</sup>H NMR:**  $\delta$  (400 MHz; DMSO-d<sub>6</sub>; 300K): 7.35 (m, 5H, aromatic Hs, O-benzyl); 7.15 (m, 4H, aromatic Hs, H tetrahydroisoquinoline); 6.51 (m, 1H, NHBoc); 5.12 (s, 2H, CH<sub>2</sub>-Ph); 4.76 (d, 1H, H tetrahydroisoquinoline); 4.51 (m, 1H, H tetrahydroisoquinoline); 4.36 (d, 1H, H tetrahydroisoquinoline); 2.95 (m, 3H, H tetrahydroisoquinoline + CH<sub>2</sub>NHBoc); 2.71 (d, 1H, H tetrahydroisoquinoline); 1.34 (s, 9H, NHBoc)

**IR:**  $\nu$ : NH: 3351 cm<sup>-1</sup>;  $\nu$ : <C=O: 1686 cm<sup>-1</sup>

**Step E:** *tert-Butyl [(3S)-1,2,3,4-tetrahydroisoquinolin-3-ylmethyl]carbamate*

To a solution of 21 g (53 mmol) of the compound obtained in Step D in 600 mL of ethyl acetate there are added 2.1 g of palladium-on-carbon 10 %. The batch is stirred at ambient temperature under a pressure of 1.3 bars of dihydrogen for 5 hours. The reaction mixture is then filtered and then concentrated to dryness. The title product is obtained in the form of a solid.

**<sup>1</sup>H NMR:**  $\delta$  (400 MHz; DMSO-d<sub>6</sub>; 300K): 7.15 (m, 4H, aromatic Hs, H tetrahydroisoquinoline); 6.85 (t, 1H, NHBoc); 3.90 (m, 2H, H tetrahydroisoquinoline); 3.00 (m, 2H, CH<sub>2</sub>NHBoc); 2.80 (m, 1H, H tetrahydroisoquinoline); 2.65 (dd, 1H, H tetrahydroisoquinoline); 2.40 (dd, 1H, H tetrahydroisoquinoline); 1.40 (s, 9H, NHBoc)

**IR:**  $\nu$ : NH: 3386-3205 cm<sup>-1</sup> (NH amide);  $\nu$ : <C=O: 1688 cm<sup>-1</sup>;  $\nu$ : NH: 1526 cm<sup>-1</sup> (NH amine)



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

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

To a solution of 5 g of (3S)-2-[(benzyloxy)carbonyl]-1,2,3,4-tetrahydro-3-  
5 isoquinolinecarboxylic acid (16 mmol) in 160 mL of dichloromethane there are added  
1.5 mL of morpholine (17.6 mmol), then 9 mL of *N,N,N*-triethylamine (64 mmol), 3.3 g of  
1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (EDC) (19.2 mmol) and 2.6 g of  
hydroxybenzotriazole (HOBt) (19.2 mmol). The reaction mixture is stirred at ambient  
temperature overnight; it is then poured into ammonium chloride solution and extracted  
10 with ethyl acetate. The organic phase is then dried over  $\text{MgSO}_4$ , and then filtered and  
evaporated to dryness. The crude product thereby obtained is then purified by  
chromatography over silica gel using dichloromethane and methanol as eluants. The  
product is obtained in the form of a foam.

$^1\text{H}$  NMR:  $\delta$  (400 MHz;  $\text{dmsO-d}_6$ ; 353K): 7.30 (m, 5H benzyl); 7.15 (m, 4H, aromatic Hs);  
15 5.2-5.0 (m, 3H, 2H benzyl, 1H dihydroisoquinoline); 4.75-4.5 (2d, 2H  
dihydroisoquinoline); 3.55-3.3 (m, 8H morpholine); 3.15-2.9 (2dd, 2H  
dihydroisoquinoline)

IR:  $\nu$ :  $>\text{C}=\text{O}$ : 1694; 1650  $\text{cm}^{-1}$

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

20 To a solution of 5.3 g of the product obtained in Step A (13.9 mmol) in 278 mL of  
tetrahydrofuran there are added 14 mL of borane-dimethylsulphide complex ( $\text{BH}_3\text{Me}_2\text{S}$ )  
(27.8 mmol) at ambient temperature. The batch is heated for 4 hours at 80°C. It is allowed  
to return to ambient temperature and there are then added 7 mL (14 mmol) of  $\text{BH}_3\text{Me}_2\text{S}$ .  
The reaction mixture is again heated at 80°C for 2 hours. The tetrahydrofuran is then  
25 evaporated off and then there is slowly added methanol and then 5.6 mL of 5N aqueous  
HCl solution (27.8 mmol). The mixture is stirred at ambient temperature overnight, and  
then at 80°C for 1 hour. Saturated aqueous  $\text{NaHCO}_3$  solution is then added to the reaction  
mixture placed at 0°C until a pH of 8 is obtained, and extraction with ethyl acetate is then

carried out. The organic phase is then dried over  $\text{MgSO}_4$ , and then filtered and evaporated to dryness. The title product is obtained in the form of an oil.

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

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

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

To a solution of 4.9 g of the compound of Step B (13,4 mmol) in 67 mL of ethanol there is added 0.980 g of palladium dihydroxide (20 % by weight) at ambient temperature. The reaction mixture is placed under 1.2 bars of hydrogen at ambient temperature for 4 hours. It is then passed through a Whatman filter and the palladium is then rinsed several times  
15 with ethanol. The filtrate is evaporated to dryness. The title product is obtained in the form of an oil.

$^1\text{H}$  NMR:  $\delta$  (400 MHz;  $\text{dms}\text{-d}_6$ ; 300K): 7.12-7.0 (unresolved peak, 4H, aromatic Hs); 3.92 (s, 2H tetrahydroisoquinoline); 3.60 (t, 4H morpholine); 2.98 (m, 1H tetrahydroisoquinoline); 2.68 (dd, 1H tetrahydroisoquinoline); 2.5-2.3 (unresolved peak,  
20 8H, 1H tetrahydroisoquinoline, 6H morpholine, 1H NH)

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

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

The procedure is in accordance with the process of Preparation 3', replacing the  
25 morpholine used in Step A by 1-methyl-piperazine.

**Preparation 5':**      **(3*S*)-3-[2-(Morpholin-4-yl)ethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride**

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

5    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, still dropwise 4.3 mL (30.9 mmol) of triethylamine, 2.20 g (12.40 mmol) of EDC and 1.70 g (1.68 mmol) of HOBT (hydroxybenzotriazole). The batch is stirred at ambient temperature for 15 hours. The  
10    reaction mixture is then diluted with dichloromethane, successively washed with 1M HCl solution, saturated aqueous NaHCO<sub>3</sub> solution and then brine until neutral. The organic phase is then dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. After purification by chromatography over silica gel using dichloromethane and methanol as eluants, the title product is obtained in the form of an oil.

15    **<sup>1</sup>H NMR:** δ (400 MHz; dmso-d<sub>6</sub>; 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<sub>2</sub> 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<sub>2</sub>CO); 1.40 (s, 9H, <sup>1</sup>Bu)

20    **IR:** ν: C=O: 1687; 1625 cm<sup>-1</sup>

**Step B:**      *1-(Morpholin-4-yl)-2-[(3*S*)-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 1M solution of HCl in  
25    ether. The batch is stirred at ambient temperature for 15 hours, and then the suspension is filtered and the precipitate washed with ether. After drying, the title product is obtained in the form of a solid.

**<sup>1</sup>H NMR:**  $\delta$  (400 MHz; dmso-d<sub>6</sub>; 300K): 9.80-9.50 (m, 2H, NH<sub>2</sub><sup>+</sup>); 7.30-7.10 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.30 (m, 2H, aliphatic Hs, CH<sub>2</sub> 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<sub>2</sub> tetrahydroisoquinoline and CH<sub>2</sub>CO)

**IR:**  $\nu$ : -NH<sub>2</sub><sup>+</sup>: 2800-1900 cm<sup>-1</sup>;  $\nu$ : C=O: 1620 cm<sup>-1</sup>

***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<sub>4</sub> 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.

**<sup>1</sup>H NMR:**  $\delta$  (400 MHz; dmso-d<sub>6</sub>; 300K): 11.35 + 9.80 (2m, 2H, NH<sub>2</sub><sup>+</sup>); 10.00 (m, H, NH<sup>+</sup>); 7.20 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.30 (s, 2H, aliphatic Hs, CH<sub>2</sub> alpha to N tetrahydroisoquinoline); 4.00 + 3.85 (2m, 4H, aliphatic Hs, CH<sub>2</sub> 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<sub>2</sub>-morpholine); 3.15 (dd, 1H, aliphatic H, CH<sub>2</sub> tetrahydroisoquinoline); 3.10 (m, 2H, aliphatic H, CH alpha to O morpholine); 2.90 (dd, 1H, aliphatic H, CH<sub>2</sub> tetrahydroisoquinoline); 2.30 + 2.15 (2m, 2H, aliphatic H, CH<sub>2</sub>-tetrahydroisoquinoline)

**IR:**  $\nu$ : NH<sup>+</sup> / -NH<sub>2</sub><sup>+</sup>: between 3500 and 2250 cm<sup>-1</sup>;  $\nu$ : C=C: weak 1593 cm<sup>-1</sup>;  $\nu$ : aromatic C-H: 765 cm<sup>-1</sup>

**Preparation 6': (3R)-3-[3-(Morpholin-4-yl)propyl]-1,2,3,4-tetrahydroisoquinoline**

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

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

5 **Step B: 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  
10 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 aqueous ammonium chloride solution are added. The resulting solution is extracted with dichloromethane. The organic phase is then dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. After purification by chromatography over silica gel using dichloromethane and MeOH as eluants, the expected  
15 product is obtained in the form of an oil.

<sup>1</sup>H NMR (500 MHz, dmso-d<sub>6</sub>) 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, 4 H), 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)

20 **IR (ATR) cm<sup>-1</sup>**: ν: >C=O: 1731 (ester); ν: >C=O: 1644 (amide); ν: -SO<sub>2</sub>: 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  
25 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.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) 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<sup>-1</sup>: ν: -OH: 3500 to 2000; ν: >C=O: 1727 (acid); ν: >C=O: 1634 (amide); ν: -SO<sub>2</sub>: 1330-1155

**Step D:** 3-[(3*R*)-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 (NaCl) and then, dropwise, 5 mL of water. The batch is stirred at 130°C for 1 hour and then the solution is concentrated to ¼. The reaction mixture is then diluted with dichloromethane and washed successively with saturated aqueous lithium chloride solution and then with brine. The organic phase is then dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. After purification by chromatography over silica gel using cyclohexane and ethyl acetate as eluants, the expected product is obtained in the form of an oil.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) 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<sup>-1</sup>: ν: >C=O: 1639; ν: -SO<sub>2</sub>: 1331-1156; γ: >CH-Ar: 815-675

**Step E:** (3*R*)-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<sub>4</sub>, filtered and concentrated to dryness. After

purification by chromatography over silica gel using dichloromethane and ammonia-in-ethanol as eluants, the expected product is obtained in the form of an oil.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) 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),  
5 2.25 (t, 4 H), 2.2 (t, 2 H), 1.4/1.3 (2m, 4 H).

IR (ATR) cm<sup>-1</sup>: ν: -SO<sub>2</sub>: 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  
10 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 chromatography over silica gel using dichloromethane and ammonia-in-ethanol as eluants, the expected product is obtained in the form of an oil.

15 <sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) 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<sup>-1</sup>: ν: >NH<sub>2</sub>+ /NH+: 3500-2300; ν: >C-O-C<: 1115

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

20 Empirical formula: C<sub>16</sub> H<sub>24</sub> N<sub>2</sub> O

[M+H]<sup>+</sup> calculated: 261.1961

[M+H]<sup>+</sup> measured: 261.1959

**Preparation 7': (3*S*)-3-[(9*aS*)-Octahdropiperazino[2,1-*c*]morpholin-8-ylmethyl]-1,2,3,4-tetrahydroisoquinoline trihydrochloride**

**Step A: *tert*-Butyl (9*aS*)-4-oxo-octahdropiperazino[2,1-*c*]morpholine-8-carboxylate**

The synthesis of this compound is known in the literature (*J. Med. Chem.* **2012**, *55*, 5887  
5 for the opposite enantiomer).

**Step B: (9*aS*)-Octahdropiperazino[2,1-*c*]morpholin-4-one hydrochloride**

A 4M solution of HCl in dioxane (60 mL, 240 mmol) is added to the compound *tert*-butyl  
(9*aS*)-4-oxo-octahdropiperazino[2,1-*c*]morpholine-8-carboxylate (11.8 g, 46.0 mmol)  
cooled using an ice bath. The solution is then stirred at ambient temperature for 2 hours,  
10 and then at 50-60°C for 1.5 hours. The solution is then evaporated to dryness. The residue  
is co-evaporated with dioxane (3 x 20 mL) and then dried *in vacuo* to obtain the expected  
compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, dmso-*d*<sub>6</sub>) δ ppm: 2.80 - 2.94 (m, 2 H), 2.94 - 3.05 (m, 1 H), 3.23 -  
3.37 (m, 2 H), 3.59 - 3.69 (m, 1 H), 3.83 - 3.93 (m, 1 H), 3.95 - 4.04 (m, 1 H), 4.02 - 4.13  
15 (m, 2 H), 4.45 - 4.55 (m, 1 H), 9.58 (br s, 2 H)

**Step C: *tert*-Butyl (3*S*)-3-[(9*aS*)-4-oxo-octahdropiperazino[2,1-*c*]morpholine-8-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate**

EDC (3.90 g, 20.3 mmol) is added to a solution of the compound of Step B (3.02 g,  
15.7 mmol), (3*S*)-2-[(*tert*-butoxy)carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic  
20 acid (4.6 g, 16.6 mmol), triethylamine (8.0 mL, 57.4 mmol) and HOBt (2.72 g, 20.1 mmol)  
in dichloromethane (150 mL). The mixture is stirred at ambient temperature for 21 hours.  
1N aqueous HCl solution (105 mL) is added and the precipitate formed is filtered off using  
a Buchner funnel. The phases of the filtrate are separated. The aqueous phase is extracted  
with dichloromethane (2 x 10 mL). The combined organic phases are washed with 3N  
25 aqueous HCl solution (35 mL), then with aqueous 5 % potassium bicarbonate solution (2 x  
35 mL) and finally with brine (35 mL). The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub>, filtered  
and then concentrated under reduced pressure. The product is purified by chromatography  
over silica gel using ethyl acetate and heptane as eluants to obtain the expected compound  
in the form of a solid.



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 1.38 - 1.57 (m, 9 H), 2.39 - 2.89 (m, 2 H), 2.89 - 3.34 (m, 3 H), 3.34 - 3.70 (m, 2 H), 3.90 - 4.06 (m, 1 H), 4.09 - 4.27 (m, 2 H), 4.30 - 5.00 (m, 5 H), 5.20 - 5.37 (m, 1 H), 7.03 - 7.24 (m, 4 H)

**Step D:** (3*S*)-3-[(9*aS*)-Octahdropiperazino[2,1-*c*]morpholin-8-ylmethyl]-1,2,3,4-tetrahydroisoquinoline trihydrochloride

4M HCl solution in dioxane (45 mL, 180 mmol) is added to the compound of Step C (6.6 g, 46.0 mmol) cooled in an ice bath. The suspension is then stirred at ambient temperature for 24 hours and then it is evaporated to dryness. The residue is co-evaporated with MTBE and then dried *in vacuo*. The solid thereby obtained is suspended in tetrahydrofuran (160 mL), and then LiAlH<sub>4</sub> (3.0 g, 79.1 mmol) is added. The suspension is refluxed for 6.5 hours, and it is then cooled in an ice bath. Water (3 mL) is then added over a period of 7 minutes. After 0.5 hours, 2N aqueous sodium hydroxide solution (6 mL) is added. Water (6 mL) is again added 0.25 hours later. Finally, Celite (7 g) and Na<sub>2</sub>SO<sub>4</sub> (25 g) are added 0.5 hours later. The suspension is filtered over Celite and rinsed with tetrahydrofuran (2 x 100 mL). The filtrate is concentrated to dryness. The oil thereby obtained is dissolved in MTBE (50 mL). The resulting solution is filtered and the filtrate concentrated. The residue is dissolved in methanol (60 mL), and then 4M HCl solution in dioxane (20 mL) is added. The solution is heated to 40°C and treated with activated charcoal (0.66 g), with stirring, for 1 hour. The suspension is filtered over Celite and rinsed with warm methanol. The filtrate is concentrated until the product starts to crystallise out. Crystallisation is allowed to continue for 16 hours at ambient temperature. The solid obtained is filtered off and rinsed with a mixture of 2-propanol / MTBE (4/6) (2 x 20 mL), and then with MTBE (2 x 20 mL). After drying, the expected compound is obtained.

<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ ppm: 2.28 - 2.44 (m, 1 H), 2.74 - 3.00 (m, 4 H), 3.08 - 3.27 (m, 3 H), 3.27 - 3.42 (m, 2 H), 3.43 - 3.56 (m, 2 H), 3.56 - 3.69 (m, 2 H), 3.76 - 3.95 (m, 2 H), 4.00 - 4.22 (m, 2 H), 4.35 - 4.50 (m, 2 H), 7.20 - 7.41 (m, 4 H)

<sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O) δ ppm: 29.00, 44.58, 50.30, 51.08, 51.17, 52.75, 53.17, 58.08, 61.60, 64.61, 66.37, 127.14, 127.71, 128.00, 128.77, 129.55, 131.15

MS (ESI): [M+H]<sup>+</sup> 288.16

**Preparation 8': (3S)-3-(1-Oxa-6-azaspiro[3.3]hept-6-ylmethyl)-1,2,3,4-tetrahydro-isoquinoline**

**Step A: (3S)-3-(Iodomethyl)-2-[(4-methylphenyl)sulphonyl]-1,2,3,4-tetrahydro-isoquinoline**

5 The compound of Step A of Preparation 6' (4.0 g; 8.48 mmol) in acetonitrile (10 mL) is placed in a 27-ml microwave tube and then sodium iodide (1.40 g; 9.33 mmol) is added. The reaction mixture is heated for 5 hours at 100°C using microwaves (200 W). It is then filtered and the solid is washed with dichloromethane. The filtrate is evaporated to dryness and then the residue is purified by chromatography over silica gel using heptane and ethyl  
10 acetate as eluants. The title compound is obtained in the form of an oil.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 7.64 (d, 2 H), 7.28 (d, 2 H), 7.15-7 (m, 4 H), 4.5/4.3 (2d, 2 H), 4.14 (m, 1 H), 3.22 (m, 2 H), 2.82 (m, 2 H), 2.31 (s, 3 H)

IR (ATR) cm<sup>-1</sup>: 1897 ν -Ar, 1333 + 1156 ν -SO<sub>2</sub>

**Step B: (3S)-2-[(4-Methylphenyl)sulphonyl]-3-(1-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-1,2,3,4-tetrahydroisoquinoline**

15 The iodinated compound (2.5 g; 5.85 mmol) obtained in the preceding Step is dissolved in acetonitrile (50 mL). 1-Oxa-6-azaspiro[3.3]heptane oxalate (1.21 g; 6.36 mmol) is added, followed by potassium carbonate (1.61 g; 11.7 mmol). The reaction mixture is heated for 15 hours at reflux. The reaction mixture is filtered and washed with acetonitrile, and then is  
20 evaporated to dryness.

The compound is purified by chromatography over silica gel using dichloromethane and ammonia-in-methanol as eluants. The title compound is obtained in the form of an oil.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 7.68 (d, 2 H), 7.32 (d, 2 H), 7.14-7 (m, 4 H), 4.53/4.2 (dd, 2 H), 4.34 (t, 2 H), 3.95 (m, 1 H), 3.5/3.4/2.98 (3m, 4 H), 2.7 (t, 2 H), 2.68-  
25 2.58 (m, 2 H), 2.34 (s, 3 H), 2.31-2.24 (m, 2 H)

IR (ATR) cm<sup>-1</sup>: 1333 + 1156 ν -SO<sub>2</sub>

**Step C: (3S)-3-(1-Oxa-6-azaspiro[3.3]hept-6-ylmethyl)-1,2,3,4-tetrahydroisoquinoline**

The tosylated compound of the above Step (1.3 g; 3.26 mmol) is dissolved in 10 mL of methanol. Powdered magnesium (633 mg; 26.08 mmol) is added in portions of 160 mg every 3 hours. The reaction mixture is stirred in an ultrasound bath 15 hours. It is then  
5 filtered over Celite, washed with copious amounts of methanol, and then evaporated to dryness. The compound is purified by chromatography over silica gel using dichloromethane and ammonia-in-methanol as eluants. The compound is obtained in the form of an oil.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 7.01 (m, 4 H), 4.46 (t, 2 H), 3.85 (s, 2 H), 3.51/3.05  
10 (dd, 2 H), 2.73 (t, 2 H), 2.61/2.4 (m, 4 H), 2.4 (m, 1 H), 2.4 (m, 1 H)

IR (ATR) cm<sup>-1</sup>: 3325 ν >NH

**Preparation 9': (3S)-3-[(9aR)-Octahdropiperazino[2,1-c]morpholin-8-ylmethyl]-1,2,3,4-tetrahydroisoquinoline trihydrochloride**

**Step A: tert-Butyl (9aR)-4-oxo-octahdropiperazino[2,1-c]morpholine-8-carboxylate**

15 Synthesis of this compound is described in the literature (*J. Med. Chem.* **2012**, *55*, 5887).

**Step B: (9aR)-Octahdropiperazino[2,1-c]morpholin-4-one hydrochloride**

A 4M solution of HCl in dioxane (39 mL, 154 mmol) is added to the compound of Step A (11.3 g, 44.1 mmol). The solution is then stirred at ambient temperature for 5 hours, and then a 4M solution of HCl in dioxane (12 mL, 48 mmol) is added again. The mixture is  
20 stirred for 16 hours. The solution is then evaporated to dryness to yield the expected product in the form of a solid.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 2.79 - 2.93 (m, 2 H), 3.02 (td, *J* = 13.1, 2.7 Hz, 1 H), 3.22 - 3.34 (m, 2 H), 3.59 - 3.67 (m, 1 H), 3.86 - 3.96 (m, 1 H), 3.96 - 4.01 (m, 1 H), 4.05 (AB q, *J* = 13.3 Hz, 2 H), 4.48 (dd, *J* = 14.1, 2.5 Hz, 1 H), 9.71 (br. s, 1 H), 9.91 (br.  
25 s, 1 H)

**Step C:** *tert-Butyl (3S)-3-[(9aR)-4-oxo-octahydropiperazino[2,1-c]morpholine-8-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate*

EDC (5.17 g, 27.0 mmol) is added to a solution of the compound of the above Step (4.0 g, 20.7 mmol), (3S)-2-[(*tert*-butoxy)carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (6.04 g, 21.8 mmol), triethylamine (11.6 mL, 83.1 mmol) and HOBt (3.65 g, 27.0 mmol) in dichloromethane (100 mL). The mixture is stirred at ambient temperature for 16 hours. 1N aqueous HCl solution (70 mL) is added and the precipitate formed is filtered off using a Buchner funnel. The phases of the filtrate are separated. The organic phase is washed with saturated aqueous potassium carbonate solution and is then concentrated under reduced pressure. The residue is pre-absorbed onto silica gel and is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to yield the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 1.25 - 1.58 (m, 9 H), 2.50 - 2.76 (m, 2 H), 2.76 - 3.25 (m, 3 H), 3.37 - 3.76 (m, 2 H), 3.92 - 4.50 (m, 5 H), 4.06 (s, 2 H), 4.66 (d, *J* = 15.6 Hz, 1 H), 4.76 - 5.28 (m, 1 H), 7.05 - 7.31 (m, 4 H)

**Step D:** *(3S)-3-[(9aR)-Octahydropiperazino[2,1-c]morpholin-8-ylmethyl]-1,2,3,4-tetrahydroisoquinoline trihydrochloride*

A 4M solution of HCl in dioxane (24.0 mL, 96.2 mmol) is added to a solution of the compound of Step C (8.00 g, 12.25 mmol) in dichloromethane (25 mL). The mixture is stirred at ambient temperature for 16 hours and is then concentrated to dryness. The crude product obtained is added to a suspension of LiAlH<sub>4</sub> (1.97 g, 51.91 mmol) in tetrahydrofuran (140 mL). The mixture is refluxed until the reaction (monitored by LC-MS) is complete and it is then cooled to 0°C. Water (2.5 mL) is added dropwise. After stirring for 10 minutes, aqueous 2M sodium hydroxide solution (5 mL) is added dropwise. Water (5 mL) is again added after stirring for 10 minutes. There are finally added Celite (4 g) and Na<sub>2</sub>SO<sub>4</sub> (12 g) after stirring for an additional 10 minutes. The suspension is filtered over Celite and the filtrate is concentrated to dryness. The crude residue thereby obtained is dissolved in methanol (80 mL), and then a 4M solution of HCl in dioxane (16.75 mL, 67.0 mmol) is added. The mixture is stirred at ambient temperature for 3 hours, and then concentrated to dryness. The residue is dissolved in a minimum of warm

methanol (70 mL), and then MTBE (3-5 mL) is added. The solution is cooled at 0°C for 1 hour in an ice-cold water bath, and the product precipitates out. A little MTBE (2-3 mL) is again added and the mixture is allowed to stand for a further 1 hour at 0°C. The solid obtained is filtered over a Buchner funnel and dried *in vacuo* to yield the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm: 2.65 (t, *J* = 11.1 Hz, 1 H), 2.74 - 2.97 (m, 4 H), 3.10 (d, *J* = 12.5 Hz, 1 H), 3.19 (dd, *J* = 17.6, 4.8 Hz, 1 H), 3.25 - 3.55 (m, 5 H), 3.59 - 3.74 (m, 2 H), 3.82 - 4.15 (m, 4 H), 4.45 (AB q, *J* = 15.9 Hz, 2 H), 7.21 - 7.35 (m, 4 H).

<sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD) δ ppm: 30.21, 45.67, 50.22, 51.99, 52.90, 53.58, 53.71, 59.25, 62.58, 65.30, 67.07, 127.76, 128.40, 129.08, 129.36, 130.16, 131.95

MS (ESI): [M+H]<sup>+</sup> 288.2

**Preparation 1'':**     *N*-[4-[*tert*-Butyl(dimethyl)silyl]oxyphenyl]-1-methyl-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).

<sup>1</sup>H NMR: δ (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300K): 6.45-6.55 (dd, 4H, aromatic Hs); 4.60 (m, 2H, NH<sub>2</sub>-Ph); 0.90 (s, 9H, Si (CH<sub>2</sub>)<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>); 0.10 (s, 6H, Si (CH<sub>2</sub>)<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)

IR: ν: -NH<sub>2</sub><sup>+</sup>: 3300-3400 cm<sup>-1</sup>

**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<sub>2</sub>(dba)<sub>3</sub> (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 using dichloromethane and ethyl acetate as eluants to provide the expected product in the form of a solid.

**<sup>1</sup>H NMR:**  $\delta$  (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300K): 7.55 (s, 1H, pyrazole); 7.23 (s, 1H, pyrazole); 7.18 (broad s, 1H, NH<sub>2</sub>-Ph); 6.64 (m, 4H, aromatic Hs); 3.77 (s, 3H, CH<sub>3</sub>-pyrazole); 0.90 (s, 9H, Si (CH<sub>2</sub>)<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>); 0.12 (s, 6H, Si (CH<sub>2</sub>)<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)

**IR:**  $\nu$  -NH<sup>+</sup>: 3275 cm<sup>-1</sup>;  $\nu$  Ar and C=N: 1577 and 1502 cm<sup>-1</sup>;  $\nu$  -Si-C-: 1236 cm<sup>-1</sup>;  $\nu$  -Si-O-: 898 cm<sup>-1</sup>;  $\nu$  -Si-C-: 828, 774 cm<sup>-1</sup>

**Preparation 2'': 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(dimethyl)silyl chloride (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 MgSO<sub>4</sub>, then filtered and evaporated to dryness. The crude product thereby obtained is then purified by chromatography over silica gel using petroleum ether and dichloromethane as eluants. The title product is obtained in the form of a powder.

**<sup>1</sup>H NMR:**  $\delta$  (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 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:**  $\nu$ : >NH: 3403 cm<sup>-1</sup>;  $\nu$ : >Ar: 1597 cm<sup>-1</sup>

**Preparation 3'': *tert*-Butyl 5-[(4-[[*tert*-butyl(dimethyl)silyl]oxy]phenyl)amino]-1*H*-indole-1-carboxylate**

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 *tert*-butyl 5-bromo-1*H*-indole-1-carboxylate.

<sup>1</sup>H NMR: δ (400 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300K): 7.85 (d, 1H); 7.78 (s, 1H); 7.55 (d, 1H); 7.15 (d, 1H); 6.95 (m, 3H); 6.75 (d, 2H); 6.58 (d, 1H); 1.65 (s, 9H); 1.00 (s, 9H); 0.2 (s, 6H)

**Preparation 4'':**     *N*-(4-{{*tert*-Butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indol-5-amine

5     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 5-bromo-1-methyl-1*H*-indole.

**Preparation 5'':**     *N*-(4-{{*tert*-Butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-indazol-5-amine

10     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 5-bromo-1-methyl-1*H*-indazole.

**Preparation 6'':**     *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 by 4-bromo-2-fluoro-1-methylbenzene.

15     **Preparation 7'':**     *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 by 1-bromo-3-fluorobenzene.

**Preparation 8'':**     4-Benzoyloxy-*N*-phenyl-aniline

20     To a solution of 4-hydroxy-*N*-phenyl-aniline (30 g; 162 mmol) in acetonitrile (400 mL) there are added 58 g of Cs<sub>2</sub>CO<sub>3</sub> (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 purified by chromatography over silica gel using petroleum ether and ethyl acetate as eluants. The title product is then obtained in the  
25     form of a colourless solid.

**<sup>1</sup>H NMR:**  $\delta$  (400 MHz; dmso-d<sub>6</sub>; 300K): 7.80 (m, 1H, NH); 7.45 (m, 2H, aryl); 7.40 (m, 2H, aryl); 7.30 (m, 1H, aryl); 7.15 (s, 2H, aryl); 7.05 (d, 2H, aryl); 6.9-7.0 (m, 4H, aryl); 6.70 (t, 1H, aryl); 5.05 (s, 2H, benzyl).

**IR:**  $\nu$ : >NH: 3408 cm<sup>-1</sup>

5 **Preparation 9'':** *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 by 4-bromopyridine.

**IR:**  $\nu$  -NH-: 3200 and 2500 cm<sup>-1</sup>;  $\nu$ :-Si-O-: 902 cm<sup>-1</sup>;  $\nu$ :-Si-C-: 820 cm<sup>-1</sup>

**Preparation 10'':** *N*-(4-{{*tert*-Butyl(dimethyl)silyl}oxy}phenyl)-4-fluoroaniline

10 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 1-bromo-4-fluorobenzene.

**Preparation 11'':** *N*-(4-{{*tert*-Butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-amine

15 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 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:**  $\nu$ :-NH-: 3278 cm<sup>-1</sup>;  $\nu$ : aromatic -C=C- moieties: 1605 cm<sup>-1</sup>

20 **Preparation 12'':** *N*-(4-{{*tert*-Butyl(dimethyl)silyl}oxy}phenyl)-2-methoxy-pyrimidin-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 by 5-bromo-2-methoxypyrimidine.



**Preparation 13'':** *N*-(4-{{*tert*-Butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-2,3-dihydro-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 by 5-bromo-1-methyl-2,3-dihydro-1*H*-pyrrolo-  
5 [2,3-*b*]pyridine.

**Preparation 14'':** *N*-(4-{{*tert*-Butyl(dimethyl)silyl}oxy}phenyl)-1-methyl-1*H*-benzimidazol-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 by 5-bromo-1-methyl-1*H*-benzimidazole.

10 **Preparation 15'':** *N*<sup>4</sup>-(4-{{*tert*-Butyl(dimethyl)silyl}oxy}phenyl)-*N*<sup>2</sup>,*N*<sup>2</sup>-dimethylpyridine-2,4-diamine

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 4-bromo-*N,N*-dimethylpyridin-2-amine.

15 **Preparation 16'':** *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 by 6-bromopyrazolo[1,5-*a*]pyrimidine.

**IR:**  $\nu$  -NH-: 3272 cm<sup>-1</sup>;  $\nu$  -C=N-: 1634 cm<sup>-1</sup>;  $\nu$  -C=C-: 1616 cm<sup>-1</sup>

20 **Preparation 17'':** *N*-[4-{{*tert*-Butyl(dimethyl)silyl}oxy}phenyl]-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 by 5-bromo-1-methyl-pyrazolo[3,4-*b*]pyridine (obtained in accordance with a protocol from the literature: WO 2006/052568 starting from 2-methyl-pyrazol-3-amine and 2-bromopropanedial).

