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**Quinoxaline and pyridopyrazine derivatives as p13Kbeta inhibitors**

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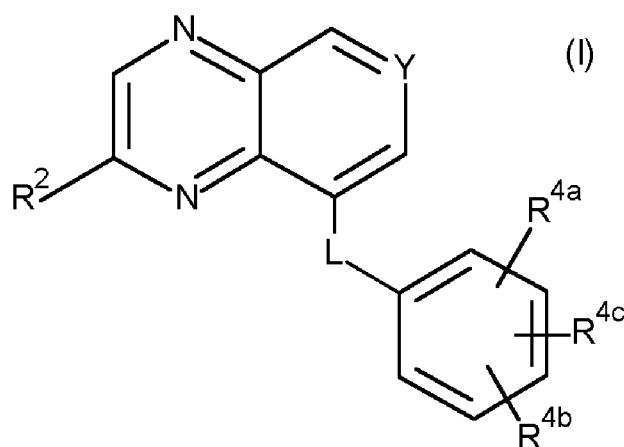
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(54) Title: QUINOXALINE AND PYRIDOPYRAZINE DERIVATIVES AS PI3KBETA INHIBITORS



(57) Abstract: The present invention relates to substituted quinoxaline and pyridopyrazine derivatives of Formula (I) wherein the variables have the meaning defined in the claims. The compounds according to the present invention are useful as p13Kβ inhibitors. The invention further relates to pharmaceutical compositions comprising said compounds as an active ingredient as well as the use of said compounds as a medicament.



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QUINOXALINE AND PYRIDOPYRAZINE DERIVATIVES  
AS PI3K $\beta$  INHIBITORS

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Field of the Invention

- 5 The present invention relates to substituted quinoxaline and pyridopyrazine derivatives useful as PI3K $\beta$  inhibitors. The invention further relates to pharmaceutical compositions comprising said compounds as an active ingredient as well as the use of said compounds as a medicament.

Background of the invention

- 10 Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.
- There are three classes of phosphoinositide-3-kinases (PI3Ks): class I, class II and class III. Class I PI3Ks are the most associated with human cancer [K.D Courtney, R.B. Corcoran and J.A. Engelman (2010), *Journal of Clinical Oncology.*, 28; 1075].
- 15 The class I phosphoinositide-3-kinases (PI3Ks) are divided into 2 subclasses: class I<sub>A</sub>, composed of a p110 catalytic subunit (p110a, p110b or p110d) and a p85 regulatory subunit (p85a, p55a and p50a, p85b or p55g) and class I<sub>B</sub> PI3K represented by the p110g catalytic subunit and the p101 and p84 regulatory subunits [B. Vanhaesebroeck
- 20 and M.D. Waterfield (1999) *Experimental Cell Research.*, 253, 239-254]. The class I<sub>A</sub> PI3Ks are activated in a variety of solid and non-solid tumors via mutation or deletion of the tumor suppressor PTEN (phosphatase and tensin homolog) or in the case of p110a by activating mutations [K.D Courtney, R.B. Corcoran and J.A. Engelman (2010), *Journal of Clinical Oncology.*, 28; 1075]. PI3Ks can also be activated by
- 25 receptor tyrosine kinases (RTKs); p110b can be activated by G-protein coupled receptors [K.D Courtney, R.B. Corcoran and J.A. Engelman (2010), *Journal of Clinical Oncology.*, 28; 1075]. Once activated the phosphoinositide-3-kinases catalyze the phosphorylation of phosphatidyl 4,5-diphosphate leading to the generation of phosphatidyl, 3, 4, 5-triphosphate (PIP3) [Zhao L., Vogt P. K.(2008) *Oncogene* 27,
- 30 5486–5496]. PTEN antagonizes the activity of the PI3Ks through the dephosphorylation PIP3 [Myers M. P., Pass I., Batty I. H., Van der Kaay J., Stolarov J. P., Hemmings B. A., Wigler M. H., Downes C. P., Tonks N. K.(1998) *Proc. Natl. Acad. Sci. U.S.A.* 95, 13513–13518]. The PIP3 generated by activation of PI3K or sustained by the inactivation of PTEN binds to a subset of lipid-binding domains in
- 35 downstream targets such as the pleckstrin homology domain of the oncogene Akt thereby recruiting it to the plasma membrane [Stokoe D., Stephens L. R., Copeland T.,

Gaffney P. R., Reese C. B., Painter G. F., Holmes A. B., McCormick F., Hawkins P. T. (1997) *Science* 277, 567–570]. Once at the plasma membrane Akt phosphorylates several effector molecules that are involved in numerous biologically relevant processes such as metabolism, differentiation, proliferation, longevity and apoptosis [D. R. Calnan and A. Brunet (2008) *Oncogene* 27; 2276].

Several studies suggest a key role for p110b in PTEN-deficient tumors. For example the genetic knockout of p110b, but not p110a, is able to block tumor formation and Akt activation driven by Pten loss in the anterior prostate in a mouse model [Jia S, Liu Z, Zhang S, Liu P, Zhang L, Lee SH, Zhang J, Signoretti S, Loda M, Roberts TM, Zhao JJ. *Nature* 2008; 454:776–9]. Furthermore other studies have shown that a subset of PTEN-deficient human tumor cell lines is sensitive to inactivation of p110b rather than p110a [Wee S, Wiederschain D, Maira SM, Loo A, Miller C, deBeaumont R, Stegmeier F, Yao YM, Lengauer C (2008) *Proc. Natl. Acad. Sci (USA)*; 105 13057]. PTEN deficiency either by genetic inactivation or reduced expression frequently occurs in human cancers such as GBM, endometrial, lung, breast cancers and prostate cancer among others [K.D Courtney, R.B. Corcoran and J.A. Engelman (2010), *Journal of Clinical Oncology.*, 28; 1075].

These studies suggest that treatment of PTEN-deficient cancer with agents that inhibition p110b may be therapeutically beneficial. In addition to its role in cancer, p110b may be a target for antithrombotic therapy. It has been reported in mouse models that PI3K $\beta$  inhibition can prevent stable integrin  $\alpha_{IIb}\beta_3$  adhesion contacts that eliminates occlusive thrombus formation without prolongation of bleed time [S. P. Jackson *et al.* (2005) *Nature Medicine.*, 11, 507-514].

Furthermore, the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/AKT pathway is frequently activated during prostate cancer (PCa) progression through loss or mutation of the phosphatase and tensin homolog (PTEN) gene. Following the androgen receptor (AR) pathway, it is the second major driver of PCa growth. Combination with hormonal therapy improved efficacy of PI3K/AKT-targeted agents in PTEN-negative PCa models. Upregulation of AR-target genes upon PI3K/AKT inhibition suggests a compensatory crosstalk between the PI3K–AR pathways which, for optimal efficacy treatment, could require cotargeting of the AR axis [Marques RB, et al., High Efficacy of Combination Therapy Using PI3K/AKT Inhibitors with Androgen Deprivation in Prostate Cancer Preclinical Models. *Eur Urol* (2014), <http://dx.doi.org/10.1016/j.eururo.2014.08.053>]. Therefore PI3K $\beta$  inhibitors can be advantageously combined with anti-androgen therapies including androgen receptor antagonists and inhibitors of androgen biosynthesis in PTEN-negative prostate cancers.

WO 2012/116237 discloses heterocyclic entities that modulate PI3 kinase activity.  
WO 2011/123751 describes heterocyclic compounds as selective inhibitors of PI3K activity.

WO 2011/022439 discloses heterocyclic entities that modulate PI3 kinase activity.

5 WO 2008/014219 describes thiozolidinedione derivatives as PI3 kinase inhibitors.

WO 2013/028263 relates to pyrazolopyrimidine derivatives as PI3 kinase inhibitors.

WO 2012/047538 relates to benzimidazole derivatives as PI3 kinase inhibitors.

WO 2013/095761 relates to imidazopyridine derivatives as PI3 kinase inhibitors.

10 US 2013/0157977 relates to benzimidazole boronic acid derivatives as PI3 kinase inhibitors.

WO 2009/021083 describes quinoxaline derivatives as PI3 kinase inhibitors.

WO 2007/103756 describes the preparation of thiazolones for use as PI3 kinase inhibitors.

15 WO 2011/041399 describes benzimidazolyl (morpholinyl)purines and related compounds as PI3K $\delta$  inhibitors and their preparation and use for the treatment of PI3K-mediated diseases.

WO 2009/088990 describes the preparation of pyrazolo pyrimidines and other heterocyclic compounds as therapeutic PI3 kinase modulators.

20 WO2016/097347 relates to substituted imidazopyridazine derivatives useful as PI3K $\beta$  inhibitors.

WO2016/097359 relates to relates to heterocyclyl linked imidazopyridazine derivatives useful as PI3K $\beta$  inhibitors.

It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

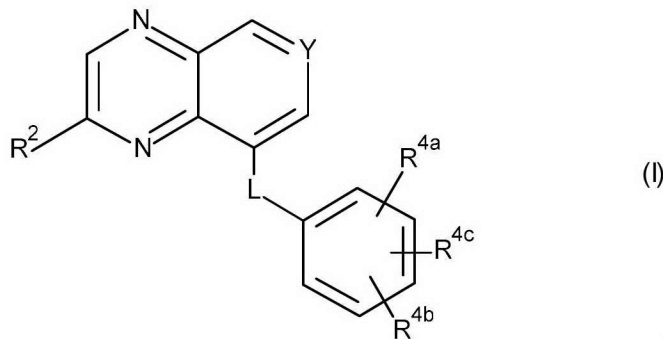
25 There is a strong need for novel PI3K $\beta$  kinase inhibitors thereby opening new avenues for the treatment or prevention of cancer, in particular PTEN-deficient cancers, more in particular prostate cancer. It is accordingly an object of a preferred embodiment of the present invention to provide such compounds.

30 Summary of the invention

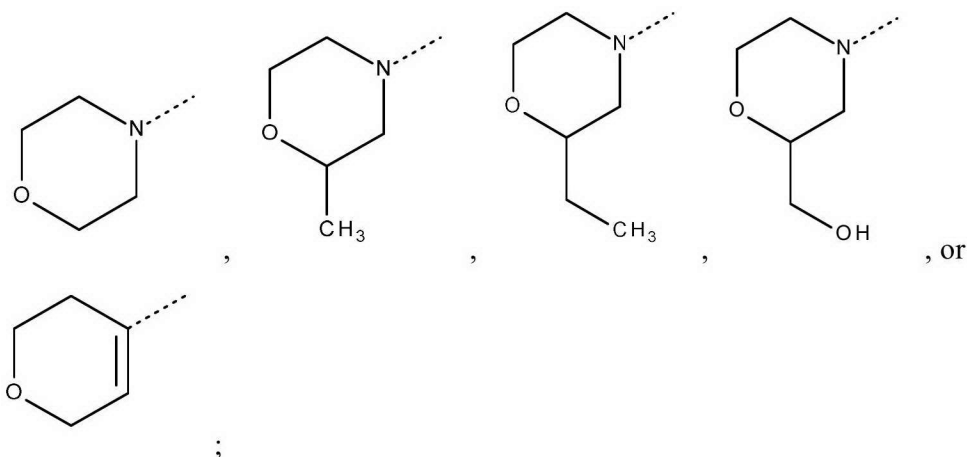
It has been found that the compounds of the present invention are useful as PI3K $\beta$  inhibitors. The compounds according to the invention and compositions thereof, may be useful for the treatment or prevention, in particular for the treatment, of diseases such as cancer, autoimmune disorders, cardiovascular diseases, inflammatory diseases,  
35 neurodegenerative diseases, allergy, pancreatitis, asthma, multiorgan failure, kidney

diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, lung injuries and the like.

In a first aspect, this invention concerns compounds of Formula (I)



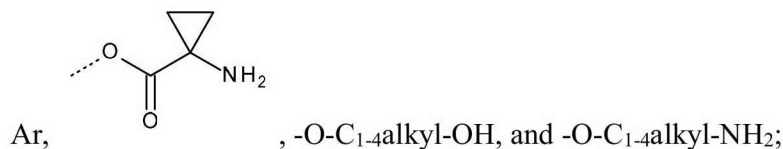
- 5 tautomers and stereoisomeric forms thereof, wherein  
 Y represents CR<sup>3</sup> or N;  
 L represents -CH(C<sub>1-4</sub>alkyl)-CH<sub>2</sub>-, -CH<sub>2</sub>-CH(C<sub>1-4</sub>alkyl)-,  
 -CH(C<sub>1-4</sub>alkyl)-CH(C<sub>1-4</sub>alkyl)-, -CHR<sup>1a</sup>-X-, or -X-CHR<sup>1c</sup>-;  
 X represents O, S, or NR<sup>1b</sup>;  
 10 R<sup>1a</sup> represents hydrogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkyl substituted with one -OH;  
 R<sup>1c</sup> represents hydrogen or C<sub>1-4</sub>alkyl;  
 R<sup>1b</sup> represents hydrogen, C<sub>1-4</sub>alkyl, -CH<sub>2</sub>-C(=O)-NR<sup>6a</sup>R<sup>6b</sup>, or C<sub>1-4</sub>alkyl substituted with  
 one substituent selected from the group consisting of hydroxyl, -O-C<sub>1-4</sub>alkyl, and  
 -NR<sup>6c</sup>R<sup>6d</sup>;  
 15 or R<sup>1b</sup> is taken together with R<sup>1a</sup> or R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>3</sub>-;  
 or R<sup>1b</sup> is taken together with R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>2</sub>- or -(CH<sub>2</sub>)<sub>4</sub>-;  
 R<sup>2</sup> represents



$R^{6a}$  and  $R^{6b}$  each independently are selected from the group consisting of hydrogen and  $C_{1-4}$ alkyl;

$R^{6c}$  and  $R^{6d}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$ , and  $-N(C_{1-4}alkyl)_2$ ;

$R^3$  represents  $R^7$ ,  $-(C=O)H$ ,  $-(C=O)-C_{1-4}alkyl$ ,  $-(C=O)-NR^{5a}R^{5b}$ ,  $-(C=O)-OR^{5c}$ ,  $-(C=O)-Het^1$ ,  $-(C=O)-NH-Het^2$ ,  $-(C=O)-NH-C_{1-4}alkyl-Het^1$ ,  $-(C=O)-N(C_{1-4}alkyl)-C_{1-4}alkyl-Het^1$ ,  $-(C=O)-N(C_{1-4}alkyl)-Het^2$ ,  $C_{1-4}alkyl$ ,  $-CH=N-OH$ ,  $-CH(OH)-CH_2-NR^{5d}R^{5e}$ ,  $-CH(OH)-CH_2-Het^1$ ,  $-CH(OH)-C_{1-4}alkyl$ ,  $-C(OH)(C_{1-4}alkyl)_2$ , halo, or  $R^3$  represents  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl, fluoro,  $-NR^{5f}R^{5g}$ ,  $Het^1$ ,  $-O-(C=O)-CH(NH_2)-C_{1-4}alkyl$ ,  $-O-(C=O)-CH(NH_2)-C_{1-4}alkyl$ ;



$R^{5a}$  and  $R^{5b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-NH_2$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{3-6}cycloalkyl$ ,  $C_{1-4}$ alkyl substituted with one or more halo atoms, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-O-C_{1-4}alkyl-NH_2$ ,  $-O-C_{1-4}alkyl-NH(C_{1-4}alkyl)$ ,  $-O-C_{1-4}alkyl-N(C_{1-4}alkyl)_2$ ,  $-(C=O)-O-C_{1-4}alkyl$ ,  $-(C=O)-OH$ ,  $-(C=O)-C_{1-4}alkyl$ ,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$  and  $-N(C_{1-4}alkyl)_2$ ;

$R^{5c}$  represents hydrogen or  $C_{1-4}$ alkyl;

$R^{5d}$  and  $R^{5e}$  each independently are selected from the group consisting of hydrogen and  $C_{1-4}$ alkyl;

$R^{5f}$  and  $R^{5g}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkyl substituted with one or more halo atoms, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$ , and  $-N(C_{1-4}alkyl)_2$ ;

$R^{4a}$ ,  $R^{4b}$  and  $R^{4c}$  each independently are selected from the group consisting of hydrogen, cyano,  $C_{1-4}$ alkyl, halo,  $-(C=O)H$ ,  $-NR^{6e}R^{6f}$ ,  $-O-C_{1-4}alkyl$ , and  $C_{1-4}$ alkyl substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, and  $-NR^{6g}R^{6h}$ ;

R<sup>6e</sup> and R<sup>6f</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl), and hydroxyl;

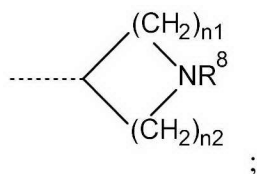
5 R<sup>6g</sup> and R<sup>6h</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl), and hydroxyl;

10 Het<sup>1</sup> represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N; or Het<sup>1</sup> represents a bicyclic 8-, 9- or 10-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N;

each optionally substituted with one or two substituents each independently selected from the group consisting of halo, -NR<sup>9a</sup>R<sup>9b</sup>, C<sub>1-4</sub>alkyl, -(C=O)-OR<sup>5h</sup>, -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -C<sub>1-4</sub>alkyl-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, hydroxyl, -O-C<sub>1-4</sub>alkyl, cyano, C<sub>1-4</sub>alkyl substituted with  
15 one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl) and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>; or two substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A;

20 R<sup>9a</sup> and R<sup>9b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

Het<sup>2</sup> represents



n1 represents 1 or 2;

n2 represents 1 or 2;

25 R<sup>8</sup> represents hydrogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

R<sup>5h</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

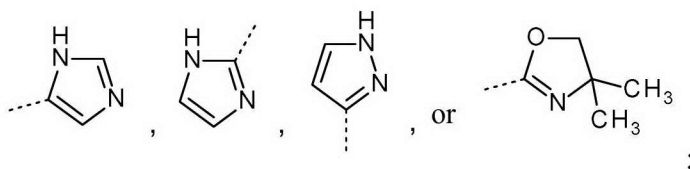
30 Ring A represents cyclobutyl, cyclopentyl, cyclohexyl, or a 4-, 5- or 6-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N; said cyclobutyl, cyclopentyl, cyclohexyl, or 4-, 5- or 6-membered saturated heterocyclyl is optionally substituted with one or two C<sub>1-4</sub>alkyl substituents, with one C<sub>1-4</sub>alkyl and one hydroxy substituent, or with one hydroxy substituent;



p represents 1 or 2;

Ar represents phenyl optionally substituted with one hydroxyl;

R<sup>7</sup> represents



- 5 and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

In a second aspect, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to the first aspect.

- 10 In a third aspect, the present invention provides a method of inhibition of PI3K $\beta$ , the method comprising administering to a subject in need thereof an effective amount of a compound according to the first aspect or a pharmaceutical composition according to the second aspect.

- 15 In a fourth aspect, the present invention provides a method of treatment or prevention of a disease or condition modulated by PI3K $\beta$ , the method comprising administering to a subject in need thereof an effective amount of a compound according to the first aspect or a pharmaceutical composition according to the second aspect.

- 20 The present invention also provides a method of treatment or prevention of a disease or condition according to the fourth aspect, wherein the disease or condition is selected from cancer, autoimmune disorders, cardiovascular diseases, inflammatory diseases, neurodegenerative diseases, allergy, pancreatitis, asthma, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, and lung injuries.

- 25 In a fifth aspect, the present invention provides use of a compound according to the first aspect, or a pharmaceutical composition according to the second aspect, in the manufacture of a medicament for inhibition of PI3K $\beta$ .

- 30 In a sixth aspect, the present invention provides use of a compound according to the first aspect, or a pharmaceutical composition according to the second aspect, in the manufacture of a medicament for treatment or prevention of a disease or condition modulated by PI3K $\beta$ .

The present invention further provides use of a compound or a pharmaceutical composition in the manufacture of a medicament according to the seventh aspect, wherein the disease or condition is selected from cancer, autoimmune disorders, cardiovascular diseases, inflammatory diseases, neurodegenerative diseases, allergy, pancreatitis, asthma, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, and lung injuries.

The present invention also concerns methods for the preparation of compounds of the present invention.

The compounds of the present invention were found to inhibit PI3K $\beta$  per se or can undergo metabolism to a (more) active form in vivo (prodrugs), and therefore may be useful in the treatment or prevention, in particular in the treatment, of diseases such as cancer, autoimmune disorders, cardiovascular diseases, inflammatory diseases, neurodegenerative diseases, allergy, pancreatitis, asthma, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, lung injuries and the like.

In view of the aforementioned pharmacology of the compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, it follows that they may be suitable for use as a medicament.

In particular the compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, may be suitable in the treatment or prevention, in particular in the treatment, of cancer.

The present invention also concerns the use of compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament for the inhibition of PI3K $\beta$ , for the treatment or prevention of cancer.

The present invention will now be further described. In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

#### Detailed description

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise.

Unless the context clearly requires otherwise, throughout the description and the claims, the words “comprise”, “comprising”, and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of “including, but not limited to”.

- 5 When any variable occurs more than one time in any constituent or in any formula (e.g. Formula (I)), its definition in each occurrence is independent of its definition at every other occurrence.

- Whenever the term “substituted” is used in the present invention, it is meant, unless otherwise is indicated or is clear from the context, to indicate that one or more hydrogens, in particular from 1 to 3 hydrogens, preferably 1 or 2 hydrogens, more preferably 1 hydrogen, on the atom or radical indicated in the expression using “substituted” are replaced with a selection from the indicated group, provided that the normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.
- 10  
15

When two or more substituents are present on a moiety they may, unless otherwise is indicated or is clear from the context, replace hydrogens on the same atom or they may replace hydrogen atoms on different atoms in the moiety.

- It will be clear for the skilled person that, unless otherwise is indicated or is clear from the context, a substituent on a heterocyclyl group may replace any hydrogen atom on a ring carbon atom or on a ring heteroatom.
- 20

- The prefix “C<sub>x-y</sub>” (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C<sub>1-6</sub>alkyl group contains from 1 to 6 carbon atoms, a C<sub>1-4</sub>alkyl group contains from 1 to 4 carbon atoms, a C<sub>1-3</sub>alkyl group contains from 1 to 3 carbon atoms, a C<sub>3-6</sub>cycloalkyl group contains from 3 to 6 carbon atoms, and so on.
- 25

The term “halo” as a group or part of a group is generic for fluoro, chloro, bromo, iodo unless otherwise is indicated or is clear from the context.

- The term “C<sub>1-6</sub>alkyl” as a group or part of a group refers to a hydrocarbyl radical of Formula C<sub>n</sub>H<sub>2n+1</sub> wherein n is a number ranging from 1 to 6. C<sub>1-6</sub>alkyl groups comprise from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms, more preferably from 1 to 3 carbon atoms, still more preferably 1 to 2 carbon atoms. Alkyl groups may be linear or branched and may be substituted as indicated herein. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. Thus, for example, C<sub>1-6</sub>alkyl includes all linear, or
- 30  
35

branched alkyl groups with between 1 and 6 carbon atoms, and thus includes such as for example methyl, ethyl, *n*-propyl, *i*-propyl, 2-methyl-ethyl, butyl and its isomers (e.g. *n*-butyl, *isobutyl* and *tert*-butyl), pentyl and its isomers, hexyl and its isomers, and the like.

- 5 The term "C<sub>1-4</sub>alkyl" as a group or part of a group refers to a hydrocarbyl radical of Formula C<sub>n</sub>H<sub>2n+1</sub> wherein n is a number ranging from 1 to 4. C<sub>1-4</sub>alkyl groups comprise from 1 to 4 carbon atoms, preferably from 1 to 3 carbon atoms, more preferably 1 to 2 carbon atoms. C<sub>1-4</sub>alkyl groups may be linear or branched and may be substituted as indicated herein. When a subscript is used herein following a carbon atom, the
- 10 subscript refers to the number of carbon atoms that the named group may contain. C<sub>1-4</sub>alkyl includes all linear, or branched alkyl groups with between 1 and 4 carbon atoms, and thus includes methyl, ethyl, *n*-propyl, *i*-propyl, 2-methyl-ethyl, butyl and its isomers (e.g. *n*-butyl, *isobutyl* and *tert*-butyl), and the like.

- The term "C<sub>3-6</sub>cycloalkyl" alone or in combination, refers to a cyclic saturated
- 15 hydrocarbon radical having from 3 to 6 carbon atoms. Non-limiting examples of suitable C<sub>3-6</sub>cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Examples of compounds wherein R<sup>1b</sup> and R<sup>1a</sup> are taken together to form -(CH<sub>2</sub>)<sub>3</sub>- are compounds 1-4, 10, 14-19, 23-52, 54-55, 57-58, 62-67, 69-72, 75-77, 93-96, 101-103, 106-107, 112, 249-255.

- 20 Examples of compounds wherein R<sup>1b</sup> and R<sup>1c</sup> are taken together to form -(CH<sub>2</sub>)<sub>3</sub>- are compounds 244-245.

In case L represents -CH(C<sub>1-4</sub>alkyl)-CH<sub>2</sub>-, it is intended that the C-atom with the two hydrogens (-CH<sub>2</sub>-) is attached to the phenyl ring in the structure of formula (I).

- In case L represents -CH<sub>2</sub>-CH(C<sub>1-4</sub>alkyl)-, it is intended that the C-atom with the C<sub>1-4</sub>alkyl substituent (-CH(C<sub>1-4</sub>alkyl)-) is attached to the phenyl ring in the structure of
- 25 formula (I).

In case L represents -CHR<sup>1a</sup>-X-, it is intended that 'X' is attached to the phenyl ring in the structure of formula (I).

- In case L represents -X-CHR<sup>1c</sup>-, it is intended that the C-atom with the R<sup>1c</sup> substituent
- 30 (-CHR<sup>1c</sup>-) is attached to the phenyl ring in the structure of formula (I).

In an embodiment the expression 'at least one heteroatom' is restricted to '1, 2 or 3 heteroatoms', in a particular embodiment to '1 or 2 heteroatoms', in a more particular embodiment to '1 heteroatom'.

- Examples of a 4-, 5- or 6-membered saturated heterocyclyl containing at least one
- 35 heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N (e.g. in Ring A),

include, but are not limited to azetidiny, morpholinyl, piperidinyl, pyrrolidinyl, 1,1-dioxido-thietanyl, 1,1-dioxido-thiomorpholinyl, piperazinyl, dioxolanyl, oxazolidinyl, oxetanyl, tetrahydrofuranyl, and the like.

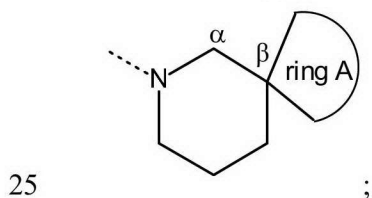
5 Examples of a 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N (e.g. in Het<sup>1</sup>), include, but are not limited to azetidiny, morpholinyl, piperidinyl, pyrrolidinyl, 1,1-dioxido-thietanyl, 1,1-dioxido-thiomorpholinyl, piperazinyl, dioxolanyl, oxazolidinyl, oxetanyl, tetrahydrofuranyl, 4,5-dihydro-1,3-oxazolyl, hexahydro-1H-1,4-diazepinyl, and the like.

10 Examples of a bicyclic 8-, 9- or 10-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N (e.g. in Het<sup>1</sup>), include, but are not limited to 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazinyl, octahydro-pyrrolo[1,2-*a*]pyrazinyl, and the like.

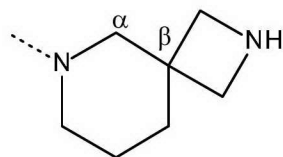
Het<sup>1</sup> representing a bicyclic heterocyclyl, in particular is a fused bicyclic heterocyclyl.

15 Het<sup>1</sup> may be attached to the remainder of the molecule of Formula (I) through any available ring carbon atom or ring heteroatom as appropriate, if not otherwise specified. In a particular embodiment Het<sup>1</sup> is attached to the remainder of the molecule of Formula (I) via a nitrogen atom.

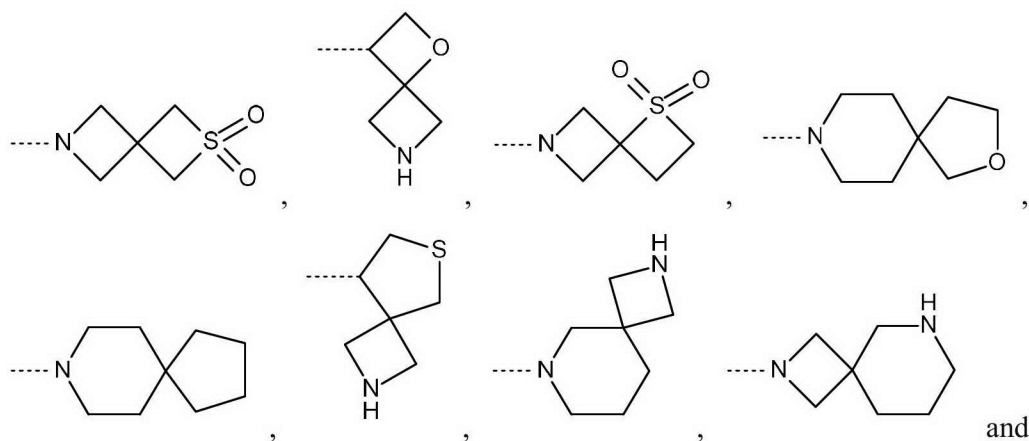
It will be clear that when two substituents on the same carbon atom in the Het<sup>1</sup> definition are taken together to form together with the common carbon atom to which they are attached Ring A, a spiro moiety is formed. For example, when Het<sup>1</sup> represents 1-piperidinyl wherein two substituents on the carbon atom in position β are taken together to form together with the common carbon atom to which they are attached ring A, the following spiro moiety is formed:



in particular if in the above example ring A represents 3-azetidiny, the following spiro moiety is formed:



Examples of such spiro moieties, include, but are not limited to



the like.

- 5 Whenever substituents are represented by chemical structure, “---” represents the bond of attachment to the remainder of the molecule of Formula (I).

Whenever one of the ring systems, is substituted with one or more substituents, those substituents may replace, unless otherwise is indicated or is clear from the context, any hydrogen atom bound to a carbon or nitrogen atom of the ring system.

- 10 The term “subject” as used herein, refers to an animal, preferably a mammal (e.g. cat, dog, primate or human), more preferably a human, who is or has been the object of treatment, observation or experiment.

The term “therapeutically effective amount” as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal

- 15 response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medicinal doctor or other clinician, which includes alleviation or reversal of the symptoms of the disease or disorder being treated.

The term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or

- 20 indirectly, from combinations of the specified ingredients in the specified amounts.

The term “treatment”, as used herein, is intended to refer to all processes wherein there may be a slowing, interrupting, arresting or stopping of the progression of a disease, but does not necessarily indicate a total elimination of all symptoms.

The term “compounds of the invention” as used herein, is meant to include the

- 25 compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof.

As used herein, any chemical formula with bonds shown only as solid lines and not as solid wedged or hashed wedged bonds, or otherwise indicated as having a particular configuration (e.g. *R*, *S*) around one or more atoms, contemplates each possible stereoisomer, or mixture of two or more stereoisomers.

- 5 Hereinbefore and hereinafter, the term “compound of Formula (I)” is meant to include the stereoisomers thereof and the tautomeric forms thereof.

The terms “stereoisomers”, “stereoisomeric forms” or “stereochemically isomeric forms” hereinbefore or hereinafter are used interchangeably.

- 10 The invention includes all stereoisomers of the compounds of the invention either as a pure stereoisomer or as a mixture of two or more stereoisomers.

Enantiomers are stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemate or racemic mixture.

- 15 Atropisomers (or atropoisomers) are stereoisomers which have a particular spatial configuration, resulting from a restricted rotation about a single bond, due to large steric hindrance. All atropisomeric forms of the compounds of Formula (I) are intended to be included within the scope of the present invention.

- 20 Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, i.e. they are not related as mirror images. If a compound contains a double bond, the substituents may be in the *E* or the *Z* configuration. Substituents on bivalent cyclic (partially) saturated radicals may have either the *cis*- or *trans*-configuration; for example if a compound contains a disubstituted cycloalkyl group, the substituents may be in the *cis* or *trans* configuration. Therefore, the invention includes enantiomers, atropisomers, diastereomers, racemates, *E* isomers, *Z* isomers, *cis* isomers, *trans* isomers and mixtures thereof, whenever chemically possible.

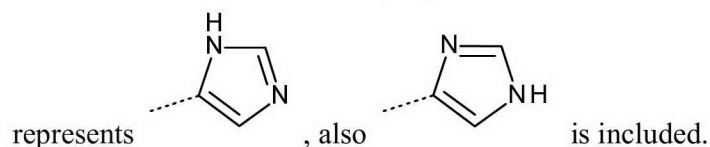
- 25 The meaning of all those terms, i.e. enantiomers, atropisomers, diastereomers, racemates, *E* isomers, *Z* isomers, *cis* isomers, *trans* isomers and mixtures thereof are known to the skilled person.

- 30 The absolute configuration is specified according to the Cahn-Ingold-Prelog system. The configuration at an asymmetric atom is specified by either *R* or *S*. Resolved stereoisomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light. For instance, resolved enantiomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light.



When a specific stereoisomer is identified, this means that said stereoisomer is substantially free, i.e. associated with less than 50%, preferably less than 20%, more preferably less than 10%, even more preferably less than 5%, in particular less than 2% and most preferably less than 1%, of the other stereoisomers. Thus, when a compound of Formula (I) is for instance specified as (R), this means that the compound is substantially free of the (S) isomer; when a compound of Formula (I) is for instance specified as E, this means that the compound is substantially free of the Z isomer; when a compound of Formula (I) is for instance specified as cis, this means that the compound is substantially free of the trans isomer.

Some of the compounds of Formula (I) may also exist in their tautomeric form. Such forms in so far as they may exist, are intended to be included within the scope of the present invention. It follows that a single compound may exist in both stereoisomeric and tautomeric form. For example, it will be clear for the skilled person that when R<sup>7</sup>



For therapeutic use, salts of the compounds of Formula (I), N-oxides and solvates thereof, are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable addition salts as mentioned hereinabove or hereinafter are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of Formula (I), N-oxides and solvates thereof, are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids. Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.



The compounds of Formula (I), N-oxides and solvates thereof containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline; the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term solvate comprises the hydrates and solvent addition forms which the compounds of Formula (I) are able to form, as well as N-oxides and pharmaceutically acceptable addition salts thereof. Examples of such forms are e.g. hydrates, alcoholates and the like.

The compounds of the invention as prepared in the processes described below may be synthesized in the form of mixtures of enantiomers, in particular racemic mixtures of enantiomers, that can be separated from one another following art-known resolution procedures. A manner of separating the enantiomeric forms of the compounds of Formula (I), and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

In the framework of this application, an element, in particular when mentioned in relation to a compound of Formula (I), comprises all isotopes and isotopic mixtures of this element, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. Radiolabelled compounds of Formula (I) may comprise a radioactive isotope selected from the group of  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{11}\text{C}$ ,  $^{18}\text{F}$ ,  $^{122}\text{I}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{75}\text{Br}$ ,  $^{76}\text{Br}$ ,  $^{77}\text{Br}$  and  $^{82}\text{Br}$ . Preferably, the radioactive isotope is selected from the group of  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{11}\text{C}$  and  $^{18}\text{F}$ . More preferably, the radioactive isotope is  $^2\text{H}$ . In particular, deuterated compounds are intended to be included within the scope of the

present invention.

In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein

5 Y represents  $\text{CR}^3$  or N;

L represents  $-\text{CH}(\text{C}_{1-4}\text{alkyl})-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}(\text{C}_{1-4}\text{alkyl})-$ ,  $-\text{CH}(\text{C}_{1-4}\text{alkyl})-\text{CH}(\text{C}_{1-4}\text{alkyl})-$ ,  $-\text{CHR}^{1a}-\text{X}-$ , or  $-\text{X}-\text{CHR}^{1c}-$ ;

X represents O, S, or  $\text{NR}^{1b}$ ;

$\text{R}^{1a}$  represents hydrogen,  $\text{C}_{1-4}\text{alkyl}$ , or  $\text{C}_{1-4}\text{alkyl}$  substituted with one  $-\text{OH}$ ;

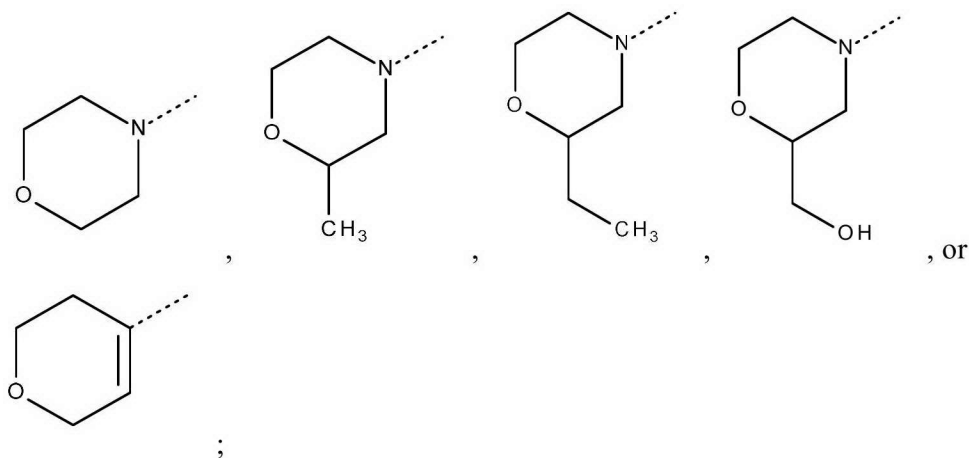
10  $\text{R}^{1c}$  represents hydrogen or  $\text{C}_{1-4}\text{alkyl}$ ;

$\text{R}^{1b}$  represents hydrogen,  $\text{C}_{1-4}\text{alkyl}$ ,  $-\text{CH}_2-\text{C}(=\text{O})-\text{NR}^{6a}\text{R}^{6b}$ , or  $\text{C}_{1-4}\text{alkyl}$  substituted with one substituent selected from the group consisting of hydroxyl,  $-\text{O}-\text{C}_{1-4}\text{alkyl}$ , and  $-\text{NR}^{6c}\text{R}^{6d}$ ;

or  $\text{R}^{1b}$  is taken together with  $\text{R}^{1a}$  or  $\text{R}^{1c}$  to form  $-(\text{CH}_2)_3-$ ;

15 or  $\text{R}^{1b}$  is taken together with  $\text{R}^{1c}$  to form  $-(\text{CH}_2)_2-$  or  $-(\text{CH}_2)_4-$ ;

$\text{R}^2$  represents

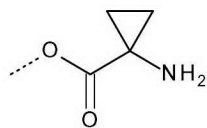


20  $\text{R}^{6a}$  and  $\text{R}^{6b}$  each independently are selected from the group consisting of hydrogen and  $\text{C}_{1-4}\text{alkyl}$ ;

$\text{R}^{6c}$  and  $\text{R}^{6d}$  each independently are selected from the group consisting of hydrogen,  $\text{C}_{1-4}\text{alkyl}$ , and  $\text{C}_{1-4}\text{alkyl}$  substituted with one substituent selected from the group consisting of hydroxyl,  $-\text{NH}_2$ ,  $-\text{NH}(\text{C}_{1-4}\text{alkyl})$ , and  $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$ ;

25  $\text{R}^3$  represents  $\text{R}^7$ ,  $-(\text{C}=\text{O})\text{H}$ ,  $-(\text{C}=\text{O})-\text{C}_{1-4}\text{alkyl}$ ,  $-(\text{C}=\text{O})-\text{NR}^{5a}\text{R}^{5b}$ ,  $-(\text{C}=\text{O})-\text{OR}^{5c}$ ,  $-\text{C}(=\text{O})-\text{Het}^1$ ,  $-\text{C}(=\text{O})-\text{NH}-\text{Het}^2$ ,  $\text{C}_{1-4}\text{alkyl}$ ,  $-\text{CH}=\text{N}-\text{OH}$ ,  $-\text{CH}(\text{OH})-\text{CH}_2-\text{NR}^{5d}\text{R}^{5e}$ ,  $-\text{CH}(\text{OH})-\text{CH}_2-\text{Het}^1$ ,  $-\text{CH}(\text{OH})-\text{C}_{1-4}\text{alkyl}$ ,  $-\text{C}(\text{OH})(\text{C}_{1-4}\text{alkyl})_2$ , halo, or  $\text{R}^3$  represents  $\text{C}_{1-4}\text{alkyl}$  substituted with one substituent selected from the group consisting of hydroxyl, fluoro,

$-NR^{5f}R^{5g}$ ,  $Het^1$ ,  $-O-(C=O)-CH(NH_2)-C_{1-4}alkyl$ ,  $-O-(C=O)-CH(NH_2)-C_{1-4}alkyl-Ar$ ,



,  $-O-C_{1-4}alkyl-OH$ , and  $-O-C_{1-4}alkyl-NH_2$ ;

- $R^{5a}$  and  $R^{5b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}alkyl$ ,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-NH_2$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{3-6}cycloalkyl$ ,  
5  $C_{1-4}alkyl$  substituted with one or more halo atoms, and

$C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-O-C_{1-4}alkyl-NH_2$ ,  $-O-C_{1-4}alkyl-NH(C_{1-4}alkyl)$ ,  $-O-C_{1-4}alkyl-N(C_{1-4}alkyl)_2$ ,  $-(C=O)-O-C_{1-4}alkyl$ ,  $-(C=O)-OH$ ,  $-(C=O)-C_{1-4}alkyl$ ,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$  and  $-N(C_{1-4}alkyl)_2$ ;

- 10  $R^{5c}$  represents hydrogen or  $C_{1-4}alkyl$ ;

$R^{5d}$  and  $R^{5e}$  each independently are selected from the group consisting of hydrogen and  $C_{1-4}alkyl$ ;

$R^{5f}$  and  $R^{5g}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}alkyl$ ,  $C_{1-4}alkyl$  substituted with one or more halo atoms, and

- 15  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$ , and  $-N(C_{1-4}alkyl)_2$ ;

$R^{4a}$ ,  $R^{4b}$  and  $R^{4c}$  each independently are selected from the group consisting of hydrogen, cyano,  $C_{1-4}alkyl$ , halo,  $-C(=O)H$ ,  $-NR^{6e}R^{6f}$ ,  $-O-C_{1-4}alkyl$ , and  $C_{1-4}alkyl$  substituted with one or more substituents each independently selected from the group  
20 consisting of hydroxyl, halo, and  $-NR^{6g}R^{6h}$ ;

$R^{6e}$  and  $R^{6f}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}alkyl$ , and  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$ , and hydroxyl;

- 25  $R^{6g}$  and  $R^{6h}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}alkyl$ , and  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$ , and hydroxyl;

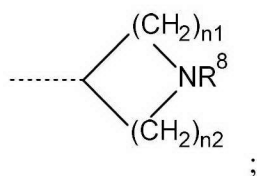
- $Het^1$  represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $S(=O)_p$  and N; or  $Het^1$  represents a bicyclic 8-, 9- or 10-membered saturated or partially  
30 saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $S(=O)_p$  and N;

each optionally substituted with one or two substituents each independently selected

from the group consisting of halo,  $\text{-NR}^{\text{9a}}\text{R}^{\text{9b}}$ ,  $\text{C}_{1-4}\text{alkyl}$ ,  $\text{-(C=O)-OR}^{\text{5h}}$ ,  $\text{-S(=O)}_2\text{-C}_{1-6}\text{alkyl}$ ,  $\text{-C}_{1-4}\text{alkyl-S(=O)}_2\text{-C}_{1-6}\text{alkyl}$ , hydroxyl,  $\text{-O-C}_{1-4}\text{alkyl}$ , cyano,  $\text{C}_{1-4}\text{alkyl}$  substituted with one or more halo atoms, and  $\text{C}_{1-4}\text{alkyl}$  substituted with one substituent selected from the group consisting of hydroxyl,  $\text{-NH}_2$ ,  $\text{-NH(C}_{1-4}\text{alkyl)}$  and  $\text{-N(C}_{1-4}\text{alkyl)}_2$ ; or two substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A;

R<sup>9a</sup> and R<sup>9b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

Het<sup>2</sup> represents



n1 represents 1 or 2;

n2 represents 1 or 2;

R<sup>8</sup> represents hydrogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

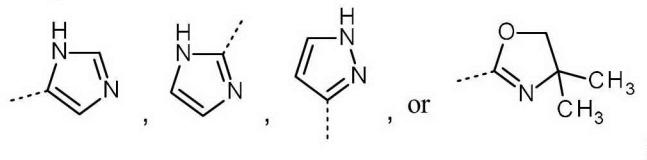
R<sup>5h</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

15 Ring A represents cyclobutyl, cyclopentyl, cyclohexyl, or a 4-, 5- or 6-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N; said cyclobutyl, cyclopentyl, cyclohexyl, or 4-, 5- or 6-membered saturated heterocyclyl is optionally substituted with one or two C<sub>1-4</sub>alkyl substituents, with one C<sub>1-4</sub>alkyl and one hydroxy substituent, or with one hydroxy  
20 substituent;

p represents 1 or 2;

Ar represents phenyl optionally substituted with one hydroxyl;

$R^7$  represents



25 and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein

Y represents  $\text{CR}^3$  or N;

L represents  $-\text{CH}(\text{C}_{1-4}\text{alkyl})-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}(\text{C}_{1-4}\text{alkyl})-$ ,  $-\text{CH}(\text{C}_{1-4}\text{alkyl})-\text{CH}(\text{C}_{1-4}\text{alkyl})-$ ,  $-\text{CHR}^{1a}-\text{X}-$ , or  $-\text{X}-\text{CHR}^{1c}-$ ;

X represents O, S, or  $\text{NR}^{1b}$ ;

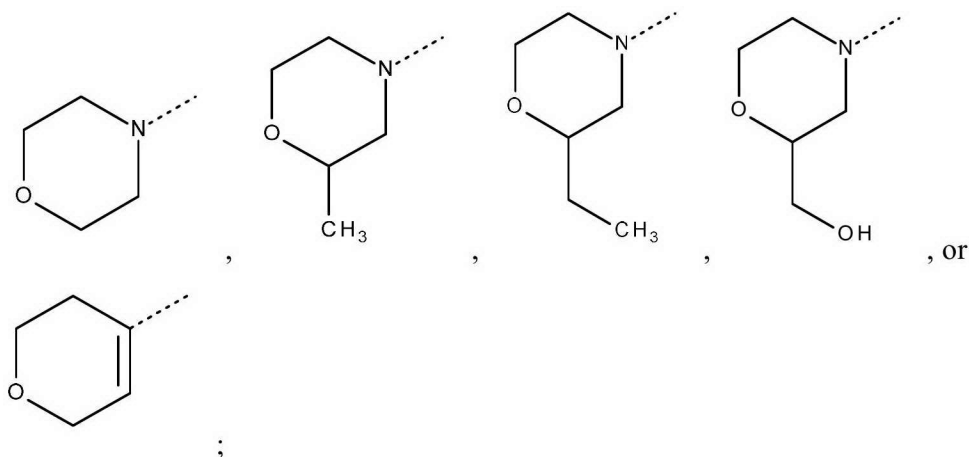
5  $\text{R}^{1a}$  represents  $\text{C}_{1-4}\text{alkyl}$ ;

$\text{R}^{1c}$  represents hydrogen or  $\text{C}_{1-4}\text{alkyl}$ ;

$\text{R}^{1b}$  represents hydrogen,  $\text{C}_{1-4}\text{alkyl}$ ,  $-\text{CH}_2-\text{C}(=\text{O})-\text{NR}^{6a}\text{R}^{6b}$ , or  $\text{C}_{1-4}\text{alkyl}$  substituted with one substituent selected from the group consisting of hydroxyl,  $-\text{O}-\text{C}_{1-4}\text{alkyl}$ , and  $-\text{NR}^{6c}\text{R}^{6d}$ ;

10 or  $\text{R}^{1b}$  is taken together with  $\text{R}^{1a}$  or  $\text{R}^{1c}$  to form  $-(\text{CH}_2)_3-$ ;  
or  $\text{R}^{1b}$  is taken together with  $\text{R}^{1c}$  to form  $-(\text{CH}_2)_2-$  or  $-(\text{CH}_2)_4-$ ;

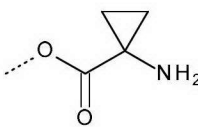
$\text{R}^2$  represents



15  $\text{R}^{6a}$  and  $\text{R}^{6b}$  each independently are selected from the group consisting of hydrogen and  $\text{C}_{1-4}\text{alkyl}$ ;

$\text{R}^{6c}$  and  $\text{R}^{6d}$  each independently are selected from the group consisting of hydrogen,  $\text{C}_{1-4}\text{alkyl}$ , and  $\text{C}_{1-4}\text{alkyl}$  substituted with one substituent selected from the group consisting of hydroxyl,  $-\text{NH}_2$ ,  $-\text{NH}(\text{C}_{1-4}\text{alkyl})$ , and  $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$ ;

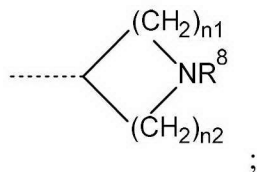
20  $\text{R}^3$  represents  $\text{R}^7$ ,  $-(\text{C}=\text{O})\text{H}$ ,  $-(\text{C}=\text{O})-\text{C}_{1-4}\text{alkyl}$ ,  $-(\text{C}=\text{O})-\text{NR}^{5a}\text{R}^{5b}$ ,  $-(\text{C}=\text{O})-\text{OR}^{5c}$ ,  $-(\text{C}=\text{O})-\text{Het}^1$ ,  $-(\text{C}=\text{O})-\text{NH}-\text{Het}^2$ ,  $\text{C}_{1-4}\text{alkyl}$ ,  $-\text{CH}=\text{N}-\text{OH}$ ,  $-\text{CH}(\text{OH})-\text{CH}_2-\text{NR}^{5d}\text{R}^{5e}$ ,  $-\text{CH}(\text{OH})-\text{CH}_2-\text{Het}^1$ ,  $-\text{CH}(\text{OH})-\text{C}_{1-4}\text{alkyl}$ ,  $-\text{C}(\text{OH})(\text{C}_{1-4}\text{alkyl})_2$ , halo, or  $\text{R}^3$  represents  $\text{C}_{1-4}\text{alkyl}$  substituted with one substituent selected from the group consisting of hydroxyl, fluoro,  $-\text{NR}^{5f}\text{R}^{5g}$ ,  $\text{Het}^1$ ,  $-\text{O}-\text{C}(=\text{O})-\text{CH}(\text{NH}_2)-\text{C}_{1-4}\text{alkyl}$ ,  $-\text{O}-\text{C}(=\text{O})-\text{CH}(\text{NH}_2)-\text{C}_{1-4}\text{alkyl}-\text{Ar}$ ,

25  ,  $-\text{O}-\text{C}_{1-4}\text{alkyl}-\text{OH}$ , and  $-\text{O}-\text{C}_{1-4}\text{alkyl}-\text{NH}_2$ ;

- $R^{5a}$  and  $R^{5b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl,  $-O-C_{1-4}$ alkyl,  $-S(=O)_2-NH_2$ ,  $-S(=O)_2-C_{1-4}$ alkyl,  $-S(=O)_2-C_{3-6}$ cycloalkyl,  $C_{1-4}$ alkyl substituted with one or more halo atoms, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of
- 5 hydroxyl,  $-O-C_{1-4}$ alkyl,  $-S(=O)_2-C_{1-4}$ alkyl,  $-O-C_{1-4}$ alkyl- $NH_2$ ,  $-O-C_{1-4}$ alkyl- $NH(C_{1-4}$ alkyl),  $-O-C_{1-4}$ alkyl- $N(C_{1-4}$ alkyl) $_2$ ,  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl) and  $-N(C_{1-4}$ alkyl) $_2$ ;
- $R^{5c}$  represents hydrogen or  $C_{1-4}$ alkyl;
- $R^{5d}$  and  $R^{5e}$  each independently are selected from the group consisting of hydrogen and  $C_{1-4}$ alkyl;
- 10  $R^{5f}$  and  $R^{5g}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkyl substituted with one or more halo atoms, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}$ alkyl,  $-S(=O)_2-C_{1-4}$ alkyl,  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl), and  $-N(C_{1-4}$ alkyl) $_2$ ;
- $R^{4a}$ ,  $R^{4b}$  and  $R^{4c}$  each independently are selected from the group consisting of
- 15 hydrogen, cyano,  $C_{1-4}$ alkyl, halo,  $-C(=O)H$ ,  $-NR^{6e}R^{6f}$ ,  $-O-C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, and  $-NR^{6g}R^{6h}$ ;
- $R^{6e}$  and  $R^{6f}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of
- 20  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl), and hydroxyl;
- $R^{6g}$  and  $R^{6h}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl), and hydroxyl;
- Het<sup>1</sup> represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated
- 25 heterocyclyl containing at least one heteroatom each independently selected from O, S,  $S(=O)_p$  and N; or Het<sup>1</sup> represents a bicyclic 8-, 9- or 10-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $S(=O)_p$  and N;
- each optionally substituted with one or two substituents each independently selected
- 30 from the group consisting of halo,  $-NR^{9a}R^{9b}$ ,  $C_{1-4}$ alkyl,  $-(C=O)-OR^{5h}$ ,  $-S(=O)_2-C_{1-6}$ alkyl,  $-C_{1-4}$ alkyl- $S(=O)_2-C_{1-6}$ alkyl, hydroxyl,  $-O-C_{1-4}$ alkyl, cyano,  $C_{1-4}$ alkyl substituted with one or more halo atoms, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl) and  $-N(C_{1-4}$ alkyl) $_2$ ; or two substituents on the same carbon atom of said heterocyclyl are taken together to form
- 35 together with the common carbon atom to which they are attached Ring A;

$R^{9a}$  and  $R^{9b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one or more halo atoms;

Het<sup>2</sup> represents



5  $n_1$  represents 1 or 2;

$n_2$  represents 1 or 2;

$R^8$  represents hydrogen,  $C_{1-4}$ alkyl, or  $C_{1-4}$ alkyl substituted with one or more halo atoms;

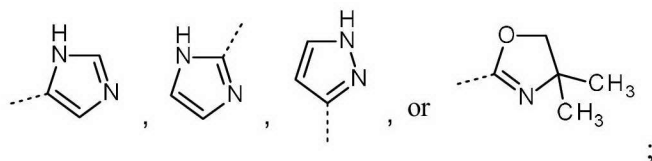
$R^{5h}$  represents hydrogen or  $C_{1-4}$ alkyl;

10 Ring A represents cyclobutyl, cyclopentyl, cyclohexyl, or a 4-, 5- or 6-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $S(=O)_p$  and N; said cyclobutyl, cyclopentyl, cyclohexyl, or 4-, 5- or 6-membered saturated heterocyclyl is optionally substituted with one or two  $C_{1-4}$ alkyl substituents, with one  $C_{1-4}$ alkyl and one hydroxy substituent, or with one hydroxy substituent;

15  $p$  represents 1 or 2;

Ar represents phenyl optionally substituted with one hydroxyl;

$R^7$  represents



20 and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein

25 Y represents  $CR^3$  or N;

L represents  $-CH(C_{1-4}alkyl)-CH_2-$ ,  $-CH_2-CH(C_{1-4}alkyl)-$ ,  $-CH(C_{1-4}alkyl)-CH(C_{1-4}alkyl)-$ ,  $-CHR^{1a}-X-$ , or  $-X-CHR^{1c}-$ ;

X represents O, S, or  $NR^{1b}$ ;

$R^{1a}$  represents  $C_{1-4}$ alkyl;

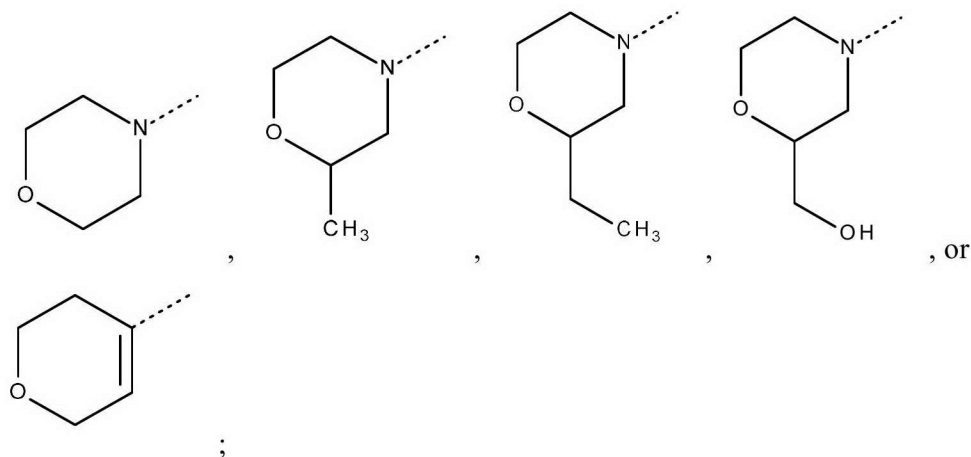
$R^{1c}$  represents hydrogen or  $C_{1-4}$ alkyl;

$R^{1b}$  represents hydrogen,  $C_{1-4}$ alkyl, or  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}$ alkyl, and  $-NR^{6c}R^{6d}$ ;

or  $R^{1b}$  is taken together with  $R^{1a}$  or  $R^{1c}$  to form  $-(CH_2)_3-$ ;

5 or  $R^{1b}$  is taken together with  $R^{1c}$  to form  $-(CH_2)_2-$  or  $-(CH_2)_4-$ ;

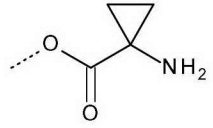
$R^2$  represents



10  $R^{6c}$  and  $R^{6d}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$ , and  $-N(C_{1-4}alkyl)_2$ ;

$R^3$  represents  $R^7$ ,  $-(C=O)H$ ,  $-(C=O)-C_{1-4}alkyl$ ,  $-(C=O)-NR^{5a}R^{5b}$ ,  $-(C=O)-OR^{5c}$ ,  $-C(=O)-Het^1$ ,  $-C(=O)-NH-Het^2$ ,  $C_{1-4}alkyl$ ,  $-CH=N-OH$ ,  $-CH(OH)-CH_2-NR^{5d}R^{5e}$ ,  $-CH(OH)-CH_2-Het^1$ ,  $-CH(OH)-C_{1-4}alkyl$ ,  $-C(OH)(C_{1-4}alkyl)_2$ , halo, or  $R^3$  represents  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl, fluoro,

15

$-NR^{5f}R^{5g}$ ,  $Het^1$ ,  $-O-(C=O)-CH(NH_2)-C_{1-4}alkyl$ , ,  $-O-C_{1-4}alkyl-OH$ , and  $-O-C_{1-4}alkyl-NH_2$ ;

$R^{5a}$  and  $R^{5b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-NH_2$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{3-6}cycloalkyl$ ,  $C_{1-4}alkyl$  substituted with one or more halo atoms, and  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-O-C_{1-4}alkyl-NH_2$ ,  $-O-C_{1-4}alkyl-NH(C_{1-4}alkyl)$ ,  $-O-C_{1-4}alkyl-N(C_{1-4}alkyl)_2$ ,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$  and  $-N(C_{1-4}alkyl)_2$ ;

20

$R^{5c}$  represents hydrogen or  $C_{1-4}$ alkyl;



$R^{5d}$  and  $R^{5e}$  each independently are selected from the group consisting of hydrogen and  $C_{1-4}$ alkyl;

$R^{5f}$  and  $R^{5g}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkyl substituted with one or more halo atoms, and

- 5  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}$ alkyl,  $-S(=O)_2-C_{1-4}$ alkyl,  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl), and  $-N(C_{1-4}$ alkyl) $_2$ ;

- $R^{4a}$ ,  $R^{4b}$  and  $R^{4c}$  each independently are selected from the group consisting of hydrogen, cyano,  $C_{1-4}$ alkyl, halo,  $-C(=O)H$ ,  $-NR^{6e}R^{6f}$ ,  $-O-C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one or more substituents each independently selected from the group  
10 consisting of hydroxyl, halo, and  $-NR^{6g}R^{6h}$ ;

$R^{6e}$  and  $R^{6f}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl), and hydroxyl;

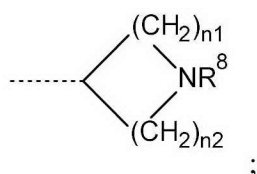
- $R^{6g}$  and  $R^{6h}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting  
15 of  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl), and hydroxyl;

- Het<sup>1</sup> represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $S(=O)_p$  and N; or Het<sup>1</sup> represents a bicyclic 8-, 9- or 10-membered saturated or partially  
20 saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $S(=O)_p$  and N;

- each optionally substituted with one or two substituents each independently selected from the group consisting of halo,  $-NR^{9a}R^{9b}$ ,  $C_{1-4}$ alkyl,  $-(C=O)-OR^{5h}$ ,  $-S(=O)_2-C_{1-6}$ alkyl,  $-C_{1-4}$ alkyl- $S(=O)_2-C_{1-6}$ alkyl, hydroxyl,  $-O-C_{1-4}$ alkyl, cyano,  $C_{1-4}$ alkyl substituted with  
25 one or more halo atoms, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl) and  $-N(C_{1-4}$ alkyl) $_2$ ; or two substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A;

- $R^{9a}$  and  $R^{9b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one or more halo atoms;  
30

Het<sup>2</sup> represents



n1 represents 1 or 2;

n2 represents 1 or 2;

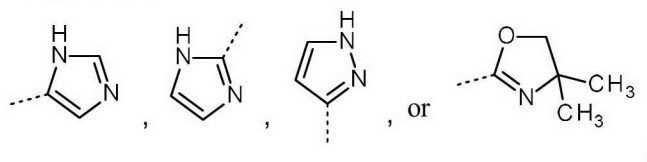
R<sup>8</sup> represents hydrogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

R<sup>5h</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

- 5 Ring A represents cyclobutyl, cyclopentyl, cyclohexyl, or a 4-, 5- or 6-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N; said cyclobutyl, cyclopentyl, cyclohexyl, or 4-, 5- or 6-membered saturated heterocyclyl is optionally substituted with one or two C<sub>1-4</sub>alkyl substituents, with one C<sub>1-4</sub>alkyl and one hydroxy substituent, or with one hydroxy
- 10 substituent;

p represents 1 or 2;

R<sup>7</sup> represents



- and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates
- 15 thereof.