**Preparation 18'':** 4-({4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}amino)-1,5-dimethyl-1*H*-pyrrole-2-carbonitrile

**Step A:** 4-Bromo-1,5-dimethyl-1*H*-pyrrole-2-carbonitrile

A solution of bromine (6.58 mL, 0.13 mol) in acetic acid (60 mL) is added dropwise, with the aid of a dropping funnel, to a solution of 1,5-dimethyl-1*H*-pyrrole-2-carbonitrile (15.0 g, 0.12 mol) in acetic acid (300 mL). The batch is stirred at ambient temperature for 24 hours. The reaction mixture is then poured into a beaker containing 300 mL of water. The solid formed is filtered off and rinsed with water. It is then dissolved in dichloromethane (300 mL) and the organic phase is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to yield the expected product in the form of a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ ppm: 2.25 (s, 3 H), 3.67 (s, 3 H), 6.74 (s, 1 H)

**Step B:** 4-({4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}amino)-1,5-dimethyl-1*H*-pyrrole-2-carbonitrile

A solution of the compound of the above Step (1.5 g, 7.53 mmol), 4-[(*tert*-butyldimethylsilyl)oxy]aniline (2.02 g, 9.04 mmol), sodium *tert*-butylate (1.45 g, 15.06 mmol) and 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (0.13 g, 0.30 mmol) in toluene (20 mL) is purged with nitrogen. Tris(dibenzylideneacetone)-dipalladium(0) (0.28 g, 0.30 mmol) is added, and then the reaction mixture is heated at 90°C until the reaction is complete (monitored by TLC). Heating is stopped and the mixture is allowed to return to ambient temperature. Water (75 mL) is added and the mixture is extracted with ethyl acetate (3 x 75 mL). The combined organic phases are washed with brine and then concentrated. The crude product is absorbed onto silica gel and purified by chromatography over silica gel using ethyl acetate and heptane as eluants. The product thereby obtained is dissolved in heptane in the warm state and is allowed to precipitate, with stirring, at ambient temperature, and then at 0°C. The solid is filtered off and the operation is repeated on the filtrate to yield the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 0.15 (s, 6 H), 0.97 (s, 9 H), 2.13 (s, 3 H), 3.66 (s, 3 H), 4.68 (br. s, 1 H), 6.49 (d, *J* = 8.5 Hz, 2 H), 6.64 (s, 1 H), 6.66 (d, *J* = 8.7 Hz, 2 H)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm: 4.34, 9.72, 18.30, 25.88, 32.94, 101.27, 114.37, 114.70, 116.41, 120.73, 124.52, 131.23, 141.54, 148.27

5 MS (ESI<sup>+</sup>): [M+H]<sup>+</sup> measured: 342.3

**Preparation 19'': 4-[(4-{*tert*-Butyl(dimethyl)silyl}oxy)phenyl]amino]-1-methyl-1*H*-pyrrole-2-carbonitrile**

**Step A: 1-Methyl-1*H*-pyrrole-2-carbonitrile**

10 *N,N*-Dimethylformamide (3 mL) and 1,4-diazabicyclo[2.2.2]octane (0.49 g, 4.3 mmol) are added to a solution of pyrrole-2-carbonitrile (4 g, 43.4 mmol) in dimethyl carbonate (56 mL). The solution is stirred at 90°C for 15 hours, and is then heated at 110°C for 8 hours. The mixture is cooled to ambient temperature, and then ethyl acetate (80 mL) is added. The phases are separated and the organic phase is washed with water (2 x 80 mL) and 1N aqueous HCl solution (1 x 80 mL). The combined aqueous phases are extracted  
15 again with ethyl acetate (1 x 80 mL). The combined organic phases are washed with brine (1 x 80 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to obtain the expected product in the form of a liquid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 3.78 (m, 2 H), 6.12 - 6.18 (m, 1 H), 6.74 - 6.82 (m, 1 H)

20 **Step B: 4-Bromo-1-methyl-1*H*-pyrrole-2-carbonitrile**

*N*-Bromosuccinimide (6.2 g, 34.9 mmol) is added to a solution of 1-methyl-1*H*-pyrrole-2-carbonitrile (3.7 g, 34.9 mmol) in *N,N*-dimethylformamide (150 mL). The solution is stirred for 15 hours at ambient temperature. Another amount of *N*-bromosuccinimide (2.0 g, 11 mmol) is added and the mixture is stirred for 3 hours. Silica (7 g) is then added  
25 and the suspension is then evaporated to dryness. The material pre-absorbed onto the silica is placed on a silica gel column and the product is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to obtain the expected product in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 3.77 (s, 3 H), 6.75 (d, *J* = 1.7 Hz, 1 H), 6.80 (d, *J* = 1.7 Hz, 1 H)

**Step C:**      ***4-[(tert-Butyldimethylsilyl)oxy]phenyl}amino)-1-methyl-1H-pyrrole-2-carbonitrile***

5 Nitrogen is bubbled through a solution of 4-bromo-1-methyl-1H-pyrrole-2-carbonitrile (2.82 g, 15.2 mmol) and 4-[(*tert*-butyldimethylsilyl)oxy]aniline (4.08 g, 18.3 mmol) in toluene (55 mL) for 5 minutes. Sodium *tert*-butylate (2.92 g, 30.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (556 mg, 0.6 mmol) and 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (255 mg, 0.6 mmol) are then added to the  
10 reaction mixture. The mixture is stirred for 1 hour at 80°C under nitrogen. The suspension is then cooled to ambient temperature and filtered over Celite. The Celite cake is then rinsed with ethyl acetate. The filtrate is washed with water and then with brine. The organic phase is dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The product is purified twice by chromatography over silica gel using ethyl acetate and heptane as  
15 eluants, and then by trituration in heptane to obtain the expected product in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 0.16 (s, 6 H), 0.97 (s, 9 H), 3.73 (s, 3 H), 6.57 (d, *J* = 1.9 Hz, 1 H), 6.64 - 6.66 (m, 1 H), 6.70 (s, 4 H); NMR

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm: -4.48, 18.17, 25.72, 35.46, 103.01, 113.56, 113.69,  
20 115.92, 119.55, 120.67, 129.04, 139.94, 148.85

MS (ESI<sup>+</sup>): [M+H]<sup>+</sup> 328.25

**Preparation 20'':** ***N-[4-[tert-Butyl(dimethyl)silyl]oxy-3-fluoro-phenyl]-1-methyl-1H-pyrazol-4-amine***

25 The procedure is in accordance with the protocol of Preparation 1'', replacing the 4-aminophenol used in Step A by 2-fluoro-4-aminophenol.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 7.59 (bs, 1 H), 7.39 (m, 1 H), 7.24 (d, 1 H), 6.74 (dd, 1 H), 6.52 (dd, 1 H), 6.42 (ddd, 1 H), 3.76 (s, 3 H), 0.92 (s, 9 H), 0.1 (d, 6 H)

**Preparation 21'': 2-({4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}amino)pyridine-4-carbonitrile**

A solution composed of 2-bromo-4-pyridinecarbonitrile (5.00 g, 36.1 mmol), 4-[(*tert*-butyldimethylsilyl)oxy]aniline (8.06 g, 36.1 mmol), sodium *tert*-butylate (4.50 g, 46.9 mmol) and 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (0.458 g, 1.08 mmol) in toluene (50 mL) is purged with nitrogen. Tris(dibenzylideneacetone)-dipalladium(0) (0.99 g, 1.08 mmol) is then added to the reaction mixture, and then the batch is heated at 50°C for 1.5 hours. The mixture is then allowed to cool to ambient temperature. Water is added and the reaction mixture is extracted with ethyl acetate (3 x 20 mL). The combined organic phases are washed with brine, and then concentrated under reduced pressure. The crude product is absorbed onto silica gel and purified by chromatography over silica gel using ethyl acetate and heptane as eluants. The product obtained is dissolved in the warm state in heptane and precipitates, with stirring, at ambient temperature, and then at 0°C. After filtration, the expected compound is obtained in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 0.22 (s, 6 H), 1.00 (s, 9 H), 6.61 (br. s, 1 H), 6.81 - 6.84 (m, 2 H), 6.84 - 6.89 (m, 2 H), 7.12 - 7.17 (m, 2 H), 8.26 (dd, *J* = 5.1, 0.9 Hz, 1 H)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm: -4.29, 18.31, 25.78, 109.11, 114.73, 117.23, 121.17, 121.74, 124.93, 132.12, 149.79, 153.45, 158.00

MS (ESI<sup>+</sup>): [M+H]<sup>+</sup> 326.19

**Preparation 22'': *N*-[4-[(*tert*-Butyl(dimethyl)silyl]oxyphenyl]-1-tetrahydrofuran-3-yl-pyrazol-4-amine**

4-[(*tert*-Butyl(dimethyl)silyl)oxy]aniline (0.92 g, 3.48 mmol) and 4-iodo-1-tetrahydrofuran-3-yl-pyrazole (0.78 g, 3.48 mmol) dissolved in anhydrous tetrahydrofuran (20 mL) are stirred for one hour at ambient temperature in the presence of sodium *tert*-butylate (1.7 mL, 2M solution in THF) and chloro(2-di-*tert*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (84 mg, 0.122 mmol). The reaction mixture is filtered over Celite and then evaporated to dryness. The residue is crystallised from a mixture of heptane/ethyl acetate, filtered and washed with heptane and then purified

by chromatography over silica gel using dichloromethane and methanol as eluants to yield the expected product.

**<sup>1</sup>H NMR** (500 MHz, dmso-d<sub>6</sub>, 300 K) δ ppm: 7.62 (d, 1H, pyrazole-H5), 7.29 (d, 1H, pyrazole-H3), 7.26 (s, 1H, NH), 6.68 (d, 2H, Ar-H), 6.64 (d, 2H, Ar-H), 4.93 (m, 1H, THF-3'H), 3.95 (m, 1H, THF-5'H), 3.94 (m, 1H, THF-2'H), 3.87 (m, 1H, THF-2'H), 3.80 (m, 1H, THF-5'H), 2.33 (m, 1H, THF-4'H), 2.27 (m, 1H, THF-4'H), 0.93 (s, 9H, <sup>t</sup>Bu), 0.12 (s, 6H, Me)

**IR:** ν C-H: 2857 cm<sup>-1</sup>; ν aromatic: 1505 cm<sup>-1</sup>; ν Si-C: 1249 cm<sup>-1</sup>

**Preparation 23'': 6-({4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}amino)pyridine-2-carbonitrile**

4-Aminophenol (3.3 g, 30.2 mmol) is added to a solution of 6-chloropyridine-2-carbonitrile (3.5 g, 25.3 mmol) in 1-methyl-2-pyrrolidinone (70 mL). The reaction mixture is heated at 140-150°C for 16 hours in a sealed flask. The batch is then cooled to ambient temperature. Imidazole (3.4 g, 49.9 mmol) and *tert*-butyl(dimethyl)silyl chloride (7.6 g, 50.4 mmol) are subsequently added and the mixture is stirred for 16 hours at ambient temperature. The mixture is diluted with water (140 mL) and the product is extracted with AcOEt (4 x 50 mL). The organic phases are combined and washed with water (3 x 50 mL), and then brine (1 x 50 mL). The organic phase is then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to obtain the title product.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ ppm: 0.20 (s, 6 H), 0.99 (s, 9 H), 6.74 (dd, *J* = 7.6, 4.9 Hz, 1 H), 6.81 - 6.88 (m, 3 H), 7.36 - 7.42 (m, 2 H), 7.74 (dd, *J* = 7.6, 1.9 Hz, 1 H), 8.34 (dd, *J* = 4.9, 1.9 Hz, 1 H)

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ ppm: -4.38, 18.21, 25.73, 92.58, 113.50, 116.53, 120.30, 123.20, 131.97, 141.67, 152.42, 152.45, 156.51

**MS (ESI):** [M+H]<sup>+</sup> 326.24

**Preparation 24'': 4-({4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}amino)pyrimidine-2-carbonitrile**

**Step A: *N*-{4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}-2-chloropyrimidin-4-amine**

4-Aminophenol (8.8 g, 80.6 mmol) and triethylamine (18.6 mL, 133.4 mmol) are added to a solution of 2,4-dichloropyrimidine (10.0 g, 67.1 mmol) in ethanol (150 mL). The reaction mixture is heated at 150°C for 14 hours in a sealed flask. The batch is then cooled to ambient temperature and the solvent is evaporated off *in vacuo*. Dichloromethane (200 mL) is added to the residue, and then imidazole (9.1 g, 133.7 mmol) and *tert*-butyl(dimethyl)silyl chloride (12.1 g, 80.3 mmol) are added. The mixture is stirred for 15 hours at ambient temperature. The reaction mixture is diluted with water (200 mL). The phases are separated and the organic phase is washed with brine (1 x 100 mL). It is then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to obtain a solid. The latter is triturated in heptane, filtered off and rinsed with heptane to yield the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 0.22 (s, 6 H), 0.99 (s, 9 H), 6.42 (d, *J* = 5.9 Hz, 1 H), 6.81 (br. s, 1 H), 6.85 - 6.90 (m, 1 H), 7.13 (d, *J* = 8.7 Hz, 2 H), 8.07 (d, *J* = 5.9 Hz, 2 H)

**Step B: 4-({4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}amino)pyrimidine-2-carbonitrile**

Anhydrous *N,N*-dimethylformamide (10 mL) is placed under nitrogen in a flask and then the compound of Step A (670 mg, 2.0 mmol) is added. Zinc cyanide (468 mg, 4.0 mmol) and tetrakis(triphenylphosphine)palladium(0) (404 mg, 0.3 mmol) are subsequently added. Nitrogen is bubbled through the solution for 5 minutes and then the reaction mixture is stirred at 120°C for 2 hours under a nitrogen atmosphere. The reaction, monitored by LC-MS, is complete. The mixture is cooled to ambient temperature, and then water (15 mL) is added thereto. The product is extracted with AcOEt (3 x 25 mL). The organic phases are combined and washed with water (4 x 25 mL), and then with brine (1 x 25 mL). The organic phase is dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue is

purified by chromatography over silica gel using ethyl acetate and heptane as eluants to obtain the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 0.22 (s, 6 H), 0.99 (s, 9 H), 6.63 (d, *J* = 6.1 Hz, 1 H), 6.86 - 6.92 (m, 2 H), 7.03 (br. s, 1 H), 7.17 (d, *J* = 8.5 Hz, 2 H), 8.22 (d, *J* = 6.1 Hz, 1 H)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm: -4.51, 18.10, 25.55, 106.32, 115.92, 121.00, 125.22, 129.73, 144.55, 154.16, 156.07, 161.56

**Preparation 25'': *N*-{4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}-1-trideuteriomethyl-1*H*-pyrazol-4-amine**

**Step A: 4-Bromo-1-trideuteriomethyl-1*H*-pyrazole**

4-Bromo-1*H*-pyrazole (9.05 g, 61.6 mmol) is added in portions to a suspension of NaH (60 % in oil) (2.83 g, 70.8 mmol) in tetrahydrofuran (90 mL) cooled in an ice bath. After having taken away the ice bath, the solution is stirred at ambient temperature for 0.5 hours. It is again cooled in an ice bath and iodomethane-*d*<sub>3</sub> (5.0 mL, 80.3 mmol) is added. The solution is stirred at ambient temperature for 19 hours. The suspension is then concentrated. The evaporation residue is triturated with MTBE (90 mL) and filtered. The filtrate is concentrated *in vacuo* to obtain the expected compound in the form of an oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 7.37 (s, 1 H), 7.43 (s, 1 H)

**Step B: *N*-{4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}-1-trideuteriomethyl-1*H*-pyrazol-4-amine**

4-Bromo-1-trideuteriomethyl-1*H*-pyrazole (9.6 g, 58.5 mmol), 4-[(*tert*-butyldimethylsilyl)oxy]aniline (14.4 g, 64.6 mmol) and toluene (150 mL) are added to a 500-ml three-necked flask. The solution is degassed with nitrogen for 15 minutes, and then sodium *tert*-butylate (11.4 g, 0.12 mol), 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (0.77 g, 1.81 mmol) and tris(dibenzylideneacetone)dipalladium(0) (1.64 g, 1.79 mmol) are successively added. The suspension is heated at 85°C for 1.5 hours. The reaction mixture is then cooled to ambient temperature and water (270 mL) is added. The mixture is stirred for 30 minutes. Celite (30 g) is then added and the suspension is filtered on a bed of Celite.



The phases of the filtrate are separated and the aqueous phase is extracted with ethyl acetate (3 x 200 mL). The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. Silica (36 g) is added to the filtrate and the batch is evaporated to dryness. The product is purified by chromatography over silica gel using ethyl acetate and heptane as eluants. The product obtained is recrystallised from heptane (80 mL) to obtain the expected compound.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 0.16 (s, 6 H), 0.97 (s, 9 H), 4.92 (s, 1 H), 6.61 – 6.73 (m, 4 H), 7.25 (s, 1 H), 7.36 (s, 1 H)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm: -4.37, 18.28, 25.86, 38.67 (sept., <sup>1</sup>J<sub>C-D</sub> = 21.0 Hz), 115.12, 120.73, 123.76, 126.52, 134.74, 141.07, 148.43

MS (ESI): [M+H]<sup>+</sup> 307.08

**Preparation 26'': *N*-[4-[*tert*-Butyl(dimethyl)silyl]oxyphenyl]-1-(oxetan-3-yl)-1*H*-pyrazol-4-amine**

**Step A: 4-Bromo-1-(oxetan-3-yl)-1*H*-pyrazole**

4-Bromo-1*H*-pyrazole (1.53 g, 10.7 mmol) is dissolved in anhydrous dimethylformamide (15 mL). 3-Bromooxetane (2.0 g, 14.6 mmol) and caesium carbonate (4.7 g, 14 mmol) are successively added thereto. The reaction mixture is heated for 8 hours at 130°C in a sealed flask. At the end of the reaction, the solvent is evaporated off *in vacuo* and the residue is purified by chromatography over silica gel using dichloromethane containing diethylamine and methanol as eluants to yield the expected compound.

**Step B: *N*-[4-[*tert*-Butyl(dimethyl)silyl]oxyphenyl]-1-(oxetan-3-yl)-1*H*-pyrazol-4-amine**

4-[*tert*-Butyl(dimethyl)silyl]oxyaniline (1.5 g, 7.2 mmol) and 4-bromo-1-(oxetan-3-yl)-pyrazole (1.6 g, 7.2 mmol) dissolved in anhydrous tetrahydrofuran (25 mL) are stirred for 3 hours at ambient temperature in the presence of sodium *tert*-butylate (3.7 mL, 2M solution in THF) and chloro(2-di-*tert*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (101 mg, 0.145 mmol). The reaction mixture is filtered over Celite and then evaporated to dryness. The residue is purified by chromatography over silica gel using dichloromethane containing diethylamine and ethyl acetate as eluants to yield the expected product.

<sup>1</sup>H NMR (500 MHz, dms<sub>o</sub>-d<sub>6</sub>, 300 K) δ ppm: 7.76 (s, 1H, pyrazole-5'H), 7.40 (s, 1H, pyrazole-3'H), 7.34 (br s, 1H, NH), 6.70 (d, 2H, Ar-H), 6.65 (d, 2H, Ar-H), 5.49 (m, 1H, oxetane), 4.89 (d, 4H, oxetane), 0.93 (s, 9H, <sup>t</sup>Bu), 0.13 (s, 6H, Me)

IR: ν: C-H: 2955 cm<sup>-1</sup>; aromatic: 1505 cm<sup>-1</sup>; Si-C: 1237 cm<sup>-1</sup>

5 **Preparation 27'': Mixture of *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1,5-dimethyl-1*H*-pyrazol-4-amine and *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1,3-dimethyl-1*H*-pyrazol-4-amine**

**Step A: Mixture of 4-bromo-1,5-dimethyl-1*H*-pyrazole and 4-bromo-1,3-dimethyl-1*H*-pyrazole**

10 To a suspension of NaH 60 % in oil (0.3 g; 7.45 mmol) in tetrahydrofuran (150 mL) there is added, at 10°C, 4-bromo-3-methyl-1*H*-pyrazole dissolved in 15 mL of tetrahydrofuran dropwise, over 15 minutes. After stirring for 40 minutes at ambient temperature, iodomethane (0.45 mL; 7.45 mmol) is added dropwise, and then the reaction mixture is stirred overnight. After adding water, the reaction mixture is evaporated and taken up in  
15 dichloromethane. The organic phase is separated off and dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. The residue is purified by chromatography over silica gel to yield a mixture of the title compounds (4-bromo-1,3-dimethyl-pyrazole and 4-bromo-1,5-dimethyl-pyrazole respectively in a ratio of 4:6).

**4-bromo-1,5-dimethyl-1*H*-pyrazole:**

20 <sup>1</sup>H NMR (500 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 7.41 (s, 1 H), 3.76 (s, 3 H), 2.22 (s, 3 H)

**4-bromo-1,3-dimethyl-1*H*-pyrazole:**

<sup>1</sup>H NMR (500 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 7.81 (s, 1 H), 3.74 (s, 3 H), 2.09 (s, 3 H)

**Step B: Mixture of *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1,5-dimethyl-1*H*-pyrazol-4-amine and *N*-(4-{{*tert*-butyl(dimethyl)silyl}oxy}phenyl)-1,3-dimethyl-1*H*-pyrazol-4-amine**

25 The procedure is in accordance with Step B of Preparation 1'', replacing the 4-bromo-1-methyl-1*H*-pyrazole by the mixture of isomers from Step A. A mixture of isomers in a

ratio of 4:6 is obtained (respectively *N*-(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1,5-dimethyl-1*H*-pyrazol-4-amine and *N*-(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-1,3-dimethyl-1*H*-pyrazol-4-amine).

**Preparation 28''': *N*-[4-[*tert*-Butyl(dimethyl)silyl]oxyphenyl]-1-cyclopropyl-1*H*-pyrazol-4-amine**

**Step A: 4-Bromo-1-cyclopropyl-1*H*-pyrazole**

4-Bromo-1*H*-pyrazole (1.76 g, 12 mmol) is dissolved in anhydrous dimethylformamide (15 mL). Cyclopropyl bromide (2.9 mL, 36 mmol) and caesium carbonate (7.8 g, 24 mmol) are successively added thereto. The reaction mixture is heated for 15 hours at 160°C in a sealed flask. At the end of the reaction, the solvent is evaporated off *in vacuo* and the residue is purified by chromatography over silica gel using heptane and dichloromethane as eluants to yield the expected compound.

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

4-[*tert*-Butyl(dimethyl)silyl]oxyaniline (1.64 g, 7.3 mmol) and 4-bromo-1-cyclopropyl-1*H*-pyrazole (1.4 g, 7.3 mmol) dissolved in anhydrous tetrahydrofuran (30 mL) are stirred for 3 hours at ambient temperature in the presence of sodium *tert*-butylate (3.7 mL, 2M solution in THF) and chloro(2-di-*tert*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (101 mg, 0.146 mmol). The reaction mixture is filtered over Celite and then evaporated to dryness. The residue is purified by chromatography over silica gel using heptane and ethyl acetate as eluants to yield the expected product.

**<sup>1</sup>H NMR** (500 MHz, dms<sub>o</sub>-d<sub>6</sub>, 300 K) δ ppm: 7.61 (s, 1H, pyrazole-5'H), 7.23 (s, 1H, pyrazole-3'H), 7.22 (br s, 1H, NH), 6.65 (d, 2H, Ar-H), 6.63 (d, 2H, Ar-H), 3.64 (m, 1H, cyclopropyl-H), 1.00 – 0.91 (m, 4H, cyclopropyl), 0.93 (s, 9H, <sup>t</sup>Bu), 0.12 (s, 6H, Me)

**IR:** ν: C-H: 2930 cm<sup>-1</sup>; aromatic: 1504 cm<sup>-1</sup>; Si-C: 1237 cm<sup>-1</sup>

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

Empirical formula: C<sub>18</sub>H<sub>27</sub>N<sub>3</sub>OSi

[M+H]<sup>+</sup> calculated: 330.2003

[M+H]<sup>+</sup> measured: 330.1989

5     **Preparation 29'': 1,5-Dimethyl-4-(phenylamino)-1*H*-pyrrole-2-carbonitrile**

The procedure is in accordance with the protocol of Preparation 1'', replacing the 4-{{*tert*-butyl(dimethyl)silyl}oxy}aniline used in Step B by aniline.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 7.19 (s, 1 H), 7.05 (t, 2 H), 6.79 (s, 1 H), 6.6 (m, 3 H), 3.61 (s, 3 H), 2.1 (s, 3 H)

10    **Preparation 30'': 1-Methyl-*N*-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-amine**

The procedure is in accordance with the protocol of Step B of Preparation 1'' using aniline and 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).

15    <sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 8.1 (d, 1 H), 7.9 (s, 1 H), 7.7 (d, 1 H), 7.45 (d, 1 H), 7.17 (t, 2 H), 6.9 (d, 2 H), 6.7 (t, 1 H), 6.38 (d, 1 H), 3.8 (s, 3 H)

**Preparation 31'': *N*-(4-{{*tert*-Butyl(dimethyl)silyl}oxy}phenyl)-1-trideuteriomethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-amine**

20    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 5-bromo-1-(trideuteriomethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (obtained in accordance with a protocol from the literature *Heterocycles*, 60(4), 865, 2003, replacing the methyl iodide by trideuterated methyl iodide).

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 8.05 (d, 1 H), 7.6 (m+d, 2 H), 7.4 (d, 1 H), 6.85/6.7 (2d, 4 H), 6.3 (d, 1 H), 0.95 (s, 9 H), 0.15 (s, 6 H)

**Preparation 32'': 4-({4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}amino)-1-trideuteriomethyl-1*H*-pyrrole-2-carbonitrile**

**Step A: 1-Trideuteriomethyl-1*H*-pyrrole-2-carbonitrile**

NaH (60 % in oil) (2.61 g, 65.2 mmol) is suspended in tetrahydrofuran (110 mL) at 0°C. 1*H*-Pyrrole-2-carbonitrile (5 g, 54.3 mmol) is added dropwise over 10 minutes. The reaction mixture is then warmed up to ambient temperature over 30 minutes. It is again cooled to 0°C, and then iodomethane-*d*<sub>3</sub> (10.23 g, 70.6 mmol) is added. The reaction mixture is stirred for 16 hours under nitrogen at ambient temperature. The reaction mixture is then evaporated under reduced pressure, and then ethyl acetate (200 mL) and water (200 mL) are added. The phases are separated, and the aqueous phase is extracted with ethyl acetate (2 x 200 mL). The combined organic phases are washed with brine (1 x 80 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue is purified by chromatography over silica gel using ethyl acetate and heptane as eluants. The fractions are combined and evaporated *in vacuo* to obtain the expected compound.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 6.13 (dd, *J* = 2.7, 3.9 Hz, 1 H), 6.75 (dd, *J* = 1.5, 4.1 Hz, 1 H), 6.79 (dd, *J* = 1.7, 2.6 Hz, 1 H)

**Step B: 4-Bromo-1-trideuteriomethyl-1*H*-pyrrole-2-carbonitrile**

*N*-Bromosuccinimide (6.68 g, 37.5 mmol) is added to a solution of the compound of the above Step (4.09 g, 37.5 mmol) in *N,N*-dimethylformamide (188 mL). The solution is stirred for 16 hours at ambient temperature. The residue is purified by chromatography using ethyl acetate and heptane as eluants to obtain the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 6.75 (d, *J* = 1.7 Hz, 1H), 6.80 (d, *J* = 1.7 Hz, 1 H)

**Step C: 4-({4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}amino)-1-trideuteriomethyl-1*H*-pyrrole-2-carbonitrile**

Nitrogen is bubbled through a solution composed of the compound obtained in the above Step (5.85 g, 31.1 mmol), 4-[(*tert*-butyldimethylsilyl)oxy]aniline (8 g, 35.8 mmol), sodium

*tert*-butylate (3.88 g, 40.4 mmol) and 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (662 mg, 1.56 mmol) in toluene (260 mL) for 5 minutes. Tris(dibenzylideneacetone)-dipalladium(0) (1.43 g, 1.56 mmol) is then added. The mixture is stirred for 1 hour at 70°C under nitrogen. The suspension is then cooled to ambient temperature, diluted with ethyl acetate and filtered over Celite. The Celite cake is then rinsed with ethyl acetate. The filtrate is washed with water (3 times), and then brine (once). The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The product is purified twice by chromatography over silica gel using ethyl acetate and heptane as eluants, and then by reverse-phase chromatography using methanol and water as eluants to obtain the expected compound in the form of a powder.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 0.17 (s, 6 H), 0.98 (s, 9 H), 4.96 (br. s, 1 H), 6.57 (d, *J* = 1.9 Hz, 1 H), 6.64 (d, *J* = 1.8 Hz, 1 H), 6.70 (br. s, 4 H)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm: -4.38, 18.26, 25.83, 34.83, 102.96, 113.69, 113.71, 115.95, 119.58, 120.75, 129.14, 140.10, 148.84

MS (ESI): [M+H]<sup>+</sup> 331.09

**Preparation 33'': 4-({4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}amino)-1-trideuterio-methyl-5-methyl-1*H*-pyrrole-2-carbonitrile**

**Step A: 5-Methyl-1*H*-pyrrole-2-carbonitrile**

The compound is prepared in accordance with the protocol described in *Heterocycles* **2011**, 82, 1503.

**Step B: 1-Trideuteriomethyl-5-methyl-1*H*-pyrrole-2-carbonitrile**

A solution of 5-methyl-1*H*-pyrrole-2-carbonitrile (0.30 g, 2.82 mmol) in *N,N*-dimethyl-formamide (5 mL) is cooled to 0°C. NaH (60 % in oil) (0.118 g, 2.96 mmol) is added in portions, and the reaction mixture is stirred at 0°C for 30 minutes. Iodomethane-*d*<sub>3</sub> (4.15 mL, 67.2 mmol) is added in a single portion, and the reaction mixture is stirred at ambient temperature until the reaction is complete. It is then diluted with water (30 mL) and ethyl acetate (15 mL). The phases are separated and the aqueous phase is extracted a second time with ethyl acetate (15 mL). The combined organic phases are washed with

water (1 x 50 mL), and then brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the residue is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to yield the expected compound in the form of a solid.

5     <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 2.25 (s, 3 H), 5.91 (dd, *J* = 3.9, 0.6 Hz, 1 H), 6.69 (d, *J* = 3.9 Hz, 1 H)

**Step C: 4-Bromo-1-trideuteriomethyl-5-methyl-1H-pyrrole-2-carbonitrile**

10     A solution of bromine (0.133 mL, 2.60 mmol) in acetic acid (1.5 mL) is added dropwise to a solution of the compound obtained in the above Step (0.305 g, 2.48 mmol) in acetic acid (5.5 mL) previously cooled to 0°C. The reaction mixture is stirred and gradually warmed up to ambient temperature over a period of 20 hours. The reaction mixture is poured into water (50 mL) and the mixture is extracted with dichloromethane (2 x 50 mL). The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to yield the expected compound in the form of a solid.

15     <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 2.24 (s, 3 H), 6.73 (s, 1 H)

**Step D: 4-({4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}amino)-1-trideuteriomethyl-5-methyl-1H-pyrrole-2-carbonitrile**

20     A solution composed of the compound obtained in the above Step (7.00 g, 34.6 mmol), 4-[(*tert*-butyldimethylsilyl)oxy]aniline (8.90 g, 39.8 mmol), sodium *tert*-butylate (4.33 g, 45.0 mmol) and 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (0.441 g, 1.04 mmol) in toluene (70 mL) is purged with nitrogen. Tris(dibenzylideneacetone)-dipalladium(0) (0.951 g, 1.04 mmol) is added, and then the reaction mixture is heated at 65°C until the reaction, monitored by TLC, is complete. Heating is stopped and the mixture is cooled to ambient temperature. Water (200 mL) is added and the mixture is  
25     extracted with ethyl acetate (3 times). The combined organic phases are washed with brine, and then concentrated. The crude product is purified by chromatography over silica gel using ethyl acetate and heptane as eluants. The product obtained is dissolved in heptane in

the warm state; it is allowed to precipitate out at ambient temperature and then at 0°C to yield the expected product in the form of crystals.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 0.15 (s, 6 H), 0.96 (s, 9 H), 2.12 (s, 3 H), 4.66 (br. s, 1 H), 6.46 - 6.51 (m, 2 H), 6.64 (s, 1 H), 6.64 - 6.69 (m, 2 H)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm: -4.37, 9.64, 18.26, 25.84, 31.62 - 32.87 (m), 101.14, 114.35, 114.66, 116.33, 120.68, 124.51, 131.17, 141.53, 148.18

MS (ESI): [M+H]<sup>+</sup> 345.13

**Preparation 34'': 5-[(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)amino]-1-methyl-1*H*-pyrazole-3-carbonitrile**

**Step A: 5-Amino-1-methyl-1*H*-pyrazole-3-carbonitrile**

To a suspension of 1-methyl-5-nitro-1*H*-pyrazole-3-carbonitrile (2 g; 13.1 mmol) in a mixture of water (14 mL) and ethanol (120 mL) there are added HCl 37 % (170 μL) and iron filings (5.1 g; 91 mmol). The reaction mixture is heated for 5 hours at 50°C. After cooling to ambient temperature, the reaction mixture is filtered. The filtrate is concentrated to dryness and then purified by chromatography over silica gel using dichloromethane and ethyl acetate as eluants to yield the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 5.8 (s, 1 H), 5.7 (m, 2 H), 3.6 (s, 3 H)

**Step B: 5-[(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)amino]-1-methyl-1*H*-pyrazole-3-carbonitrile**

The procedure is in accordance with the protocol of Step B of Preparation 1'', replacing the 4-bromo-1-methyl-1*H*-pyrazole by (4-bromophenoxy)-(*tert*-butyl)dimethyl-silane and the 4-{[*tert*-butyl(dimethyl)silyl]oxy}aniline by the compound from Step A.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 8.15 (s, 1 H), 6.9 (d, 2 H), 6.75 (d, 2 H), 6.45 (s, 1 H), 3.75 (s, 3 H), 0.95 (s, 9 H), 0.15 (s, 6 H)



**Preparation 35'':** 4-[(4-{*tert*-Butyl(dimethyl)silyl}oxy)phenyl]amino]-5-methyl-1-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-2-carbonitrile

The procedure is in accordance with the process of Preparation 33'', replacing the iodomethane-*d*<sub>3</sub> in Step B by 2-(chloroethyl)morpholine hydrochloride.

5     <sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 6.85 (s, 1 H), 6.75 (s, 1 H), 6.6 (d, 2 H), 6.5 (d, 2 H), 4.1 (t, 2 H), 3.55 (t, 4 H), 2.6 (t, 2 H), 2.4 (t, 4 H), 2.1 (s, 3 H), 0.9 (s, 9 H), 0.1 (s, 6 H)

**Preparation 36'':** *N*-(4-{*tert*-Butyl(dimethyl)silyl}oxy)phenyl)-2-[2-(morpholin-4-yl)ethoxy]pyrimidin-5-amine

10     **Step A:** 4-[2-(5-Bromopyrimidin-2-yl)oxyethyl]morpholine

NaH (1.0 g, 25.0 mmol, 60 % in oil) suspended in anhydrous tetrahydrofuran is cooled at 0°C in an ice bath under argon, and then 2-morpholinoethanol (2.7 g, 20.7 mmol) is added dropwise. The ice bath is withdrawn and the suspension is stirred for 1 hour at ambient temperature. 5-Bromo-2-chloro-pyrimidine (4.0 g, 20.7 mmol) is then added at ambient  
15     temperature and the reaction mixture is stirred for 16 hours at ambient temperature. Saturated aqueous ammonium chloride solution (10 mL) and water (10 mL) are added to the reaction mixture; the pH is adjusted to 9 by adding saturated aqueous NaHCO<sub>3</sub> solution. The resulting solution is extracted 3 times with ethyl acetate, the organic phase is then washed with brine, dried over MgSO<sub>4</sub>, and then evaporated to dryness. The expected  
20     compound precipitates out by means of the addition of petroleum ether.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 8.75 (s, 2 H), 4.4 (t, 2 H), 3.55 (t, 4 H), 2.7 (t, 2 H), 2.45 (t, 4 H)

IR (ATR) cm<sup>-1</sup>: 1562 ν >C=C< and C=N, 787 ν -C-H Ar

25     **Step B:** *N*-(4-{*tert*-Butyl(dimethyl)silyl}oxy)phenyl)-2-[2-(morpholin-4-yl)ethoxy]pyrimidin-5-amine

The procedure is in accordance with the protocol of Step B of Preparation 1'', replacing the 4-bromo-1-methyl-1*H*-pyrazole by the compound from Step A.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 8.3 (s, 2 H), 7.8 (s, 1 H), 6.9/6.75 (2d, 4 H), 4.35 (t, 2 H), 3.55 (t, 4 H), 2.7 (t, 2 H), 2.45 (t, 4 H), 0.95 (s, 9 H), 0.15 (s, 6 H)

IR (ATR) cm<sup>-1</sup>: 3300 ν -NH, 1506 ν -NH, 837 ν -Si-Me, 837 and 778 ν -CH Ar

**Preparation 37'**: 4-({4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}amino)-1,3-dimethyl-1*H*-pyrrole-2-carbonitrile

**Step A**: 4-Methyl-*N*-(prop-2-en-1-yl)benzene-1-sulphonamide

Allylamine (10.6 mL, 0.14 mol) is added over a period of 4 minutes to a solution of tosyl chloride (25.1 g, 0.13 mol) in dichloromethane (250 mL) cooled in an ice bath. Triethylamine (24 mL, 0.18 mol) is added and then the solution is stirred at ambient temperature for 1.25 hours. Aqueous 3N HCl solution (60 mL) is added and the phases are then separated. The organic phase is washed with another amount of aqueous 3N HCl solution (60 mL) and then with 5 % aqueous sodium bicarbonate solution (60 mL). The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to obtain the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 2.43 (s, 3 H), 3.54 - 3.63 (m, 2 H), 4.50 (ls, 1 H), 5.05 - 5.22 (m, 2 H), 5.66 - 5.79 (m, 1H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.76 (d, *J* = 8.1 Hz, 2 H)

**Step B**: 4-Methyl-*N*-(2-methylprop-2-en-1-yl)-*N*-(prop-2-en-1-yl)benzene-1-sulphonamide

3-Chloro-2-methylpropene (20 mL, 0.20 mol) is added over a period of 5 minutes to a suspension of 4-methyl-*N*-(prop-2-en-1-yl)benzene-1-sulphonamide (27.9 g, 0.13 mol) and potassium carbonate (28.1 g, 0.20 mol) in *N,N*-dimethylformamide (200 mL) cooled in an ice bath. After 20 minutes, the suspension is stirred at ambient temperature for 18 hours. The suspension is concentrated to dryness. The residue is taken up in ethyl acetate (250 mL) and water (110 mL). The aqueous phase is extracted with ethyl acetate (2 x 50 mL). The combined organic phases are washed successively with aqueous 3N HCl solution (50 mL), water (3 x 50 mL), aqueous 5 % potassium bicarbonate solution

(50 mL), and finally brine (50 mL). The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to obtain the expected compound in the form of an oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 1.69 (s, 3 H), 2.43 (s, 3 H), 3.70 (s, 2H), 3.75 - 3.79 (m, 2 H), 4.87 (d, *J* = 25.1 Hz, 1 H), 5.04 - 5.09 (m, 1 H), 5.09 - 5.12 (m, 1 H), 5.45 - 5.59 (m, 1H), 7.29 (d, *J* = 8.1 Hz, 2 H), 7.71 (d, *J* = 8.1 Hz, 2 H)

**Step C: 3-Methyl-1-(4-methylbenzenesulphonyl)-1H-pyrrole**

A solution of the compound obtained in Step B (15.2 g, 57.3 mmol) in toluene (550 mL) is heated at 80°C in the presence of (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)-dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium (Grubbs' catalyst, 2nd generation) (150 mg, 0.18 mmol) for 1 hour. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (16.1 g, 70.9 mmol) is then added in one portion, and the solution is heated at 80°C for 24 hours. The solution is filtered over Celite, and the filtrate is concentrated *in vacuo*. The product is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to obtain the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 2.02 (d, *J* = 1.0 Hz, 3 H), 2.39 (s, 3 H), 6.09 - 6.13 (m, 1H), 6.85 - 6.90 (m, 1 H), 7.03 - 7.07 (m, 1 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H)

**Step D: 3-Methyl-1-(4-methylbenzenesulphonyl)-1H-pyrrole-2-carbonitrile**

Aluminium chloride (19.4 g, 0.15 mol) is added all at once to a solution of 3-methyl-1-(4-methylbenzenesulphonyl)-1H-pyrrole (13.0 g, 55.3 mmol) in 1,2-dichloroethane (230 mL) at ambient temperature. After stirring for 20 minutes, cyanogen bromide (11.11 g, 0.10 mol) is added in portions over a period of 20 minutes. After 4.5 hours, an additional amount of cyanogen bromide (1.94 g, 18.3 mmol) is added. After stirring for 17 hours at ambient temperature, the reaction mixture is poured slowly into a mixture of dichloromethane (300 mL) and water (600 mL) cooled to 0°C. The resulting mixture is stirred for 1 hour. Subsequently the phases are separated and the aqueous phase is extracted with dichloromethane (3 x 150 mL). The combined organic phases are washed

with water (2 x 150 mL) and brine (150 mL). The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to obtain the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 2.18 (s, 3 H), 2.43 (s, 3 H), 6.17 (d, *J* = 3.2 Hz, 1 H), 7.33 - 7.39 (m, 3 H), 7.90 (d, *J* = 8.5 Hz, 2 H)

5     **Step E: 4-Bromo-3-methyl-1-(4-methylbenzenesulphonyl)-1H-pyrrole-2-carbonitrile**

*N*-Bromosuccinimide (12.0 g, 67.4 mmol) is added all at once to a suspension of 3-methyl-1-(4-methylbenzenesulphonyl)-1H-pyrrole-2-carbonitrile (14.45 g, 55.6 mmol) in *N,N*-dimethylformamide (60 mL) at ambient temperature. The mixture is stirred at ambient temperature for 29 hours and is then cooled in an ice bath. Saturated aqueous sodium  
10     bisulphite solution (90 mL), water (90 mL) and ethyl acetate (250 mL) are then added. The phases are separated, and then the aqueous phase is extracted with ethyl acetate (2 x 70 mL). The combined organic phases are washed with 5 % aqueous potassium bicarbonate solution (90 mL), water (3 x 90 mL), and then brine (3 x 90 mL). The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product is  
15     purified by chromatography over silica gel using toluene and heptane as eluants to obtain the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 2.13 (s, 3 H), 2.45 (s, 3 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.43 (s, 1 H), 7.92 (d, *J* = 8.4 Hz, 2 H)

**Step F: 4-Bromo-1,3-dimethyl-1H-pyrrole-2-carbonitrile**

20     Potassium hydroxide (3.65 g, 65.1 mmol) is added all at once to a suspension of 4-bromo-3-methyl-1-(4-methylbenzenesulphonyl)-1H-pyrrole-2-carbonitrile (4.66 g, 13.7 mmol) in methanol (95 mL) cooled using an ice bath. After 15 minutes, the suspension is stirred at ambient temperature for 17 hours. The methanol is evaporated to dryness. The evaporation residue is taken up in MTBE (25 mL) and washed with water (25 mL). The aqueous phase  
25     is extracted with MTBE (2 x 25 mL). The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue obtained is dissolved in tetrahydrofuran (50 mL) and the solution is cooled using an ice bath. NaH (60 % in oil) (1.02 g, 25.5 mmol) is added. After 10 minutes, iodomethane (2.4 mL, 38.6 mmol) is also added.

The mixture is stirred at ambient temperature for 1.5 hours. The tetrahydrofuran is evaporated to dryness. The residue is taken up in dichloromethane and washed with water. The aqueous phase is extracted with dichloromethane. The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to obtain the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 2.16 (s, 3 H), 3.71 (s, 3 H), 6.74 (s, 1 H)

**Step G: 4-({4-[(*tert*-Butyldimethylsilyl)oxy]phenyl}amino)-1,3-dimethyl-1*H*-pyrrole-2-carbonitrile**

4-Bromo-1,3-dimethyl-1*H*-pyrrole-2-carbonitrile (2.03 g, 10.2 mmol) and 4-[(*tert*-butyldimethylsilyl)oxy]aniline (3.41 g, 15.3 mmol) are dissolved in toluene (40 mL). The solution is degassed with nitrogen for 10 minutes. Sodium *tert*-butylate (1.18 g, 12.2 mmol), 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (0.17 g, 0.41 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.187 g, 0.2 mmol) are then added. The mixture is heated at 100°C for 30 minutes and then cooled to ambient temperature. Water (50 mL) and Celite (6 g) are added. The suspension is filtered over Celite, and the filtrate is diluted with MTBE. The phases are separated and the aqueous phase is extracted with MTBE (2 x 50 mL). The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The residue is purified by chromatography over silica gel using ethyl acetate and heptane as eluants followed by reverse-phase chromatography using methanol and water as eluants. The product obtained is lyophilised to provide the expected compound in the form of a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 0.15 (s, 6 H), 0.98 (s, 9 H), 2.05 (s, 3 H), 3.70 (s, 3 H), 4.69 (br. s, 1 H), 6.55 - 6.57 (m, 2 H), 6.64 - 6.69 (m, 3 H)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm: -4.37, 9.42, 18.27, 25.84, 35.50, 102.59, 113.77, 115.13, 120.72, 121.91, 126.77, 126.94, 140.98, 148.39

**Preparation 38'': 4-[(4-[(*tert*-Butyl(dimethyl)silyl]oxy)phenyl)amino]-1-ethyl-5-methyl-1*H*-pyrrole-2-carbonitrile**

The procedure is in accordance with the process of Preparation 33'', replacing the iodomethane-*d*<sub>3</sub> in Step B by iodoethane.

<sup>1</sup>H NMR (400 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 6.85 (s, 1 H), 6.75 (s, 1 H), 6.6/6.5 (2d, 4 H), 4 (quad, 2 H), 2.1 (s, 3 H), 1.3 (s, 3 H), 0.9 (s, 9 H), 0.1 (s, 6 H)

**Preparation 39'': *N*-[4-[*tert*-Butyl(dimethyl)silyl]oxyphenyl]-2-ethoxy-pyrimidin-5-amine**

5 **Step A: 5-Bromo-2-ethoxy-pyrimidine**

5-Bromo-2-chloro-pyrimidine (5.0 g, 25 mmol) is dissolved in ethanol (55 mL) and sodium ethylate (1.81 g, 26.6 mmol) is added in portions. The reaction mixture is stirred for 15 hours at ambient temperature. When the reaction is complete, the solvent is evaporated off, water (200 mL) is added, and then the reaction mixture is extracted with  
10 dichloromethane (2 x 100mL). The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub>, and then evaporated to dryness to yield 5-bromo-2-ethoxy-pyrimidine.

**Step B: *N*-[4-[*tert*-Butyl(dimethyl)silyl]oxyphenyl]-2-ethoxy-pyrimidin-5-amine**

4-[*tert*-Butyl(dimethyl)silyl]oxyaniline (1.8 g, 8 mmol) and 5-bromo-2-ethoxy-pyrimidine (1.6 g, 8 mmol) dissolved in anhydrous tetrahydrofuran (30 mL) are stirred for 1 hour at  
15 ambient temperature in the presence of sodium *tert*-butylate (4 mL, 2M solution in THF) and chloro(2-di-*tert*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)-phenyl]palladium(II) (111 mg, 0.16 mmol). The reaction mixture is filtered over Celite and then evaporated to dryness. The residue is triturated in heptane to obtain the expected compound after filtration.

20 <sup>1</sup>H NMR (500 MHz, dms<sub>o</sub>-d<sub>6</sub>, 300 K) δ ppm: 8.31 (s, 2H, pyrimidine-H), 7.80 (s, 1H, NH), 6.73 (d, 2H, Ar-H), 6.68 (d, 2H, Ar-H), 4.26 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 1.31 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>), 0.94 (s, 9H, <sup>t</sup>Bu), 0.15 (s, 6H, Me)

IR: ν: aromatic: 1504 cm<sup>-1</sup>; Si-C: 1247 cm<sup>-1</sup>; C-O-C: 1057 cm<sup>-1</sup>

**Preparation 40'': *tert*-Butyl 6-[(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)amino]-pyridin-3-yl carbonate**

**Step A: 6-Bromopyridin-3-yl *tert*-butyl carbonate**

To a solution of 5 g of 6-bromopyridin-3-ol (28.7 mmol) and 7.53 g of di-*tert*-butyl dicarbonate (34.5 mmol) in 50 mL of tetrahydrofuran there is added 0.18 g of 4-dimethylaminopyridine (1.4 mmol). The mixture is stirred at ambient temperature for 6 hours and then concentrated. The residue obtained is dissolved in a mixture of ethyl ether and water. After separation of the phases, the separated-off organic phase is dried over MgSO<sub>4</sub> and concentrated to dryness. The title product is obtained in the form of a solid which is used in the next Step without being otherwise purified.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 8.4 (s, 1 H), 7.71 (s, 2 H), 1.5 (s, 9 H)

**Step B: *tert*-Butyl 6-[(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)amino]pyridin-3-yl carbonate**

To a solution of 2.79 g of the compound obtained in Step A (10.2 mmol) in 15 mL of toluene and 15 mL of tetrahydrofuran there are added 1.18 g of sodium *tert*-butylate (12.2 mmol), and then the batch is stirred under argon for 15 minutes. There is then added 0.35 g of palladium catalyst (0.5 mmol). The reaction mixture is then stirred at ambient temperature for 16 hours and then filtered. The filtrate is concentrated and taken up in a mixture of dichloromethane and water. The organic phase is separated off and then washed with water, dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. The crude product thereby obtained is purified by chromatography over silica gel using dichloromethane and ethyl acetate as eluants. The residue is then taken up in a minimum of isopropyl ether. The solid then obtained is filtered off, washed with ether and then dried. The title product is obtained in the form of a solid, which is subsequently used without being otherwise purified.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 9 (s, 1 H), 8.35 (wd, 1 H), 8.3 (wd, 1 H), 8 (wd, 1 H), 7.45 (dd, 1 H), 7.45 (wd, 1 H), 6.8 (d, 1 H), 6.4 (wd, 1 H), 3.8 (s, 3 H), 1.5 (s, 9 H)

**Preparation 41'': 3-[4-[*tert*-Butyl(dimethyl)silyl]oxyanilino]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 by 3-bromobenzonitrile.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 8.3 (s, 1 H), 7.3 (t, 1 H), 7.2/7.1 (2 dd, 2 H), 7.15 (t, 1 H), 7.05 (d, 2 H), 6.8 (d, 2 H), 0.95 (s, 9 H), 0.2 (s, 6 H)

**Preparation 42'': 4-[4-[*tert*-Butyl(dimethyl)silyl]oxyanilino]thiophene-2-carbonitrile**

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 4-bromothiophene-2-carbonitrile.

<sup>1</sup>H NMR (400 MHz, dmso-d<sub>6</sub>) δ ppm: 8.35 (s, 1 H), 7.59 (wd, 1 H), 7.08 (wd, 1 H), 6.95 (d, 2 H), 6.75 (d, 2 H), 0.94 (s, 9 H), 0.16 (s, 6 H)

The amines NHR<sub>3</sub>R<sub>4</sub> wherein R<sub>3</sub> and R<sub>4</sub>, 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 2'' can be applied to various secondary amines NHR<sub>3</sub>R<sub>4</sub> (as defined hereinbefore) having one or more hydroxy functions, when they are available commercially. Alternatively, the secondary amines having at least one hydroxy substituent may be synthesised directly in a protected form, i.e. starting from reagents whose hydroxy function has been protected beforehand. Among the protecting groups, *tert*-butyl(dimethyl)silyloxy and benzyloxy are especially preferred.

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



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

**Preparation I: *tert*-Butyl [2-(3-iodo-4-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)ethyl]carbamate**

**Step A: 4-[2-(*tert*-Butoxycarbonylamino)ethyl]benzoic acid**

*tert*-Butyl dicarbonate (1.64 g; 7.5 mmol) is dissolved in 1,4-dioxane (5 mL) and the solution is added to a well-stirred solution of 4-(2-aminoethyl)benzoic acid (1.0 g; 5 mmol) in 1M aqueous sodium hydroxide solution (25 mL) and 1,4-dioxane (10 mL), and the mixture is then stirred at ambient temperature for 3 hours. The 1,4-dioxane is removed by evaporation *in vacuo*, and then ethyl acetate (200 mL) is added to the residue. The pH of the aqueous phase is adjusted to 1.5 with 2M aqueous HCl solution. The organic phase is separated off and the aqueous phase is then extracted with ethyl acetate (100 mL). The combined organic extracts are washed with water, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to a volume of 10 mL. Heptane is added to the residue and then the solid precipitate is filtered off to yield the title compound.

**<sup>1</sup>H NMR (500 MHz, dms<sub>o</sub>-d<sub>6</sub>, 300K):** 12.81 (br s, 1H, COOH), 7.85 (m, 2H, Ar-2' and 6'H), 7.31 (m, 2H, Ar-3' and 5'H), 6.91 and 6.51 (2x br s, 1H, NH), 3.16 (m, 2H, CH<sub>2</sub>), 2.75 (t, 2H, CH<sub>2</sub>), 1.35 and 1.31 (2 x br s, 9H, Bu<sup>t</sup>); **<sup>13</sup>C NMR (125 MHz, dms<sub>o</sub>-d<sub>6</sub>, 300 K):** 167.8 (q), 156.0 (CH), 145.3 (q), 129.8 (2 x CH), 129.3 (2 x CH), 129.1 (q), 78.0 (q), 41.5 (CH<sub>2</sub>), 35.9 (CH<sub>2</sub>), 28.7 (CH<sub>3</sub>)

**Step B: 4-[2-(*tert*-Butoxycarbonylamino)ethyl]-2-iodo-benzoic acid**

The compound of the above Step (0.88 g; 3.31 mmol), iodobenzene diacetate (1.07 g; 3.31 mmol), tetrabutylammonium iodide (1.22 g; 3.31 mmol), iodine (0.84 g; 3.31 mmol) and diacetoxypalladium (0.04 g; 0.165 mmol) are dissolved in 1,2-dichloroethane (8 mL), and the mixture is then heated in a microwave reactor at 80°C for 90 minutes. The cooled mixture is partitioned between saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (30 mL) and the original solvent. The organic phase is separated off and the aqueous residue is extracted with diethyl ether (2 x 15 mL). The pH of the resulting aqueous solution is adjusted to 2 with 2M aqueous HCl solution and the product is then extracted with ethyl acetate (2 x 75 mL). The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The crude product is purified by chromatography over silica gel to yield the mixture of regioisomers, which are separated

by preparative HPLC using water-TFA and acetonitrile as eluants. The pH of the appropriate combined fractions is adjusted to 5 with NaHCO<sub>3</sub>, and then the acetonitrile is evaporated off under reduced pressure. The precipitate is recovered by filtration and then dried to yield the title compound.

5 <sup>1</sup>H NMR (500 MHz, dms<sup>o</sup>-d<sub>6</sub>, 300K): 13.16 (broad s, 1H, COOH), 7.81 (s, 1H, Ar-3'H), 7.66 (d, 1H, Ar-6'H), 7.29 (d, 1H, Ar-5'H), 6.89 (t, 1H, NH), 3.14 (t, 1H, CH<sub>2</sub>), 2.69 (t, 1H, CH<sub>2</sub>), 1.35 (s, 9H, Boc)

***Step C: tert-Butyl [2-(3-iodo-4-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl)ethyl]carbamate***

10 The compound of the above Step (0.714 g; 1.82 mmol), TBTU (0.73 g; 2.28 mmol), *N*-ethyl-*N*-isopropyl-propan-2-amine (0.94 mL; 5.46 mmol) and *N,N*-dimethylpyridin-4-amine (22 mg) are stirred in dichloromethane (20 mL) for 5 minutes, and then (3R)-3-methyl-1,2,3,4-tetrahydroisoquinoline (0.282 g; 1.92 mmol) (*cf.* Preparation 1') is added. The mixture is stirred for three more hours. The reaction mixture is diluted with  
15 dichloromethane (150 mL) and then washed with water (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The crude product is purified by chromatography over silica gel using dichloromethane and methanol as eluants to yield the title compound.

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

Empirical formula: C<sub>24</sub>H<sub>29</sub>IN<sub>2</sub>O<sub>3</sub>

20 [M+H]<sup>+</sup> calculated: 521.1303

[M+H]<sup>+</sup> measured: 521.1282

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**IR:** ν: C-H: 2931 cm<sup>-1</sup>; >C=O: 1706, 1627 cm<sup>-1</sup>; amide: 1505 cm<sup>-1</sup>; C-O-C: 1248, 1166 cm<sup>-1</sup>

**Preparation II: *tert*-Butyl (4-Iodo-3-[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}benzyl)carbamate**

**Step A: 2-Iodo-5-methyl-benzoic acid**

3-Methylbenzoic acid (6.12 g; 45 mmol), iodobenzene diacetate (14.49 g; 45 mmol),  
5 tetrabutylammonium iodide (16.62 g, 45 mmol), iodine (11.43 g; 45 mmol) and  
diacetoxypalladium (0.5 g; 2.2 mmol) are dissolved in 1,2-dichloroethane, and then the  
mixture is heated in a sealed tube at 85°C for 1 hour and 45 minutes. The cooled solution is  
purified by chromatography over silica gel using dichloromethane and methanol as eluants  
to yield the title compound.

10 **Step B: Methyl 2-iodo-5-methyl-benzoate**

The compound of the above Step (6.25 g, 23.9 mmol) is dissolved in anhydrous methanol  
(100 mL), and then SOCl<sub>2</sub> (3.6 mL, 49 mmol) is added dropwise to the well-stirred  
solution. The solution is refluxed for 18 hours and then evaporated to a volume of 25 mL  
and then poured into crushed ice (100 g). The resulting mixture is extracted with diethyl  
15 ether (2 x 75 mL). The organic phase is washed with saturated aqueous NaHCO<sub>3</sub> solution  
and then brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to yield the title compound.

**Step C: Methyl 5-(bromomethyl)-2-iodo-benzoate**

The compound of the above Step (5.7 g; 20.7 mmol), *N*-bromo-succinimide (3.67 g;  
20.7 mmol) and dibenzoyl peroxide (0.24 g; 1 mmol) are dissolved in carbon tetrachloride  
20 (40 mL) and then refluxed for 5 hours. New portions of *N*-bromosuccinimide (1.0 g;  
5.6 mmol) and dibenzoyl peroxide (0.05 g; 0.2 mmol) are then added and heating is  
continued for 4 more hours. The reaction mixture is cooled to ambient temperature. The  
insoluble parts are removed by filtration, and the concentrated filtrate is then purified by  
chromatography over silica gel using heptane and ethyl acetate as eluants to yield the title  
25 compound.

**Step D: Methyl 5-(aminomethyl)-2-iodo-benzoate**

The compound of the above Step (0.53 g; 1.5 mmol) is dissolved in 7M methanolic  
ammonia (20 mL) and then stirred at ambient temperature for 1 hour. The solution is

evaporated to dryness to yield the title compound, which was used in the next Step without purification.

**Step E: 5-[(tert-Butoxycarbonylamino)methyl]-2-iodo-benzoic acid**

Methyl 5-(aminomethyl)-2-iodo-benzoate hydrobromide (0.56 g; 1.5 mmol) was dissolved in pyridine (10 mL), then di-*tert*-butyl dicarbonate (0.80 g; 3.6 mmol) is added and the mixture is stirred at ambient temperature for 30 minutes and then evaporated to dryness. The residue is redissolved in methanol (10 mL), and then 2M aqueous NaOH solution (3 mL) and 2 mL of water are added. The resulting solution is stirred for 2 hours at 50°C, then diluted with water (20 mL), and the methanol is evaporated off under reduced pressure. The pH of the resulting aqueous solution is adjusted to 3 with 2M aqueous HCl solution; the product is then extracted with ethyl acetate. The organic phase is washed with brine, and then dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product is triturated with DCM. The solid formed is recovered by filtration to yield the title compound.

**<sup>1</sup>H NMR (500 MHz, dms<sub>o</sub>-d<sub>6</sub>, 300 K):** 13.24 (broad s, 1H, COOH), 7.91 (d, 1H, Ar-3'H), 7.58 (d, 1H, Ar-6'H), 7.47 (t, 1H, NH), 7.09 (d, 1H, (Ar-5'H), 4.09 (d, 2H, CH<sub>2</sub>), 1.38 (s, 9H, Boc); **<sup>13</sup>C NMR (125 MHz, dms<sub>o</sub>-d<sub>6</sub>, 300K):** 168.6 (q), 156.3 (q), 141.1 (q), 140.9 (CH), 137.1 (q), 131.6 (CH), 129.1 (CH), 92.2 (q), 78.5 (q), 28.7 (CH<sub>3</sub>)

**Step F: tert-Butyl (4-iodo-3-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)-benzyl)carbamate**

The compound of the above Step (1.62 g; 4.3 mmol), TBTU (2.76 g; 8.59 mmol), *N*-ethyl-*N*-isopropyl-propan-2-amine (1.48 mL; 8.59 mmol) and *N,N*-dimethylpyridin-4-amine (10 mg) are stirred in DCM (50 mL) for 5 minutes; (3R)-3-methyl-1,2,3,4-tetrahydroisoquinoline (0.76 g; 5.15 mmol) (*cf.* Preparation 1') is then added and the mixture is stirred for 15 minutes more. The insoluble parts are removed by filtration, and then the concentrated filtrate is purified by chromatography over silica gel using dichloromethane and methanol as eluants to yield the title compound.

**Preparation III: *tert*-Butyl (3-bromo-4-[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}benzyl)carbamate**

**Step A: Methyl 4-(aminomethyl)-2-bromo-benzoate**

A solution of methyl 2-bromo-4-(bromomethyl)benzoate (4.57 g; 14.84 mmol) in 50 mL of methanol is added dropwise to a well-stirred solution of ammonia in methanol (7M; 315 mL) at ambient temperature, and the solution is then stirred for 3 hours. All the solvents are evaporated off and the residue is purified by chromatography over silica gel using dichloromethane-methanol as eluants to yield the title compound.

**Step B: 2-Bromo-4-[(*tert*-butoxycarbonylamino)methyl]benzoic acid**

The compound of the above Step (4.04 g; 16.6 mmol) is dissolved in pyridine (55 mL) and then di-*tert*-butyl dicarbonate (5.43 g; 24.9 mmol) is added and the mixture is stirred at ambient temperature for 16 hours; it is then evaporated to dryness. The residue is redissolved in methanol (100 mL), and then 1M aqueous NaOH solution (54 mL) is added. The resulting solution is stirred for 1.5 hours at 50°C and is then allowed to cool to ambient temperature. The pH of the solution is adjusted to 7 using 2M aqueous HCl solution; the methanol is then evaporated off under reduced pressure. The resulting aqueous solution is diluted with water (50 mL), and then the pH is adjusted to 3 using 2M aqueous HCl solution. The product is extracted with dichloromethane (2 x 100 mL). The organic phase is washed with brine, then dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to yield the title compound which is used in the next Step without purification.

**IR:**  $\nu$ : N-H: 3359 cm<sup>-1</sup>; C-H: 2983 cm<sup>-1</sup>; >C=O: 1685, 1603 cm<sup>-1</sup>; amide: 1519 cm<sup>-1</sup>; C-O-C: 1248, 1162, 1057 cm<sup>-1</sup>

**Step C: *tert*-Butyl (3-bromo-4-[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}benzyl)carbamate**

The compound of the above Step (3.7 g; 11.2 mmol), TBTU (7.19 g; 22.4 mmol), *N*-ethyl-*N*-isopropyl-propan-2-amine (3.86 mL; 22.4 mmol) and *N,N*-dimethylpyridin-4-amine (48 mg) are stirred in dichloromethane (100 mL) for 5 minutes, and then (3*R*)-3-methyl-1,2,3,4-tetrahydroisoquinoline (1.98 g, 13.44 mmol) (cf. Preparation 1') is added, and the

mixture is stirred for 1 hour more. The insoluble parts are removed by filtration, and then the concentrated filtrate is purified by chromatography over silica gel using dichloromethane and methanol as eluants to yield the title compound.

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

5 Empirical formula: C<sub>23</sub>H<sub>27</sub>BrN<sub>2</sub>O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 459.1285

[M+H]<sup>+</sup> measured: 459.1282

<sup>1</sup>H NMR (500 MHz, dms<sub>o</sub>-d<sub>6</sub>, 300K, presence of amide rotamers): 7.66-6.87 (m, 7H, aromatic), 5.34 and 4.12 (d, 2H, CH<sub>2</sub>-isoquinoline), 5.02 and 4.97 and 3.87 and 3.83 (m, 10 1H, CH<sub>2</sub>-isoquinoline), 4.17 (d, 2H, CH<sub>2</sub>-benzyl), 3.18-2.48 (m, 1H, CH<sub>2</sub>-isoquinoline), 1.16 and 1.14 and 1.10 and 0.98 (d, 3H, isoquinoline CH<sub>3</sub>), 1.31 and 1.41 (s, 9H, Boc).

**Example 1.** 5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

15 **Step A:** Ethyl 5-(5-chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1,2-dimethyl-1H-pyrrole-3-carboxylate

To a solution of 1.4 g of the compound obtained in Preparation 1 (4.35 mmol) in 50 mL of dichloromethane there are successively added 0.7 g of the compound obtained in Preparation 1' (4.79 mmol), 0.7 g of HOBT (5.22 mmol), 0.81 g of EDC (5.22 mmol) and 20 1.6 mL of triethylamine (21.7 mmol). The batch is then stirred overnight at ambient temperature. The reaction mixture is then diluted with dichloromethane and washed 3 times with saturated aqueous NaHCO<sub>3</sub> solution. The organic phase is then dried over MgSO<sub>4</sub>, filtered, concentrated to dryness, and then purified by chromatography over silica gel using dichloromethane and methanol as eluants.

25 <sup>1</sup>H NMR: δ (500 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300K): 7.6-7.3 (m, 3H, aromatic Hs, 4-chlorophenyl); 7.2-6.85 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 6.45-6.3 (m, 1H, H pyrrole); 5.0-4.8-3.8 (m, 1H, aliphatic H, tetrahydroisoquinoline); 5.3-3.75 (dd, 2H, aliphatic Hs

tetrahydroisoquinoline); 4.2-4.0 (m, 2H, OCH<sub>2</sub>CH<sub>3</sub>); 3.25 (s, 3H, CH<sub>3</sub>-N-pyrrole); 3.0-2.2 (m, 2H, aliphatic Hs, tetrahydroisoquinoline); 2.5 (s, 3H, CH<sub>3</sub>-pyrrole); 1.25 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>); 1.05 (d, 3H, tetrahydroisoquinoline-CH<sub>3</sub>)

IR:  $\nu$ : >C=O: 1693 cm<sup>-1</sup> ester;  $\nu$ : >C=O: 1625 cm<sup>-1</sup> amide

5 **Step B:** *5-(5-Chloro-2-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-phenyl)-1,2-dimethyl-1H-pyrrole-3-carboxylic acid*

To a solution of 1.7 g of the compound obtained in Step A (3.77 mmol) in 5 mL of dioxane there is added 0.317 g of LiOH (7.5 mmol) dissolved in 5 mL of water. The batch is heated in a microwave apparatus for 4 hours at 100°C (power 140 W). The reaction mixture is  
10 then filtered and concentrated to dryness. The residue thereby obtained is taken up in dichloromethane (50 mL) and then saturated aqueous NH<sub>4</sub>Cl solution is added thereto. The organic phase is washed with water and then with brine, dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. The title product is obtained in the form of a solid and is used directly in the next Step.

15 <sup>1</sup>H NMR:  $\delta$  (500 MHz; dmso-d<sub>6</sub>; 300K): 11.05 (broad s, 1H, COOH), 7.5-7.2 (m, 3H, aromatic Hs, 4-chlorophenyl); 7.2-6.9 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 6.45-6.2 (m, 1H, aliphatic H, H pyrrole); 5.3-3.75 (dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 5.0-4.8-3.8 (m, 1H, aliphatic H, tetrahydroisoquinoline); 3.5-3.2 (s, 3H, CH<sub>3</sub>-N-pyrrole); 3.0-2.1 (aliphatic Hs, CH<sub>3</sub>-tetraisoquinoline); 2.5-2.4-1.98 (m, 3H, CH<sub>3</sub>-pyrrole); 1.05-  
20 0.52 (m, 3H, aliphatic Hs, CH<sub>3</sub>-tetraisoquinoline)

IR :  $\nu$ : -OH: 3500-2000 cm<sup>-1</sup> carboxylic acid;  $\nu$ : >C=O: 1699 + 1658 cm<sup>-1</sup> carboxylic acid;  $\nu$ : >C=N-: 1625 cm<sup>-1</sup> amide

25 **Step C:** *N-(4-[(tert-Butyl(dimethyl)silyl]oxy]phenyl)-5-(5-chloro-2-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide*

To a solution of 0.65 g of the compound obtained in Step B (1.54 mmol) in 15 mL of dichloroethane there is added, dropwise, 0.244 mL of 1-chloro-N,N,2-trimethyl-prop-1-en-1-amine. The reaction mixture is stirred at ambient temperature for 1 hour, and there are then added 0.56 g of the compound of Preparation 1" (1.84 mmol), 10 mL of



dichloroethane and 0.376 g of 4-dimethylaminopyridine (DMAP) (3.07 mmol). The batch is stirred at 110°C overnight. The reaction mixture is concentrated, dissolved in dichloromethane and washed with saturated aqueous NaHCO<sub>3</sub> solution. The title product is obtained in the form of an oil and is used directly in the next Step.

5 ***Step D: 5-(5-Chloro-2-(((3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl)-phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide***

To a solution of 0.8 g of the compound obtained in Step C (1.03 mmol) in 2 mL of methanol, there are added 1.55 mL of a 1M solution of potassium hydroxide in methanol  
10 (1.55 mmol). The batch is stirred at ambient temperature for 30 minutes. The reaction mixture is then diluted with dichloromethane and successively washed with 1M aqueous HCl solution, saturated aqueous NaHCO<sub>3</sub> solution and then brine until neutral. The organic phase is then dried over MgSO<sub>4</sub>, filtered and evaporated. The crude product thereby obtained is purified by chromatography over silica gel using dichloromethane and  
15 methanol as eluants. The solid thereby obtained is dissolved in a mixture of water/acetonitrile until dissolution is complete, filtered and then lyophilised.

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

%C=68.74:68.25; %H=5.43:5.69; %N=11.79:11.66; %Cl=5.97:5.95

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

20 Empirical formula: C<sub>34</sub>H<sub>32</sub>ClN<sub>5</sub>O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 594.2266

[M+H]<sup>+</sup> measured: 594.2289

**Example 2.** 5-(2-[[*(3S)*-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]phenyl)-1-methyl-*N,N*-diphenyl-1*H*-pyrrole-3-carboxamide

**Step A:** *tert*-Butyl {[*(3S)*-2-{2-[4-(diphenylcarbamoyl)-1-methyl-1*H*-pyrrol-2-yl]benzoyl}-1,2,3,4-tetrahydroisoquinolin-3-yl]methyl}carbamate

5 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 2 and *tert*-butyl [*(3S)*-1,2,3,4-tetrahydroisoquinolin-3-ylmethyl]carbamate (see Preparation 2') in Step A, and *N*-phenylaniline in Step C.

**Step B:** 5-(2-[[*(3S)*-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]phenyl)-1-methyl-*N,N*-diphenyl-1*H*-pyrrole-3-carboxamide

10 A solution of the NH-Boc compound of Step A in dichloromethane is placed at 0°C. 10 molar equivalents of trifluoroacetic acid are added thereto dropwise. The batch is stirred at ambient temperature for 4 hours until the starting material has disappeared completely. The reaction mixture is then concentrated to dryness, taken up again and co-evaporated twice with toluene, then taken up in a mixture of acetonitrile/H<sub>2</sub>O and finally lyophilised.

15 The title product is then obtained after a neutralisation step.

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

%C=77.75:77.27; %H=5.97:5.73; %N=10.36:10.44

**Example 3.** 5-(5-Chloro-2-[[*(3S)*-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-3-carboxamide

**Step A:** *tert*-Butyl 5-[(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl){5-(5-chloro-2-[[*(3S)*-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]phenyl)-1-methyl-1*H*-pyrrol-3-yl]carbonyl]amino]-1*H*-indole-1-carboxylate

25 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 3 and (*3S*)-3-[(4-methyl-1-piperazinyl)methyl]-1,2,3,4-tetrahydroisoquinoline (see Preparation 4') in Step A, and the compound of Preparation 3" in Step C.

***Step B: 5-(5-Chloro-2-((3S)-3-((4-methylpiperazin-1-yl)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl}phenyl)-N-(4-hydroxyphenyl)-N-(1H-indol-5-yl)-1-methyl-1H-pyrrole-3-carboxamide***

To a solution of 455 mg (0.49 mmol) of the product obtained in Step A in 5 mL of methanol there are added 135 mg (2.5 mmol) of KOH. After stirring for 3 hours at ambient temperature, the reaction mixture is concentrated, treated with saturated aqueous NaHCO<sub>3</sub> solution and extracted with methylene chloride. The organic phase is then dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The crude product thereby obtained is then purified by chromatography over silica gel using dichloromethane and methanol as eluants to yield the expected product in the form of a foam.

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

%C=70.72:68.54; %H=5.79:5.37; %N=11.78:11.41; %Cl=4.97:4.79

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

Empirical formula: C<sub>42</sub>H<sub>41</sub>ClN<sub>6</sub>O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 713.3007

[M+H]<sup>+</sup> measured: 713.2973

***Example 4. N-(4-Hydroxyphenyl)-N-(1H-indol-5-yl)-1-methyl-5-(6-((3S)-3-((4-methylpiperazin-1-yl)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl)-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide***

The title compound is obtained in accordance with the process of Example 3 using the compound of Preparation 4 in Step A.

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

%C=71.45:69.32; %H=5.86:5.22; %N=11.63:11.08

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

Empirical formula: C<sub>43</sub>H<sub>42</sub>N<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 723.3295

[M+H]<sup>+</sup> measured: 723.3262

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 32 and (ii) the appropriate tetrahydroisoquinoline compound obtained according to one of Preparations 1' to 9' and, in Step C: (iii) the suitable  $\text{NHR}_3\text{R}_4$  amine (a non-exhaustive list is proposed in Preparations 1'' to 42''). The compounds thereby obtained are optionally subjected to a step of conversion into salt form in the presence of HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the hydrochloride of the expected compound is obtained.