In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein

Y represents CR<sup>3</sup> or N;

- 20 L represents -CH(C<sub>1-4</sub>alkyl)-CH<sub>2</sub>-, -CH<sub>2</sub>-CH(C<sub>1-4</sub>alkyl)-, -CH(C<sub>1-4</sub>alkyl)-CH(C<sub>1-4</sub>alkyl)-, -CHR<sup>1a</sup>-X-, or -X-CHR<sup>1c</sup>-;

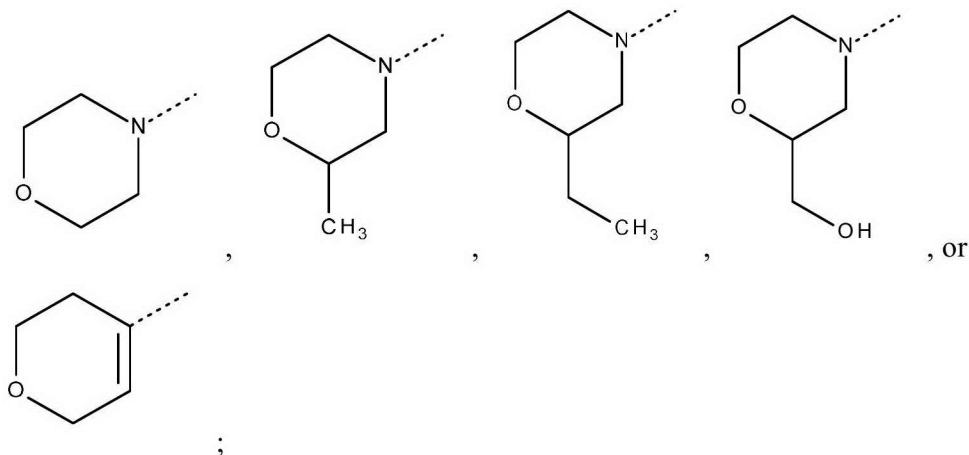
X represents O, S, or NR<sup>1b</sup>;

R<sup>1a</sup> represents hydrogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkyl substituted with one -OH;

R<sup>1c</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

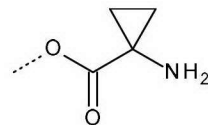
- 25 R<sup>1b</sup> represents hydrogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -O-C<sub>1-4</sub>alkyl, and -NR<sup>6c</sup>R<sup>6d</sup>;
- or R<sup>1b</sup> is taken together with R<sup>1a</sup> or R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>3</sub>-;
- or R<sup>1b</sup> is taken together with R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>2</sub>- or -(CH<sub>2</sub>)<sub>4</sub>-;

R<sup>2</sup> represents



R<sup>6c</sup> and R<sup>6d</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl), and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>;

R<sup>3</sup> represents R<sup>7</sup>, -(C=O)H, -(C=O)-C<sub>1-4</sub>alkyl, -(C=O)-NR<sup>5a</sup>R<sup>5b</sup>, -(C=O)-OR<sup>5c</sup>, -C(=O)-Het<sup>1</sup>, -C(=O)-NH-Het<sup>2</sup>, -C(=O)-NH-C<sub>1-4</sub>alkyl-Het<sup>1</sup>, -C(=O)-N(C<sub>1-4</sub>alkyl)-C<sub>1-4</sub>alkyl-Het<sup>1</sup>, -C(=O)-N(C<sub>1-4</sub>alkyl)-Het<sup>2</sup>, C<sub>1-4</sub>alkyl, -CH=N-OH, -CH(OH)-CH<sub>2</sub>-NR<sup>5d</sup>R<sup>5e</sup>, -CH(OH)-CH<sub>2</sub>-Het<sup>1</sup>, -CH(OH)-C<sub>1-4</sub>alkyl, -C(OH)(C<sub>1-4</sub>alkyl)<sub>2</sub>, halo, or R<sup>3</sup> represents C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of



hydroxyl, fluoro, -NR<sup>5f</sup>R<sup>5g</sup>, Het<sup>1</sup>, -O-(C=O)-CH(NH<sub>2</sub>)-C<sub>1-4</sub>alkyl, O-C<sub>1-4</sub>alkyl-OH, and -O-C<sub>1-4</sub>alkyl-NH<sub>2</sub>;

R<sup>5a</sup> and R<sup>5b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, -O-C<sub>1-4</sub>alkyl, -S(=O)<sub>2</sub>-NH<sub>2</sub>, -S(=O)<sub>2</sub>-C<sub>1-4</sub>alkyl, -S(=O)<sub>2</sub>-C<sub>3-6</sub>cycloalkyl, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -O-C<sub>1-4</sub>alkyl, -S(=O)<sub>2</sub>-C<sub>1-4</sub>alkyl, -O-C<sub>1-4</sub>alkyl-NH<sub>2</sub>, -O-C<sub>1-4</sub>alkyl-NH(C<sub>1-4</sub>alkyl), -O-C<sub>1-4</sub>alkyl-N(C<sub>1-4</sub>alkyl)<sub>2</sub>, -(C=O)-O-C<sub>1-4</sub>alkyl, -(C=O)-OH, -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl) and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>;

R<sup>5c</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

R<sup>5d</sup> and R<sup>5e</sup> each independently are selected from the group consisting of hydrogen and C<sub>1-4</sub>alkyl;

$R^{5f}$  and  $R^{5g}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkyl substituted with one or more halo atoms, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}$ alkyl,  $-S(=O)_2-C_{1-4}$ alkyl,  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl), and  $-N(C_{1-4}$ alkyl) $_2$ ;

- 5  $R^{4a}$ ,  $R^{4b}$  and  $R^{4c}$  each independently are selected from the group consisting of hydrogen, cyano,  $C_{1-4}$ alkyl, halo,  $-C(=O)H$ ,  $-NR^{6e}R^{6f}$ ,  $-O-C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, and  $-NR^{6g}R^{6h}$ ;

- 10  $R^{6e}$  and  $R^{6f}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl), and hydroxyl;

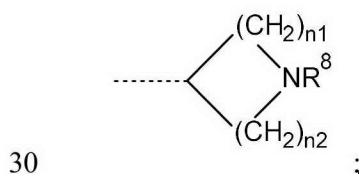
$R^{6g}$  and  $R^{6h}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl), and hydroxyl;

- 15  $Het^1$  represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $S(=O)_p$  and N; or  $Het^1$  represents a bicyclic 8-, 9- or 10-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $S(=O)_p$  and N;

- 20 each optionally substituted with one or two substituents each independently selected from the group consisting of halo,  $-NR^{9a}R^{9b}$ ,  $C_{1-4}$ alkyl,  $-(C=O)-OR^{5h}$ ,  $-S(=O)_2-C_{1-6}$ alkyl,  $-C_{1-4}$ alkyl- $S(=O)_2-C_{1-6}$ alkyl, hydroxyl,  $-O-C_{1-4}$ alkyl, cyano,  $C_{1-4}$ alkyl substituted with one or more halo atoms, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl) and  $-N(C_{1-4}$ alkyl) $_2$ ; or two substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A;

$R^{9a}$  and  $R^{9b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one or more halo atoms;

$Het^2$  represents



$n1$  represents 1 or 2;

$n2$  represents 1 or 2;

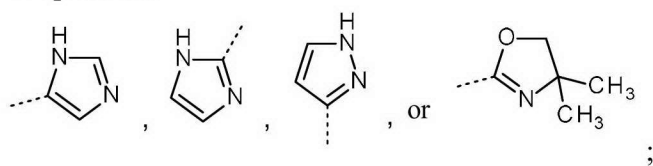
$R^8$  represents hydrogen,  $C_{1-4}$ alkyl, or  $C_{1-4}$ alkyl substituted with one or more halo atoms;

$R^{5h}$  represents hydrogen or  $C_{1-4}$ alkyl;

- Ring A represents cyclobutyl, cyclopentyl, cyclohexyl, or a 4-, 5- or 6-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $S(=O)_p$  and N; said cyclobutyl, cyclopentyl, cyclohexyl, or 4-, 5- or 6-membered saturated heterocyclyl is optionally substituted with one or two  $C_{1-4}$ alkyl substituents, with one  $C_{1-4}$ alkyl and one hydroxy substituent, or with one hydroxy substituent;

p represents 1 or 2;

- 10  $R^7$  represents



and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

- 15 In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein

Y represents  $CR^3$  or N;

L represents  $-CH(C_{1-4}alkyl)-CH_2-$ ,  $-CHR^{1a}-X-$ , or  $-X-CHR^{1c}-$ ;

X represents O, S, or  $NR^{1b}$ ;

- 20  $R^{1a}$  represents hydrogen,  $C_{1-4}$ alkyl, or  $C_{1-4}$ alkyl substituted with one -OH;

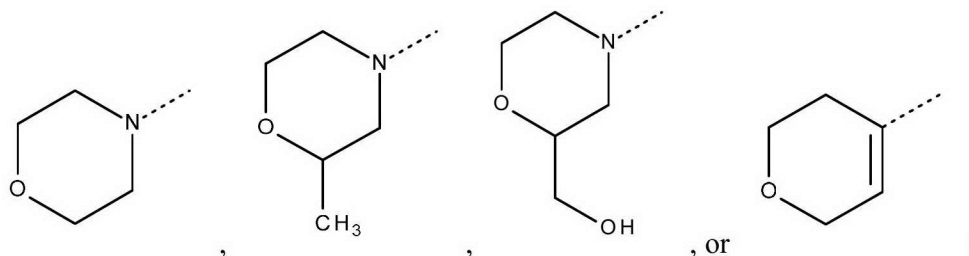
$R^{1c}$  represents hydrogen or  $C_{1-4}$ alkyl;

$R^{1b}$  represents hydrogen or  $C_{1-4}$ alkyl;

or  $R^{1b}$  is taken together with  $R^{1a}$  or  $R^{1c}$  to form  $-(CH_2)_3-$ ;

or  $R^{1b}$  is taken together with  $R^{1c}$  to form  $-(CH_2)_2-$ ;

- 25  $R^2$  represents



R<sup>3</sup> represents R<sup>7</sup>, -(C=O)H, -(C=O)-NR<sup>5a</sup>R<sup>5b</sup>, -(C=O)-OR<sup>5c</sup>, -(C=O)-Het<sup>1</sup>, -(C=O)-NH-Het<sup>2</sup>, -(C=O)-NH-C<sub>1-4</sub>alkyl-Het<sup>1</sup>, -(C=O)-N(C<sub>1-4</sub>alkyl)-Het<sup>2</sup>, C<sub>1-4</sub>alkyl, -CH=N-OH, -CH(OH)-CH<sub>2</sub>-NR<sup>5d</sup>R<sup>5e</sup>, -CH(OH)-CH<sub>2</sub>-Het<sup>1</sup>, -CH(OH)-C<sub>1-4</sub>alkyl, halo, or R<sup>3</sup> represents C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, fluoro, -NR<sup>5f</sup>R<sup>5g</sup>, Het<sup>1</sup>, and -O-C<sub>1-4</sub>alkyl-OH;

R<sup>5a</sup> and R<sup>5b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, -O-C<sub>1-4</sub>alkyl, -S(=O)<sub>2</sub>-NH<sub>2</sub>, -S(=O)<sub>2</sub>-C<sub>3-6</sub>cycloalkyl, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -O-C<sub>1-4</sub>alkyl, -O-C<sub>1-4</sub>alkyl-NH<sub>2</sub>, -O-C<sub>1-4</sub>alkyl-NH(C<sub>1-4</sub>alkyl), -(C=O)-O-C<sub>1-4</sub>alkyl, -(C=O)-OH, -NH(C<sub>1-4</sub>alkyl) and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>;

R<sup>5c</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

R<sup>5d</sup> and R<sup>5e</sup> each independently are selected from the group consisting of hydrogen and C<sub>1-4</sub>alkyl;

R<sup>5f</sup> and R<sup>5g</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -O-C<sub>1-4</sub>alkyl, and -S(=O)<sub>2</sub>-C<sub>1-4</sub>alkyl;

R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> each independently are selected from the group consisting of hydrogen, cyano, C<sub>1-4</sub>alkyl, halo, -(C=O)H, -NR<sup>6e</sup>R<sup>6f</sup>, -O-C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, and -NR<sup>6g</sup>R<sup>6h</sup>;

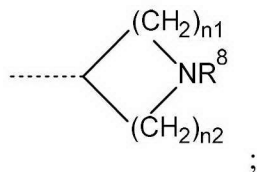
R<sup>6e</sup> and R<sup>6f</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one hydroxyl substituent;

Het<sup>1</sup> represents a monocyclic 4-, 5-, 6- or 7-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, S(=O)<sub>p</sub> and N; or Het<sup>1</sup> represents a bicyclic 9-membered saturated or partially saturated heterocyclyl containing at least one N-atom;

each optionally substituted with one or two substituents each independently selected from the group consisting of -NR<sup>9a</sup>R<sup>9b</sup>, C<sub>1-4</sub>alkyl, -(C=O)-OR<sup>5h</sup>, hydroxyl, -O-C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl and -NH(C<sub>1-4</sub>alkyl); or two substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A;

R<sup>9a</sup> and R<sup>9b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

Het<sup>2</sup> represents



5 n1 represents 1;

n2 represents 1 or 2;

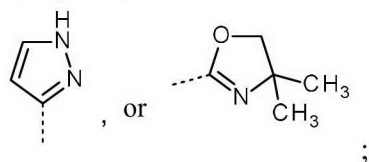
R<sup>8</sup> represents hydrogen, or C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

R<sup>5h</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

10 Ring A represents a 4-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, and S(=O)<sub>p</sub>;

p represents 2;

R<sup>7</sup> represents



15 and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein

Y represents CR<sup>3</sup> or N;

20 L represents -CHR<sup>1a</sup>-X-, or -X-CHR<sup>1c</sup>-;

X represents O, S, or NR<sup>1b</sup>;

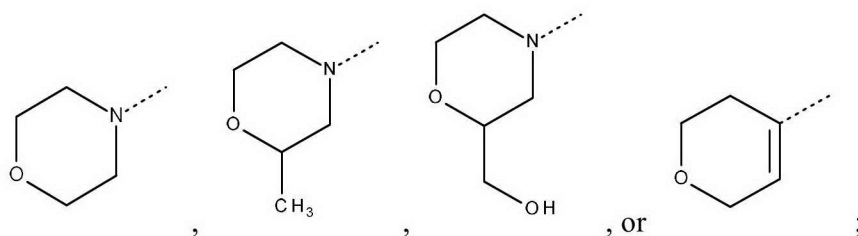
R<sup>1a</sup> represents C<sub>1-4</sub>alkyl;

R<sup>1c</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

R<sup>1b</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

25 or R<sup>1b</sup> is taken together with R<sup>1a</sup> or R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>3</sub>-;

R<sup>2</sup> represents



- R<sup>3</sup> represents R<sup>7</sup>, -(C=O)H, -(C=O)-NR<sup>5a</sup>R<sup>5b</sup>, -(C=O)-OR<sup>5c</sup>, -C(=O)-Het<sup>1</sup>, -C(=O)-NH-Het<sup>2</sup>, C<sub>1-4</sub>alkyl, -CH=N-OH, -CH(OH)-CH<sub>2</sub>-NR<sup>5d</sup>R<sup>5e</sup>, -CH(OH)-CH<sub>2</sub>-Het<sup>1</sup>, -CH(OH)-C<sub>1-4</sub>alkyl, halo, or R<sup>3</sup> represents C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -NR<sup>5f</sup>R<sup>5g</sup>, Het<sup>1</sup>, and -O-C<sub>1-4</sub>alkyl-OH;

- R<sup>5a</sup> and R<sup>5b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, -O-C<sub>1-4</sub>alkyl, -S(=O)<sub>2</sub>-NH<sub>2</sub>, -S(=O)<sub>2</sub>-C<sub>3-6</sub>cycloalkyl, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -O-C<sub>1-4</sub>alkyl, -O-C<sub>1-4</sub>alkyl-NH<sub>2</sub>, -O-C<sub>1-4</sub>alkyl-NH(C<sub>1-4</sub>alkyl), -NH(C<sub>1-4</sub>alkyl) and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>;

R<sup>5c</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

- R<sup>5d</sup> and R<sup>5e</sup> each independently are selected from the group consisting of hydrogen and C<sub>1-4</sub>alkyl;

R<sup>5f</sup> and R<sup>5g</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -O-C<sub>1-4</sub>alkyl, and -S(=O)<sub>2</sub>-C<sub>1-4</sub>alkyl;

- R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> each independently are selected from the group consisting of hydrogen, cyano, C<sub>1-4</sub>alkyl, halo, -C(=O)H, -NR<sup>6e</sup>R<sup>6f</sup>, -O-C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, and -NR<sup>6g</sup>R<sup>6h</sup>;

- R<sup>6e</sup> and R<sup>6f</sup> each independently are selected from the group consisting of hydrogen, and C<sub>1-4</sub>alkyl substituted with one -NH<sub>2</sub> substituent;

R<sup>6g</sup> and R<sup>6h</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one hydroxyl substituent;

- Het<sup>1</sup> represents a monocyclic 4-, 5-, or 6-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, S(=O)<sub>p</sub> and N; or Het<sup>1</sup> represents a bicyclic 9-membered partially saturated heterocyclyl containing at least

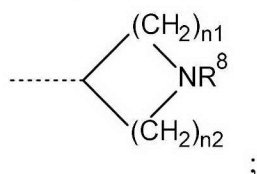


one N-atom;

each optionally substituted with one or two substituents each independently selected from the group consisting of  $\text{-NR}^{\text{9a}}\text{R}^{\text{9b}}$ ,  $\text{C}_{1-4}\text{alkyl}$ ,  $\text{-(C=O)-OR}^{\text{5h}}$ , hydroxyl,  $\text{-O-C}_{1-4}\text{alkyl}$ ,  $\text{C}_{1-4}\text{alkyl}$  substituted with one or more halo atoms, and  $\text{C}_{1-4}\text{alkyl}$  substituted with one substituent selected from the group consisting of hydroxyl, and  $\text{-NH(C}_{1-4}\text{alkyl)}$ ; or two substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A;

R<sup>9a</sup> and R<sup>9b</sup> each independently are selected from the group consisting of hydrogen, and C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

10 Het<sup>2</sup> represents



$n_1$  represents 1;

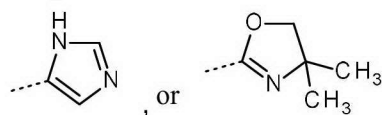
$n_2$  represents 1;



R<sup>8</sup> represents C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

15 R<sup>5h</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

Ring A represents a 4-membered saturated heterocyclcyl containing at least one heteroatom each independently selected from O and S(=O)<sub>p</sub>;

p represents 2;

 $R^7$  represents

20 , or ; and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

Another embodiment of the present invention relates to those compounds of Formula

(I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments wherein one or more of the following restrictions apply:

(i) L represents  $-\text{CHR}^{1a}-\text{X}-$ , or  $-\text{X}-\text{CHR}^{1c}-$ ;

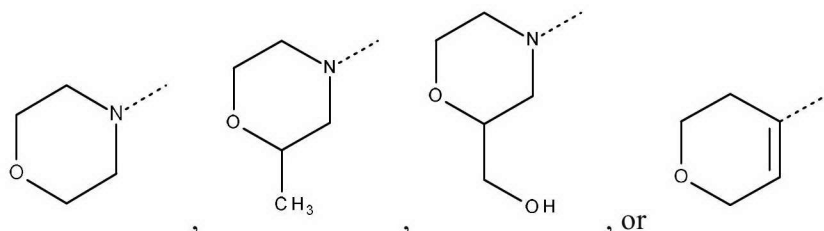
(ii) R<sup>1a</sup> represents C<sub>1-4</sub>alkyl;

R<sup>1c</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

30 R<sup>1b</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

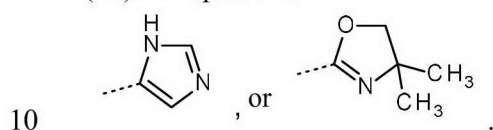
or R<sup>1b</sup> is taken together with R<sup>1a</sup> or R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>3</sub>-;

(iii) R<sup>2</sup> represents



- (iv) R<sup>3</sup> represents R<sup>7</sup>, -(C=O)H, -(C=O)-NR<sup>5a</sup>R<sup>5b</sup>, -(C=O)-OR<sup>5c</sup>, -(C=O)-Het<sup>1</sup>, -(C=O)-NH-Het<sup>2</sup>, C<sub>1-4</sub>alkyl, -CH=N-OH, -CH(OH)-CH<sub>2</sub>-NR<sup>5d</sup>R<sup>5e</sup>, -CH(OH)-CH<sub>2</sub>-Het<sup>1</sup>, -CH(OH)-C<sub>1-4</sub>alkyl, halo, or R<sup>3</sup> represents C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -NR<sup>5f</sup>R<sup>5g</sup>, Het<sup>1</sup>, and -O-C<sub>1-4</sub>alkyl-OH;
- (v) R<sup>5a</sup> and R<sup>5b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, -O-C<sub>1-4</sub>alkyl, -S(=O)<sub>2</sub>-NH<sub>2</sub>, -S(=O)<sub>2</sub>-C<sub>3-6</sub>cycloalkyl, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -O-C<sub>1-4</sub>alkyl, -O-C<sub>1-4</sub>alkyl-NH<sub>2</sub>, -O-C<sub>1-4</sub>alkyl-NH(C<sub>1-4</sub>alkyl), -NH(C<sub>1-4</sub>alkyl) and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>;
- (vi) R<sup>5f</sup> and R<sup>5g</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -O-C<sub>1-4</sub>alkyl, and -S(=O)<sub>2</sub>-C<sub>1-4</sub>alkyl;
- (vii) R<sup>6e</sup> and R<sup>6f</sup> each independently are selected from the group consisting of hydrogen, and C<sub>1-4</sub>alkyl substituted with one -NH<sub>2</sub> substituent;
- (viii) R<sup>6g</sup> and R<sup>6h</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one hydroxyl substituent;
- (ix) Het<sup>1</sup> represents a monocyclic 4-, 5-, or 6-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, S(=O)<sub>p</sub> and N; or Het<sup>1</sup> represents a bicyclic 9-membered partially saturated heterocyclyl containing at least one N-atom;
- each optionally substituted with one or two substituents each independently selected from the group consisting of -NR<sup>9a</sup>R<sup>9b</sup>, C<sub>1-4</sub>alkyl, -(C=O)-OR<sup>5h</sup>, hydroxyl, -O-C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, and -NH(C<sub>1-4</sub>alkyl); or two substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A;

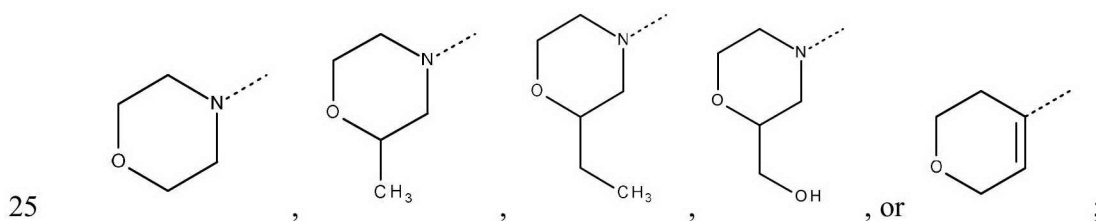
- (x)  $R^{9a}$  and  $R^{9b}$  each independently are selected from the group consisting of hydrogen, and  $C_{1-4}$ alkyl substituted with one or more halo atoms;
- (xi)  $n1$  represents 1;  
 $n2$  represents 1;
- 5 (xii)  $R^8$  represents  $C_{1-4}$ alkyl substituted with one or more halo atoms;
- (xiii) Ring A represents a 4-membered saturated heterocyclcyl containing at least one heteroatom each independently selected from O and  $S(=O)_p$ ;
- (xiv)  $p$  represents 2;
- (xv)  $R^7$  represents



In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein

- Y represents  $CR^3$  or N;
- 15 L represents  $-CH(C_{1-4}alkyl)-CH_2-$ ,  $-CH_2-CH(C_{1-4}alkyl)-$ ,  $-CH(C_{1-4}alkyl)-CH(C_{1-4}alkyl)-$ ,  $-CHR^{1a}-X-$ , or  $-X-CHR^{1c}-$ ;
- X represents O, S, or  $NR^{1b}$ ;
- $R^{1a}$  represents  $C_{1-4}$ alkyl;
- $R^{1c}$  represents hydrogen or  $C_{1-4}$ alkyl;
- 20  $R^{1b}$  represents hydrogen,  $C_{1-4}$ alkyl,  $-CH_2-C(=O)-NR^{6a}R^{6b}$ , or  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}alkyl$ , and  $-NR^{6c}R^{6d}$ ;
- or  $R^{1b}$  is taken together with  $R^{1a}$  or  $R^{1c}$  to form  $-(CH_2)_3-$ ;

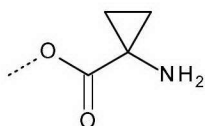
$R^2$  represents



$R^{6a}$  and  $R^{6b}$  each independently are selected from the group consisting of hydrogen and  $C_{1-4}$ alkyl;

$R^{6c}$  and  $R^{6d}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$ , and  $-N(C_{1-4}alkyl)_2$ ;

- 5  $R^3$  represents  $R^7$ ,  $-(C=O)H$ ,  $-(C=O)-C_{1-4}alkyl$ ,  $-(C=O)-NR^{5a}R^{5b}$ ,  $-(C=O)-OR^{5c}$ ,  $-(C=O)-Het^1$ ,  $-(C=O)-NH-Het^2$ ,  $C_{1-4}alkyl$ ,  $-CH=N-OH$ ,  $-CH(OH)-CH_2-NR^{5d}R^{5e}$ ,  $-CH(OH)-CH_2-Het^1$ ,  $-CH(OH)-C_{1-4}alkyl$ ,  $-C(OH)(C_{1-4}alkyl)_2$ , halo, or  $R^3$  represents  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of hydroxyl, fluoro,  $-NR^{5f}R^{5g}$ ,  $Het^1$ ,  $-O-(C=O)-CH(NH_2)-C_{1-4}alkyl$ ,  $-O-(C=O)-CH(NH_2)-C_{1-4}alkyl-Ar$ ,



,  $-O-C_{1-4}alkyl-OH$ , and  $-O-C_{1-4}alkyl-NH_2$ ;

- 10  $R^{5a}$  and  $R^{5b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-NH_2$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{3-6}cycloalkyl$ ,  $C_{1-4}alkyl$  substituted with one or more halo atoms, and  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-O-C_{1-4}alkyl-NH_2$ ,  $-O-C_{1-4}alkyl-NH(C_{1-4}alkyl)$ ,  $-O-C_{1-4}alkyl-N(C_{1-4}alkyl)_2$ ,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$  and  $-N(C_{1-4}alkyl)_2$ ;

$R^{5c}$  represents hydrogen or  $C_{1-4}alkyl$ ;

$R^{5d}$  and  $R^{5e}$  each independently are selected from the group consisting of hydrogen and  $C_{1-4}alkyl$ ;

- 20  $R^{5f}$  and  $R^{5g}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}alkyl$ ,  $C_{1-4}alkyl$  substituted with one or more halo atoms, and  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$ , and  $-N(C_{1-4}alkyl)_2$ ;

- 25  $R^{4a}$ ,  $R^{4b}$  and  $R^{4c}$  each independently are selected from the group consisting of hydrogen, cyano,  $C_{1-4}alkyl$ , halo,  $-(C=O)H$ ,  $-NR^{6e}R^{6f}$ ,  $-O-C_{1-4}alkyl$ , and  $C_{1-4}alkyl$  substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, and  $-NR^{6g}R^{6h}$ ;

$R^{6e}$  and  $R^{6f}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}alkyl$ , and  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$ , and hydroxyl;

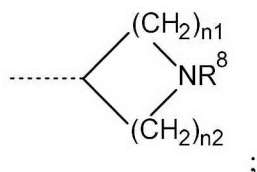
- 30  $R^{6g}$  and  $R^{6h}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}alkyl$ , and  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$ , and hydroxyl;

Het<sup>1</sup> represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N;

- each optionally substituted with one or two substituents each independently selected  
 5 from the group consisting of halo, -NR<sup>9a</sup>R<sup>9b</sup>, C<sub>1-4</sub>alkyl, -(C=O)-OR<sup>5h</sup>, -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -C<sub>1-4</sub>alkyl-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, hydroxyl, -O-C<sub>1-4</sub>alkyl, cyano, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl) and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>; or two substituents on the same carbon atom of said heterocyclyl are taken together to form  
 10 together with the common carbon atom to which they are attached Ring A;

R<sup>9a</sup> and R<sup>9b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

Het<sup>2</sup> represents



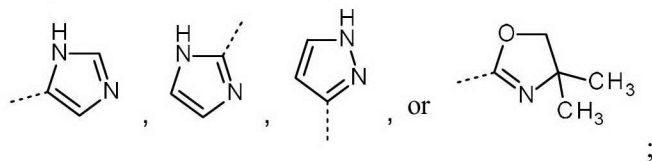
- 15 n<sub>1</sub> represents 1 or 2;  
 n<sub>2</sub> represents 1 or 2;  
 R<sup>8</sup> represents hydrogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

- Ring A represents cyclobutyl, cyclopentyl, cyclohexyl, or a 4-, 5- or 6-membered saturated heterocyclyl containing at least one heteroatom each independently selected  
 20 from O, S, S(=O)<sub>p</sub> and N; said cyclobutyl, cyclopentyl, cyclohexyl, or 4-, 5- or 6-membered saturated heterocyclyl is optionally substituted with one or two C<sub>1-4</sub>alkyl substituents, with one C<sub>1-4</sub>alkyl and one hydroxy substituent, or with one hydroxy substituent;

p represents 1 or 2;

- 25 Ar represents phenyl optionally substituted with one hydroxyl;

R<sup>7</sup> represents



and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein

Y represents  $\text{CR}^3$ ;

5 L represents  $-\text{CHR}^{1a}-\text{X}-$  or  $-\text{X}-\text{CHR}^{1c}-$ ;

X represents O, S, or  $\text{NR}^{1b}$ ;

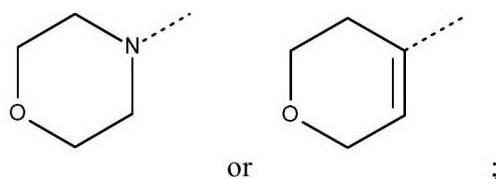
$\text{R}^{1a}$  represents hydrogen or  $\text{C}_{1-4}$ alkyl; in particular  $\text{C}_{1-4}$ alkyl;

$\text{R}^{1c}$  represents hydrogen or  $\text{C}_{1-4}$ alkyl;

$\text{R}^{1b}$  represents hydrogen or  $\text{C}_{1-4}$ alkyl;

10 or  $\text{R}^{1b}$  is taken together with  $\text{R}^{1c}$  to form  $-(\text{CH}_2)_3-$ ;

$\text{R}^2$  represents



$\text{R}^3$  represents  $-(\text{C}=\text{O})\text{H}$ ,  $-(\text{C}=\text{O})-\text{C}_{1-4}$ alkyl,  $-(\text{C}=\text{O})-\text{NR}^{5a}\text{R}^{5b}$ ,  $-(\text{C}=\text{O})-\text{OR}^{5c}$ ,  $-(\text{C}=\text{O})-$

15  $\text{Het}^1$ ,  $-(\text{C}=\text{O})-\text{NH}-\text{Het}^2$  or  $\text{R}^3$  represents  $\text{C}_{1-4}$ alkyl substituted with one  $-\text{NR}^{5f}\text{R}^{5g}$  substituent;

$\text{R}^{5a}$  and  $\text{R}^{5b}$  each independently are selected from the group consisting of hydrogen,  $\text{C}_{1-4}$ alkyl,  $-\text{O}-\text{C}_{1-4}$ alkyl,  $-\text{S}(=\text{O})_2-\text{NH}_2$ ,  $-\text{S}(=\text{O})_2-\text{C}_{1-4}$ alkyl,  $-\text{S}(=\text{O})_2-\text{C}_{3-6}$ cycloalkyl,  $\text{C}_{1-4}$ alkyl substituted with one or more halo atoms, and

20  $\text{C}_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-\text{O}-\text{C}_{1-4}$ alkyl,  $-\text{S}(=\text{O})_2-\text{C}_{1-4}$ alkyl,  $-\text{O}-\text{C}_{1-4}$ alkyl- $\text{NH}_2$ ,  $-\text{O}-\text{C}_{1-4}$ alkyl- $\text{NH}(\text{C}_{1-4}$ alkyl),  $-\text{O}-\text{C}_{1-4}$ alkyl- $\text{N}(\text{C}_{1-4}$ alkyl) $_2$ ,  $-\text{NH}_2$ ,  $-\text{NH}(\text{C}_{1-4}$ alkyl) and  $-\text{N}(\text{C}_{1-4}$ alkyl) $_2$ ;

$\text{R}^{5c}$  represents hydrogen or  $\text{C}_{1-4}$ alkyl;

$\text{R}^{5f}$  and  $\text{R}^{5g}$  each independently are selected from the group consisting of hydrogen,  $\text{C}_{1-4}$ alkyl, and  $\text{C}_{1-4}$ alkyl substituted with one hydroxyl substituent;

25  $\text{R}^{4a}$ ,  $\text{R}^{4b}$  and  $\text{R}^{4c}$  each independently are selected from the group consisting of hydrogen, cyano,  $\text{C}_{1-4}$ alkyl, halo,  $-(\text{C}=\text{O})\text{H}$ ,  $-\text{NR}^{6e}\text{R}^{6f}$ ,  $-\text{O}-\text{C}_{1-4}$ alkyl, and  $\text{C}_{1-4}$ alkyl substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, and  $-\text{NR}^{6g}\text{R}^{6h}$ ;

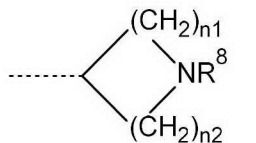
30  $\text{R}^{6e}$  and  $\text{R}^{6f}$  each independently are selected from the group consisting of hydrogen,  $\text{C}_{1-4}$ alkyl, and  $\text{C}_{1-4}$ alkyl substituted with one substituent selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{NH}(\text{C}_{1-4}$ alkyl), and hydroxyl;

$R^{6g}$  and  $R^{6h}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$ , and hydroxyl;

Het<sup>1</sup> represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N;

each optionally substituted with one or two substituents each independently selected from the group consisting of halo,  $-NR^{9a}R^{9b}$ ,  $C_{1-4}alkyl$ ,  $-(C=O)-OR^{5h}$ ,  $-S(=O)_2-C_{1-6}alkyl$ ,  $-C_{1-4}alkyl-S(=O)_2-C_{1-6}alkyl$ , hydroxyl,  $-O-C_{1-4}alkyl$ , cyano,  $C_{1-4}alkyl$  substituted with one or more halo atoms, and  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of hydroxyl,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$  and  $-N(C_{1-4}alkyl)_2$ ; or two substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A;

$R^{9a}$  and  $R^{9b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}alkyl$ , and  $C_{1-4}alkyl$  substituted with one or more halo atoms;



Het<sup>2</sup> represents ;

$n_1$  represents 1 or 2;

$n_2$  represents 1 or 2;

$R^8$  represents hydrogen,  $C_{1-4}alkyl$ , or  $C_{1-4}alkyl$  substituted with one or more halo atoms;

$R^{5h}$  represents hydrogen or  $C_{1-4}alkyl$ ;

Ring A represents cyclobutyl, cyclopentyl, cyclohexyl, or a 4-, 5- or 6-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N; said cyclobutyl, cyclopentyl, cyclohexyl, or 4-, 5- or 6-membered saturated heterocyclyl is optionally substituted with one or two  $C_{1-4}alkyl$  substituents, with one  $C_{1-4}alkyl$  and one hydroxy substituent, or with one hydroxy substituent;

$p$  represents 1 or 2;

and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

30

In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein

Y represents  $\text{CR}^3$ ;

L represents  $-\text{CHR}^{1a}-\text{X}-$  or  $-\text{X}-\text{CHR}^{1c}-$ ;

X represents  $\text{NR}^{1b}$ ;

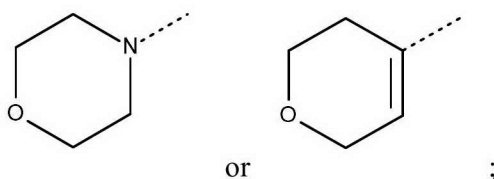
$\text{R}^{1a}$  represents hydrogen or  $\text{C}_{1-4}$ alkyl; in particular  $\text{C}_{1-4}$ alkyl;

5  $\text{R}^{1c}$  represents hydrogen or  $\text{C}_{1-4}$ alkyl;

$\text{R}^{1b}$  represents hydrogen;

or  $\text{R}^{1b}$  is taken together with  $\text{R}^{1c}$  to form  $-(\text{CH}_2)_3-$ ;

$\text{R}^2$  represents



10  $\text{R}^3$  represents  $-(\text{C}=\text{O})-\text{NR}^{5a}\text{R}^{5b}$ ,  $-(\text{C}=\text{O})-\text{Het}^1$ , or  $\text{R}^3$  represents  $\text{C}_{1-4}$ alkyl substituted with one  $-\text{NR}^{5f}\text{R}^{5g}$  substituent;

$\text{R}^{5a}$  and  $\text{R}^{5b}$  each independently are selected from the group consisting of hydrogen,  $\text{C}_{1-4}$ alkyl, and  $\text{C}_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-\text{NH}_2$ ,  $-\text{NH}(\text{C}_{1-4}\text{alkyl})$  and  $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$ ;

15  $\text{R}^{5f}$  and  $\text{R}^{5g}$  each independently are selected from the group consisting of hydrogen,  $\text{C}_{1-4}$ alkyl, and  $\text{C}_{1-4}$ alkyl substituted with one hydroxyl substituent;

$\text{R}^{4a}$ ,  $\text{R}^{4b}$  and  $\text{R}^{4c}$  each independently are selected from the group consisting of hydrogen, cyano,  $\text{C}_{1-4}$ alkyl, and halo;

20  $\text{Het}^1$  represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $\text{S}(=\text{O})_p$  and N;

each optionally substituted with one or two substituents each independently selected from the group consisting of  $\text{C}_{1-4}$ alkyl;

25 and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein

Y represents  $\text{CR}^3$ ;

30 L represents  $-\text{CHR}^{1a}-\text{X}-$ ;

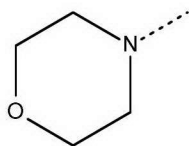
X represents O, S, or  $\text{NR}^{1b}$ ;

$\text{R}^{1a}$  represents  $\text{C}_{1-4}$ alkyl;



$R^{1b}$  represents hydrogen or  $C_{1-4}$ alkyl;

$R^2$  represents



;

$R^3$  represents  $-(C=O)H$ ,  $-(C=O)-C_{1-4}$ alkyl,  $-(C=O)-NR^{5a}R^{5b}$ ,  $-(C=O)-OR^{5c}$ ,  $-C(=O)-$   
 5 Het<sup>1</sup>,  $-C(=O)-NH-Het^2$ ;

$R^{5a}$  and  $R^{5b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl,  $-O-C_{1-4}$ alkyl,  $-S(=O)_2-NH_2$ ,  $-S(=O)_2-C_{1-4}$ alkyl,  $-S(=O)_2-C_{3-6}$ cycloalkyl,  $C_{1-4}$ alkyl substituted with one or more halo atoms, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of  
 10 hydroxyl,  $-O-C_{1-4}$ alkyl,  $-S(=O)_2-C_{1-4}$ alkyl,  $-O-C_{1-4}$ alkyl- $NH_2$ ,  $-O-C_{1-4}$ alkyl- $NH(C_{1-4}$ alkyl),  $-O-C_{1-4}$ alkyl- $N(C_{1-4}$ alkyl)<sub>2</sub>,  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl) and  $-N(C_{1-4}$ alkyl)<sub>2</sub>;

$R^{5c}$  represents hydrogen or  $C_{1-4}$ alkyl;

$R^{4a}$ ,  $R^{4b}$  and  $R^{4c}$  each independently are selected from the group consisting of hydrogen, cyano,  $C_{1-4}$ alkyl, halo,  $-C(=O)H$ ,  $-NR^{6e}R^{6f}$ ,  $-O-C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl  
 15 substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, and  $-NR^{6g}R^{6h}$ ;

$R^{6e}$  and  $R^{6f}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl), and hydroxyl;

20  $R^{6g}$  and  $R^{6h}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl), and hydroxyl;

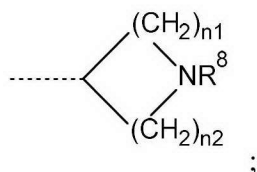
Het<sup>1</sup> represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  
 25  $S(=O)_p$  and N;

each optionally substituted with one or two substituents each independently selected from the group consisting of halo,  $-NR^{9a}R^{9b}$ ,  $C_{1-4}$ alkyl,  $-(C=O)-OR^{5h}$ ,  $-S(=O)_2-C_{1-6}$ alkyl,  $-C_{1-4}$ alkyl- $S(=O)_2-C_{1-6}$ alkyl, hydroxyl,  $-O-C_{1-4}$ alkyl, cyano,  $C_{1-4}$ alkyl substituted with one or more halo atoms, and  $C_{1-4}$ alkyl substituted with one substituent selected from  
 30 the group consisting of hydroxyl,  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl) and  $-N(C_{1-4}$ alkyl)<sub>2</sub>; or two

substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A;

R<sup>9a</sup> and R<sup>9b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

5 Het<sup>2</sup> represents



n1 represents 1 or 2;

n2 represents 1 or 2;

R<sup>8</sup> represents hydrogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

10 R<sup>5h</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

Ring A represents cyclobutyl, cyclopentyl, cyclohexyl, or a 4-, 5- or 6-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N; said cyclobutyl, cyclopentyl, cyclohexyl, or 4-, 5- or 6-membered saturated heterocyclyl is optionally substituted with one or two C<sub>1-4</sub>alkyl substituents, with one C<sub>1-4</sub>alkyl and one hydroxy substituent, or with one hydroxy substituent;

p represents 1 or 2;

and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

20

In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein

Y represents CR<sup>3</sup>;

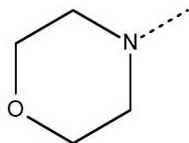
L represents -CHR<sup>1a</sup>-X-;

25 X represents O, S, or NR<sup>1b</sup>;

R<sup>1a</sup> represents C<sub>1-4</sub>alkyl;

R<sup>1b</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

R<sup>2</sup> represents



;

R<sup>3</sup> represents  $-(C=O)H$ ,  $-(C=O)-C_{1-4}alkyl$ ,  $-(C=O)-NR^{5a}R^{5b}$ ;

- 5 R<sup>5a</sup> and R<sup>5b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-NH_2$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{3-6}cycloalkyl$ , C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-O-C_{1-4}alkyl-NH_2$ ,  $-O-C_{1-4}alkyl-NH(C_{1-4}alkyl)$ ,  $-O-C_{1-4}alkyl-N(C_{1-4}alkyl)_2$ ,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$  and  $-N(C_{1-4}alkyl)_2$ ;

- 10 R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> each independently are selected from the group consisting of hydrogen, cyano, C<sub>1-4</sub>alkyl, halo, and  $-O-C_{1-4}alkyl$ ;

and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

- 15 In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein

Y represents CR<sup>3</sup>;

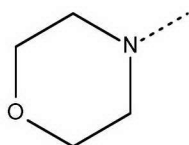
L represents  $-CHR^{1a}-X-$ ;

X represents NR<sup>1b</sup>;

- 20 R<sup>1a</sup> represents C<sub>1-4</sub>alkyl;

R<sup>1b</sup> represents hydrogen or C<sub>1-4</sub>alkyl; in particular hydrogen;

R<sup>2</sup> represents



;

R<sup>3</sup> represents  $-(C=O)-NR^{5a}R^{5b}$ ;

- 25 R<sup>5a</sup> and R<sup>5b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl and  $-O-C_{1-4}alkyl$ ;

$R^{4a}$ ,  $R^{4b}$  and  $R^{4c}$  each independently are selected from the group consisting of hydrogen and halo;

and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

- 5 In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  $R^{1b}$  represents hydrogen,  $C_{1-4}$ alkyl,  $-CH_2-C(=O)-NR^{6a}R^{6b}$ , or  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}$ alkyl, and
- 10  $-NR^{6c}R^{6d}$ ,  
or  $R^{1b}$  is taken together with  $R^{1a}$  or  $R^{1c}$  to form  $-(CH_2)_3-$ ;  
Het<sup>1</sup> represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $S(=O)_p$  and N;
- 15 each optionally substituted with one or two substituents each independently selected from the group consisting of halo,  $-NR^{9a}R^{9b}$ ,  $C_{1-4}$ alkyl,  $-(C=O)-OR^{5h}$ ,  $-S(=O)_2-C_{1-6}$ alkyl,  $-C_{1-4}$ alkyl- $S(=O)_2-C_{1-6}$ alkyl, hydroxyl,  $-O-C_{1-4}$ alkyl, cyano,  $C_{1-4}$ alkyl substituted with one or more halo atoms, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl) and  $-N(C_{1-4}$ alkyl)<sub>2</sub>; or two
- 20 substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A.

- In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
- 25  $R^{1a}$  represents  $C_{1-4}$ alkyl, or  $C_{1-4}$ alkyl substituted with one  $-OH$ .

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  $R^{1a}$  represents  $C_{1-4}$ alkyl.

- 30 In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  $R^{1a}$  represents  $C_{1-4}$ alkyl;  
 $R^{1c}$  represents hydrogen or  $C_{1-4}$ alkyl;
- 35  $R^{1b}$  represents hydrogen,  $C_{1-4}$ alkyl, or  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}$ alkyl, and  $-NR^{6c}R^{6d}$ .

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  $R^{1b}$  is always taken together with  $R^{1a}$  or  $R^{1c}$  to form  $-(CH_2)_3-$ .

5 In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

Y represents  $CR^3$ ;

L represents  $-CHR^{1a}-X-$  or  $-X-CHR^{1c}-$ ;

10 X represents  $NR^{1b}$ ;

$R^{1a}$  represents  $C_{1-4}$ alkyl;

$R^{1c}$  represents hydrogen or  $C_{1-4}$ alkyl;

$R^{1b}$  represents hydrogen;

or  $R^{1b}$  is taken together with  $R^{1c}$  to form  $-(CH_2)_3-$ .

15 In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

Y represents  $CR^3$ ;

L represents  $-CHR^{1a}-X-$  or  $-X-CHR^{1c}-$ ;

20 X represents  $NR^{1b}$ ;

$R^{1a}$  represents  $C_{1-4}$ alkyl;

$R^{1c}$  represents hydrogen or  $C_{1-4}$ alkyl;

$R^{1b}$  represents hydrogen.

In an embodiment, the present invention relates to those compounds of Formula (I) and  
25 the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

Y represents  $CR^3$ .

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof,  
30 or any subgroup thereof as mentioned in any of the other embodiments, wherein

Y represents  $CR^3$ ;

$R^3$  represents  $-(C=O)-NR^{5a}R^{5b}$ .

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof,

or any subgroup thereof as mentioned in any of the other embodiments, wherein Y represents N.

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof,  
5 or any subgroup thereof as mentioned in any of the other embodiments, wherein L represents  $-\text{CHR}^{1a}-\text{X}-$  or  $-\text{X}-\text{CHR}^{1c}-$ .

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  
10 X represents  $\text{NR}^{1b}$ .

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  $\text{R}^{5c}$  represents hydrogen.

15 In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  $\text{R}^{1b}$  is not taken together with  $\text{R}^{1a}$  or  $\text{R}^{1c}$ .

In an embodiment, the present invention relates to those compounds of Formula (I) and  
20 the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  $\text{Het}^1$  represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $\text{S}(=\text{O})_p$  and N; each optionally substituted with one or two substituents each  
25 independently selected from the group consisting of halo,  $-\text{NR}^{9a}\text{R}^{9b}$ ,  $\text{C}_{1-4}\text{alkyl}$ ,  $-(\text{C}=\text{O})-\text{OR}^{5h}$ ,  $-\text{S}(=\text{O})_2-\text{C}_{1-6}\text{alkyl}$ ,  $-\text{C}_{1-4}\text{alkyl}-\text{S}(=\text{O})_2-\text{C}_{1-6}\text{alkyl}$ , hydroxyl,  $-\text{O}-\text{C}_{1-4}\text{alkyl}$ , cyano,  $\text{C}_{1-4}\text{alkyl}$  substituted with one or more halo atoms, and  $\text{C}_{1-4}\text{alkyl}$  substituted with one substituent selected from the group consisting of hydroxyl,  $-\text{NH}_2$ ,  $-\text{NH}(\text{C}_{1-4}\text{alkyl})$  and  $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$ ; or two substituents on the same carbon atom of said heterocyclyl are  
30 taken together to form together with the common carbon atom to which they are attached Ring A.

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  $\text{Het}^1$   
35 represents a bicyclic 8-, 9- or 10-membered saturated or partially saturated heterocyclyl

containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N; each optionally substituted with one or two substituents each independently selected from the group consisting of halo, -NR<sup>9a</sup>R<sup>9b</sup>, C<sub>1-4</sub>alkyl, -(C=O)-OR<sup>5h</sup>, -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -C<sub>1-4</sub>alkyl-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, hydroxyl, -O-C<sub>1-4</sub>alkyl, cyano, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl) and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>; or two substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A.

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het<sup>1</sup> represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N; wherein two substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A.

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein L represents -CH(CH<sub>3</sub>)-NH-.

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein L represents -CH(CH<sub>3</sub>)-NH- (R stereochemistry).

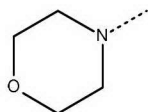
In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het<sup>1</sup> as defined in any of the other embodiments is attached to the remainder of the molecule via a N-atom.

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het<sup>1</sup> is piperazin-1-yl optionally substituted as defined in any of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het<sup>1</sup> is piperazin-1-yl substituted with two C<sub>1-4</sub>alkyl substituents.

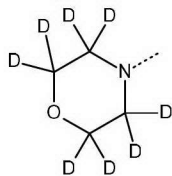
In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het<sup>1</sup> is piperazin-1-yl substituted with one C<sub>1-4</sub>alkyl substituent in position 3 and one C<sub>1-4</sub>alkyl substituent in position 5.

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R<sup>2</sup> represents



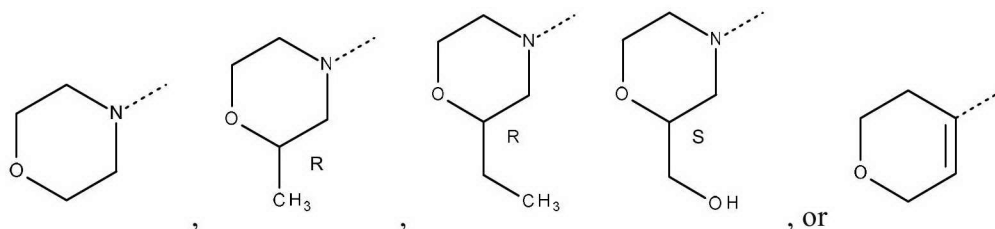
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In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R<sup>2</sup> represents



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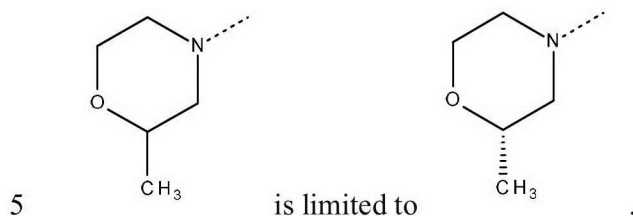
In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R<sup>2</sup> represents



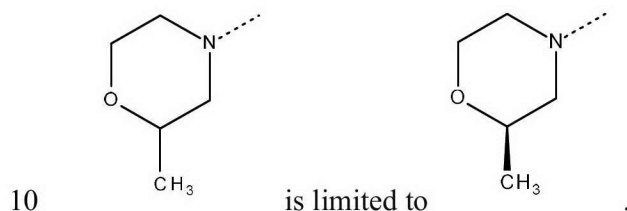
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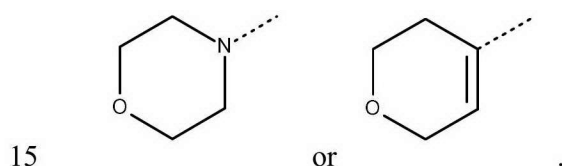
In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  $R^2$  representing



In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  $R^2$  representing



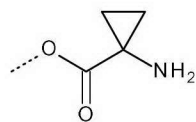
In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  $R^2$  represents



In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein  $R^3$  represents  $-(C=O)H$ ,  $-(C=O)-C_{1-4}alkyl$ ,  $-(C=O)-NR^{5a}R^{5b}$ ,  $-(C=O)-OR^{5c}$ ,  $-(C=O)-Het^1$ ,  $-C(=O)-NH-Het^2$ ,  $C_{1-4}alkyl$ ,  $-CH=N-OH$ ,  $-CH(OH)-CH_2-NR^{5d}R^{5e}$ ,  $-CH(OH)-CH_2-Het^1$ ,  $-CH(OH)-C_{1-4}alkyl$ ,  $-C(OH)(C_{1-4}alkyl)_2$ , halo, or  $R^3$  represents  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of hydroxyl, fluoro,  $-NR^{5f}R^{5g}$ ,

20

Het<sup>1</sup>, -O-(C=O)-CH(NH<sub>2</sub>)-C<sub>1-4</sub>alkyl, -O-(C=O)-CH(NH<sub>2</sub>)-C<sub>1-4</sub>alkyl-Ar,



, -O-C<sub>1-4</sub>alkyl-OH, and -O-C<sub>1-4</sub>alkyl-NH<sub>2</sub>.

In an embodiment, the present invention relates to those compounds of Formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R<sup>3</sup> is other than R<sup>7</sup>.

In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 12, 14, 39, 117, 158, 184 and 276, tautomers and stereoisomeric forms thereof, and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 12, 14, 39, 117, 158, 184, 328, 211 and 276, tautomers and stereoisomeric forms thereof, and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment the compound of Formula (I) is selected from the group consisting of compound 117, tautomers and stereoisomeric forms thereof, and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment the compound of Formula (I) is compound 117.

In an embodiment the compound of Formula (I) is selected from the group consisting of compound 184, tautomers and stereoisomeric forms thereof, and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment the compound of Formula (I) is compound 184.

In an embodiment the compound of Formula (I) is selected from the group consisting of compound 276, tautomers and stereoisomeric forms thereof, and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment the compound of Formula (I) is compound 276.

In an embodiment the compound of Formula (I) is selected from the group consisting of compound 158, tautomers and stereoisomeric forms thereof, and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

- 5 In an embodiment the compound of Formula (I) is compound 158.

In an embodiment the compound of Formula (I) is selected from the group consisting of compound 14, tautomers and stereoisomeric forms thereof, and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

- 10 In an embodiment the compound of Formula (I) is compound 14.

In an embodiment the compound of Formula (I) is selected from the group consisting of compound 12, tautomers and stereoisomeric forms thereof, and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

- 15 In an embodiment the compound of Formula (I) is compound 12.

In an embodiment the compound of Formula (I) is selected from the group consisting of compound 39, tautomers and stereoisomeric forms thereof, and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

- 20 In an embodiment the compound of Formula (I) is compound 39.

In an embodiment the compound of Formula (I) is selected from the group consisting of compound 328, tautomers and stereoisomeric forms thereof, and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

- 25 In an embodiment the compound of Formula (I) is compound 328.

In an embodiment the compound of Formula (I) is selected from the group consisting of compound 211, tautomers and stereoisomeric forms thereof, and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

- 30 In an embodiment the compound of Formula (I) is compound 211.

All possible combinations of the above-indicated embodiments are considered to be embraced within the scope of this invention.

### Methods for the Preparation of Compounds of Formula (I)

In this section, as in all other sections unless the context indicates otherwise, references to Formula (I) also include all other sub-groups and examples thereof as defined herein.

- 5 The general preparation of some typical examples of the compounds of Formula (I) is described hereunder and in the specific examples, and are generally prepared from starting materials which are either commercially available or prepared by standard synthetic processes commonly used by those skilled in the art. The following schemes are only meant to represent examples of the invention and are in no way meant to be a  
10 limit of the invention. For example, the skilled person will realize that some of the general schemes wherein Y is Y<sup>1</sup> may, dependent on the reaction conditions, also apply for cases wherein Y represents -(C=O)-O-H or C<sub>1-4</sub>alkyl substituted with OH.

- Alternatively, compounds of the present invention may also be prepared by analogous reaction protocols as described in the general schemes below, combined with standard  
15 synthetic processes commonly used by those skilled in the art of organic chemistry.

- The skilled person will realize that in the reactions described in the Schemes, although this is not always explicitly shown, it may be necessary to protect reactive functional groups (for example hydroxy, amino, or carboxy groups) where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional  
20 protecting groups can be used in accordance with standard practice. The protecting groups may be removed at a convenient subsequent stage using methods known from the art. This is illustrated in the specific examples. For example, a skilled person will realize that e.g. preparation of compound 17 according to Scheme 1 requires cleavage of the the *tert*-butoxycarbonyl (Boc) in acidic media such as for example hydrochloric  
25 acid 4N in acetonitrile at 0°C or room temperature. For example compound 244 is obtained after cleavage of the *tert*-butyldimethylsilyl in the presence of tetrabutylammonium Fluoride (1M in tetrahydrofuran) in tetrahydrofuran at room temperature. For example compound 79 is prepared according to Scheme 3 from compound 78 by a palladium catalyzed amination reaction using *N*-*boc*-1,2-  
30 diaminoethane followed by cleavage of the *tert*-butoxycarbonyl (Boc) with trifluoroacetic acid as the acid source.

The skilled person will realize that in the reactions described in the Schemes, it may be advisable or necessary to perform the reaction under an inert atmosphere, such as for example under N<sub>2</sub>-gas atmosphere.

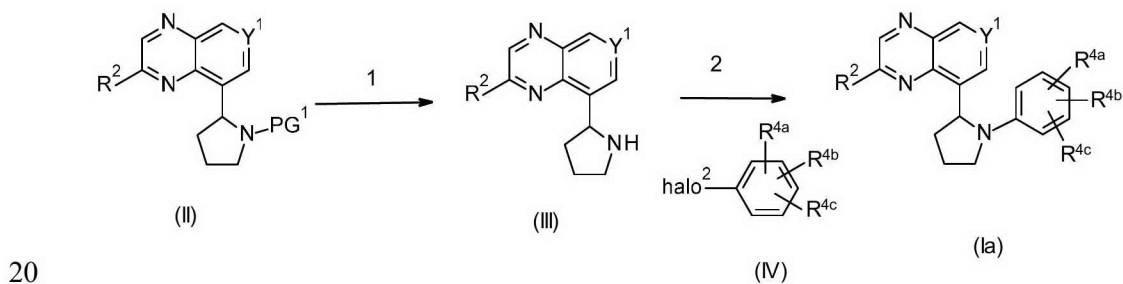
It will be apparent for the skilled person that it may be necessary to cool the reaction mixture before reaction work-up (refers to the series of manipulations required to isolate and purify the product(s) of a chemical reaction such as for example quenching, column chromatography, extraction).

- 5 The skilled person will realize that heating the reaction mixture under stirring may enhance the reaction outcome. In some reactions microwave heating may be used instead of conventional heating to shorten the overall reaction time.

The skilled person will realize that another sequence of the chemical reactions shown in the Schemes below, may also result in the desired compound of formula (I).

- 10 The skilled person will realize that intermediates and final compounds shown in the schemes below may be further functionalized according to methods well-known by the person skilled in the art.

In general, compounds of formula (I) wherein L is defined as shown in scheme 1 and Y is Y<sup>1</sup> being N or CR<sup>3</sup> wherein R<sup>3</sup> is defined as -C<sub>1-4</sub>alkyl, -(C=O)-O-C<sub>1-4</sub>alkyl, -(C=O)-NR<sup>5a</sup>R<sup>5b</sup>, -C(=O)-Het<sup>1</sup> or halo, said compounds being represented by formula (Ia) can be prepared according to the following reaction Scheme 1 wherein PG<sup>1</sup> is a protecting group such as for example a tert-Butyloxycarbonyl (Boc) and halo<sup>2</sup> is defined as Cl, Br or I. All other variables in Scheme 1 are defined according to the scope of the present invention.