**Example 5.** 5-(5-Chloro-2-{[(3*S*)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-indol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=64.54:64.9; %H=5.67:5.49; %N=10.5:10.4; %Cl=13.29:12.52; %Cl=8.86:7.39

**Example 6.** 5-(5-Chloro-2-{[(3*S*)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-ethyl-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-1*H*-pyrrole-3-carboxamide

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

Empirical formula:  $\text{C}_{44}\text{H}_{45}\text{ClN}_6\text{O}_3$

$[\text{M}+\text{H}]^+$  calculated: 741.3320

$[\text{M}+\text{H}]^+$  measured: 741.3326

**Example 7.** 5-(5-Chloro-2-{[(3*S*)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-cyclopropyl-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-1*H*-pyrrole-3-carboxamide

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

Empirical formula: C<sub>45</sub>H<sub>45</sub>ClN<sub>6</sub>O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 753.3320

[M+H]<sup>+</sup> measured: 753.3306

- 5     **Example 8.** 5-(5-Chloro-2-{[(3*S*)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(1-methyl-1*H*-indol-5-yl)-1-(propan-2-yl)-1*H*-pyrrole-3-carboxamide

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

Empirical formula: C<sub>45</sub>H<sub>47</sub>ClN<sub>6</sub>O<sub>3</sub>

10    [M+H]<sup>+</sup> calculated: 755.3476

[M+H]<sup>+</sup> measured: 755.3466

**Example 9.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-indol-5-yl)-5-(6-{[(3*S*)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=65.26:65.8; %H=5.73:5.47; %N=10.38:10.48; %Cl=8.76:8.46; %Cl=8.76:8.02

**Example 10.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=69.11:68.56; %H=5.8:5.31; %N=8.06:8.13; %Cl=5.1:4.68

**Example 11.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-(3-hydroxypropyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

**Step A:** 1-[3-(Benzyloxy)propyl]-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 10 and the compound of Preparation 3' in Step A, and the compound of Preparation 2" in Step C.

**Step B:** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-(3-hydroxypropyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

The compound of Step A is subjected to a deprotection reaction in accordance with a protocol analogous to that described in Step B of Example 23.

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

%C=68.24:67.96; %H=6.5.79; %N=7.58:7.61; %Cl=4.8:4.75

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

Empirical formula: C<sub>42</sub>H<sub>43</sub>FN<sub>4</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 703.3296

[M+H]<sup>+</sup> measured: 703.33294

**Example 12.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-indazol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=67.33:67.39; %H=5.65:5.18; %N=11.22:11.52; %Cl=4.73:3.82

**Example 13.** *N*-(3-Fluoro-4-methylphenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-  
{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-  
benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

5     %C=66.97:66.72; %H=5.62:5.21; %N=7.44:7.59; %Cl=4.71:4.54

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

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

10    %C=66.62:66.59; %H=5.59:4.67; %N=10.84:10.85; %Cl=4.57:4.24

**Example 15.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3*S*)-3-(morpholin-4-  
ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-  
1*H*-pyrrole-3-carboxamide hydrochloride

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

15    %C=68.28:67.07; %H=5.73:5.09; %N=7.77:7.75; %Cl=4.92:5.71

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

Empirical formula: C<sub>41</sub>H<sub>40</sub>N<sub>4</sub>O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 685.3026

[M+H]<sup>+</sup> measured: 685.3033

20    **Example 16.** *N*-(3-Fluorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3*S*)-3-  
(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-  
5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=66.62:66.11; %H=5.45:5.2; %N=7.58:7.89; %Cl=4.8:5.59

**Example 17.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

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

5 %C=67.51:66.91; %H=5.66:5.05; %N=7.87:7.88; %Cl=4.98:5.75

**Example 18.** 1-(2-Hydroxyethyl)-*N*-(4-hydroxyphenyl)-2-methyl-5-(6-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

10 **Step A:** 1-[2-(Benzyloxy)ethyl]-*N*-[4-(benzyloxy)phenyl]-2-methyl-5-(6-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 9 and (3*S*)-3-[2-(morpholin-4-yl)ethyl]-1,2,3,4-tetrahydroisoquinoline (see Preparation 5') in Step A, and 4-(benzyloxy)-*N*-phenylaniline (see Preparation 8'') in Step C.

**Step B:** 1-(2-Hydroxyethyl)-*N*-(4-hydroxyphenyl)-2-methyl-5-(6-{[(3*S*)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

20 The compound of Step A is subjected to a deprotection reaction in accordance with a protocol analogous to that described in Step B of Example 23.

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

Empirical formula: C<sub>38</sub>H<sub>40</sub>N<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 729.3283

[M+H]<sup>+</sup> measured: 729.3282

25 **Example 19.** *N*-(4-Hydroxyphenyl)-5-(5-methoxy-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride



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

%C=69.63:69.45; %H=6.13:5.94; %N=7.92:7.79; %Cl=5.01:4.58

**Example 20.** *N*-(4-Hydroxyphenyl)-5-(5-methoxy-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=69.39:69.66; %H=5.66:5.46; %N=8.99:8.92; %Cl=5.69:5.29

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

Empirical formula: C<sub>36</sub>H<sub>35</sub>N<sub>4</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 587.2653

[M+H]<sup>+</sup> measured: 587.2649

**Example 21.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(7-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-2,3-dihydro-1,4-benzodioxin-6-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=64.99:64.67; %H=5.86:5.67; %N=11.37:11.27; %Cl=4.8:4.71

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

Empirical formula: C<sub>40</sub>H<sub>43</sub>N<sub>6</sub>O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 703.3236

[M+H]<sup>+</sup> measured: 703.3239

**Example 22.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-5-(7-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-2,3-dihydro-1,4-benzodioxin-6-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=68.61:67.97; %H=5.89:5.59; %N=7.62:7.55; %Cl=4.82:4.27

**Example 23.** 1-(2-Hydroxyethyl)-N-(4-hydroxyphenyl)-2-methyl-5-(6- $\{[(3R)$ -3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

**Step A:** 1-[2-(Benzyloxy)ethyl]-N-(4- $\{[tert$ -butyl(dimethyl)silyl]oxy}phenyl)-2-methyl-5-(6- $\{[(3R)$ -3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 9 and the compound of Preparation 1" in Step C.

**Step B:** N-(4- $\{[tert$ -Butyl(dimethyl)silyl]oxy}phenyl)-1-(2-hydroxyethyl)-2-methyl-5-(6- $\{[(3R)$ -3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

To a solution of 6.86 g (8.19 mmol) of the compound of Step A in 70 mL of anhydrous methanol there are added 1.37 g of Pd/C 10%. The batch is degassed for 0.5 hours and then stirred at ambient temperature under dihydrogen pressure (1.5 bar) for 12 hours. The reaction mixture is then filtered and then concentrated to dryness. The expected product is obtained in the form of a solid.

**<sup>1</sup>H NMR:**  $\delta$  (500 MHz; dmso-d<sub>6</sub>; 300K): 7.7-7.4 (s, 1H, H pyrazole); 7.1-6.8 (s, 1H, H pyrazole); 7.3-6.9 (m, 4H, aromatic Hs, H tetrahydroisoquinoline); 7.0-6.7 (m, 2H, aromatic Hs); 6.9-6.4 (m, 2H, aromatic Hs); 6.8-6.4 (m, 2H, aromatic Hs); 6.1 (m, 2H, OCH<sub>2</sub>O); 5.2, 5.0, 4.7 (4s, H, H-pyrrole (presence of conformational isomers); 5.15 (d, 1H, aliphatic H, H tetrahydroisoquinoline); 4.9 (m, 1H, aliphatic H, H tetrahydroisoquinoline); 4.9-4.8 (m, 1H, CH<sub>2</sub>OH); 4.7 (m, 1H, aliphatic H, H tetrahydroisoquinoline); 3.9 (d, 1H, aliphatic H, H tetrahydroisoquinoline); 3.85 (m, 1H, aliphatic H, H tetrahydroisoquinoline); 3.7 (m, 2H, aliphatic Hs, CH<sub>2</sub>CH<sub>2</sub>OH); 3.75 (2s, 3H, ); 3.5-3.2 (m, 2H, aliphatic Hs, CH<sub>2</sub>CH<sub>2</sub>OH); 3.0-2.4 (m, 2H, aliphatic H, H tetrahydroisoquinoline); 2.4-2.3 (4s, 3H, CH<sub>3</sub>-pyrrole); 1.5, 0.95, 0.75 (4 d, 3H, CH<sub>3</sub>-THIQ); 0.85 (broad s, 9H, Si(CH<sub>3</sub>)<sub>2</sub>(CH(CH<sub>3</sub>)<sub>2</sub>); 0.15 (m, 6H, Si(CH<sub>3</sub>)<sub>2</sub>(CH(CH<sub>3</sub>)<sub>2</sub>))

IR: v: -OH: 3346 cm<sup>-1</sup> carboxylic acid; v: >C=O: 1621 cm<sup>-1</sup>

**Step C:** 1-(2-Hydroxyethyl)-N-(4-hydroxyphenyl)-2-methyl-5-(6-{{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl}carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

5 The phenol function of the compound of Step B is deprotected following the process of Step D of Example 1.

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

%C=68.23:68.12; %H=5.57:5.29; %N=11.05:10.79

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

10 Empirical formula: C<sub>36</sub>H<sub>36</sub>N<sub>5</sub>O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 634.2662

[M+H]<sup>+</sup> measured: 634.2660

**Example 24.** N-(4-Hydroxyphenyl)-5-(5-methoxy-2-{{(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl}carbonyl}phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

15

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

%C=65.86:64.47; %H=6.09:5.88; %N=11.82:11.45; %Cl=4.98:6.7

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

Empirical formula: C<sub>39</sub>H<sub>42</sub>N<sub>6</sub>O<sub>5</sub>

20 [M+H]<sup>+</sup> calculated: 675.3289

[M+H]<sup>+</sup> measured: 675.3287

**Example 25.** 5-(5-Chloro-2-{{(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl}carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

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

%C=63.77:62.83; %H=5.63:5.83; %N=11.74:11.29; %Cl=4.95:5.42

**Example 26.** *N*-(4-Hydroxyphenyl)-2-methyl-1-[2-(methylamino)ethyl]-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with Steps A, B and C of the process of Example 30 replacing the sodium azide used in Step B by methylamine. After purification over silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> gradient), the compound obtained, 0.3 g (0.46 mmol), is dissolved in 5 mL of anhydrous methanol and there is added, dropwise, 0.464 mL (0.47 mmol) of 1M HCl solution in ether. The batch is stirred for 0.5 hours at ambient temperature. The precipitate thereby obtained is filtered off and dried and then dissolved in a mixture of CH<sub>3</sub>CN/H<sub>2</sub>O before being lyophilised at low temperature. The expected product is obtained in the form of a solid.

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

%C=65.05:64.64; %H=5.75:5.43; %N=12.3:12.3; %Cl=5.19:5.39

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

Empirical formula: C<sub>37</sub>H<sub>38</sub>N<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 647.2903

[M+H]<sup>+</sup> measured: 647.2922

**Example 27.** 1-[2-(Dimethylamino)ethyl]-*N*-(4-hydroxyphenyl)-2-methyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the process of Example 26, replacing the methylamine in Step B by dimethylamine.

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

%C=65.46:65.07; %H=5.93:5.87; %N=12.05:12.06; %Cl=5.08:5.55

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

Empirical formula: C<sub>38</sub>H<sub>40</sub>N<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 661.3060

[M+H]<sup>+</sup> measured: 661.3045

5     **Example 28.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=66.99:66.88; %H=5.14:5.28; %N=8.93:8.87; %Cl=5.65:4.98

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

Empirical formula: C<sub>35</sub>H<sub>32</sub>ClN<sub>4</sub>O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 591.2157

[M+H]<sup>+</sup> measured: 591.2178

15    **Example 29.** 5-(5-Chloro-2-{[(3*S*)-3-{[2-(morpholin-4-yl)ethoxy]methyl}-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

***Step A: Methyl 5-(5-chloro-2-{[(3*S*)-3-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxylate***

20    To a solution of 4.9 g of the compound of Preparation 1 in a mixture of 40 mL of dimethylformamide and 40 mL of tetrahydrofuran there are added 2.73 g (1.1 equivalents) of (3*S*)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline, 7.95 mL of diisopropylethylamine and 9.84 g (1.7 equivalents) of HATU. After stirring for 2 hours at ambient temperature, the reaction mixture is dried, taken up in ethyl acetate and then washed with 10 % aqueous citric acid solution and water. The combined aqueous phases are extracted  
25    with ethyl acetate. The organic phases thereby obtained are combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product obtained is purified by chromatography over silica gel using dichloromethane and ethanol as eluants to yield the title compound.

<sup>1</sup>H NMR: δ (500 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300K): 7.6-7.4 (m, 3H, Cl-Ph); 7.2-6.9 (m, 4H, Ar(THIQ)); 6.5-6.15 (broad 4s, 1H, pyrrole); 4.9-3.8 (6 d, 2H, NCH<sub>2</sub> THIQ); 4.85-3.6 (m, 1H, NCH THIQ); 4.2-4.0 (m, 2H, OCH<sub>2</sub> ester), 3.45-3.2 (3s, 3H, N-CH<sub>3</sub>); 3.35-3.0 (3m, 2H, HOCH<sub>2</sub>); 3.0-2.0 (m, 2H, THIQ); 2.5-2.1 (m, 3H, CH<sub>3</sub> pyrrole); 1.25-1.1 (m, 3H, CH<sub>3</sub> ester)

IR: ν -OH: 3388 cm<sup>-1</sup>, ν >C=O: 1693 cm<sup>-1</sup> (conjugated ester), ν >C=O: 1620 cm<sup>-1</sup> (amide)

***Step B: Methyl 5-(5-chloro-2-{[(3S)-3-{[2-(morpholin-4-yl)ethoxy]methyl}-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1,2-dimethyl-1H-pyrrole-3-carboxylate***

A solution of 1.7 g (3.2 mmol) of the compound obtained in the above Step in 20 mL of dimethylformamide is added, dropwise at 0°C, to a suspension of 0.280 g of NaH 60 % in oil (2.2 equivalents) in 10 mL of dimethylformamide. After stirring for 5 minutes at ambient temperature, a suspension of 0.68 g of 4-(2-bromoethyl)morpholine hydrobromide (1.1 equivalents) is added dropwise. The reaction mixture is stirred at ambient temperature for 45 minutes. There are then added, in two steps over 20 hours, 2.2 equivalents of 4-(2-bromoethyl)morpholine hydrobromide, and then 3 equivalents of NaH 60 % in oil. The reaction mixture is then poured into a mixture of 10 % aqueous ammonium chloride and ethyl acetate. The resulting organic phase is successively washed with water, and then with saturated aqueous LiCl solution and brine. It is then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The oil obtained is purified by chromatography over silica gel using dichloromethane and ethanol as eluants to provide the expected product.

<sup>1</sup>H NMR: δ (500 MHz; dms<sub>o</sub>-d<sub>6</sub>; 300K): 7.6-7.3 (m, 3H, Cl-Ph); 7.2-6.85 (m, 4H, Ar(THIQ)); 6.5-6.15 (broad s, 1H, pyrrole); 5.25-3.8 (m, 2H, NCH<sub>2</sub> THIQ); 5.05-3.75 (m, 1H, NCH THIQ); 4.2-4.0 (m, 2H, OCH<sub>2</sub> ester), 3.5-3.25 (m, 3H, N-CH<sub>3</sub>); 3.6-2.75 (m, 8H, OCH<sub>2</sub> morpholinoethoxymethyl); 2.95-2.05 (m, 2H, THIQ); 2.55-2.15 (m, 6H, NCH<sub>2</sub> morpholinoethoxymethyl); 2.55-2.05 (m, 3H, CH<sub>3</sub> pyrrole), 1.25-1.1 (m, 3H, CH<sub>3</sub> ester)

IR: ν >C=O: 1694 cm<sup>-1</sup> (conjugated ester), ν >C=O: 1629 cm<sup>-1</sup> (amide)

**Step C:** 5-(5-Chloro-2- $\{[(3S)$ -3- $\{[2$ -(morpholin-4-yl)ethoxy]methyl}-3,4-dihydro-isoquinolin-2(1H)-yl]carbonyl}phenyl)-1,2-dimethyl-1H-pyrrole-3-carboxylic acid

To a solution of 1.46 g of the compound of the above Step in 5 mL of dioxane there are added 5 mL of 1M aqueous LiOH solution. The batch is heated in a microwave apparatus (100 W) at 100°C for 2 hours. The reaction mixture is poured into water and then extracted with ethyl ether. The ethereal phase is extracted again with 10 mL of water. The aqueous phases are acidified to pH 5-6 by adding saturated aqueous ammonium chloride solution and then extracted twice with dichloromethane. The dichloromethane phase is dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to dryness. The title product is obtained in the form of a meringue.

**<sup>1</sup>H NMR:**  $\delta$  (500 MHz; dmso-d<sub>6</sub>; 300K): 11.4 (broad s, 1H, CO<sub>2</sub>H), 7.6-7.3 (m, 3H, Cl-Ph); 7.2-6.8 (m, 4H, Ar(THIQ)); 6.5-6.2 (broad 4s, 1H, pyrrole); 5.25-3.75 (m, 2H, NCH<sub>2</sub> THIQ); 5.05-3.7 (3m, 1H, NCH THIQ); 3.5-3.2 (3s, 3H, N-CH<sub>3</sub>); 3.6-2.7 (m, 8H, OCH<sub>2</sub> morpholinoethoxymethyl); 2.5-2.2 (m, 6H, NCH<sub>2</sub> morpholinoethoxymethyl); 3.0-2.0 (m, 2H, THIQ), 2.5-2.0 (3s, 3H, CH<sub>3</sub> pyrrole)

**IR:**  $\nu$  -OH: 3300-2200 cm<sup>-1</sup>,  $\nu$  >C=O: 1697-1662 cm<sup>-1</sup> (double band, carboxylic acid),  $\nu$  >C=O: 1628 cm<sup>-1</sup> (amide)

**Step D:** N-(4- $\{[tert$ -Butyl(dimethyl)silyl]oxy}phenyl)-5-(5-chloro-2- $\{[(3S)$ -3- $\{[2$ -(morpholin-4-yl)ethoxy]methyl}-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide

The acid obtained in Step C (1.48 g) is suspended in 15 mL of 1,2-dichloroethane. 1.1 equivalents of 1-chloro-N,N,2-trimethylpropenylamine are added thereto. After stirring for 1 hour at ambient temperature, there are added 15 mL of toluene and 1.05 equivalents of the compound of Preparation 2". The reaction mixture is heated for 14 hours at 110°C and then dried. The crude product thereby obtained is purified by chromatography over silica gel using dichloromethane and ethanol as eluants to yield the expected product.

**<sup>1</sup>H NMR:**  $\delta$  (500 MHz; dmso-d<sub>6</sub>; 300K): 7.55-7.25 (m, 3H, Cl-Ph); 7.25-6.6 (m, 9H, Ar(THIQ)+phenyl); 6.8-6.5 (m, 2H, phenoxy); 7.0-6.6 (m, 2H, phenoxy); 5.7-5.05 (broad 4s, 1H, pyrrole); 5.2-3.6 (8d, 2H, THIQ); 5.05-3.6 (4m, 1H, NCH THIQ), 3.6-2.9 (m, 8H,

aliphatic morpholinoethoxymethyl); 3.4-3.2 (broad 3s, 3H, N-CH<sub>3</sub>); 3.0-2.1 (m, 2H, THIQ), 2.35 (m, 2H, NCH<sub>2</sub> morpholinoethoxymethyl); 2.4-2.2 (m, 4H, NCH<sub>2</sub> morpholine); 2.4-2.15 (broad 3s, 3H, CH<sub>3</sub> pyrrole); 0.8 (broad 2s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>); 0.1 (4s, 6 H, SiCH<sub>3</sub>)  
**IR:**  $\nu$  >C=O: 1635-1595 cm<sup>-1</sup> (double band),  $\nu$  Si-O: 1117 cm<sup>-1</sup>,  $\nu$  Si-C: 837 cm<sup>-1</sup>

5 **Step E:** 5-(5-Chloro-2-{{(3S)-3-{{2-(morpholin-4-yl)ethoxy}methyl}-3,4-dihydroisoquinolin-2(1H)-yl}carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

To a solution of 0.7 g of the compound of Step D in 5 mL of methanol there is added 0.92 mL of a 1M solution of potassium hydroxide in methanol. After stirring for 1 hour  
10 10 minutes at ambient temperature, saturated aqueous sodium bicarbonate solution is added. The product which precipitates is extracted with ethyl acetate and then washed with water and brine. The resulting aqueous phases are extracted again with ethyl acetate. The organic phases thereby obtained are dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product obtained is purified by chromatography over silica gel  
15 using dichloromethane and ammonia-in-ethanol as eluants to provide 0.536 g of the title product, in the form of the base. The latter is dissolved in acetonitrile and converted into salt form using 1M aqueous HCl solution. After a lyophilisation step, the expected product is obtained in the form of a solid.

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

20 %C=66.4(66.75);%H=5.98(5.87);%N=7.38(7.41);%Cl=9.42(9.38);%Cl<sup>-</sup>=4.57(4.69)

**Example 30.** 1-(2-Aminoethyl)-N-(4-hydroxyphenyl)-2-methyl-5-(6-{{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl}carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

25 **Step A:** 2-{3-[(4-{{tert-Butyl(dimethyl)silyl}oxy}phenyl)(1-methyl-1H-pyrazol-4-yl)carbonyl]-2-methyl-5-(6-{{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl}carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrol-1-yl}ethyl methanesulphonate

A solution of 4.65 g of the compound obtained in Step B of Example 23 (6.22 mmol) in 100 mL of anhydrous THF is placed at 0°C. There are successively added thereto 3.5 mL



(12.44 mmol) of triethylamine and then, dropwise, 0.722 mL of methanesulphonic chloride (9.33 mmol) dissolved in 20 mL of THF. The batch is then stirred at ambient temperature for 2 hours. The reaction mixture is hydrolysed by addition of saturated aqueous NaHCO<sub>3</sub> solution and then extracted twice with ethyl acetate. The organic phases are combined,  
5 dried over MgSO<sub>4</sub> and concentrated to dryness. The expected compound is obtained in the form of a glassy solid.

**<sup>1</sup>H NMR:** δ (500 MHz; dmso-d<sub>6</sub>; 300K): 7.7-7.45 (s, 1H, H pyrazole); 7.1-6.9 (s, 1H, H pyrazole); 7.2-6.4 (m, 8H, aromatic Hs); 6.95-6.65 (m, 2H, aromatic Hs); 6.1 (m, 2H, OCH<sub>2</sub>O); 5.2, 4.6 (4s, H, H-pyrrole (presence of conformational isomers); 4.9, 4.6, 3.9, 3.8  
10 (m, 1H), 5.05-3.75 (m, 1H, aliphatic H, H tetrahydroisoquinoline); 4.3-4.05 (m, 2H, aliphatic Hs, CH<sub>2</sub>CH<sub>2</sub>OSO<sub>2</sub>CH<sub>3</sub>); 4.2-3.95 (m, 2H, aliphatic Hs, CH<sub>2</sub>CH<sub>2</sub>OSO<sub>2</sub>CH<sub>3</sub>); 3.75-2.7 (2s, 3H, CH<sub>3</sub>-pyrazole); 3.0 (several s, 3H, CH<sub>2</sub>OSO<sub>2</sub>CH<sub>3</sub>); 3.05-2.5 (several m, 2H, aliphatic Hs, H tetrahydroisoquinoline); 2.45-2.3 (several s, 3H, CH<sub>3</sub>-pyrrole); 1.05, 0.75 (several d, 3H, CH<sub>3</sub>-tetraisoquinoline); 0.9 (several s, 9H, Si(CH<sub>3</sub>)<sub>2</sub>(CH(CH<sub>3</sub>)<sub>2</sub>); 0.1 (m,  
15 6H, Si(CH<sub>3</sub>)<sub>2</sub>(CH(CH<sub>3</sub>)<sub>2</sub>))

**IR:** ν: >C=O: 1626 cm<sup>-1</sup>, ν: -SO<sub>2</sub>: 1349 and 1172 cm<sup>-1</sup>

**Step B:** *1-(2-Azidoethyl)-N-(4-{{tert-butyl(dimethyl)silyl}oxy}phenyl)-2-methyl-5-(6-  
{{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl}carbonyl}-1,3-benzodioxol-5-yl)-N-(1-  
methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide*

To a solution of 2 g (2.42 mmol) of compound of Step A in 20 mL of anhydrous DMF there is added 0.472 g (7.26 mmol) of sodium azide. The batch is stirred at 65°C for 4 hours 30 minutes. The reaction mixture is poured into saturated aqueous NaHCO<sub>3</sub> solution and then extracted twice with ethyl acetate. The organic phases are combined and washed with saturated aqueous LiCl solution, dried over MgSO<sub>4</sub> and concentrated to  
25 dryness. After purification over silica gel using dichloromethane and ammonia-in-methanol as eluants, the expected product is obtained in the form of a foam.

**<sup>1</sup>H NMR:** δ (500 MHz; dmso-d<sub>6</sub>; 300K): 7.65-7.45 (several s, 1H, H pyrazole); 7.1-6.9 (several s, 1H, H pyrazole); 7.3-6.4 (several m, 6H, aromatic Hs); 7.1-6.9 (several s, 1H, aromatic Hs); 6.8, 6.5 (2m, 2H, aromatic Hs); 6.1 (several s, 2H, OCH<sub>2</sub>O); 5.25- 4.65

(several s, 1H, H-pyrrole (presence of conformational isomers); 4.9, 4.6, 3.8 (several m, 1H); 5.05-3.7 (several m, 4H, aliphatic Hs, H-THIQ +  $\text{CH}_2\text{CH}_2\text{N}_3$ ); 3.7 (several s, 3H, H  $\text{CH}_3$ -pyrazole); 3.5-3.25 (m, 2H,  $\text{CH}_2\text{CH}_2\text{N}_3$ ); 3.1-2.4 (several m, 3H,  $\text{CH}_3$ -pyrrole); 2.45-2.3 (several s, 3H,  $\text{CH}_3$ -pyrrole); 1.0-0.75 (several d, 3H,  $\text{CH}_3$ -THIQ); 0.9 (several s, 9H,  $\text{Si}(\text{CH}_3)_2(\text{CH}(\text{CH}_3)_2)$ ); 0.1 (several s, 6H,  $\text{Si}(\text{CH}_3)_2(\text{CH}(\text{CH}_3)_2)$ )

IR:  $\nu$ :-N=N=N:  $2100\text{ cm}^{-1}$ ,  $\nu$ :>C=O:  $1630\text{ cm}^{-1}$ ,  $\nu$ :-Si-O-:  $1035\text{ cm}^{-1}$

***Step C: 1-(2-Azidoethyl)-N-(4-hydroxyphenyl)-2-methyl-5-(6-((3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl)-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide***

To a solution of 1.12 g of the compound obtained in Step B (14.49 mmol) in 5 mL of methanol there are added, dropwise, 7.24 mL of 1M methanolic potassium hydroxide solution (72.45 mmol). The batch is stirred at ambient temperature for 3 hours. The reaction mixture is then concentrated to dryness, taken up in dichloromethane, hydrolysed with saturated aqueous  $\text{NaHCO}_3$  solution and then extracted twice with dichloromethane. The organic phases are then combined, washed with water, dried over  $\text{MgSO}_4$  and concentrated to dryness. The expected product is obtained in the form of a foam and used directly in the next Step.

$^1\text{H NMR}$ :  $\delta$  (500 MHz;  $\text{dmsO-d}_6$ ; 300K): 9.60 (s, 1H,  $\text{CH}_2\text{CH}_2\text{OH}$ ); 7.65-7.45 (several s, 1H, H pyrazole); 7.1-6.9 (several s, 1H, H pyrazole); 7.3-6.4 (several m, 6H, aromatic Hs); 7.1-6.9 (several s, 1H, aromatic Hs); 6.8, 6.5 (2m, 2H, aromatic Hs); 6.15 (several s, 2H,  $\text{OCH}_2\text{O}$ ); 5.35- 4.8 (several s, 1H, H-pyrrole (presence of conformational isomers); 4.9, 4.6, 3.8 (several m, 1H, aliphatic H, H tetrahydroisoquinoline); 3.7 (several s, 3H, H  $\text{CH}_3$ -pyrazole); 3.5-3.25 (m, 2H,  $\text{CH}_2\text{CH}_2\text{N}_3$ ); 3.1-2.4 (several m, 3H,  $\text{CH}_3$ -pyrrole); 2.45-2.3 (several s, 3H, H THIQ); 2.45-2.3 (several s, 3H,  $\text{CH}_3$ -pyrrole); 1.0-0.75 (several d, 3H,  $\text{CH}_3$ -THIQ)

IR:  $\nu$ :-OH:  $3171\text{ cm}^{-1}$ ,  $\nu$ :-N=N=N:  $2100\text{ cm}^{-1}$ ,  $\nu$ :>C=O:  $1617\text{ cm}^{-1}$

***Step D: 1-(2-Aminoethyl)-N-(4-hydroxyphenyl)-2-methyl-5-(6-([(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride***

To a solution of 1.27 g of the compound obtained in the above Step (1.93 mmol) in 15 mL of anhydrous ethanol there is added 0.154 g of Pd/C 10 %. The batch is degassed for 0.5 hours. It is then stirred for 12 hours at ambient temperature under hydrogen pressure (1.5 bar). The reaction mixture is then filtered and then concentrated to dryness. After purification by chromatography over silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> gradient), an oily residue is obtained. The residue is dissolved in 10 mL of anhydrous ethanol and then converted into salt form by adding two molar equivalents of a 1N solution of HCl in ethanol. The product is then dried before being dissolved in a minimum of a mixture of water and acetonitrile. After a lyophilisation step at low temperature, the expected product is obtained in the form of a solid.

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

%C=64.62:63.84; %H=5.57:5.55; %N=12.56:12.36; %Cl=5.3:5.56

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

Empirical formula: C<sub>36</sub>H<sub>36</sub>N<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 633.2820

[M+H]<sup>+</sup> measured: 633.2808

***Example 31. N-(4-Hydroxyphenyl)-5-(5-methoxy-2-([(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide***

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

%C=71.29:70.17; %H=5.98:5.98; %N=11.88:11.49

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

Empirical formula: C<sub>35</sub>H<sub>36</sub>N<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 590.2762

[M+H]<sup>+</sup> measured: 590.2778

**Example 32.** Phenyl (4-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-3-[[{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}benzyl]-carbamate

**Step A:** *N*-(4-Benzoyloxyphenyl)-*N*,1,2-trimethyl-pyrrole-3-carboxamide

5 The process is analogous to that described in Step A of Example 45.

**Step B:** *tert*-Butyl [4-(4-{[4-(benzyloxy)phenyl](methyl)carbamoyl}-1,5-dimethyl-1H-pyrrol-2-yl)-3-[[{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}benzyl]-carbamate

10 The compound of Preparation II (1.5 g; 2.96 mmol) and the compound of Step A (1.16 g; 3.44 mmol) are dissolved in dimethylacetamide (25 mL) and then nitrogen is bubbled through the solution for 5 minutes. Potassium acetate (0.586 g; 5.92 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.2 g; 0.295 mmol) are added to the mixture which is then heated to 100°C and, after stirring for 20 minutes, water (10 µL) is added. Stirring at 100°C under a nitrogen atmosphere is continued for 2 hours more. The  
15 reaction mixture is allowed to cool to ambient temperature and is then evaporated to a volume of 15 mL. The resulting mixture is filtered over a short Celite column and then purified by preparative HPLC using water-TFA and acetonitrile as eluants. The pH of the appropriate fractions is adjusted to 7 with NaHCO<sub>3</sub>, and then the acetonitrile is evaporated off under reduced pressure. The aqueous residue is extracted with DCM. The organic  
20 phase is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to yield the title compound.

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

Empirical formula: C<sub>40</sub>H<sub>41</sub>N<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 713.3705

25 [M+H]<sup>+</sup> measured: 713.3709

**Step C:** 5-[4-(Aminomethyl)-2-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl]phenyl]-N-[4-(benzyloxy)phenyl]-N,1,2-trimethyl-1H-pyrrole-3-carboxamide hydrochloride

The compound of the above Step (1.18 g, 1.66 mmol) is dissolved/suspended in 4M HCl in dioxane (20 mL). The heterogeneous mixture is stirred for 30 minutes at ambient temperature and then evaporated to dryness to yield 1.19 g of the title compound which is used in the next Step without purification.

**Step D:** Phenyl (4-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-3-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}benzyl)carbamate

The title compound is obtained starting from the compound of the above Step in accordance with the protocol of Step D of Example 45.

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

%C=72.83(72.88);%H=6.01(5.96);%N=8.02(8.72)

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

Empirical formula: C<sub>39</sub>H<sub>38</sub>N<sub>4</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 643.2922

[M+H]<sup>+</sup> measured: 643.2916

**Example 33.** 5-(5-Chloro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

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

%C=65.75(65.84);%H=5.38(5.39);%N=7.62(7.68);%Cl=9.77(9.72);%Cl=4.84(4.86)

**Example 34.** 5-(5-Chloro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(3-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

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

%C=65.61(65.84);%H=5.09(5.39);%N=7.76(7.68);%Cl=4.83(4.86)

**Example 35.** *N*-(4-Hydroxyphenyl)-*N*,1,2-trimethyl-5-(2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-4-{[(phenoxyacetyl)amino]methyl}phenyl)-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 32 using 2-phenoxyacetyl chloride as acylating agent in Step D.

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

%C=72.53(73.15);%H=5.76(6.14);%N=8.31(8.53)

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

Empirical formula: C<sub>40</sub>H<sub>40</sub>N<sub>4</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 657.3079

[M+H]<sup>+</sup> measured: 657.3061

**Example 36.** 5-(4-{[(Ethylcarbamoyl)amino]methyl}-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*,1,2-trimethyl-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 32 using ethyl isocyanate as acylating agent in Step D.

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

%C=70.88(70.8);%H=6.02(6.62);%N=11.17(11.8)

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

Empirical formula: C<sub>35</sub>H<sub>39</sub>N<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 594.3100

[M+H]<sup>+</sup> measured: 594.3083

**Example 37.** 5-(4-{[(Benzylcarbamoyl)amino]methyl}-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*,1,2-trimethyl-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 32 using benzyl isocyanate as acylating agent in Step D.

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

%C=73.21(73.26);%H=5.98(6.3);%N=10.23(10.68)

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

Empirical formula: C<sub>40</sub>H<sub>41</sub>N<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 656.3239

[M+H]<sup>+</sup> measured: 656.3256

**Example 38.** 5-(5-Chloro-2-{[(3*S*)-3-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

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

%C=70.97(71.34);%H=5.2(5.32);%N=6.96(6.93)

**Example 39.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

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

%C=69.81(69.64);%H=5.6(5.51);%N=11.55(11.6)

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

Empirical formula: C<sub>35</sub>H<sub>34</sub>N<sub>5</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 604.2554

[M+H]<sup>+</sup> measured: 604.2565

**Example 40.** Phenyl (3-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-4-[[*(3R)*-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}benzyl)-carbamate

**Step A:** *N*-(4-Benzoyloxyphenyl)-*N*,1,2-trimethyl-pyrrole-3-carboxamide

5 The process is analogous to that described in Step A of Example 45.

**Step B:** 5-[5-(Aminomethyl)-2-[[*(3R)*-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl]phenyl]-*N*-[4-(benzyloxy)phenyl]-*N*,1,2-trimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

10 The compound of Preparation III (1.84 g; 3.99 mmol) and the compound of Step A (1.60 g; 4.48 mmol) are dissolved in dimethylacetamide (20 mL) and then nitrogen is bubbled through the solution for 5 minutes. Potassium acetate (0.78 g; 7.48 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.28 g; 0.4 mmol) are added to the mixture which is then heated to 105°C and, after stirring for 10 minutes, water (11 µL) is added. Stirring at 105°C under a nitrogen atmosphere is continued for 6 hours more. The  
15 reaction mixture is allowed to cool to ambient temperature, the resulting mixture is filtered over a short Celite column and is then purified by preparative HPLC using water-TFA and acetonitrile as eluants. The pH of the appropriate fractions is adjusted to 7 with NaHCO<sub>3</sub> and then the acetonitrile is evaporated off under reduced pressure. The solid precipitate is removed by filtration and then dried (5 mbar, 45°C, 16 hours) to form *tert*-butyl [3-(4-{[4-(benzyloxy)phenyl](methyl)carbamoyl]-1,5-dimethyl-1*H*-pyrrol-2-yl}-4-[[*(3R)*-3-methyl-  
20 3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}benzyl]carbamate which is dissolved/suspended in 4M HCl in dioxane (35 mL). The heterogeneous mixture is stirred for 30 minutes at ambient temperature and then evaporated to dryness to yield the title compound which is used in the next Step without purification.

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

Empirical formula: C<sub>39</sub>H<sub>40</sub>N<sub>4</sub>O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 613.3180

[M+H]<sup>+</sup> measured: 613.3194



IR:  $\nu$ : N-H+: 2854  $\text{cm}^{-1}$ ;  $>\text{C}=\text{O}$ : 1621  $\text{cm}^{-1}$ ; C-O-C: 1234, 1120, 1011  $\text{cm}^{-1}$

**Step C:** Phenyl (3-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-4-[[{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}benzyl]carbamate

The title compound is obtained starting from the compound of the above Step in accordance with the process of Step D of Example 45.

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

%C=73.2(72.88); %H=5.83(5.96); %N=8.13(8.72)

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

Empirical formula:  $\text{C}_{39}\text{H}_{38}\text{N}_4\text{O}_5$

[M+H]<sup>+</sup> calculated: 643.2922

[M+H]<sup>+</sup> measured: 643.2902

**Example 41.** N-(3-Fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-[[{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide

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

%C=71.44(71.95); %H=4.95(5.22); %N=6.8(6.8)

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

Empirical formula:  $\text{C}_{37}\text{H}_{33}\text{FN}_3\text{O}_5$

[M+H]<sup>+</sup> calculated: 618.2399

[M+H]<sup>+</sup> measured: 618.2392

**Example 42.** N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-[[{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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

%C=71.32(71.65); %H=5.17(5.4); %N=10.67(10.71)

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

Empirical formula: C<sub>39</sub>H<sub>36</sub>N<sub>5</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 654.2711

[M+H]<sup>+</sup> measured: 654.2710

- 5     **Example 43.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide

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

%C=73.9(74.11);%H=5.16(5.55);%N=6.81(7.01)

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

Empirical formula: C<sub>37</sub>H<sub>34</sub>N<sub>3</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 600.2493

[M+H]<sup>+</sup> measured: 600.2495

- 15    **Example 44.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]-pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=66.41(66.62);%H=5.08(5.59);%N=10.85(10.84);%Cl=4.68(4.57)

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

- 20    Empirical formula: C<sub>43</sub>H<sub>42</sub>N<sub>6</sub>O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 739.3239

[M+H]<sup>+</sup> measured: 739.3246

**Example 45. Phenyl [2-(3-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-4-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-phenyl)ethyl]carbamate**

***Step A: N-(4-Benzyloxyphenyl)-N,1,2-trimethyl-pyrrole-3-carboxamide***

5 To a suspension of 1,2-dimethylpyrrole-3-carboxylic acid (2.085 g; 15 mmol) in 1,2-dichloroethane (40 mL) there is added 1-chloro-*N,N*,2-trimethyl-prop-1-en-1-amine (2.37 mL; 17.9 mmol), and the solution formed is stirred for 1 hour. To the resulting solution there is added, dropwise, an ice-cold solution of 4-benzyloxy-*N*-methyl-aniline (3.73 g; 15 mmol) and *N*-ethyl-*N*-isopropyl-propan-2-amine (7.75 mL; 45 mmol) in 1,2-  
10 dichloroethane (40 mL). The reaction mixture is stirred at ambient temperature for 1 hour; it is then diluted with dichloromethane (250 mL) and washed with water (2 x 30 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The crude product is triturated with diethyl ether and the solid formed is filtered off to yield the title compound.

IR:  $\nu$ : >C=O: 1616 cm<sup>-1</sup>; amide: 1508 cm<sup>-1</sup>; C-O-C: 1230, 1172, 1009 cm<sup>-1</sup>

15 ***Step B: tert-Butyl {2-[3-(4-{[4-(benzyloxy)phenyl](methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-4-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)ethyl}-carbamate***

The compound of Preparation I (0.869 g; 1.67 mmol) and the compound of Step A (0.558 g; 1.67 mmol) are dissolved in dimethylacetamide (8 mL) and then nitrogen is  
20 bubbled through the solution for 5 minutes. Potassium acetate (0.33 g; 3.34 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.117 g; 0.167 mmol) are added to the mixture which is then heated to 140°C and, after stirring for 10 minutes, water (80  $\mu$ L) is added. Stirring at 140°C under a nitrogen atmosphere is continued for 16 hours more. The reaction mixture is allowed to cool to ambient temperature and then evaporated. The  
25 residue is partitioned between dichloromethane (100 mL) and water (20 mL). The organic phase is washed with water (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The residue was purified by preparative HPLC using water-TFA and acetonitrile as eluants. The pH of the appropriate fractions is adjusted to 12 using aqueous NaOH solution and then the acetonitrile is evaporated off under reduced pressure. The aqueous residue is extracted with

dichloromethane (2 x 100 mL). The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to yield the title compound.

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

Empirical formula: C<sub>45</sub>H<sub>50</sub>N<sub>4</sub>O<sub>5</sub>

5 [M+H]<sup>+</sup> calculated: 727.3861

[M+H]<sup>+</sup> measured: 727.3852

**IR:**  $\nu$ : >C=O: 1705, 1618 cm<sup>-1</sup>; amide: 1509 cm<sup>-1</sup>; C-O-C: 1242, 1166, 1012 cm<sup>-1</sup>

***Step C: 5-[5-(2-Aminoethyl)-2-[[ (3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl]phenyl]-N-[4-(benzyloxy)phenyl]-N,1,2-trimethyl-1H-pyrrole-3-carboxamide hydrochloride***

10

The compound of Step B (0.35 g; 0.48 mmol) was dissolved/suspended in 4M HCl in dioxane (3 mL). The heterogeneous mixture is stirred for 30 minutes at ambient temperature and then evaporated to dryness to yield the title compound which is used in next Step without being otherwise purified.

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

Empirical formula: C<sub>40</sub>H<sub>42</sub>N<sub>4</sub>O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 627.3337

[M+H]<sup>+</sup> measured: 627.3309

**IR:**  $\nu$ : C-H: 2931 cm<sup>-1</sup>; >C=O: 1608 cm<sup>-1</sup>; amide: 1508 cm<sup>-1</sup>; C-O-C: 1233, 1012 cm<sup>-1</sup>

20 ***Step D: Phenyl 2-(3-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-4-[[ (3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)ethyl]-carbamate***

The compound of Step C (0.10 g; 0.15 mmol) is dissolved in dichloromethane. Phenyl chloroformate (0.027 g; 0.17 mmol) and diisopropylethylamine (0.097 g, 0.75 mmol) are added thereto. The reaction mixture is stirred at ambient temperature for 30 minutes. After  
25 dilution with dichloromethane (100 mL), the organic phase is washed with water (20 mL),

evaporated and concentrated. The residue is then dissolved in ethanol and a Pd/C catalyst is added (10 mg). The reaction mixture is hydrogenated at atmospheric pressure at ambient temperature. When the reaction is complete, the catalyst is removed by filtration, the filtrate is concentrated and the crude product is purified by chromatography over silica gel using dichloromethane and methanol as eluants, to yield the title product.

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

%C=72.36(73.15);%H=6.15(6.14);%N=8.14(8.53)

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

Empirical formula: C<sub>40</sub>H<sub>40</sub>N<sub>4</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 657.3077

[M+H]<sup>+</sup> measured: 657.3062

**Example 46. N-(4-Hydroxyphenyl)-N,1,2-trimethyl-5-(2-([(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)-5-{2-[(phenoxyacetyl)amino]ethyl}phenyl)-1H-pyrrole-3-carboxamide**

The title compound is obtained in accordance with the process of Example 45 using 2-phenoxyacetyl chloride as acylating agent in Step D.

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

%C=72.74(73.41);%H=6.38(6.31);%N=7.65(8.35)

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

Empirical formula: C<sub>41</sub>H<sub>42</sub>N<sub>4</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 671.3235

[M+H]<sup>+</sup> measured: 671.3226

**Example 47. N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-([(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide hydrochloride**

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

%C=64.25(64.59);%H=5.4(5.7);%N=11.41(11.59);%Cl=4.93(4.89)

**Example 48.** *N*-(4-Hydroxyphenyl)-*N*-(2-methoxypyrimidin-5-yl)-1,2-dimethyl-5-(6-  
5 {{{(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-  
pyrrole-3-carboxamide

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

%C=68.07(68.45);%H=5(5.27);%N=10.74(11.09)

**Example 49.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-  
pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-  
10 dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-  
carboxamide dihydrochloride

**Step A:** *N*-(4-{{*tert*-Butyl(dimethyl)silyl}oxy}phenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-  
pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-  
2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

15 The title compound is obtained in accordance with the process of Example 1 using the acid  
of Preparation 11 and (3*S*)-3-(4-morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline (see  
Preparation 3') in Step A, and the compound of Preparation 11" in Step C.

**Step B:** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-  
*b*]pyridin-5-yl)-5-(6-{{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-  
20 yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide dihydrochloride

To a solution of 0.21 g (0.2 mmol) of the compound of Step A in 3 mL of acetic acid there  
are added 85 mg of sodium cyanoborohydride (5 equivalents). The reaction mixture is  
stirred for 3 hours at ambient temperature and then overnight at 50°C. There are then added  
2.6 equivalents of sodium cyanoborohydride and the reaction mixture is heated at 50°C for  
25 3 hours. The operation is repeated for a second time (addition of 2.6 equivalents of sodium  
cyanoborohydride and then heating at 50°C for 3 hours). After coevaporation of the acetic  
acid in the presence of toluene, the residue is taken up in 3 mL of methanol. The pH of the  
solution is adjusted to 12 using 1M methanolic potassium hydroxide solution. After stirring

overnight at ambient temperature, the reaction mixture is poured into saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The resulting organic phase is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The product obtained is purified by chromatography over silica gel (dichloromethane/ethanol/ammonia 94/6/0.6) and then over a Lichroprep RP18 column (water/acetonitrile/trifluoroacetic acid). After evaporation of the acetonitrile, the product is neutralised with sodium bicarbonate. It is then extracted with ethyl acetate. The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue obtained is dissolved in acetonitrile and converted into salt form with 1M aqueous HCl solution. After lyophilisation, the title product is obtained in the form of a solid.

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

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

[M+H]<sup>+</sup> calculated: 741.3395

[M+H]<sup>+</sup> measured: 741.3400

**Example 50.** *N*-(4-Hydroxyphenyl)-*N*-(2-methoxypyrimidin-5-yl)-1,2-dimethyl-5-(6-  
{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-  
benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

Empirical formula: C<sub>40</sub>H<sub>40</sub>N<sub>6</sub>O<sub>7</sub>

[M+H]<sup>+</sup> calculated: 717.3031

[M+H]<sup>+</sup> measured: 717.3031

**Example 51.** 5-(5-{[(Benzylcarbamoyl)amino]methyl}-2-{[(3*R*)-3-methyl-3,4-  
dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*,1,2-trimethyl-  
1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 40 using benzyl isocyanate as acylating agent in Step C.

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

%C=73.39(73.26);%H=6.16(6.3);%N=10.08(10.68)

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

Empirical formula: C<sub>40</sub>H<sub>41</sub>N<sub>5</sub>O<sub>4</sub>

5 [M+H]<sup>+</sup> calculated: 656.3239

[M+H]<sup>+</sup> measured: 656.3226

**Example 52. 5-(5-{[(Ethylcarbamoyl)amino]methyl}-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*,1,2-trimethyl-1*H*-pyrrole-3-carboxamide**

10 The title compound is obtained in accordance with the process of Example 40 using ethyl isocyanate as acylating agent in Step C.

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

%C=71.4(70.8);%H=6.41(6.62);%N=11.24(11.8)

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

15 Empirical formula: C<sub>35</sub>H<sub>39</sub>N<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 594.3082

[M+H]<sup>+</sup> measured: 594.3069

**Example 53. *N*-(4-Hydroxyphenyl)-*N*,1,2-trimethyl-5-(2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-{[(phenoxyacetyl)amino]methyl}phenyl)-1*H*-pyrrole-3-carboxamide**

20 The title compound is obtained in accordance with the process of Example 40 using 2-phenoxyacetyl chloride as acylating agent in Step C.

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

%C=72.32(73.15);%H=6.21(6.14);%N=7.84(8.53)



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

Empirical formula: C<sub>40</sub>H<sub>40</sub>N<sub>4</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 657.3079

[M+H]<sup>+</sup> measured: 657.3105

5     **Example 54.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-5-(2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-{[(phenoxyacetyl)amino]methyl}phenyl)-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

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

%C=73.87(73.04);%H=5.47(5.74);%N=10.26(10.87)

10     **Example 55.** 5-(5-[2-({[2-(4-Fluorophenyl)ethyl]sulphonyl}amino)ethyl]-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*,1,2-trimethyl-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 45 using 2-(4-fluorophenyl)ethanesulphonyl chloride as acylating agent in Step D.

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

%C=67.42(68.12);%H=5.76(6);%N=7.27(7.75);S=3.68(4.44)

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

Empirical formula: C<sub>41</sub>H<sub>43</sub>FN<sub>4</sub>O<sub>5</sub>S

[M+H]<sup>+</sup> calculated: 723.3018

20     [M+H]<sup>+</sup> measured: 723.3011

**Example 56.** 5-(5-{2-[(Benzylcarbamoyl)amino]ethyl}-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*,1,2-trimethyl-1*H*-pyrrole-3-carboxamide

25     The title compound is obtained in accordance with the process of Example 45 using benzyl isocyanate as acylating agent in Step D.

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

%C=71.14(73.52);%H=6.47(6.47);%N=9.42(10.46)

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

Empirical formula: C<sub>41</sub>H<sub>43</sub>N<sub>5</sub>O<sub>4</sub>

5 [M+H]<sup>+</sup> calculated: 670.3395

[M+H]<sup>+</sup> measured: 670.3390

**Example 57. N-(4-Hydroxyphenyl)-N,1,2-trimethyl-5-(2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-{2-[(phenylacetyl)amino]ethyl}phenyl)-1H-pyrrole-3-carboxamide**

10 The title compound is obtained in accordance with the process of Example 45 using phenylacetyl chloride as acylating agent in Step D.

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

%C=75.46(75.21);%H=6.11(6.46);%N=8.31(8.56)

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

15 Empirical formula: C<sub>41</sub>H<sub>42</sub>N<sub>4</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 655.3286

[M+H]<sup>+</sup> measured: 655.3285

**Example 58. N-(4-Hydroxyphenyl)-N,1,2-trimethyl-5-(2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-{2-[(phenylcarbamoyl)amino]ethyl}phenyl)-1H-pyrrole-3-carboxamide**

20 The title compound is obtained in accordance with the process of Example 45 using phenyl isocyanate as acylating agent in Step D.

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

%C=71.25(73.26);%H=6.12(6.3);%N=9.61(10.68)

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

Empirical formula: C<sub>40</sub>H<sub>41</sub>N<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 656.3239

[M+H]<sup>+</sup> measured: 656.3226

5     **Example 59.** 5-(4-[(2-(4-Fluorophenyl)ethyl)sulphonyl]amino)methyl)-2-[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]phenyl)-*N*-(4-hydroxyphenyl)-*N*,1,2-trimethyl-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 32 using 2-(4-fluorophenyl)ethanesulphonyl chloride as sulphonylation agent in Step D.

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

%H=5.19(5.83);%N=7.28(7.9);S=4.45(4.52);%C=66.17(67.78)

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

Empirical formula: C<sub>40</sub>H<sub>41</sub>FN<sub>4</sub>O<sub>5</sub>S

[M+H]<sup>+</sup> calculated: 709.2866

15     [M+H]<sup>+</sup> measured: 709.2866

**Example 60.** 5-(5-Chloro-2-[(3*S*)-3-[(2-(dimethylamino)ethoxy)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]phenyl)-*N*-(4-hydroxy phenyl)-1,2-dimethyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

20     The process of Example 29 is used, on the one hand replacing the 4-(2-bromoethyl)morpholine hydrobromide used in Step B by 2-chloroethyldimethylamine hydrochloride and on the other hand adding a catalytic amount of tetrabutylammonium iodide.

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

Empirical formula: C<sub>40</sub>H<sub>41</sub>ClN<sub>4</sub>O<sub>4</sub>

25     [M+H]<sup>+</sup> calculated: 677.2890

[M+H]<sup>+</sup> measured: 677.2887

**Example 61.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

5 Empirical formula: C<sub>36</sub>H<sub>32</sub>N<sub>4</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 601.2445

[M+H]<sup>+</sup> measured: 601.2424

**Example 62.** 5-(5-Fluoro-4-methoxy-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

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

%C=68.99(69.18);%H=5.89(5.64);%N=11.35(11.52)

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

Empirical formula: C<sub>35</sub>H<sub>34</sub>FN<sub>5</sub>O<sub>4</sub>

15 [M+H]<sup>+</sup> calculated: 608.2668

[M+H]<sup>+</sup> measured: 608.2640

**Example 63.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]-pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

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

%C=70.48(70.85);%H=5.67(5.32);%N=11.2(10.87)

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

Empirical formula: C<sub>38</sub>H<sub>34</sub>ClN<sub>5</sub>O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 666.2242

25 [M+H]<sup>+</sup> measured: 666.2235

**Example 64.** *N*,1,2-Trimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-  
{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-  
benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

5 Empirical formula: C<sub>38</sub>H<sub>40</sub>N<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 661.3133

[M+H]<sup>+</sup> measured: 661.3125

**Example 65.** 1,2-Dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-  
(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-  
5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

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

Empirical formula: C<sub>43</sub>H<sub>42</sub>N<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 723.3289

[M+H]<sup>+</sup> measured: 723.3287

**Example 66.** 4-Methylphenyl (4-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-  
dimethyl-1*H*-pyrrol-2-yl}-3-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-  
carbonyl}benzyl)carbamate

The title compound is obtained in accordance with the process of Example 32 using 4-  
methylphenyl chloroformate as acylating agent in Step D.

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

Empirical formula: C<sub>40</sub>H<sub>40</sub>N<sub>4</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 657.3079

[M+H]<sup>+</sup> measured: 657.3076

**Example 67.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-  
2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-  
pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=65.69(65.28);%H=5.38(5.77);%N=11.18(12.02);%Cl=5.61(5.07)

**Example 68.** 5-(5-Fluoro-4-hydroxy-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

A 1N solution of tribromoborane (1.3 equivalents) in dichloromethane is poured rapidly, at ambient temperature, into a solution of the compound of Example 62 in dichloromethane. This operation is repeated twice in order to complete the reaction in 5 hours. The reaction mixture is poured into anhydrous ethanol at 5°C. After stirring for 10 minutes, saturated aqueous NaHCO<sub>3</sub> solution is added. The mixture is extracted with dichloromethane, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to dryness. The crude product obtained is purified by preparative HPLC using water, TFA and acetonitrile as eluants. The pH of the appropriate fractions is adjusted to 12 with saturated aqueous NaHCO<sub>3</sub> solution, and then the acetonitrile is evaporated off under reduced pressure. The aqueous residue is extracted with dichloromethane. The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to yield the title compound.

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

Empirical formula: C<sub>34</sub>H<sub>32</sub>FN<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 594.2511

[M+H]<sup>+</sup> measured: 594.2517

**Example 69.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3*S*)-3-[(4-methylpiperazin-1-yl)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)-1*H*-pyrrole-3-carboxamide hydrochloride

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

Empirical formula: C<sub>44</sub>H<sub>45</sub>N<sub>7</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 752.3555

[M+H]<sup>+</sup> measured: 752.3552

**Example 70.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3*S*)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

5 Empirical formula: C<sub>41</sub>H<sub>42</sub>N<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 699.3289

[M+H]<sup>+</sup> measured: 699.3293

**Example 71.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

Empirical formula: C<sub>42</sub>H<sub>41</sub>ClN<sub>6</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 723.3289

[M+H]<sup>+</sup> measured: 723.3287

15 **Example 72.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-benzimidazol-5-yl)-1*H*-pyrrole-3-carboxamide

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

%C=68.90(69.17);%H=5.32(5.67);%N=11.40(11.52)

20 **Example 73.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide dihydrochloride

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

Empirical formula: C<sub>40</sub>H<sub>39</sub>N<sub>5</sub>O<sub>6</sub>

25 [M+H]<sup>+</sup> calculated: 686.2973

[M+H]<sup>+</sup> measured: 686.2971

**Example 74.** 5-(5-Chloro-2-[[[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

5 Empirical formula: C<sub>39</sub>H<sub>38</sub>ClN<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 676.2685

[M+H]<sup>+</sup> measured: 676.2684

**Example 75.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-[[[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]-1,3-benzodioxol-5-yl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=60.12:59.77; %H=4.92:4.76; %N=10.79:10.39 %Cl=4.55:5.17

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

Empirical formula: C<sub>39</sub> H<sub>37</sub> F<sub>3</sub> N<sub>6</sub> O<sub>6</sub>

15 [M+H]<sup>+</sup> calculated: 743.2799

[M+H]<sup>+</sup> measured: 742.2802

**Example 76.** 2-(Difluoromethyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-[[[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

20 **Example 77.** *N*-(4-Hydroxyphenyl)-2-(methoxymethyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-[[[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 78.** 2-(2,2-Difluoroethyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-[[[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

25



**Example 79.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-  
{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-  
benzodioxol-5-yl)-2-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 80.** *N*-(4-Hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-*N*-(1-methyl-1*H*-  
pyrazol-4-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-  
yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 81.** *N*-(4-Hydroxyphenyl)-1-methyl-5-(6-{[(3*R*)-3-methyl-3,4-  
dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-1*H*-  
pyrazol-4-yl)-2-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the general protocol of Example 1 using the  
compound of Preparation 22 in Step A. The product obtained is finally dissolved in  
acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a  
lyophilisation step, the expected compound is obtained in the form of a solid.

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

Empirical formula: C<sub>40</sub> H<sub>42</sub> N<sub>6</sub> O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 703.3239

[M+H]<sup>+</sup> measured: 703.3236

**Example 82.** *N*-(4-Hydroxyphenyl)-1-methyl-5-(6-{[(3*R*)-3-methyl-3,4-  
dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-1*H*-  
pyrazol-4-yl)-2-(morpholin-4-ylmethyl)-1*H*-pyrrole-3-carboxamide

The procedure is in accordance with the general protocol of Example 1 using the  
compound of Preparation 23 in Step A.

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

Empirical formula: C<sub>39</sub> H<sub>40</sub> N<sub>6</sub> O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 689.3082

[M+H]<sup>+</sup> measured: 689.3085

**Example 83.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxamide

**Example 84.** 2-(Difluoromethyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 85.** *N*-(4-Hydroxyphenyl)-2-(methoxymethyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 86.** 2-(2,2-Difluoroethyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 87.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-2-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 88.** *N*-(4-Hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

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

%C=65.97:66.15; %H=5.78:5.46; %N=10.26:10.24; %Cl=4.33:4.76

***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):***

Empirical formula: C<sub>45</sub> H<sub>46</sub> N<sub>6</sub> O<sub>7</sub>

5 [M+H]<sup>+</sup> calculated: 783.3501

[M+H]<sup>+</sup> measured: 783.3502

**Example 89.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-[2-(morpholin-4-yl)ethyl]-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

10 **Example 90.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(morpholin-4-ylmethyl)-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 91.** *N*-(4-Hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 92.** 1-Ethyl-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

20 The procedure is in accordance with the protocol described in Example 1, using the compounds from Preparations 20 and 3' in Step A and the compound from Preparation 1" in Step C. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

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

25 %C=64.99:65.61; %H=5.86:5.39; %N=11.37:11.43; %Cl=4.80:4.42

$[M+H]^+$  measured: 703.3236

**Example 93.** *N*-(4-Hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-([*(3S)*-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl))-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=64.01:64.10; %H=5.90:5.63; %N=10.92:10.88; %Cl=4.61:4.70.

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

Empirical formula: C<sub>41</sub> H<sub>44</sub> N<sub>6</sub> O<sub>7</sub>

$[M+H]^+$  calculated: 733.3344

10  $[M+H]^+$  measured: 733.3345

**Example 94.** 1-(2-Fluoroethyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-([*(3S)*-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl))-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

15 The procedure is in accordance with the protocol described in Steps A-D of Example 1, using the compounds from Preparations 21 and 3' in Step A and the compound from Preparation 1'' in Step C. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

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

20 %C=63.44:63.25; %H=5.59:5.09; %N=11.10:11.02; %Cl=4.68:4.74

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

Empirical formula: C<sub>40</sub>H<sub>41</sub>FN<sub>6</sub>O<sub>6</sub>

$[M+H]^+$  calculated: 721.3144

$[M+H]^+$  measured: 721.3147

**Example 95.** 1-(2,2-Difluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-([(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 32 and the compound of Preparation 3' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=61.97:61.89; %H=5.33:5.04; %N=10.84:10.85; %Cl<sup>-</sup>=4.57:4.55

**High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>40</sub> H<sub>40</sub> F<sub>2</sub> N<sub>6</sub> O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 739.3050

[M+H]<sup>+</sup> measured: 739.3052

**Example 96.** N-(4-Hydroxyphenyl)-2-methyl-5-(6-([(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide hydrochloride

**Step A:** N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1-(2-morpholinoethyl)pyrrole-3-carboxamide

The compound obtained in Step E of Example 99 is dissolved in 6 mL of tetrahydrofuran. Sodium iodide (100 mg, 0.67 mmol) is added, followed by morpholine (0.21 mL, 2.53 mmol) dropwise. The reaction mixture is heated in a sealed flask at 90°C for 72 hours. After cooling, the solution is evaporated to dryness and the residue is purified by chromatography over silica gel using dichloromethane and methanol as eluants. The expected product is obtained in the form of a foam.

<sup>1</sup>H NMR (500 MHz, dms<sup>o</sup>-d<sub>6</sub>) δ ppm: 7.7-7.45 (4 bs, 1 H), 7.2-6.9 (m, 4 H), 7.1-6.4 (m, 2 H), 7.1-6.9 (4 bs, 1 H), 7-6.8 (4 m, 2 H), 6.75/6.48 (d+bs, 2 H), 6.1 (4 bs, 2 H), 5.25-4.7

(4 bs, 1 H), 5.2-3.8 (m, 2 H), 4.9/4.65/3.8 (3 m, 1 H), 3.75 (4 s, 3 H), 3.5 (bs, 4 H), 3-2 (m, 10 H), 2.41/2.3 (2 bs, 3 H), 1.02/0.95/0.78 (3 bd, 3 H), 0.88 (m, 9 H), 0.1 (m, 6 H)

IR (ATR)  $\text{cm}^{-1}$ : 1626  $\delta$  >C=O amides

**Step B:** *N*-(4-Hydroxyphenyl)-2-methyl-5-(6- $\{[(3R)$ -3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the protocol described in Step D of Example 1. The product obtained is finally subjected to a step of conversion into salt form in the presence of HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

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

Empirical formula:  $\text{C}_{40} \text{H}_{42} \text{N}_6 \text{O}_6$

$[\text{M}+\text{H}]^+$  calculated: 703.3239

$[\text{M}+\text{H}]^+$  measured: 703.3238

**Example 97.** *N*-(4-Hydroxyphenyl)-2-methyl-5-(6- $\{[(3R)$ -3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1-[2-(morpholin-4-yl)ethyl]-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the protocol described in Example 96 replacing the compound of Preparation 1" by that of Preparation 2".

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

%C=68.61:68.12; %H=5.89:5.23; %N=7.62:7.54; %Cl=4.82:4.66

**High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):**

Empirical formula:  $\text{C}_{42} \text{H}_{42} \text{N}_4 \text{O}_6$

$[\text{M}+\text{H}]^+$  calculated: 699.3177

$[\text{M}+\text{H}]^+$  measured: 699.3173

**Example 98.** 1-[2-(Dimethylamino)ethyl]-N-(4-hydroxyphenyl)-2-methyl-5-(6-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)-1,3-benzodioxol-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the protocol described in Example 27 replacing the compound of Preparation 1" by that of Preparation 2". The product obtained is finally subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

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

%C=69.30:69.20; %H=5.96:5.48; %N=8.08:8.08; %Cl=5.11:5.03

*High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):*

Empirical formula: C<sub>40</sub> H<sub>40</sub> N<sub>4</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 657.3071

[M+H]<sup>+</sup> measured: 657.3066

**Example 99.** N-(4-Hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-5-(6-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

**Step A:** Ethyl 1-(2-benzyloxyethyl)-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]pyrrole-3-carboxylate

The procedure is in accordance with the protocol described in Step A of Example 1 replacing the compound of Preparation 1 by that of Preparation 19.

<sup>1</sup>H NMR (500 MHz, dmso-d<sub>6</sub>) δ ppm: 7.35-6.95 (m, 9 H), 7-6.8 (several s, 2 H), 6.35-5.85 (several s, 1 H), 6.15 (several s, 2 H), 5.15-3.5 (several m, 4 H), 4.9/4.7/3.95 (several m, 1 H), 4.4 (m, 2 H), 4.2-3.95 (m, 2 H), 3.55 (m, 2 H), 3.1-2.35 (several m, 2 H), 2.5-2.2 (several s, 3 H), 1.25-1.1 (several m, 3 H), 1.05-0.7 (several d, 3 H)

**Step B:** *1-(2-Benzoyloxyethyl)-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]pyrrole-3-carboxylic acid*

The procedure is in accordance with the protocol described in Step B of Example 1.

**IR (ATR)  $\text{cm}^{-1}$ :** 3000-2500  $\nu$  -OH, 1675-1625  $\nu$  -C=O carboxylic acid + amide

5 **Step C:** *1-(2-Benzoyloxyethyl)-N-[4-[tert-butyl(dimethyl)silyl]oxyphenyl]-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)pyrrole-3-carboxamide*

The procedure is in accordance with the protocol described in Step C of Example 1.

10  **$^1\text{H}$  NMR** (500 MHz,  $\text{dms}\text{-d}_6$ )  $\delta$  ppm: 7.7-7.5 (several s, 1 H), 7.35-6.5 (several m, 11 H), 7.1-6.9 (several s, 1 H), 6.95-6.5 (several s, 2 H), 6.8/6.5 (m, 2 H), 6.05 (several s, 2 H), 5.25-4.7 (several s, 1 H), 5.1-3.6 (several m, 4 H), 4.85/4.6/3.75 (several m, 1 H), 4.3 (m, 2 H), 3.7 (2xs, 3 H), 3.4 (m, 2 H), 3.05-2.4 (several m, 2 H), 2.4-2.25 (several s, 3 H), 1-0.75 (several d, 3 H), 0.9 (several s, 9 H), 0.1 (several s, 6 H)

**IR (ATR)  $\text{cm}^{-1}$ :** 1629  $\nu$  >C=O amides

15 **Step D:** *N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-1-(2-hydroxyethyl)-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)pyrrole-3-carboxamide*

20 In a hydrogenating reactor, the compound of the above Step is dissolved in 30 mL of methanol. The solution is degassed by bubbling argon in, and palladium-on-carbon 10 % (550 mg) is added. The resulting suspension is stirred under a pressure of 1 bar of hydrogen for 15 hours, and then passed through a Whatman® filter. The catalyst is rinsed with methanol and the filtrate is evaporated *in vacuo*. The residue thereby obtained is purified by chromatography over silica gel using dichloromethane and methanol as eluants. The expected product is obtained in the form of an oil.

25  **$^1\text{H}$  NMR** (500 MHz,  $\text{pyridine-d}_5$ )  $\delta$  ppm: 7.7-7.4 (4 s, 1 H), 7.3-6.9 (m, 4 H), 7.1-6.8 (4 s, 1 H), 7-6.7 (m, 2 H), 6.9-6.4 (m, 2 H), 6.8-6.4 (4 m, 2 H), 6.1 (m, 2 H), 5.2/5/4.7 (4 s, 1 H), 5.15-3.9 (8 d, 2 H), 4.9-4.8 (m, 1 H), 4.9/4.7/3.85 (3 m, 1 H), 3.9-3.7 (m, 2 H), 3.75 (2 s, 3



H), 3.5-3.2 (m, 2 H), 3-2.4 (m, 2 H), 2.4-2.3 (4 s, 3 H), 1.05/0.95/0.75 (4 d, 3 H), 0.85 (bs, 9 H), 0.15-0 (m, 6 H)

**IR (ATR)  $\text{cm}^{-1}$ :** 3346  $\nu$  -OH primary alcohol, 1621  $\nu$  -C=O amides

**Step E:** *2-[3-[[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-(1-methyl-1H-pyrazol-4-yl)-carbamoyl]-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]pyrrol-1-yl]ethyl methanesulphonate*

The compound of the above Step (2.37 g, 3.17 mmol) is dissolved in 30 mL of tetrahydrofuran. The reaction mixture is cooled to 0°C and there are successively added triethylamine (1.8 mL, 13.9 mmol) and, dropwise, methanesulphonyl chloride (0.40 mL, 5.17 mmol). The reaction mixture is stirred for 2 hours at 0°C. The reaction mixture is then poured into saturated aqueous sodium hydrogen carbonate solution and extracted 3 times with ethyl acetate. The organic phase is washed 3 times with brine, dried over  $\text{MgSO}_4$ , filtered and then evaporated to dryness. The evaporation residue is used without purification in the next Step.

**$^1\text{H}$  NMR** (500 MHz,  $\text{dms}\text{-d}_6$ )  $\delta$  ppm: 7.7-7.45 (several s, 1 H), 7.25-6.4 (m, 8 H), 7.1-6.9 (several s, 1 H), 6.95-6.65 (several s, 2 H), 6.1 (several s, 2 H), 5.2-4.6 (several s, 1 H), 5.05-3.75 (several d, 2 H), 4.9/4.6/3.9/3.8 (several m, 1 H), 4.3-4.05 (m, 2 H), 4.2-3.95 (m, 2 H), 3.75/3.7 (2 s, 3 H), 3.05-2.5 (several m, 2 H), 3 (several s, 3 H), 2.45-2.3 (several s, 3 H), 1.05-0.75 (several d, 3 H), 0.9 (several s, 9 H), 0.1 (several s, 6 H)

**IR (ATR)  $\text{cm}^{-1}$ :** 1626  $\nu$  -C=O, 1349  $\nu$  - $\text{SO}_2$ , 1249  $\delta$  - $\text{CH}_3$ , 1172  $\nu$  - $\text{SO}_2$

**Step F:** *N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-1-[2-[2-methoxyethyl(methyl)amino]ethyl]-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)pyrrole-3-carboxamide*

The compound of the above Step (1.33 mg, 1.61 mmol) is dissolved in 6 mL of tetrahydrofuran. Sodium iodide (100 mg, 0.67 mmol) is added, followed by dimethylamine (0.172 g, 1.932 mmol) dropwise. The reaction mixture is heated in a sealed flask at 60°C for 36 hours. After cooling, it is evaporated to dryness and purified by chromatography over silica gel using dichloromethane and ammonia-in-methanol as eluants. The expected product is obtained in the form of a foam.