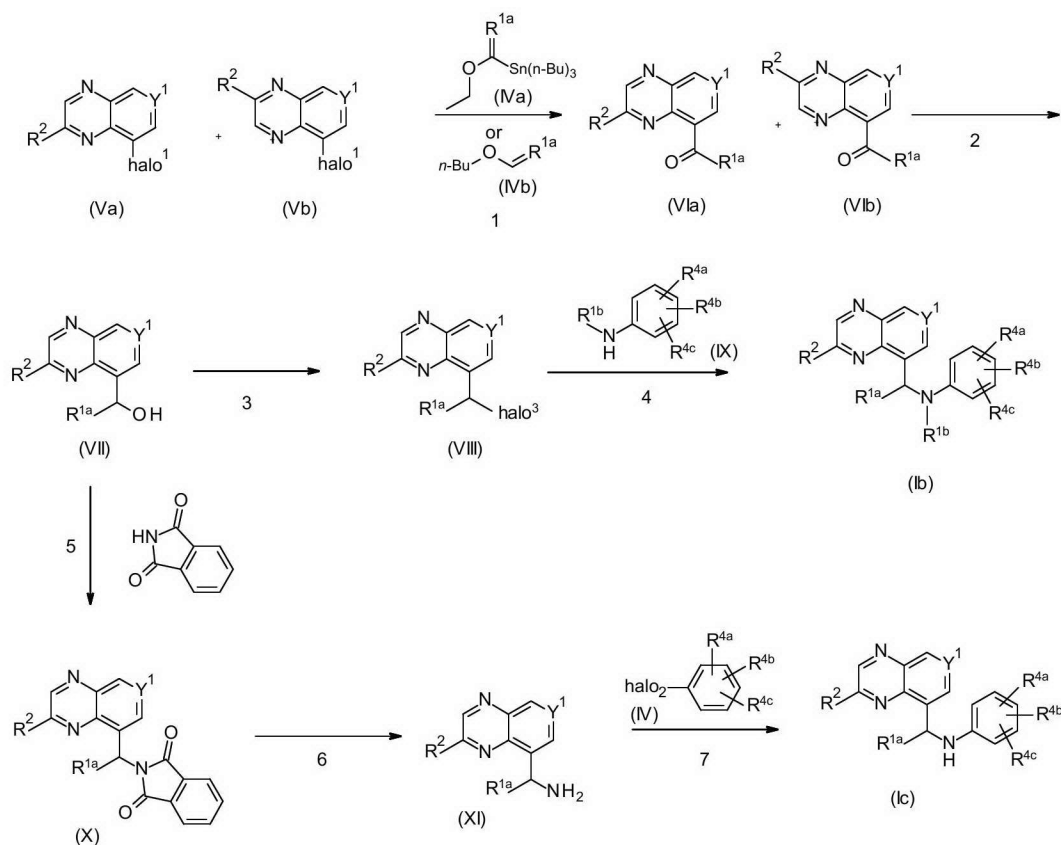
Scheme 1

In Scheme 1, the following reaction conditions apply:

- 1: in the presence of a suitable acid such as for example hydrochloric acid (HCl) or trifluoroacetic acid (TFA), a suitable solvent such as for example dichloromethane (DCM), at a suitable temperature such as room temperature;
- 25 2: in the presence of a suitable catalyst such as for example palladium acetate (Pd(OAc)<sub>2</sub>) or tris(dibenzylideneacetone)dipalladium(0) (Pd<sub>2</sub>dba<sub>3</sub>), a suitable ligand such as for example Xanthphos or 2-(di-tert-butylphosphino)biphenyl a suitable base

such as for example cesium carbonate or sodium tert-butoxide, a suitable solvent such as for example 1,4-dioxane, at a suitable temperature such as 100°C, in a sealed vessel;

In general, compounds of formula (I) wherein L is defined as shown in scheme 2 and Y is Y<sup>1</sup> being N or CR<sup>3</sup> wherein R<sup>3</sup> is defined as -C<sub>1-4</sub>alkyl, -(C=O)-O-C<sub>1-4</sub>alkyl, -(C=O)-NR<sup>5a</sup>R<sup>5b</sup>, -C(=O)-Het<sup>1</sup> or halo, and R<sup>1a</sup> is defined as C<sub>1-4</sub>alkyl, said compounds being represented by formula (Ib) and (Ic) can be prepared according to the following reaction Scheme 2 wherein halo<sup>1</sup> is defined as Cl, Br and I, and halo<sup>3</sup> is defined as Cl or Br. 'n-Bu' means n-butyl. All other variables in Scheme 2 are defined according to the scope of the present invention.



Scheme 2

In Scheme 2, the following reaction conditions apply:

- 1: In case of reagent (IVa), in the presence of a suitable catalyst such as for example dichlorobis(triphenylphosphine) palladium (II) or tetrakis(triphenylphosphine)palladium(0) (Pd(Ph<sub>3</sub>)<sub>4</sub>), a suitable solvent such as for example 1,4-dioxane, at a suitable temperature such as 100°C in a sealed or an open

vessel; Then, in the presence of a suitable acid such as for example aqueous HCl, at a suitable temperature such as room temperature;

In case of reagent (IVb), in the presence of a suitable catalyst such as for example Pd(OAc)<sub>2</sub>, a suitable ligand such as for example 1,3-Bis(diphenylphosphino)propane (DPPP), a suitable base such as for example triethylamine, a suitable solvent such as for example dimethylsulfoxide, at a suitable temperature such as 100°C; Then, in the presence of a suitable acid such as for example HCl, at a suitable temperature such as 0°C;

2: in the presence of a suitable reducing reagent such as for example sodium borohydride, a suitable solvent such as for example a mixture of methanol and dichloromethane, at a suitable temperature such as room temperature, in the presence or not of a suitable additive such as for example cerium (III) chloride;

3: in the presence of a suitable halogenating reagent such as for example phosphorous tribromide or thionyl chloride, a suitable solvent such as for example dichloromethane, at a suitable temperature such as for example 10°C or room temperature;

4: in the presence of a suitable solvent such as for example *N,N*-dimethylformamide, at a suitable temperature such as for example 50 or 60°C, in a sealed vessel;

5: in the presence of a suitable reagent such as for example di-*tert*-butyl azodicarboxylate, a suitable phosphine such as for example triphenylphosphine, a suitable solvent such as for example tetrahydrofuran, at a suitable temperature such as for example room temperature;

6: in the presence of a suitable reagent such as for example hydrazine monohydrate, a suitable solvent such as for example ethanol, at a suitable temperature such as for example 80°C;

7: in the presence of a suitable catalyst such as for example chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II) (Brettphos precatalyst first gen), a suitable base such as for example cesium carbonate, a suitable solvent such as for example 2-methyl-2-butanol, at a suitable temperature such as 100°C, in a sealed vessel.

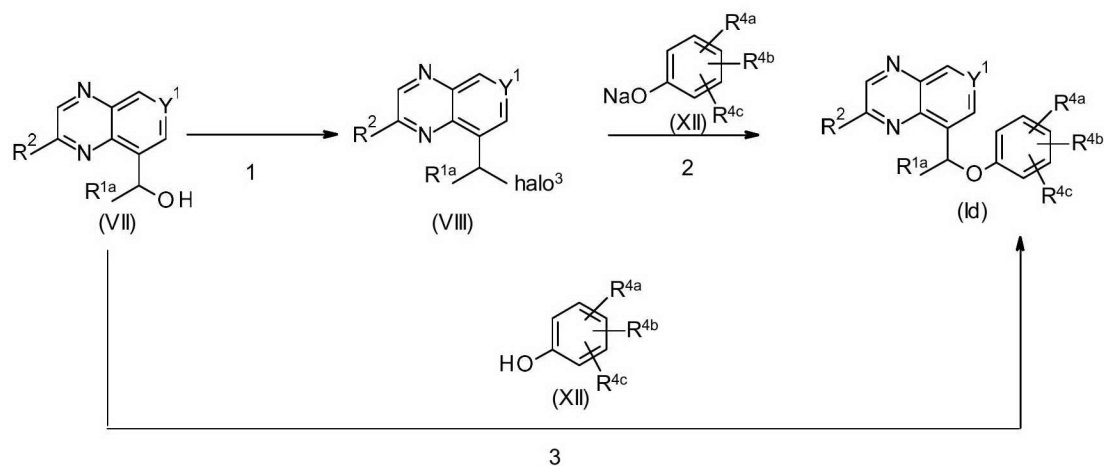
In general, compounds of formula (I) wherein

L is defined as shown in scheme 3;

Y is Y<sup>1</sup> being N or CR<sup>3</sup> wherein R<sup>3</sup> is defined as -C<sub>1-4</sub>alkyl, -(C=O)-O-C<sub>1-4</sub>alkyl, -(C=O)-NR<sup>5a</sup>R<sup>5b</sup>, -C(=O)-Het<sup>1</sup> or halo;

$R^{1a}$  is defined as  $C_{1-4}$ alkyl or hydrogen for step 1 and 2, and is defined according to the scope of the present invention for step 3);

said compounds being represented by formula (Id) can be prepared according to the following reaction Scheme 3 wherein halo<sup>1</sup> is defined as Cl, Br or I and halo<sup>3</sup> is defined as Cl or Br. All other variables in Scheme 3 are defined according to the scope of the present invention.



Scheme 3

In Scheme 3, the following reaction conditions apply:

1: in the presence of a suitable halogenating reagent such as for example phosphorous tribromide or thionyl chloride, a suitable solvent such as for example dichloromethane, at a suitable temperature such as for example 10°C or room temperature;

2: in the presence of a suitable solvent such as for example *N,N*-dimethylformamide, at a suitable temperature such as for example 50 or 60°C, in a sealed vessel;

3: in the presence of a suitable reagent such as for example di-*tert*-butylazodicarboxylate, a suitable phosphine such as for example triphenylphosphine, a solvent such as for example tetrahydrofuran, at a suitable temperature such as for example room temperature;

Alternatively, in the presence of a suitable reagent such as for example cyanoethylenetriethylphosphorane, a solvent such as for example toluene, at a suitable temperature such as for example 60°C, in a sealed vessel.

In general, compounds of formula (I) wherein

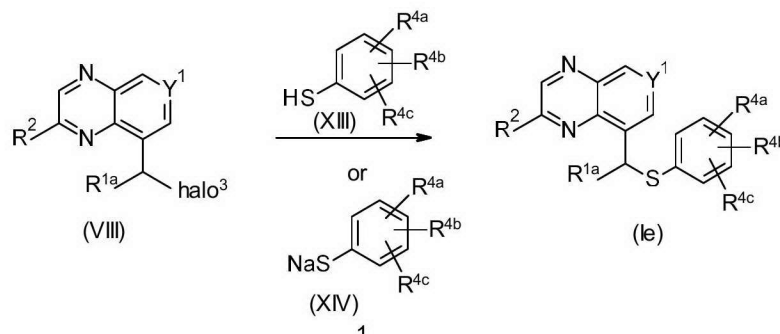
L is defined as shown in scheme 4;



Y is  $Y^1$  being N or  $CR^3$  wherein  $R^3$  is defined as  $-C_{1-4}alkyl$ ,  $-(C=O)-O-C_{1-4}alkyl$ ,  $-(C=O)-NR^{5a}R^{5b}$ ,  $-C(=O)-Het^1$  or halo;

$R^{1a}$  is defined as  $C_{1-4}alkyl$  or hydrogen;

- said compounds being represented by formula (Ie), can be prepared according to the following reaction Scheme 4 wherein halo<sup>3</sup> is defined as Cl or Br. All other variables in Scheme 4 are defined according to the scope of the present invention.

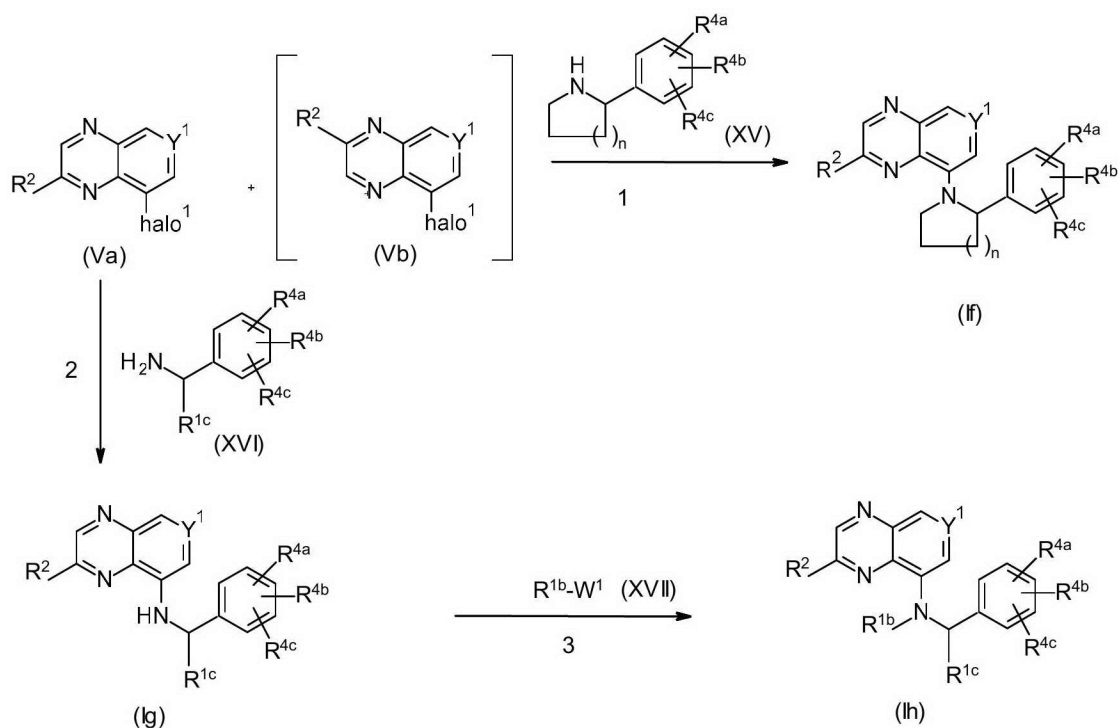


Scheme 4

- In Scheme 4, the following reaction conditions apply:

1: in the presence of a suitable solvent such as for example *N,N*-dimethylformamide, at a suitable temperature such as for example 50 or 60°C, in a sealed vessel.

- In general, compounds of formula (I) wherein L is defined as shown in scheme 5 and Y is  $Y^1$  being N or  $CR^3$  wherein  $R^3$  is defined as  $-C_{1-4}alkyl$ ,  $-(C=O)-O-C_{1-4}alkyl$ ,  $-(C=O)-NR^{5a}R^{5b}$ ,  $-C(=O)-Het^1$  or halo, said compounds being represented by formula (If) can be prepared according to the following reaction Scheme 5 wherein halo<sup>1</sup> is defined as Cl, Br or I,  $W^1$  is a leaving group such as for example Cl, Br or I, and n is 0, 1 or 2. Moreover  $R^{5a}$  and  $R^{5b}$  are other than hydrogen for the purpose of Scheme 5. All other variables in Scheme 5 are defined according to the scope of the present invention.



Scheme 5

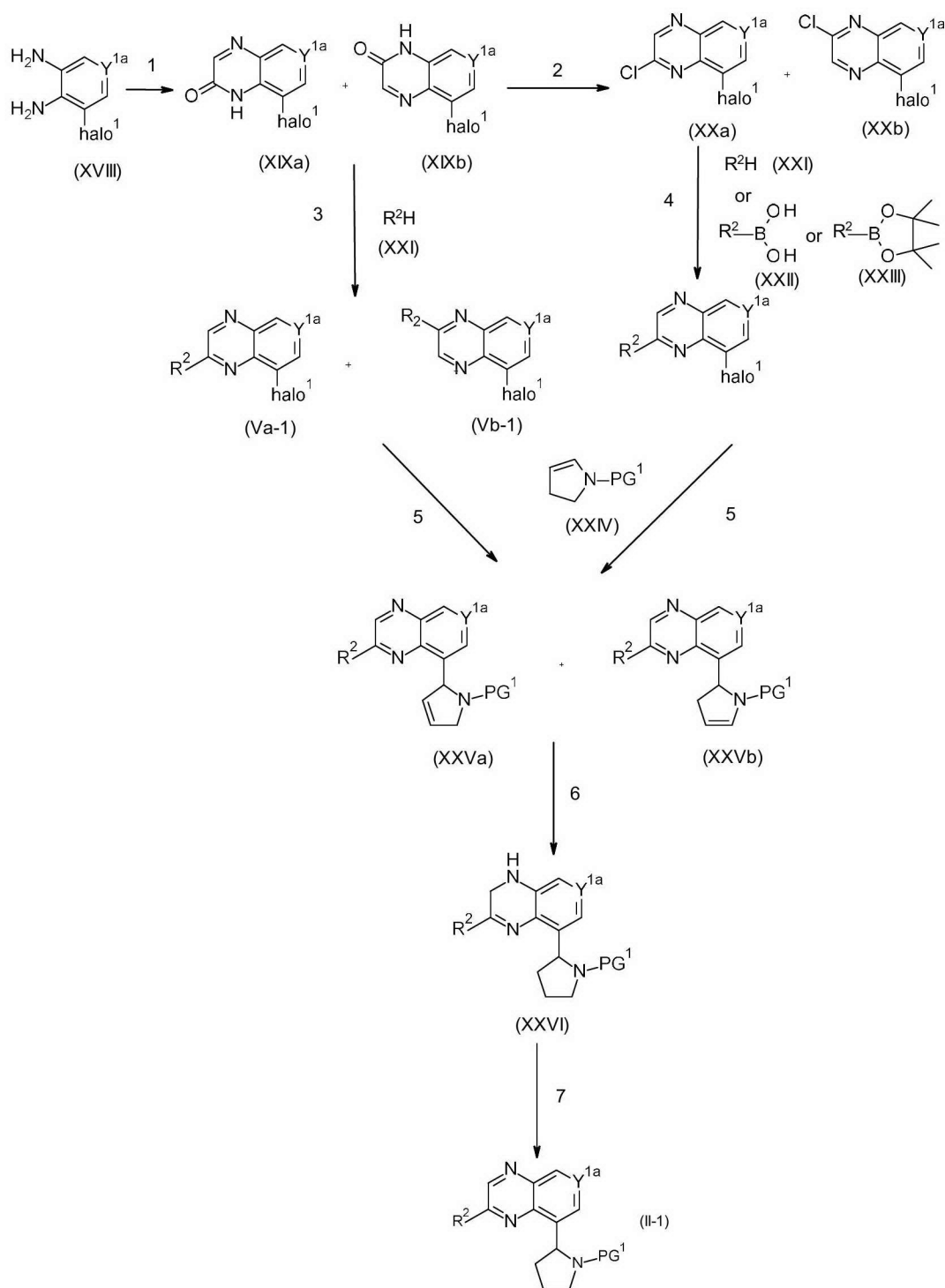
In Scheme 5, the following reaction conditions apply:

- 5 1: in the presence of a suitable catalyst such as for example chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II) (Brettphos precatalyst first gen), with or without a suitable ligand such as for example 2-dicyclohexylphosphino-2,6'-diisopropoxy-1,1'-biphenyl, a suitable base such as for example cesium carbonate, a suitable solvent such as for example *tert*-amyl alcohol (2-methyl-2-butanol) or toluene, at a suitable temperature such as 100°C, in a sealed vessel;
- 10 2: in the presence of a suitable catalyst such as for example chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II) (Brettphos precatalyst first gen) or palladium acetate, with or without a suitable ligand such as for example 2-dicyclohexylphosphino-2,6'-diisopropoxy-1,1'-biphenyl or 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, a suitable base such as for example cesium carbonate, a suitable solvent such as for example *tert*-amyl alcohol, toluene or dioxane, at a suitable temperature ranged from 80 to 100°C, in a sealed vessel;
- 15

3: in the presence of a suitable deprotonating agent such as for example sodium hydride, a suitable solvent such as for example dimethylformamide, at a suitable temperature such as for example room temperature.

- 5 A subgroup of the Intermediates of formula (II) used in the above Scheme 1, hereby named Intermediates of formula (II-1) wherein L is limited according to scheme 6 and Y is Y<sup>1a</sup> being N, -C-C<sub>1-4</sub>alkyl, -C-(C=O)-O-C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkyl can be prepared according to the following reaction Scheme 6 wherein PG<sup>1</sup> is a protecting group such as for example a Boc, and halo<sup>2</sup> is defined as Cl, Br or I. All other variables in Scheme
- 10 6 are defined according to the scope of the present invention.

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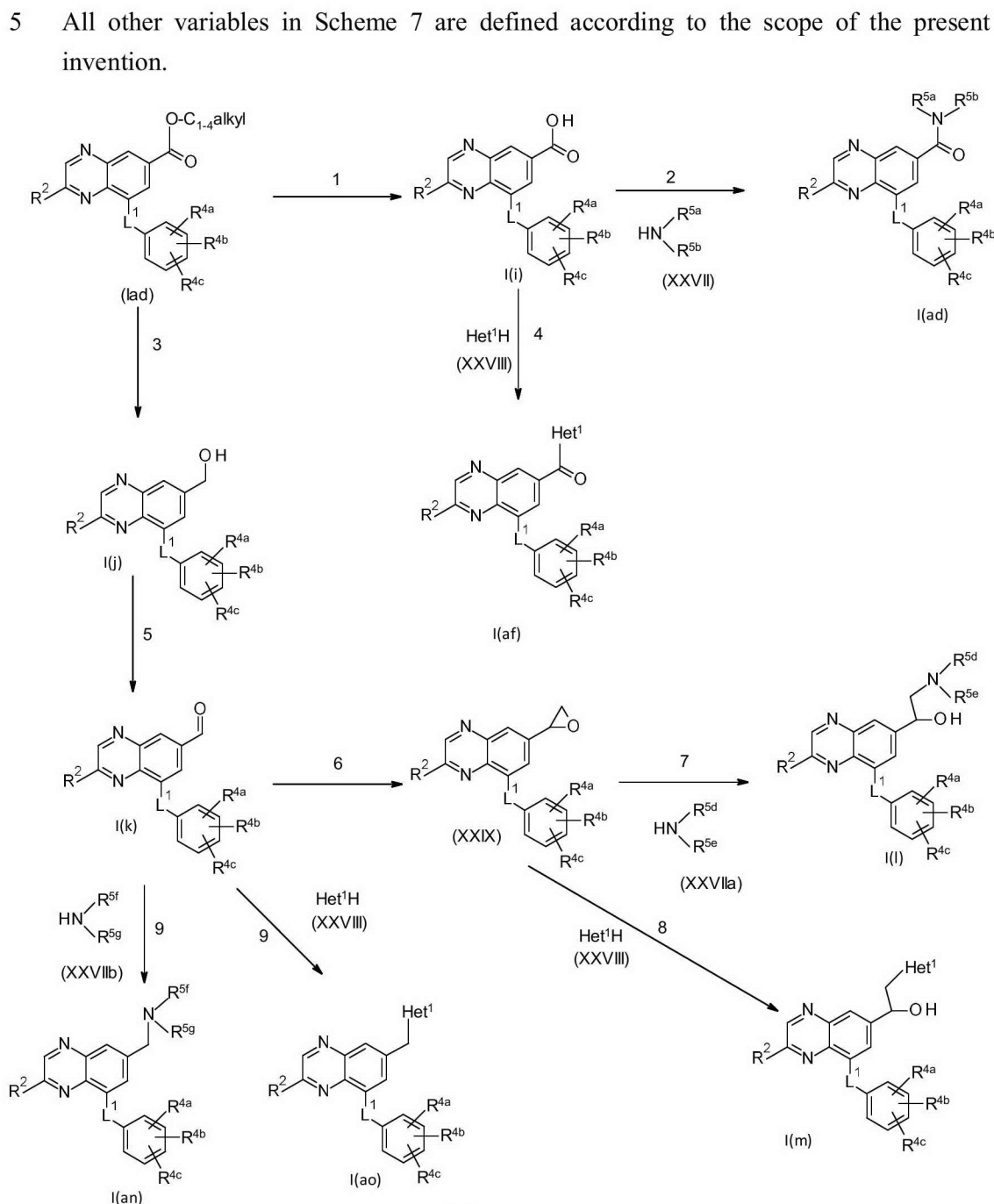
Scheme 6

In Scheme 6, the following reaction conditions apply:

- 1: in the presence of a suitable reagent such as for example 2,2-dihydroxy acetic acid, a suitable solvent such as for example a mixture of water and methanol , at a suitable temperature such as room temperature;
- 5 Alternatively, in the presence of a suitable reagent such as for example an ethyl glyoxalate solution in toluene, a suitable solvent such as for example ethanol , at a suitable temperature such as solvent reflux;
- 2: in the presence of a suitable chlorinating reagent such as for example phosphoryl trichloride ( $\text{POCl}_3$ ), at a suitable temperature such as  $80^\circ\text{C}$ ;
- 10 3: in the presence of a suitable coupling reagent such as for example phosphoryl bromo-tris-pyrrolidino-phosphonium hexafluorophosphate, a suitable base such as for example triethylamine, a suitable solvent such as for example tetrahydrofuran, at a suitable temperature such as room temperature;
- 4: in case of an intermediate of formula (XXI): in the presence of a suitable solvent  
15 such as for example tetrahydrofuran, at a suitable temperature such as solvent reflux;  
in case of an intermediate of formula (XXII) or in case of an intermediate of formula (XXIII): in the presence of a suitable catalyst such as for example [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane , suitable base such as for example potassium phosphate, a  
20 suitable solvent such as for example 1,4-dioxane, at a suitable temperature such as for example  $80^\circ\text{C}$ , in a sealed vessel;
- 5: in the presence of a suitable catalyst such as for example  $\text{Pd}(\text{OAc})_2$ , a suitable phosphine such as for example triphenylphosphine, a suitable base such as for example potassium carbonate, a suitable solvent such as for example *N,N*-dimethylformamide or  
25 1,4-dioxane, at a suitable temperature such as for example  $100^\circ\text{C}$ , in a sealed vessel;
- 6: in the presence of hydrogen, a suitable catalyst such as for example platinum (IV) oxide, a suitable solvent such as for example methanol, at a suitable temperature such as for example room temperature;
- 7: in the presence of a suitable oxidative reagent such as for example manganese oxide,  
30 a suitable solvent such as for example dichloromethane, at a suitable temperature such as for example room temperature.

In general, compounds of formula (I) wherein L is  $\text{L}^1$  being  $-\text{CHR}^{1a}-\text{X}-$  or  $-\text{X}-\text{CHR}^{1c}-$ ; and Y is  $\text{Y}^a$  being  $\text{CR}^3$  wherein  $\text{R}^3$  is defined as  $-\text{COOH}$ ,  $-\text{CH}_2\text{OH}$ ,  $-(\text{C}=\text{O})\text{H}$ ,  $-\text{CH}(\text{OH})-$

$\text{CH}_2\text{-NR}^{5d}\text{R}^{5e}$ ,  $\text{-CH(OH)-CH}_2\text{-Het}^1$ ,  $\text{-(C=O)-NR}^{5a}\text{R}^{5b}$ ,  $\text{-C(=O)-Het}^1$ ,  $\text{-CH}_2\text{-NR}^{5f}\text{R}^{5g}$  or  $\text{-CH}_2\text{-Het}^1$ , said compounds being represented respectively by compounds of formula (Ii), (Ij), (Ik), (Il), (Im), (Iad), I(ae), I(an) and I(ao), can be prepared according to the following reaction Scheme 7.



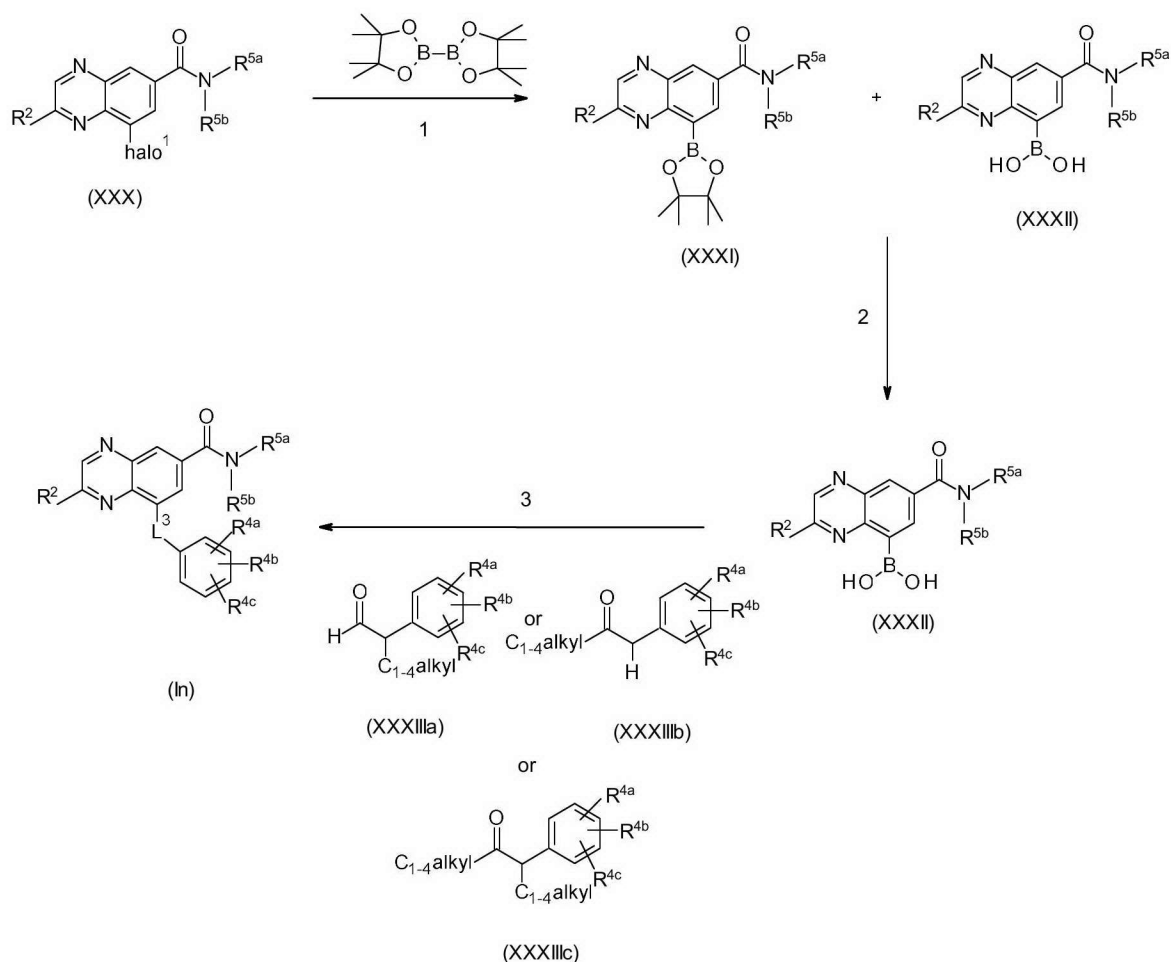
Scheme 7

In Scheme 7, the following reaction conditions apply:

- 1: in the presence of a suitable base such as for example lithium hydroxide monohydrate or sodium carbonate, a suitable solvent such as for example a mixture of water and tetrahydrofuran or a mixture of water, methanol and tetrahydrofuran, at a suitable temperature such as for example 50°C or room temperature;
- 5 2: in the presence of a suitable coupling reagent such as for example *N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate, *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), (1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU), 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) or 1,1'-carbonyldiimidazole, a suitable base such as
- 10 for example diisopropylethylamine, triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene, a suitable solvent such as for example *N,N*-dimethylformamide or methyltetrahydrofuran, at a suitable temperature such as for example room temperature;
- 15 3: in the presence of a suitable reducing reagent such as for example diisobutylaluminium hydride, a suitable solvent such as for example tetrahydrofuran, at a suitable temperature such as for example -70°C;
- 4: in the presence of a suitable coupling reagent such as for example HBTU, COMU, HATU or 1,1'-carbonyldiimidazole, a suitable base such as for example diisopropylethylamine, triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene, a suitable
- 20 solvent such as for example *N,N*-dimethylformamide or methyltetrahydrofuran, at a suitable temperature such as for example room temperature;
- 5: in the presence of a suitable oxidative reagent such as for example manganese dioxide, a suitable solvent such as for example dichloromethane, at a suitable temperature such as for example room temperature;
- 25 6: in the presence of a suitable reagent such as for example trimethylsulfonium iodide, a suitable deprotonating reagent such as for example sodium hydride, a suitable solvent such as for example tetrahydrofuran, at a suitable temperature such as for example 70°C;
- 7: in the presence of a suitable solvent such as for example tetrahydrofuran, at a
- 30 suitable temperature such as for example 100°C, in a sealed vessel;
- 8: in the presence of a suitable solvent such as for example tetrahydrofuran, at a suitable temperature such as for example 100°C, in a sealed vessel;

9: in the presence of a suitable reducing agent such as for example sodium borohydride, eventually a suitable base such as for example sodium acetate, in a suitable solvent such as for example methanol at a suitable temperature such as room temperature.

- 5 In general, compounds of formula (I) wherein L is L<sup>3</sup> defined as  $-\text{CH}(\text{C}_{1-4}\text{alkyl})-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}(\text{C}_{1-4}\text{alkyl})-$ , or  $-\text{CH}(\text{C}_{1-4}\text{alkyl})-\text{CH}(\text{C}_{1-4}\text{alkyl})-$  and Y is defined as  $\text{CR}^3$  and  $\text{R}^3$  is defined as  $-(\text{C}=\text{O})-\text{NR}^{5a}\text{R}^{5b}$ , said compounds being represented by formula (In), can be prepared according to the following reaction Scheme 8 wherein halo<sup>1</sup> is defined as Cl, Br or I. All other variables in Scheme 8 are defined as above or according to the
- 10 scope of the present invention.



Scheme 8

- 15 In Scheme 8, the following reaction conditions apply:



1: in the presence of a suitable reagent such as for example Bis(pinacolato)diboron, a suitable catalyst such as for example [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), a suitable base such as for example potassium acetate, a suitable solvent such as for example 1,4-dioxane, at a  
5 suitable temperature such as for example 100°C;

2: in the presence of a suitable reagent such as for example sodium periodate, a suitable acid such as for example hydrochloric acid, a suitable solvent such as for example a mixture of water and tetrahydrofuran, at a suitable temperature such as for example room temperature;

10 3: in the presence of a suitable reagent such as for example *N*-tosylhydrazine, a suitable base such as for example potassium carbonate, a suitable solvent such as for example 1,4-dioxane, at a suitable temperature such as for example ranged between 80°C and 110°C.

In general, compounds of formula (I) wherein L is L<sup>2</sup> being -CH(C<sub>1-4</sub>alkyl)-CH<sub>2</sub>-, -CH<sub>2</sub>-CH(C<sub>1-4</sub>alkyl)-, -CH(C<sub>1-4</sub>alkyl)-CH(C<sub>1-4</sub>alkyl)-, CHR<sup>1a</sup>-X-, or -X-CHR<sup>1c</sup>-; and  
15 wherein Y is Y<sup>2</sup> being CR<sup>3</sup> and R<sup>3</sup> is defined as -CH(OH)C<sub>1-4</sub>alkyl or -C(OH)(C<sub>1-4</sub>alkyl)<sub>2</sub>, said compounds being respectively represented by formula (Io) and (Ip), can be prepared according to the following reaction Scheme 9.

For the purpose of Scheme 9, halo<sup>4</sup> is defined as Cl or Br;

20 X represents O, S, or NR<sup>1b</sup>;

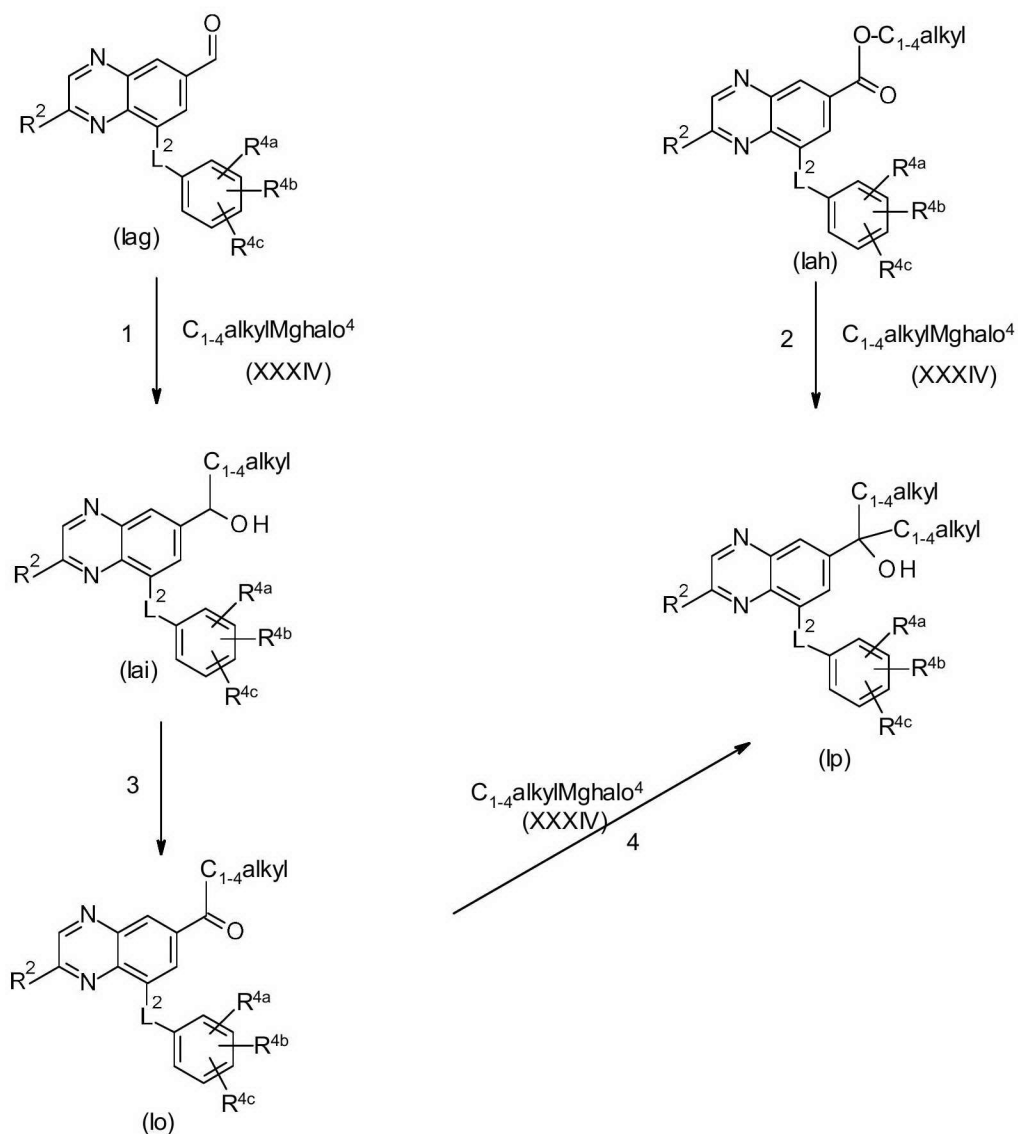
R<sup>1a</sup> represents C<sub>1-4</sub>alkyl;

R<sup>1b</sup> represents C<sub>1-4</sub>alkyl

or R<sup>1b</sup> is taken together with R<sup>1a</sup> or R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>3</sub>-;

or R<sup>1b</sup> is taken together with R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>2</sub>- or -(CH<sub>2</sub>)<sub>4</sub>-.

25 All other variables in Scheme 9 are defined according to the scope of the present invention.



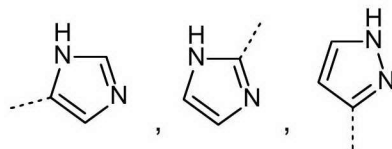
Scheme 9

In Scheme 9, the following reaction conditions apply:

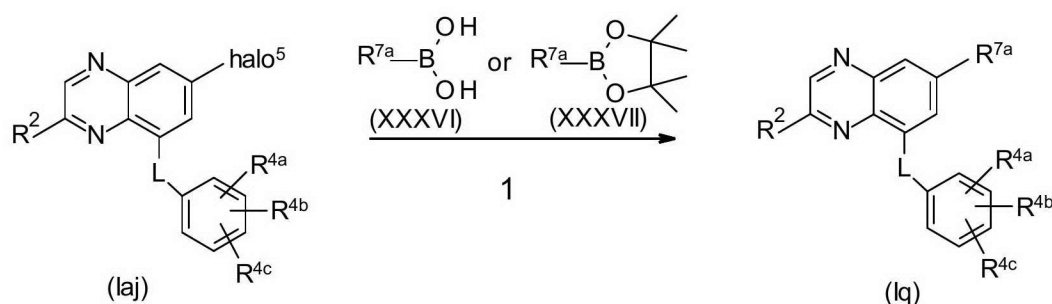
- 1: in the presence of a suitable solvent such as for example tetrahydrofuran, at a suitable temperature such as for example 10°C;
- 2: in the presence of a suitable solvent such as for example tetrahydrofuran, at a suitable temperature such as for example 10 °C;
- 3: in the presence of a suitable oxidative reagent such as for example manganese dioxide, a suitable solvent such as for example dichloromethane, at a suitable temperature such as room temperature;

4: in the presence of a suitable solvent such as for example tetrahydrofuran, at a suitable temperature such as for example 10 °C.

In general, compounds of formula (I) wherein Y is Y<sup>3</sup> being CR<sup>3</sup> and R<sup>3</sup> is restricted to



5 R<sup>7a</sup> being defined as , said compounds being represented by formula (Iq), can be prepared according to the following reaction Scheme 10 wherein halo<sup>5</sup> is defined as Cl, Br or I. All other variables in Scheme 10 are defined according to the scope of the present invention.

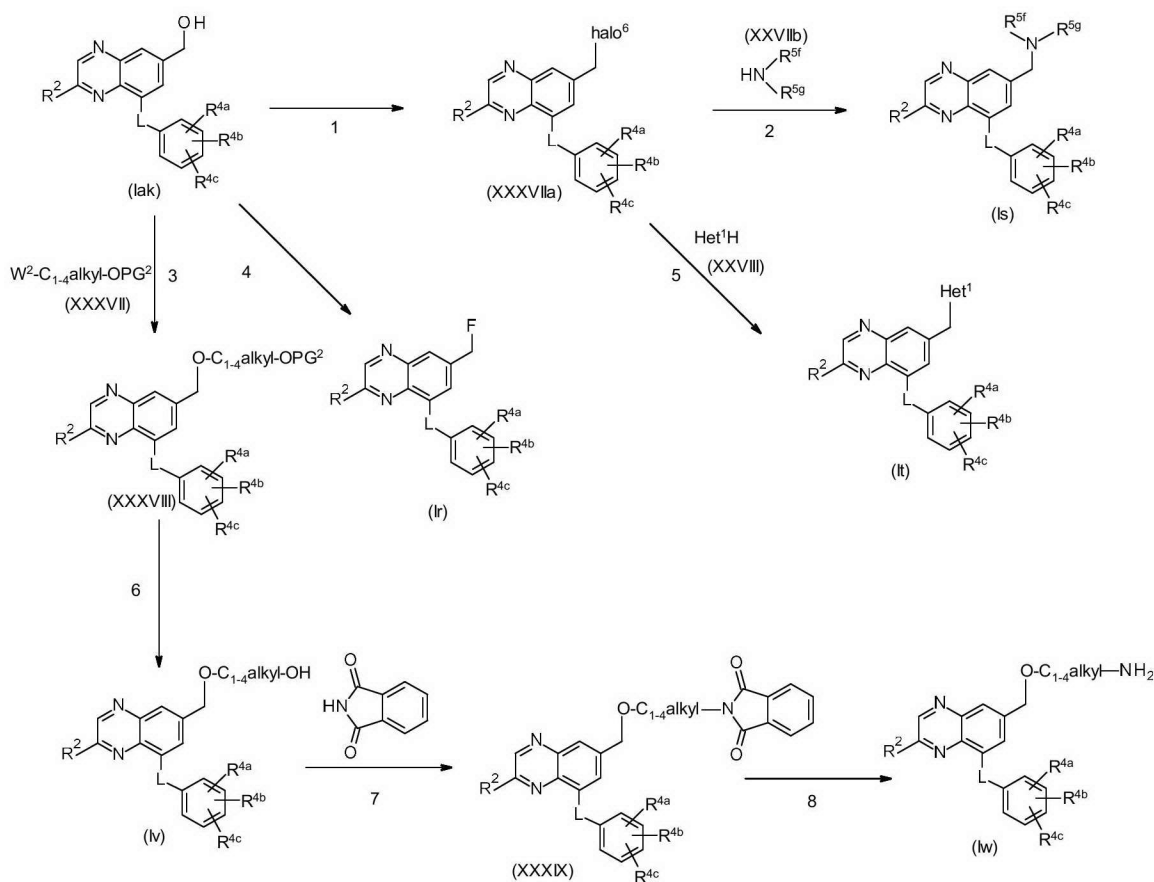


Scheme 10

In Scheme 10, the following reaction conditions apply:

1: in the presence of a suitable catalyst such as for example 1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane, a suitable solvent such as for example tetrahydrofuran, at a suitable temperature such as for example 95°C, and eventually followed by protective groups cleavage using state of the art methods.

In general, compounds of formula (I) wherein Y is Y<sup>4</sup> being CR<sup>3</sup> and R<sup>3</sup> is defined as CH<sub>2</sub> substituted with one substituent selected from the group consisting of fluoro, -NR<sup>5f</sup>R<sup>5g</sup>, Het<sup>1</sup>, -O-C<sub>1-4</sub>alkyl-OH, and -O-C<sub>1-4</sub>alkyl-NH<sub>2</sub>, said compounds being respectively represented by formula (Ir), (Is), (It), (Iu), (Iv) and (Iw) can be prepared according to the following reaction Scheme 11 wherein halo<sup>6</sup> is defined as Cl or Br, W<sup>2</sup> as a leaving group such as for example Cl or Br and PG<sup>2</sup> a protective group such as for example a *tert*-Butyldimethylsilyl (TBDMS). All other variables in Scheme 11 are defined according to the scope of the present invention.



Scheme 11

In Scheme 11, the following reaction conditions apply:

- 5    1: in the presence of a suitable halogenating reagent such as for example thionyl chloride, in the presence of a suitable solvent such as for example dichloromethane, at a suitable temperature such as for example room temperature;
- 2: in the presence of a suitable solvent such as for example acetonitrile, at a suitable temperature such as for example 80°C;
- 10   3: in the presence of a suitable deprotonating reagent such as for example sodium hydride, a suitable solvent such as for example N,N-dimethylformamide, at a suitable temperature such as for example room temperature;
- 4: in the presence of a suitable fluorinating reagent such as for example diethylaminosulfur trifluoride, a suitable solvent such as for example dichloromethane,
- 15   at a suitable temperature such as for example room temperature;
- 5: in the presence of a suitable solvent such as for example acetonitrile, at a suitable temperature such as for example 80°C;

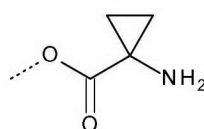
6: in the presence of a suitable acid such as for example trifluoroacetic acid, a suitable solvent such as for example methanol, at a suitable temperature such as room temperature;

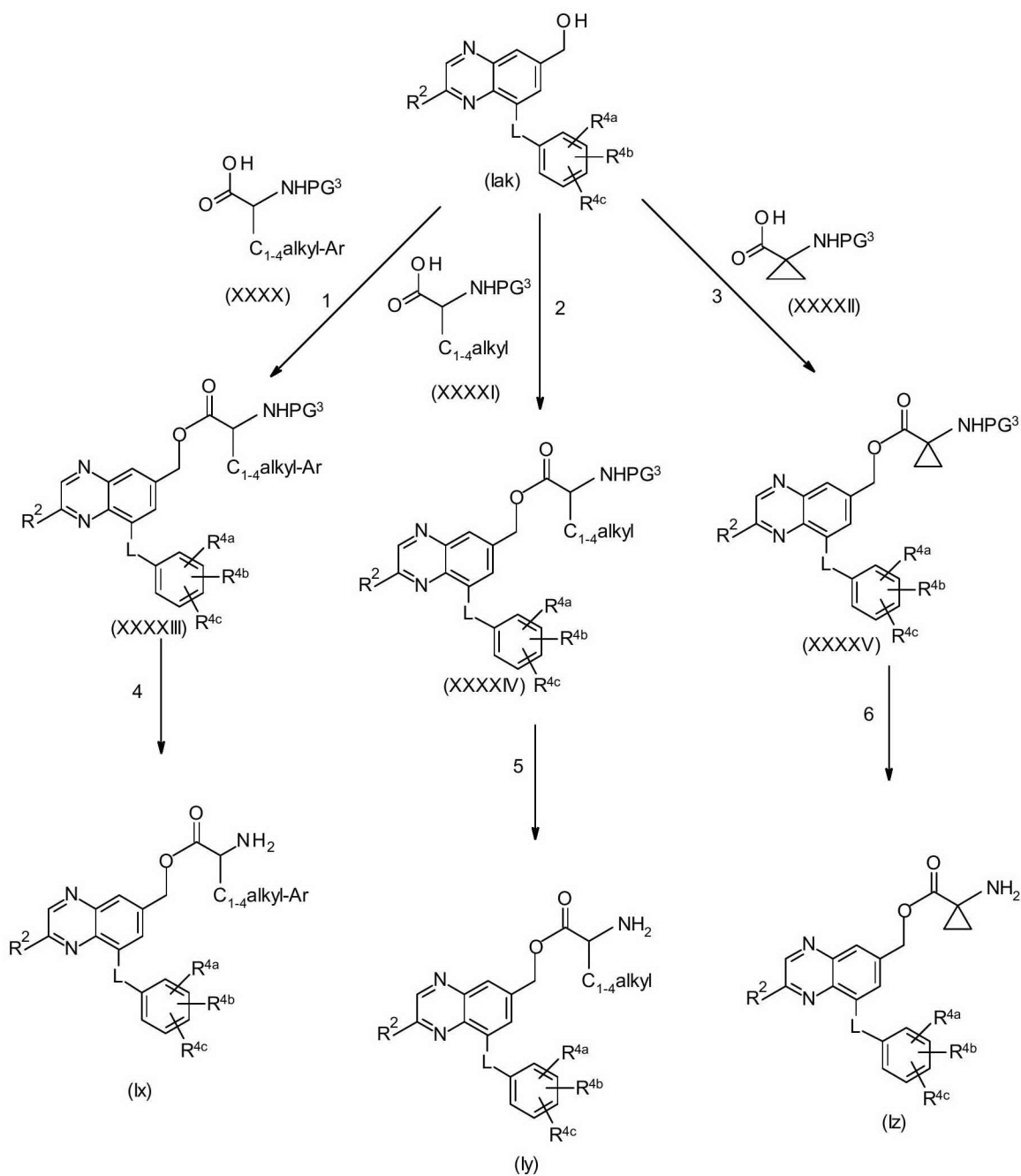
7: in the presence of a suitable reagent such as for example di-tert-butyl azodicarboxylate, a suitable phosphine such as for example triphenylphosphine, a suitable solvent such as for example tetrahydrofuran, at a suitable temperature such as for example room temperature;

8: in the presence of a suitable reagent such as for example hydrazine monohydrate, a suitable solvent such as for example ethanol, at a suitable temperature such as for example 80°C.

Compounds of formula (I) wherein Y is Y<sup>5</sup> being CR<sup>3</sup> and R<sup>3</sup> is defined C<sub>2-4</sub>alkyl substituted with one substituent selected from the group consisting of fluoro, -NR<sup>5f</sup>R<sup>5g</sup>, Het<sup>1</sup>, -O-C<sub>1-4</sub>alkyl-OH, and -O-C<sub>1-4</sub>alkyl-NH<sub>2</sub> can be prepared from the aldehyde I(k) using coupling such as Wittig or Horner Emmons olefination with the appropriate coupling partner followed by reduction of the double bond.

In general, compounds of formula (I) wherein Y is Y<sup>6</sup> being CR<sup>3</sup> and R<sup>3</sup> is defined as C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of -O-

(C=O)-CH(NH<sub>2</sub>)-C<sub>1-4</sub>alkyl, -O-(C=O)-CH(NH<sub>2</sub>)-C<sub>1-4</sub>alkyl-Ar and , said compounds being respectively represented by formula (Ix), (Iy) and (Iz) can be prepared according to the following reaction Scheme 12 wherein PG<sup>3</sup> is defined as a protective group such for example Boc. All other variables in Scheme 12 are defined as above or according to the scope of the present invention.



Scheme 12

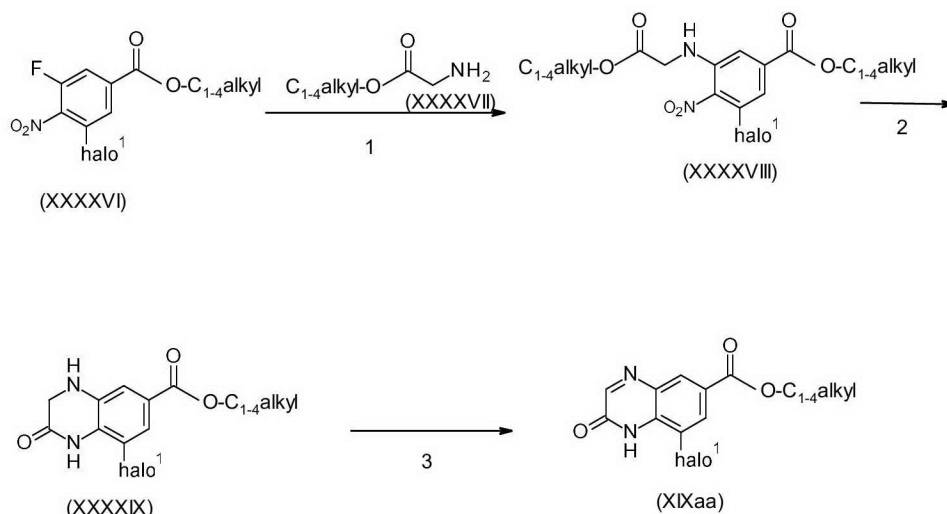
In Scheme 12, the following reaction conditions apply:

- 5 1: in the presence of a suitable coupling reagent such as for example 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-Triazolo[4,5-*b*]pyridinium, 3-oxide, a suitable additive such as for example dimethylaminopyridine, a suitable base such as for example diisopropylethylamine, and in a suitable solvent such as for example of DMF;

2: in the presence of an acide such as for example trifluoroacetic acid or hydrogen chloride in a suitable solvent such as for exemple dichloromethane or methanol. Alternatively, in the presence of palladium on charcoal, in a suitable solvent such as methanol under an atmosphere of hydrogen.

5

Intermediates of formula (XIXaa) when Y is Y<sup>7</sup> being CR<sup>3</sup> wherein R<sup>3</sup> is defined as - (C=O)-O-C<sub>1-4</sub>alkyl used in the above Scheme 6 can alternatively be prepared according to the following reaction scheme 13 wherein halo<sup>1</sup> is defined as above. All other variables in Scheme 13 are defined according to the scope of the present invention.



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Scheme 13

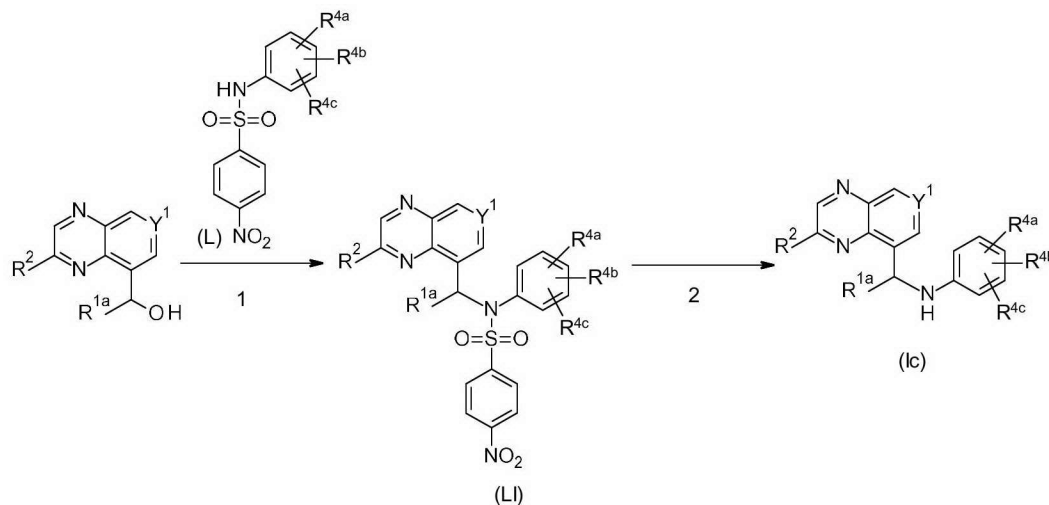
In Scheme 13, the following reaction conditions apply:

- 1: in the presence of a suitable base such as for example diisopropylethylamine, a suitable solvent such as for example dimethylacetamide, at a suitable temperature such as room temperature;
- 2: in the presence of a suitable reducing reagent such as for example Tin(II) chloride dihydrate, a suitable solvent such as for example ethanol, at a suitable temperature such as 80°C;
- 3: in the presence of a suitable oxidative reagent such as for example manganese dioxide, a suitable solvent such as for example dichloromethane at a suitable temperature such as room temperature.

20

In general, compounds of formula (I), wherein Y is Y<sub>1</sub> being N or CR<sup>3</sup> wherein R<sup>3</sup> is defined as -C<sub>1-4</sub>alkyl, -(C=O)-O-C<sub>1-4</sub>alkyl, -(C=O)-O-NR<sup>5a</sup>R<sup>5b</sup>, -C(=O)-Het<sup>1</sup> or halo,

said compounds being represented by formula (Ic), already described in scheme 2, can alternatively be prepared according to the following reaction Scheme 14. All variables in Scheme 14 are defined according to the scope of the present invention.



5

Scheme 14

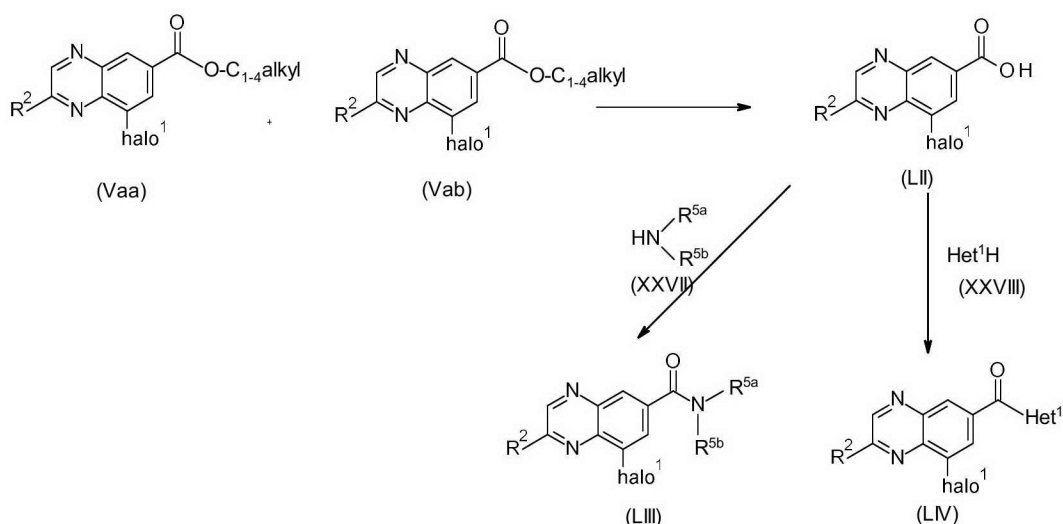
In Scheme 14, the following reaction conditions apply:

- 1: in the presence of a suitable reagent such as for example cyanomethylenetriethylphosphorane, a suitable solvent such as for example toluene, at a suitable temperature such as for example 60°C, optionally in a sealed vessel;
- 10 Alternatively, in the presence of a suitable reagent such as for example diisopropylazodicarboxylate, a suitable phosphine such as for example tributylphosphine, in a suitable solvent such as for example tetrahydrofuran, keeping temperature at 0°C during reagents addition and then, increase to 30°C;
- 2: in the presence of a suitable acid such as for example thioglycolic acid, a suitable
- 15 base such as for example 1,8-diazabicyclo(5.4.0)undec-7-ene, a suitable solvent solvent such as for example acetonitrile, at a suitable temperature such as room temperature.

Intermediates of formula (LIII) and (LIV), wherein Y is Y<sup>8</sup> being CR<sup>3</sup> wherein R<sup>3</sup> is defined as -(C=O)-O- NR<sup>5a</sup>R<sup>5b</sup>, -C(=O)-Het<sup>1</sup>, which may be used as starting material in

20 the above Schemes 2 and 5 can be prepared according to the following reaction Scheme 15. All variables in Scheme 15 are defined as before or according to the scope of the present invention.



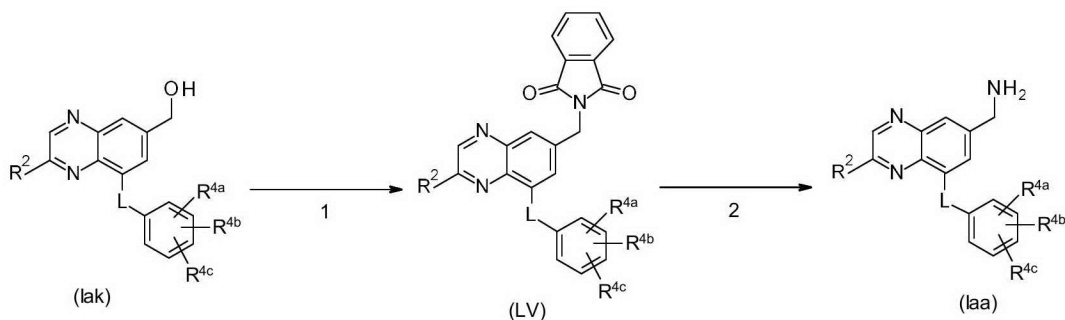


Scheme 15

In Scheme 15, the following reaction conditions apply:

- 1: in the presence of a suitable base such as for example lithium hydroxide monohydrate or sodium hydroxide, a suitable solvent such as for example a mixture of water and tetrahydrofuran or a mixture of water, ethanol and tetrahydrofuran, at a suitable temperature such as room temperature;
- 2: in the presence of a suitable coupling reagent such as for example HBTU or 1,1'-carbonyldiimidazole, a suitable base such as for example  $N,N$ -diisopropylethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene, a suitable solvent such as for example  $N,N$ -dimethylformamide or methyltetrahydrofuran, at a suitable temperature such as for example room temperature.

In general, compounds of formula (I) wherein Y is  $Y^9$  being  $CR^3$  and  $R^3$  is defined as  $-CH_2-NH_2$ , said compounds being represented by formula (Iaa) can be prepared according to the following reaction Scheme 16. All variables in Scheme 16 are defined as above or according to the scope of the present invention.