<sup>1</sup>H NMR (500 MHz, dms<sup>o</sup>-d<sub>6</sub>) δ ppm 7.7-7.45 (4 bs, 1 H), 7.2-6.9 (m, 4 H), 7.1-6.9 (4 bs, 1 H), 7-6.7 (4 m, 2 H), 7/6.45 (2 m, 2 H), 6.8/6.45 (2 m, 2 H), 6.1 (m, 2 H), 5.22/5.05/4.7 (4 bs, 1 H), 5.2-3.8 (m, 2 H), 4.91/4.65/3.9 (3 m, 1 H), 3.75 (2 bs, 3 H), 3.7 (m, 2 H), 3.2 (bs, 3 H), 3-2 (m, 2 H), 2.7-2 (ml, 6 H), 2.7-2 (m, 3 H), 2.45/2.35 (2 bs, 3 H),  
5 1.05/0.95/0.8 (3 bd, 3 H), 0.9 (m, 9 H), 0.1 (m, 6 H)

IR (ATR) cm<sup>-1</sup>: 1628 (shoulder) δ -C=O amides

***Step G: N-(4-hydroxyphenyl)-1-[2-[2-methoxyethyl(methyl)amino]ethyl]-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)pyrrole-3-carboxamide hydrochloride***

10 The procedure is in accordance with the protocol described in Step D of Example 1. The product obtained is finally subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

15 IR (ATR) cm<sup>-1</sup>: 2000 to 3500 ν -NH<sup>+</sup>/OH, 1615 ν >C=O amides, 1237-1161 δ >C-O-C<, 745 ν >CH-Ar

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

Empirical formula: C<sub>40</sub> H<sub>44</sub> N<sub>6</sub> O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 705.3395

[M+H]<sup>+</sup> measured: 705.3391

20 ***Example 100. 5-(5-Fluoro-4-methoxy-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride***

The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations. The product obtained is finally dissolved in acetonitrile and

converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

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

%C=64.23:64.31; %H=5.80:5.43; %N=11.52:11.46; %Cl=4.86:4.95

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

Empirical formula: C<sub>39</sub> H<sub>41</sub> F N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 693.3195

[M+H]<sup>+</sup> measured: 693.3194

10 **Example 101. 5-(4-Fluoro-5-methoxy-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride**

15 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 27 and the compound of Preparation 3' in Step A, and the compound of Preparation 1'' in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=64.23:63.12; %H=5.80:5.20; %N=11.52:11.38. %Cl=4.86:5.03

***High-resolution mass spectrometry (ESI+/HR, ESI-/LR):***

Empirical formula: C<sub>39</sub> H<sub>41</sub> F N<sub>6</sub> O<sub>5</sub>

20 [M+H]<sup>+</sup> calculated: 693.3195

[M+H]<sup>+</sup> measured: 693.3195

**Example 102. 5-(5-Chloro-2-{[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide trihydrochloride**

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

Empirical formula: C<sub>43</sub> H<sub>44</sub> Cl N<sub>7</sub> O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 742.3267

[M+H]<sup>+</sup> measured: 742.3268

5     **Example 103.** 5-(5-Chloro-2-{[(3*S*)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide

10     **Example 104.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 105.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

15     **Example 106.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide

The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations, it being understood that Step D is not carried out. The expected product is obtained in free base form.

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

%C=70.72:69.77; %H=5.79:5.96; %N=11.78:11.43

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

Empirical formula: C<sub>42</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 713.3001

25     [M+H]<sup>+</sup> measured: 713.2998

**Example 107.** 5-(5-Chloro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(4-fluorophenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 108.** 5-(5-Chloro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(5-cyano-1-methyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and (3*S*)-3-(4-morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline (see Preparation 3') in Step A, and the compound of Preparation 19" in Step C. The product obtained is finally subjected to a step of conversion into salt form in the presence of HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

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

%C=64.95:65.09; %H=5.45:5.20; %N=11.36:11.26; %Cl=4.79:4.62

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

Empirical formula: C<sub>40</sub> H<sub>39</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 703.2794

[M+H]<sup>+</sup> measured: 703.2789

**Example 109.** 5-(5-Chloro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(6-cyanopyridin-2-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 23" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

*High-resolution mass spectrometry (ESI<sup>+</sup>/FLA/HR, ESI/FLA):*

Empirical formula: C<sub>40</sub> H<sub>37</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 701.2638

[M+H]<sup>+</sup> measured: 701.2639

- 5     **Example 110.** 5-(5-Chloro-2-([(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-cyanopyridin-2-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=65.13:65.72; %H=5.19:4.76; %N=11.39:12.04; %Cl=4.81:4.45

- 10    *High-resolution mass spectrometry (ESI<sup>+</sup>/FLA/HR, ESI/FLA):*

Empirical formula: C<sub>40</sub> H<sub>37</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 701.2638

[M+H]<sup>+</sup> measured: 701.2643

- 15    **Example 111.** 5-(5-Chloro-2-([(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-cyanopyrimidin-2-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

**Example 112.** 5-(5-Chloro-2-([(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-[2-(dimethylamino)pyridin-4-yl]-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

- 20    **Example 113.** 5-(5-Chloro-2-([(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-benzimidazol-5-yl)-1*H*-pyrrole-3-carboxamide

- 25    **Example 114.** 5-(5-Chloro-2-([(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(pyrazolo[1,5-*a*]pyrimidin-6-yl)-1*H*-pyrrole-3-carboxamide

**Example 115.** 5-(5-Chloro-2-{[(3*S*)-3-[(9*aS*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide dihydrochloride

5 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 7' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

10 %C=61.01:60.17; %H=5.74:5.09; %N=12.15:12.02; %Cl=8.78:9.81

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

Empirical formula: C<sub>41</sub> H<sub>44</sub> Cl N<sub>7</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 734.3216

[M+H]<sup>+</sup> measured: 734.3220

15 **Example 116.** 5-(5-Chloro-2-{[(3*S*)-3-[(9*aR*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide dihydrochloride

20 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 9' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=61.01:61.90; %H=5.74:5.65; %N=12.15:12.14; %Cl=13.15:11.51

***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):***

Empirical formula: C<sub>41</sub> H<sub>44</sub> Cl N<sub>7</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 734.3216

[M+H]<sup>+</sup> measured: 734.3218

5     **Example 117.** 5-(5-Chloro-2-{[(3*S*)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

10     **Example 118.** 5-(5-Chloro-2-{[(3*S*)-3-(difluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 119.** 5-(5-Chloro-2-{[(3*S*)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

15     **Example 120.** 5-(5-Chloro-2-{[(3*S*)-3-[(3-cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 121.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(1-ethyl-1*H*-pyrazol-4-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

20     **Example 122.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(1-cyclopropyl-1*H*-pyrazol-4-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

25     The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 28" in Step C.



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

%C=68.12:67.94; %H=5.86:5.77; %N=11.92:11.65

***High-resolution mass spectrometry (ESI+/HR, ESI-/LR):***

Empirical formula: C<sub>40</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>4</sub>

5 [M+H]<sup>+</sup> calculated: 705.2951

[M+H]<sup>+</sup> measured: 705.2952

**Example 123.** 5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(trifluoromethyl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide

10 **Example 124.** 5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-[1-(difluoromethyl)-1H-pyrazol-4-yl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

**Example 125.** 5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N-[1-(2-methoxyethyl)-1H-pyrazol-4-yl]-1,2-dimethyl-1H-pyrrole-3-carboxamide

15

**Example 126.** 5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(oxetan-3-yl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 26" in Step C.

20

***High-resolution mass spectrometry (ESI+/HR, ESI-/LR):***

Empirical formula: C<sub>40</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 721.2900

25 [M+H]<sup>+</sup> measured: 721.2902

**Example 127.** 5-(5-Chloro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-[1-(tetrahydrofuran-3-yl)-1*H*-pyrazol-4-yl]-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 22" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=63.81:63.63; %H=5.75:5.74; %N=10.89:10.71; %Cl=4.59:4.52

**High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>41</sub> H<sub>43</sub> Cl N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 735.3056

[M+H]<sup>+</sup> measured: 735.3061

**Example 128.** 5-(5-Chloro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-[1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl]-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

**Example 129.** 5-(5-Chloro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridin-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process described in Step B of Example 49 using Example 106 as starting material, it being understood that the product is not subjected to the step of conversion into salt form.

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

%C=70.53:70.51; %H=6.06:5.81; %N=11.75:11.71

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

Empirical formula: C<sub>42</sub> H<sub>43</sub> Cl N<sub>6</sub> O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 715.3158

[M+H]<sup>+</sup> measured: 715.3159

5     **Example 130.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-fluorophenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

10     **Example 131.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*,1,2-trimethyl-1*H*-pyrrole-3-carboxamide

**Example 132.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

15     **Example 133.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 134.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

20     **Example 135.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

25     **Example 136.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 137.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

5 **Example 138.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 139.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

10 **Example 140.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

15 **Example 141.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 142.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-ethyl-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

20 **Example 143.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-ethyl-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 144.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-ethyl-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 145.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

5 **Example 146.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 147.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

10 **Example 148.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-(2-fluoroethyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

15 **Example 149.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-(2-fluoroethyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 150.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-(2-fluoroethyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

20 **Example 151.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-(2,2-difluoroethyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 152.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-(2,2-difluoroethyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

Example 153. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-(2,2-difluoroethyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

Example 154. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

Example 155. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

Example 156. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

Example 157. 5-(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*-pyrazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

Example 158. 5-(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*-pyrrolo[2,3-*b*]pyridin-5-yl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

Example 159. 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

Example 160. 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-1-[2-(morpholin-4-yl)ethyl]-*N*-phenyl-1*H*-pyrrole-3-carboxamide

**Example 161.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-[2-(dimethylamino)ethyl]-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 162.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-[2-(dimethylamino)ethyl]-*N*-(4-hydroxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

**Example 163.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-[2-(dimethylamino)ethyl]-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 164.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1-[2-(dimethylamino)ethyl]-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 165.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 166.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 167.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 168.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxamide

**Example 169.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxamide

**Example 170.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxamide

**Example 171.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-2-(difluoromethyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 172.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-2-(difluoromethyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 173.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-2-(difluoromethyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 174.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-(methoxymethyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 175.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-(methoxymethyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide



**Example 176.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-(methoxymethyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 177.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 178.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 179.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 180.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-2-(2,2-difluoroethyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 181.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-2-(2,2-difluoroethyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 182.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-2-(2,2-difluoroethyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 183.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 184.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

5 **Example 185.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 186.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-2-(morpholin-4-ylmethyl)-1*H*-pyrrole-3-carboxamide

10 **Example 187.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(morpholin-4-ylmethyl)-1*H*-pyrrole-3-carboxamide

15 **Example 188.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(morpholin-4-ylmethyl)-1*H*-pyrrole-3-carboxamide

**Example 189.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-2-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

20 **Example 190.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

**Example 191.** 5-(5-Chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

**Example 192.** 5-(5-Chloro-2-{[(3*S*)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 193.** 5-(5-Chloro-2-{[(3*S*)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 194.** 5-(5-Chloro-2-{[(3*S*)-3-(difluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 195.** 5-(5-Chloro-2-{[(3*S*)-3-(difluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 196.** 5-(5-Chloro-2-{[(3*S*)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 197.** 5-(5-Chloro-2-{[(3*S*)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 198.** 5-(5-Chloro-2-{[(3*S*)-3-[(9*aS*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 199.** 5-(5-Chloro-2-{[(3*S*)-3-[(9*aS*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-

hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 200.** 5-(5-Chloro-2-{[(3*S*)-3-[(9*aR*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 201.** 5-(5-Chloro-2-{[(3*S*)-3-[(9*aR*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 202.** 5-(2-{[(3*S*)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-chlorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 203.** 5-(2-{[(3*S*)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-chlorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 204.** 5-(2-{[(3*S*)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-chlorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 205.** 5-(5-Chloro-2-{[(3*S*)-3-[(3-cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 206.** 5-(5-Chloro-2-{[(3*S*)-3-[(3-cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 207.** 5-(5-Chloro-2-{[(3*S*)-3-(1-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 8' in Step A, and the compound of Preparation 1" in Step C.

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

Empirical formula: C<sub>39</sub> H<sub>39</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 691.2794

[M+H]<sup>+</sup> measured: 691.2796

**Example 208.** 5-(5-Chloro-2-{[(3*S*)-3-(1-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 209.** 5-(5-Fluoro-4-methoxy-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

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

%C=66.27:66.84; %H=5.69:5.15; %N=10.78:10.71; %Cl=4.55:4.46

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

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

[M+H]<sup>+</sup> calculated: 743.3352

[M+H]<sup>+</sup> measured: 743.3353

**Example 210.** 5-(5-Fluoro-4-methoxy-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

5 **Step A:** 5-(5-Fluoro-4-methoxy-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the compound of Preparation 14 and (3*S*)-3-(4-morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline (see Preparation 3') in Step A, and the compound of Preparation 11" in Step C.

10 **Step B:** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

15 The title compound is obtained in accordance with the process described in Step B of Example 49 starting from compound of the above Step, it being understood that the product is finally subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected product is obtained.

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

20 %C=60.12:59.77; %H=4.92:4.76; %N=10.79:10.39; %Cl=4.55:5.17

**High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):**

Empirical formula: C<sub>40</sub> H<sub>40</sub> N<sub>4</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 657.3071

[M+H]<sup>+</sup> measured: 657.3066

**Example 211.** 5-(4-Fluoro-5-methoxy-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 212.** 5-(4-Fluoro-5-methoxy-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 213.** *N*-(1-Ethyl-1*H*-pyrazol-4-yl)-5-(5-fluoro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

**Example 214.** *N*-(1-Cyclopropyl-1*H*-pyrazol-4-yl)-5-(5-fluoro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 28" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=66.24:66.53; %H=5.84:5.39; %N=10.59:10.92 %Cl=4.89:5.68

**Example 215.** 5-(5-Fluoro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-[1-(trifluoromethyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrole-3-carboxamide

**Example 216.** *N*-[1-(Difluoromethyl)-1*H*-pyrazol-4-yl]-5-(5-fluoro-2-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

**Example 217.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-[1-(2-methoxyethyl)-1*H*-pyrazol-4-yl]-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

**Example 218.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-[1-(oxetan-3-yl)-1*H*-pyrazol-4-yl]-1*H*-pyrrole-3-carboxamide

**Example 219.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-[1-(tetrahydrofuran-3-yl)-1*H*-pyrazol-4-yl]-1*H*-pyrrole-3-carboxamide

**Example 220.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-[1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl]-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

**Example 221.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide

**Example 222.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide

**Example 223.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-fluorophenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 224.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-fluorophenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide



**Example 225.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*,1,2-trimethyl-1*H*-pyrrole-3-carboxamide

**Example 226.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

**Example 227.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 228.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 229.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 230.** *N*-(5-Cyano-1-methyl-1*H*-pyrrol-3-yl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 19" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=66.43:67.09; %H=5.57:5.21; %N=11.62:11.48 %Cl=4.90:4.75

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

Empirical formula: C<sub>40</sub>H<sub>39</sub>FN<sub>6</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 687.3097

[M+H]<sup>+</sup> measured: 687.3073

5     **Example 231.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

10     **Example 232.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 233.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

15     **Example 234.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 235.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

20     **Example 236.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

25     **Example 237.** 1-Ethyl-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 238.** 1-Ethyl-5-(5-fluoro-2-[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 239.** 1-Ethyl-5-(5-fluoro-2-[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 240.** 5-(5-Fluoro-2-[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 241.** 5-(5-Fluoro-2-[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 242.** 5-(5-Fluoro-2-[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 243.** 1-(2-Fluoroethyl)-5-(5-fluoro-2-[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 244.** 1-(2-Fluoroethyl)-5-(5-fluoro-2-[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 245.** 1-(2-Fluoroethyl)-5-(5-fluoro-2-[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 246.** 1-(2,2-Difluoroethyl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 247.** 1-(2,2-Difluoroethyl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 248.** 1-(2,2-Difluoroethyl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 249.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 250.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 251.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 252.** 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

**Example 253.** 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

**Example 254.** 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

**Example 255.** 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-1-[2-(morpholin-4-yl)ethyl]-*N*-phenyl-1*H*-pyrrole-3-carboxamide

**Example 256.** 1-[2-(Dimethylamino)ethyl]-5-(5-fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 257.** 1-[2-(Dimethylamino)ethyl]-5-(5-fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

**Example 258.** 1-[2-(Dimethylamino)ethyl]-5-(5-fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 259.** 1-[2-(Dimethylamino)ethyl]-5-(5-fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 260.** 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 261.** 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 262.** 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

5 **Example 263.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxamide

10 **Example 264.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxamide

**Example 265.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxamide

15 **Example 266.** 2-(Difluoromethyl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 267.** 2-(Difluoromethyl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

20 **Example 268.** 2-(Difluoromethyl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 269.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-(methoxymethyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 270.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-(methoxymethyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 271.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-(methoxymethyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 272.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 273.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 274.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 275.** 2-(2,2-Difluoroethyl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 276.** 2-(2,2-Difluoroethyl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 277.** 2-(2,2-Difluoroethyl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 278.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 279.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 280.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 281.** 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-2-(morpholin-4-ylmethyl)-1*H*-pyrrole-3-carboxamide

**Example 282.** 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(morpholin-4-ylmethyl)-1*H*-pyrrole-3-carboxamide

**Example 283.** 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(morpholin-4-ylmethyl)-1*H*-pyrrole-3-carboxamide

**Example 284.** 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-2-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide



Example 285. 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

5 Example 286. 5-(5-Fluoro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

Example 287. 5-(5-Fluoro-2-{[(3*S*)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

10 Example 288. 5-(5-Fluoro-2-{[(3*S*)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

15 Example 289. 5-(5-Fluoro-2-{[(3*S*)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

Example 290. 5-(2-{[(3*S*)-3-(Difluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-fluorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

20 Example 291. 5-(2-{[(3*S*)-3-(Difluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-fluorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

Example 292. 5-(2-{[(3*S*)-3-(Difluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-fluorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 293.** 5-(5-Fluoro-2-{[(3*S*)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 294.** 5-(5-Fluoro-2-{[(3*S*)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 295.** 5-(5-Fluoro-2-{[(3*S*)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 296.** 5-(5-Fluoro-2-{[(3*S*)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 297.** 5-(5-Fluoro-2-{[(3*S*)-3-[(9*aS*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 298.** 5-(5-Fluoro-2-{[(3*S*)-3-[(9*aS*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 299.** 5-(5-Fluoro-2-{[(3*S*)-3-[(9*aR*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

Example 300. 5-(5-Fluoro-2-{[(3*S*)-3-[(9*aR*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

5 Example 301. 5-(5-Fluoro-2-{[(3*S*)-3-[(9*aR*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

10 Example 302. 5-(2-{[(3*S*)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-fluorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

Example 303. 5-(2-{[(3*S*)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-fluorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

15 Example 304. 5-(2-{[(3*S*)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-fluorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

20 Example 305. 5-(2-{[(3*S*)-3-[(3-Cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-fluorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

Example 306. 5-(2-{[(3*S*)-3-[(3-Cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-fluorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 307.** 5-(2-{{(3*S*)-3-[(3-Cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-5-fluorophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 308.** 5-(5-Fluoro-2-{{(3*S*)-3-(1-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 309.** 5-(5-Fluoro-2-{{(3*S*)-3-(1-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 310.** *N*-(1-Ethyl-1*H*-pyrazol-4-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 311.** *N*-(1-Cyclopropyl-1*H*-pyrazol-4-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 312.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-[1-(trifluoromethyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrole-3-carboxamide

**Example 313.** *N*-[1-(Difluoromethyl)-1*H*-pyrazol-4-yl]-*N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 314.** *N*-(4-Hydroxyphenyl)-*N*-[1-(2-methoxyethyl)-1*H*-pyrazol-4-yl]-1,2-dimethyl-5-(6-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 315.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}-1,3-benzodioxol-5-yl)-*N*-[1-(oxetan-3-yl)-1*H*-pyrazol-4-yl]-1*H*-pyrrole-3-carboxamide

**Example 316.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}-1,3-benzodioxol-5-yl)-*N*-[1-(tetrahydrofuran-3-yl)-1*H*-pyrazol-4-yl]-1*H*-pyrrole-3-carboxamide

**Example 317.** *N*-[1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl]-*N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 318.** 1,2-Dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide

**Example 319.** 1,2-Dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide

**Example 320.** *N*-(4-Fluorophenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 321.** *N*-(4-Fluorophenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 322.** *N*-(4-Hydroxyphenyl)-*N*,1,2-trimethyl-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 323.** *N*-(2-Hydroxypyrimidin-5-yl)-1,2-dimethyl-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide

**Example 324.** *N*-(2-Hydroxypyrimidin-5-yl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 325.** *N*-(2-Hydroxypyrimidin-5-yl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 326.** *N*-(2-Hydroxypyrimidin-5-yl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 327.** *N*-(5-Cyano-1-methyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 328.** *N*-(4-Hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 329.** *N*-(4-Hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 330.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-  
{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-  
benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 331.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-  
5-yl)-5-(6-{{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-  
yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 332.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo-  
[2,3-*b*]pyridin-5-yl)-5-(6-{{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-  
2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 333.** 1-Ethyl-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]-  
pyridin-5-yl)-5-(6-{{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-  
carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 334.** 1-Ethyl-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-  
pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroiso-  
quinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 335.** *N*-(4-Hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-*N*-(1-methyl-1*H*-  
pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroiso-  
quinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 336.** *N*-(4-Hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-*N*-(1-methyl-2,3-  
dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-  
dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-  
carboxamide

**Example 337.** 1-(2-Fluoroethyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 338.** 1-(2-Fluoroethyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 339.** 1-(2,2-Difluoroethyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 340.** 1-(2,2-Difluoroethyl)-*N*-(4-hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 341.** *N*-(4-Hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 342.** *N*-(4-Hydroxyphenyl)-2-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 343.** *N*-(4-Hydroxyphenyl)-2-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide



**Example 344.** *N*-(4-Hydroxyphenyl)-2-methyl-5-(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)-1-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

**Example 345.** *N*-(4-Hydroxyphenyl)-2-methyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

**Example 346.** 1-[2-(Dimethylamino)ethyl]-*N*-(4-hydroxyphenyl)-2-methyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 347.** 1-[2-(Dimethylamino)ethyl]-*N*-(4-hydroxyphenyl)-2-methyl-5-(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)-1*H*-pyrrole-3-carboxamide

**Example 348.** 1-[2-(Dimethylamino)ethyl]-*N*-(4-hydroxyphenyl)-2-methyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 349.** *N*-(4-Hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-5-(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)-1*H*-pyrrole-3-carboxamide

**Example 350.** *N*-(4-Hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 351.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-yl)methyl]-3,4-dihydroisoquinolin-

2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxamide

**Example 352.** 2-(Difluoromethyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 353.** *N*-(4-Hydroxyphenyl)-2-(methoxymethyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 354.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-2-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 355.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-2-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 356.** *N*-(4-Hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-2-(2,2,2-trifluoroethyl)-1*H*-pyrrole-3-carboxamide

**Example 357.** 2-(2,2-Difluoroethyl)-*N*-(4-hydroxyphenyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 358.** *N*-(4-Hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

- 5 The title compound is obtained in accordance with the process described in Step B of Example 49 using Example 88 as starting material, it being understood that the product is finally dissolved in acetonitrile and converted into salt form in 0.1M aqueous HCl solution. After a lyophilisation step, the expected product is obtained in the form of a solid.

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

- 10 %C=65.80:64.71; %H=6.01:5.74; %N=10.23:10.03; %Cl=4.32:6.47

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

Empirical formula: C<sub>45</sub> H<sub>48</sub> N<sub>6</sub> O<sub>7</sub>

[M+H]<sup>+</sup> calculated: 785.3657

[M+H]<sup>+</sup> measured: 785.3658

- 15 **Example 359.** *N*-(4-Hydroxyphenyl)-1-methyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(morpholin-4-ylmethyl)-1*H*-pyrrole-3-carboxamide

- 20 **Example 360.** *N*-(4-Hydroxyphenyl)-1-methyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-[2-(morpholin-4-yl)ethyl]-1*H*-pyrrole-3-carboxamide

**Example 361.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-{[(3*S*)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

- 25 **Example 362.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 363.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 364.** 5-(6-{[(3*S*)-3-(Difluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 365.** 5-(6-{[(3*S*)-3-(Difluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 366.** 5-(6-{[(3*S*)-3-(Difluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 367.** 5-(6-{[(3*S*)-3-(Fluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 368.** 5-(6-{[(3*S*)-3-(Fluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 369.** 5-(6-{[(3*S*)-3-(Fluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 370.** 5-(6-{[(3*S*)-3-[(9*aS*)-Hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-

hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 371.** 5-(6-{[(3*S*)-3-[(9*aS*)-Hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 372.** 5-(6-{[(3*S*)-3-[(9*aS*)-Hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 373.** 5-(6-{[(3*S*)-3-[(9*aR*)-Hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 374.** 5-(6-{[(3*S*)-3-[(9*aR*)-Hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 375.** 5-(6-{[(3*S*)-3-[(9*aR*)-Hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 376.** 5-(6-{[(3*S*)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 377.** 5-(6-{[(3*S*)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 378.** 5-(6-{[(3*S*)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 379.** 5-(6-{[(3*S*)-3-[(3-Cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide

**Example 380.** 5-(6-{[(3*S*)-3-[(3-Cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 381.** 5-(6-{[(3*S*)-3-[(3-Cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 382.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-{[(3*S*)-3-(1-oxa-6-azaspiro[3.3]hept-6-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 383.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-(6-{[(3*S*)-3-(1-oxa-6-azaspiro[3.3]hept-6-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide

**Example 384.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-yl)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=67.28:67.73; %H=5.65:5.30; %N=10.06:9.41 %Cl=5.09:5.79

**Example 385.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

Empirical formula: C<sub>41</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 713.3253

[M+H]<sup>+</sup> measured: 713.3272

**Example 386.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

**Step A:** *N*-[4-[*tert*-Butyl(dimethyl)silyloxyphenyl]-5-[5-chloro-2-[(3*S*)-3-(morpholino-methyl)-3,4-dihydro-1*H*-isoquinoline-2-carbonyl]phenyl]-*N*-(5-cyano-1,2-dimethyl-pyrrol-3-yl)-1,2-dimethyl-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C.

IR:  $\nu$  -CN-: 2210 cm<sup>-1</sup>;  $\nu$  -C=O-: 1631 cm<sup>-1</sup>

**Step B:** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

The compound of Step A is deprotected in accordance with the protocol described in Step D of Example 1. The product thereby obtained is finally subjected to a step of conversion into salt form in the presence of HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected product is obtained.

<sup>1</sup>H NMR (500 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm: 11.2 (bs, 1H), 9.39 (bs, 1H), 7.83 (d, 1 H), 7.54 (d, 1 H), 7.33 (s, 1 H), 7.14 (m, 2 H), 7 (m, 2 H), 6.8 (d, 2 H), 6.62 (d, 2 H), 6.57 (bs, 1 H), 5.26 (s, 1 H), 5.26 (m, 1 H), 4.64/4.03 (AB, 2 H), 4.01/3.92 (2m, 4 H), 3.75/3.43/3.15/3.02 (4m, 4 H), 3.59 (s, 3 H), 3.3/3.15 (2m, 2 H), 2.97 (s, 3 H), 2.69/2.52 (dd+d, 2 H), 2.06 (s, 3 H), 1.91 (s, 3 H)

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

%C=65.34:65.50; %H=5.62:5.15; %N=11.15:10.84 %Cl=4.70:4.44

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

Empirical formula: C<sub>41</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 717.2952

[M+H]<sup>+</sup> measured: 717.2951

**Example 387.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-5-yl)-5-(6-([(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=66.62:66.36; %H=5.59:5.62; %N=10.84:10.72 %Cl=4.57:4.55

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

Empirical formula: C<sub>43</sub> H<sub>42</sub> N<sub>6</sub> O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 739.3239

[M+H]<sup>+</sup> measured: 739.3241

**Example 388.** 5-(5-Chloro-2-([(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl)phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide dihydrochloride

The title compound is obtained in accordance with the process described in Step B of Example 49 using Example 71 as starting material, it being understood that the product is



finally subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

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

5    %C=62.73:62.96; %H=5.64:4.95; %N=10.45:10.32; %Cl=13.23:12.91

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

Empirical formula: C<sub>42</sub> H<sub>43</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 731.3107

[M+H]<sup>+</sup> measured: 731.3111

10    **Example 389.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

15    The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

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

%C=65.88:66.28; %H=5.53:5.15; %N=10.98:10.95; %Cl=4.63:4.47

***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):***

20    Empirical formula: C<sub>42</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 729.2951

[M+H]<sup>+</sup> measured: 729.2954

**Example 390.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide

5 The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations, it being understood that Step D is not carried out. The expected product is obtained in free base form.

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

%C=70.72:69.77; %H=5.79:5.96; %N=11.78:11.43

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

10 Empirical formula: C<sub>42</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 713.3001

[M+H]<sup>+</sup> measured: 713.2998

**Example 391.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

15

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

%C=65.88:65.69; %H=5.33:4.87; %N=10.98:10.86; %Cl=4.63:4.51

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

Empirical formula: C<sub>42</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>4</sub>

20 [M+H]<sup>+</sup> calculated: 729.2951

[M+H]<sup>+</sup> measured: 729.2953

**Example 392.** 5-(5-Chloro-2-{[(3*R*)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=68.19:68.33; %H=6.00:5.49; %N=10.78:10.71; %Cl=4.55:4.46; %Cl = 9.58:9.78

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

Empirical formula: C<sub>42</sub> H<sub>43</sub> Cl N<sub>4</sub> O<sub>4</sub>

5 [M+H]<sup>+</sup> calculated: 703.3046

[M+H]<sup>+</sup> measured: 703.3042

**Example 393. 5-(5-Chloro-2-{[(3*R*)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride**

10 ***High-resolution mass spectrometry (ESI+/-/FIA):***

Empirical formula: C<sub>44</sub> H<sub>45</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 757.3264

[M+H]<sup>+</sup> measured: 757.3263

**Example 394. 5-(5-Chloro-2-{[(3*R*)-3-[3-(morpholin-4-yl)propyl]-3,4-**

15 ***dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide***

The title compound is obtained in accordance with the process described in Step B of Example 49 using Example 393 as starting material, it being understood that the product is not subjected to the step of conversion into salt form.

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

%C=69.60:69.56; %H=6.21:6.24; %N=11.07:11.08

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

Empirical formula: C<sub>44</sub> H<sub>47</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 759.3420

25 [M+H]<sup>+</sup> measured: 759.3422

**Example 395. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(3-cyano-4-methoxyphenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):***

Empirical formula: C<sub>42</sub> H<sub>40</sub> Cl N<sub>5</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 730.2791

[M+H]<sup>+</sup> measured: 730.2790

**Example 396. *N*-(3-Fluoro-4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 11 and (3*S*)-3-(4-morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline (see Preparation 3') in Step A, and the compound of Preparation 20" in Step C. The product obtained is finally subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

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

%C=65.79:65.43; %H=5.39:5.19; %N=11.31:11.21; %Cl=4.77:4.34

***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):***

Empirical formula: C<sub>39</sub> H<sub>39</sub> F N<sub>6</sub> O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 707.2988

[M+H]<sup>+</sup> measured: 707.2988

**Example 397.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(2-methoxypyrimidin-5-yl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

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

5 Empirical formula: C<sub>39</sub> H<sub>39</sub> Cl N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 707.2743

[M+H]<sup>+</sup> measured: 707.2746

**Example 398.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(3-cyanophenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=66.85:66.75; %H=5.34:5.42; %N=9.51:9.73; %Cl=9.62:9.67; %Cl<sup>-</sup>=4.81:4.71

*High-resolution mass spectrometry (ESI+/-/FLA/HR, ESI-/FLA):*

Empirical formula: C<sub>41</sub> H<sub>38</sub> Cl N<sub>5</sub> O<sub>4</sub>

15 [M+H]<sup>+</sup> calculated: 700.2685

[M+H]<sup>+</sup> measured: 700.2686

**Example 399.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(3-fluoro-4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide hydrochloride

20 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and (3*S*)-3-(4-morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline (see Preparation 3') in Step A, and the compound of Preparation 20" in Step C. The product obtained is finally subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the  
25 expected compound is obtained.

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

%C=62.21:61.32; %H=5.36:5.18; %N=11.46:11.14; %Cl= 9.66:10.16; %Cl<sup>-</sup>=4.83:5.23

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

Empirical formula: C<sub>38</sub> H<sub>38</sub> Cl F N<sub>6</sub> O<sub>4</sub>

5 [M+H]<sup>+</sup> calculated: 697.2700

[M+H]<sup>+</sup> measured: 697.2704

**Example 400. Methyl 2-[[5-(5-chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydro-isoquinolin-2(1H)-yl]carbonyl]phenyl)-1,2-dimethyl-1H-pyrrol-3-yl]carbonyl](4-hydroxyphenyl)amino]pyridine-4-carboxylate hydrochloride**

10 The title compound is a secondary product which forms in the course of synthesis of Example 110 (in the final Step before the step of conversion into salt form) owing to hydrolysis of the nitrile function into a methyl ester function. The compound is separated from that of Example 110 by chromatography over silica gel in a mixture of methanol and dichloromethane.

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

%C=63.90:64.43; %H=5.36:5.01; %N=9.09:9.34; %Cl<sup>-</sup>=4.60:4.46

***High-resolution mass spectrometry (ESI+/HR and ESI-/LR):***

Empirical formula: C<sub>41</sub> H<sub>40</sub> Cl N<sub>5</sub> O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 734.2740

20 [M+H]<sup>+</sup> measured: 734.2743

**Example 401. 5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(3-cyano-4-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride**

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

25 %C=65.25:64.23; %H=5.07:4.71; %N=9.28:9.36; %Cl= 9.40:9.59; %Cl<sup>-</sup>=4.70:4.50

***High-resolution mass spectrometry (ESI<sup>+</sup>/FIA/HR, ESI<sup>-</sup>/FIA):***

Empirical formula: C<sub>41</sub> H<sub>37</sub> Cl F N<sub>5</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 718.2591

[M+H]<sup>+</sup> measured: 718.2593

5 **Example 402.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-{1-[(3*S* or *R*)-tetrahydrofuran-3-yl]-1*H*-pyrazol-4-yl}-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=65.20:65.92; %H=5.87:5.78; %N=11.13:10.36 %Cl<sup>-</sup>=4.69:4.79)

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

Empirical formula: C<sub>41</sub>H<sub>43</sub>FN<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 719.3359

[M+H]<sup>+</sup> measured: 719.3362

and

15 **Example 403.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-{1-[(3*R* or *S*)-tetrahydrofuran-3-yl]-1*H*-pyrazol-4-yl}-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=65.20:66.04; %H=5.87:5.87; %N=11.13:10.62; %Cl<sup>-</sup>=4.69:4.76

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

Empirical formula: C<sub>41</sub>H<sub>43</sub>FN<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 719.3359

[M+H]<sup>+</sup> measured: 719.3350

The compounds of Examples 402 and 403 are obtained in accordance with the process of  
25 Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A,

and the compound of Preparation 22" in Step C. The diastereoisomers obtained are separated by chiral chromatography and then converted into salt form and lyophilised as described in the general process to yield the title compounds.