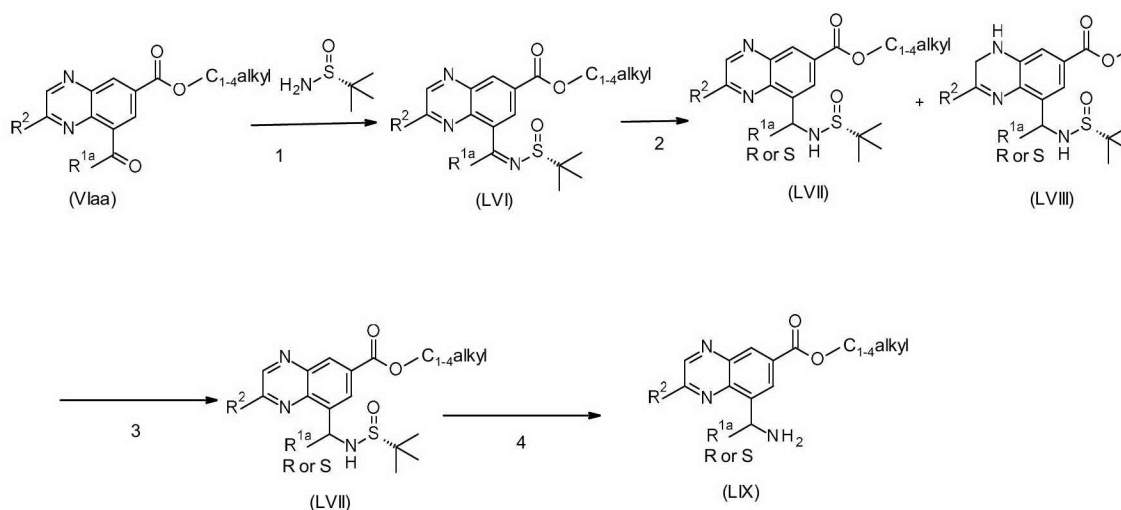
Scheme 16

In Scheme 16, the following reaction conditions apply:

1: in the presence of a suitable reagent such as for example di-tert-butyl azodicarboxylate, a suitable phosphine such as for example triphenylphosphine, a suitable solvent such as for example tetrahydrofuran, at a suitable temperature such as for example 40°C;

2: in the presence of a suitable reagent such as for example hydrazine monohydrate, a suitable solvent such as for example methanol, at a suitable temperature such as for example 70 °C.

10 Intermediates of formula (LIX) (subgroup of intermediates of formula (XI) used in the above Scheme 2) wherein Y is Y<sup>10</sup> being CR<sup>3</sup> wherein R<sup>3</sup> is defined as -(C=O)-O-C<sub>1-4</sub>alkyl, can be prepared in enantiomerically pure form according to the following reaction Scheme 17. All variables in Scheme 17 are defined according to the scope of the present invention.



Scheme 17

In Scheme 17, the following reaction conditions apply:

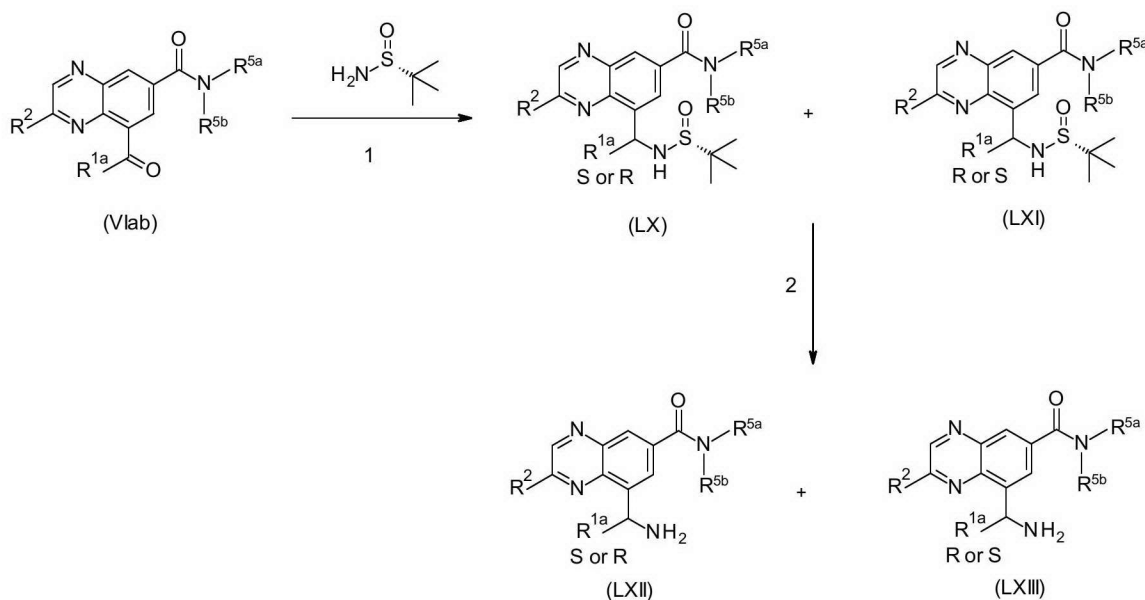
1: in the presence of a suitable reagent such as for example titanium (IV) ethoxide, a suitable solvent such as for example tetrahydrofuran or cyclopentyl methyl ether, at a suitable temperature such as for example room temperature;

2: in the presence of a suitable reducing reagent such as for example sodium cyanoborohydride, a suitable acid such as for example acetic acid, a suitable solvent such as for example a mixture of methanol and dichloromethane, at a suitable temperature such as for example -15°C;

3: in the presence of a suitable oxidative reagent such as for example manganese dioxide, a suitable solvent such as for example dichloromethane, at a suitable temperature such as for example room temperature;

4: in the presence of a suitable acid such as for example hydrochloric acid, a suitable solvent such as for example a mixture of acetonitrile and 1,4-dioxane, at a suitable temperature such as for example room temperature.

Intermediates of formula (LXII) and (LXIII) (subgroups of intermediates of formula (XI) used in the above Scheme 2) wherein Y is Y<sup>11</sup> being CR<sup>3</sup> wherein R<sup>3</sup> is defined as  
 10 -(C=O)-O- NR<sup>5a</sup>R<sup>5b</sup>, can be prepared according to the following reaction Scheme 18. All variables in Scheme 18 are defined according to the scope of the present invention.



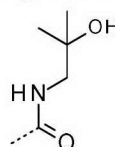
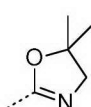
Scheme 18

15 In Scheme 18, the following reaction conditions apply:

1: in the presence of a suitable reagent such as for example titanium (IV) ethoxide, a suitable solvent such as for example tetrahydrofuran or cyclopentyl methyl ether, at a suitable temperature such as for example ranged from room temperature to solvent reflux ; then, in the presence of a suitable reducing reagent such as for example sodium  
 20 borohydride, at a suitable temperature such as for example ranged between -50°C and room temperature;

2: in the presence of a suitable acid such as for example hydrochloric acid, a suitable solvent such as for example 1,4-dioxane, at a suitable temperature such as for example room temperature.

In general, compounds of formula (I) wherein L is L<sup>1</sup> being -CHR<sup>1a</sup>-X- or -X-CHR<sup>1c</sup>;

- 5 and Y is Y<sup>12</sup> being CR<sup>3</sup> wherein R<sup>3</sup> is defined as  or  said compounds being represented respectively by formula (Iab) and (Iac), can be prepared according to the following reaction Scheme 19.

For the purpose of Scheme 19, X represents O, S, or NR<sup>1b</sup>;

R<sup>1a</sup> represents C<sub>1-4</sub>alkyl;

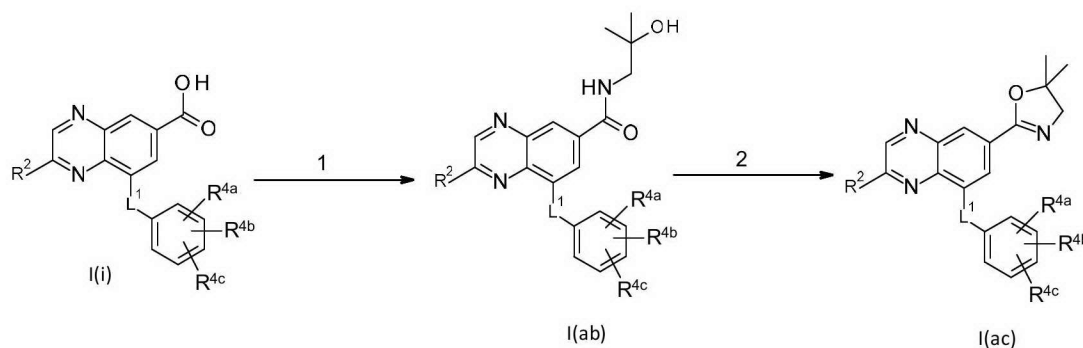
- 10 R<sup>1c</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

R<sup>1b</sup> represents hydrogen, C<sub>1-4</sub>alkyl, -CH<sub>2</sub>-C(=O)-NR<sup>6a</sup>R<sup>6b</sup>, or C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -O-C<sub>1-4</sub>alkyl, and -NR<sup>6c</sup>R<sup>6d</sup>;

or R<sup>1b</sup> is taken together with R<sup>1a</sup> or R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>3</sub>;

- 15 or R<sup>1b</sup> is taken together with R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>2</sub>- or -(CH<sub>2</sub>)<sub>4</sub>.

All other variables in Scheme 19 are defined according to the scope of the present invention.



Scheme 19

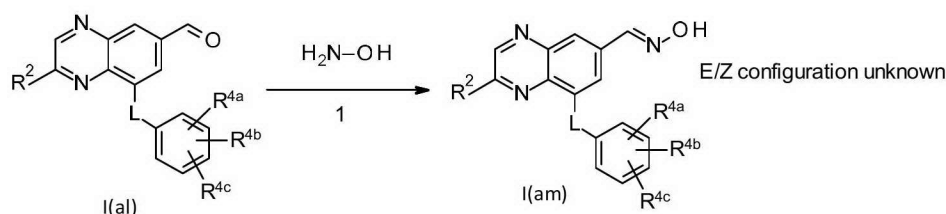
- 20 In Scheme 19, the following reaction conditions apply:

1: in the presence of a suitable coupling reagent such as for example HBTU or 1,1'-carbonyldiimidazole, a suitable base such as for example diisopropylethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene, a suitable solvent such as for example *N,N*-dimethylformamide or methyltetrahydrofuran, at a suitable temperature such as for example room temperature;

25

2: in the presence of a suitable halogenating reagent such as for example thionyl chlorine, a suitable solvent such as for example dichloromethane, at a suitable temperature such as for example room temperature.

5 In general, compounds of formula (I) wherein Y is Y<sup>13</sup> being CR<sup>3</sup> wherein R<sup>3</sup> is defined as -CH=N-OH, said compounds being respectively represented by formula (Iam), can be prepared according to the following reaction Scheme 20 wherein all other variables are defined according to the scope of the present invention.



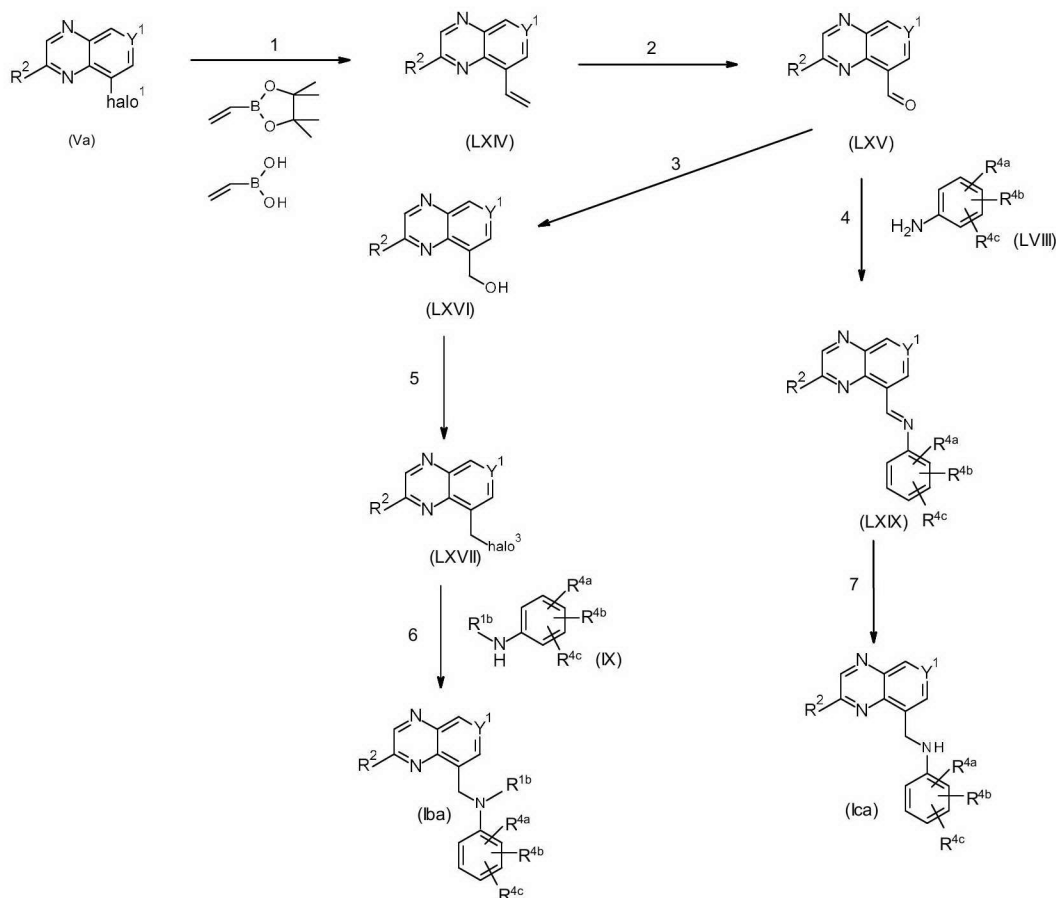
Scheme 20

10 In Scheme 20, the following reaction conditions apply:

1: in the presence of a suitable solvent such as for example ethanol, at a suitable temperature such as for example 100°C.

15 In general, compounds of formula (I) wherein L is defined as -CH<sub>2</sub>-X-; and Y is Y<sup>1</sup> being being N or CR<sup>3</sup> wherein R<sup>3</sup> is defined as -C<sub>1-4</sub>alkyl, -(C=O)-O-C<sub>1-4</sub>alkyl, -(C=O)-NR<sup>5a</sup>R<sup>5b</sup>, -C(=O)-Het<sup>1</sup> or halo; said compounds being represented respectively by formula (Iba) and (Ica), can be prepared according to the following reaction Scheme 21.

20 All other variables in Scheme 21 are defined as above or according to the scope of the present invention.



Scheme 21

In Scheme 21, the following reaction conditions apply:

- 1: in the presence of a suitable catalyst such as for example [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane, a suitable base such as for example potassium phosphate, in a suitable solvent such as for example a mixture of dioxane and water, at a suitable temperature such as 90°C, optionally in a sealed reactor;
- 2: in the presence of a suitable oxidative agent such as for example osmium tetroxide and sodium periodate, in a suitable solvent such as for example tetrahydrofuran;
- 3: in the presence of a suitable reducing reagent such as for example sodium borohydride, a suitable solvent such as for example a mixture of methanol and dichloromethane, at a suitable temperature such as room temperature, in the presence or not of a suitable additive such as for example cerium (III) chloride;

4: in the presence of molecular sieve 4Å, in a suitable solvent such as for example dichloromethane, optionally in a sealed reactor;

5: in the presence of a suitable halogenating reagent such as for example phosphorous tribromide or thionyl chloride, a suitable solvent such as for example dichloromethane, at a suitable temperature such as for example 10°C or room temperature;

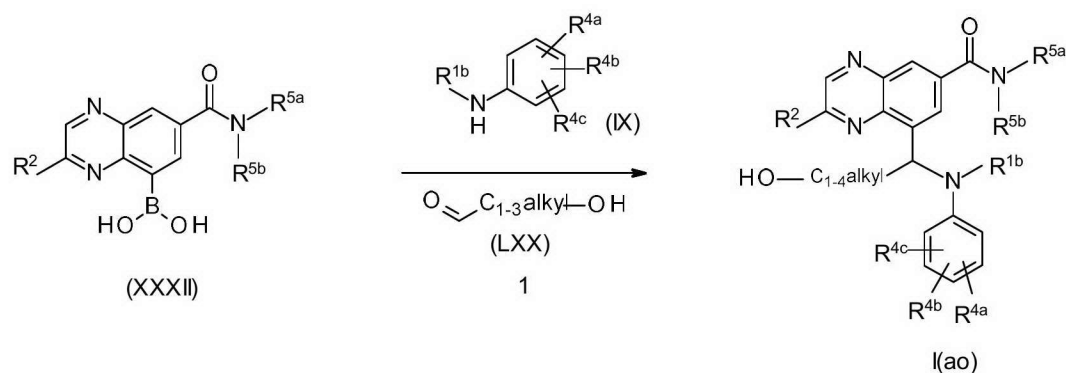
6: in the presence of a suitable solvent such as for example *N,N*-dimethylformamide, at a suitable temperature such as for example 50 or 60°C, in a sealed vessel;

7: in the presence of a suitable reducing agent such as for example sodium triacetoxyborohydride, in a suitable solvent such as for example dichloromethane;

10

In general, compounds of formula (I) wherein L is defined as  $-\text{CH}(\text{C}_{1-4}\text{alkyl-OH})-\text{X}-$ , and Y is defined as  $\text{CR}^3$  wherein  $\text{R}^3$  is defined as  $-(\text{C}=\text{O})-\text{NR}^{5a}\text{R}^{5b}$ ; said compounds being represented by formula I(ao), can be prepared according to the following reaction Scheme 22. All other variables in Scheme 22 are defined as above or according to the scope of the present invention.

15



Scheme 22

In Scheme 22, the following reaction conditions apply:

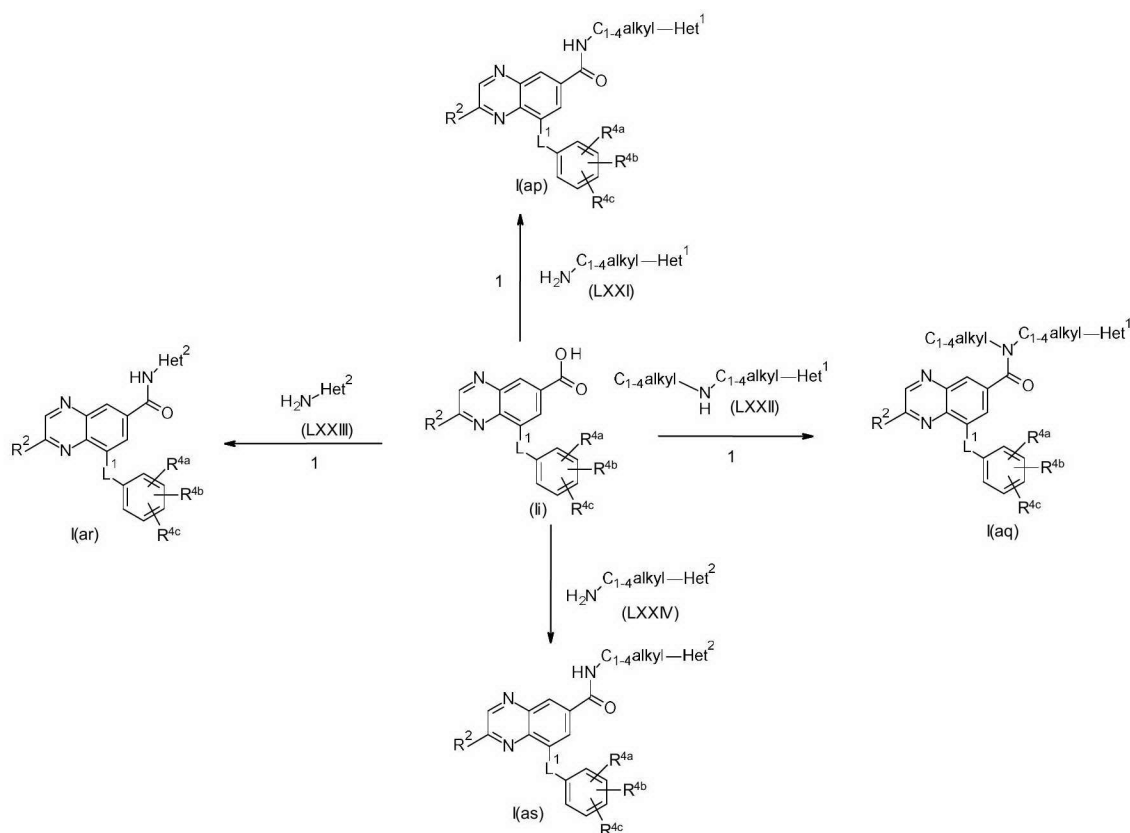
1: in a suitable solvent such as for example hexafluoroisopropanol.

20

In general, compounds of formula (I) wherein L is  $\text{L}^1$  being  $-\text{CHR}^{1a}-\text{X}-$  or  $-\text{X}-\text{CHR}^{1c}-$ ; and Y is  $\text{Y}^a$  being  $\text{CR}^3$  wherein  $\text{R}^3$  is defined as  $-(\text{C}=\text{O})-\text{NH}-\text{C}_{1-4}\text{alkyl}-\text{Het}^1$ ,  $-(\text{C}=\text{O})-\text{N}(\text{C}_{1-4}\text{alkyl})-\text{C}_{1-4}\text{alkyl}-\text{Het}^1$ ,  $-\text{CH}_2-\text{NHHet}^2$  or as  $-(\text{C}=\text{O})-\text{NH}-\text{C}_{1-4}\text{alkyl}-\text{Het}^2$ , said compounds being represented respectively by compounds of formula I(ap), I(aq), I(ar), and I(as), can be prepared according to the following reaction Scheme 23.

25

All other variables in Scheme 23 are defined according to the scope of the present invention.



5

Scheme 23

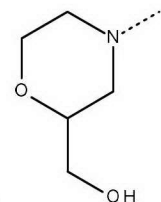
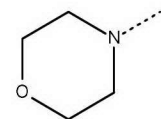
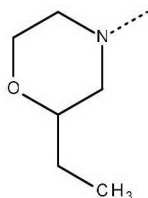
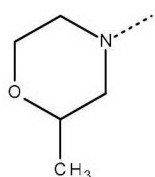
In Scheme 23, the following reaction conditions apply:

- 1: in the presence of a suitable coupling reagent such as for example *N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate, *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), (1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU), 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) or 1,1'-carbonyldiimidazole, a suitable base such as for example diisopropylethylamine, triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene, a suitable solvent such as for example *N,N*-dimethylformamide or methyltetrahydrofuran, at a suitable temperature such as for example room temperature.



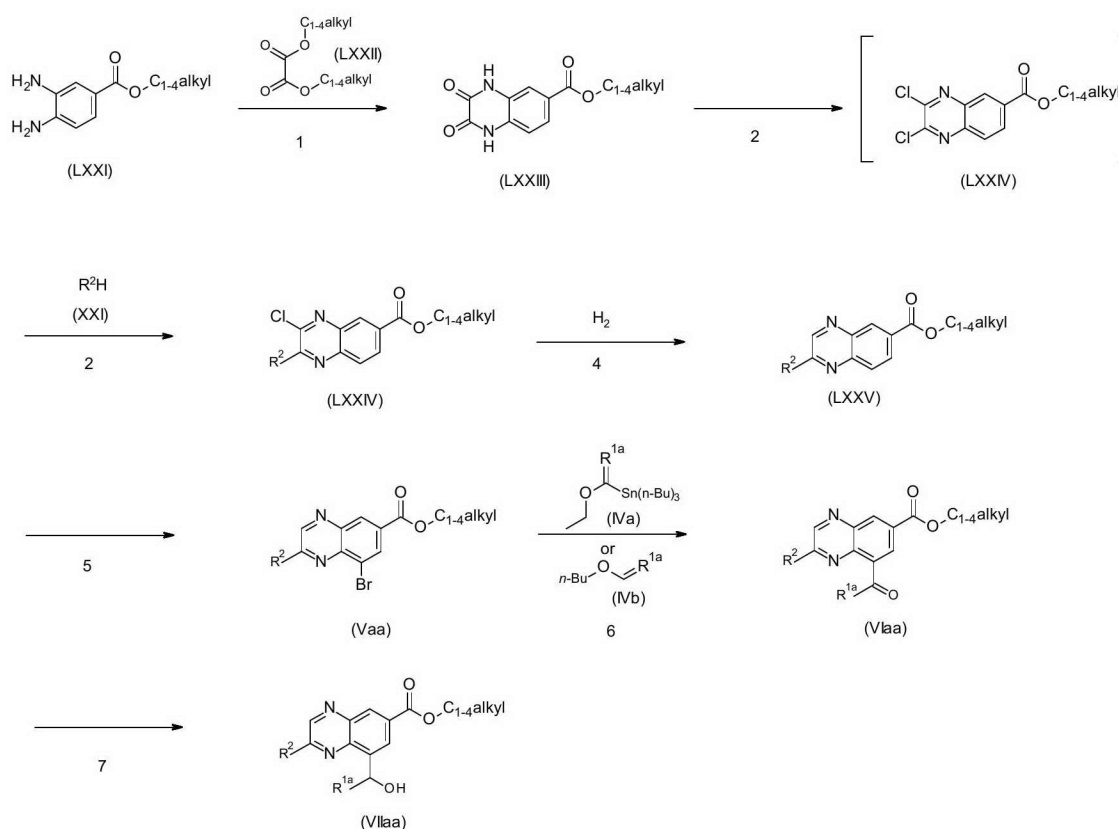
A subgroup of the Intermediates of formula (VII) used in the above Scheme 2, hereby

named Intermediates of formula (VIIaa) wherein  $R^2$  is restricted to



and

and Y is restricted to  $-C(C=O)-O-C_{1-4}\text{alkyl}$  can be prepared according to the following reaction Scheme 24. All other variables in Scheme 24 are defined according to the scope of the present invention.



10

Scheme 24

In Scheme 24, the following reaction conditions apply:

- 1: in a suitable solvent such as for example toluene at a suitable temperature such as reflux;
- 2: in the presence of a suitable chlorinating reagent such as for example thionyl chloride, a suitable additive such as for example dimethylformide, in a suitable solvent  
5 such as for example 1,2-dichloroethane at a suitable temperature such as 80°C;
- 3: in the presence of a suitable base such as for example trimethylamine, in a suitable solvent such as for example 2-methyltetrahydrofuran;
- 4: in the presence of a suitable base such as for example 1,8-Diazabicyclo[5.4.0]undec-  
7-ene, a suitable catalyst such as for example palladium on carbon (Pd/C), in a suitable  
10 solvent such as for example dichloromethane;
- Then, after filtration of the catalyst, filtrate is treated with a suitable oxydating agent such as manganese dioxide, at a suitable temperature such as for exmaple 30 to 40°C;
- 5: in the presence of a suitable halogenating agent such as for example dimethyldibromohydantoin, in a suitable solvent such as for example dichloromethane  
15 at a suitable temperature such as for exmaple 30 to 40°C;
- 6: In case of reagent (IVa), in the presence of a suitable catalyst such as for example dichlorobis(triphenylphosphine) palladium (II) or tetrakis(triphenylphosphine)palladium(0) (Pd(Ph<sub>3</sub>)<sub>4</sub>), a suitable solvent such as for  
example 1,4-dioxane, at a suitable temperature such as 100°C in a sealed or an open  
20 vessel; Then, in the presence of a suitable acid such as for example aqueous HCl, at a suitable temperature such as room temperature;
- In case of reagent (IVb), in the presence of a suitable catalyst such as for example Pd(OAc)<sub>2</sub>, a suitable ligand such as for example 1,3-Bis(diphenylphosphino)propane (DPPP), a suitable base such as for example triethylamine, a suitable solvent such as  
25 for example dimethylsulfoxide, at a suitable temperature such as 100°C; Then, in the presence of a suitable acid such as for example HCl, at a suitable temperature such as 0°C;
- 7: in the presence of an enantioselective reducing agent such as for example (-)-*B*-chlorodiisopinocampheylborane, in a suitable solvent such as for example  
30 dichloromethane, at a suitable temperature such as -35°C.

In all these preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known  
35 in the art such as, for example, extraction, crystallization, trituration and chromatography.

The chirally pure forms of the compounds of Formula (I) form a preferred group of compounds. It is therefore that the chirally pure forms of the intermediates and their salt forms are particularly useful in the preparation of chirally pure compounds of Formula (I). Also enantiomeric mixtures of the intermediates are useful in the preparation of compounds of Formula (I) with the corresponding configuration.

### Pharmacology

It has been found that the compounds of the present invention inhibit PI3K $\beta$  kinase activity, and optionally also have PI3K $\delta$  inhibitory activity.

It is therefore anticipated that the compounds according to the present invention or pharmaceutical compositions thereof may be useful for treating or preventing, in particular treating, of diseases such as cancer, autoimmune disorders, cardiovascular diseases, inflammatory diseases, neurodegenerative diseases, allergy, pancreatitis, asthma, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, lung injuries and the like; in particular cancer.

Because the pharmaceutically active compounds of the present invention are active as PI3K $\beta$  inhibitors, they exhibit therapeutic utility in treatment or prevention, in particular treatment, of susceptible neoplasms, particularly those neoplasms that exhibit a PTEN deficiency.

As used herein, the phrase "PTEN deficient" or "PTEN deficiency" shall describe tumors with deficiencies of the tumor suppressor function of PTEN (Phosphatase and Tensin Homolog). Such deficiency includes mutation in the PTEN gene, reduction or absence of PTEN proteins when compared to PTEN wild-type, or mutation or absence of other genes that cause suppression of PTEN function.

"Susceptible neoplasm" as used herein refers to neoplasms which are susceptible to treatment by a kinase inhibitor and particularly neoplasms that are susceptible to treatment by a PI3K $\beta$  inhibitor. Neoplasms which have been associated with inappropriate activity of the PTEN phosphatase and particularly neoplasms which exhibit mutation of PTEN, or mutation of an upstream activator of PI3K $\beta$  kinase or overexpression of an upstream activator of PI3K $\beta$  kinase, and are therefore susceptible to treatment with an PI3K $\beta$  inhibitor, are known in the art, and include both primary and metastatic tumors and cancers. According to an embodiment, description of the treatment of a susceptible neoplasm may be used interchangeably with description of the treatment of a cancer.

According to one embodiment, "susceptible neoplasms" include but are not limited to PTEN-deficient neoplasms listed as follows: brain (gliomas), glioblastomas, leukemias,

Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast cancer, inflammatory breast cancer, colorectal cancer Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon cancer, head and neck cancer, liver cancer, kidney cancer, lung cancer, melanoma, squamous cell carcinoma, ovarian cancer, pancreatic cancer, prostate cancer, sarcoma cancer, osteosarcoma, giant cell tumor of bone, thyroid cancer, lymphoblastic T cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic neutrophilic leukemia, acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma, Megakaryoblastic leukemia, Acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia, malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, cervical cancer, vulval cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor), and testicular cancer.

According to an alternative embodiment, the term "susceptible neoplasm" includes and is limited to hormone refractory prostate cancer, non-small-cell lung cancer, endometrial cancer, gastric cancer, melanoma, head and neck cancer, breast cancer, including tripnegative breast cancer, and glioma.

In an embodiment, the term "susceptible neoplasm" includes and is limited to prostate cancer, in particular hormone refractory prostate cancer.

The compounds of the present invention may also have therapeutic applications in sensitising tumour cells for radiotherapy and chemotherapy.

Hence the compounds of the present invention may be used as "radiosensitizer" and/or "chemosensitizer" or can be given in combination with another "radiosensitizer" and/or "chemosensitizer".

The term "radiosensitizer", as used herein, is defined as a molecule, preferably a low molecular weight molecule, administered to animals in therapeutically effective amounts to increase the sensitivity of the cells to ionizing radiation and/or to promote the treatment of diseases which are treatable with ionizing radiation.

The term "chemosensitizer", as used herein, is defined as a molecule, preferably a low molecular weight molecule, administered to animals in therapeutically effective

amounts to increase the sensitivity of cells to chemotherapy and/or promote the treatment of diseases which are treatable with chemotherapeutics.

Several mechanisms for the mode of action of radiosensitizers have been suggested in the literature including: hypoxic cell radiosensitizers ( e.g., 2- nitroimidazole  
5 compounds, and benzotriazine dioxide compounds) mimicking oxygen or alternatively behave like bioreductive agents under hypoxia; non-hypoxic cell radiosensitizers (e.g., halogenated pyrimidines) can be analogues of DNA bases and preferentially incorporate into the DNA of cancer cells and thereby promote the radiation-induced breaking of DNA molecules and/or prevent the normal DNA repair mechanisms; and  
10 various other potential mechanisms of action have been hypothesized for radiosensitizers in the treatment of disease.

Many cancer treatment protocols currently employ radiosensitizers in conjunction with radiation of x-rays. Examples of x-ray activated radiosensitizers include, but are not limited to, the following: metronidazole, misonidazole, desmethylmisonidazole,  
15 pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, EO9, RB 6145, nicotinamide, 5-bromodeoxyuridine (BUdR), 5- iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FudR), hydroxyurea, cisplatin, and therapeutically effective analogs and derivatives of the same.

Photodynamic therapy (PDT) of cancers employs visible light as the radiation activator  
20 of the sensitizing agent. Examples of photodynamic radiosensitizers include the following, but are not limited to: hematoporphyrin derivatives, Photofrin, benzoporphyrin derivatives, tin etioporphyrin, pheoborbide-a, bacteriochlorophyll-a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, and therapeutically effective analogs and derivatives of the same.

25 Radiosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds which promote the incorporation of radiosensitizers to the target cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the target cells; chemotherapeutic agents which act on the tumour with or without additional radiation;  
30 or other therapeutically effective compounds for treating cancer or other diseases.

Chemosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds which promote the incorporation of chemosensitizers to the target cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the target cells;  
35 chemotherapeutic agents which act on the tumour or other therapeutically effective compounds for treating cancer or other disease. Calcium antagonists, for example

verapamil, are found useful in combination with antineoplastic agents to establish chemosensitivity in tumor cells resistant to accepted chemotherapeutic agents and to potentiate the efficacy of such compounds in drug-sensitive malignancies.

5 The invention relates to compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for use as a medicament.

The invention also relates to compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for use in the inhibition of PI3K $\beta$  kinase activity and optionally also for use in the inhibition of PI3K $\delta$ .

10 The compounds of the present invention can be "anti-cancer agents", which term also encompasses "anti-tumor cell growth agents" and "anti-neoplastic agents".

The invention also relates to compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for use in the treatment of diseases mentioned above.

15 The invention also relates to compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for the treatment or prevention, in particular for the treatment, of said diseases.

The invention also relates to compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for the treatment or prevention, in particular in the treatment, of PI3K $\beta$  mediated diseases or conditions.

20 The invention also relates to compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for the treatment or prevention, in particular in the treatment, of PI3K $\beta$  and optionally PI3K $\delta$  mediated diseases or conditions.

25 The invention also relates to the use of compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament.

The invention also relates to the use of compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament for the inhibition of PI3K $\beta$ .

30 The invention also relates to the use of compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament for the inhibition of PI3K $\beta$  and optionally also for the inhibition of PI3K $\delta$ .

The invention also relates to the use of compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament for the treatment or prevention, in particular for the treatment, of any one of the disease conditions mentioned hereinbefore.

- 5 The invention also relates to the use of compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament for the treatment of any one of the disease conditions mentioned hereinbefore.

10 The compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, can be administered to mammals, preferably humans for the treatment or prevention of any one of the diseases mentioned hereinbefore.

In view of the utility of the compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, there is provided a method of treating warm-blooded animals, including humans, suffering from or a method of preventing  
15 warm-blooded animals, including humans, to suffer from any one of the diseases mentioned hereinbefore.

Said methods comprise the administration, i.e. the systemic or topical administration, preferably oral administration, of an effective amount of a compound of Formula (I) or a N-oxide, a pharmaceutically acceptable addition salt, or a solvate thereof, to warm-  
20 blooded animals, including humans.

Those of skill in the treatment of such diseases could determine the effective therapeutic daily amount from the test results presented hereinafter. An effective therapeutic daily amount would be from about 0.005 mg/kg to 50 mg/kg, in particular 0.01 mg/kg to 50 mg/kg body weight, more in particular from 0.01 mg/kg to 25 mg/kg  
25 body weight, preferably from about 0.01 mg/kg to about 15 mg/kg, more preferably from about 0.01 mg/kg to about 10 mg/kg, even more preferably from about 0.01 mg/kg to about 1 mg/kg, most preferably from about 0.05 mg/kg to about 1 mg/kg body weight. The amount of a compound according to the present invention, also referred to here as the active ingredient, which is required to achieve a therapeutically effect will  
30 of course, vary on case-by-case basis, for example with the particular compound, the route of administration, the age and condition of the recipient, and the particular disorder or disease being treated.

A method of treatment may also include administering the active ingredient on a regimen of between one and four intakes per day. In these methods of treatment the  
35 compounds according to the invention are preferably formulated prior to



administration. As described herein below, suitable pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

The compounds of the present invention, that can be suitable to treat or prevent cancer or cancer-related conditions, may be administered alone or in combination with one or  
5 more additional therapeutic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of Formula (I), a N-oxide, a pharmaceutically acceptable addition salt, or a solvate thereof, and one or more additional therapeutic agents, as well as administration of the compound of  
10 Formula (I), a N-oxide, a pharmaceutically acceptable addition salt, or a solvate thereof, and each additional therapeutic agents in its own separate pharmaceutical dosage formulation. For example, a compound of Formula (I), a N-oxide, a pharmaceutically acceptable addition salt, or a solvate thereof, and a therapeutic agent may be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent may be administered in separate oral dosage  
15 formulations.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition.

Accordingly, the present invention further provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a  
20 therapeutically effective amount of a compound of Formula (I), a N-oxide, a pharmaceutically acceptable addition salt, or a solvate thereof.

The carrier or diluent must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

For ease of administration, the subject compounds may be formulated into various  
25 pharmaceutical forms for administration purposes. The compounds according to the invention, in particular the compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup or combination thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for  
30 systemically administering drugs.

To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These  
35 pharmaceutical compositions are desirable in unitary dosage form suitable, in



particular, for administration orally, rectally, percutaneously, by parenteral injection or by inhalation. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing a compound of Formula (I), a N-oxide, a pharmaceutically acceptable addition salt, or a solvate thereof, may be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut oil, sesame oil, cottonseed oil, corn oil, soybean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid or base addition salts of compounds of Formula (I) due to their increased water solubility over the corresponding base or acid form, are more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including

scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

In order to enhance the solubility and/or the stability of the compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, in  
5 pharmaceutical compositions, it can be advantageous to employ  $\alpha$ -,  $\beta$ - or  $\gamma$ -cyclodextrins or their derivatives, in particular hydroxyalkyl substituted cyclodextrins, e.g. 2-hydroxypropyl- $\beta$ -cyclodextrin or sulfobutyl- $\beta$ -cyclodextrin. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds according to the invention in pharmaceutical compositions.

10 Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight, even more preferably from 0.1 to 50 % by weight of the compound of Formula (I), a N-oxide, a pharmaceutically acceptable addition salt, or a solvate thereof, and  
15 preferably from 1 to 99.95 % by weight, more preferably from 30 to 99.9 % by weight, even more preferably from 50 to 99.9 % by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the composition.

As another aspect of the present invention, a combination of a compound of the present invention with another anticancer agent is envisaged, especially for use as a medicine, more specifically for use in the treatment of cancer or related diseases.

20 For the treatment of the above conditions, the compounds of the invention may be advantageously employed in combination with one or more other medicinal agents, more particularly, with other anti-cancer agents or adjuvants in cancer therapy. Examples of anti-cancer agents or adjuvants (supporting agents in the therapy) include but are not limited to:

- 25 - platinum coordination compounds for example cisplatin optionally combined with amifostine, carboplatin or oxaliplatin;
- taxane compounds for example paclitaxel, paclitaxel protein bound particles (Abraxane<sup>TM</sup>) or docetaxel;
- topoisomerase I inhibitors such as camptothecin compounds for example  
30 irinotecan, SN-38, topotecan, topotecan hcl;
- topoisomerase II inhibitors such as anti-tumour epipodophyllotoxins or podophyllotoxin derivatives for example etoposide, etoposide phosphate or teniposide;
- anti-tumour vinca alkaloids for example vinblastine, vincristine or vinorelbine;
- 35 - anti-tumour nucleoside derivatives for example 5-fluorouracil, leucovorin, gemcitabine, gemcitabine hcl, capecitabine, cladribine, fludarabine, nelarabine;

- alkylating agents such as nitrogen mustard or nitrosourea for example cyclophosphamide, chlorambucil, carmustine, thiotepa, mephalan (melphalan), lomustine, altretamine, busulfan, dacarbazine, estramustine, ifosfamide optionally in combination with mesna, pipobroman, procarbazine, streptozocin, temozolomide, uracil;
- anti-tumour anthracycline derivatives for example daunorubicin, doxorubicin optionally in combination with dexrazoxane, doxil, idarubicin, mitoxantrone, epirubicin, epirubicin hcl, valrubicin;
- molecules that target the IGF-1 receptor for example picropodophilin;
- tetracarcin derivatives for example tetrocarcin A;
- glucocorticoids for example prednisone;
- antibodies for example trastuzumab (HER2 antibody), rituximab (CD20 antibody), gemtuzumab, gemtuzumab ozogamicin, cetuximab, pertuzumab, bevacizumab, alemtuzumab, eculizumab, ibritumomab tiuxetan, nofetumomab, panitumumab, tositumomab, CNTO 328;
- estrogen receptor antagonists or selective estrogen receptor modulators or inhibitors of estrogen synthesis for example tamoxifen, fulvestrant, toremifene, droloxifene, faslodex, raloxifene or letrozole;
- aromatase inhibitors such as exemestane, anastrozole, letrozole, testolactone and vorozole;
- differentiating agents such as retinoids, vitamin D or retinoic acid and retinoic acid metabolism blocking agents (RAMBA) for example accutane;
- DNA methyl transferase inhibitors for example azacytidine or decitabine;
- antifolates for example premetrexed disodium;
- antibiotics for example antinomycin D, bleomycin, mitomycin C, dactinomycin, carminomycin, daunomycin, levamisole, plicamycin, mithramycin;
- antimetabolites for example clofarabine, aminopterin, cytosine arabinoside or methotrexate, azacitidine, cytarabine, floxuridine, pentostatin, thioguanine;
- apoptosis inducing agents and antiangiogenic agents such as Bcl-2 inhibitors for example YC 137, BH 312, ABT 737, gossypol, HA 14-1, TW 37 or decanoic acid;
- tubuline-binding agents for example combrestatin, colchicines or nocodazole;
- kinase inhibitors (e.g. EGFR (epithelial growth factor receptor) inhibitors, MTKI (multi target kinase inhibitors), mTOR inhibitors) for example flavoperidol, imatinib mesylate, erlotinib, gefitinib, dasatinib, lapatinib, lapatinib ditosylate, sorafenib, sunitinib, sunitinib maleate, temsirolimus;
- farnesyltransferase inhibitors for example tipifarnib;

- histone deacetylase (HDAC) inhibitors for example sodium butyrate, suberoylanilide hydroxamic acid (SAHA), depsipeptide (FR 901228), NVP-LAQ824, R306465, JNJ-26481585, trichostatin A, vorinostat;
- Inhibitors of the ubiquitin-proteasome pathway for example PS-341, MLN .41 or bortezomib;
- Yondelis;
- Telomerase inhibitors for example telomestatin;
- Matrix metalloproteinase inhibitors for example batimastat, marimastat, prinostat or metastat;
- Recombinant interleukins for example aldesleukin, denileukin diftitox, interferon alfa 2a, interferon alfa 2b, peginterferon alfa 2b;
- MAPK inhibitors;
- Retinoids for example alitretinoin, bexarotene, tretinoin;
- Arsenic trioxide;
- Asparaginase;
- Steroids for example dromostanolone propionate, megestrol acetate, nandrolone (decanoate, phenpropionate), dexamethasone;
- Gonadotropin releasing hormone agonists or antagonists for example abarelix, goserelin acetate, histrelin acetate, leuprolide acetate;
- Thalidomide, lenalidomide;
- Mercaptopurine, mitotane, pamidronate, pegademase, pegaspargase, rasburicase;
- BH3 mimetics for example ABT-737;
- MEK inhibitors for example PD98059, AZD6244, CI-1040;
- colony-stimulating factor analogs for example filgrastim, pegfilgrastim, sargramostim; erythropoietin or analogues thereof (e.g. darbepoetin alfa); interleukin 11; oprelvekin; zoledronate, zoledronic acid; fentanyl; bisphosphonate; palifermin;
- a steroidal cytochrome P450 17alpha-hydroxylase-17,20-lyase inhibitor (CYP17), e.g. abiraterone, abiraterone acetate;
- Glycolysis inhibitors, such as 2-deoxyglucose;
- mTOR inhibitors such as rapamycins and rapalogs, and mTOR kinase inhibitors;
- PI3K inhibitors and dual mTOR/PI3K inhibitors;
- autophagy inhibitors, such as chloroquine and hydroxy-chloroquine;

- antibodies that re-activate the immune response to tumors, for example nivolumab (anti-PD-1), lambrolizumab (anti-PD-1), ipilimumab (anti-CTLA4), and MPDL3280A (anti-PD-L1).

5 The compounds of the invention can also be advantageously combined with anti-androgen therapies including androgen receptor antagonists and inhibitors of androgen biosynthesis in PTEN-negative prostate cancers.

The present invention further relates to a product containing as first active ingredient a compound according to the invention and as further active ingredient one or more  
10 anticancer agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

The one or more other medicinal agents and the compound according to the present invention may be administered simultaneously (e.g. in separate or unitary  
15 compositions) or sequentially in either order. In the latter case, the two or more compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the  
20 particular other medicinal agent and compound of the present invention being administered, their route of administration, the particular tumour being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

25 The weight ratio of the compound according to the present invention and the one or more other anticancer agent(s) when given as a combination may be determined by the person skilled in the art. Said ratio and the exact dosage and frequency of administration depends on the particular compound according to the invention and the other anticancer agent(s) used, the particular condition being treated, the severity of the  
30 condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of  
35 the physician prescribing the compounds of the instant invention. A particular weight ratio for the present compound of Formula (I) and another anticancer agent may range

from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

5 The platinum coordination compound is advantageously administered in a dosage of 1 to 500mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 50 to 400  $\text{mg}/\text{m}^2$ , particularly for cisplatin in a dosage of about 75  $\text{mg}/\text{m}^2$  and for carboplatin in about 300 $\text{mg}/\text{m}^2$  per course of treatment.

10 The taxane compound is advantageously administered in a dosage of 50 to 400 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 75 to 250  $\text{mg}/\text{m}^2$ , particularly for paclitaxel in a dosage of about 175 to 250  $\text{mg}/\text{m}^2$  and for docetaxel in about 75 to 150  $\text{mg}/\text{m}^2$  per course of treatment.

15 The camptothecin compound is advantageously administered in a dosage of 0.1 to 400 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 1 to 300  $\text{mg}/\text{m}^2$ , particularly for irinotecan in a dosage of about 100 to 350  $\text{mg}/\text{m}^2$  and for topotecan in about 1 to 2  $\text{mg}/\text{m}^2$  per course of treatment.

20 The anti-tumour podophyllotoxin derivative is advantageously administered in a dosage of 30 to 300 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 50 to 250 $\text{mg}/\text{m}^2$ , particularly for etoposide in a dosage of about 35 to 100  $\text{mg}/\text{m}^2$  and for teniposide in about 50 to 250  $\text{mg}/\text{m}^2$  per course of treatment.

25 The anti-tumour vinca alkaloid is advantageously administered in a dosage of 2 to 30 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, particularly for vinblastine in a dosage of about 3 to 12  $\text{mg}/\text{m}^2$ , for vincristine in a dosage of about 1 to 2  $\text{mg}/\text{m}^2$ , and for vinorelbine in dosage of about 10 to 30  $\text{mg}/\text{m}^2$  per course of treatment.

30 The anti-tumour nucleoside derivative is advantageously administered in a dosage of 200 to 2500 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 700 to 1500  $\text{mg}/\text{m}^2$ , particularly for 5-FU in a dosage of 200 to 500 $\text{mg}/\text{m}^2$ , for gemcitabine in a dosage of about 800 to 1200  $\text{mg}/\text{m}^2$  and for capecitabine in about 1000 to 2500  $\text{mg}/\text{m}^2$  per course of treatment.

35 The alkylating agents such as nitrogen mustard or nitrosourea is advantageously administered in a dosage of 100 to 500 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 120 to 200  $\text{mg}/\text{m}^2$ , particularly for cyclophosphamide in a dosage of



about 100 to 500 mg/m<sup>2</sup>, for chlorambucil in a dosage of about 0.1 to 0.2 mg/kg, for carmustine in a dosage of about 150 to 200 mg/m<sup>2</sup>, and for lomustine in a dosage of about 100 to 150 mg/m<sup>2</sup> per course of treatment.

- 5 The anti-tumour anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter (mg/m<sup>2</sup>) of body surface area, for example 15 to 60 mg/m<sup>2</sup>, particularly for doxorubicin in a dosage of about 40 to 75 mg/m<sup>2</sup>, for daunorubicin in a dosage of about 25 to 45mg/m<sup>2</sup>, and for idarubicin in a dosage of about 10 to 15 mg/m<sup>2</sup> per course of treatment.

10

The antiestrogen agent is advantageously administered in a dosage of about 1 to 100 mg daily depending on the particular agent and the condition being treated. Tamoxifen is advantageously administered orally in a dosage of 5 to 50 mg, preferably 10 to 20 mg twice a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Toremifene is advantageously administered orally in a dosage of about 60mg once a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Anastrozole is advantageously administered orally in a dosage of about 1mg once a day. Droloxifene is advantageously administered orally in a dosage of about 20-100mg once a day. Raloxifene is advantageously administered orally in a dosage of about 60mg once a day. Exemestane is advantageously administered orally in a dosage of about 25mg once a day.

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Antibodies are advantageously administered in a dosage of about 1 to 5 mg per square meter (mg/m<sup>2</sup>) of body surface area, or as known in the art, if different. Trastuzumab is advantageously administered in a dosage of 1 to 5 mg per square meter (mg/m<sup>2</sup>) of body surface area, particularly 2 to 4mg/m<sup>2</sup> per course of treatment.

These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7, 14, 21 or 28 days.

30

### **Examples**

The following examples illustrate the present invention.

35

Hereinafter, the term 'BOC', 'Boc' or 'boc' means *tert*-butoxycarbonyl, means 'DCM' means dichloromethane, 'MeOH' means methanol, 'EtOH' means ethanol, 'ACN' means acetonitrile, 'THF' means tetrahydrofuran, 'Me-THF' means methyltetrahydrofuran, 'DMF' means dimethylformamide, 'EtOAc' means ethyl acetate, 'H<sub>2</sub>O' means water, 'DMA' means dimethylacetamide, 'DME' means ethylene

glycol dimethyl ether, 'Et<sub>2</sub>O' means diethyl ether, 'iPrOH' means isopropanol, 'K<sub>2</sub>CO<sub>3</sub>' means potassium carbonate, 'K<sub>3</sub>PO<sub>4</sub>' means potassium phosphate, 'NH<sub>4</sub>OH' means ammonia aqueous solution, 'NaHCO<sub>3</sub>' means sodium bicarbonate, 'NaOH' means sodium hydroxide, 'NaCl' means sodium chloride, 'NH<sub>4</sub>Cl' means ammonium chloride, 'celite®' means diatomaceous earth, 'NMP' means *N*-methylpyrrolidine, 'LiCl' means lithium chloride, 'NH<sub>4</sub>HCO<sub>3</sub>' means ammonium bicarbonate, 'KOAc' means potassium acetate, 'DIPEA' means diisopropylethylamine, 'iPrNH<sub>2</sub>' means isopropylamine, 'MgSO<sub>4</sub>' means magnesium sulfate, 'Na<sub>2</sub>SO<sub>4</sub>' means sodium sulfate, 'N<sub>2</sub>' means nitrogen, 'HCl' means hydrochloric acid, 'quant.' means quantitative, 'TFA' means trifluoroacetic acid, 'NaBH<sub>4</sub>' means sodium borohydride, 'LiAlH<sub>4</sub>' means lithium aluminium hydride, 'MnO<sub>2</sub>' means manganese(IV) oxide, 'CO<sub>2</sub>' means carbon dioxide, 'CO' means carbon monoxide, 'SFC' means supercritical fluid chromatography, 'HBTU' means *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate, *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, 'TBAF' means tetrabutylammonium fluoride, 'PPh<sub>3</sub>' means triphenylphosphine, 'Pd(OAc)<sub>2</sub>' means palladium(II) acetate, 'Pd<sub>2</sub>(dba)<sub>3</sub>' means tris(dibenzylideneacetone)dipalladium(0), 'Pd(PPh<sub>3</sub>)<sub>4</sub>' means tetrakis(triphenylphosphine) palladium(0), 'Pd.Cl<sub>2</sub>(dppf).DCM' means dichloro [1,1'-bis(diphenylphosphino) ferrocene] palladium(II) dichloromethane adduct, 'BrettPhos' means 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl, 'rt' means room temperature, 'OR' means optical rotation, 'BrettPhos Precatalyst First Gen' means chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II), 'Xantphos' means 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, 'de' means diastereomeric excess, 'ee' or 'e.e.' means enantiomeric excess, 'M.P.' means melting point, 'DSC' means differential scanning calorimetry, 'K' means Kofler; 'COMU' means (1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate, 'HATU' means 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate, 'MeTHF' means 2-methyltetrahydrofuran.

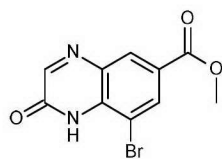
When a stereocenter is indicated with 'RS' this means that a racemic mixture was obtained.

#### A. Preparation of the intermediates

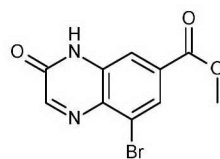
##### Example A1

Preparation of intermediate 1a and intermediate 1b





intermediate 1a



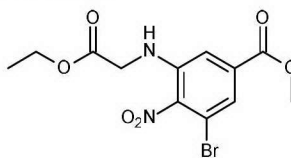
intermediate 1b

At -40°C, 2,2-dihydroxy-acetic acid (85.61 g; 930mmol) in H<sub>2</sub>O (35 mL) was added dropwise to a solution of methyl-3,4-diamino-5-bromobenzoate (190 g; 775.28 mmol) in MeOH (2 L). Then, the reaction mixture was allowed to warm to rt and stirred for 2h. The solid was filtered, washed with Et<sub>2</sub>O and dried under vacuum to give 214 g (98%) of a mixture of two intermediates 1a and 1b (ratio ~85/15 by <sup>1</sup>H NMR).

#### Alternative pathway:

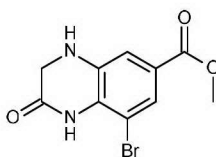
Ethyl glyoxalate solution (6.6 mL; 66.1 mmol; 50% in toluene) was added to a solution of methyl-3,4-diamino-5-bromobenzoate (8.1 g; 33.05 mmol) in EtOH (150 mL). The reaction mixture was heated at reflux for 3h. The mixture was cooled down to rt and the precipitate was filtered, washed with diethylether and dried under vacuum to give 7.3 g (78%) of a mixture of intermediates 1a and 1b.

#### Alternative preparation of intermediate 1a



#### Preparation of intermediate 1c:

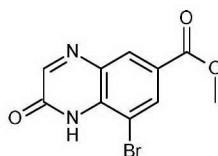
To a solution of methyl-3-bromo-5-fluoro-4-nitrobenzoate (2 g; 7.2 mmol) and glycine ethyl ester hydrochloride (1.1 g; 7.9 mmol) in DMA (20mL) was added DIPEA (4.9mL; 28.8 mmol) at rt. The mixture was stirred at rt for 2 days. H<sub>2</sub>O and EtOAc were added. The organic layer was extracted, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness under vacuum to give 3.3g of crude intermediate. A purification was performed by silica gel chromatography (irregular SiOH 20-45 μm, 40g, mobile phase: gradient from 100% heptane to 70% heptane, 30% EtOAc). The fractions containing the product were mixed and evaporated to give 2.1g (81%) of intermediate 1c.



#### Preparation of intermediate 1d:

Intermediate 1c (200 mg; 0.55 mmol) was dissolved in EtOH (5mL). Tin (II) chloride dihydrate (315 mg; 1.66 mmol) was added and the mixture was heated at 80°C for 4 hours and cooled down to rt. The resulting precipitate was filtered, washed with EtOH and dried (vacuum, 60°C, overnight) to give 90 mg (57%) of intermediate 1d.

5

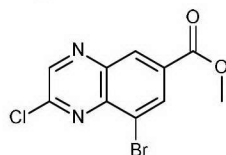


Preparation of intermediate 1a:

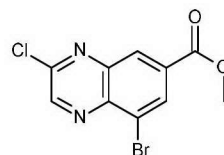
To a solution of intermediate 1d (90 mg; 0.32mmol) in DCM (10mL) was added manganese dioxide (110 mg; 1.26 mmol). The solution was stirred at rt for 2 hours. Manganese dioxide (55mg; 0.63mmol) was again added and the solution was stirred overnight at rt. The mixture was filtered through a pad of celite®, washed with DCM and the solvent was evaporated to dryness to give 58 mg (65%) of intermediate 1a.

10

Preparation of intermediate 2a and intermediate 2b



intermediate 2a



intermediate 2b

A mixture of intermediate 1a and 1b (85/15) (25 g; 75.07 mmol) was added slowly to POCl<sub>3</sub> (300 mL). The reaction mixture was heated at 80°C for 3h. POCl<sub>3</sub> was evaporated and DCM was added to the residue. The mixture was poured into ice-water and extracted with DCM. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated. The residue was purified by chromatography over silica gel (eluent: from 9/1 petroleum ether/EtOAc to 4/1 petroleum ether/EtOAc). The pure fractions were collected and the solvent was evaporated to give 17 g (75%) of intermediate 2a and 3 g (13%) of intermediate 2b.

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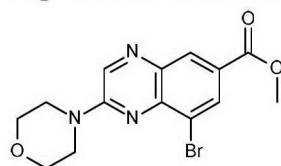
Alternative pathway:

A mixture of intermediate 1a (5 g; 17.7 mmol) in POCl<sub>3</sub> (75 mL) was heated at 80°C for 4h. The mixture was evaporated under vacuum and the residue was taken-up in ice water and DCM. The mixture was slowly basified with a 10% aqueous solution of K<sub>2</sub>CO<sub>3</sub> and stirred at rt for 2h. The aqueous layer was separated and extracted with DCM (2x). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and evaporated under vacuum to give 4.89 g (92%, beige solid) of intermediate 2a.

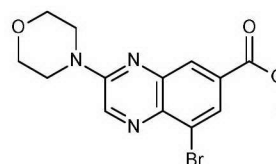
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## Preparation of intermediate 3a and intermediate 3b



intermediate 3a



intermediate 3b

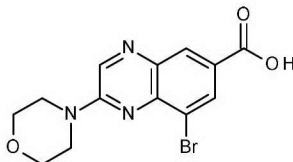
Triethylamine (95.4 mL; 660 mmol) was added to a mixture of intermediates 1a and 1b  
 5 (75 g; 132.47 mmol) (ratio 1a/1b undetermined) in THF (3 L) at 0°C. The reaction mixture was stirred at 0°C for 10min. Then, morpholine (55.8 mL; 634 mmol) and bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (135.2 g; 290 mmol) were added. The reaction mixture was stirred at rt for 12h. The solvent was evaporated and the residue was washed with H<sub>2</sub>O. The solid (yellow) was filtered, washed with ACN,  
 10 then Et<sub>2</sub>O and dried under vacuum to give 80 g (85%) of a mixture intermediates 3a and 3b (ratio ~4/1 by <sup>1</sup>H NMR).

## Alternative pathway:

A mixture of intermediate 2a (3.3 g; 10.94 mmol) and morpholine (2.9 mL; 32.83  
 15 mmol) in THF (50 mL) was heated at reflux for 3h. The reaction mixture was cooled down to rt, then poured into ice-water and extracted with EtOAc. The organic layer was washed with brine (2x), then water, dried over MgSO<sub>4</sub>, filtered and evaporated to give 3.7 g (95%) of intermediate 3a.

## 20 Alternative preparation of intermediate 3a:

Intermediate 186 was dissolved in dichloromethane (10 volumes) and dimethyl dibromohydantoin (0.8 equivalents) was added. After reacting at 30-40 °C for 30 hours, the reaction mixture was washed with a saturated solution of ammonium chloride and the organic phase was concentrated to give intermediate 3a in quantitative yield (78  
 25 purity).



## Preparation of intermediate 4:

A solution of lithium hydroxide monohydrate (5.96 g; 141.97 mmol) in H<sub>2</sub>O (60 mL) was added to a solution of a mixture of intermediates 3a and 3b (5/1) (10 g; 28.39 mmol) in THF (200 mL) at rt. The reaction mixture was stirred at rt overnight. At 0°C,

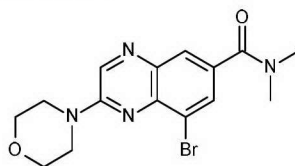
the solution was slowly acidified with a 3N aqueous solution of HCl and stirred at 10°C for 1h. The precipitate was filtered, then washed with water and dried to give 7.4 g (70%. yellow solid. 91% of purity evaluated by LC/MS) of intermediate 4. M.P.: >260°C (Köfler).