**Example 404.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(2-cyanopyrimidin-4-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

**Example 405.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-(pyridazin-4-yl)-1*H*-pyrrole-3-carboxamide dihydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C, it being understood that Step D is not carried out. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

**High-resolution mass spectrometry (ESI<sup>+</sup>-/FIA/HR, ESI-/FIA):**

Empirical formula: C<sub>40</sub> H<sub>39</sub> Cl N<sub>8</sub> O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 715.2906

[M+H]<sup>+</sup> measured: 715.2909

**Example 406.** *N*-(5-Cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 25 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=68.46:68.27; %H=6.03:5.12; %N=11.68:11.75; %Cl=4.93:4.73



***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI-/FLA):***

Empirical formula: C<sub>41</sub> H<sub>42</sub> N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 683.3340

[M+H]<sup>+</sup> measured: 683.3334

5 **Example 407. *N*-(3-Fluoro-4-hydroxyphenyl)-5-(5-methoxy-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 12 and the compound of Preparation 3' in Step A, and the compound of  
10 Preparation 20" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=64.23:63.94; %H=5.80:5.00; %N=11.52:11.56; %Cl=4.86:4.99

***High-resolution mass spectrometry (ESI+/-/FIA/HR and MS/MS, ESI-/FLA):***

15 Empirical formula: C<sub>39</sub> H<sub>41</sub> F N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 693.3195

[M+H]<sup>+</sup> measured: 693.3191

20 **Example 408. *N*-(5-Cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-5-(5-methoxy-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 12 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=67.32:67.30; %H=6.05:5.28; %N=11.22:11.15; %Cl=4.73:4.59

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

Empirical formula: C<sub>42</sub> H<sub>44</sub> N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 713.3446

[M+H]<sup>+</sup> measured: 713.3443

5 **Example 409. N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]-pyridin-5-yl)-5-(2-([(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl})phenyl)-1H-pyrrole-3-carboxamide hydrochloride**

10 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 25 and the compound of Preparation 3' in Step A, and the compound of Preparation 11" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=68.98:68.95; %H=5.93:4.76; %N=11.49:11.43

*High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):*

15 Empirical formula: C<sub>42</sub> H<sub>42</sub> N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 695.3340

[M+H]<sup>+</sup> measured: 695.3341

20 **Example 410. N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(2-([(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl})phenyl)-1H-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process described in Step B of Example 49 using Example 409 as starting material. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

***High-resolution mass spectrometry (ESI/FIA/HR and ESI-/FIA):***

Empirical formula: C<sub>42</sub> H<sub>44</sub> N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 697.3497

[M+H]<sup>+</sup> measured: 697.3497

5     **Example 411. 5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide hydrochloride**

10     The title compound is obtained in accordance with the process of Example 96 using the acid of Preparation 30, the compound of Preparation 1', and the compound of Preparation 1". The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):***

Empirical formula: C<sub>39</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 693.2951

15     [M+H]<sup>+</sup> measured: 693.2947

**Example 412. 5-(5-Chloro-2-{[(3R)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride**

20     The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 6' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=66.06:65.61; %H=5.93:5.22; %N=10.75:10.69; %Cl=4.53:4.68

***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI-/FIA):***

Empirical formula: C<sub>43</sub> H<sub>45</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 745.3264

[M+H]<sup>+</sup> measured: 745.3260

5 **Example 413. *N*-(5-Cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(7-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}-2,3-dihydro-1,4-benzodioxin-6-yl)-1*H*-pyrrole-3-carboxamide hydrochloride**

10 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 13 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=66.44:66.40; %H=5.83:4.84; %N=10.81:10.79; %Cl=4.56:4.22

15 ***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI-/FIA):***

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

[M+H]<sup>+</sup> calculated: 741.3395

[M+H]<sup>+</sup> measured: 741.3397

20 **Example 414. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(5-methyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)-1*H*-pyrrole-3-carboxamide hydrochloride**

25 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=64.23:64.38; %H=5.39:5.25; %N=12.79:12.62; %Cl=4.62:4.39

***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI-/FIA):***

Empirical formula: C<sub>41</sub> H<sub>40</sub> Cl N<sub>7</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 730.2903

[M+H]<sup>+</sup> measured: 730.2904

5 **Example 415. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1-methyl-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 3 and the compound of Preparation 3' in Step A, and the compound of  
10 Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=64.95:65.14; %H=5.45:5.34; %N=11.36:11.36; %Cl=4.79:4.67

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

15 Empirical formula: C<sub>40</sub> H<sub>39</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 703.2794

[M+H]<sup>+</sup> measured: 703.2795

20 **Example 416. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-[1-(trideuterio-methyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 25" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=63.51:63.41; %H=5.63:5.42; %N=11.69:11.61; %Cl=4.93:4.85

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

Empirical formula: C<sub>38</sub> H<sub>36</sub> Cl D<sub>3</sub> N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 682.2982

[M+H]<sup>+</sup> measured: 682.2986

5 **Example 417. *N*-(5-Cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-5-(4-methoxy-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

10 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 31 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=67.32:67.56; %H=6.05:5.84; %N=11.22:11.21; %Cl<sup>-</sup>=4.73:4.71

***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI-/FIA):***

15 Empirical formula: C<sub>42</sub> H<sub>44</sub> N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 713.3446

[M+H]<sup>+</sup> measured: 713.3446

20 **Example 418. *N*-(4-Hydroxyphenyl)-5-(4-methoxy-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 31 and the compound of Preparation 3' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=65.86:65.51; %H=6.09:6.09; %N=11.82:11.73; %Cl<sup>-</sup>=4.98:5.14

***High-resolution mass spectrometry (ESI/FIA/HR, ESI/FIA):***

Empirical formula: C<sub>39</sub> H<sub>42</sub> N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 675.3289

[M+H]<sup>+</sup> measured: 675.3286

5 **Example 419.** *N*-(3-Cyanophenyl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of  
10 Preparation 41" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

Empirical formula: C<sub>41</sub>H<sub>38</sub>FN<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 684.2988

15 [M+H]<sup>+</sup> measured: 684.2975

**Example 420.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-[1-(trideuterio-methyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid  
20 of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 25" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

Empirical formula: C<sub>38</sub>D<sub>3</sub>H<sub>36</sub>FN<sub>6</sub>O<sub>4</sub>

25 [M+H]<sup>+</sup> calculated: 666.3285

[M+H]<sup>+</sup> measured: 666.3265

**Example 421.** *N*-(5-Cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

**High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):**

Empirical formula: C<sub>41</sub> H<sub>41</sub> F N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 701.3246

[M+H]<sup>+</sup> measured: 701.3282

**Example 422.** *N*-(4-Hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 25 and the compound of Preparation 3' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=67.00:67.47; %H=6.07:5.54; %N=12.34:12.46; %Cl=5.20:4.58

**High-resolution mass spectrometry (ESI<sup>+</sup>/FIA/HR, ESI-/FIA):**

Empirical formula: C<sub>38</sub> H<sub>40</sub> N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 645.3184

[M+H]<sup>+</sup> measured: 645.3182



**Example 423.** 5-(5-Fluoro-2-[[{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-[1-(oxetan-3-yl)-1*H*-pyrazol-4-yl]-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 26" in Step C.

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

%C=68.17:67.82; %H=5.86:5.97; %N=11.92:11.48

**High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):**

Empirical formula: C<sub>40</sub>H<sub>41</sub>FN<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 705.3202

[M+H]<sup>+</sup> measured: 705.3207

**Example 424.** *N*-(4-Hydroxyphenyl)-*N*-(2-methoxypyrimidin-5-yl)-1,2-dimethyl-5-(2-[[{(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 25 and the compound of Preparation 3' in Step A, and the compound of Preparation 12" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=66.05:65.63; %H=5.83:5.45; %N=11.85:11.93; %Cl<sup>-</sup>=5.00:4.91

**High-resolution mass spectrometry (ESI<sup>+</sup>-/FIA/HR, ESI-/FIA):**

Empirical formula: C<sub>39</sub> H<sub>40</sub> N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 673.3133

[M+H]<sup>+</sup> measured: 673.3129

**Example 425.** *N*-(3-Cyano-5-methoxyphenyl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=67.25:66.55; %H=5.51:5.28; %N=9.33:8.55 %Cl<sup>-</sup>=4.73:4.67

**Example 426.** 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(2-methoxypyrimidin-5-yl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 12" in Step C.

*High-resolution mass spectrometry (ESI/FLA/HR and MS/MS):*

Empirical formula: C<sub>39</sub>H<sub>39</sub>FN<sub>6</sub>O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 691.3038

[M+H]<sup>+</sup> measured: 691.3060

**Example 427.** *N*-(3-Cyano-4-methoxyphenyl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=67.24:66.41; %H=5.51:5.35; %N=9.33:8.97 %Cl<sup>-</sup>=4.73:4.81

**Example 428. *N*-(5-Cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-5-(4-fluoro-2- $\{[(3S)$ -3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 26 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=66.79:66.97; %H=5.74:5.36; %N=11.40:11.45; %Cl<sup>-</sup>=4.81:4.53

***High-resolution mass spectrometry (ESI<sup>+</sup>-/FIA/HR, ESI-/FIA):***

Empirical formula: C<sub>41</sub> H<sub>41</sub> F N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 701.3246

[M+H]<sup>+</sup> measured: 701.3245

**Example 429. *N*-(5-Cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-5-(4-fluoro-5-methoxy-2- $\{[(3S)$ -3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 27 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=65.75:65.43; %H=5.78:5.57; %N=10.95:10.81; %Cl<sup>-</sup>=4.62:4.54

***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI-/FIA):***

Empirical formula: C<sub>42</sub> H<sub>43</sub> F N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 731.3352

[M+H]<sup>+</sup> measured: 731.3351

5     **Example 430.** 5-(5-Chloro-2-{{3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl}-carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]-pyridin-5-yl)-1H-pyrrole-3-carboxamide

10     The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and racemic 3-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline in Step A, and the compound of Preparation 11" in Step C.

***High-resolution mass spectrometry (ESI+/FIA/HR and MS/MS, ESI-/FIA):***

Empirical formula: C<sub>38</sub> H<sub>31</sub> Cl F<sub>3</sub> N<sub>5</sub> O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 698.2140

[M+H]<sup>+</sup> measured: 698.2144

15     **Example 431.** 5-(5-Chloro-2-{{(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl}carbonyl}phenyl)-N-(1,3-dimethyl-1H-pyrazol-4-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

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

%C=64.19:64.37; %H=5.80:5.18; %N=11.52:11.55; %Cl=4.86:4.68

20     ***High-resolution mass spectrometry (ESI+/FIA/HR, ESI-/FIA):***

Empirical formula: C<sub>39</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 693.2951

[M+H]<sup>+</sup> measured: 693.2952

and

**Example 432.** 5-(5-Chloro-2-{{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(1,5-dimethyl-1*H*-pyrazol-4-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

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

5    %C=64.19:64.43; %H=5.80:5.22; %N=11.52:11.60; %Cl=4.86:4.66

*High-resolution mass spectrometry (ESI+/-/FLA/HR, ESI-/FLA):*

Empirical formula: C<sub>39</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 693.2951

[M+H]<sup>+</sup> measured: 693.2953

10    The compounds of Examples 431 and 432 are obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the mixture of Preparation 27'' in Step C. At the end of Step D, the isomers are separated by preparative HPLC using acetonitrile and water-TFA as eluants. After evaporating off the solvent and neutralising with sodium bicarbonate, the products are  
15    subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the title products are obtained.

**Example 433.** *N*-(5-Cyano-1-methyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(2-{{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-1*H*-pyrrole-3-carboxamide hydrochloride

20    The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 25 and the compound of Preparation 3' in Step A, and the compound of Preparation 19'' in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=68.12:68.29; %H=5.86:5.40; %N=11.92:12.05; %Cl=5.03:4.92

**High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):**

Empirical formula: C<sub>40</sub> H<sub>40</sub> N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 669.3184

[M+H]<sup>+</sup> measured: 669.3184

5     **Example 434. 5-(5-Fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide hydrochloride**

10     The title compound is obtained in accordance with the process described in Step B of Example 49 using Example 385 as starting material. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=67.15:68.03; %H=5.90:5.50; %N=11.19:10.59 %Cl<sup>-</sup>=4.72:5.55

15     **Example 435. *N*-(4-Cyanopyridin-2-yl)-5-(5-fluoro-4-methoxy-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

20     The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 14 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

**High-resolution mass spectrometry (ESI<sup>+</sup>/FIA/HR, ESI<sup>-</sup>/FIA):**

Empirical formula: C<sub>41</sub> H<sub>39</sub> F N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 715.3039

[M+H]<sup>+</sup> measured: 715.3040

**Example 436. 5-(5-Chloro-2-[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyanothiophen-2-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=63.07:63.09; %H=5.02:4.78; %N=9.43:9.35; %S=4.32:4.09; %Cl=4.77:4.59

***High-resolution mass spectrometry (ESI/FLA/HR and MS/MS, ESI+/-/FLA):***

Empirical formula: C<sub>39</sub> H<sub>36</sub> Cl N<sub>5</sub> O<sub>4</sub> S

[M+H]<sup>+</sup> calculated: 706.2249;

[M+H]<sup>+</sup> measured: 706.2250

**Example 437. *N*-(3-Cyano-4-fluorophenyl)-5-(5-fluoro-2-[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

***High-resolution mass spectrometry (ES+):***

Empirical formula: C<sub>41</sub>H<sub>37</sub>F<sub>2</sub>N<sub>5</sub>O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 702.2894

[M+H]<sup>+</sup> measured: 702.2886

**Example 438. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(pyrazin-2-yl)-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=63.95:63.96; %H=5.37:5.17; %N=11.78:11.61; %Cl=4.97:4.57

***High-resolution mass spectrometry (ESI+/HR, ESI-/LR):***

Empirical formula: C<sub>38</sub> H<sub>37</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 677.2638

[M+H]<sup>+</sup> measured: 677.2639

**Example 439. 5-(5-Fluoro-4-methoxy-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-*N*-(2-methoxypyrimidin-5-yl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 14 and the compound of Preparation 3' in Step A, and the compound of Preparation 12" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI-/FIA):***

Empirical formula: C<sub>40</sub> H<sub>41</sub> F N<sub>6</sub> O<sub>6</sub>

[M+H]<sup>+</sup> calculated: 721.3144

[M+H]<sup>+</sup> measured: 721.3144



**Example 440.** *N*-(5-Cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-5-(5-fluoro-4-methoxy-2-  
{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-  
*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid  
of Preparation 14 and the compound of Preparation 3' in Step A, and the compound of  
Preparation 18" in Step C. The compound obtained is converted into salt form and  
lyophilised as described in the general process to obtain the title compound.

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

%C=65.75:65.98; %H=5.78:5.50; %N=10.95:10.87; %Cl=4.62:4.42

**High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>42</sub> H<sub>43</sub> F N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 731.3352

[M+H]<sup>+</sup> measured: 731.3353

**Example 441.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-  
2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-1,2-dimethyl-*N*-  
phenyl-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid  
of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of  
Preparation 29" in Step C, it being understood that Step D is not carried out. The  
compound obtained is converted into salt form and lyophilised as described in the general  
process to obtain the title compound.

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

%C=66.75:66.44; %H=5.74:5.59; %N=11.39:11.45; %Cl=4.81:4.43

**High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>41</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 701.3001

[M+H]<sup>+</sup> measured: 701.2998

**Example 442. 5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(5-cyanothiophen-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 42" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=63.07:63.14; %H=5.02:4.87; %N=9.43:9.41; %S=4.32:4.24; %Cl<sup>-</sup>=4.77:4.57

***High-resolution mass spectrometry (ESI+/HR, ESI-/LR):***

Empirical formula: C<sub>39</sub> H<sub>36</sub> Cl N<sub>5</sub> O<sub>4</sub> S

[M+H]<sup>+</sup> calculated: 706.2249

[M+H]<sup>+</sup> measured: 706.2252

**Example 443. 5-(5-Fluoro-4-hydroxy-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide**

***Step A: 5-(5-Fluoro-4-methoxy-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide***

The title compound is obtained in accordance with the process of Example 1 (Steps A to C) using the acid of Preparation 28 and the compound from Preparation 3' in Step A, and the compound of Preparation 30" in Step C.

**Step B: 5-(5-Fluoro-4-hydroxy-2-[[*(3S)*-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]phenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide**

To a solution of the compound of Step A (1 g; 1.37 mmol) in anhydrous dichloromethane (10 mL) there is added, dropwise at 0°C, a 1M solution of boron tribromide in dichloromethane (1.8 mL; 1.8 mmol). After stirring for 15 hours at ambient temperature, the reaction mixture is poured dropwise into a solution of ethanol (15 mL) at -10°C. After stirring for one hour, saturated aqueous sodium bicarbonate solution is added, and the reaction mixture is extracted with dichloromethane. After drying over MgSO<sub>4</sub>, the residue is purified on a silica gel column using a mixture of dichloromethane and methanol as eluant to yield the expected product.

***High-resolution mass spectrometry (ESI+/HR, ESI-/LR):***

Empirical formula: C<sub>42</sub> H<sub>41</sub> F N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 713.3246

[M+H]<sup>+</sup> measured: 713.3244

**Example 444. 5-(5-Chloro-2-[[*(3S)*-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]phenyl)-*N*-(4-hydroxyphenyl)-*N*-(5-methoxypyrazin-2-yl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=62.99:62.72; %H=5.42:5.24; %N=11.30:11.19; %Cl=4.77:4.67

***High-resolution mass spectrometry (ESI+/HR, ESI-/LR):***

Empirical formula: C<sub>39</sub> H<sub>39</sub> Cl N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 707.2743

[M+H]<sup>+</sup> measured: 707.2747

**Example 445.** 5-(5-Chloro-2-[[*(3S)*-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-[1-(trideuteriomethyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-1*H*-pyrrole-3-carboxamide hydrochloride

5     **Step A:** 5-(5-Chloro-2-[[*(3S)*-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-[1-(trideuteriomethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-1*H*-pyrrole-3-carboxamide

The intermediate is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of  
10     Preparation 31" in Step C.

**Step B:** 5-(5-Chloro-2-[[*(3S)*-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-[1-(trideuteriomethyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-1*H*-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the protocol described in Step B of Example 49, it  
15     being understood that the product is then subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the title product is obtained.

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

%C=65.45:65.33; %H=5.78:5.59; %N=10.90:10.82; %Cl=4.60:4.28

20     **High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>42</sub> H<sub>40</sub> Cl D<sub>3</sub> N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 734.3295

[M+H]<sup>+</sup> measured: 734.3300

**Example 446. 5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-fluoropyrazin-2-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=62.28:62.16; %H=5.10:4.97; %N=11.04:11.35; %Cl<sup>-</sup>=4.85:4.48

**High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>38</sub> H<sub>36</sub> Cl F N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 695.2543

[M+H]<sup>+</sup> measured: 695.2545

**Example 447. 5-(4-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 26 and the compound of Preparation 3' in Step A, and the compound of Preparation 1'' in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=65.28:65.27; %H=5.77:5.51; %N=12.02:1.90; %Cl<sup>-</sup>=5.07:4.74

**High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>38</sub> H<sub>39</sub> F N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 663.3090

[M+H]<sup>+</sup> measured: 663.3084

**Example 448.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-[5-cyano-1-(trideuteriomethyl)-1*H*-pyrrol-3-yl]-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 32" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=64.69:64.23; %H=5.45:5.47; %N=11.32:11.16; %Cl=4.77:4.56

**High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>40</sub> H<sub>36</sub> Cl D<sub>3</sub> N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 706.2982

[M+H]<sup>+</sup> measured: 706.2985

**Example 449.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-[5-cyano-2-methyl-1-(trideuteriomethyl)-1*H*-pyrrol-3-yl]-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 33" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=65.07:64.55; %H=5.62:5.51; %N=11.11:10.98; %Cl=4.68:4.58

**High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>41</sub> H<sub>38</sub> Cl D<sub>3</sub> N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 720.3139

[M+H]<sup>+</sup> measured: 720.3143

**Example 450. 5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(3-cyano-1-methyl-1H-pyrazol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 34" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=63.24:62.62; %H=5.31:5.09; %N=13.24:13.04; %Cl=4.79:4.37

**High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>39</sub> H<sub>38</sub> Cl N<sub>7</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 704.2747

[M+H]<sup>+</sup> measured: 704.2747

**Example 451. 5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 17" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=65.64:66.28; %H=5.51:5.45; %N=13.07:12.17 %Cl=4.73:5.51

**Example 452. N-(1,3-Dimethyl-1H-pyrazol-4-yl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride**

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

%C=65.68:64.77; %H=5.94:5.55; %N=11.78:10.69 %Cl=4.97:6.48

and

**Example 453.** *N*-(1,5-Dimethyl-1*H*-pyrazol-4-yl)-5-(5-fluoro-2-[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride

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

%C=65.68:65.43; %H=5.94:5.62; %N=11.78:10.95 %Cl=4.97:5.60

The compounds of Examples 452 and 453 are obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the mixture of Preparation 27" in Step C. At the end of Step D, the isomers are separated by preparative HPLC using acetonitrile and water-TFA as eluants. After evaporating off the solvent and neutralising with sodium bicarbonate, the products are subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the title products are obtained.

**Example 454.** 5-(5-Chloro-2-[[3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid from Preparation 1 and racemic 3-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline in Step A, and the compound of Preparation 18" in Step C.

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

%C=64.77:64.81; %H=4.55:4.52; %N=10.21:10.33



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

Empirical formula: C<sub>37</sub> H<sub>31</sub> Cl F<sub>3</sub> N<sub>5</sub> O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 686.2140

[M+H]<sup>+</sup> measured: 686.2145

5 **Example 455. 5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl)-N-{5-cyano-2-methyl-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrol-3-yl}-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 1' in Step A, and the compound of Preparation 35" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=65.71:66.07; %H=5.78:5.82; %N=10.95:10.66; %Cl=4.62:4.45

***High-resolution mass spectrometry (ESI+/HR, ESI-/LR):***

15 Empirical formula: C<sub>42</sub> H<sub>43</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 731.3107

[M+H]<sup>+</sup> measured: 731.3109

20 **Example 456. 5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-{2-[2-(morpholin-4-yl)-ethoxy]pyrimidin-5-yl}-1H-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 1' in Step A, and the compound of Preparation 36" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=63.41:63.51; %H=5.59:5.26; %N=11.09:11.10; %Cl=4.68:4.46

**High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>40</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 721.2900

[M+H]<sup>+</sup> measured: 721.2907

5     **Example 457. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(6-cyano-5-methoxypyridin-2-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

10     The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=64.15:63.95; %H=5.25:4.79; %N=10.95:10.97; %Cl=4.62:4.22

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

15     Empirical formula: C<sub>41</sub> H<sub>39</sub> Cl N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 731.2743

[M+H]<sup>+</sup> measured: 731.2746

20     **Example 458. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1,4-dimethyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 37" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=65.34:65.68; %H=5.62:5.31; %N=11.15:11.15; %Cl=4.70:4.33

***High-resolution mass spectrometry (ESI+/HR, ESI-/LR):***

Empirical formula: C<sub>41</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 717.2951

[M+H]<sup>+</sup> measured: 717.2954

5 **Example 459. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1-ethyl-2-methyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride**

10 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 38" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=65.71;65.29; %H=5.78;5.51; %N=10.95;10.95; %Cl=4.62;4.39

***High-resolution mass spectrometry (ESI+/HR, ESI-/LR):***

15 Empirical formula: C<sub>42</sub> H<sub>43</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 731.3107

[M+H]<sup>+</sup> measured: 731.3109

20 **Example 460. 5-(5-Chloro-2-{[(3*R*)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-[1-(tetrahydrofuran-3-yl)-1*H*-pyrazol-4-yl]-1*H*-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 6' in Step A, and the compound of Preparation 22" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=64.58;64.24; %H=6.05;5.88; %N=10.51;10.53; %Cl=4.43;4.39

***High-resolution mass spectrometry (ESI+/HR, ESI-/LR):***

Empirical formula: C<sub>43</sub> H<sub>47</sub> Cl N<sub>6</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 763.3369

[M+H]<sup>+</sup> measured: 763.3371

5     **Example 461. 5-(5-Chloro-2-{[(3*R*)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-1,2-dimethyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride**

10     The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 6' in Step A, and the compound of Preparation 29" in Step C, it being understood that Step D is not carried out. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=67.44:66.68; %H=6.05:5.80; %N=10.97:10.95; %Cl<sup>-</sup>=4.63:4.57

15     ***High-resolution mass spectrometry (ESI+/HR):***

Empirical formula: C<sub>43</sub> H<sub>45</sub> Cl N<sub>6</sub> O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 729.3314

[M+H]<sup>+</sup> measured: 729.3316

20     **Example 462. 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(5-methyl-1,2-oxazol-3-yl)-1*H*-pyrrole-3-carboxamide**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C.

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

%C=67.10:66.64; %H=5.63:5.40; %N=10.30:10.24

**High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>38</sub> H<sub>38</sub> Cl N<sub>5</sub> O<sub>5</sub>

[M+H]<sup>+</sup> calculated: 680.2634

[M+H]<sup>+</sup> measured: 680.2637

5 **Example 463.** *N*-(2-Ethoxypyrimidin-5-yl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide

10 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 39" in Step C.

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

%C=68.17:67.52; %H=5.86:5.60; %N=11.92:11.43

15 **Example 464.** 5-(5-Chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-hydroxypyridin-2-yl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide dihydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 40" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

20 **High-resolution mass spectrometry (ESI+/HR, ESI-/LR):**

Empirical formula: C<sub>41</sub> H<sub>40</sub> Cl N<sub>7</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 730.2903

[M+H]<sup>+</sup> measured: 730.2907

**Example 465. 5-(4-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 29 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=65.34:64.81; %H=5.62:5.27; %N=11.15:10.95 %Cl<sup>-</sup>=4.70:5.09

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

Empirical formula: C<sub>41</sub> H<sub>41</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 717.2951

[M+H]<sup>+</sup> measured: 717.2952

**Example 466. 5-(4-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 29 and the compound of Preparation 3' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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

%C=66.77:62.82; %H=5.63:5.29; %N=11.74:11.75; %Cl<sup>-</sup>=5.01:5.23

***High-resolution mass spectrometry (ESI<sup>+</sup>/HR, ESI<sup>-</sup>/LR):***

Empirical formula: C<sub>38</sub> H<sub>39</sub> Cl N<sub>6</sub> O<sub>4</sub>

[M+H]<sup>+</sup> calculated: 679.2794

[M+H]<sup>+</sup> measured: 679.2796

**Example 467. 5-(5-Chloro-2-{[3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide**

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and 1,2,3,4-tetrahydroisoquinoline in Step A, and the compound of Preparation 2" in Step C.

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

%C=72.97;72.93; %H=5.25;5.08; %N=7.29;7.34

***High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):***

Empirical formula: C<sub>35</sub> H<sub>30</sub> Cl N<sub>3</sub> O<sub>3</sub>

[M+H]<sup>+</sup> calculated: 576.2048

[M+H]<sup>+</sup> measured: 576.2067

## **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<sup>®</sup> primary  
5 accession number: P10415), at a final concentration of  $2.50 \times 10^{-8}$  M, is mixed with a  
fluorescent peptide (Fluorescein-REIGAQLRRMADDLNAQY), at a final concentration of  
 $1.00 \times 10^{-8}$  M in a buffer solution (Hepes 10 mM, NaCl 150 mM, Tween20 0.05%, pH 7.4),  
in the presence or absence of increasing concentrations of test compounds. After  
incubation for 2 hours, the fluorescence polarisation is measured.

10 The results are expressed in IC<sub>50</sub> (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**

15 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<sub>50</sub> (the concentration of compound that inhibits cell viability  
20 by 50 %) and are presented in Table 1 below.

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



**Table 1: IC<sub>50</sub> of Bcl-2 inhibition (fluorescence polarisation test)  
and of cytotoxicity for RS4;11 cells**

|                   | IC <sub>50</sub> (nM) Bcl-2 FP | IC <sub>50</sub> (nM) MTT RS4;11 |                   | IC <sub>50</sub> (nM) Bcl-2 FP | IC <sub>50</sub> (nM) MTT RS4;11 |
|-------------------|--------------------------------|----------------------------------|-------------------|--------------------------------|----------------------------------|
| <b>Example 1</b>  | 5.0                            | 33.6                             | <b>Example 29</b> | 6.6                            | 47.5                             |
| <b>Example 2</b>  | ND                             | 1660                             | <b>Example 30</b> | 4.7                            | 771                              |
| <b>Example 3</b>  | 24.6                           | 94.9                             | <b>Example 31</b> | 7.2                            | 89.3                             |
| <b>Example 4</b>  | ND                             | 231                              | <b>Example 32</b> | 13.3                           | 240                              |
| <b>Example 5</b>  | 21.2                           | 44.8                             | <b>Example 33</b> | 10.9                           | 57.8                             |
| <b>Example 6</b>  | 25.2                           | 69                               | <b>Example 34</b> | 8.2                            | 47                               |
| <b>Example 7</b>  | 25.6                           | 90.6                             | <b>Example 35</b> | 50.0                           | 560                              |
| <b>Example 8</b>  | ND                             | 255                              | <b>Example 36</b> | 71.4                           | >600                             |
| <b>Example 9</b>  | 22.4                           | 87.5                             | <b>Example 37</b> | 60.4                           | >600                             |
| <b>Example 10</b> | 16.2                           | 205                              | <b>Example 38</b> | 7.5                            | 134                              |
| <b>Example 11</b> | 14.2                           | 202                              | <b>Example 39</b> | 7.2                            | 19.7                             |
| <b>Example 12</b> | 5.5                            | 39.6                             | <b>Example 40</b> | 64.4                           | 431                              |
| <b>Example 13</b> | 4.4                            | 19.8                             | <b>Example 41</b> | 10.0                           | 22.6                             |
| <b>Example 14</b> | 3.7                            | 8.23                             | <b>Example 42</b> | 5.2                            | 4.36                             |
| <b>Example 15</b> | 11.1                           | 69.4                             | <b>Example 43</b> | 5.1                            | 28.9                             |
| <b>Example 16</b> | 12.6                           | 22.7                             | <b>Example 44</b> | 3.0                            | 5.41                             |
| <b>Example 17</b> | 8.0                            | 75.2                             | <b>Example 45</b> | 38.9                           | 403                              |
| <b>Example 18</b> | 3.9                            | 27.6                             | <b>Example 46</b> | 76.6                           | >600                             |
| <b>Example 19</b> | 6.0                            | 65.5                             | <b>Example 47</b> | 5.9                            | 44.5                             |
| <b>Example 20</b> | 4.9                            | 164                              | <b>Example 48</b> | 4.4                            | 14.9                             |
| <b>Example 21</b> | 4.7                            | 79.9                             | <b>Example 49</b> | 4.0                            | 14.1                             |
| <b>Example 22</b> | 6.6                            | 45.7                             | <b>Example 50</b> | 5.9                            | 33.1                             |
| <b>Example 23</b> | 3.6                            | 25.4                             | <b>Example 51</b> | 26.7                           | 354                              |
| <b>Example 24</b> | 6.2                            | 79.1                             | <b>Example 52</b> | 28.9                           | 433                              |
| <b>Example 25</b> | 4.0                            | 33.3                             | <b>Example 53</b> | 43.5                           | 293                              |
| <b>Example 26</b> | 4.1                            | 541                              | <b>Example 54</b> | 18.0                           | 30.5                             |
| <b>Example 27</b> | 5.2                            | 93.4                             | <b>Example 55</b> | 209.6                          | >600                             |
| <b>Example 28</b> | 7.5                            | 95.3                             | <b>Example 56</b> | 75.0                           | >600                             |

|                    | IC <sub>50</sub> (nM) Bcl-2 FP | IC <sub>50</sub> (nM) MTT RS4;11 |                    | IC <sub>50</sub> (nM) Bcl-2 FP | IC <sub>50</sub> (nM) MTT RS4;11 |
|--------------------|--------------------------------|----------------------------------|--------------------|--------------------------------|----------------------------------|
| <b>Example 57</b>  | 80.0                           | >600                             | <b>Example 102</b> | 2                              | 6.51                             |
| <b>Example 58</b>  | 133.3                          | >600                             | <b>Example 108</b> | 3.9                            | 15.4                             |
| <b>Example 59</b>  | 134.0                          | >600                             | <b>Example 109</b> | 91.5                           | 930                              |
| <b>Example 60</b>  | ND                             | 18.3                             | <b>Example 110</b> | 8.5                            | 39.5                             |
| <b>Example 61</b>  | 4.5                            | 37.8                             | <b>Example 115</b> | 3.6                            | 18.3                             |
| <b>Example 62</b>  | 14.3                           | 127                              | <b>Example 116</b> | 3.4                            | 47.8                             |
| <b>Example 63</b>  | 5.1                            | 11.2                             | <b>Example 122</b> | 3.4                            | 82.4                             |
| <b>Example 65</b>  | 21.9                           | 113                              | <b>Example 126</b> | 4.2                            | 49.2                             |
| <b>Example 66</b>  | 16.9                           | 241                              | <b>Example 127</b> | 5.3                            | 111                              |
| <b>Example 67</b>  | 12.5                           | 98.6                             | <b>Example 129</b> | 18.1                           | 275                              |
| <b>Example 68</b>  | 2.1                            | 20.7                             | <b>Example 207</b> | 4.6                            | 32.2                             |
| <b>Example 69</b>  | 5.3                            | 3.68                             | <b>Example 209</b> | 7.4                            | 25.4                             |
| <b>Example 70</b>  | 8.5                            | 63.5                             | <b>Example 210</b> | 8.8                            | 47.2                             |
| <b>Example 71</b>  | 6.1                            | 12.9                             | <b>Example 214</b> | 6.3                            | 236                              |
| <b>Example 72</b>  | 7.7                            | 43.6                             | <b>Example 230</b> | 5.1                            | 18.3                             |
| <b>Example 73</b>  | 8                              | 42.6                             | <b>Example 358</b> | 14.8                           | 165                              |
| <b>Example 74</b>  | 4                              | 45.4                             | <b>Example 384</b> | 9.7                            | 216                              |
| <b>Example 75</b>  | 52.9                           | 367                              | <b>Example 385</b> | 5.7                            | 28.7                             |
| <b>Example 81</b>  | ND                             | 249                              | <b>Example 386</b> | 2.6                            | 9.23                             |
| <b>Example 82</b>  | 19.5                           | 427                              | <b>Example 387</b> | 20.6                           | 243                              |
| <b>Example 88</b>  | 15.9                           | 69.6                             | <b>Example 388</b> | 3.6                            | 16.5                             |
| <b>Example 92</b>  | 8.4                            | 37.8                             | <b>Example 389</b> | 14.7                           | 208                              |
| <b>Example 93</b>  | 19.7                           | 368                              | <b>Example 390</b> | 21.2                           | 173                              |
| <b>Example 94</b>  | 8.6                            | 104                              | <b>Example 391</b> | 30.3                           | 255                              |
| <b>Example 95</b>  | 7                              | 174                              | <b>Example 392</b> | 3.8                            | 11.4                             |
| <b>Example 96</b>  | 13.5                           | 161                              | <b>Example 393</b> | 2.1                            | 1.95                             |
| <b>Example 97</b>  | 19                             | 98                               | <b>Example 394</b> | 2.5                            | 2.76                             |
| <b>Example 98</b>  | 7.6                            | 68.3                             | <b>Example 395</b> | 3.5                            | 7.57                             |
| <b>Example 99</b>  | 6.4                            | 108                              | <b>Example 396</b> | 15.7                           | 116                              |
| <b>Example 100</b> | 22.9                           | 193                              | <b>Example 397</b> | 4.5                            | 37.1                             |
| <b>Example 101</b> | 21.1                           | 743                              | <b>Example 398</b> | 3.9                            | 13.4                             |

|                    | IC <sub>50</sub> (nM) Bcl-2 FP | IC <sub>50</sub> (nM) MTT RS4;11 |                    | IC <sub>50</sub> (nM) Bcl-2 FP | IC <sub>50</sub> (nM) MTT RS4;11 |
|--------------------|--------------------------------|----------------------------------|--------------------|--------------------------------|----------------------------------|
| <b>Example 399</b> | 9.9                            | 155                              | <b>Example 432</b> | 3.4                            | 76.6                             |
| <b>Example 400</b> | 49                             | 469                              | <b>Example 433</b> | 2.6                            | 48.2                             |
| <b>Example 401</b> | 8                              | 24.3                             | <b>Example 434</b> | 3.5                            | 45.7                             |
| <b>Example 402</b> | 26.1                           | 241                              | <b>Example 435</b> | 14.9                           | 441                              |
| <b>Example 403</b> | 24.2                           | 289                              | <b>Example 436</b> | 49.1                           | 338                              |
| <b>Example 404</b> | 24.4                           | 85.5                             | <b>Example 437</b> | 4.4                            | 70.5                             |
| <b>Example 406</b> | 4.2                            | 10.6                             | <b>Example 438</b> | 11.3                           | 379                              |
| <b>Example 407</b> | 20.6                           | 150                              | <b>Example 439</b> | 6.1                            | 329                              |
| <b>Example 408</b> | 5.4                            | 4.46                             | <b>Example 440</b> | 2.6                            | 13.6                             |
| <b>Example 409</b> | 12.2                           | 41.9                             | <b>Example 441</b> | 3.5                            | 132                              |
| <b>Example 410</b> | 9.9                            | 61.6                             | <b>Example 442</b> | 3                              | 42.8                             |
| <b>Example 411</b> | 5.5                            | 32.8                             | <b>Example 443</b> | ND                             | 57.9                             |
| <b>Example 412</b> | 3.1                            | 0.398                            | <b>Example 444</b> | 5.5                            | 181                              |
| <b>Example 413</b> | 3.1                            | 9.43                             | <b>Example 445</b> | 2                              | 19                               |
| <b>Example 415</b> | 3.8                            | 29.9                             | <b>Example 446</b> | 7.8                            | 249                              |
| <b>Example 416</b> | 2.9                            | 42.5                             | <b>Example 447</b> | 20                             | >600                             |
| <b>Example 417</b> | 3                              | 11                               | <b>Example 448</b> | 2.4                            | 12.1                             |
| <b>Example 418</b> | 10.1                           | 159                              | <b>Example 449</b> | 1.7                            | 11.9                             |
| <b>Example 419</b> | 2.8                            | 15.8                             | <b>Example 450</b> | 2.7                            | 53.2                             |
| <b>Example 420</b> | 6.1                            | 51.8                             | <b>Example 451</b> | 2.9                            | 102                              |
| <b>Example 421</b> | 2.5                            | 3.73                             | <b>Example 452</b> | 8.3                            | 112                              |
| <b>Example 422</b> | 9.2                            | 101                              | <b>Example 453</b> | 6.9                            | 99.9                             |
| <b>Example 423</b> | 11.7                           | 344                              | <b>Example 454</b> | 6.5                            | 158                              |
| <b>Example 424</b> | 13.6                           | 102                              | <b>Example 455</b> | 1.9                            | 11.8                             |
| <b>Example 425</b> | 4.2                            | 62                               | <b>Example 456</b> | 2.7                            | 80.6                             |
| <b>Example 426</b> | 5.2                            | 139                              | <b>Example 457</b> | ND                             | 80.4                             |
| <b>Example 427</b> | 2.2                            | 23.3                             | <b>Example 458</b> | 10.5                           | 197                              |
| <b>Example 428</b> | 3.5                            | 59.2                             | <b>Example 459</b> | 2.5                            | 5.93                             |
| <b>Example 429</b> | 3.1                            | 109                              | <b>Example 460</b> | 2.8                            | 22.9                             |
| <b>Example 430</b> | 19.9                           | 328                              | <b>Example 461</b> | 3.1                            | 18.6                             |
| <b>Example 431</b> | 3                              | 89                               | <b>Example 462</b> | 13.3                           | 368                              |

|                    | IC <sub>50</sub> (nM) Bcl-2 FP | IC <sub>50</sub> (nM) MTT RS4;11 |                    | IC <sub>50</sub> (nM) Bcl-2 FP | IC <sub>50</sub> (nM) MTT RS4;11 |
|--------------------|--------------------------------|----------------------------------|--------------------|--------------------------------|----------------------------------|
| <b>Example 463</b> | ND                             | 40.8                             | <b>Example 466</b> | ND                             | 493                              |
| <b>Example 464</b> | 36.6                           | 723                              | <b>Example 467</b> | 19.2                           | 188                              |
| <b>Example 465</b> | ND                             | 50.6                             |                    |                                |                                  |

ND: not determined

**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.

5     1x10<sup>7</sup> RS4;11 cells are grafted sub-cutaneously into immunosuppressed mice (SCID strain). 25 to 30 days after the graft, the animals are treated orally with the various compounds. Sixteen hours after treatment, the tumour masses are recovered and lysed, and the caspase 3 activity is measured in the tumour lysates.