5

Alternative pathway:

A 3M aqueous solution of NaOH (11.6 mL; 34.8 mmol) was added to a mixture of intermediates 3a and 3b (4.08 g; 11.6 mmol) in EtOH (60 mL) and THF (60 mL). The reaction mixture was stirred at rt overnight and evaporated under vacuum. The residue was acidified with a 0.5 N aqueous solution of HCl to give a precipitate. The solid was filtered off, washed with water, then diethylether and dried under vacuum to give 3.86 g (99%, yellow solid) of intermediate 4.

10

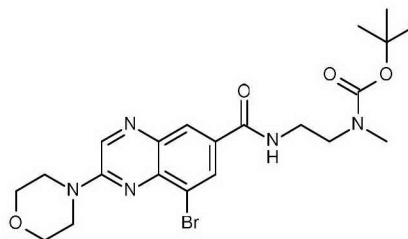


Preparation of intermediate 5:

At 10°C, HBTU (10.7 g; 28.1 mmol) was added portion wise to a mixture of intermediate 4 (9.5 g; 28.1 mmol), DIPEA (12.3 mL; 70.2 mmol) and dimethylamine (2M in THF) (21.1 mL; 42.1 mmol) in DMF (180 mL). The reaction mixture was stirred at rt for the week-end. The solution was poured into ice-water, extracted with EtOAc (2x). The organic layer was washed with brine (2x), then dried over MgSO<sub>4</sub>, filtered and evaporated until dryness. The residue was taken-up with diethylether, filtered and dried to give 9.5 g (93%) of intermediate 5.

15

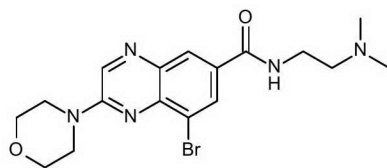
20



Preparation of intermediate 217

Intermediate 217 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 4 and *N*-(2-aminoethyl)-*N*-Methyl carbamic acid tert-butyl ester as starting materials (720mg g; 49%).

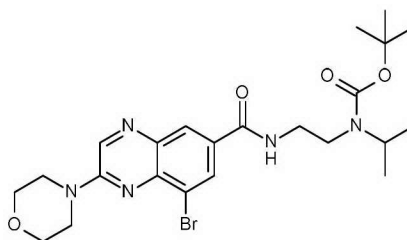
25



#### Preparation of intermediate 237

Intermediate 237 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 4 and N,N-Dimethylethylenediamine as starting materials (420mg g; 70%).

5



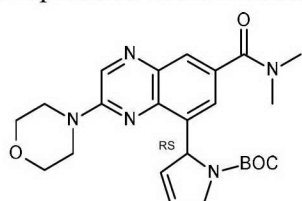
#### Preparation of intermediate 238

Intermediate 238 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 4 and 2-Amino-Ethyl)isopropyl-carbamic acid tert-butylester as starting materials (5.6g; 81%).

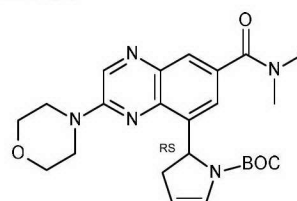
10

#### Example A2

##### Preparation of intermediate 6a and intermediate 6b



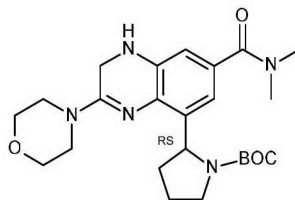
intermediate 6a



intermediate 6b

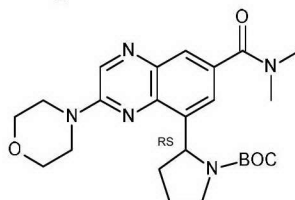
- 15 In a sealed vessel, a mixture of intermediate 5 (8 g; 21.9 mmol), N-boc-2,3-dihydro-1H-pyrrole (5.3 mL; 30.67 mmol) and K<sub>2</sub>CO<sub>3</sub> (9.08 g; 65.71 mmol) in anhydrous DMF (200 mL) was degazed under N<sub>2</sub>. PPh<sub>3</sub> (1.15 g; 4.38 mmol) then Pd(OAc)<sub>2</sub> (492 mg; 2.19 mmol) were added and the reaction mixture was heated at 100°C for 15h. The reaction was cooled down to rt, poured into H<sub>2</sub>O and EtOAc was added. The mixture
- 20 was filtered through a pad of celite® and the filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and evaporated until dryness. The residue (12 g) was purified by chromatography over silica gel (irregular SiOH; 15-40 μm; 120 g; gradient: from 0.1% NH<sub>4</sub>OH, 96% DCM, 4% MeOH to 0.1%

NH<sub>4</sub>OH, 92% DCM, 8% MeOH). The pure fractions were collected and the solvent was evaporated to give 6.2 g (62%, 50/50 by LCMS) of a mixture of intermediates 6a and 6b.



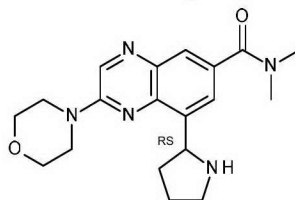
Preparation of intermediate 7:

- 5 A mixture of intermediates 6a and 6b (7 g; 15.43 mmol) and platinum (IV) oxide (713 mg; 3.09 mmol) in EtOH (200 mL) was hydrogenated at rt under a pressure of 1.2 bar of H<sub>2</sub> for 4h. The reaction was filtered through a pad of celite<sup>®</sup>, rinsed with MeOH and the filtrate was evaporated to give 6.8 g (97%) of intermediate 7. The product was used without purification for the next step.



- 10 Preparation of intermediate 8:

A mixture of intermediate 7 (6.8 g; 14.86 mmol), manganese oxide (3.9 g; 44.58 mmol) in DCM (150 mL) was stirred at rt for 1h. The reaction mixture was filtered through a pad of celite<sup>®</sup>, rinsed with MeOH and the filtrate was evaporated to give 7 g (quant.) of intermediate 8. The product was used without purification for the next step.



- 15 Preparation of intermediate 9:

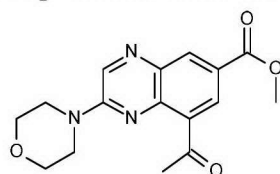
The experiment was performed twice on 3.5g of intermediate 8:

- At 10°C, HCl (4M in 1,4-dioxane) (9.6 mL; 38.41 mmol) was added dropwise to a solution of intermediate 8 (3.5 g; 7.68 mmol) in DCM (115 mL). The reaction mixture was stirred at rt for 5h. The mixture was taken-up with DCM and iced-water, basified with NH<sub>4</sub>OH and extracted with DCM. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The combined residues (5.46 g obtained from 2 experiments) was purified by chromatography over silica gel (irregular SiOH; 15-40 μm; 120 g; mobile phase: 0.1% NH<sub>4</sub>OH, 90% DCM, 10% MeOH). The pure fractions were collected and the solvent was evaporated to give 3.94 g (72%) of intermediate 9.

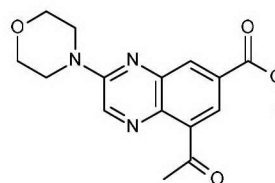
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## Example A3

Preparation of intermediate 10a and intermediate 10b



intermediate 10a



intermediate 10b

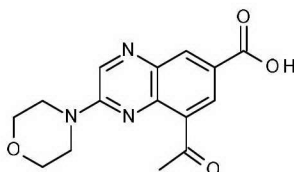
Tributyl(1-ethoxyvinyl)tin (67.68 g; 187.40 mmol) was added to a solution of a mixture  
 of intermediates 3a and 3b (60 g; 85.18 mmol) in anhydrous 1,4-dioxane (1.2 L) under  
 N<sub>2</sub>. Dichlorobis(triphenylphosphine) palladium (II) (3.59 g; 5.11 mmol) was added and  
 the mixture was purged again with N<sub>2</sub>. The reaction mixture was heated at 100°C  
 overnight. After cooling down to rt, a 3M aqueous solution of HCl was added and the  
 mixture was stirred at rt for 40min. The mixture was slowly basified with a saturated  
 aqueous solution of NaHCO<sub>3</sub> and EtOAc was added. The mixture was extracted with  
 EtOAc and the organic layer was washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub> and  
 evaporated. The residue was purified by column chromatography over silica gel  
 (eluent: from DCM/EtOAc 10/1 to DCM/EtOAc 8/1). The pure fractions were  
 collected and the solvent was evaporated to give a 10 g of mixture of intermediate 10a  
 and intermediate 10b and 30.5 g (54%) of intermediate 10a. The 10 g mixture of  
 intermediate 10a and intermediate 10b was further purified by chromatography over  
 silica gel (eluent: from DCM/EtOAc 10/1 to DCM/EtOAc 4/1). The pure fractions were  
 collected and the solvent was evaporated to give 1.6 g (3%) of intermediate 10b and 7 g  
 of mixture (intermediate 10a and intermediate 10b) (ratio 1/1 by NMR).

## Alternative preparation:

To a solution of a mixture of intermediates 3a and 3b (75/25 evaluated by LC/MS)  
 (195g, 554 mmol) in DMSO (2000 mL) was added vinylbutylether (166 g, 1661.  
 mmol) and TEA (400 mL, 2768 mmol, 0.7g/mL) under N<sub>2</sub> atmosphere. Pd(OAc)<sub>2</sub>  
 (12.4g, 55mmol) and DPPP (45.6g, 111mmol) were added. The mixture was purged  
 again with N<sub>2</sub> and heated to 100 °C overnight. After cooling down to room  
 temperature, HCl (3M, 1845mL, 5536 mmol) was added portionwise under ice batch  
 and the mixture was stirred for 1 hour. The pH of the mixture was adjusted to 8 with  
 NaHCO<sub>3</sub>. The mixture was filtered. The cake was washed with ethyl acetate (1000  
 mL), then dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1500 mL\*2) and filtered. The filtrate was washed with  
 brine (500 mL), evaporated to give a crude yellow solid (200 g) mainly containing  
 intermediate 10a. This residue was purified by silica gel chromatography (eluent: ethyl

acetate= 100%). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 100 g (57%) of intermediate 10a as yellow solid.

Alternatively, the previous reaction was also carried out using EtOH as solvent at a temperature of 70°C.

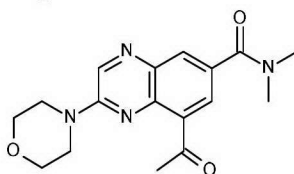


5 Preparation of intermediate 11:

Intermediate 11 was prepared according to an analogous procedure as described for the synthesis of intermediate 4, using intermediate 10a as starting material. The aqueous layer was extracted with DCM (2x). The organic layers were separated, washed with water, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The crude product was taken-up with diethylether, the precipitate was filtered off and dried under vacuum to give 3 g (63%, yellow solid) of intermediate 11. The product was used without purification for the next step.

Alternative pathway:

15 A 1M aqueous solution of NaOH (89 mL; 89.0 mmol) was added to a solution of intermediate 10a (9.35 g; 29.7 mmol) in THF (140 mL) and MeOH (140 mL). The reaction mixture was stirred at rt for 1h then evaporated until dryness under vacuum. The solid obtained was slowly acidified with 1N aqueous solution of HCl and filtered. The cake was dried under vacuum then taken-up in EtOH and evaporated under vacuum to give 8.90 g (quant., yellow solid) of intermediate 11. The product was used without purification for the next step.



Preparation of intermediate 12:

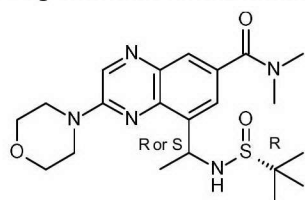
Intermediate 12 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 11 as starting material. The reaction mixture was stirred at rt for 1h then evaporated under vacuum. The residue was taken-up in EtOAc and a mixture of a saturated aqueous solution of NaHCO<sub>3</sub> and water (50/50) was added. The aqueous layer was separated and extracted with EtOAc (3x). The combined organic layers were washed with a saturated aqueous solution of brine (3x), dried over MgSO<sub>4</sub>, filtered off and evaporated in vacuum. The residue (14.2 g, orange foam) was purified by chromatography over silica gel (Irregular SiOH; 15-40



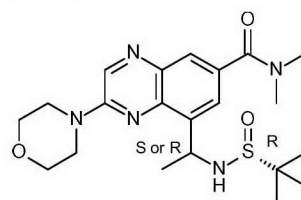
$\mu\text{m}$ ; 300 g; mobile phase: 30% heptane, 70% EtOAc/MeOH (9/1)). The pure fractions were collected and the solvent was evaporated to give 7.80 g (80%, yellow solid) of intermediate 12.

#### 5 Example A4

Preparation of intermediate 13a and intermediate 13b



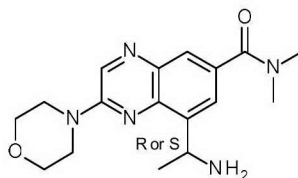
intermediate 13a



intermediate 13b

Intermediate 12 (1.30 g; 3.96 mmol) was added to a solution of (R)-(+)-2-methyl-2-propanesulfonamide (1.44 g; 11.9 mmol) and titanium(IV) ethoxide (4.98 mL; 23.8 mmol) in THF (42 mL) at rt. The reaction mixture was heated at reflux (70°C) for 18h. Then, the reaction mixture was cooled down to -50°C and NaBH<sub>4</sub> (150 mg; 3.96 mmol) was added portionwise. The mixture was allowed to slowly warm to rt and stirred for 1h. The mixture was cooled down to 0°C and MeOH was slowly added (bubbling in the mixture). The crude was then poured into a saturated aqueous solution of NaCl and filtered. The cake was rinsed with EtOAc and the filtrate was extracted with EtOAc. The organic layer was separated, washed with water, dried over MgSO<sub>4</sub>, filtered off and evaporated under vacuum. The residue (2.30 g) was purified by chromatography over silica gel (Irregular SiOH; 15-40  $\mu\text{m}$ ; 80 g; mobile phase: 70% heptane, 30% iPrOH/NH<sub>4</sub>OH (9/1)). The pure fractions were collected and the solvent was evaporated. The residue (800 mg) was combined with another little batch (34 mg) and the mixture was purified by chromatography over silica gel (Irregular SiOH; 15-40  $\mu\text{m}$ ; 30 g; gradient: from 100% DCM to 90% DCM, 10% iPrOH). The pure fractions were collected and the solvent was evaporated to give 260 mg (15%) of intermediate 13a and 175 mg (10%) of intermediate 13b (first product eluted by chromatography).

25



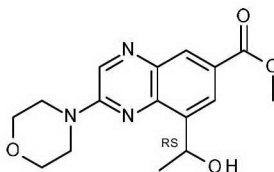
Preparation of intermediate 14:

HCl (4M in 1,4-dioxane) (192  $\mu\text{L}$ ; 767  $\mu\text{mol}$ ) was added to a solution of intermediate 13a (334 mg; 767  $\mu\text{mol}$ ) in 1,4-dioxane (7.6 mL). The reaction mixture was stirred at rt

for 1h. The mixture was combined with another batch coming from a reaction performed on 20 mg of intermediate 13a and basified with a saturated aqueous solution of NaHCO<sub>3</sub>. The aqueous layer was separated and extracted with EtOAc (3x). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and evaporated under vacuum. The residue (265 mg) was purified by chromatography over silica gel (Irregular SiOH; 15-40 µm; 10 g; gradient: from 100% DCM to 90% DCM, 10% (9/1) MeOH/NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated to give 95 mg (37%, yellow foam) of fraction 1 and 53 mg (21%, yellow foam) of fraction 2. Fraction 2 was purified by achiral SFC (CHIRALPAK AD-H; 5 µm 250x20 mm; mobile phase: 75% CO<sub>2</sub>, 25% MeOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 37 mg (15%, yellow film) of intermediate 14.

Fraction 1 was purified by chromatography over silica gel (Irregular SiOH; 15-40 µm; 10 g; gradient: from 100% DCM to 90% DCM, 10% (9/1) MeOH/NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated. The residue (yellow foam) was purified by chiral SFC (CHIRALPAK AD-H 5 µm 250x20 mm; mobile phase: 75% CO<sub>2</sub>, 25% MeOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 59 mg (23%, pale yellow film) of intermediate 14.

## Example A5



Preparation of intermediate 15:

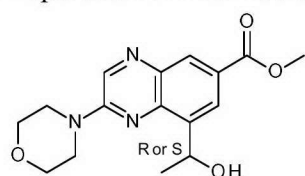
Cerium(III) chloride (8.2 g; 33.3 mmol) was added to a solution of intermediate 10a (10 g; 31.7 mmol) in MeOH (220 mL) and DCM (100 mL). The reaction mixture was stirred at rt for 30min. The mixture was cooled down to 0°C and NaBH<sub>4</sub> (1.32 g; 34.9 mmol) was added portionwise (bubbling in the mixture). The reaction mixture was stirred at rt for 1h30. Then, DCM and water were added. The layers were separated, the aqueous layer was extracted with DCM (2x) and the combined organics layers were dried over MgSO<sub>4</sub>, filtered off and evaporated in vacuum. The residue (9.65 g) was recrystallized with MeOH and diethylether. The precipitate was filtered and dried to give 7.98 g (79%) of intermediate 15.

Alternative pathway:

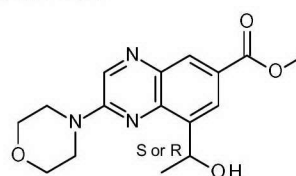
NaBH<sub>4</sub> (1.01 g; 26.6 mmol) was added to a solution of intermediate 10a (7.94 g; 22.2 mmol) in MeOH (140 mL) and DCM (70 mL) at 0°C. The reaction mixture was slowly

warmed to rt and stirred for 30min. The mixture was slowly quenched with water. DCM was added and the layers were separated. The aqueous layer was extracted with DCM (2x). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and evaporated under vacuum. The residue (7.9 g, orange solid) was purified by chromatography over silica gel (regular SiOH; 30 μm; 300 g; gradient: from 70% DCM, 30% EtOAc to 30% DCM, 70% EtOAc). The pure fractions were collected and the solvent was evaporated. The residue (5.35 g, yellow solid) was triturated in diethylether and filtered to give 4.95 g (70%, pale yellow solid) of intermediate 15.

#### 10 Preparation of intermediate 15a and intermediate 15b



intermediate 15a

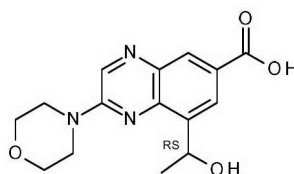


intermediate 15b

Intermediate 15a and intermediate 15b were obtained after chiral SFC (Stationary phase: CHIRALPAK IC 5μm 250x30mm, Mobile phase: 55% CO<sub>2</sub>, 45% EtOH (0.3% iPrNH<sub>2</sub>)) of intermediate 15. Crystallization from ACN and diethylether afforded 444 mg (22%) of intermediate 15a (M.P.: 163°C, DSC) and 593 mg (30%) of intermediate 15b (M.P.: 146°C, DSC).

#### Alternative preparation of intermediate 15b

Intermediate 10a and (-)-*B*-chlorodiisopinocampheylborane (1.25 eq.) were stirred in dichloromethane (10 volumes) at -35 °C. After complete conversion, diethanolamine (2.7 eq.) was added to remove the boron byproducts. The mixture was refluxed for two hours and the solid formed was filtered and discarded. The filtrate was washed twice with water, concentrated to 1-2 volumes and petrol ether was added. The solid was filtered and re-slurried in methyl tertiobutylether. The procedure was executed on 50 g, 200 g and 300 g scale of intermediate 10a in 93% average yield (e.e.: 90%).



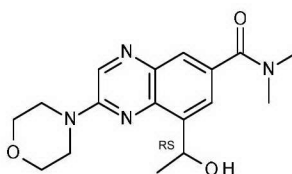
#### Preparation of intermediate 16:

Intermediate 16 was prepared according to an analogous procedure as described for the synthesis of intermediate 4, using intermediate 15 as starting material. At 0°C, the

solution was acidified with 3N aqueous solution of HCl slowly and stirred at 10°C for 1h. The precipitate was filtered and dried to give 1.4 g (39%) of intermediate 16. The filtrate was extracted with DCM (2x). The organic layers were combined, washed with water, dried over MgSO<sub>4</sub>, filtered and evaporated to give additional 1.8 g (50%, yellow solid) of intermediate 16. The 2 batches were combined to give 3.2 g (89% global yield) of intermediate 16 directly use in the next step without any further purification.

Alternative pathway:

Intermediate 16 was prepared according to an analogous procedure as described for the synthesis of intermediate 11 (alternative preparation), using intermediate 15 as starting material. The reaction mixture was stirred at rt overnight then evaporated until dryness under vacuum. The solid obtained was slowly acidified with a 1N aqueous solution of HCl and filtered on a glass frit to give 1.4 g (100%, off-white solid) of intermediate 16.



Preparation of intermediate 17:

Intermediate 17 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 16 as starting material. The residue was taken-up in EtOAc and a mixture of a saturated aqueous solution of NaHCO<sub>3</sub> was added. The aqueous layer was separated and extracted with EtOAc (2x) and DCM/MeOH (9/1) (2x). The combined organic layers were dried over MgSO<sub>4</sub>, filtered off and evaporated under vacuum. The residue (2.1 g, orange oil) was purified by chromatography over silica gel (regular SiOH; 30 µm; 80 g; gradient: 100% DCM to 30% DCM, 70% EtOAc). The pure fractions were collected and the solvent was evaporated to give 220 mg (14%, orange foam, not pure by NMR) of intermediate 17 and 905 mg (59%, yellow foam) of intermediate 17.

Alternative pathway:

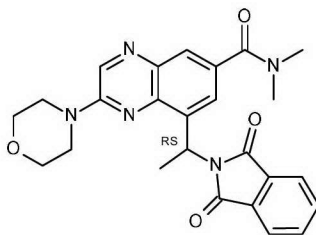
Intermediate 17 was prepared according to an analogous procedure as described for the synthesis of intermediate 15 (alternative pathway), using intermediate 12 as starting material. The reaction mixture was stirred at 0°C for 15min. The mixture was quenched with water and slowly warmed to rt. The aqueous layer was extracted with DCM (2x), then DCM/MeOH (9/1) (2x). The combined organics layers were dried over MgSO<sub>4</sub>, filtered off and evaporated in vacuum. The residue (1.68 g, pale yellow foam) was purified by chromatography over silica gel (irregular SiOH; 15-40 µm; 50 g; eluent:

from 100% DCM to 96% DCM, 4% MeOH). The pure fractions were collected and the solvent was evaporated to give 1.29 g (79%, pale yellow foam) of intermediate 17.

Alternative pathway:

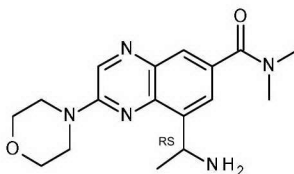
- 5 Intermediate 17 was prepared according to an analogous procedure as described for the synthesis of intermediate 15, using intermediate 12 as starting material. The reaction mixture was stirred at rt for 15h. Then, DCM and ice-water were added and the mixture was stirred at rt for 1h. The aqueous layer was extracted with DCM (2x) and the combined organics layers were dried over MgSO<sub>4</sub>, filtered off and evaporated in
- 10 vacuum. The residue was taken-up with diethylether, the precipitate was filtered and dried to give 1.73 g (87%) of intermediate 17.

#### 15 Example A6



Preparation of intermediate 18:

- Phtalimide (2.54 g; 17.3 mmol), PPh<sub>3</sub> (4.53 g; 17.3 mmol) and di-tert-butyl azodicarboxylate (3.97 g, 17.3 mmol) were added to a solution of intermediate 17 (3.80 g; 11.5 mmol) in THF (110 mL). The reaction mixture was stirred at rt for 18h. Then,
- 20 the mixture was evaporated under vacuum and the residue (16 g, orange foam) was purified by chromatography over silica gel (regular SiOH; 30 µm; 300 g; gradient: from 70% heptane, 30% EtOAc/MeOH (9/1) to 30% heptane, 70% EtOAc/MeOH (9/1)). The pure fractions were collected and the solvent was evaporated to give 4.62 g (49%, pale brown foam) of intermediate 18.



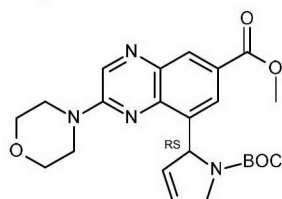
#### 25 Preparation of intermediate 19:

Hydrazine monohydrate (1.50 mL; 24.5 mmol) was added to a suspension of intermediate 18 (2.35 g; 2.46 mmol) in EtOH (24 mL). The reaction mixture was heated at 80°C for 18h. Then, the mixture was cooled down to rt and filtered. The solid was rinsed with EtOH and the filtrate was evaporated under vacuum. The residue (2.35

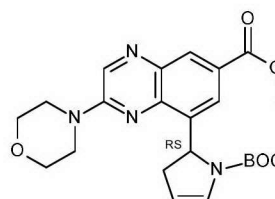
g, orange solid) was combined with another batch coming from a reaction performed on 2.27 g of intermediate 18, and the resulting product was diluted in DCM/MeOH (9/1). The precipitate was filtered on a glass frit and the filtrate was evaporated under vacuum and purified by chromatography over silica gel (regular SiOH; 30  $\mu$ m; 200 g; gradient: from 100% DCM to 90% DCM, 10% MeOH/NH<sub>4</sub>OH (9/1)). The pure fractions were collected and the solvent was evaporated to give 835 mg (45%, brown oil) of intermediate 19.

#### Example A7

Preparation of intermediate 20a and intermediate 20b



intermediate 20a

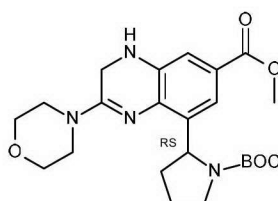


intermediate 20b

A mixture of intermediate 20a and intermediate 20b was prepared according to an analogous procedure as described for the synthesis of intermediate 6, using intermediate 3a as starting material. The residue (3.2 g) was purified by chromatography over silica gel (irregular SiOH; 15-40  $\mu$ m; 80 g; eluent: 99% DCM, 1% MeOH). The pure fractions were collected and the solvent was evaporated to give 1.9 g (79%) of a mixture of intermediate 20a and intermediate 20b.

#### Alternative pathway:

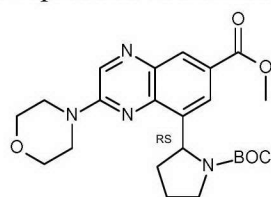
In a sealed glassware, a mixture of intermediate 3a and intermediate 3b (75/25) (10 g; 28.39 mmol), N-boc-2,3-dihydro-1H-pyrrole (6.86 mL; 39.75 mmol) and K<sub>2</sub>CO<sub>3</sub> (11.8 g; 85.18 mmol) in 1,4-dioxane (250 mL) was bubbled with N<sub>2</sub>. Then, PPh<sub>3</sub> (1.49 g; 5.68 mmol) and Pd(OAc)<sub>2</sub> (640 mg; 2.84 mmol) were added. The reaction mixture was heated to 100°C for 5h. The reaction mixture was cooled down to rt, poured onto water and extracted with EtOAc. The organic layer was decanted, washed with brine, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (21 g) was purified by chromatography over silica gel (irregular SiOH; 20-45  $\mu$ m; 450 g; mobile phase: 62% heptane, 3% MeOH (+10% NH<sub>4</sub>OH), 35% EtOAc). The pure fractions were collected and evaporated to dryness yielding 2.3 g (17%, impure) of intermediate 20a and 8.2 g (59%) of intermediate 20a.



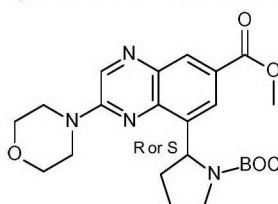
Preparation of intermediate 21:

Intermediate 21 was prepared according to an analogous procedure as described for the synthesis of intermediate 7, using intermediate 20a as starting material. The reaction mixture was stirred at rt for 45min. intermediate 21 (11 g, 100%) was directly used without any further purification in the next step.

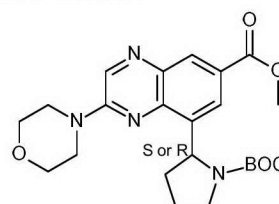
Preparation of intermediate 22a, intermediate 22b and intermediate 22c



Intermediate 22a

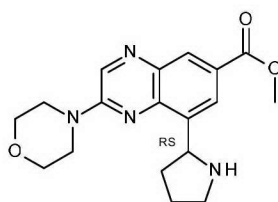


Intermediate 22b



Intermediate 22c

Intermediate 22a were prepared according to an analogous procedure as described for the synthesis of intermediate 8, using intermediate 21 as starting material. The residue (12 g) was purified by chromatography over silica gel (irregular SiOH; 15-40  $\mu$ m; 800 g; mobile phase: 99% DCM, 1% MeOH). The pure fractions were collected and the solvent was evaporated to give respectively 3.7 g (31%) of intermediate 22a and additional 7.3 g (61%) of intermediate 22a. This last fraction was purified by chiral SFC (Whelk O1 (S,S) 5  $\mu$ m; 250\*21.1 mm; mobile phase: 60% CO<sub>2</sub>, 40% EtOH). The pure fractions were collected and the solvent was evaporated to give 3.45 g (29%) of intermediate 22b and 3.38 g (28%) of intermediate 22c.

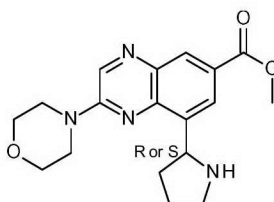


Preparation of intermediate 23:

Intermediate 23 was prepared according to an analogous procedure as described for the synthesis of intermediate 9, using intermediate 22a as starting material. The reaction mixture was stirred at rt for 15h. The mixture was poured into DCM and a saturated aqueous solution of NaHCO<sub>3</sub> then, extracted with DCM (3x). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue was

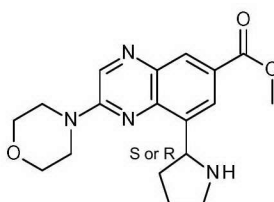


taken-up with Et<sub>2</sub>O. The precipitate was filtered and dried to give 3.5 g (90%) of intermediate 23.



Preparation of intermediate 24:

- Intermediate 24 was prepared according to an analogous procedure as described for the  
 5 synthesis of intermediate 23, using intermediate 22b as starting material. 8.4 g (88%) of intermediate 24 was obtained.

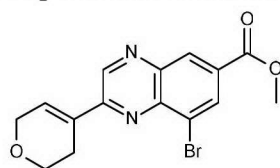


Preparation of intermediate 25:

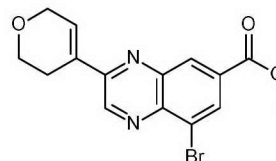
- Intermediate 25 was prepared according to an analogous procedure as described for the  
 synthesis of intermediate 23, using intermediate 22c as starting material. 2 1.68 g  
 10 (75%) of intermediate 25 was obtained.

#### Example A8

Preparation of intermediate 26a and intermediate 26b



intermediate 26a



intermediate 26b

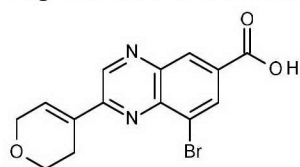
- 15 In a Schlenk tube, a mixture of intermediate 2a (4.0 g; 13.27 mmol), 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (3.34 g; 15.92 mmol), K<sub>3</sub>PO<sub>4</sub> (8.45 g; 39.80 mmol) in 1,4-dioxane (80 mL) and H<sub>2</sub>O (8 mL) was carefully degassed under vacuum and back-filled with N<sub>2</sub> (3x). Then, Pd.Cl<sub>2</sub>(dppf).DCM (0.54 g; 0.66 mmol) was added. The mixture was carefully degassed under vacuum and back-filled with N<sub>2</sub> (3x) and then  
 20 stirred at 80°C for 8 h. After cooling down to rt, the mixture was diluted with DCM and filtered through a pad of celite®. The filtrate was evaporated under vacuum. The residue (brown) was purified by chromatography over silica gel (Regular SiOH; 30 µm; 200 g; eluent: from 100% DCM to 85% DCM, 15% EtOAc). The pure fractions were collected and the solvent was concentrated until precipitation. The solid was filtered



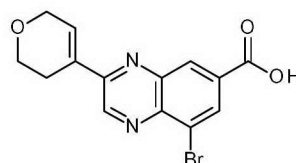
and dried to give 2.7 g (58%, beige solid) of a mixture of intermediate 26a and 26b (92/8 evaluated by  $^1\text{H}$  NMR). The filtrate was evaporated under vacuum to give additional 455 mg (10%, pale brown solid) of a mixture of intermediate 26a and 26b (80/20 evaluated by  $^1\text{H}$  NMR).

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#### Preparation of intermediate 27a and intermediate 27b



intermediate 27a

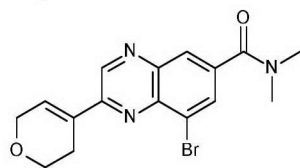


intermediate 27b

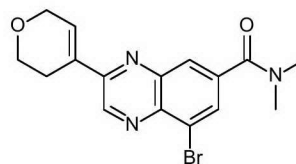
In a round bottom flask, at  $0^\circ\text{C}$ , to a mixture of intermediate 26a and 26b (2.7g; 7.35 mmol; 92/8) in EtOH (50 mL) and THF (50 mL) was added 1M aqueous NaOH (14.7 mL, 14.7 mmol). The reaction mixture was stirred allowing the temperature to reach rt over 1h. Additional THF (20 mL) and EtOH (20 mL) were added and the stirring was continue for 1 hour. Then, the solvent were evaporated. The resulting residue was diluted with water and acidified with 1M aqueous solution of HCl to pH 2. The aqueous layer was extracted with a mixture of DCM/MeOH (9/1, 7x). The combined organic layers were washed with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ , dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated to give 2.27 g (92%, beige solid) of a mixture of intermediate 27a and 27b (93/7 evaluated by  $^1\text{H}$  NMR).

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#### Preparation of intermediate 28a and intermediate 28b



intermediate 28a



intermediate 28b

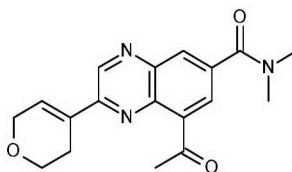
20

A mixture of intermediate 28a and 28b was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using a mixture of intermediate 27a and 27b as starting material. The reaction mixture was stirred at rt for 18h. The residue (6.6 g) was mixed with crude coming from a reaction performed on 380 mg of a mixture of intermediate 27a and 27b (~85/15, evaluated by  $^1\text{H}$  NMR) and the resulting residue was purified by chromatography over silica gel (regular SiOH; 30  $\mu\text{m}$ ; 200 g; mobile phase: from 100% DCM to 98% DCM, 2% MeOH). The pure

25

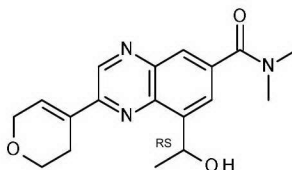
fractions were collected and the solvent was evaporated. The residue (4.03 g, sticky yellow solid) was dried under vacuum for 16 h to give 3.40 g (yellow sticky solid) which was triturated in Et<sub>2</sub>O (~10 mL). The supernatant was removed and the solid was triturated once more with Et<sub>2</sub>O (~10 mL). The supernatant was removed and the solid was dried to give 3.24 g (yellow solid, impure) of a mixture of intermediate 28a and 28b (92/8 evaluated by <sup>1</sup>H NMR). The product was used without further purification for the next step.

#### Example A9



#### 10 Preparation of intermediate 29:

Intermediate 29 was prepared according to an analogous procedure as described for the synthesis of intermediate 10, using intermediate 28 as starting material. The reaction mixture was stirred at 80°C for 8h. The residue was purified by chromatography over silica gel (regular SiOH; 30 μm; 200 g; gradient: from 99% DCM, 1% iPrOH to 95% DCM, 5% iPrOH). The pure fractions were collected and the solvent was evaporated to give 969 mg (40%, clear orange solid) of intermediate 29.

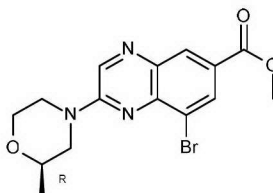


#### Preparation of intermediate 30:

Intermediate 30 was prepared according to an analogous procedure as described for the synthesis of intermediate 15, using intermediate 29 as starting material. The reaction mixture was stirred at rt for 15h. The residue was purified by chromatography over silica gel (irregular 15-40 μm; 24 g; mobile phase: from 50% heptane, 5% MeOH, 35% EtOAc). The pure fractions were collected and the solvent was evaporated to give 600 mg (73%) of intermediate 30.

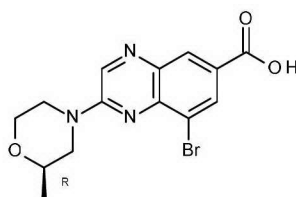
25

#### Example A10



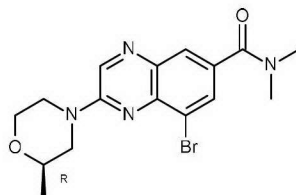
#### Preparation of intermediate 31:

- (R)-2-methylmorpholine hydrochloride (1.53 g; 11.11 mmol) and triethylamine (3.09 mL; 22.22 mmol) were added to a solution of intermediates 2a and 2b (67/23) (5 g; 11.11 mmol) in THF (100 mL). The reaction mixture was stirred at rt for 2h. The precipitate was filtered off and the cake was washed with EtOAc. The filtrate was evaporated under vacuum and the residue (6.52 g, brown oil) was purified by chromatography over silica gel (irregular SiOH 15-40  $\mu$ m; 200 g; mobile phase: from 100% DCM to 70% DCM, 30% EtOAc). The pure fractions were collected and the solvent was evaporated to give 2.61 g (59%, yellow solid) of intermediate 31.



#### 10 Preparation of intermediate 32:

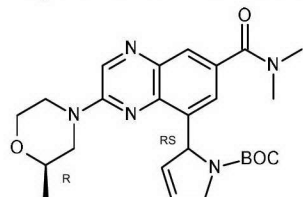
Intermediate 32 was prepared according to an analogous procedure as described for the synthesis of intermediate 4, using intermediate 31 as starting material (2.06 g, 90%, yellow solid).



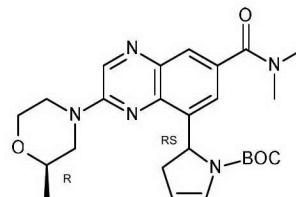
#### Preparation of intermediate 33:

- 15 Intermediate 33 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 32 as starting material (1.97 g, quant., orange foam).

#### Preparation of intermediate 34a and intermediate 34b



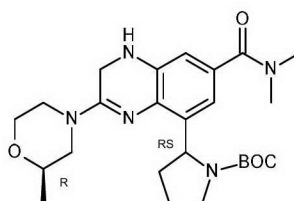
intermediate 34a



intermediate 34b

#### 20

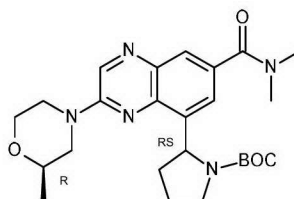
A mixture of intermediates 34a and 34b was prepared according to an analogous procedure as described for the synthesis of intermediate 6, using intermediate 33 and N-boc-2,3-dihydro-1H-pyrrole as starting material (1.88 g, 82%, yellow foam).



Preparation of intermediate 35:

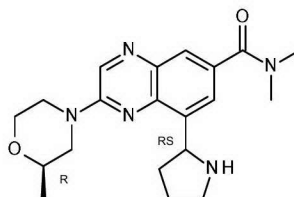
Intermediate 35 was prepared according to an analogous procedure as described for the synthesis of intermediate 7, using a mixture of intermediate 34a and 34b as starting material (1.76 g, 93%, green foam).

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Preparation of intermediate 36:

Intermediate 36 was prepared according to an analogous procedure as described for the synthesis of intermediate 8, using intermediate 35 as starting material (1.79 g, 100%, yellow foam).



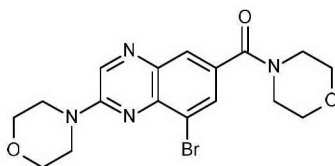
10 Preparation of intermediate 37:

HCl (4M in 1,4-dioxane) (4.67 mL; 18.68 mmol) was added to a solution of intermediate 36 (1.79 g; 3.74 mmol) in 1,4-dioxane (37 mL). The reaction mixture was stirred at 50°C overnight. The mixture was cooled to rt and evaporated under vacuum. The residue was taken-up in DCM and water. The aqueous layer was slowly basified with NaHCO<sub>3</sub> (solid). The layers were separated and the aqueous layer was extracted with DCM (2x) and with DCM/MeOH (9/1) (2x). The combined organic layer were dried over MgSO<sub>4</sub>, filtered and evaporated under vacuum. The residue (1.32 g, orange foam) was purified by chromatography over silica gel (irregular SiOH 15-40 μm; 50 g; gradient: from 100% DCM to 90% DCM, 10% MeOH (+5% NH<sub>4</sub>OH)). The pure fractions were collected and the solvent was evaporated to give 1.08 g (77%, yellow foam) of intermediate 37.

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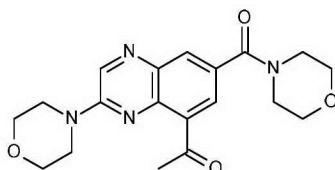
Example A11



Preparation of intermediate 40:

Intermediate 40 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 4 and morpholine as starting material (1.61 g, 84%).

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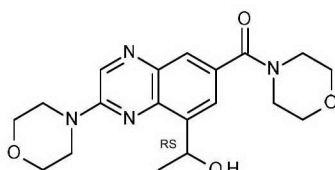


Preparation of intermediate 41:

Intermediate 41 was prepared according to an analogous procedure as described for the synthesis of intermediate 10, using intermediate 40 as starting material (1.28 g, 87%).

10 Alternative pathway:

Intermediate 41 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 11 and morpholine as starting material (2.6 g, 85%).



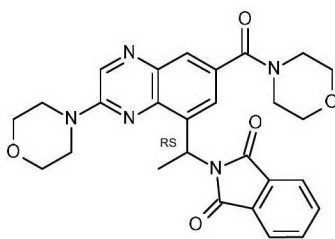
Preparation of intermediate 42:

15 Intermediate 42 was prepared according to an analogous procedure as described for the synthesis of intermediate 15, using intermediate 41 as starting material (1 g, 83%).

Alternative pathway:

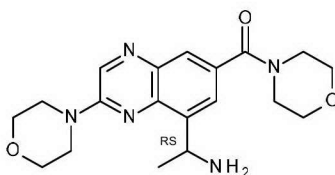
20 Intermediate 42 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 16 and morpholine as starting material (3 g, 76%).

Example A12



Preparation of intermediate 43:

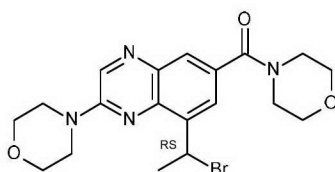
Intermediate 43 was prepared according to an analogous procedure as described for the synthesis of intermediate 18, using intermediate 42 and phthalimide as starting material (386 mg, 79%).



5 Preparation of intermediate 44:

Intermediate 44 was prepared according to an analogous procedure as described for the synthesis of intermediate 19, using intermediate 43 and hydrazine monohydrate as starting material (152 mg, 53%).

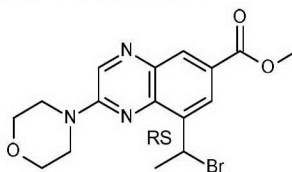
10 Example A13



Preparation of intermediate 45:

In a sealed tube, at 10°C, phosphorus tribromide (0.67 mL; 7.05 mmol) was added dropwise to a solution of intermediate 42 (1.75 g; 4.70 mmol) in DCM (20 mL). The reaction mixture was stirred at rt for 72h. A precipitate was filtered, washed with Et<sub>2</sub>O and dried to give 1.5 g (62%) of intermediate 45.

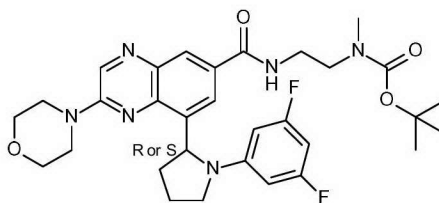
15



Preparation of intermediate 87:

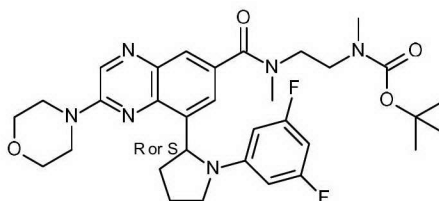
Intermediate 87 was prepared according to an analogous procedure as described for the synthesis of intermediate 45, using intermediate 15 as starting material (3.3 g, 57%).

20 Example A14



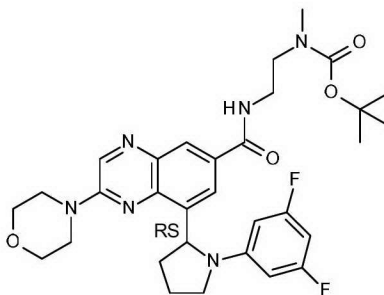
Preparation of intermediate 49:

Under N<sub>2</sub>, N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester (108  $\mu$ L; 0.59 mmol) was added to a solution of compound 251 (130 mg; 0.30 mmol), HBTU (224 mg; 0.59 mmol) and DIPEA (305  $\mu$ L; 1.77 mmol) in DMF (4 mL) at rt. The solution was stirred at rt for 72h. The solution was poured into ice-water. The product was extracted with EtOAc and washed with brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (190 mg) was purified by chromatography over silica gel (irregular 15-40  $\mu$ m; 24 g; mobile phase: 95% DCM, 5% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated to give 150 mg (85%) of intermediate 49.



Preparation of intermediate 50:

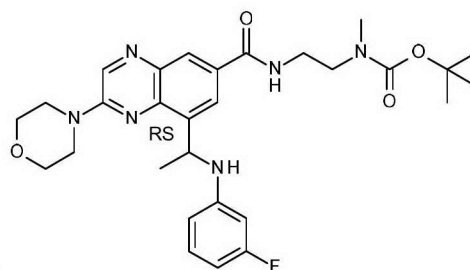
Intermediate 50 was prepared according to an analogous procedure as described for the synthesis of intermediate 49, using compound 251 and N-methyl-N-[2-(methylamino)ethyl]-1,1-dimethylethyl ester carbamic acid as starting material (450 mg, >100%).



Preparation of intermediate 85:

Intermediate 85 was prepared according to an analogous procedure as described for the synthesis of intermediate 49, using compound 62 and N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester as starting materials (193 mg, 71%).

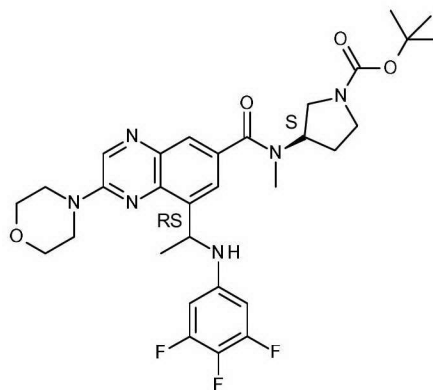
118



Preparation of intermediate 187:

Intermediate 187 was prepared according to an analogous procedure as described for the synthesis of intermediate 49 using compound 263 as starting materials (1.17g, used without purification for the next step).

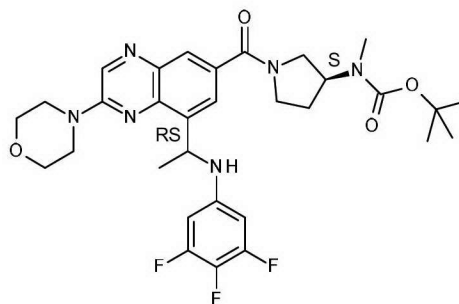
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Preparation of intermediate 188 :

Intermediate 188 was prepared according to an analogous procedure as described for the synthesis of intermediate 49, using compound 170 and (S)-tert-Butyl 3-(methylamino)pyrrolidine-1-carboxylate as starting materials (1.02g; 44% of purity evaluated by LC/MS).

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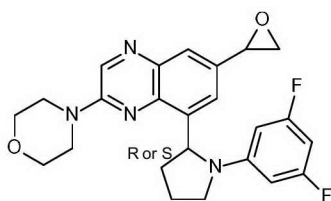
Preparation of intermediate 189 :

Intermediate 189 was prepared according to an analogous procedure as described for the synthesis of intermediate 49 using compound 170 and (S)-3-(N-Boc-N-methylamino)pyrrolidine as starting materials (760 mg, used without purification).

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Example A15



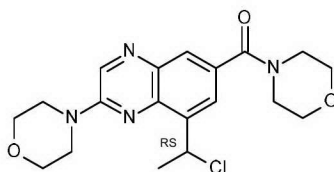


Preparation of intermediate 51:

Sodium hydride (71 mg; 1.77 mmol) was added to a solution of trimethylsulfonium iodide (361 mg; 1.77 mmol) in THF (10 mL) at rt under N<sub>2</sub> flow. After 1h at 50°C, a solution of compound 250 (500 mg; 1.18 mmol) in THF (10mL) was added dropwise.

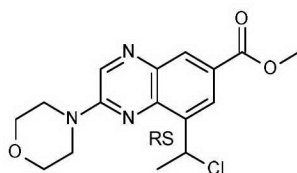
- 5 The reaction mixture was heated at 70°C for 1h. The mixture was poured into water and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and evaporated. The residue (650 mg) was purified by chromatography over silica gel (50 g; mobile phase: 98% DCM, 2% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated to give 450 mg (87%) of intermediate 51.

Example A16



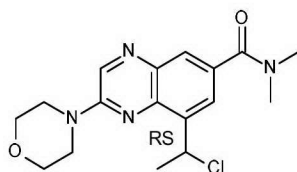
Preparation of intermediate 52:

- 15 At 10°C, thionyl chloride (0.39 mL; 5.37 mmol) was added to a solution of intermediate 42 (1 g; 2.69 mmol) in DCM (20 mL) under N<sub>2</sub>. The solution was stirred at 10°C for 4h. The mixture was evaporated to give 1.05 g (100%) of intermediate 52. The crude intermediate was directly used without purification in the next step.



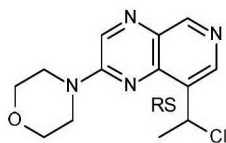
Preparation of intermediate 105:

- 20 Intermediate 105 was prepared according to an analogous procedure as described for the synthesis of intermediate 52, using intermediate 15 as starting material (15 g).



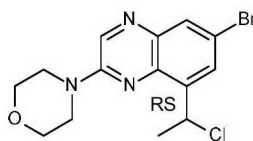
Preparation of intermediate 119:

Intermediate 119 was prepared according to an analogous procedure as described for the synthesis of intermediate 52, using intermediate 17 as starting material (1 g, >100%). The crude product was used without purification in the next step.



5 Preparation of intermediate 139:

Intermediate 139 was prepared according to an analogous procedure as described for the synthesis of intermediate 52, using intermediate 138 as starting material (370 mg, quant.). The product was used without purification in the next step.

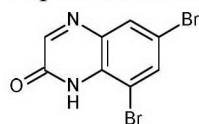


10 Preparation of intermediate 145:

Intermediate 145 was prepared according to an analogous procedure as described for the synthesis of intermediate 52, using intermediate 56 as starting material (9 g, quant.). The product was used without purification for the next step.

15 Example A17

Preparation of intermediate 53a: and intermediate 53b



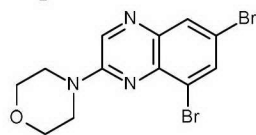
intermediate 53a



intermediate 53b

A mixture of intermediate 53a and intermediate 53b was prepared according to an analogous procedure as described for the synthesis of intermediate 1a, using 3,5-dibromo-1,2-benzenediamine and 2,2-dihydroxy-acetic acid as starting material (59 g, 90%).

Preparation of intermediate 54a and intermediate 54b



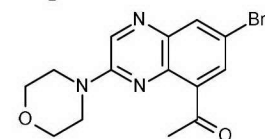
intermediate 54a



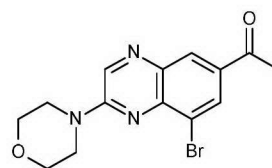
intermediate 54b

A mixture of intermediate 54a and intermediate 54b was prepared according to an analogous procedure as described for the synthesis of intermediate 3a, using a mixture of intermediates 54a and 54b and morpholine as starting material (41.5 g, 92%).

### 5 Preparation of intermediate 55a and intermediate 55b



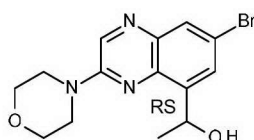
intermediate 55a



intermediate 55b

The experiment was performed twice on the same quantity (15 g; 40.2 mmol) of a mixture of intermediates 54a and 54b:

In a Schlenk reactor, a solution of mixture of intermediates 54a and 54b (15 g; 40.2 mmol) and tributyl(1-ethoxyvinyl)tin (14.9 mL; 44.2 mmol) in 1,4-dioxane (400 mL) was degassed under N<sub>2</sub>. Pd(PPh<sub>3</sub>)<sub>4</sub> (2.32 g; 2.01 mmol) was added and the mixture was degassed under N<sub>2</sub> and was heated at 100°C overnight. Then, more Pd(PPh<sub>3</sub>)<sub>4</sub> (2.32 g; 2.01 mmol) was added. The reaction mixture was degassed under N<sub>2</sub> and heated at 100°C for 24h. The mixture was quenched with a 1M aqueous solution of HCl (120 mL) and stirred at rt for 30min. The resulting solution was basified with NaHCO<sub>3</sub> solid. The 2 batches were combined and filtered through a pad of celite®. The cake was washed with water and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered and evaporated under vacuum. The crude product was triturated in Et<sub>2</sub>O and filtered. The precipitate (23 g, yellow solid) was purified by chromatography over silica gel (irregular SiOH; 15-40 µm; 330+220 g; gradient: 63% heptane, 35% EtOAc, 2% MeOH). The fractions containing the product were collected and the solvent was evaporated. The residue (15 g, pale yellow solid) was further purified by chromatography over silica gel (Irregular SiOH 20-45 µm; 450 g; mobile phase: 99.5% DCM, 0.5% MeOH) and then by achiral SFC (CHIRALPAK IC 5 µm 250x30 mm; mobile phase: 45% CO<sub>2</sub>, 55% MeOH (0.3% iPrNH<sub>2</sub>) (7.3% DCM)). The pure fractions were collected and the solvent was evaporated to give 2.7 g (9%, pale yellow solid) of intermediate 54a, 3.0 g (11%, yellow solid) of intermediate 55a and 1.06 g (3%, yellow solid) of intermediate 55b.

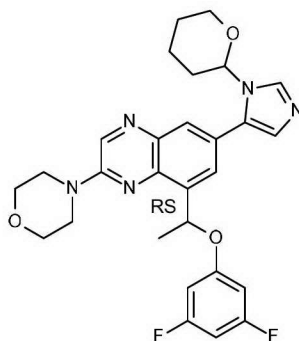


### 30 Preparation of intermediate 56:

Intermediate 56 was prepared according to an analogous procedure as described for the synthesis of intermediate 15, using intermediate 55a as starting material (200 mg, 99%).

5 Alternative pathway:

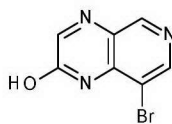
Intermediate 56 was prepared according to an analogous procedure as described for the synthesis of intermediate 15 (alternative pathway), using intermediate 55a as starting material (396 mg, 54%).



Preparation of intermediate 58:

- 10 A solution of compound 277 (282 mg; 0.63 mmol), 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-imidazole (226 mg; 0.81 mmol) and  $K_2CO_3$  (173 mg; 1.25 mmol) in 1,4-dioxane (4.27 mL) and water (0.64 mL) was degassed under  $N_2$ .  $PdCl_2(dppf)$ .DCM (51 mg; 62.6  $\mu$ mol) was added and the reaction mixture was heated at 95°C overnight. The resulting suspension was quenched with
- 15 water (10 mL) and extracted with EtOAc (3x20 mL). The combined organic layers were dried over  $MgSO_4$ , filtered and evaporated under reduced pressure. The residue was purified by chromatography over silica gel (irregular SiOH; 15-40  $\mu$ m; 12 g; gradient: from 100% heptane to 90% EtOAc, 10% MeOH (+5%  $NH_4OH$ )). The pure fractions were collected and the solvent was evaporated to give 127 mg (39%, brown
- 20 solid) of intermediate 58.

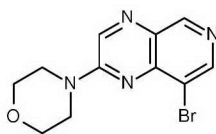
Example A18



Preparation of intermediate 59:

- Intermediate 59 was prepared according to an analogous procedure as described for the synthesis of intermediate 1a, using intermediate 5-bromo-3,4-pyridinediamine and ethyl glyoxalate solution (50% in toluene) as starting materials (53.5 g, 47%).
- 25

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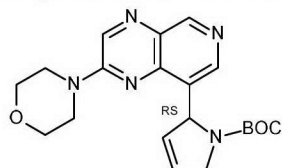


Preparation of intermediate 60:

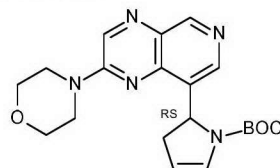
Intermediate 60 was prepared according to an analogous procedure as described for the synthesis of intermediate 3a, using intermediate intermediate 59 and morpholine as starting materials (30 g, 44%).

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Preparation of intermediate 61a and intermediate 61b



intermediate 61a

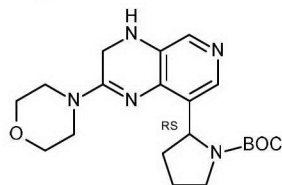


intermediate 61b

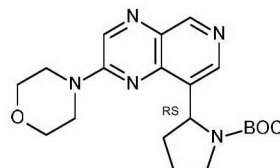
A mixture of intermediate 61a and 61b was prepared according to an analogous procedure as described for the synthesis of intermediate 6a and intermediate 6b, using intermediate 60 and N-boc-2,3-dihydro-1H-pyrrole as starting materials (800 mg, 62%).

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Preparation of intermediate 62a and intermediate 62b



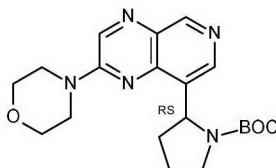
intermediate 62a



intermediate 62b

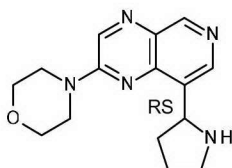
A mixture of intermediates 62a and 62b was prepared according to an analogous procedure as described for the synthesis of intermediate 7, using a mixture of intermediates 61a and 61b and platinum (IV) oxide as starting materials at atmospheric pressure for 3h (750 mg, quant.).

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Preparation of intermediate 63:

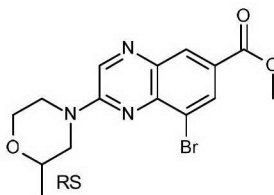
Intermediate 63 was prepared according to an analogous procedure as described for the synthesis of intermediate 8, using a mixture of intermediates 62a and 62b and manganese oxide as starting materials (623 mg, 83%).



5 Preparation of intermediate 64:

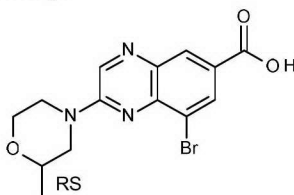
Intermediate 64 was prepared according to an analogous procedure as described for the synthesis of intermediate 9, using intermediate 63 as starting material (300 mg, 65%).

Example A19



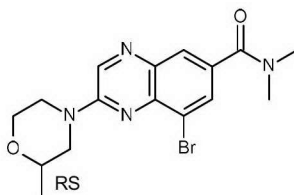
10 Preparation of intermediate 65:

Intermediate 65 was prepared according to an analogous procedure as described for the synthesis of intermediate 3a, using intermediate 2a and 2-methylmorpholine as starting materials (1.58 g, 81%, yellow solid).



Preparation of intermediate 66:

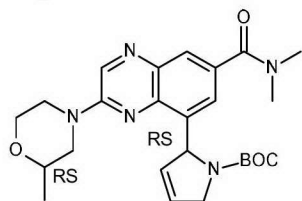
- 15 Intermediate 36 was prepared according to an analogous procedure as described for the synthesis of intermediate 4, using intermediate 65 as starting material (1.39 g, 92%, yellow solid).



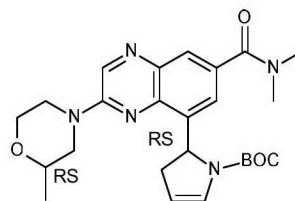
Preparation of intermediate 67:

- 20 Intermediate 67 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 66 as starting material (1.43 g, 96%, yellow foam).

## Preparation of intermediate 68a and intermediate 68b

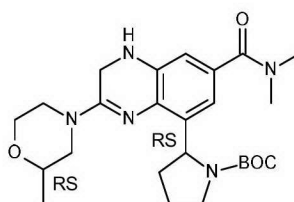


intermediate 68a



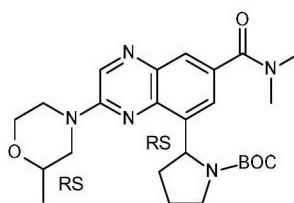
intermediate 68b

A mixture of intermediates 68a and 68b was prepared according to an analogous procedure as described for the synthesis of intermediate 6, using intermediate 67 and N-boc-2,3-dihydro-1H-pyrrole as starting materials (370 mg, 81%, yellow oil).



## Preparation of intermediate 69:

A mixture of intermediates 68a and 68b (370 mg; 0.79 mmol) and platinum (IV) oxide (37 mg; 0.16 mmol) in MeOH (4 mL) and THF (4 mL) was hydrogenated at rt under pressure of 1 bar of H<sub>2</sub> for 16h. Then, more platinum (IV) oxide (18 mg; 0.08 mmol) was added and the mixture was hydrogenated at rt under pressure of 1 bar of H<sub>2</sub> for 16h. The reaction was filtered through a pad of celite® and rinsed with MeOH. The filtrate was combined with another batch from 30mg of intermediates 68a and 68b and was evaporated to give 355 mg (82%) of intermediate 69. The product was directly used in the next step without any further purification.



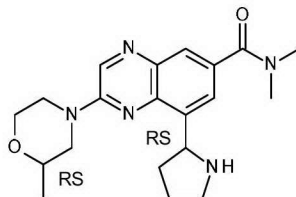
## Preparation of intermediate 70:

Intermediate 70 was prepared according to an analogous procedure as described for the synthesis of intermediate 8, using intermediate 69 as starting material (279 mg, 79%, yellow foam).

## Alternative pathway:

Sec-Butyllithium (1.3M in THF) (2.29 mL; 2.97 mmol) was added to a solution of N-Boc-pyrrolidine (521  $\mu$ L; 2.97 mmol) and N,N,N',N'-tetramethylenediamine (446  $\mu$ L;

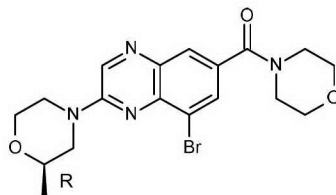
- 2.97 mmol) in THF (3.72 mL) under N<sub>2</sub> at -78°C. The solution was stirred 1h30 at -78°C. Zinc chloride (2M in Me-THF) (1.49 mL; 2.97 mmol) was added slowly. The reaction was stirred 30min at -78°C then 1h at rt. Intermediate 67 (600 mg; 1.49 mmol), Pd(OAc)<sub>2</sub> (13 mg; 0.06 mmol) and tri-tert-butylphosphonium tetrafluoroborate (35 mg; 0.12 mmol) were added. Then, the reaction mixture was heated at 60°C for 30min. The mixture was combined with another batch coming from a reaction performed on 500 mg of intermediate 67. The mixture was quenched with a saturated solution of NH<sub>4</sub>Cl and extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated in vacuum. The residue (2.2 g, orange oil) was purified by chromatography over silica gel (regular SiOH 30 µm; 80 g; gradient: from 80% DCM, 20% EtOAc to 100% EtOAc). The pure fractions were collected and the solvent was evaporated to give 156 mg (12%, yellow foam) of intermediate 70.



Preparation of intermediate 71:

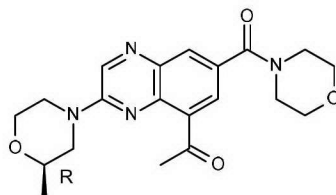
- Intermediate 71 was prepared according to an analogous procedure as described for the synthesis of intermediate 37, using intermediate 70 as starting material (157 mg, 69%, orange oil).

Example A20



- Preparation of intermediate 74:

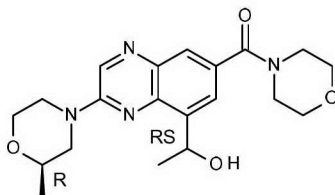
Intermediate 74 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 32 and (R)-2-methylmorpholine as starting materials (2.76 g, quant.). The product was directly used without any purification in the next step.



- Preparation of intermediate 75:



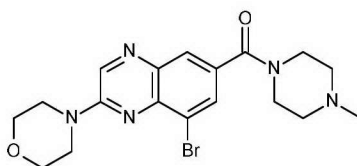
Intermediate 75 was prepared according to an analogous procedure as described for the synthesis of intermediate 10a, using intermediate 74 as starting material (316 mg, 74%).



Preparation of intermediate 76:

- 5 Intermediate 76 was prepared according to an analogous procedure as described for the synthesis of intermediate 15, using intermediate 75 as starting material (81 mg, 67%).

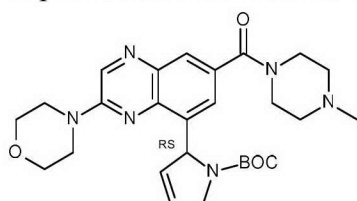
Example A21



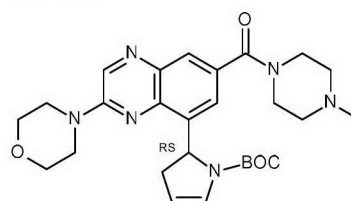
Preparation of intermediate 77:

- 10 Intermediate 77 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 4 and 1-methylpiperazine as starting materials (1.6 g, 86%).

Preparation of intermediate 78a and intermediate 78b



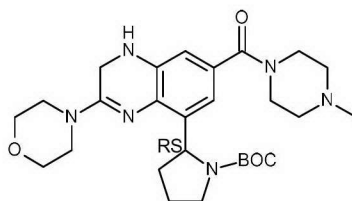
intermediate 78a



intermediate 78b

- 15 A mixture of intermediate 78a and 78b was prepared according to an analogous procedure as described for the synthesis of intermediates 6a and 6b, using intermediate 77 and N-boc-2,3-dihydro-1H-pyrrole as starting materials (1.2 g, 62%, ratio by <sup>1</sup>H NMR: 65/35).

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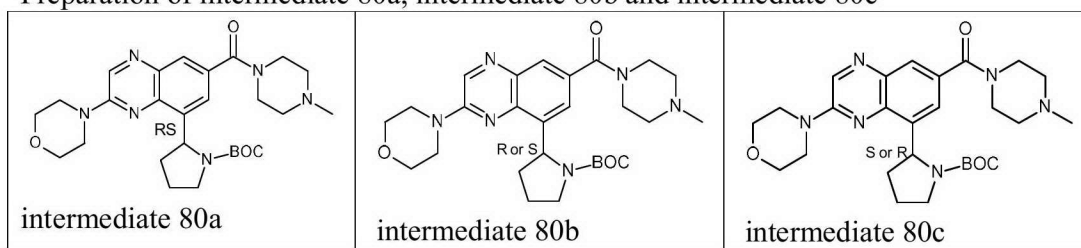


Preparation of intermediate 79:

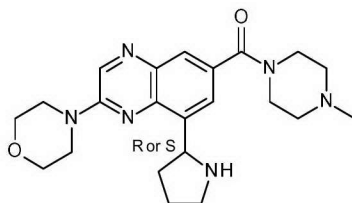
Intermediate 79 was prepared according to an analogous procedure as described for the synthesis of intermediate 7, using a mixture of intermediates 78a and 78b in MeOH as starting materials (1.2 g, quant.).

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Preparation of intermediate 80a, intermediate 80b and intermediate 80c



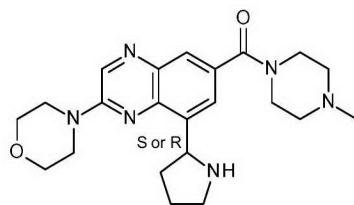
A mixture of intermediate 79 (1.2 g; 2.34 mmol), manganese oxide (0.61g; 7.02 mmol) in DCM (30 mL) was stirred at rt for 1h. The reaction mixture was filtered through a pad of celite®, rinsed with MeOH and the filtrate was evaporated. The residue (1.1 g) was purified by chromatography over silica gel (irregular 15-40  $\mu$ m; 50 g; mobile phase: 40% heptane, 10% MeOH (+10%  $\text{NH}_4\text{OH}$ ), 50% EtOAc). The pure fractions were collected and the solvent was evaporated to give 0.58 g (48%) of intermediate 80a. The racemic product was purified by chiral SFC (Whelk O1 (S,S) 5  $\mu$ m 250\*21.1 mm; mobile phase: 45%  $\text{CO}_2$ , 55% MeOH). The pure fractions were collected and the solvent was evaporated to give 265 mg (22%) of intermediate 80b and 265 mg (22%) of intermediate 80c.



Preparation of intermediate 81

Intermediate 81 was prepared according to an analogous procedure as described for the synthesis of intermediate 9, using intermediate 80b as starting material (100 mg, 47%).

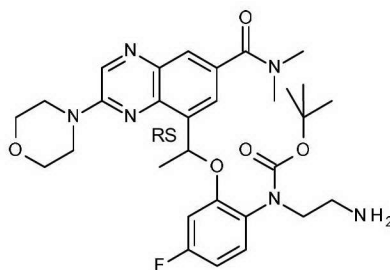
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#### Preparation of intermediate 82

Intermediate 82 was prepared according to an analogous procedure as described for the synthesis of intermediate 9, using intermediate 80c as starting material (120 mg, 56%).

#### 5 Example A22



#### Preparation intermediate 86:

In a sealed tube, a mixture of compound 78 (290 mg; 0.57 mmol), N-boc-1,2-diaminoethane (179  $\mu$ L; 1.13 mmol) and  $\text{Cs}_2\text{CO}_3$  (554 mg; 1.70 mmol) in 2-methyl-2-butanol (2.76 mL) was carefully degassed under vacuum and back-filled with  $\text{N}_2$ .  
 10 BrettPhos Precatalyst First Gen (23 mg; 0.03 mmol) and BrettPhos (6 mg; 0.01 mmol) were added. The reaction mixture was carefully degassed under vacuum and back-filled with  $\text{N}_2$  and heated at  $110^\circ\text{C}$  for 3h. After cooling down to rt, BrettPhos Precatalyst First Gen (23 mg; 0.03 mmol) and BrettPhos (6 mg; 0.01 mmol) were added. The reaction mixture was degassed in vacuum and back-filled with  $\text{N}_2$  and heated at  $110^\circ\text{C}$   
 15 for 4h. After cooling down to rt, the mixture was combined with a batch coming from a reaction performed on 40 mg of compound 78. The crude was diluted with EtOAc and filtered through a pad of celite<sup>®</sup>. The filtrate was evaporated in vacuum to dryness. The residue (758 mg, brown oil) was purified by chromatography over silica gel (Irregular SiOH 15-40  $\mu\text{m}$ ; 40 g; gradient: from 85% heptane, 13.5% EtOAc, 1.5% MeOH to  
 20 50% heptane, 45% EtOAc, 5% MeOH). The pure fractions were collected and the solvent was evaporated. The residue (309 mg) was purified by chromatography over silica gel (Irregular bare silica; 40 g; mobile phase: 53% heptane, 7% MeOH (+10%  $\text{NH}_4\text{OH}$ ), 35% EtOAc). The pure fractions were collected and the solvent was evaporated to give 180 mg (55%, pale yellow foam) of intermediate 86.

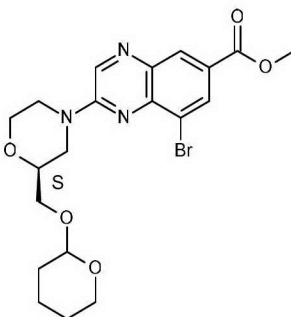
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#### Example A23



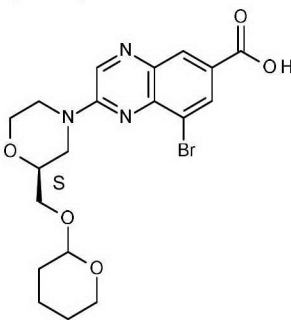
Preparation of intermediate 88:

- Pyridinium p-toluenesulfonate (409 mg; 1.63 mmol) and 3,4-dihydro-2H-pyran (2.98 mL; 32.6 mmol) were added to a solution of (S)-2-hydroxymethylmorpholine hydrochloride (2.5 g; 16.28 mmol) in DCM (160 mL). The reaction mixture was stirred at rt overnight. Then, a saturated aqueous solution of NaHCO<sub>3</sub> was added and the layers were separated. The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum to give 2.29 g (70%, yellow oil) of intermediate 88.



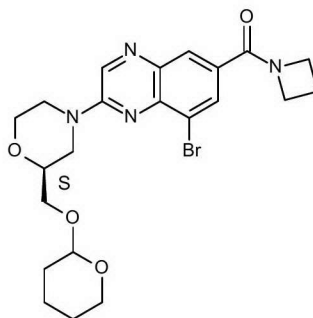
Preparation of intermediate 89:

- Intermediate 89 was prepared according to an analogous procedure as described for the synthesis of intermediate 31, using intermediate 2a and intermediate 88 as starting materials (1.42 g, 92%, yellow crystals).



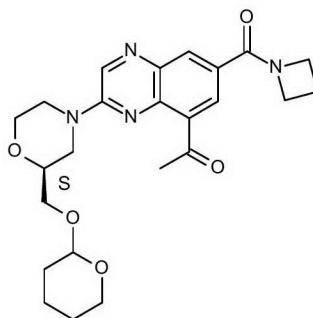
Preparation of intermediate 90:

- Intermediate 90 was prepared according to an analogous procedure as described for the synthesis of intermediate 11, using intermediate 89 as starting material. The reaction mixture was stirred at rt overnight. The mixture was evaporated under vacuum and the residue was slowly acidified with 10% aqueous solution of NH<sub>4</sub>Cl. Then, DCM was added and the layers were separated. The organic layer was washed with saturated aqueous solution of NH<sub>4</sub>Cl and the product was extracted with DCM/MeOH (9/1) (3x). The combined organic layer were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under vacuum to give 1.5 g (yellow solid) of intermediate 90.



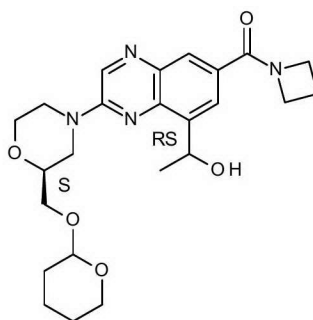
Preparation of intermediate 91:

Intermediate 81 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 90 and azetidine hydrochloride as starting materials (407 mg, 55%, yellow foam).



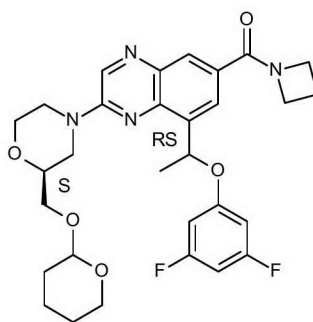
Preparation of intermediate 92:

Intermediate 92 was prepared according to an analogous procedure as described for the synthesis of intermediate 10a, using intermediate 91 as starting material (110 mg, 33%, yellow oil).



Preparation of intermediate 93:

Intermediate 93 was prepared according to an analogous procedure as described for the synthesis of intermediate 15 (alternative pathway), using intermediate 92 as starting material (116 mg, pale yellow foam).

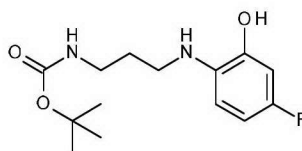


Preparation of intermediate 94:

Intermediate 94 was prepared according to an analogous procedure as described for the synthesis of compound 247, using intermediate 93 and 3,5-difluorophenol as starting materials (46 mg, 34%, colorless oil).

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Example A24

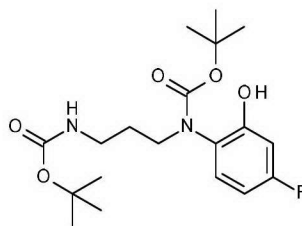


Preparation of intermediate 95:

Tert-butyl 3-aminopropylcarbamate (1.31 mL; 7.49 mmol) was added to a solution of 4-fluoro-2-hydroxybenzaldehyde (1 g; 7.14 mmol) in MeOH (70 mL). The reaction mixture was stirred at rt overnight. Then, sodium borohydride (540 mg; 14.27 mmol) was added portionwise and the reaction mixture was stirred at rt for 1h30. The mixture was slowly quenched with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ . The mixture was evaporated under vacuum and the residue was taken-up with EtOAc and water. The layers were separated. The organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated in vacuum. The residue (2.25 g, pale yellow oil) was triturated in  $\text{Et}_2\text{O}$  and evaporated under vacuum (2x) to give 2.10 g (99%, white solid) of intermediate 95.

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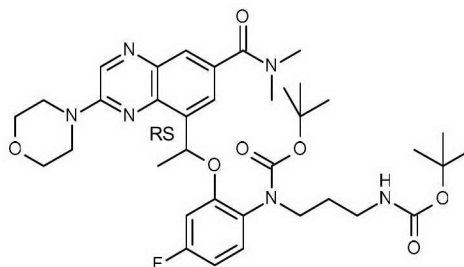


Preparation of intermediate 96:

Ditert-butyl dicarbonate (878 mg; 4.02 mmol) was added to a solution of intermediate 95 (1 g; 3.35 mmol) and triethylamine (1.40 mL; 10.06 mmol) in DCM (34 mL) at  $0^\circ\text{C}$ . The reaction mixture was stirred at rt overnight. Then, the mixture was washed with a saturated aqueous solution of  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated under vacuum. The residue (1.7 g, colourless oil) was purified

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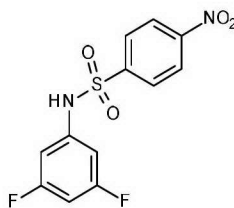
by chromatography over silica gel (irregular SiOH; 15-40  $\mu$ m; 80 g; eluent: from 90% heptane, 10% DCM to 10% heptane, 90% DCM). The pure fractions were collected and the solvent was evaporated to give 614 mg (46%, white foam) of intermediate 96.



#### 5 Preparation of intermediate 97:

Intermediate 97 was prepared according to an analogous procedure as described for the synthesis of compound 247, using intermediate 17 and intermediate 96 as starting materials (435 mg, 61%, yellow foam).

#### 10 Example A25

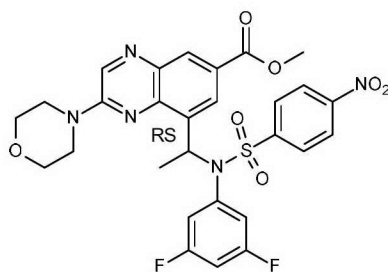


#### Preparation of intermediate 98:

A solution of 3,5-difluoroaniline (2 g; 15.49 mmol), 4-nitrobenzenesulfonyl chloride (3.61 g; 16.27 mmol) and 4-dimethylaminopyridine (37.9 mg; 0.31 mmol) in pyridine (60 mL) was heated at 100°C for 18h. After cooling down to rt, the solution was evaporated under vacuum and taken-up in DCM. The organic layer was successively washed with 1N aqueous solution of HCl (x2), water and a saturated aqueous solution of NaCl. Then, it was dried over MgSO<sub>4</sub>, filtered and evaporated under vacuum to give 4.5 g (92%, beige solid) of intermediate 98.

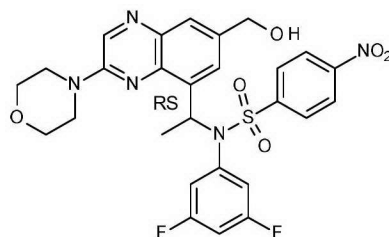
#### 20 Alternative pathway:

In a microwave tube, 4-nitrobenzenesulfonyl chloride (2.7 g; 12.20 mmol) was added to a mixture of 3,5-difluoroaniline (1.5 g; 11.62 mmol) and 4-dimethylaminopyridine (28 mg; 232  $\mu$ mol) in pyridine (15 mL). The mixture was heated at 100°C using one single mode microwave with a power output ranging from 0 to 400 W for 30min. The mixture was then evaporated under vacuum and taken-up in DCM. The organic layer was successively washed with 1N aqueous solution of HCl (x2), water and a saturated aqueous solution of NaCl. Then, it was dried over MgSO<sub>4</sub>, filtered and evaporated under vacuum to give 2.9 g (79%, beige solid) of intermediate 98.



#### Preparation of intermediate 99:

Intermediate 99 was prepared according to an analogous procedure as described for the synthesis of compound 277, using intermediate 15 and intermediate 98 as starting materials. The reaction mixture was heated at 110°C overnight. The mixture was cooled down to rt, poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular 15-40 µm; 50 g; mobile phase: 98% DCM, 2% MeOH). The pure fractions were collected and the solvent was evaporated. The residue (0.85 g) was purified by chromatography over silica gel (irregular 15-40 µm; 50 g; mobile phase: 50% heptane, 45% EtOAc, 5% MeOH). The pure fractions were collected and the solvent was evaporated to give 430 mg (45%) of intermediate 99.

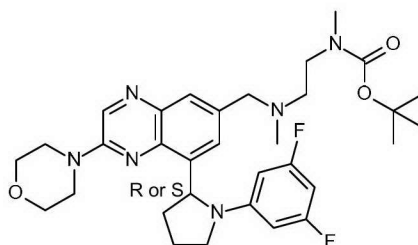


#### Preparation of intermediate 100:

Diisobutylaluminum hydride (Solution 20% in toluene) (3 mL; 3.59 mmol) was added dropwise to a solution of intermediate 99 (440 mg; 0.72 mmol) in THF (15 mL) at -70°C under N<sub>2</sub>. The reaction mixture was stirred for 4h at -70°C. The mixture was poured carefully into a solution of ice and NH<sub>4</sub>Cl, then extracted with DCM. The organic layer was washed with water and dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (450 mg) was purified by chromatography over silica gel (irregular 15-40 µm; 40 g; gradient: from 0.1% NH<sub>4</sub>OH, 3% MeOH, 97% DCM to 0.1% NH<sub>4</sub>OH, 5% MeOH, 95% DCM). The pure fractions were collected and the solvent was evaporated to give 100 mg (24%) of intermediate 100.

Example A26



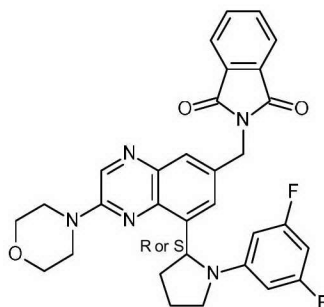


Preparation of intermediate 103:

Compound 250 (100 mg; 0.24 mmol) was added to a solution of tert-butyl methyl[2-methylamino]ethyl]carbamate (221 mg; 1.18 mmol) and sodium acetate (97 mg; 1.18 mmol) in MeOH (3 mL). The reaction mixture was stirred at rt for 4h. Then, sodium borohydride (18 mg; 0.47 mmol) was added portionwise at 0°C and the reaction mixture was stirred at rt for 1h30. Then, water was added and the product extracted with EtOAc. The organic layer was washed with brine (x2), then dried over MgSO<sub>4</sub>, filtered and evaporated to give 279 mg (quant.) of intermediate 103. The crude product was used without purification in the next step.

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Example A27



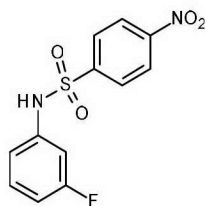
Preparation of intermediate 104:

Diisopropyl azodicarboxylate (277  $\mu$ L; 1.41 mmol) and PPh<sub>3</sub> (369 mg; 1.41 mmol) in THF (5 mL) was stirred at rt for 15min. A solution of compound 10 (200 mg; 0.47 mmol) and phthalimide (207 mg; 1.41 mmol) in THF (5 mL) was added dropwise and the reaction mixture was heated at 40°C for 24h. The mixture was evaporated until dryness. The residue (985 mg) was purified by chromatography over silica gel (irregular 15-40  $\mu$ m; 40 g; mobile phase: 60% heptane, 5% MeOH, 35% EtOAc). The pure fractions were collected and evaporated to give 750 mg (quant.) of intermediate 104.

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Example A28

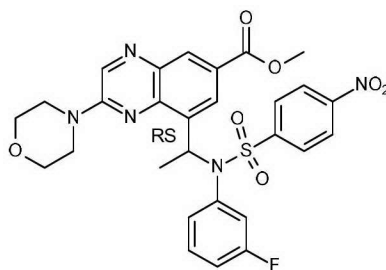
136



Preparation of intermediate 106:

Intermediate 106 was prepared according to an analogous procedure as described for the synthesis of intermediate 98, using 3-fluoroaniline and 4-nitrobenzenesulfonyl chloride as starting material (4.97 g, 93%, pale brown solid).

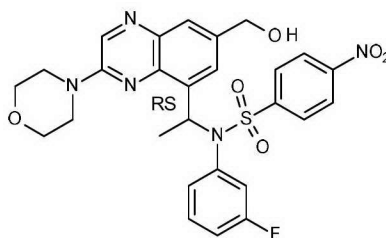
5



Preparation of intermediate 107:

Intermediate 107 was prepared according to an analogous procedure as described for the synthesis of compound 277, using intermediate 15 and intermediate 106 as starting materials (2.63 g, 47%, brown solid). The reaction mixture was heated at 120°C for 18h.

10



Preparation of intermediate 108:

Intermediate 108 was prepared according to an analogous procedure as described for the synthesis of intermediate 100, using intermediate 107 as starting material (73 mg, 33%, yellow solid).

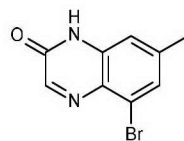
15

Example A29

Preparation of intermediate 109a and intermediate 109b



intermediate 109a

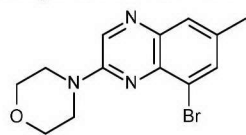


intermediate 109b

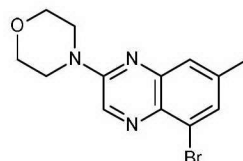
A mixture of intermediates 109a and 109b was prepared according to an analogous procedure as described for the synthesis of intermediate 1, using 3-bromo-5-

methylbenzene-1,2-diamine and 2,2-dihydroxy-acetic acid as starting materials (21 g, 100%).

#### Preparation of intermediate 110a and intermediate 110b



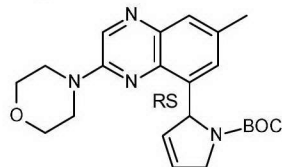
intermediate 110a



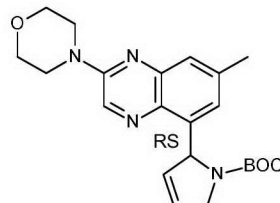
intermediate 110b

- 5 A mixture of intermediates 110a and 110b was prepared according to an analogous procedure as described for the synthesis of intermediates 3a and 3b, using a mixture of intermediates 109a and 109b and morpholine as starting materials (14.3 g, 52%, ration 1/1 by NMR).

#### 10 Preparation of intermediate 111a:and intermediate 111b



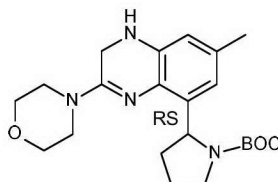
intermediate 111a



intermediate 111b

Intermediates 111a and 111b were prepared according to an analogous procedure as described for the synthesis of intermediate 20a (alternative pathway), using a mixture of intermediates 110a and 110b and N-boc-2,3-dihydro-1H-pyrrole as starting materials (257 mg, 13% of intermediate 111b and 833 mg, 43% of intermediate 111a).

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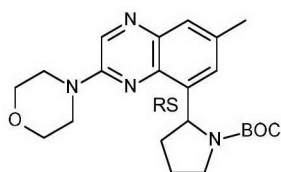


#### Preparation of intermediate 112:

Intermediate 112 was prepared according to an analogous procedure as described for the synthesis of intermediate 7, using intermediate 111a as starting material (879 mg, quant.). The reaction mixture was stirred for 1h30. The crude was used without purification for the next step.

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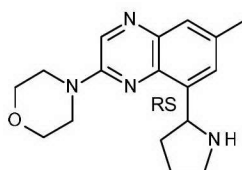
138



Preparation of intermediate 113:

Intermediate 113 was prepared according to an analogous procedure as described for the synthesis of intermediate 8, using intermediate 112 as starting material (782 mg, 94%). The reaction mixture was stirred at rt for 18h.

5



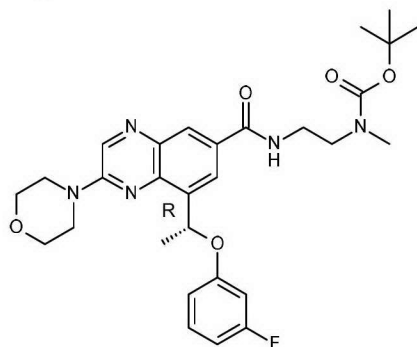
Preparation of intermediate 114:

Intermediate 114 was prepared according to an analogous procedure as described for the synthesis of intermediate 9, using intermediate 113 as starting material (405 mg, 74%). The reaction mixture was stirred at rt for 15h.

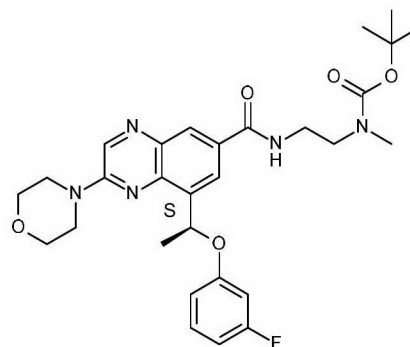
10

Example A30

Preparation of intermediate 118a and intermediate 118b



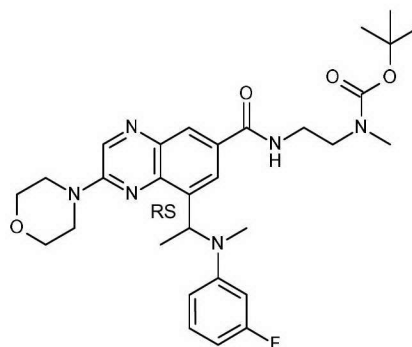
intermediate 118a



intermediate 118b

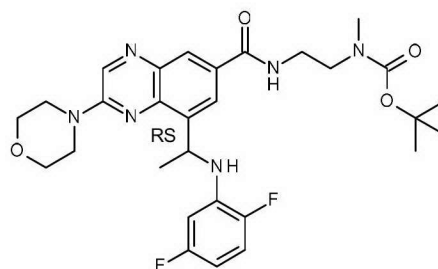
Intermediate 118a and intermediate 118b were prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 257a and N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester as starting materials (163 mg, 34%, pale yellow oil of intermediate 118a and 172 mg, 32%, pale yellow oil of intermediate 118b .

15



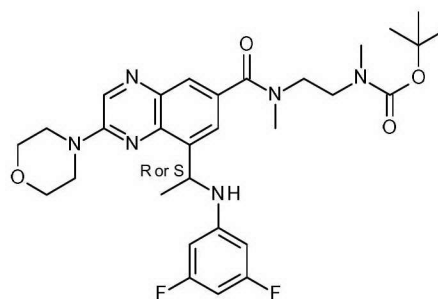
Preparation of intermediate 122:

Intermediate 122 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 98 as starting material (324 mg, 77%).



5 Preparation of intermediate 125:

Intermediate 125 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 261 and N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester as starting materials (450 mg, quant.).



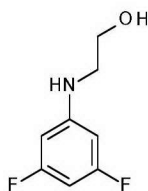
10 Preparation of intermediate 129:

Intermediate 129 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 83b and N-methyl-N-[2-(methylamino)ethyl]-1,1-dimethylethyl ester carbamic acid as starting materials (95 mg, 27%).

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Example A31

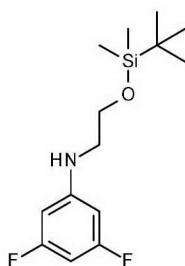
140



Preparation of intermediate 120:

A mixture of 3,5-difluoroaniline (15 g; 116.2 mmol), 2-bromoethanol (14.5 g; 116.2 mmol) and DIPEA (140 mL) was heated at 140°C overnight in a sealed vessel. The reaction mixture was filtered to give 18 g (90%) of intermediate 120.

5



Preparation of intermediate 121:

A mixture of intermediate 120 (10 g; 57.8 mmol), tert-butyldimethylsilyl chloride (8.7 g; 57.8 mmol), imidazole (3.9 g; 57.8 mmol) in DMF (300 mL) was stirred at rt overnight. The reaction was poured into water and extracted with EtOAc. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was evaporated to give 12 g (75%) of intermediate 121.

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Alternative pathway:

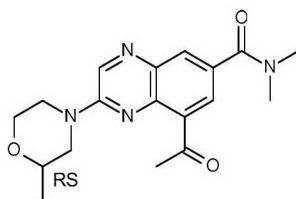
In a sealed tube, a mixture of 3,5-difluoroaniline (1 g; 7.75 mmol), (2-bromoethoxy)-tertbutyldimethylsilane (1.83 mL; 8.52 mmol) and DIPEA (3.3 mL) was stirred at 140°C overnight. The reaction mixture was poured into water, extracted with DCM, washed with brine then with H<sub>2</sub>O(2x). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated until dryness. The residue (3 g, brown oil) was purified by chromatography over silica gel (irregular 15-40 µm; 50 g; mobile phase: 98% heptane, 2% EtOAc). The pure fractions were collected and evaporated until dryness to give 0.5 g (22%) of intermediate 121 and 1.5 g (not pure) which was purified by chromatography over silica gel (irregular 15-40 µm; 80 g; mobile phase: 99% heptane, 1% EtOAc). The pure fractions were collected and evaporated to give additional 650 mg (29%) of intermediate 121.

20

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Example A32

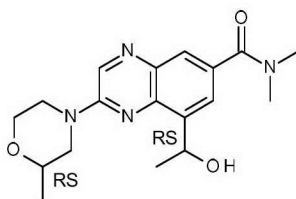
141



Preparation of intermediate 126:

Intermediate 126 was prepared according to an analogous procedure as described for the synthesis of intermediate 10, using intermediate 67 and tributyl(1-ethoxyvinyl)tin as starting materials (385 mg, 69%, yellow solid).

5

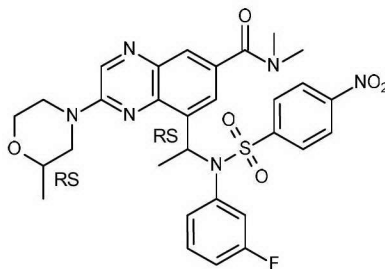


Preparation of intermediate 127:

Intermediate 127 (undetermined mixture of 4 diastereoisomers) was prepared according to an analogous procedure as described for the synthesis of intermediate 15 (alternative pathway), using intermediate 126 as starting material (254 mg, 66%, yellow foam).

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Example A33



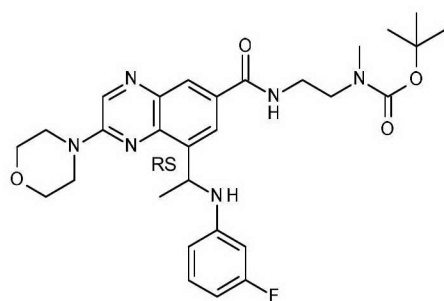
Preparation of intermediate 128:

Intermediate 128 (undetermined mixture of 4 diastereoisomers) was prepared according to an analogous procedure as described for the synthesis of compound 277, using intermediate 127 and intermediate 106 as starting materials (126 mg, 18%, yellow solid). The reaction mixture was stirred at 110°C for 18h.

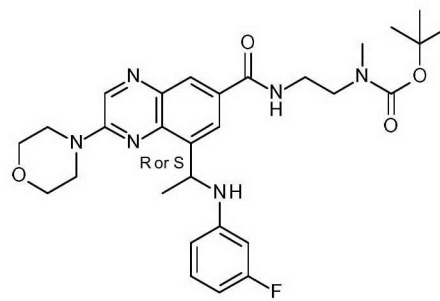
15

Example A34

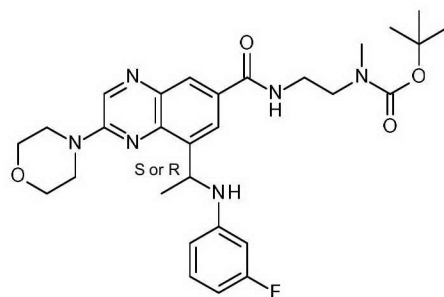
Preparation of intermediate 132a, intermediate 132b and intermediate 132c



Intermediate 132a

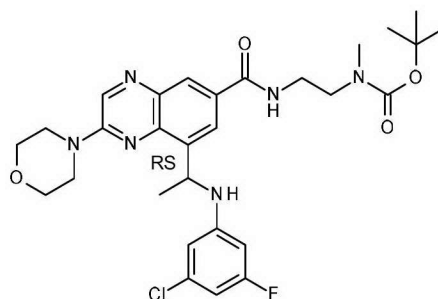


Intermediate 132b



Intermediate 132c

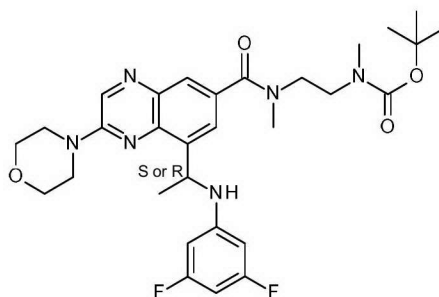
Intermediate 132a were prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 263 and N-Boc-N-methylethylenediamine as starting materials. The residue (593 mg, orange oil) was purified by chromatography over silica gel (Irregular SiOH 15-40  $\mu$ m; 24 g; gradient: from 100% DCM to 90% DCM, 10% iPrOH/NH<sub>4</sub>OH (95/5)). The pure fractions were collected and the solvent was evaporated. The residue (186 mg, yellow foam, intermediate 132a) was purified by chiral SFC (CHIRALCEL OJ-H 5  $\mu$ m; 250x20 mm; mobile phase: 75% CO<sub>2</sub>, 25% iPrOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give two fractions which were separately dissolved in a minimum of DCM, precipitated with pentane then evaporated and dried under vacuum to give respectively 89 mg (38%, yellow solid) of intermediate 132b and 90 mg (38%, yellow solid) of intermediate 132c.



15 Preparation of intermediate 135:



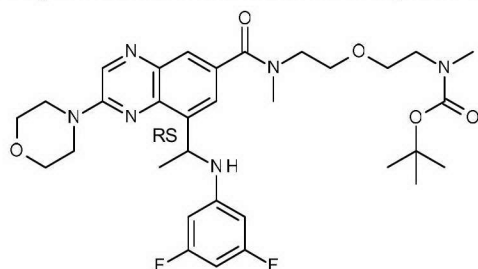
Intermediate 135 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 265 and N-Boc-N-methylethylenediamine as starting materials (240 mg, quant.).



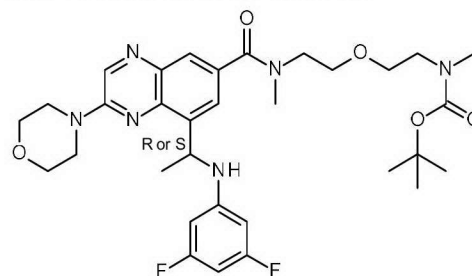
## 5 Preparation of intermediate 136:

Intermediate 136 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 83c and (N-Boc-N,N'-dimethyl)ethylenediamine as starting materials (200 mg, 59%).

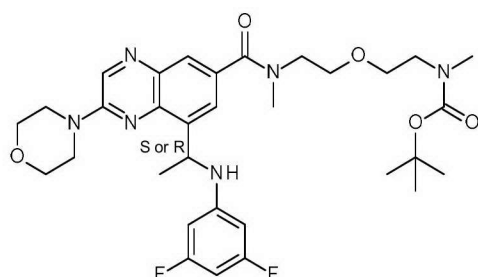
10 Preparation of intermediate 148a, intermediate 148b and intermediate 148c



Intermediate 148a

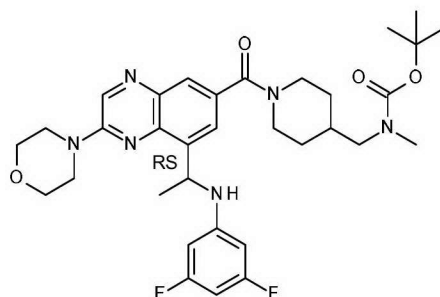


Intermediate 148b



Intermediate 148c

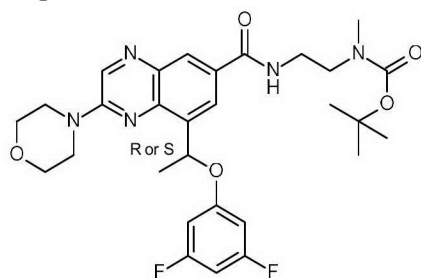
Intermediate 148a was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 83a and intermediate 147 as starting material. Intermediate 148a (346 mg; 91%) was purified by chiral SFC (Chiralpak AS-H 5  $\mu$ m; 250\*20 mm; mobile phase: 80% CO<sub>2</sub>, 20% EtOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 103 mg (27%) of intermediate 148b and 100 mg (26%) of intermediate 148c.



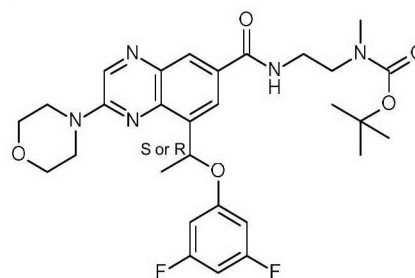
Preparation of intermediate 149:

Intermediate 149 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 83a and tert-butyl methyl(piperidin-4-ylmethyl)carbamate as starting materials (370 mg; quant.). The product was used without purification in the next step.

Preparation of intermediate 144 and intermediate 145

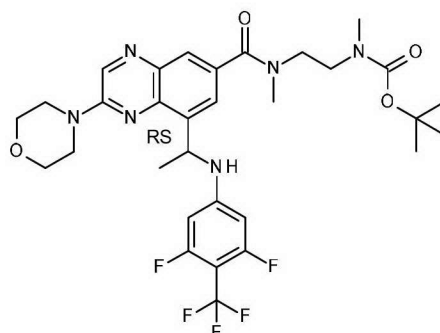


intermediate 144



intermediate 145

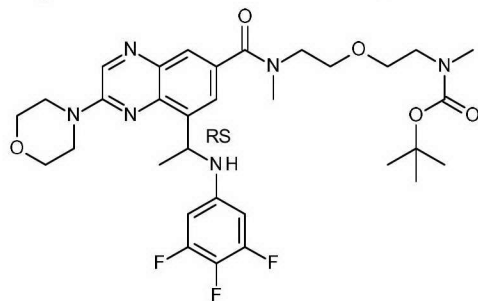
Intermediate 144 and intermediate 145 were prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 248 as starting materials. The racemic (737 mg) was purified by chiral SFC (CHIRALCEL OJ-H 5  $\mu$ m; 250x20 mm; mobile phase: 90% CO<sub>2</sub>, 10% EtOH). The pure fractions were collected and the solvent was evaporated to give respectively 297 mg (27%) of intermediate 144 and 339 mg (31%) of intermediate 145.



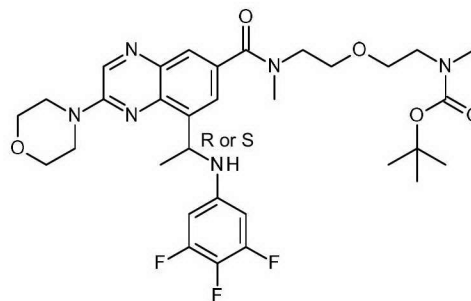
Preparation of intermediate 160:

Intermediate 160 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 270 as starting material (500 mg; 63%).

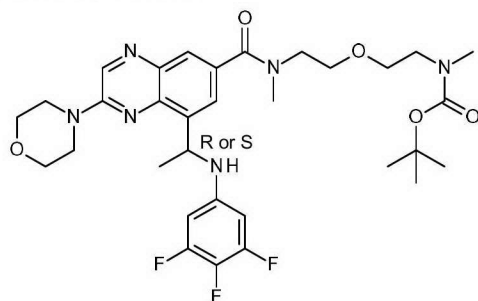
5 Preparation of intermediate 195, intermediate 195a and intermediate 195b



Intermediate 195



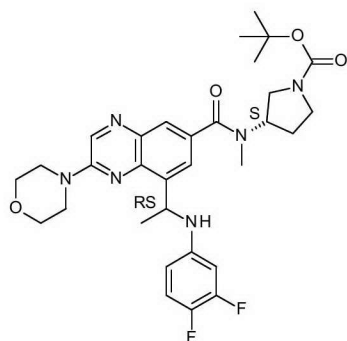
Intermediate 195a



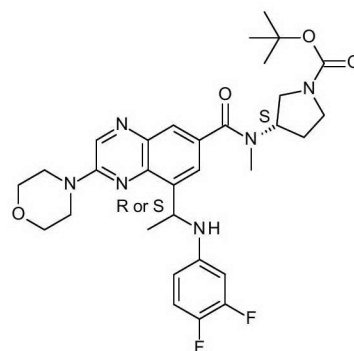
Intermediate 195b

Intermediate 195 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 170 as starting materials (520 mg; 50%). Intermediate 195 was purified by preparative SFC (Stationary phase: Chiralpak Diacel AS 20 x 250 mm, Mobile phase: CO<sub>2</sub>, iPrOH + 0.4 iPrNH<sub>2</sub>). The fractions containing the products were collected and evaporated until dryness to give 228mg (22%) of intermediate 195a and 296mg (28%) of intermediate 195b.

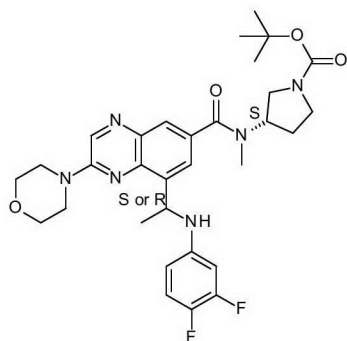
15 Preparation of intermediate 206, intermediate 206a and intermediate 206b



Intermediate 206



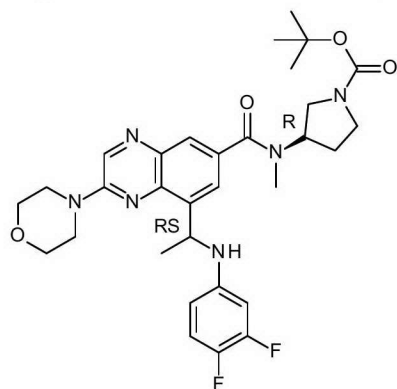
Intermediate 206a



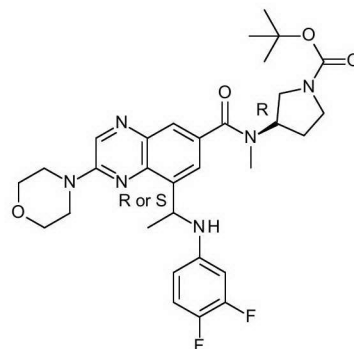
Intermediate 206b

- Intermediate 206 was prepared according to an analogous procedure as described for the synthesis of intermediate 5 using compound 234 and (S)-tert-Butyl 3-(methylamino)pyrrolidine-1-carboxylate as starting materials (1.1g; 95%). The separation of the enantiomers from 1.1 g of intermediate 206 was performed by chiral SFC (CHIRALPAK AS-H 5  $\mu$ m 250x20 mm; mobile phase: 70% CO<sub>2</sub>, 30% EtOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 462mg (40%) of intermediate 206a and 495 mg (43%) of intermediate 206b.

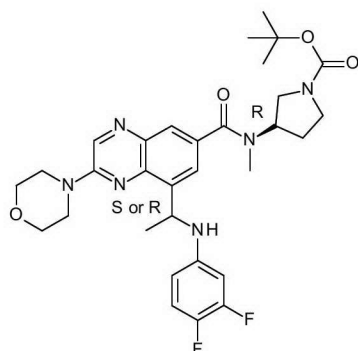
#### 10 Preparation of intermediate 207, intermediate 207a and intermediate 207b



Intermediate 207



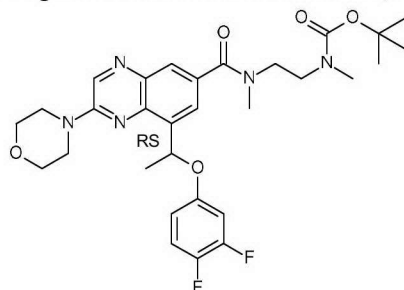
Intermediate 207a



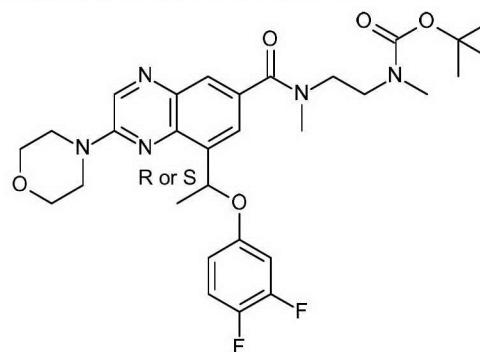
Intermediate 207b

Intermediate 207 was prepared according to an analogous procedure as described for the synthesis of intermediate 5 using compound 234 and (R)-1-Boc-3-Methylaminopyrrolidine as starting materials (1.05g; 91%). The separation of the enantiomers from 1.05 g of intermediate 207 was performed by chiral SFC (CHIRALPAK DIACEL 250x20 mm; mobile phase: CO<sub>2</sub>, EtOH (0.4% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 480mg (42%) of intermediate 207a and 504 mg (44%) of intermediate 207b.

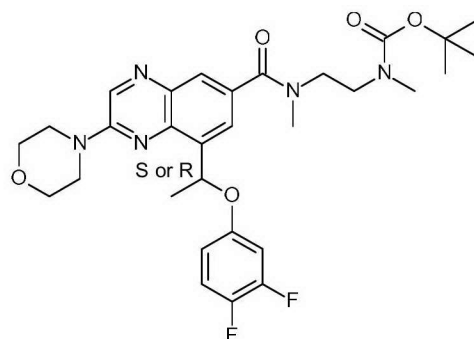
#### 10 Preparation of intermediate 208, intermediate 208a and intermediate 208b



Intermediate 208



Intermediate 208a

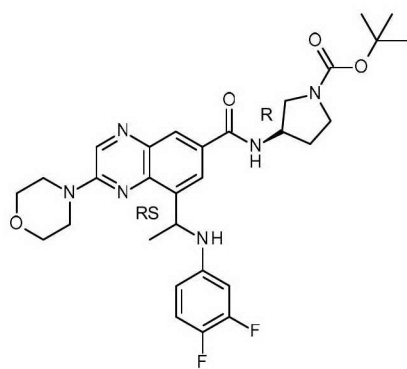


Intermediate 208b

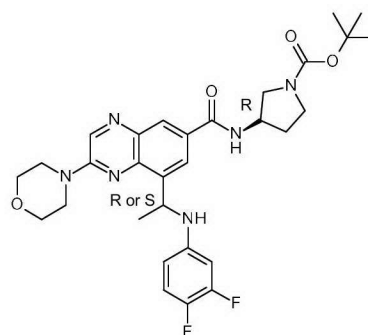
Intermediate 208 was prepared according to an analogous procedure as described for the synthesis of intermediate 5 using compound 285 and N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester as starting materials (1.12g; 79%). The separation of the enantiomers from 1.12 g of intermediate 208 was performed by chiral SFC (CHIRALPAK DIACEL AD 250x20 mm; mobile phase: CO<sub>2</sub>, EtOH (0.4% iPrNH<sub>2</sub>)).

5 The pure fractions were collected and the solvent was evaporated to give 518mg (37%) of intermediate 208a and 533 mg (38%) of intermediate 208b.

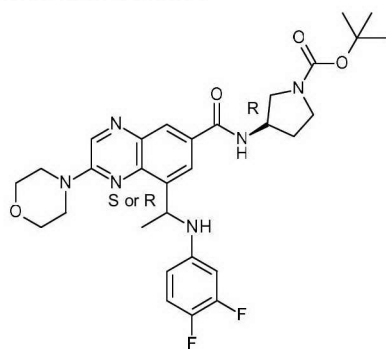
10 Preparation of intermediate 209, intermediate 209a and intermediate 209b



Intermediate 209



Intermediate 209a

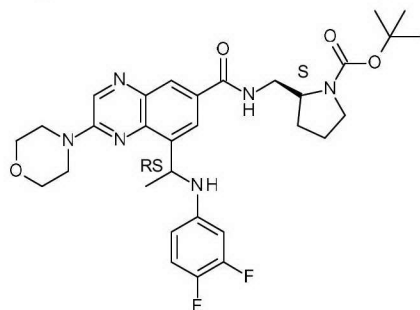


Intermediate 209b

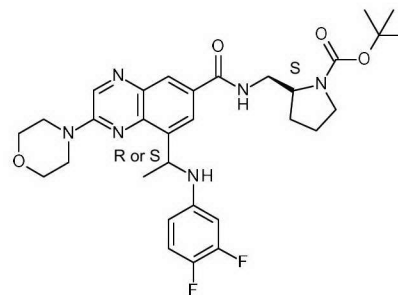
Intermediate 209 prepared according to an analogous procedure as described for the synthesis of intermediate 5 using compound 234 and (R) -1-boc-3-aminopyrrolidine as starting materials (960 mg; 93%). The separation of the enantiomers from 960 mg of intermediate 209 was performed by chiral SFC (CHIRALPAK AD-H 5μm 250x30 mm; mobile phase: 50% CO<sub>2</sub>, 50% iPrOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 407mg (39%) of intermediate 209a and 420 mg (41%) of intermediate 209b.

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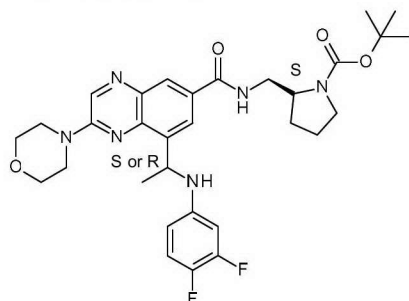
## Preparation of intermediate 213, intermediate 213a and intermediate 213b



Intermediate 213



Intermediate 213a

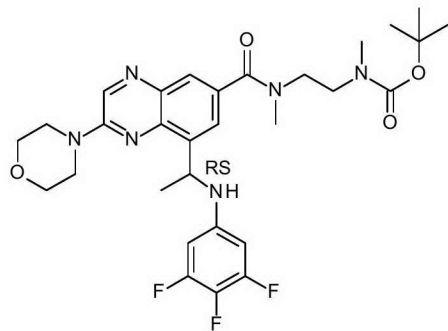


Intermediate 213b

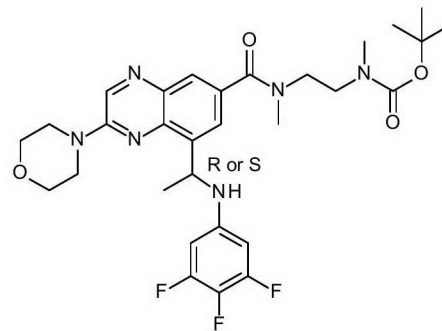
Intermediate 213 was prepared according to an analogous procedure as described for the synthesis of intermediate 5 using compound 234 and (S) – 2-aminomethyl-1-boc-pyrrolidine as starting materials (1g; 86%). The separation of the enantiomers from 1 g intermediate 213 was performed by chiral SFC (CHIRALPAK AD-H 5 $\mu$ m 250x30 mm; mobile phase: 60% CO<sub>2</sub>, 40% MeOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 416mg (36%) of intermediate 213a and 445 mg (38%) of intermediate 213b.

10

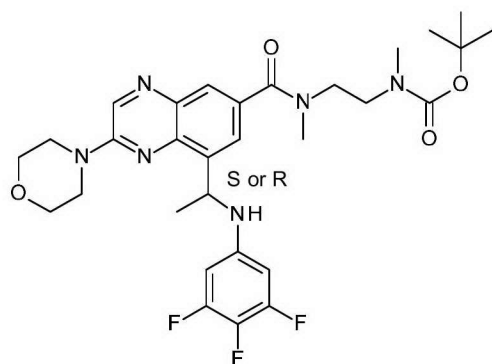
## Preparation of intermediate 215, intermediate 215a and intermediate 215b



Intermediate 215



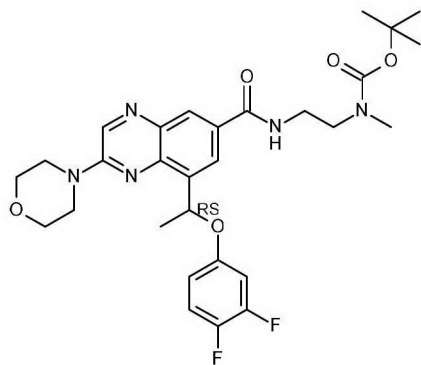
Intermediate 215a



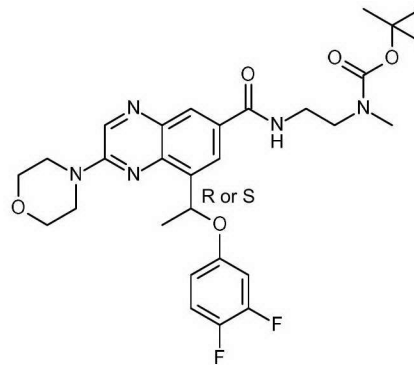
Intermediate 215b

Intermediate 215 was prepared according to an analogous procedure as described for the synthesis of intermediate 5 using compound 170 and N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester as starting materials (550 mg; 99%). The separation of the enantiomers from 550 mg intermediate 215 was performed by chiral SFC (Stationary phase: Chiralpak AD-H 5 $\mu$ m 250\*30mm, Mobile phase: 85% CO<sub>2</sub>, 15% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 200mg (36%) of intermediate 215a and 237 mg (43%) of intermediate 215b.

Preparation of intermediate 220, intermediate 220a and intermediate 220b

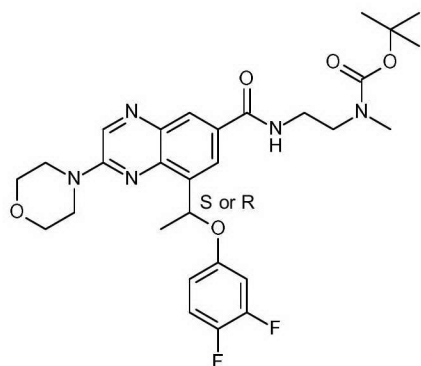


Intermediate 220



Intermediate 220a



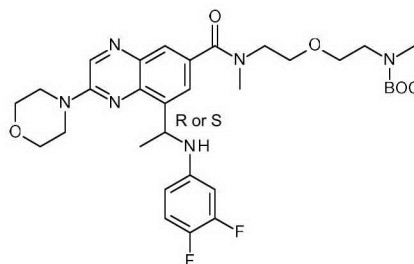


Intermediate 220b

Intermediate 220 was prepared according to an analogous procedure as described for the synthesis of intermediate 5 using compound 285 and *N*-(2-aminoethyl)-*N*-Methyl carbamic acid tert-butyl ester as starting materials (1.28g; 77%).

- 5 The separation of the enantiomers from 1.28g intermediate 220 was performed via chiral SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu$ m 250x20mm, Mobile phase: 70% CO<sub>2</sub>, 30% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fraction were collected and evaporated until dryness to give 730 mg (44%) of intermediate 220a and 716 mg (43%) of intermediate 220b.

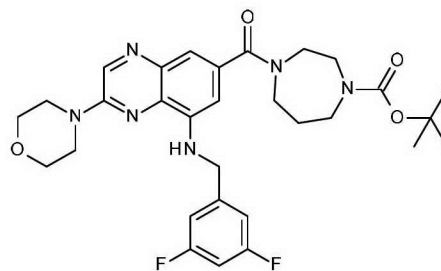
10



Preparation of intermediate 221:

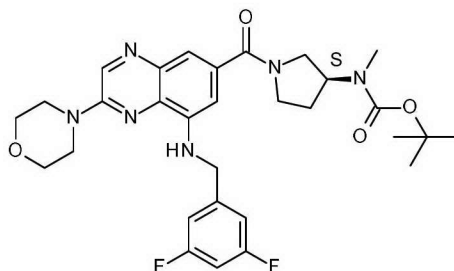
Intermediate 221 was prepared according to an analogous procedure as described for the synthesis of intermediate 5 using compound 234 and carbamic acid, *N*-methyl-*N*-[2-[2-(methylamino)ethoxy]ethyl]-, 1,1-dimethylethyl ester as starting materials (950mg; 78%).

15



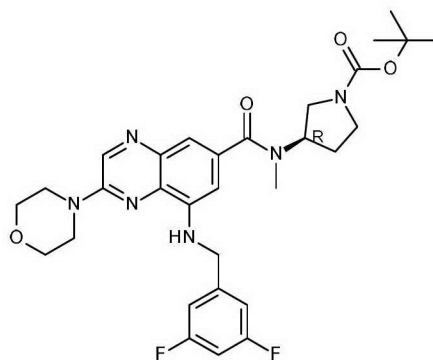
Preparation of intermediate 222:

Intermediate 222 was prepared according to an analogous procedure as described for the synthesis of intermediate 5 using compound 289 and *tert*-butyl 1,4-diazepane-1-carboxylate as starting materials (860mg, 100%).



5 Preparation of intermediate 223:

Intermediate 223 was prepared according to an analogous procedure as described for the synthesis of intermediate 5 using compound 289 and (S)-3-(*N*-3-Boc-Nmethylamino)pyrrolidine as starting materials (390mg g; 89%).

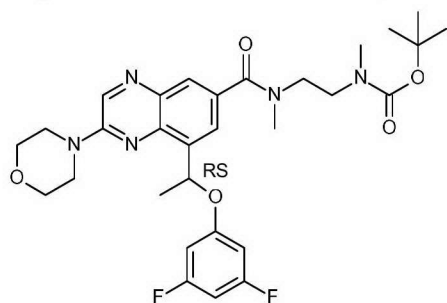


10 Preparation of intermediate 224:

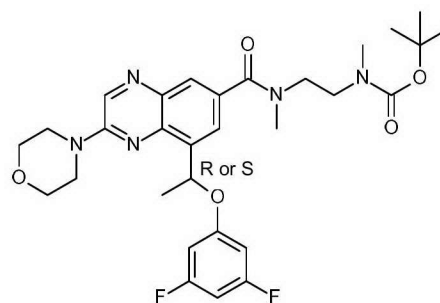
Intermediate 224 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 289 and (R)-3-(methylamino)pyrrolidine-1-carboxylic acid *tert*-butyl ester as starting materials (780mg g; 100%).

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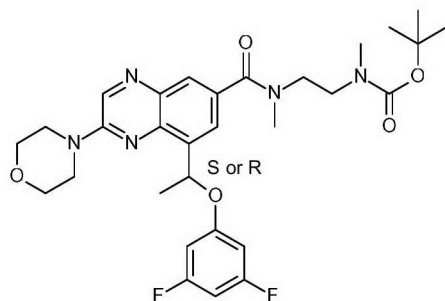
Preparation of intermediate 225, intermediate 225a and intermediate 225b



Intermediate 225



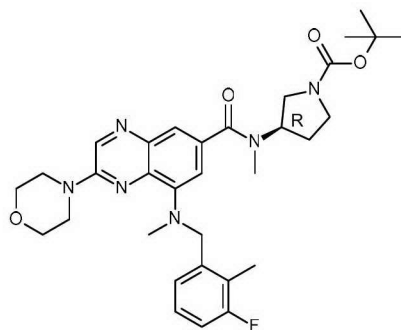
Intermediate 225a



Intermediate 225b

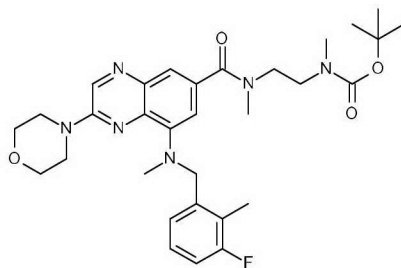
Intermediate 225 was prepared according to an analogous procedure as described for the synthesis of intermediate 5 using compound 248 and N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester as starting materials (220 mg).