10     This enzymatic measurement is carried out by assaying the appearance of a fluorogenic cleavage product (DEVDase activity, Promega). It is expressed in the form of an activation factor corresponding to the ratio between the two caspase activities: the activity for the treated mice divided by the activity for the control mice.

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

15     **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.

20     1x10<sup>7</sup> RS4;11 cells are grafted sub-cutaneously into immunosuppressed mice (SCID strain). 25 to 30 days after the graft, the animals are treated orally with the various compounds. After treatment, the tumour masses are recovered and lysed, and the cleaved (activated) form of caspase 3 is quantified in the tumour 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 $\pm$ SEM (versus control) |
|-----------------|---------------------------------------------------|----------------------------------------------|
| Example 25      | 2 hours                                           | 45.7 $\pm$ 2.0 (25 mg/kg)                    |
| Example 28      | 2 hours                                           | 72.3 $\pm$ 5.4 (12.5 mg/kg)                  |
| Example 47      | 2 hours                                           | 12.3 $\pm$ 2.4 (25 mg/kg)                    |
| Example 61      | 2 hours                                           | 76.0 $\pm$ 5.2 (12.5 mg/kg)                  |
| Example 67      | 2 hours                                           | 29.8 $\pm$ 4.0 (25 mg/kg)                    |
| Example 71      | 2 hours                                           | 46.8 $\pm$ 16.1 (25 mg/kg)                   |
| Example 74      | 2 hours                                           | 24.5 $\pm$ 7.4 (12.5 mg/kg)                  |
| Example 108     | 2 hours                                           | 22.6 $\pm$ 2.4 (12.5 mg/kg)                  |
| Example 230     | 2 hours                                           | 42.2 $\pm$ 9.3 (25 mg/kg)                    |
| Example 386     | 2 hours                                           | 52.0 $\pm$ 8.6 (12.5 mg/kg)                  |
| Example 388     | 2 hours                                           | 85.7 $\pm$ 3.7 (25 mg/kg)                    |
| Example 421     | 2 hours                                           | 38.7 $\pm$ 10.7 (12.5 mg/kg)                 |
| Example 449     | 2 hours                                           | 50.5 $\pm$ 3.4 (12.5 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.

$1 \times 10^7$  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  $150 \text{ mm}^3$ , 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).

5 The tumour mass is measured twice weekly from the start of treatment.

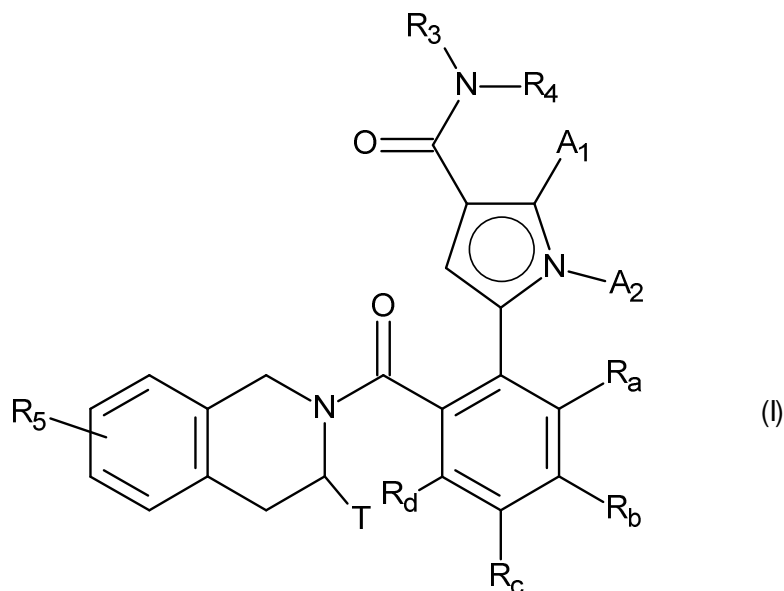
The results obtained accordingly show that the compounds of the invention are capable of inducing significant tumour regression, which can be total, during the treatment period.

**EXAMPLE F: Pharmaceutical composition: Tablets**

|    |                                                                                      |      |
|----|--------------------------------------------------------------------------------------|------|
|    | 1000 tablets containing a dose of 5 mg of a compound selected from Examples 1 to 467 | 5 g  |
| 10 | Wheat starch.....                                                                    | 20 g |
|    | Maize starch .....                                                                   | 20 g |
|    | Lactose .....                                                                        | 30 g |
|    | Magnesium stearate.....                                                              | 2 g  |
|    | Silica.....                                                                          | 1 g  |
| 15 | Hydroxypropylcellulose .....                                                         | 2 g  |

**WHAT WE CLAIM IS:**

**1.**Compound of formula (I):



wherein:

- 5
- ◆  $A_1$  and  $A_2$ , each independently of the other, represent a hydrogen or halogen atom, a linear or branched  $(C_1-C_6)$ polyhaloalkyl group, a linear or branched  $(C_1-C_6)$ alkyl group or a cycloalkyl 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  $(C_1-C_4)$ alkyl- $NR_1R_2$ , or a

10

  - group  $(C_1-C_4)$ alkyl- $OR_6$ ,
  - ◆  $R_1$  and  $R_2$ , each independently of the other, 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 or branched  $(C_1-C_6)$ alkyl group, a linear or branched

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  - $(C_2-C_6)$ alkenyl group, a linear or branched  $(C_2-C_6)$ alkynyl group, a cycloalkyl group, a  $(C_3-C_{10})$ cycloalkyl- $(C_1-C_6)$ alkyl group wherein the alkyl moiety is linear or branched, a heterocycloalkyl group, an aryl group or a heteroaryl group, 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 an aryl group, a heteroaryl group, a cycloalkyl group or a linear or branched  $(C_1-C_6)$ alkyl group, it being understood that one or more of the carbon atoms of the preceding groups, or of their 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,

◆  $R_a$ ,  $R_b$ ,  $R_c$  and  $R_d$ , each independently of the others, represent  $R_7$ , a halogen atom, a linear or branched  $(C_1-C_6)$ alkoxy group, a hydroxy group, a linear or branched  $(C_1-C_6)$ polyhaloalkyl group, a trifluoromethoxy group,  $-NR_7R_7'$ , nitro,  $R_7-CO-(C_0-C_6)$ alkyl-,  $R_7-CO-NH-(C_0-C_6)$ alkyl-,  $NR_7R_7'-CO-(C_0-C_6)$ alkyl-,  $NR_7R_7'-CO-(C_0-C_6)$ alkyl-O-,  $R_7-SO_2-NH-(C_0-C_6)$ alkyl-,  $R_7-NH-CO-NH-(C_0-C_6)$ alkyl-,  $R_7-O-CO-NH-(C_0-C_6)$ alkyl-, a heterocycloalkyl group, or the substituents of one of the pairs  $(R_a, R_b)$ ,  $(R_b, R_c)$  or  $(R_c, R_d)$  form together with the carbon atoms carrying them a ring composed of from 5 to 7 ring members, which may contain from one to 2 hetero atoms selected from oxygen and sulphur, it also being understood that one or more carbon atoms of the ring defined hereinbefore may be deuterated or substituted by from one to 3 groups selected from halogen and linear or branched  $(C_1-C_6)$ alkyl,

◆  $R_7$  and  $R_7'$ , each independently of the other, represent a hydrogen, a linear or branched  $(C_1-C_6)$ alkyl, a linear or branched  $(C_2-C_6)$ alkenyl, a linear or branched  $(C_2-C_6)$ alkynyl, an aryl or a heteroaryl, or  $R_7$  and  $R_7'$ , together with the nitrogen atom carrying them, form a heterocycle composed of from 5 to 7 ring members,

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 from 3 to 10 ring members and containing from 1 to 3 hetero atoms selected from oxygen, sulphur, SO, SO<sub>2</sub> 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<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted by a group selected from methoxy, hydroxy or morpholine; (C<sub>3</sub>-C<sub>6</sub>)spiro; linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted by a morpholine; (C<sub>1</sub>-C<sub>6</sub>)alkyl-S-; hydroxy; oxo (or *N*-oxide where appropriate); nitro; cyano; -COOR'; -OCOR'; NR'R"; linear or branched (C<sub>1</sub>-C<sub>6</sub>)polyhaloalkyl; trifluoromethoxy; (C<sub>1</sub>-C<sub>6</sub>)alkylsulphonyl; halogen; aryl optionally substituted by one or more halogen atoms; 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 linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group optionally substituted by a methoxy,

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

**2.**Compound of formula (I) according to claim 1, wherein A<sub>1</sub> represents a hydrogen atom or a methyl group.

**3.**Compound of formula (I) according to claim 1 or claim 2, wherein A<sub>2</sub> represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group optionally substituted by a group selected from halogen, hydroxy, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, NR'R" and morpholine.

**4.**Compound of formula (I) according to claim 1 or claim 2, wherein A<sub>2</sub> represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)polyhaloalkyl group or a cyclopropyl group.

**5.**Compound of formula (I) according to one of claims 1 to 3, wherein A<sub>1</sub> and A<sub>2</sub> both represent a methyl group.

**6.**Compound of formula (I) according to one of claims 1 to 5, wherein T represents a methyl, aminomethyl, (morpholin-4-yl)methyl, (4-methylpipérazin-1-yl)methyl, 2-(morpholin-4-yl)ethyl, [2-(morpholin-4-yl)ethoxy]methyl, hydroxymethyl, [2-(dimethylamino)ethoxy]methyl, hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-ylmethyl, 1-oxa-6-azaspiro[3.3]hept-6-ylmethyl, 3-(morpholin-4-yl)propyl or trifluoromethyl group.

**7.**Compound of formula (I) according to one of claims 1 to 6, wherein R<sub>a</sub> and R<sub>d</sub> each represent a hydrogen atom and (R<sub>b</sub>,R<sub>c</sub>), together with the carbon atoms carrying them, form a 1,3-dioxolane group or a 1,4-dioxane group; or R<sub>a</sub>, R<sub>c</sub> and R<sub>d</sub> each represent a hydrogen atom and R<sub>b</sub> represents a hydrogen or halogen atom or a methoxy group.

**8.**Compound of formula (I) according to one of claims 1 to 6, wherein: R<sub>a</sub> and R<sub>d</sub> each represent a hydrogen atom, R<sub>b</sub> represents a hydrogen or halogen atom and R<sub>c</sub> represents a hydroxy or methoxy group; or: R<sub>a</sub> and R<sub>d</sub> each represent a hydrogen atom, R<sub>b</sub> represents a hydroxy or methoxy group and R<sub>c</sub> represents a halogen atom.

**9.**Compound of formula (I) according to one of claims 1 to 6, wherein R<sub>a</sub>, R<sub>b</sub> and R<sub>d</sub> each represent a hydrogen atom and R<sub>c</sub> represents a group selected from R<sub>7</sub>-CO-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl-, R<sub>7</sub>-SO<sub>2</sub>-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl-, R<sub>7</sub>-NH-CO-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl- and R<sub>7</sub>-O-CO-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl-.

**10.**Compound of formula (I) according to one of claims 1 to 9, wherein R<sub>4</sub> represents a phenyl, 4-hydroxyphenyl, 3-fluoro-4-hydroxyphenyl, 2-hydroxypyrimidine or 3-hydroxypyridine group.

**11.**Compound of formula (I) according to one of claims 1 to 10, wherein R<sub>3</sub> represents an aryl or heteroaryl group.

**12.**Compound of formula (I) according to one of claims 1 to 10, wherein R<sub>3</sub> represents a group selected from methyl, phenyl, 1*H*-pyrazole, 1*H*-indole, 1*H*-indazole, pyridine, pyrimidine, 1*H*-pyrrolo[2,3-*b*]pyridine, 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine, 1*H*-benzimidazole, 1*H*-pyrrole, 1*H*-pyrrolo[2,3-*c*]pyridine, 1*H*-pyrrolo[3,2-*b*]pyridine, 5*H*-

pyrrolo[3,2-*d*]pyrimidine, thiophene, pyrazine, 1*H*-pyrazolo[3,4-*b*]pyridine, 1,2-oxazole, and 1*H*-pyrazolo[1,5-*a*]pyrimidine, those groups optionally having one or more substituents selected from halogen, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, cyano, cyclopropyl, oxetane, tetrahydrofuran, -CO-O-CH<sub>3</sub>,  
5 trideuteriomethyl, 2-(morpholin-4-yl)ethyl and 2-(morpholin-4-yl)ethoxy.

**13.**Compound of formula (I) according to claim 9, wherein R<sub>3</sub> represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl or a heteroaryl optionally substituted by a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, and R<sub>4</sub> represents a 4-hydroxyphenyl group.

**14.**Compound of formula (I) according to claim 1, selected from the following group:

10 -5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide,

-5-(5-chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide,

15 -*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide,

-*N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-  
20 carboxamide,

-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide,

25 -5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide,

-5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide,

30 -5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-carbonyl}phenyl)-*N*-(5-cyano-1-methyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide,

-*N*-(5-cyano-1-methyl-1*H*-pyrrol-3-yl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide,

5      -5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide,

-5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide,

10      -*N*-(5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide,

15      -5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-[5-cyano-2-methyl-1-(trideuteriomethyl)-1*H*-pyrrol-3-yl]-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide,

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

**15.**Compound of formula (I) according to claim 1 which is 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide.

**16.**Compound of formula (I) according to claim 1 which is 5-(5-chloro-2-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide.

**17.**Compound of formula (I) according to claim 1 which is *N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-5-(6-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1*H*-pyrrole-3-carboxamide.

**18.**Compound of formula (I) according to claim 1 which is *N*-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3*R*)-3-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}-1,3-benzodioxol-5-yl)-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide.

5 **19.**Compound of formula (I) according to claim 1 which is 5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-3-carboxamide.

10 **20.**Compound of formula (I) according to claim 1 which is 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide.

15 **21.**Compound of formula (I) according to claim 1 which is 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-*N*-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide.

20 **22.**Compound of formula (I) according to claim 1 which is 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1-methyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide.

25 **23.**Compound of formula (I) according to claim 1 which is *N*-(5-cyano-1-methyl-1*H*-pyrrol-3-yl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide.

**24.**Compound of formula (I) according to claim 1 which is 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide.

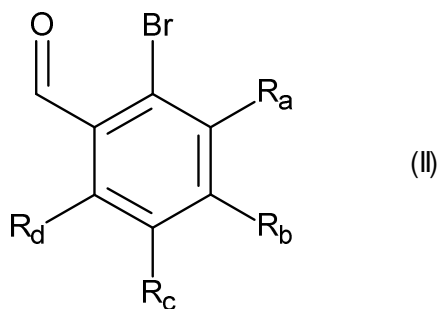
30 **25.**Compound of formula (I) according to claim 1 which is 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-

hydroxyphenyl)-1,2-dimethyl-*N*-(1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrrole-3-carboxamide.

**26.**Compound of formula (I) according to claim 1 which is *N*-(5-cyano-1,2-dimethyl-1*H*-pyrrol-3-yl)-5-(5-fluoro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide.

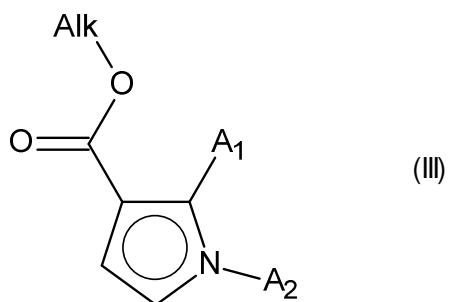
**27.**Compound of formula (I) according to claim 1 which is 5-(5-chloro-2-{[(3*S*)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}phenyl)-*N*-[5-cyano-2-methyl-1-(trideuteriomethyl)-1*H*-pyrrol-3-yl]-*N*-(4-hydroxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide.

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



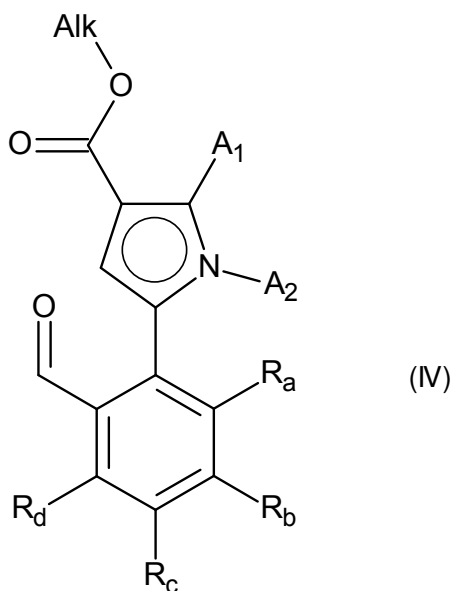
wherein  $R_a$ ,  $R_b$ ,  $R_c$  and  $R_d$  are as defined for formula (I),

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):



wherein the groups  $A_1$  and  $A_2$  are as defined for formula (I) and Alk represents a linear or branched ( $C_1$ - $C_6$ )alkyl,

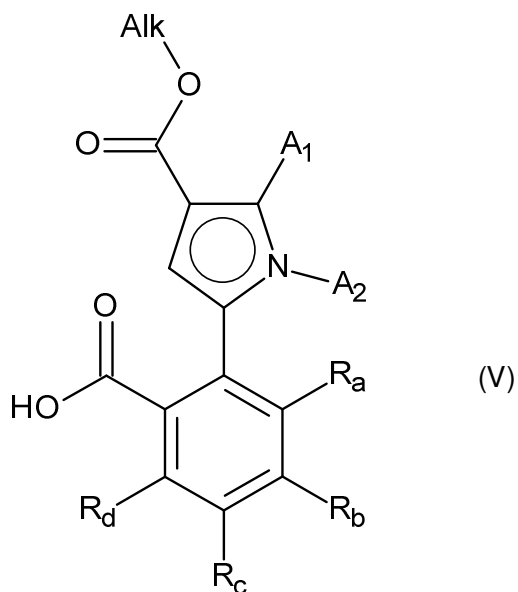
to obtain the compound of formula (IV):



5

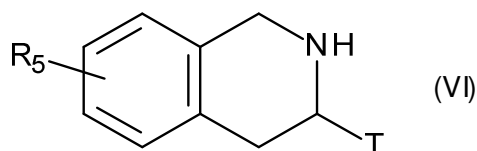
wherein  $A_1$ ,  $A_2$ ,  $R_a$ ,  $R_b$ ,  $R_c$  and  $R_d$  are as defined for formula (I) and Alk is as defined hereinbefore,

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



wherein A<sub>1</sub>, A<sub>2</sub>, R<sub>a</sub>, R<sub>b</sub>, R<sub>c</sub> and R<sub>d</sub> are as defined for formula (I) and Alk is as defined hereinbefore,

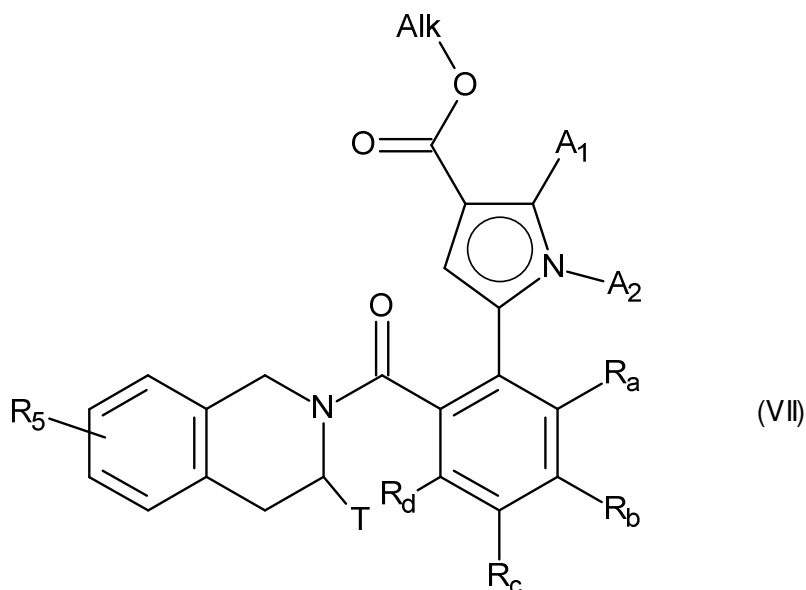
which compound of formula (V) is then subjected to peptide coupling with a compound of  
5 formula (VI):



wherein T and R<sub>5</sub> are as defined for formula (I),

to yield the compound of formula (VII):





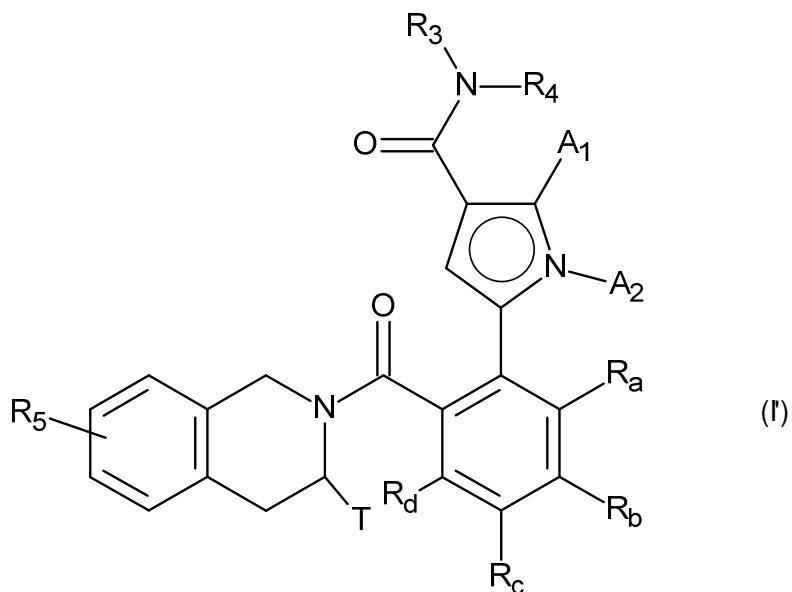
wherein  $A_1$ ,  $A_2$ ,  $R_a$ ,  $R_b$ ,  $R_c$ ,  $R_d$ ,  $T$  and  $R_5$  are as defined for formula (I) and  $Alk$  is as defined hereinbefore,

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.

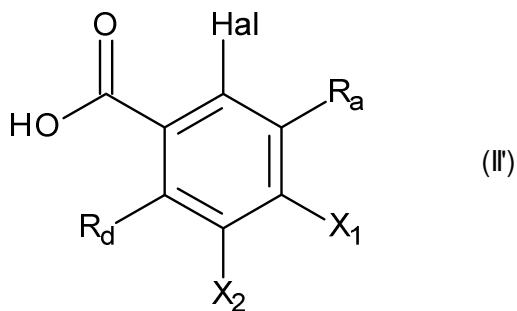
**29.** Process for the preparation of compounds of formula (I'), particular cases of the compounds of formula (I) according to claim 1 as defined hereinbelow:



wherein:

- A<sub>1</sub>, A<sub>2</sub>, R<sub>a</sub>, R<sub>d</sub>, R<sub>3</sub>, R<sub>4</sub>, T and R<sub>5</sub> are as defined for formula (I),
- R<sub>b</sub> and R<sub>c</sub> are such that one represents a hydrogen and the other a group selected from R<sub>7</sub>-CO-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl-, R<sub>7</sub>-SO<sub>2</sub>-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl-, R<sub>7</sub>-NH-CO-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl- and R<sub>7</sub>-O-CO-NH-(C<sub>0</sub>-C<sub>6</sub>)alkyl-, R<sub>7</sub> being as defined for formula (I),

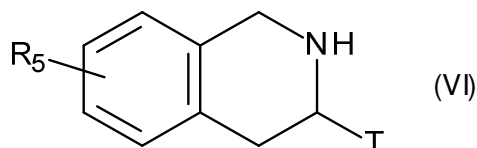
which preparation process uses as starting material a compound of formula (II):



wherein:

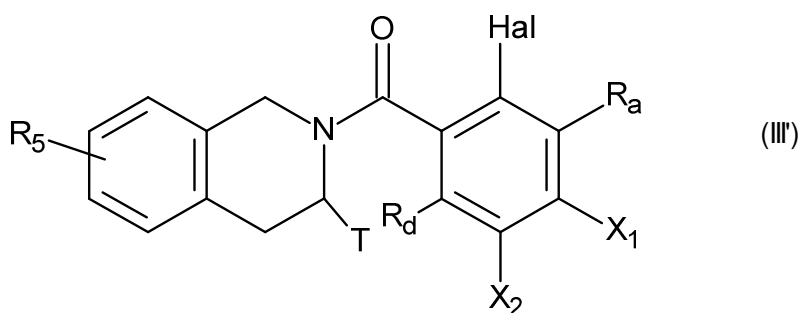
- R<sub>a</sub> and R<sub>d</sub> are as defined for formula (I),
- Hal represents a halogen atom,
- X<sub>1</sub> and X<sub>2</sub> are such that one represents a (C<sub>0</sub>-C<sub>6</sub>)alkyl-NH<sub>2</sub> group while the other represents a hydrogen atom,

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



wherein T and R<sub>5</sub> are as defined for formula (I),

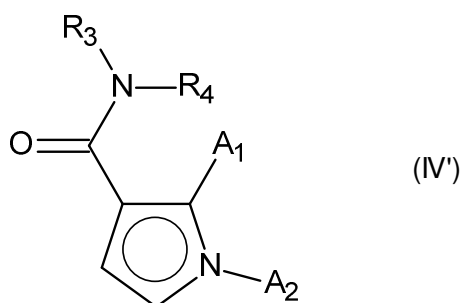
5 to yield the compound of formula (III'):



wherein:

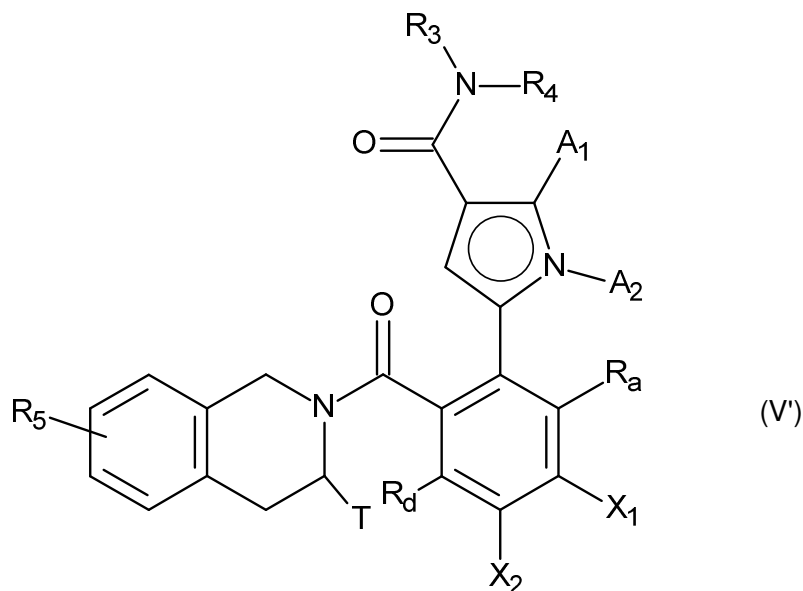
- R<sub>a</sub>, R<sub>d</sub>, T and R<sub>5</sub> are as defined for formula (I),
- Hal represents a halogen atom,
- X<sub>1</sub> and X<sub>2</sub> are such that one represents a (C<sub>0</sub>-C<sub>6</sub>)alkyl-NH<sub>2</sub> group while the other represents a hydrogen atom,

which compound of formula (III') 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 a compound of formula (IV'):



wherein A<sub>1</sub>, A<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as defined for formula (I),

to form the compound of formula (V'):



wherein:

- A<sub>1</sub>, A<sub>2</sub>, R<sub>a</sub>, R<sub>d</sub>, R<sub>3</sub>, R<sub>4</sub>, T and R<sub>5</sub> are as defined for formula (I),
- X<sub>1</sub> and X<sub>2</sub> are such that one represents a (C<sub>0</sub>-C<sub>6</sub>)alkyl-NH<sub>2</sub> group while the other represents a hydrogen atom,

which compound of formula (V') is then subjected to an acylation or sulfonylation reaction 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.

**30.** Process according to claim 28 or 29 for the preparation of a compound of formula (I) wherein one of the groups  $R_3$  or  $R_4$  is substituted by a hydroxy function, characterised in that the amine  $NHR_3R_4$  is subjected beforehand to a reaction protecting the hydroxy function 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.

**31.** Pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 27 or an addition salt thereof with a pharmaceutically acceptable acid or base in combination with one or more pharmaceutically acceptable excipients.

**32.** Pharmaceutical composition according to claim 31 for use as a pro-apoptotic agent.

**33.** Pharmaceutical composition according to claim 31 for use in the treatment of cancers, auto-immune diseases and diseases of the immune system.

**34.** Pharmaceutical composition according to claim 31 for use in the treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukaemias, colorectal cancer, cancers of the oesophagus and liver, lymphoblastic leukaemias, non-Hodgkin lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer and small-cell lung cancer.

**35.** Use of a pharmaceutical composition according to claim 31 in the manufacture of a medicament for use as a pro-apoptotic agent.

**36.** Use of a pharmaceutical composition according to claim 31 in the manufacture of a medicament intended for the treatment of cancers, diseases of the immune system and auto-immune diseases.

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

**38.** Compound of formula (I) according to one of claims 1 to 27, or an addition salt thereof with a pharmaceutically acceptable acid or base, for use in the treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukaemias, colorectal cancer, cancers of the oesophagus and liver, lymphoblastic leukaemias, non-Hodgkin lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer and small-cell lung cancer.

**39.** Use of a compound of formula (I) according to one of claims 1 to 27, or an addition salt thereof with a pharmaceutically acceptable acid or base, in the manufacture of a medicament intended for the treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukaemias, colorectal cancer, cancers of the oesophagus and liver, lymphoblastic leukaemias, non-Hodgkin lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer and small-cell lung cancer.

**40.** Combination of a compound of formula (I) according to any one of claims 1 to 27 with an anti-cancer agent selected from genotoxic agents, mitotic poisons, anti-metabolites, proteasome inhibitors, kinase inhibitors and antibodies.

**41.** Pharmaceutical composition comprising a combination of formula (I) according to any one of claims 1 to 27 and an anti-cancer agent selected from genotoxic agents, mitotic poisons, anti-metabolites, proteasome inhibitors, kinase inhibitors and antibodies, in combination with one or more pharmaceutically acceptable excipients.

**42.** Combination according to claim 40 for use in the treatment of cancers.

**43.** Use of a compound of formula (I) according to any one of claims 1 to 27 and an anti-cancer agent selected from genotoxic agents, mitotic poisons, anti-metabolites, proteasome inhibitors, kinase inhibitors and antibodies, in the manufacture of a medicament for use in the treatment of cancers.

5      **44.** Use of a compound of formula (I) according to any one of claims 1 to 27 in the manufacture of a medicament for use in the treatment of cancers wherein the medicament is for sequential or simultaneous administration with an anti-cancer agent selected from genotoxic agents, mitotic poisons, anti-metabolites, proteasome inhibitors, kinase inhibitors and antibodies

10      **45.** Compound of formula (I) according to any one of claims 1 to 27 for use in association with radiotherapy in the treatment of cancers.

15      **46.** A compound of claim 1, substantially as herein described with reference to any example thereof.

**47.** A process of claim 28 or 29, substantially as herein described with reference to any example thereof.

20      **48.** A pharmaceutical composition of claim 31, substantially as herein described with reference to any example thereof.

**49.** A use of any one of claims 35-37, 39, 43 and 44, substantially as herein described with reference to any example thereof.

25      **50.** A combination of claim 40, substantially as herein described with reference to any example thereof.