- 5 The separation of the enantiomers was performed from 220 mg of intermediate 225 via chiral SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu$ m 250x20mm, Mobile phase: 80% CO<sub>2</sub>, 20% EtOH). The pure fractions were collected and evaporated until dryness to give 43 mg (6%) of intermediate 225a and 45 mg (6%) of intermediate 225b (.



- 10 Preparation of intermediate 226

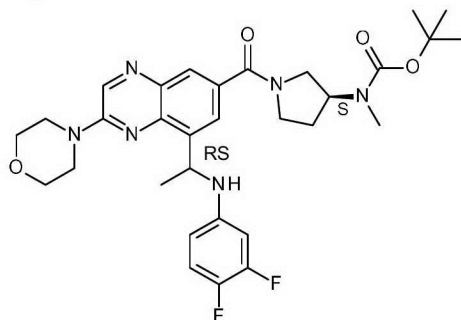
Intermediate 226 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 307 and (R)-3-(methylamino)pyrrolidine-1-carboxylic acid tert-butyl ester as starting materials (298mg, 100%).



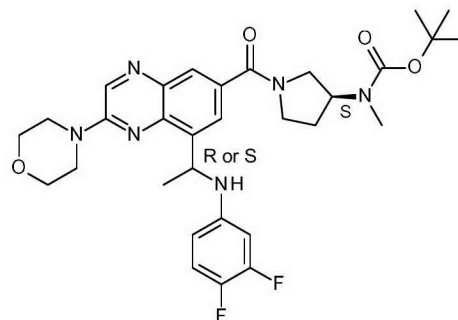
- 15 Preparation of intermediate 227

Intermediate 227 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 307 as starting material (346 mg, 82%).

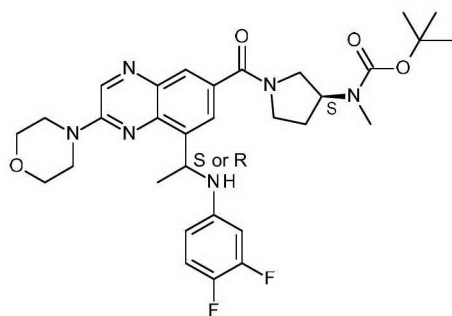
5 Preparation of intermediate 228, intermediate 228a and intermediate 228b



Intermediate 228

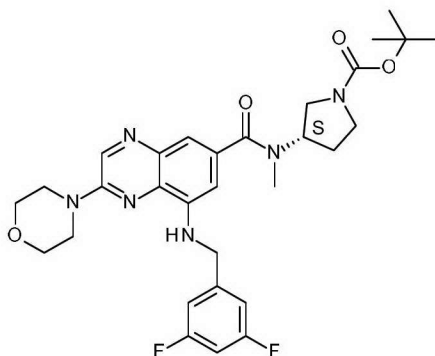


Intermediate 228a



Intermediate 228b

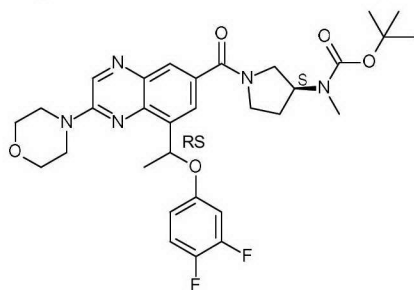
- Intermediate 228 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 234 and (S)-Tert-butylmethyl(pyrrolidin-3-yl)carbamate as starting materials (675 mg; 78%). The separation of the enantiomers was performed by SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu$ m 250x20mm, Mobile phase: 60% CO<sub>2</sub>, 40% EtOH(0.3% iPrNH<sub>2</sub>)). The fractions containing the product were mixed and concentrated to afford 179 mg of intermediate 228a and 190 mg of intermediate 228b.



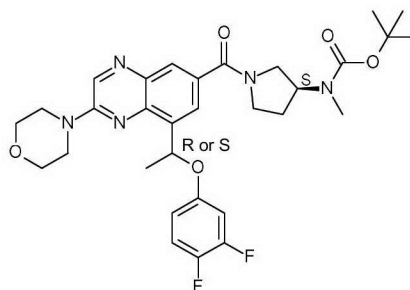
#### Preparation of intermediate 229

Intermediate 229 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 289 and (S)-1-Boc-3-  
 5 (methylamino)pyrrolidine as starting material (1.1g, 100%).

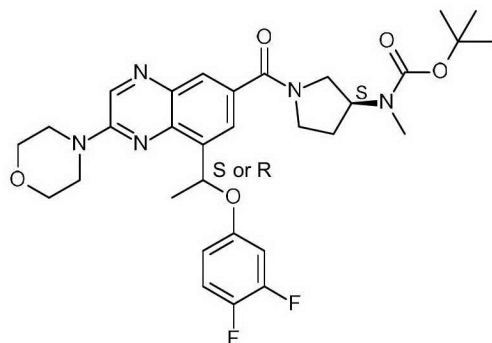
#### Preparation of intermediate 230, intermediate 230a and intermediate 230b



Intermediate 230



Intermediate 230a

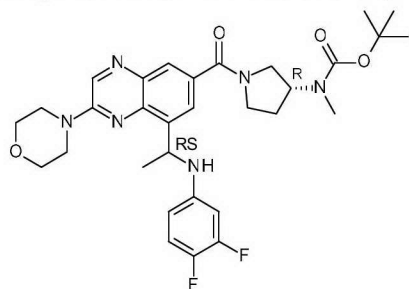


Intermediate 230b

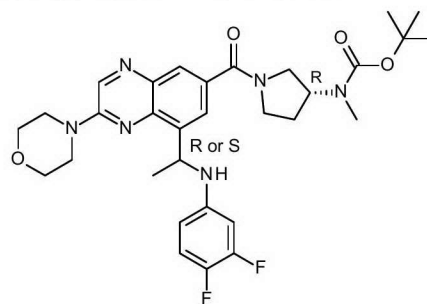
Intermediate 230 was prepared according to an analogous procedure as described for the synthesis of of intermediate 5, using compound 285 and (S)-tert-butylmethyl(pyrrolidin-3-yl)carbamate as starting materials (900 mg). The separation  
 10 of the enantiomers from 900 mg of intermediate 230 was performed via chiral SFC (Stationary phase: CHIRALPAK DIACEL AD 250x20mm, Mobile phase: CO<sub>2</sub>, EtOH +0.4% iPrNH<sub>2</sub>). The pure fractions were collected, evaporated until dryness and

crystallized from pentane to give 450 mg of intermediate 230a and 500 mg of intermediate 230b.

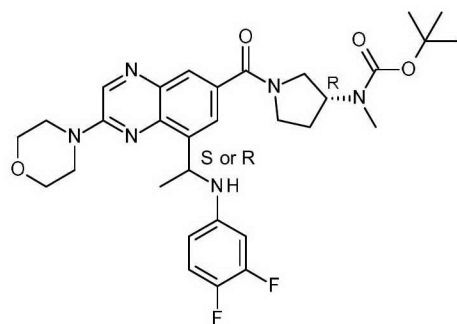
Preparation of intermediate 231, intermediate 231a and intermediate 231b



Intermediate 231



Intermediate 231a

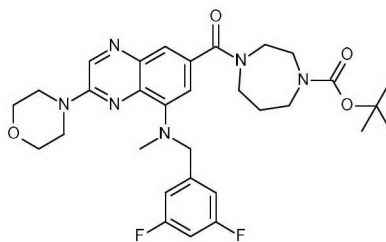


Intermediate 231b

5

Intermediate 231 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 234 and (R)-3-(*N*-Boc-*N*-methylamino)pyrrolidine as starting materials (1.03g; 89%). The separation of the enantiomers from 1.03g of intermediate 231 was performed via chiral SFC (Stationary phase: CHIRALPAK IC 250x30mm, Mobile phase: 60% CO<sub>2</sub>, 40% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected, evaporated until dryness and crystallized from pentane to give 481 mg (42%) of intermediate 231a and 435 mg (38%) of intermediate 231b.

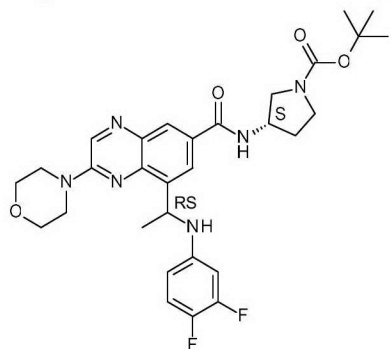
15



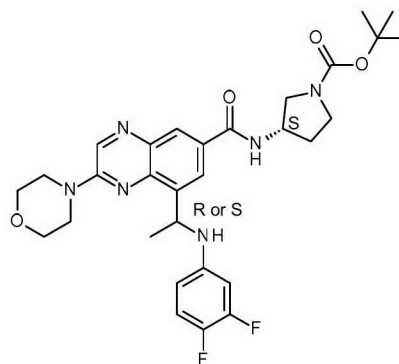
Preparation of intermediate 232:

Intermediate 232 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 291 and *tert*-butyl-1,4-diazepane-1-carboxylate as starting materials (228 mg, 79%).

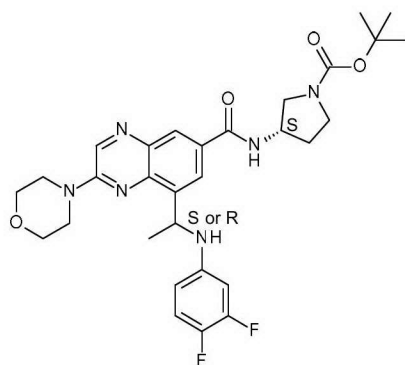
5 Preparation of intermediate 233, intermediate 233a and intermediate 233b



Intermediate 233

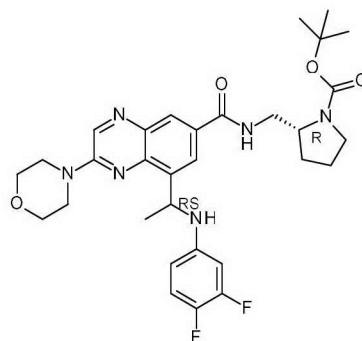


Intermediate 233a



Intermediate 233b

- Intermediate 233 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 234 and (S)-1-Boc-3-aminopyrrolidine as starting materials (845 mg; 82%). The separation of the enantiomers from 845 mg of intermediate 233 was performed via chiral SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu$ m 250x30mm, Mobile phase: 60% CO<sub>2</sub>, 40% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected, evaporated until dryness and crystallized from pentane to give 357 mg (35%) of intermediate 233a and 305 mg (31%) of intermediate 48.
- 10

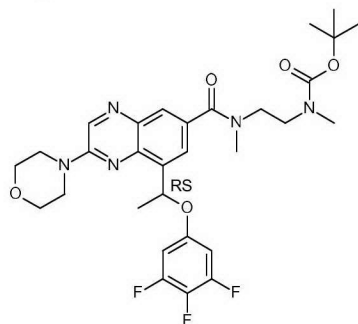


#### Preparation of intermediate 234

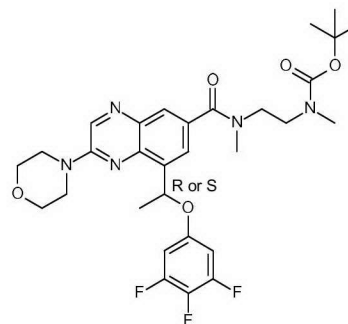
Intermediate 234 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 234 and (R)-2-(Aminoethyl)-1-Boc-pyrrolidine as starting materials (0.65g, 87%).

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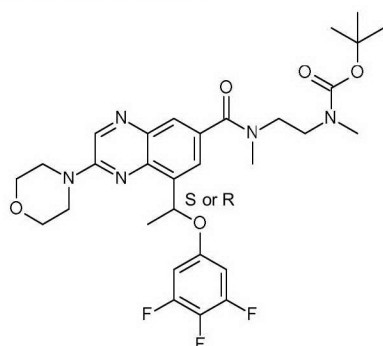
#### Preparation of intermediate 235, intermediate 235a and intermediate 235b



Intermediate 235



Intermediate 235a

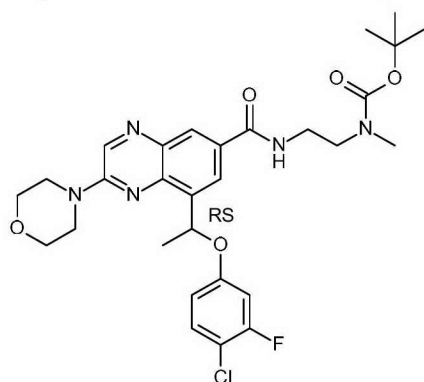


Intermediate 235b

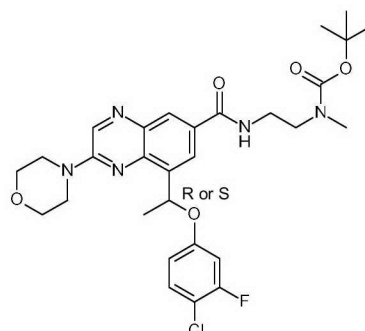
Intermediate 235 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 378 as starting material (805mg; 98%). The separation of the enantiomers from 805mg of intermediate 235 was performed via chiral SFC (Stationary phase: CHIRALPAK DIACEL 250x20mm, Mobile phase: 70% CO<sub>2</sub>, 30% EtOH(0.4% iPrNH<sub>2</sub>)). The pure fractions were collected and evaporated until dryness to give 158 mg (20%) of intermediate 235a and 150 mg (19%) of intermediate 235b.



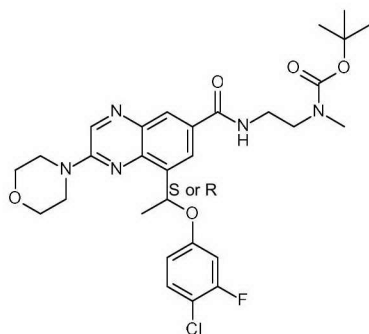
## Preparation of intermediate 236, intermediate 236a and intermediate 236b



Intermediate 236



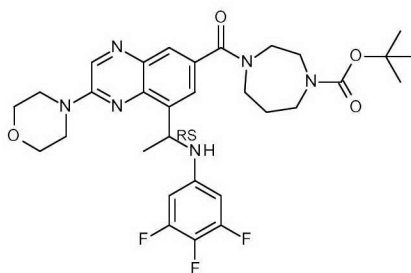
Intermediate 236a



Intermediate 236b

To a solution of compound 311 (150 mg; 0.347 mmol), N-(2-aminoethyl)-N-methylL carbamic acid tert-butyl ester (74  $\mu$ L; 0.417 mmol; 1.2eq.) and DIPEA (120  $\mu$ L; 0.695 mmol) in DMF (3 mL) was added COMU (223 mg; 0.521 mmol). The solution was stirred at rt for 18h. Additional N-(2-aminoethyl)-N-methylL carbamic acid tert-butyl ester (18.6  $\mu$ L; 0.104 mmol; 0.3 eq) was added and the solution was stirred at rt for 1h. The crude was combined with another reaction performed on 50mg of compound 311. Water and EtOAc were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with a saturated aqueous solution of NaCl (3x), dried over  $\text{MgSO}_4$ , filtered off and evaporated in vacuo. The crude (485 mg) was purified by silica gel chromatography (Stationary phase: irregular bare silica 40g, Mobile phase: 0.2%  $\text{NH}_4\text{OH}$ , 98% DCM, 2% MeOH) to give 294 mg of intermediate 236 as a yellow oil. The separation of the enantiomers from 294 mg of intermediate 236 was performed by chiral SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu$ m 250x20mm, Mobile phase: 55%  $\text{CO}_2$ , 45% MeOH) to give 116 mg (43%) of intermediate 236a as a yellow film and 115 mg (42%) of intermediate 236b as a yellow film.

160

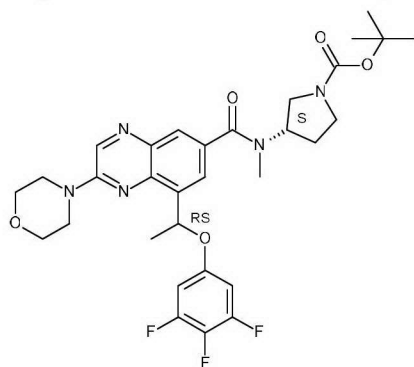


Preparation of intermediate 242

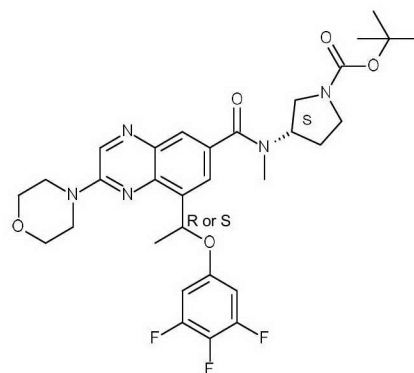
Intermediate 242 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 170 and *tert*-butyl-1,4-diazepane-1-carboxylate as starting materials (465 mg, 82%)

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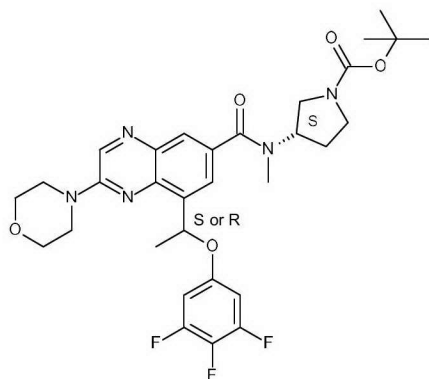
Preparation of intermediate 246, intermediate 246a and intermediate 246b



Intermediate 246



Intermediate 246a

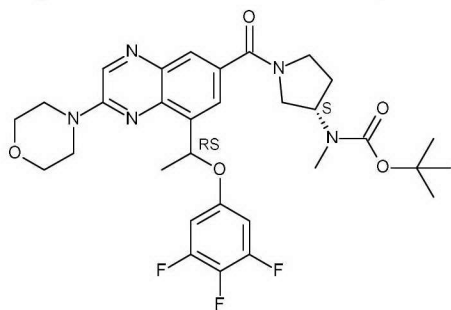


Intermediate 246b

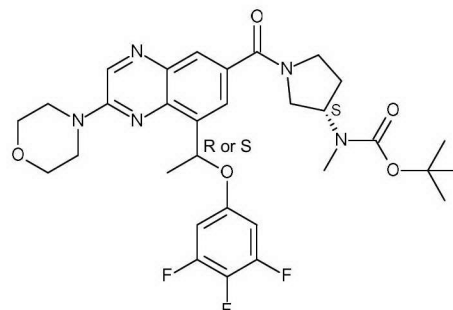
Intermediate 246 was prepared according to an analogous procedure as described for the synthesis of intermediate 236, using compound 378 and (S)- 1-Boc-(methylamino)pyrrolidine as starting materials (600 mg).

- 10 The separation of the enantiomers from 600 mg of intermediate 246 was performed by chiral SFC (Stationary phase: Chiralpak AD-H 5 $\mu$ m 250\*30mm , Mobile phase: 60% CO<sub>2</sub>, 40% EtOH) to give 210 mg (37%) of intermediate 246a as a yellow film and 223 mg (40%) of intermediate 246b as a yellow film.

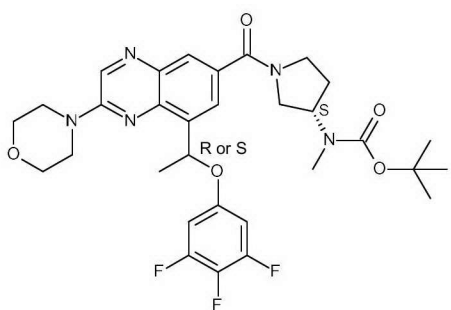
## Preparation of intermediate 247, intermediate 247a and intermediate 247b



Intermediate 247



Intermediate 247a

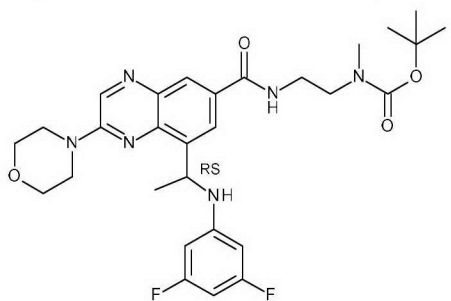


Intermediate 247b

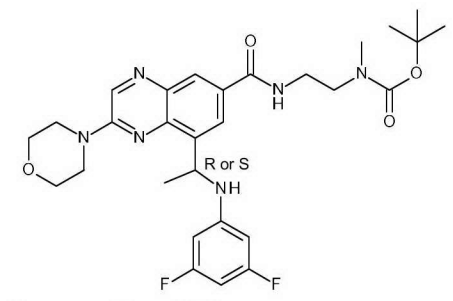
Intermediate 247 was prepared according to an analogous procedure as described for the synthesis of intermediate 236, using compound 378 and (S)-tert-butylmethyl(pyrrolidine-3-yl)carbamate as starting materials.

The separation of the enantiomers was performed by chiral SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu$ m 250x20mm, Mobile phase: 65% CO<sub>2</sub>, 35% EtOH(0.3% iPrNH<sub>2</sub>)) to give 217 mg (39%) of intermediate 247a as a yellow foam and 209 mg (37%) of intermediate 247b as a yellow foam.

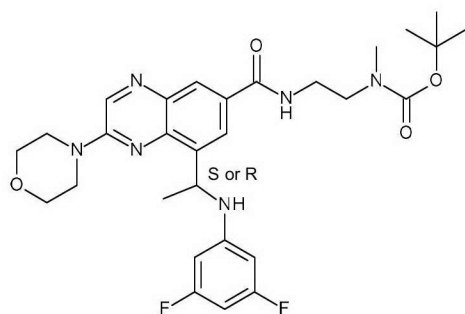
## Preparation of intermediate 248, intermediate 248a and intermediate 248b



Intermediate 248



Intermediate 248a

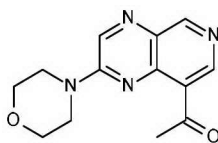


Intermediate 248b

Intermediate 248 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using compound 83a as starting material (1.4g; 78%).

The separation of the enantiomers from 1.4g of intermediate 248 was performed via chiral SFC (Stationary phase: Chiralpak AD-H 5 $\mu$ m 250\*30mm, Mobile phase: 55% CO<sub>2</sub>, 45% MeOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and evaporated until dryness to give 563 mg (31%) of intermediate 248a and 551 mg (31%) of intermediate 248b.

#### Example A35

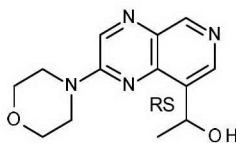


#### 10 Preparation of intermediate 137:

Tributyl(1-ethoxyvinyl)tin (14.23 g; 39.40 mmol) was added to a solution of intermediate 60 (9.12 g; 27.63 mmol) in anhydrous 1,4-dioxane (250 mL) under N<sub>2</sub>. Dichlorobis(triphenylphosphine) palladium (II) (0.97 g; 1.38 mmol) was added and the mixture was purged again with N<sub>2</sub>. The reaction mixture was heated at 100°C for 48h.

15 After cooling down to rt, formic acid (30 mL) was added and the mixture was stirred at rt overnight. The mixture was slowly basified with a saturated solution of NaHCO<sub>3</sub>, then filtered and the filtrate was evaporated under vacuum. The residue (9 g) was washed with water (2x30 mL), ACN (3x30 mL) and evaporated under vacuum to give 5 g (64%) of intermediate 137.

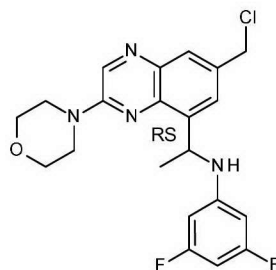
20



#### Preparation of intermediate 138:

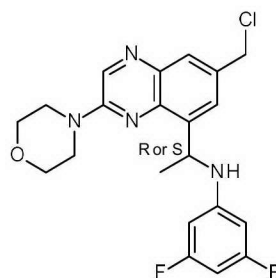
Intermediate 138 was prepared according to an analogous procedure as described for the synthesis of intermediate 15, using intermediate 137 as starting material (310 mg, 68%).

## Example A36



## Preparation of intermediate 140:

- At 0°C, thionyl chloride (200  $\mu$ L; 2.75 mmol) was added to a solution of compound 84 (550 mg; 1.37 mmol) in DCM (25 mL). The solution was allowed to warm to rt, stirred for 2h and, then evaporated under vacuum to give 575 mg (100%) of intermediate 140. The crude product was used without purification in the next step.



## Preparation of intermediate 142:

- Intermediate 142 was prepared according to an analogous procedure as described for the synthesis of intermediate 140, using compound 154a as starting material (275 mg, quant.). The product was used without purification in the next step.

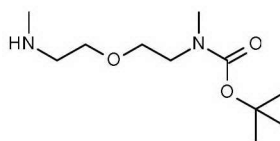


## Preparation of intermediate 143:

- Intermediate 143 was prepared according to an analogous procedure as described for the synthesis of intermediate 140, using compound 154b as starting material (234 mg, quant.). The product was used without purification in the next step.

## Example A37

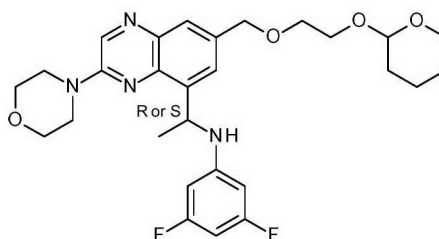
164



Preparation of intermediate 147:

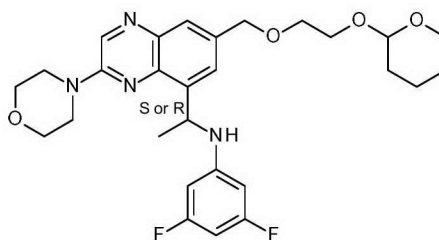
At 0°C, a solution of di-tert-butyl dicarbonate (371 mg; 1.70 mmol) in THF (5mL) was added dropwise to a solution of 2,2'-oxybis[*N*-methyl-ethanamine] (900 mg; 6.8 mmol) in THF (5 mL). The reaction mixture was stirred at rt overnight. The reaction mixture was poured into water, extracted with EtOAc. The organic layer was separated and washed with brine, then dried over MgSO<sub>4</sub>, filtered and evaporated to give 330 mg of (83%) of intermediate 147. The product was used without purification in the next step.

Example A38



Preparation of intermediate 150:

Under N<sub>2</sub> at 10°C, sodium hydride (72 mg; 1.80 mmol) was added to a solution of compound 154a (180 mg; 0.45 mmol) in DMF (2 mL). The solution was stirred at 10°C for 30min. Then, 2-(2-bromoethoxy)tetrahydro-2H-pyran (85 μL; 0.54 mmol) was added and the solution was allowed to slowly rise to rt for 5h. The solution was cooled and the mixture was poured into cooled water. The product was extracted with EtOAc. The organic layer was washed with water and dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (300 mg) was purified by chromatography over silica gel (irregular bare silica 10 g; mobile phase: 95% DCM, 5% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated to give 181 mg (76%) of intermediate 150.

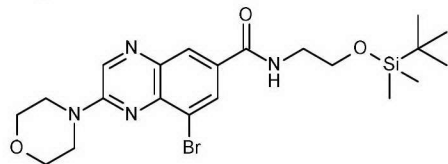


Preparation of intermediate 151:

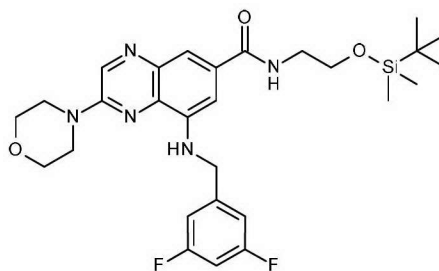
Intermediate 151 was prepared according to an analogous procedure as described for the synthesis of intermediate 150, using compound 154b and 2-(2-bromoethoxy)tetrahydro-2H-pyran as starting materials (238 mg; 72%).

## Example A39

Preparation of intermediate 162 (identical to intermediate 179):

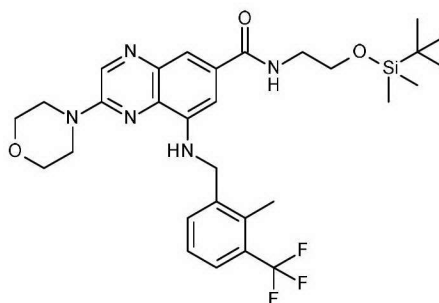


- 5 Intermediate 162 was prepared according to an analogous procedure as described for the synthesis of intermediate 5, using intermediate 4 and 2-[[1,1-dimethylethyl)dimethylsilyl]oxy]-ethanamine as starting materials (9.6 g; 73%).



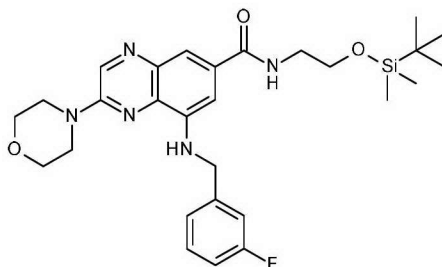
## Preparation of intermediate 163:

- 10 In a sealed tube, a mixture of intermediate 162 (1 g; 2.02 mmol), 3,5-difluorobenzylamine (0.286 mL; 2.42 mmol) and  $\text{Cs}_2\text{CO}_3$  (1.32 g; 4.04 mmol) in tert-amyl alcohol (10 mL) was degassed with  $\text{N}_2$ . 2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl (47 mg; 0.10 mmol) and BrettPhos Precatalyst First Gen (80.6 mg, 0.101 mmol) were added. The reaction mixture was purged with  $\text{N}_2$  and
- 15 heated at  $100^\circ\text{C}$  for 18 h. Water and EtOAc were added. Then the mixture was extracted. The organic layer was separated, dried over  $\text{MgSO}_4$ , filtered and evaporated. The residue (1.3 g) was purified by chromatography over silica gel (40 g of SiOH 20-45  $\mu\text{m}$ ; gradient: from 100% DCM to 95% DCM, 5% MeOH, 0.1%  $\text{NH}_4\text{OH}$ ). The pure fractions were collected and the solvent was evaporated to give 780 mg (69%) of
- 20 intermediate 163.



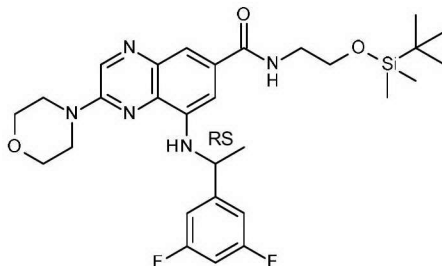
## Preparation of intermediate 164:

Intermediate 164 was prepared according to an analogous procedure as described for the synthesis of intermediate 163, using intermediate 162 and 2-methyl-3-(trifluoromethyl)benzylamine as starting materials (670 mg; 62%).



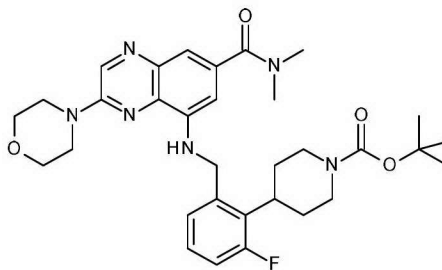
5 Preparation of intermediate 165:

Intermediate 164 was prepared according to an analogous procedure as described for the synthesis of intermediate 163, using intermediate 162 and 3-fluorobenzylamine as starting materials (765 mg; 63%).



10 Preparation of intermediate 166:

Intermediate 166 was prepared according to an analogous procedure as described for the synthesis of intermediate 163, using intermediate 162 and (RS)-1-(3,5-difluorophenyl)ethylamine as starting materials (700 mg; 61%).

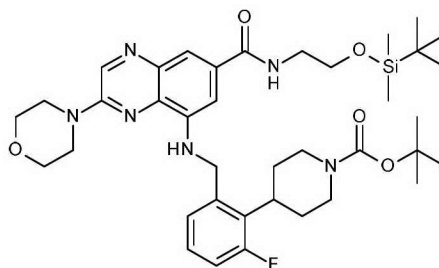


15 Preparation of intermediate 203:

Intermediate 203 was prepared according to an analogous procedure as described for the synthesis of intermediate 163 using intermediate 202 and intermediate 5 as starting materials (300 mg, 62%).

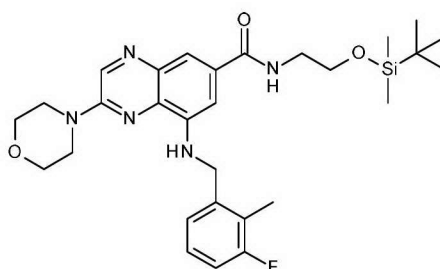


167



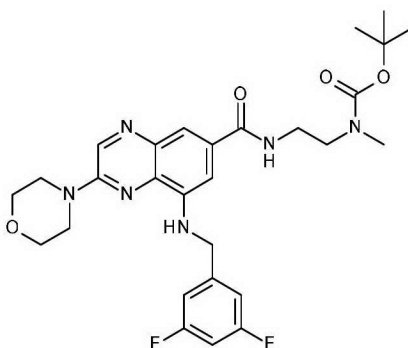
Preparation of intermediate 204:

Intermediate 204 was prepared according to an analogous procedure as described for the synthesis of intermediate 163, using intermediate 162 and intermediate 202 as starting material (410mg, 88%)



5 Preparation of intermediate 216:

Intermediate 216 was prepared according to an analogous procedure as described for the synthesis of intermediate 163, using intermediate 162 as starting material and 2-Methyl-3-fluorobenzylamine (845mg, 76%).



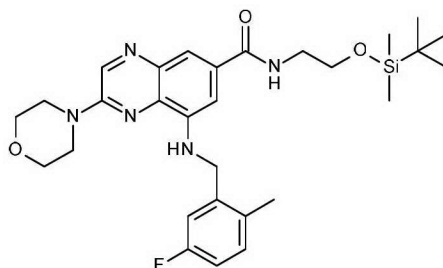
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Preparation of intermediate 218:

Intermediate 218 was prepared according to an analogous procedure as described for the synthesis of intermediate 163, using intermediate 217 as starting material and 3,5-difluorobenzylamine (310mg, 66%).

15

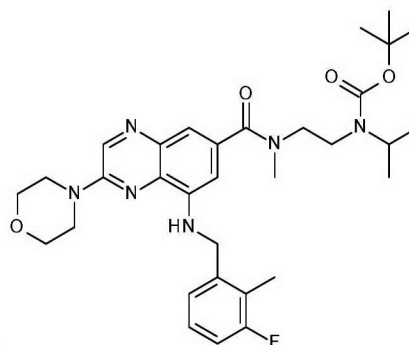
168



Preparation of intermediate 219:

intermediate 219 was prepared according to an analogous procedure as described for the synthesis of intermediate 163, using intermediate 162 as starting material and 2-methyl-5-fluorobenzylamine (420mg, 75%).

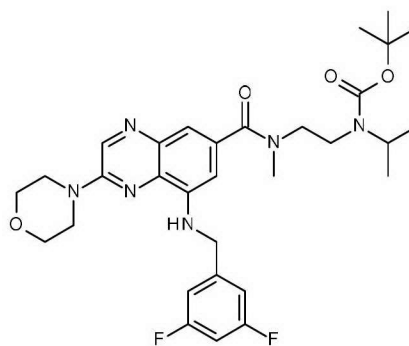
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Preparation of intermediate 240:

Intermediate 240 was prepared according to an analogous procedure as described for the synthesis of intermediate 163 using intermediate 239 and 3-Fluoro-2-methylbenzylamine as starting materials (450mg, 81%).

10

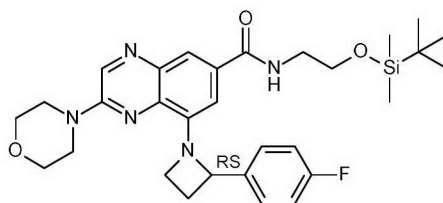


Preparation of intermediate 243:

Intermediate 243 was prepared according to an analogous procedure as described for the synthesis of intermediate 163, using intermediate 239 and 3,5-difluorobenzylamine as starting materials (460mg, 82%).

15

169

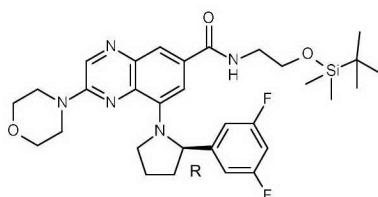


Preparation of intermediate 245:

Intermediate 245 was prepared according to an analogous procedure as described for the synthesis of intermediate 163, using intermediate 162 and 2-(4-Fluorophenyl)azetidine as starting materials (700mg, 61%).

5

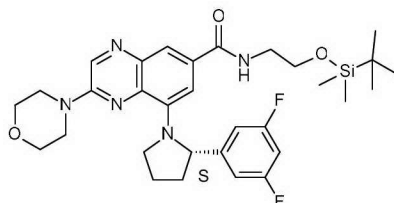
Example A40



Preparation of intermediate 174:

Intermediate 174 was prepared according to an analogous procedure as described for the synthesis of compound 1, using intermediate 162 and 2-(2R)-2-(3,5-difluorophenyl)pyrrolidine as starting materials, (200 mg; 33%) of intermediate 174.

10

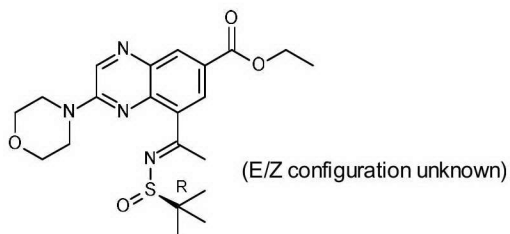


Preparation of intermediate 175:

Intermediate 175 was prepared according to an analogous procedure as described for the synthesis of compound 1, using intermediate 162 and 2-(2S)-2-(3,5-difluorophenyl)pyrrolidine as starting materials, (260 mg; 43%) of intermediate 175.

15

Example A41



Preparation of intermediate 176:

Titanium(IV) ethoxide (2.66 mL, 12.68 mmol) was added dropwise to a solution of intermediate 10a (1 g, 3.17 mmol) and (R)-(+)-2-methyl-2-propanesulfinimide (0.672 g, 5.55 mmol) in THF (25 mL) at room temperature under N<sub>2</sub>. The solution was

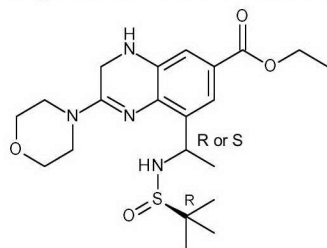
20

refluxed for 24h. The mixture was poured into brine and DCM was added. The precipitate was filtered through a short pad of Celite® which was washed with DCM. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and evaporated until dryness. The residue (1.5g) was purified by chromatography over silica gel (40 g of SiOH 15-40 μm; gradient: from 100% DCM to 95% DCM, 5% MeOH). The pure fractions were collected and the solvent was evaporated to give 600 mg (44%) of intermediate 176.

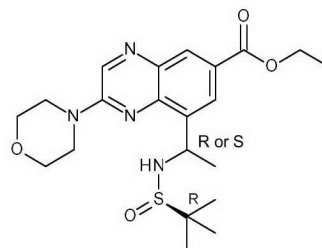
#### Alternative preparation of intermediate 176:

Titanium (IV) ethoxide (26.59 mL, 126.85 mmol) was added dropwise to a solution of intermediate 10a (10 g, 31.71 mmol) and (R)-(+)-2-methyl-2-propanesulfonamide 99% (7.68 g, 63.43 mmol) in cyclopentyl methyl ether (100 mL) at room temperature under N<sub>2</sub>. The solution was refluxed for 3h. The mixture was poured into brine and DCM was added. The precipitate was filtered through a short pad of Celite® and washed with DCM. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and evaporated until dryness. The residue was crystallized from DIPE. The precipitate was filtered off and dried under vacuum to yield 13.03 g (y = 95%, de =96.9) of intermediate 176.

#### Preparation of intermediate 177a and intermediate 177:

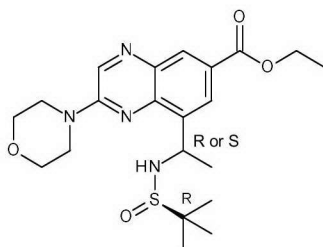


Intermediate 177a



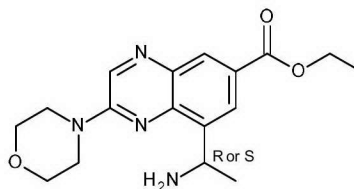
Intermediate 177

Sodium cyanoborohydride (1.1 g, 17.6 mmol) and acetic acid (2.01 mL, 35.14 mmol) were added to a solution of intermediate 176 (3.8 g, 8.78 mmol) in MeOH (50 mL) and DCM (50 mL) at -15°C. The solution was stirred at -15°C for 5h. The mixture was poured into water, basified with a 10% aqueous solution of K<sub>2</sub>CO<sub>3</sub> and the resulting aqueous mixture was extracted with DCM. The combined organic layers were washed with brine (2x), dried over MgSO<sub>4</sub>, filtered and evaporated. The residue (5.2g) was purified by silica gel chromatography (Irregular SiOH 15-40μm, 80g; gradient from 100% DCM to 95% DCM, 5% MeOH). The pure fractions were collected and the solvent was evaporated until dryness to give 2.26 g of a mixture of intermediates 177 and 177a (40/60 by LCMS).



Preparation of intermediate 177:

Manganese dioxide (0.876 g, 10.08 mmol) was added portionwise to a solution of intermediate 177a (1.1 g, 2.52 mmol) in DCM (40 mL) at room temperature. The mixture was stirred at rt for 3h. The mixture was filtered through a pad of Celite®, washed with DCM and the solvent was evaporated to dryness to give 1.34 g (100%) of intermediate 177 (de: 90%).

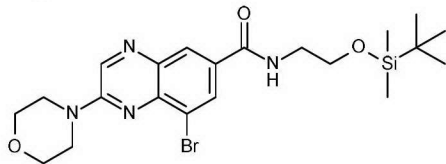


Preparation of intermediate 178:

To a solution of intermediate 177 (1.34 g, 3.08 mmol) in ACN (20 mL) was added hydrochloric acid in 1,4-Dioxane 4M (0.77 mL, 3.08 mmol). The mixture was stirred at rt for 1h. The mixture was basified with a saturated aqueous solution of NaHCO<sub>3</sub>. The aqueous layer was extracted with DCM (3x). The combined organic layers were dried over MgSO<sub>4</sub>, filtered off and evaporated. The residue (1.5g) was purified by silica gel chromatography (Irregular SiOH 15-40µm 40 g; gradient from 100% DCM to 90% DCM, 10% MeOH). The pure fractions were collected and the solvent was evaporated until dryness to give 840 mg (82%) of intermediate 178 (ee: 89.6%).

#### Example A42

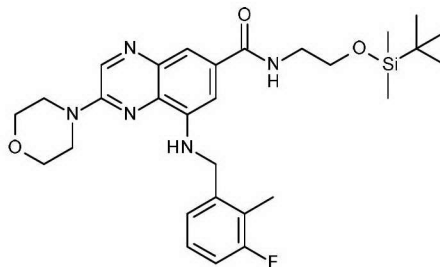
Preparation of intermediate 179 (identical to intermediate 162):



At 10°C, HBTU (10.093 g, 26.615 mmol) was added portion wise to a mixture of intermediate 4 (9 g, 26.615 mmol), *N,N*-Diisopropylethylamine (11.621 mL, 66.536 mmol) and 2-(*t*-butyldimethylsilyl)oxyethanamine (7 g, 39.922 mmol) in DMF (165 mL). The reaction mixture was stirred for 18h. H<sub>2</sub>O and EtOAc were added. The reaction mixture was extracted and the organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated to give 22g of a intermediate residue which was

taken up with DCM. The precipitate was filtered. The mother layer was concentrated and purified by silica gel chromatography (330g of SiO<sub>2</sub>, 20-45μm, gradient from 100%DCM to 95% DCM 5%MeOH 0.1% NH<sub>4</sub>OH). The pure fractions were collected and evaporated until dryness to afford 9.6g (73%) of intermediate 179.

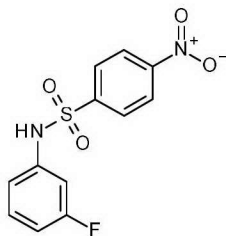
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Preparation of intermediate 180:

In a sealed tube, a mixture of intermediate 179 (1 g, 2.02 mmol), 3-fluoro-2-methylbenzylamine (0.262 mL, 2.0 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.315 g, 4.036 mmol) in *tert*-amyl alcohol (10mL) was degassed with N<sub>2</sub>. 2-Dicyclohexyphosphino-2',6'-diisopropoxy-1,1'-biphenyl (47.09 mg, 0.101 mmol) and BrettPhos Precatalyst First Gen (80.6 mg, 0.101 mmol) were added. The reaction mixture was purged with N<sub>2</sub> and heated at 100°C for 18 h. H<sub>2</sub>O and EtOAc were added. The reaction mixture was extracted. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrate. The residue (1.35g) was purified by silica gel chromatography (40g of SiO<sub>2</sub>, 20-45μm , gradient from 100%DCM to 90%DCM 10%MeOH 0.1%NH<sub>4</sub>OH). The pure fractions were collected and evaporated until dryness to afford 845 mg (76%) of intermediate 180 which was directly used in the next steps without any further purification.

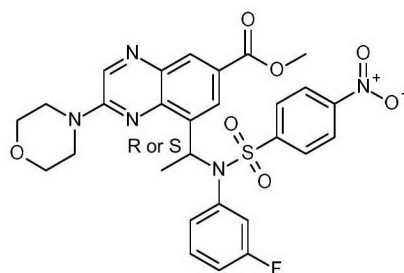
20 Example A43



Preparation of intermediate 181:

3-fluoroaniline was treated with 4-nitrophenyl sulfonyl chloride in dichloromethane using pyridine as the base. The procedure was executed on 100 and 300 g scale of fluoroaniline in 90% average yield.

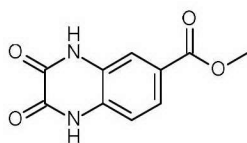
25



Preparation of intermediate 182:

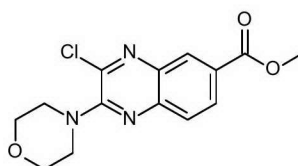
Intermediate 15b (1.0 eq.) and intermediate 181 (1.5) were dissolved in THF (10 volumes). Then, at 0 °C, tributylphosphine (*n*-Bu<sub>3</sub>P) (3-4 equivalents) and di-*iso*-propyl azodicarboxylate (DIAD) (3-4 equivalents) were added. The reaction is exothermic and keeping the temperature at 0 °C during the additions proved to be a critical parameter to avoid a significant decrease in e.e. (racemic material was obtained when the temperature was allowed to raise to 35 °C during the DIAD addition). After complete addition of the reagents, the temperature was increased to 30 °C and, after complete conversion (typically 16 hours), water was added. The solvent was switched to DCM for washing and extraction. DCM was then evaporated. The residue was slurried in 10 volumes of methanol and the precipitate was filtered. The procedure was respectively executed on 50 g scale of intermediate 15b with 3.0 equivalents of both *n*-Bu<sub>3</sub>P and DIAD to give intermediate 182 with a 76% yield (e.e.: 75.1 and on 200 g scale of intermediate 15b with 4.0 equivalents of both *n*-Bu<sub>3</sub>P and DIAD to give intermediate 182 with a 56% yield (e.e.: 82.5%) .

Example A44:



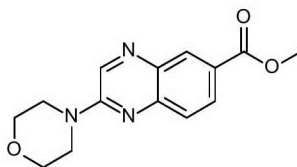
Preparation of intermediate 184:

Condensation of methyl 3,4-diaminobenzoate with diethyl oxalate (8.0 equivalents) in toluene (10 volumes) was carried out at reflux for 88 hours. After complete conversion, the mixture was concentrated to a residue which was washed with MTBE. After drying intermediate 184 was obtained in 90% yield. .



Preparation of intermediate 185:

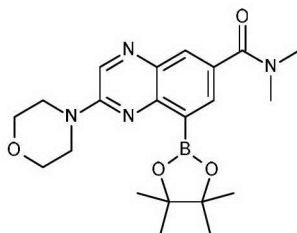
Intermediate 184 was dissolved in 1,2-dichloroethane (10 volumes). Then, dimethylformamide was added (1.0 equivalent) followed by thionyl chloride (4.0 equivalents). The mixture was heated to 80 °C for 3 hours, cooled to 15 °C and water (5 volumes) was slowly added. After phase separation, the organic layer was washed  
 5 twice with water (10 volumes) and the solvent was exchanged to 2-Me-THF (15 volumes). Triethylamine was added (3.0 equivalents) followed by morpholine (1.0 equivalents) and the reaction was stirred at room temperature. After complete conversion, water (10 volumes) was added and the layers were separated. Then, the aqueous phase was washed with 2-MeTHF (5 volumes). The combined organic layers  
 10 were washed with water (5 volumes), concentrated to a residue to obtain a solid which was slurried in MTBE (5 volumes). The precipitate was filtered and dried to give intermediate 185 in 70% yield. .



Preparation of intermediate 186:

15 Intermediate 185 was dissolved in dichloromethane (10 volumes) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.0 equivalents) was added. Pd/C (10%, 50% wet, 7% mol) was added and the mixture was hydrogenated (50 psi) for 24 hours. When the conversion was complete, the mixture was filtered through a pad of celite® and, to the filtrate, MnO<sub>2</sub> (0.1 equivalents) was added. The mixture was warmed to 30-40 °C then  
 20 filtered again on celite® and the filtrate was concentrated to 1-2 volumes. The solvent was exchanged to methyl tertiobutylether (5-7 volumes) and the mixture was cooled to 5-10 °C and stirred at the same temperature for 2 hours. The solid was filtered and dried to obtain intermediate 186 in 86% yield (99.4% purity).

25 Example A45

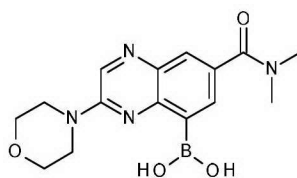


Preparation of intermediate 190:

A suspension of intermediate 5 (1.03 g, 2.72 mmol), Bis( Pinacolato)diboron (1.38 g, 5.44 mmol) and potassium acetate (1.07 g, 10.9 mmol) in 1,4-dioxane (10.5 mL) was degassed with nitrogen. Dichloro(diphenylphosphinoferrocene)palladium (99.5 mg,



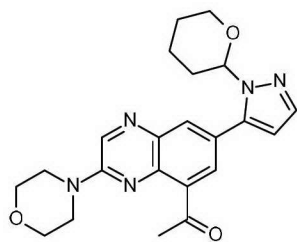
0.136 mmol) was added and the mixture was heated to 100 °C overnight. The resulting solution was cooled down to room temperature, concentrated under reduced pressure, taken up into brine (50 mL) and extracted with EtOAc (3x100 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (irregular SiOH, 15-40 μm, 50 g, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%) to give a mixture of intermediate 190 and intermediate 191 (905 mg, ratio 55/45) as an orange foam.



10 Preparation of intermediate 191:

Sodium Periodate (703 mg, 3.29 mmol) was added to a solution of a mixture of intermediate 190 and intermediate 191 (903 mg, ratio 55/45) in THF (5.52 mL) and water (17.5 mL) and the mixture was stirred at room temperature for 1h. (43.8 mL, 43.8 mmol) was added and the reaction mixture was stirred at room temperature for 1h. The resulting solution was quenched with water (50 mL) and extracted with a mixture of DCM/MeOH (8/2, 3x100 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (irregular SiOH, 15-40 μm, 50 g, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%) to give (780 mg, 100%) of intermediate 191 as a light orange powder.

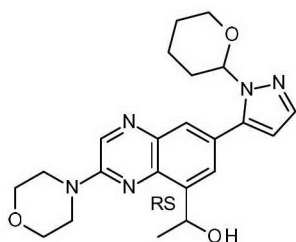
#### Example A46



Preparation of intermediate 192:

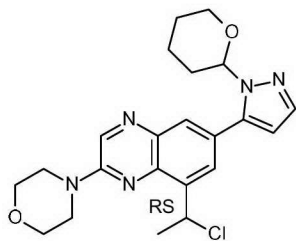
In a Schlenk tube, a solution of intermediate 55a (1g; 2.97mmol), 1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-5-boronic acid pinacol ester (1.08g; 3.87mmol) and potassium carbonate (0.82g; 5.95mmol) in 1,4-dioxane (15mL) and water (3mL) was degassed under nitrogen. Pd.Cl<sub>2</sub>(dppf).DCM (244mg; 0.3mmol) was added and the reaction mixture was heated at 95 °C for 24 hours. The mixture was cooled to rt, The mixture was poured into a mixture of water and EtOAc, then filtered through a pad of celite®.

The aqueous layer was extracted with EtOAc, The organic layer was washed with brine and dried over  $\text{MgSO}_4$ , filtered and evaporated to dryness, The resulting residue was taken-up with a mixture of Pentane and  $\text{Et}_2\text{O}$ . The precipitate was filtered to afford 0.42g (35%) of intermediate 192. The filtrate was evaporated to dryness to afford additional 0.7g (58%) of intermediate 192.



Preparation of intermediate 193:

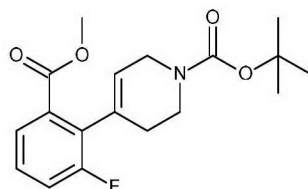
To a solution of intermediate 192 (0.42g; 1.03mmol) in MeOH(15mL) and DCM (5mL) was added sodium borohydride (43mg; 1.13mmol) and the mixture was stirred at 10°C for 2h. Then, DCM and water were added. The layers were separated. The aqueous layer was extracted with DCM (2x) and the combined organic layers were dried over  $\text{MgSO}_4$ , filtered off and evaporated in vacuo. The crude (0.45g) was purified by silica gel chromatography (Stationary phase: irregular  $\text{SiOH}$  15-40 $\mu\text{m}$  300g, Mobile phase: 45% Heptane, 50% AcOEt, 5% MeOH, 0.1%  $\text{NH}_4\text{OH}$ ) yielding 200mg (47%) of intermediate 193.



Preparation of intermediate 194:

Intermediate 194 was prepared according to an analogous procedure as described for the synthesis of intermediate 52, using intermediate 193 (as starting material (directly used without purification for the next step)).

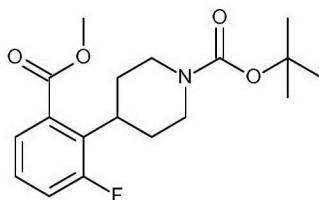
Example A47



Preparation of intermediate 197:

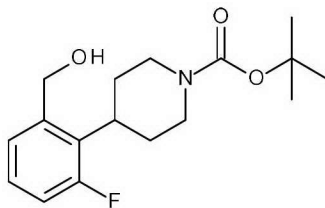
The reaction was performed twice on 12.17g of methyl-2-bromo-3-fluorobenzoate and the different reaction mixtures were mixed for the work-up and the purification.

Under N<sub>2</sub>, to a mixture of methyl-2-bromo-3-fluorobenzoate (24.34 g, 104.45 mmol),  
5 *tert*-butyl-4-(4,4,5,5-tetramethyl-1,2,3,-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2H)-  
carboxylate (48.44 g, 156.67 mmol) and K<sub>3</sub>PO<sub>4</sub> (66.51 g, 313.34 mmol) in a mixture of  
1,4-dioxane (250 mL) and distilled water (75 mL) was added [1,1'-  
Bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with  
dichloromethane (4.27 g, 5.22 mmol). The reaction mixture was heated to 100 °C  
10 overnight, poured out into water and filtered through a celite<sup>®</sup> layer. The organic layer  
was extracted with DCM, separated, dried, filtered and concentrated to dryness. The  
residue (55.6 g) was purified by column chromatography on silica gel (Irregular SiOH,  
15-40 µm, 220 g, mobile phase: 100% DCM). The fractions containing the product  
were collected and the solvent was evaporated until dryness. The resulting residue  
15 (37.9 g) was crystallized from pentane and the precipitate was filtered off and dried  
under vacuum to give 17.6 g (50%) of intermediate 197.



Preparation of intermediate 198:

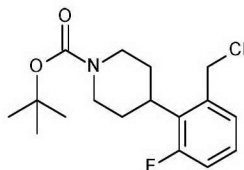
A mixture of intermediate 197 (16.50 g, 49.20 mmol) and Pearlman's catalyst (1.40 g,  
20 9.84 mmol) in MeOH (170 mL) was hydrogenated in a Parr reactor (2 atmospheres) for  
12 h at room temperature. After removal of H<sub>2</sub>, the catalyst was filtered over a pad of  
celite<sup>®</sup>, washed with DCM and the filtrate was concentrated to give 16.4 g (99%) of  
intermediate 198.



25 Preparation of intermediate 199:

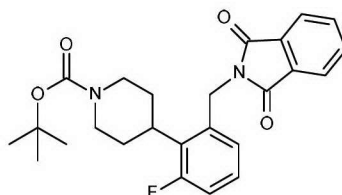
Lithium aluminium hydride (1.85 g, 48.61 mmol) was added portionwise to a mixture  
of intermediate 198 (16.40 g, 48.61 mmol) in THF (200 mL) at 5 °C under N<sub>2</sub>. The  
mixture was stirred at 5 °C for 3 h. Then, EtOAc followed by water were added  
dropwise to the mixture at -5 °C. The suspension was filtered through a pad of celite<sup>®</sup>.

The organic layer was separated, dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated to give 15.18 g (quantitative) of intermediate 199.



Preparation of intermediate 200:

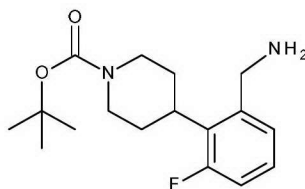
- 5 To a solution of intermediate 199 (9.23g; 29.8 mmol) in DCM (100 mL) cooled to  $0^{\circ}\text{C}$ , was slowly added trimethylamine (6.22 mL; 44.7 mmol) followed by methanesulfonylchloride (3.46 mL; 44.7 mmol). The mixture was stirred at room temperature overnight. Water was added and the product was extracted with DCM. The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated till dryness. The residue
- 10 was purified by silica gel chromatography (Irregular  $\text{SiOH}$  15-40 $\mu\text{m}$  40 g, mobile phase : gradient from 80% Heptane, 20% AcOEt to 60% Heptane, 40% AcOEt). The pure fractions were collected and the solvent was evaporated until dryness to give (9.1g, 93%) of intermediate 200 .



- 15 Preparation of intermediate 201:

A mixture of intermediate 200 (3.15g; 9.61 mmol), potassium phthalimide (1.87, 10.09mmol) in DMF (24mL) was stirred at room temperature for 3days. The insoluble was filtered off, washed with diethylether and dried to afford (4.3g, 100%) of intermediate 201.

20

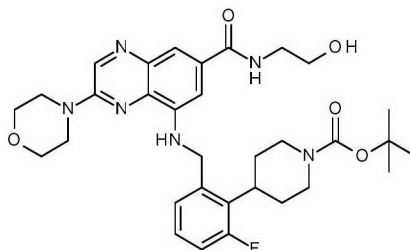


Preparation of intermediate 202:

- A mixture of intermediate 201 (4.3g, 4.81mmol), hydrazine monohydrate (2.2mL ,35.87mmol) in EtOH(142mL) was heated to  $80^{\circ}\text{C}$  for 3h30 hours. The reaction mixture was cooled to room temperature and evaporated to dryness. DCM was added
- 25 and and the residue was stirred for 10min. The insoluble was filtered and washed with DCM. The filtrate was purified by silica gel chromatography (12g of  $\text{SiOH}$  35-40 $\mu\text{m}$ ,

gradient from 100% DCM to 80% DCM 20% CH<sub>3</sub>OH 0.1% NH<sub>4</sub>OH). The fractions were collected and evaporated until dryness to give (1.75g, 58%) of intermediate 202.

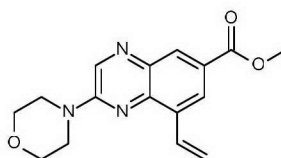
#### Example A48



#### 5 Preparation of intermediate 205:

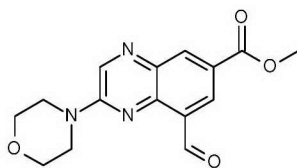
TBAF (1M in THF, 0.624 mL, 0.624 mmol) was added dropwise to a solution of intermediate 204 (0.41 g, 0.567 mmol) in THF (15 mL) at room temperature. The mixture was stirred for 3 h at room temperature. The solution was poured into ice water, extracted with EtOAc and washed with brine. The organic layer was dried over  
10 MgSO<sub>4</sub>, filtered and evaporated to dryness to give 0.56 g of intermediate 205 which was directly used in the next step.

#### Example A49:



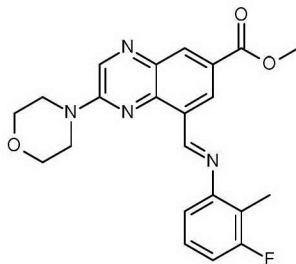
#### Preparation of intermediate 210:

- 15 In a Schlenk reactor, a solution of intermediate 3a (5.00 g; 14.2 mmol), vinylboronic acid pinacolester (3.28 g; 21.3 mmol) and potassium phosphate (4.52 g; 21.3 mmol) in dioxane (120 mL) and water (30 mL) was purged with N<sub>2</sub>. Then, PdCl<sub>2</sub>(dppf).DCM (581 mg; 710 μmol) was added. The reaction mixture was purged again with N<sub>2</sub> and heated at 90°C for 4h. After cooling down to rt, the reaction mixture was diluted with  
20 EtOAc and washed successively with water and a saturated aqueous solution of NaCl. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered off and evaporated in vacuo. The residue (7.31g) was purified by silica gel chromatography (Irregular SiOH 15-40 μm, 330 g, mobile phase: gradient from heptane 80%, EtOAc 20% to heptane 50%, EtOAc 50%) to give a pale yellow sticky solid which was triturated in Et<sub>2</sub>O. the  
25 precipitate was filtered on a glass frit to give 2.32 g (55%) of intermediate 210 as a pale yellow solid.



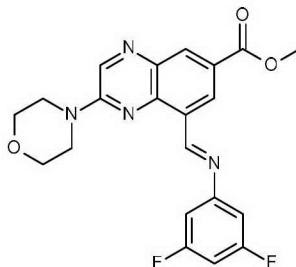
Preparation of intermediate 211:

- A solution of intermediate 210 (2.32 g; 7.75 mmol), osmium tetroxide 2,5 % in butanol (5.01 mL; 0.388 mmol), sodium periodate (5.80 g; 27.1 mmol) in THF (115 mL) and water (45 mL) was stirred at rt for 18h. The reaction mixture was poured into ice water and EtOAc was added. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered off and evaporated in vacuo. The resulting residue was triturated in MeOH and the solid was filtered on a glass frit and dried in vacuo to give 1.86 g (80%) of intermediate **211** as a yellow-brown solid.



Preparation of intermediate 212:

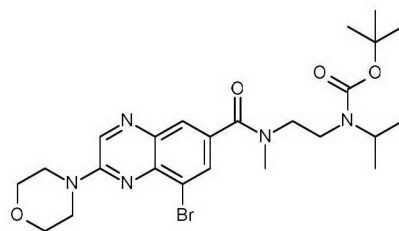
- In a sealed tube, 3-fluoro-2-methylaniline (530  $\mu$ L; 4.64 mmol) and molecular sieves 4 $\text{\AA}$  (4.60 g) were added to a solution of intermediate 211 (700 mg; 2.32 mmol) in dry DCM (22 mL). The reaction mixture was stirred at rt over the weekend. Additional molecular sieves 4 $\text{\AA}$  (1.20 g) was added and the mixture was stirred at rt for 20h. Additional 3-fluoro-2-methylaniline (132  $\mu$ L; 1.16 mmol) and molecular sieves 4 $\text{\AA}$  (500 mg) were added and the mixture was again stirred at rt for 20h. The mixture was filtered on a glass frit and the filtrate was evaporated in vacuo to give 1.41 g of intermediate 212 as a yellow solid directly used in the next step without any further purification.



Preparation of intermediate 214:

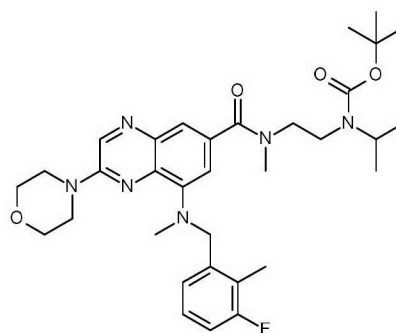
- Intermediate 214 was prepared according to an analogous procedure as described for the synthesis of intermediate 212 using intermediate 211 and 3,5-difluoroaniline as starting materials (516 mg, used without purification in the next step).

## Example A50



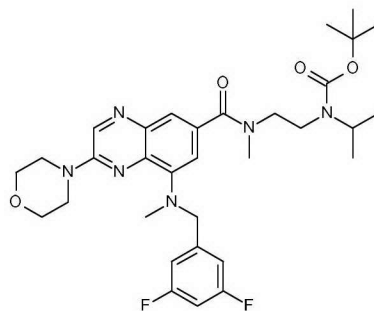
Preparation of intermediate 239:

NaH (60% dispersion in mineral oil) (948.5 mg, 23.72mmol) was added portionwise to a solution of intermediate 238( 5.6 g, 10.7 mmol) in DMF (60mL) under nitrogen cooled to 0-5 °C (ice bath cooling).The mixture was stirred at 0-5°C for 15mn then iodomethane (1.41 mL, 22.59 mmol) was added. The reaction mixture was stirred at room temperature for 16h . The reaction mixture was poured into water and the organic layer was extracted with EtOAc. The crude residue (4.5g) was purified by silica gel chromatography to afford 4g (66%) of intermediate 239.



Preparation of intermerdiaire 241

Intermediate 241 was prepared according to an analogous procedure as described for the synthesis of intermediate 239 using intermediate 240 as starting material (19mg, 4%).



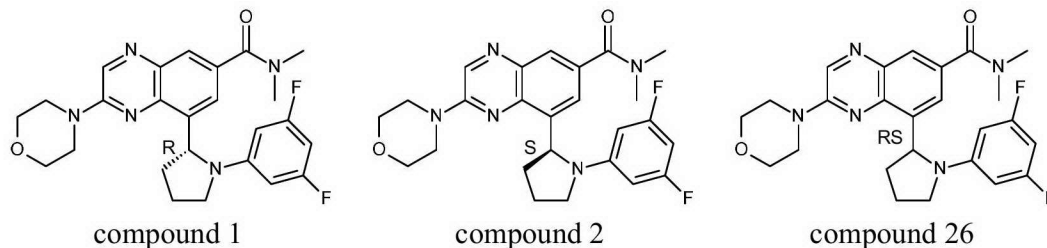
15 Preparation of intermediate 244

Intermediate 244 was prepared according to an analogous procedure as described for the synthesis of intermediate 239 using intermediate 243 as starting material (42mg, 9%).

B. Preparation of the final compounds

## Example B1:

Preparation of compound 1, compound 2 and compound 26

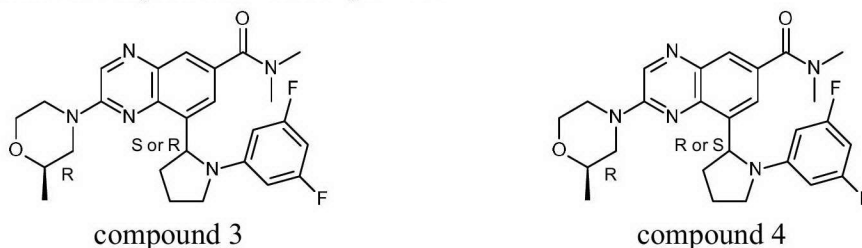


In a sealed tube, a mixture of intermediate 9 (1.1 g; 3.10 mmol), 1-bromo-3,5-difluorobenzene (0.53 mL; 4.64 mmol) and  $\text{Cs}_2\text{CO}_3$  (4.03 g; 12.38 mmol) in 1,4-dioxane (10 mL) was degazed under  $\text{N}_2$ . Xantphos (179 mg; 0.31 mmol) and  $\text{Pd}(\text{OAc})_2$  (69 mg; 0.31 mmol) were added. The reaction mixture was heated at  $100^\circ\text{C}$  for 5h. The reaction mixture was poured into ice-water. EtOAc was added and the mixture was filtered through a pad of celite<sup>®</sup>. The filtrate was separated and the organic layer was washed with brine, dried over  $\text{MgSO}_4$ , filtered and evaporated. The residue (1.54 g) was purified by chromatography over silica gel (irregular bare silica 150 g; mobile phase: 0.2%  $\text{NH}_4\text{OH}$ , 98% DCM, 2% MeOH). The pure fractions were collected and the solvent was evaporated to give 400 mg (28%) of compound 26. Compound 26 was purified by chiral SFC (CHIRALPAK AD-H; 5  $\mu\text{m}$  250x20 mm; mobile phase: 60%  $\text{CO}_2$ , 40% EtOH). The pure fractions were collected and the solvent was evaporated to give 2 fractions:

Fraction 1: 178 mg which was dissolved in ACN. Then,  $\text{Et}_2\text{O}$  and heptane were added. A precipitate was filtered and dried to give 105 mg (7%) of compound 1. M.P.:  $100^\circ\text{C}$  (K).

Fraction 2: 170 mg which was dissolved in ACN. Then,  $\text{Et}_2\text{O}$  and heptane were added. A precipitate was filtered and dried to give 93 mg (12%) of compound 2. M.P.:  $100^\circ\text{C}$  (K).

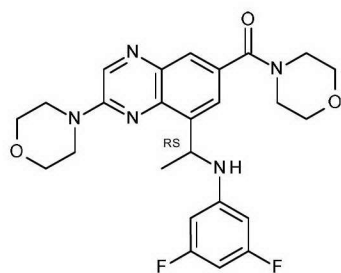
Preparation of compound 3 and compound 4



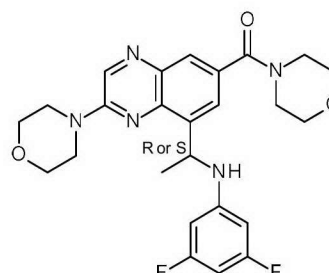


In a sealed vessel, 1-bromo-3,5-difluorobenzene (0.137 mL; 1.20 mmol) and  $\text{Cs}_2\text{CO}_3$  (779 mg; 2.39 mmol) were added to a solution of intermediate 37 (300 mg; 0.80 mmol) in 1,4-dioxane (8 mL). The mixture was carefully degassed under vacuum and back-filled with  $\text{N}_2$  (3x). Then,  $\text{Pd}(\text{OAc})_2$  (18 mg; 0.08 mmol) and xantphos (92 mg; 0.16 mmol) were added and the mixture was again carefully degassed under vacuum and back-filled with  $\text{N}_2$  (3x). The reaction mixture was stirred at  $100^\circ\text{C}$  overnight. The mixture was filtered through a pad of celite<sup>®</sup>. The cake was washed with DCM/MeOH (9/1) and the filtrate was evaporated under vacuum. The residue was taken-up with DCM and washed with an aqueous solution of  $\text{NaHCO}_3$ . The layers were separated and the aqueous layer was extracted with DCM (2x). The combined organics layers were dried over  $\text{MgSO}_4$ , filtered and evaporated under vacuum. The residue (512 mg, green foam) was purified by chromatography over silica gel (Spherical bare silica; 5  $\mu\text{m}$  150x30.0 mm; gradient: from 98% DCM, 2% MeOH (+10%  $\text{NH}_4\text{OH}$ ) to 90% DCM, 10% MeOH (+10%  $\text{NH}_4\text{OH}$ )). The pure fractions were collected and the solvent was evaporated. The residue (148 mg, green oil) was purified by achiral SFC (CHIRALPAK AD-H; 5  $\mu\text{m}$  250x20 mm; mobile phase: 70%  $\text{CO}_2$ , 30% EtOH (0.3%  $i\text{PrNH}_2$ )). The pure fractions were collected and the solvent was evaporated to give 2 fractions which were freeze-dried with water-ACN to give respectively 48 mg (13%, pale yellow fluffy solid) of compound 4 and 53 mg (14%, pale yellow fluffy solid) of compound 3.

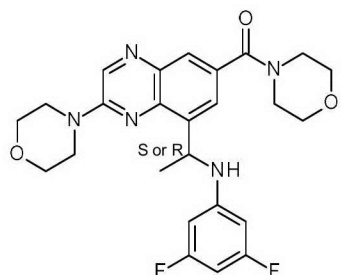
Preparation compound 7, compound 8 and compound 9



compound 7



compound 8



compound 9

In a sealed tube, a mixture of intermediate 44 (130 mg; 0.35 mmol), 1-bromo-3,5-difluorobenzene (48  $\mu$ L; 0.42 mmol) and  $\text{Cs}_2\text{CO}_3$  (228 mg; 0.70 mmol) in 2-methyl-2-butanol (1.70 mL) was purged with  $\text{N}_2$ . BrettPhos Precatalyst First Gen (14 mg; 17.5  $\mu$ mol) was added. The reaction mixture was purged with  $\text{N}_2$  and heated at 110°C for 18h. After cooling down to rt, additional 1-bromo-3,5-difluorobenzene (48  $\mu$ L; 0.42 mmol) and  $\text{Cs}_2\text{CO}_3$  (228 mg; 0.70 mmol) were added. The mixture was purged with  $\text{N}_2$  and BrettPhos Precatalyst First Gen (14 mg; 17.5  $\mu$ mol) was added. The mixture was purged with  $\text{N}_2$  and heated at 110°C for 18h. After cooling down to rt, the crude was combined with another batch coming from a reaction performed on 20 mg of intermediate 44. EtOAc and water were added. The organic layer was separated. The aqueous layer was neutralized with solid  $\text{NH}_4\text{Cl}$  and extracted with EtOAc (2x). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and evaporated under vacuum. The residue (277 mg, brown oil) was purified by chromatography over silica gel (Irregular SiOH 15-40  $\mu$ m; 10 g; gradient: from 100% DCM to 90% DCM, 10% acetone). The pure fractions were collected and the solvent was evaporated to give a yellow oil which was triturated in  $\text{Et}_2\text{O}$ . The precipitate was filtered and dried under vacuum to give 122 mg (62%, yellow foam) of compound 7. M.P.: 206°C (DSC).

86 mg of compound 7 was purified by chiral SFC (CHIRALCEL OJ-H; 5  $\mu$ m 250x20 mm; mobile phase: 75%  $\text{CO}_2$ , 25% MeOH). The pure fractions were collected and the solvent was evaporated affording two fractions which were freeze-dried with water-ACN to give respectively 39 mg (20%, pale yellow fluffy solid) of compound 8 and 41 mg (21%, pale yellow fluffy solid) of compound 9.

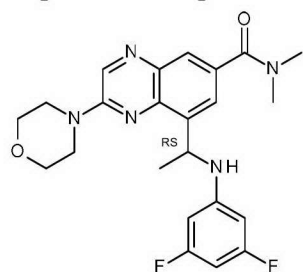
#### Alternative pathway:

In a sealed tube, a mixture of intermediate 45 (1.5 g; 20.91 mmol) and 3,5-difluoroaniline (1.9 g; 14.53 mmol) in DMF (250 mL) was stirred at 50°C for 48h. The solution was poured into ice-water. EtOAc was added and the mixture was filtered through a pad of celite<sup>®</sup>. The product was extracted with EtOAc. The organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated to dryness. The residue (200 mg) was purified by chromatography over silica gel (irregular 15-40  $\mu$ m; 40 g; mobile phase: 0.1%  $\text{NH}_4\text{OH}$ , 98% DCM, 2% MeOH). The pure fractions were collected and the solvent was evaporated to give 460 mg of compound 7.

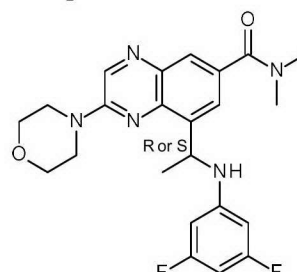
260 mg of compound 7 were purified by chiral SFC (CHIRALCEL OJ-H 5  $\mu$ m 250x20 mm; mobile phase: 75%  $\text{CO}_2$ , 25% MeOH (0.3%  $i\text{PrNH}_2$ )). The pure fractions were collected and the solvent was evaporated to give 111 mg of compound 8 (pure at 88% by  $^1\text{H}$  NMR) and 102 mg of compound 9. 111 mg of compound 8 was purified by achiral SFC (CYANO 6  $\mu$ m 150x21.2 mm; mobile phase: 85%  $\text{CO}_2$ , 15% MeOH

(0.3%  $i\text{PrNH}_2$ ). The pure fractions were collected and the solvent was evaporated. The residue (98 mg) was crystallized with pentane and  $\text{Et}_2\text{O}$ . The precipitate was filtered and dried to give 49 mg of compound 8. M.P.:  $100^\circ\text{C}$  (gum, K).

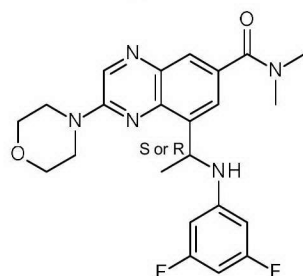
# 5 Preparation compound 11, compound 12 and compound 13



compound 11



compound 12



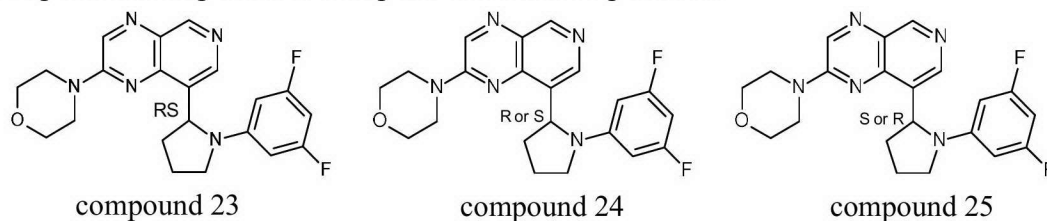
compound 13

In a sealed tube, a mixture of intermediate 19 (283 mg; 0.86 mmol), 1-bromo-3,5-difluorobenzene (147  $\mu\text{L}$ ; 1.29 mmol) and  $\text{Cs}_2\text{CO}_3$  (560 mg; 1.72 mmol) in 2-methyl-2-butanol (4.20 mL) was purged with  $\text{N}_2$ . BrettPhos Precatalyst First Gen (34 mg; 43  $\mu\text{mol}$ ) and BrettPhos (9 mg; 17  $\mu\text{mol}$ ) were added. The reaction mixture was purged with  $\text{N}_2$  and heated at  $110^\circ\text{C}$  for 18h. After cooling down to rt, 1-bromo-3,5-difluorobenzene (147  $\mu\text{L}$ ; 1.29 mmol) and  $\text{Cs}_2\text{CO}_3$  (560 mg; 1.72 mmol) were added. The mixture was purged with  $\text{N}_2$  and BrettPhos Precatalyst First Gen (34 mg; 43  $\mu\text{mol}$ ) and BrettPhos (9 mg; 17  $\mu\text{mol}$ ) were added. The reaction mixture was purged with  $\text{N}_2$  and heated at  $110^\circ\text{C}$  for 18h. After cooling down to rt, the crude was diluted with EtOAc and filtered through a pad of celite<sup>®</sup>. The filtrate was evaporated under vacuum to dryness. The residue (700 mg, brown oil) was purified by chromatography over silica gel (Irregular SiOH 15-40  $\mu\text{m}$ ; 30 g; gradient: from 100% DCM to 95% DCM, 5% ( $i\text{PrOH}/\text{NH}_4\text{OH}$  90/10)). The pure fractions were collected and the solvent was evaporated to give yellow oil which was triturated with diethylether and dried in vacuum to give 323 mg (85%, pale yellow solid) of compound 11 (M.P.:  $228^\circ\text{C}$  (DSC)). Compound 11 was purified by chiral SFC (CHIRALCEL OJ-H 5  $\mu\text{m}$  250x20 mm; mobile phase: 80%  $\text{CO}_2$ , 20% MeOH). The pure fractions were collected and the

solvent was evaporated to give two fractions which were triturated with Et<sub>2</sub>O, evaporated and dried under vacuum to give 116 mg (28%, off-white solid) of compound 12 (M.P.: 218°C (DSC)) and 117 mg (28%, off-white solid) of compound 13 (M.P.: 217°C (DSC)).

5

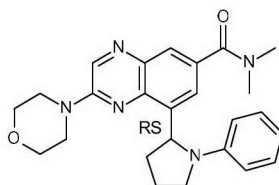
Preparation compound 23 compound 24 and compound 25



In a sealed tube, a mixture of intermediate 64 (360 mg; 1.26 mmol), 1-bromo-3,5-difluorobenzene (216  $\mu$ L; 1.89 mmol) and sodium tert-butoxide (242 mg; 2.52 mmol) in 1,4-dioxane (13 mL) was degazed under N<sub>2</sub>. Then, 2-(di-tert-butylphosphino)biphenyl (38 mg; 0.13 mmol) and Pd<sub>2</sub>(dba)<sub>3</sub> (58 mg; 0.06 mmol) were added and the reaction mixture was heated at 100°C for 18h. The mixture was poured into water and filtered through a pad of celite<sup>®</sup>. The organic layer was extracted with DCM, separated, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (400 mg) was purified by chromatography over silica gel (SiOH 15  $\mu$ m; gradient: from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated. The residue (300 mg) was taken up with DIPE/CAN (drops). A solid was filtered and dried to give 160 mg (32%) of compound 23. Compound 23 was purified by chiral SFC (CHIRALCEL OD-H 5  $\mu$ m 250x20 mm; mobile phase: 70% CO<sub>2</sub>, 30% iPrOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 64 mg (13%) of compound 24 (M.P.: 100°C (gum, K)) and 70 mg (14%) of compound 25 (M.P.: 98°C (gum, K)).

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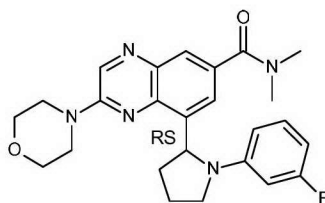
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Preparation of compound 27:

Compound 27 was prepared according to an analogous procedure as described for the synthesis of compound 1, using intermediate 9 and bromobenzene as starting materials (30 mg, 16%). M.P.: 80°C (gum, K).

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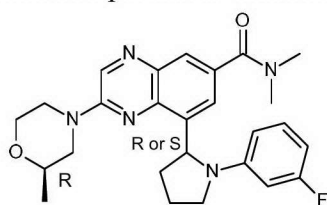


Preparation of compound 28:

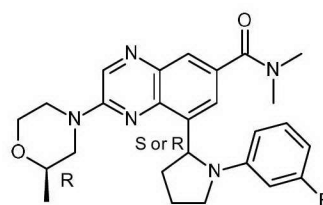
Compound 28 was prepared according to an analogous procedure as described for the synthesis of compound 1, using intermediate 9 and 1-bromo-3-fluorobenzene as starting materials (46 mg, 24%). M.P.: 80°C (gum, K).

5

Preparation compound 29 and compound 30



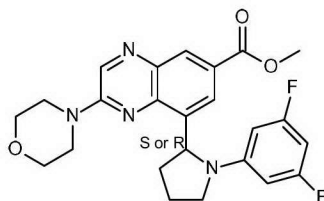
compound 29



compound 30

Compound 29 and compound 30 were prepared according to an analogous procedure as described for the synthesis of compound 3, using intermediate 37 and 1-bromo-3-fluorobenzene as starting material. The racemic compound was purified by achiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x20 mm; mobile phase: 60% CO<sub>2</sub>, 40% MeOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give two fractions which were freeze-dried with water-ACN to give respectively 39 mg (11%, pale green fluffy solid) of compound 29 and 33 mg (9%, pale green fluffy solid) of compound 30.

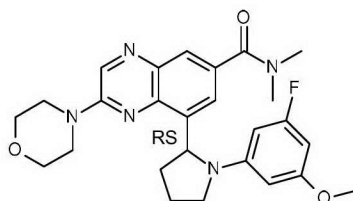
15



Preparation of compound 31:

Compound 31 was prepared according to an analogous procedure as described for the synthesis of compound 1, using intermediate 25 and 1-bromo-3,5-difluorobenzene as starting materials (300 mg, 13%). M.P.: 213°C (DSC).

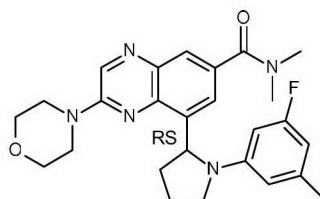
20



Preparation of compound 32:

Compound 32 was prepared according to an analogous procedure as described for the synthesis of compound 1, using intermediate 9 and 3-bromo-5-fluoroanisole as starting materials (85 mg, 25%). M.P.: 80°C (gum, K).

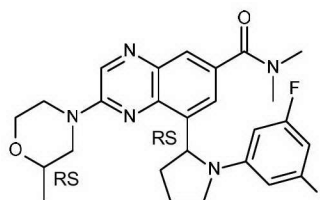
5



Preparation of compound 35:

Compound 35 was prepared according to an analogous procedure as described for the synthesis of compound 1, using intermediate 9 and 3-bromo-5-fluorotoluene as starting materials (83 mg, 25%). M.P.: 80°C (gum, K).

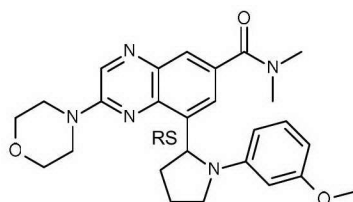
10



Preparation of compound 36:

Compound 36 was prepared according to an analogous procedure as described for the synthesis of compound 1, using intermediate 71 and 1-bromo-3,5-difluorobenzene as starting materials (90 mg, 34%). Compound 36 was obtained as a mixture of 3 diastereoisomers.

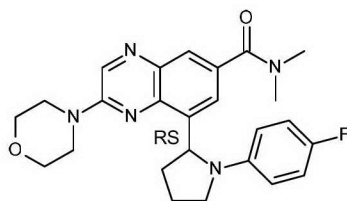
15



Preparation of compound 41:

Compound 41 was prepared according to an analogous procedure as described for the synthesis of compound 1, using intermediate 9 and 3-bromoanisole as starting materials (freeze-dried, 16 mg, 3%). M.P.: 80°C (gum, K).

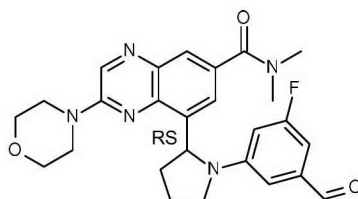
20



Preparation of compound 42:

Compound 42 was prepared according to an analogous procedure as described for the synthesis of compound 23, using intermediate 9 and 4-bromofluorobenzene as starting materials (freeze-dried, 69 mg, 27%). M.P.: 80°C (gum, K).

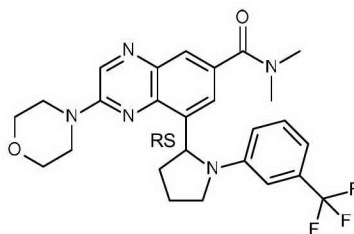
5



Preparation of compound 44:

Compound 44 was prepared according to an analogous procedure as described for the synthesis of compound 23, using intermediate 9 and 3-bromo-5-fluorobenzaldehyde as starting materials (95 mg, 24%). M.P.: 80°C (gum, K).

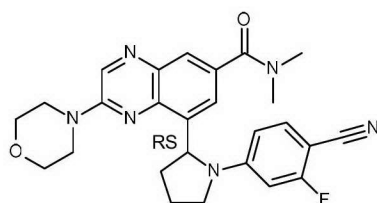
10



Preparation compound 52:

In a sealed tube, a mixture of intermediate 9 (100 mg; 0.28 mmol), 3-bromobenzotrifluoride (95 mg; 0.42 mmol) and  $\text{Cs}_2\text{CO}_3$  (183 mg; 0.56 mmol) in 1,4-dioxane (3 mL) was degazed under  $\text{N}_2$ . Then, 2-(di-tert-butylphosphino)biphenyl (17 mg; 0.06 mmol) and  $\text{Pd}_2(\text{dba})_3$  (26 mg; 0.03 mmol) were added and the reaction mixture was heated at 100°C for 24h. The mixture was poured into water and filtered through a pad of celite<sup>®</sup>. The organic layer was extracted with DCM, separated, dried over  $\text{MgSO}_4$ , filtered and evaporated to dryness. The residue (180 mg) was purified by chromatography over silica gel (Spherical bare silica 5  $\mu\text{m}$ ; 150x30.0 mm; gradient: from 98% DCM, 2% MeOH (+10%  $\text{NH}_4\text{OH}$ ) to 92% DCM, 8% MeOH (+10%  $\text{NH}_4\text{OH}$ )). The pure fractions were collected and the solvent was evaporated. The residue (33 mg) was freeze-dried with water/ACN 80/20 to give 32 mg (23%) of compound 52. M.P.: 80°C (gum, K).

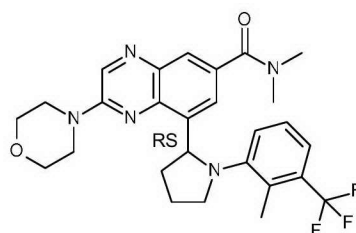
190



Preparation compound 54:

Compound 54 was prepared according to an analogous procedure as described for the synthesis of compound 52, using intermediate 9 and 4-bromo-2-fluorobenzonitrile as starting materials (freeze-dried: 37 mg, 28%). M.P.: 80°C (gum, K).

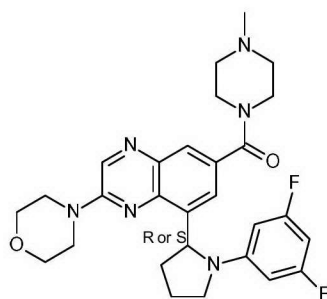
5



Preparation compound 55:

Compound 55 was prepared according to an analogous procedure as described for the synthesis of compound 52, using intermediate 9 and 2-bromo-2-methyl-3-(trifluoromethyl)benzene as starting materials (freeze-dried: 16 mg, 11%). M.P.: 80°C (gum, K).

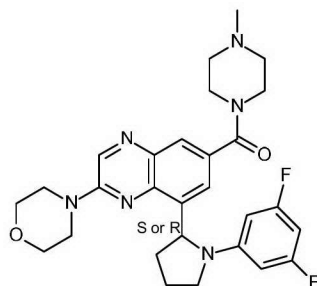
10



Preparation compound 57:

Compound 57 was prepared according to an analogous procedure as described for the synthesis of compound 52, using intermediate 81 and 1-bromo-3,5-difluorobenzene as starting materials (freeze-dried: 31 mg, 24%, white powder). M.P.: 80°C (gum, K).

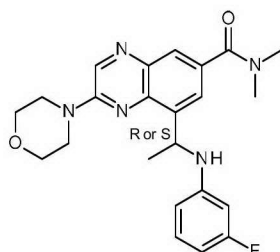
15



Preparation compound 58:



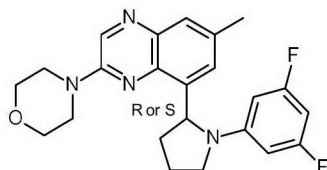
Compound 58 was prepared according to an analogous procedure as described for the synthesis of compound 52, using intermediate 82 and 1-bromo-3,5-difluorobenzene as starting materials (freeze-dried: 36 mg, 28%, white powder). M.P.: 80°C (gum, K).



### 5 Preparation compound 85:

Compound 85 was prepared according to an analogous procedure as described for the synthesis of compound 11, using intermediate 14 and 1-bromo-3-fluorobenzene as starting materials (freeze-dried: 36 mg, 29%, pale yellow fluffy solid).

### 10 Preparation of compound 106 and compound 107



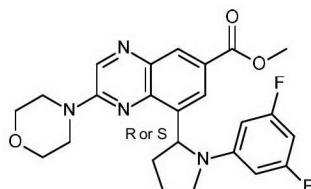
compound 106



compound 107

Compound 106 and compound 107 were prepared according to an analogous procedure as described for the synthesis of compound 52, using intermediate 114 and 1-bromo-3,5-difluorobenzene as starting materials. The residue (0.6 g) was purified by chromatography over silica gel (irregular 15-40  $\mu$ m; 40 g; mobile phase: 50% heptane, 50% EtOAc). The pure fractions were collected and the solvent was evaporated. The residue (160 mg) was purified by chiral SFC (CHIRALCEL OD-H 5  $\mu$ m; 250x20 mm; mobile phase: 80% CO<sub>2</sub>, 20% EtOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 57 mg (10%) of compound 106 (M.P.: 80°C, gum, K) and 60 mg (10%) of compound 107 (M.P.: 80-90°C, gum, K).

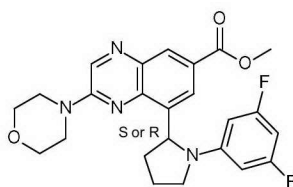
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### Preparation compound 249:

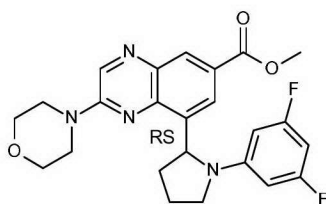
The experiment was performed 4 times on the same quantity (580 mg; 1.46 mmol) of intermediate 24.

In a sealed tube, a mixture of intermediate 24 (580 mg; 1.46 mmol), 1-bromo-3,5-difluorobenzene (0.29 mL; 2.54 mmol) and  $\text{Cs}_2\text{CO}_3$  (1.1 g; 3.39 mmol) in 1,4-dioxane (20 mL) was degazed under  $\text{N}_2$ . 2-(di-tert-butylphosphino)biphenyl (101 mg; 0.34 mmol) and  $\text{Pd}_2(\text{dba})_3$  (155 mg; 0.17 mmol) were added. The reaction mixture was heated at 100°C for 48h. The reaction mixture was poured into ice-water and EtOAc was added, filtered through a pad of celite<sup>®</sup>. The filtrate was separated and the organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated. The residue (4 g) was purified by chromatography over silica gel (irregular 15-40  $\mu\text{m}$  120 g; mobile phase: 65% heptane, 35% EtOAc). The pure fractions were collected and the solvent was evaporated to give 950 mg (31%) of compound 249. M.P.: 211°C (DSC).



Preparation of compound 252:

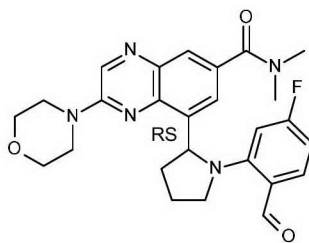
In a sealed tube, a mixture of intermediate 25 (1.73 g; 5.05 mmol), 1-bromo-3,5-difluorobenzene (750  $\mu\text{L}$ ; 6.57 mmol) and  $\text{Cs}_2\text{CO}_3$  (2.47 g; 7.58 mmol) in 1,4-dioxane (16 mL) was degazed under  $\text{N}_2$ . Xantphos (292 mg; 0.51 mmol) and  $\text{Pd}_2(\text{dba})_3$  (231 mg; 0.25 mmol) were added. Then, the reaction mixture was heated at 100°C overnight. The mixture was poured into  $\text{H}_2\text{O}$ , filtered through a pad of celite<sup>®</sup> and extracted with EtOAc. The organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated until dryness. The residue (1.5 g) was purified by chromatography over silica gel (irregular 15-40  $\mu\text{m}$ ; 80 g; mobile phase: 65% heptane, 35% EtOAc). The pure fractions were collected and the solvent was evaporated to give 1.04g (60%) of intermediate 25 and an intermediate residue was taken-up with  $\text{Et}_2\text{O}$ . The precipitate was filtered and dried under vacuum to give 300 mg (13%) of compound 252.



Preparation of compound 254:

The experiment was performed 12 times on the same quantity (475 mg; 1.39 mmol) of intermediate 23:

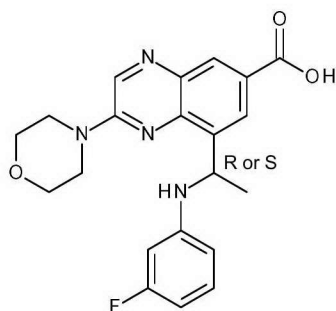
Compound 254 was prepared according to an analogous procedure as described for the synthesis of compound 249, using intermediate 23 and 1-bromo-3,5-difluorobenzene as starting materials (1.7 g, 22%).



Preparation of compound 255:

Compound 255 was prepared according to an analogous procedure as described for the synthesis of compound 249, using intermediate 9 and 2-bromo-4-fluorobenzaldehyde as starting materials (120 mg, 22%).

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Preparation of compound 274:

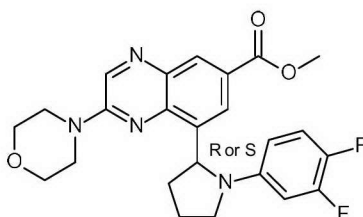
In a sealed tube, a mixture of intermediate 178 (0.2g; 0.605 mmol), 1-bromo-3-fluorobenzene (0.079 mL; 0.726 mmol) and  $\text{Cs}_2\text{CO}_3$  (0.394 g; 1.21 mmol) in tert-amyl alcohol (3 mL) was degassed with  $\text{N}_2$ . BrettPhos Precatalyst First Gen (24 mg, 0.0303 mmol) and Brettphos (6.5 mg; 0.012 mmol) were added. The reaction mixture was purged with  $\text{N}_2$  and heated at  $110^\circ\text{C}$  for 42 h. After cooling down to rt, the crude was poured into water, diluted with EtOAc and filtered on a pad of celite®. The aqueous layer was acidified and extracted with DCM, the combined layers were dried over  $\text{MgSO}_4$ , filtered and evaporated to give 94mg (39%) of the compound 274 (ee: 90%).

15

Alternative preparation of compound 274:

Compound 262a was hydrolyzed in THF (10 volumes) using NaOH (1.0 M in water, 4 eq.) at  $50^\circ\text{C}$  for 16 hours. The product was isolated by distillation of THF, dilution with water and pH adjustment to 6-7 with 2M HCl. The procedure was executed on 18 and 100 g scale of compound 262a and gave compound 274 in quantitative yield (e.e.: 97.9%).

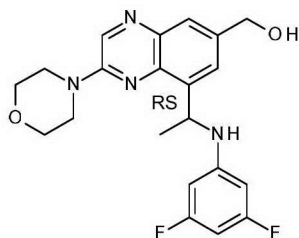
20



Preparation of compound 350:

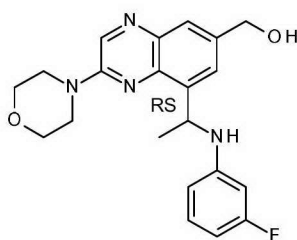
Compound 350 was prepared according to an analogous procedure as described for the synthesis of compound 52, using intermediate 24 and 4-bromo-1,2-difluorobenzene as starting materials (250 mg, 19%).

5 Example B2



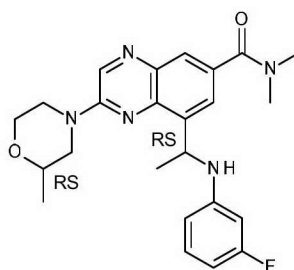
Preparation of compound 84:

A solution of thioglycolic acid (24  $\mu$ L; 0.34 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (102  $\mu$ L; 0.68 mmol) in ACN (2 mL) was added to a solution of intermediate 100 (100 mg; 0.17 mmol) in ACN (3 mL). The solution was stirred at rt for 15 min then DCM and 10% aqueous solution of  $\text{Na}_2\text{CO}_3$  were added. The organic layer was separated and the aqueous layer was extracted with DCM (2x). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and evaporated in vacuum. The residue (60 mg) was purified by chromatography over silica gel (irregular bare silica 40 g; mobile phase: 0.4%  $\text{NH}_4\text{OH}$ , 96% DCM, 4% MeOH). The pure fractions were collected and the solvent was evaporated. The residue (36 mg) was purified by reverse phase (X-  
10 Bridge-C18; 5  $\mu$ m 30\*150 mm; gradient: from 75%  $\text{NH}_4\text{HCO}_3$  0.5%, 25% ACN to 35%  $\text{NH}_4\text{HCO}_3$  0.5%, 65% ACN). The pure fractions were collected and the solvent was evaporated to give 30 mg (44%) of compound 84. M.P.: 80°C (gum, K).



20 Preparation of compound 100:

Compound 100 was prepared according to an analogous procedure as described for the synthesis of compound 84, using intermediate 108 as starting material (75 mg, 82%, pale yellow solid).



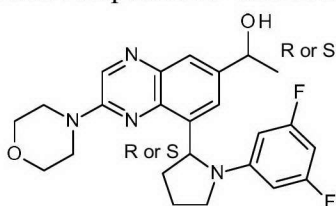
Preparation of compound 136:

Compound 136 was prepared according to an analogous procedure as described for the synthesis of compound 84, using intermediate 128 as starting material (39 mg, 44%, off-white solid. M.P.: 184°C (DSC).

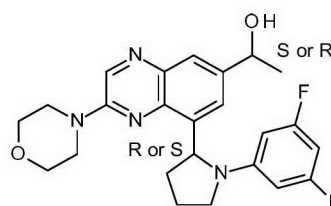
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Example B3:

Preparation compound 15 and compound 16



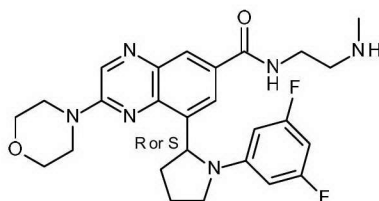
compound 185



compound 16

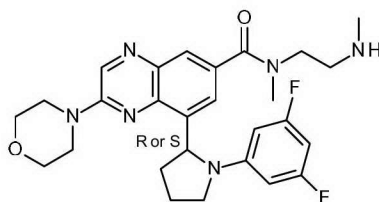
At 10°C, methylmagnesium bromide (0.27 mL; 0.82 mmol) was added to a solution of compound 250 (0.29 g; 0.68 mmol) in THF (8 mL) under N<sub>2</sub>. The solution was stirred at 10°C for 45min. The solution was poured into a saturated NH<sub>4</sub>Cl solution and the product was extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (285 mg) was purified by chromatography over silica gel (irregular 15-40 μm; 12 g; mobile phase: 96% DCM, 4% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated to give 158 mg of fraction 1 and 56 mg of fraction 2. Fraction 1 was purified by reverse phase (X-  
 10 Bridge-C18 5 μm 30\*150 mm; gradient: from 65% NH<sub>4</sub>HCO<sub>3</sub> 0.5%, 35% ACN to 25% NH<sub>4</sub>HCO<sub>3</sub> 0.5%, 75% ACN). The pure fractions were collected and the solvent was evaporated. The residue (103 mg) was combined with 56 mg of fraction 2 to give 159 mg which were purified by achiral SFC (CHIRALPAK IC 5 μm 250x20 mm; mobile  
 15 phase: 70% CO<sub>2</sub>, 30% iPrOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give two fractions which were freeze-dried with water-ACN (80/20) to give 70 mg (23%, yellow powder) of compound 15 (M.P.: 80°C (gums, K)) and 56 mg (15%, yellow powder) of compound 16 (M.P.: 80°C (gums, K)).  
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25 Example B4:



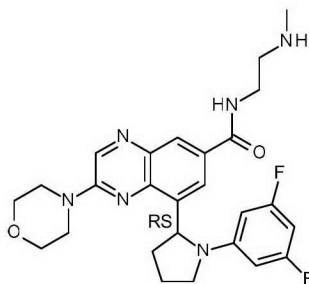
Preparation compound 17:

At 0°C, HCl (4M in 1,4-dioxane) (0.31 mL; 1.26 mmol) was added to a solution of intermediate 49 (150 mg; 0.25 mmol) in ACN (6 mL). The reaction mixture was stirred at 0°C for 1h and at rt for 3h. The solution was poured into ice-water and extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated. The residue (160 mg) was purified by chromatography over silica gel (irregular bare silica 40 g; mobile phase: 0.1% NH<sub>4</sub>OH, 90% DCM, 10% MeOH). The pure fractions were collected and the solvent was evaporated until dryness to give 45 mg (36%) of compound 17. M.P.: 170°C (K).



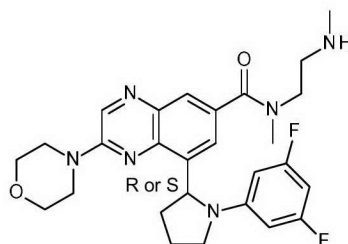
Preparation compound 18:

At 0°C, HCl (4M in 1,4-dioxane) (0.92 mL; 3.68 mmol) was added to a solution of intermediate 50 (450 mg; 0.74 mmol) in DCM (5 mL). The reaction mixture was stirred at 0°C for 1h and at rt for 3h. The solution was poured into ice-water and extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated. The residue (265 mg) was purified by chromatography over silica gel (irregular 15-40 μm; 24 g; mobile phase: 60% heptane, 5% MeOH, 35% EtOAc). The pure fractions were collected and the solvent was evaporated to give 132 mg (35%, yellow foam) of 18. M.P.: 80°C (gum, K).



Preparation of compound 72:

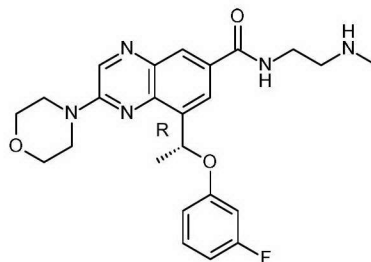
Compound 72 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 85 as starting material (freeze-dried: 72 mg, 45%, yellow powder). M.P.: 80°C (gum, K).



#### 5 Preparation compound 93:

Compound 93 was prepared according to an analogous procedure as described for the synthesis of compound 18, using intermediate 103 as starting materials (32 mg, 14%, yellow foam). M.P.: 80°C (gum, K).

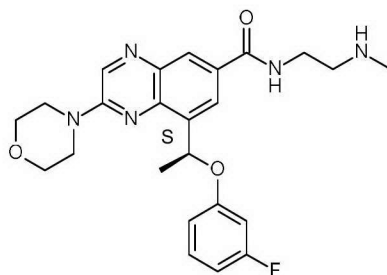
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#### Preparation compound 122:

HCl (3M in cyclopentyl methyl ether) (0.3 mL; 0.9 mmol) was added to a solution of intermediate 118a (163 mg; 0.29 mmol) in 1,4-dioxane (3 mL). The reaction mixture was stirred at 50°C for 2h30. Then, more HCl (3M in cyclopentyl methyl ether) (0.3 mL; 0.9 mmol) was added and the reaction mixture was heated at 50°C for 3h. Water was added and the mixture was slowly basified with NaHCO<sub>3</sub> (solid). The layers were separated and the aqueous layer was extracted with DCM (2x) and DCM/MeOH (9/1) (2x). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated. The residue (136 mg, orange oil) was purified by chromatography over silica gel (irregular SiOH; 15-40 μm; 4 g; gradient: from 97% DCM, 3% (MeOH/NH<sub>4</sub>OH: 95/5) to 85% DCM, 15% (MeOH/NH<sub>4</sub>OH: 95/5)). The pure fractions were collected and the solvent was evaporated. The residue (72 mg, pale yellow oil) was purified by reverse phase (X-Bridge-C18 5 μm 30\*150 mm; gradient: from 75% (aq. NH<sub>4</sub>HCO<sub>3</sub> 0.5%), 25% ACN to 35% (aq. NH<sub>4</sub>HCO<sub>3</sub> 0.5%), 65% ACN). The pure fractions were collected and the solvent was evaporated to give 37 mg (28%, yellow foam) of compound 122.

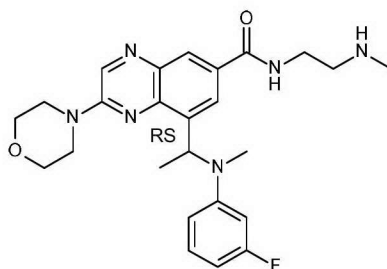
198



Preparation compound 123:

Compound 123 was prepared according to an analogous procedure as described for the synthesis of compound 122, using intermediate 118b as starting material (30 mg, 21%, pale yellow foam). M.P.: 80°C (gum, K).

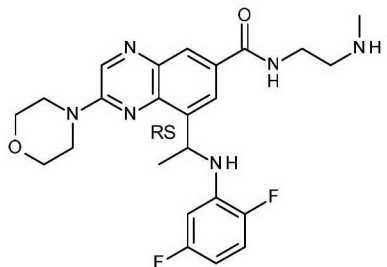
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Preparation compound 130:

Compound 130 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 122 as starting material (75 mg, 28%). M.P.: 159°C (DSC).

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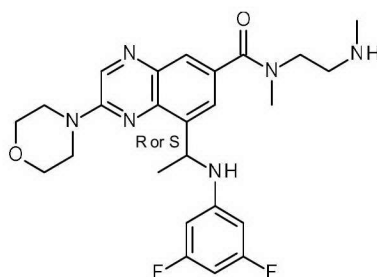
Preparation compound 132:

Compound 132 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 125 as starting material (120 mg, 36%). M.P.: 80°C (gum, K).

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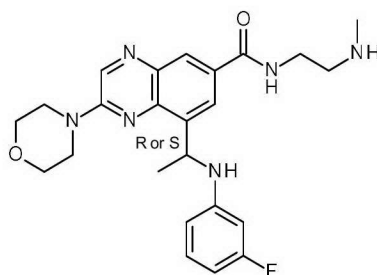
199



Preparation compound 137:

Compound 137 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 129 as starting material (27 mg, 36%). M.P.: 80°C (gum, K).

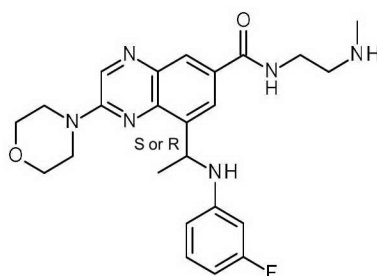
5



Preparation compound 138:

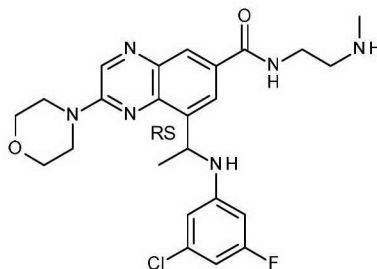
Compound 138 was prepared according to an analogous procedure as described for the synthesis of compound 122, using intermediate 132b as starting material (41 mg, 56%, yellow foam).

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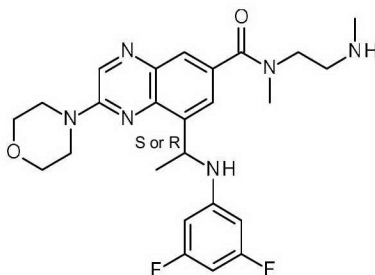
Preparation compound 139:

Compound 139 was prepared according to an analogous procedure as described for the synthesis of compound 122, using intermediate 132c as starting material (37 mg, 50%, yellow foam).



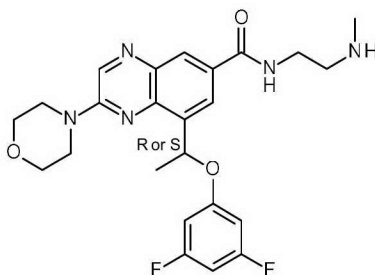
15 Preparation compound 147:

Compound 147 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 135 as starting material (40 mg, 20%). M.P.: 80°C (gum, K).



5 Preparation compound 152:

Compound 152 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 136 as starting material (40 mg, 24%). M.P.: 80°C (gum, K).

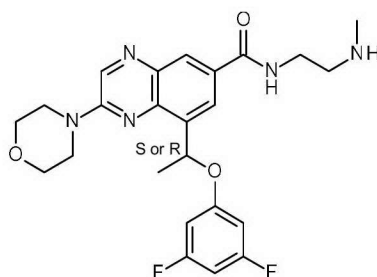


10 Preparation compound 165:

HCl (4M in 1,4-dioxane) (0.75 mL; 3.01 mmol) was added to a solution of intermediate 144 (297 mg; 0.52 mmol) in 1,4-dioxane (5 mL). The reaction mixture was stirred at 50°C for 2h30. Water was added and the mixture was slowly basified with 10% aqueous solution of K<sub>2</sub>CO<sub>3</sub>. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated. The residue (210 mg) was purified by chromatography over silica gel (40 g; mobile phase: from 90% DCM, 10% MeOH, 0.5% NH<sub>4</sub>OH to 85% DCM, 14% MeOH, 1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated to give 130 mg (53%) of compound 165. M.P.: 80°C (gum, K).

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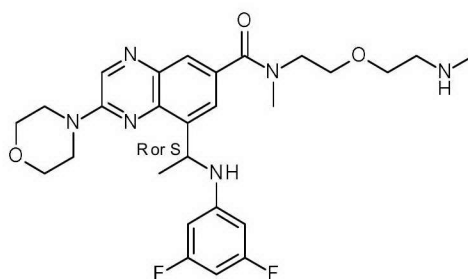
201



Preparation compound 166:

Compound 166 was prepared according to an analogous procedure as described for the synthesis of compound 165, using intermediate 145 as starting material (120 mg, 43%).  
M.P.: 80°C (gum, K).

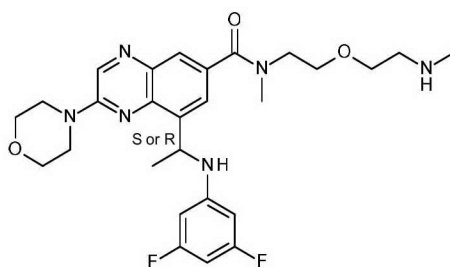
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Preparation compound 174:

Compound 174 was prepared according to an analogous procedure as described for the synthesis of compound 165, using intermediate 148b as starting material (42 mg, 49%).  
M.P.: 80°C (gum, K).

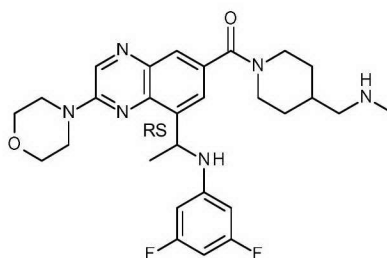
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Preparation compound 175:

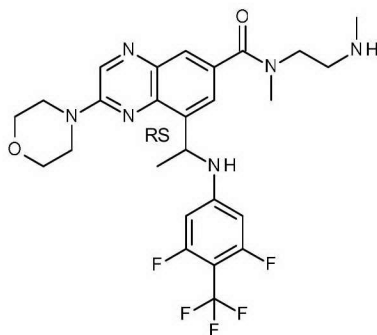
Compound 175 was prepared according to an analogous procedure as described for the synthesis of compound 165, using intermediate 148c as starting material (38 mg, 45%).  
M.P.: 80°C (gum, K).

15



Preparation compound 176:

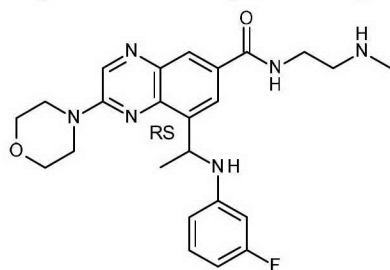
Compound 176 was prepared according to an analogous procedure as described for the synthesis of compound 165, using intermediate 149 as starting material (98 mg, 32%). The reaction mixture was stirred at 0°C for 1 and at rt for 3h.



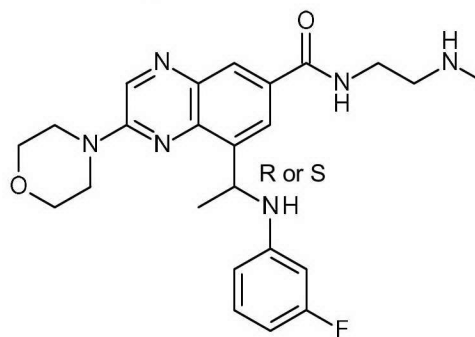
5 Preparation compound 224:

Compound 224 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 160 as starting material (crystallized from diethylether; 275 mg, 65%). M.P.: 163°C (DSC).

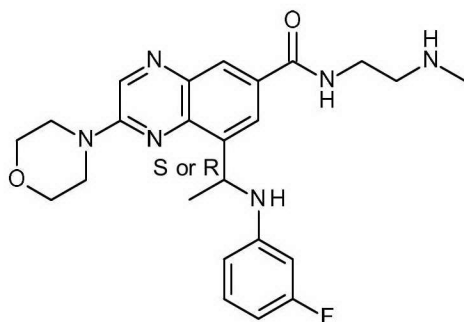
10 Preparation of compound 282, compound 282a and compound 282b



compound 282



compound 282a

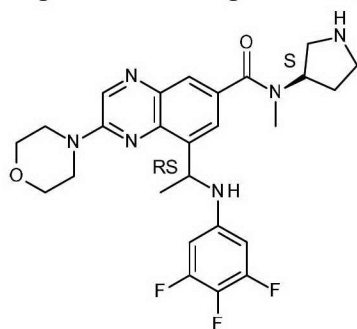


compound 282b

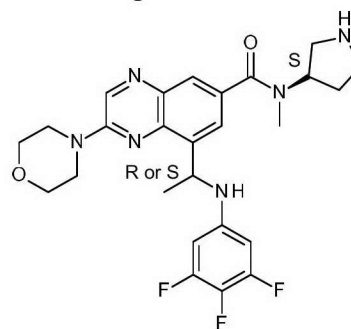
Compound 282 was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 187 as starting material. Crystallization from MeOH and Et<sub>2</sub>O gave 520 mg of compound 282 (54%), MP : 100°C, gum, K).

Compound 282 (440 mg) was purified by chiral SFC (CHIRALPAK AD-H 5 μm 250x20 mm; mobile phase: 50% CO<sub>2</sub>, 50% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 189 mg of one compound which was crystallized from Et<sub>2</sub>O giving 120mg (12%) of compound 282a (MP : 100°C, gum, K) and 195 mg of another compound which was crystallized from Et<sub>2</sub>O giving 116mg (12%) of compound 182b (MP : 100°C, gum, K).

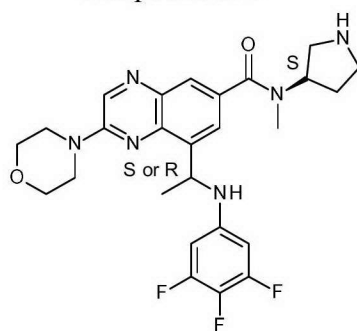
Preparation of compound 296, compound 296a and compound 296b



compound 296



compound 296a

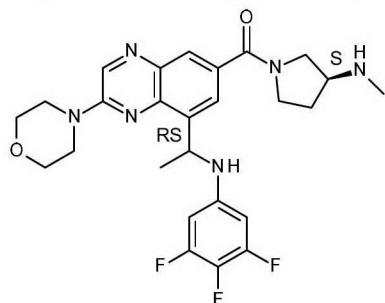


compound 296b

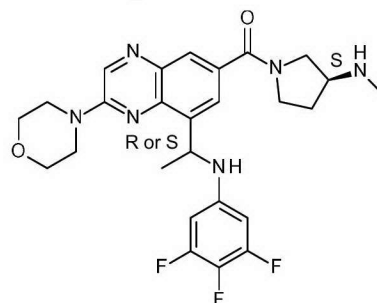
Compound 296 was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 188 as starting material (725 mg, 87%).

Compound 296 (700 mg) was purified by chiral SFC (CHIRALCEL OJ-H 5 μm 250x20 mm; mobile phase: 88.2% CO<sub>2</sub>, 11.8% MeOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 219 mg of one compound which was crystallized from pentane giving 180mg (21%) of compound 296a and 214 mg of other compound which was crystallized from pentane giving 161mg (19%) of compound 296b.

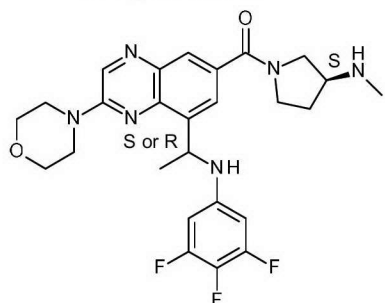
## Preparation of compound 297, compound 297a and compound 297b



compound 297



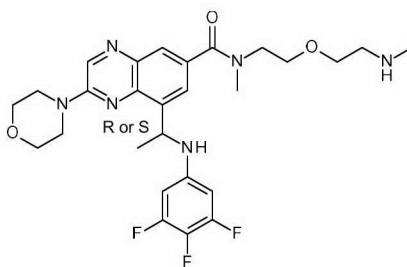
compound 297a



compound 297b

Compound 297 was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 189as starting material (465 mg, 73%). Compound 297 was purified by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x20 mm; mobile phase: 70% CO<sub>2</sub>, 30% iPrOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 179 mg of one compound which was crystallized from DIPE giving 136mg (21%) of compound 297a and 136 mg of other compound which was crystallized from DIPE giving 103mg (16%) of compound 297b.

10

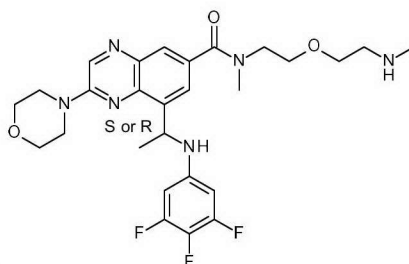


## Preparation of compound 315a

Compound 315a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 195aas starting material (84 mg, 44%, MP : 86°C, gum, K).

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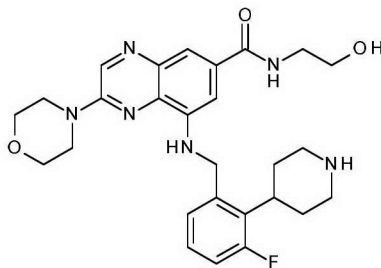
205



## Preparation of compound 315b

Compound 315b was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 195b as starting material material (96 mg, 38%, M.P.: 90°C (gum, K).

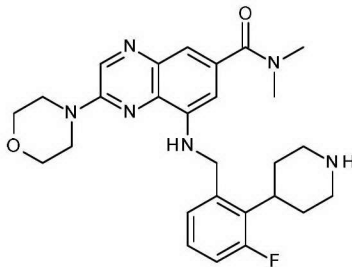
5



## Preparation of compound 317

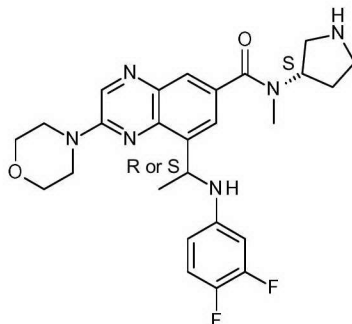
Trifluoroacetic acid (1.028 mL, 13.8 mmol) was added dropwise to a solution of intermediate 205 (0.56 g, 0.92 mmol) in DCM (15 mL) at 0°C. The solution was allowed to warm to room temperature and was stirred at room temperature overnight. The mixture was poured into water, basified with an aqueous solution of K<sub>2</sub>CO<sub>3</sub> 10% and the compound was extracted with DCM. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated. The residue (0.39g) was purified via silica gel chromatography (Stationary phase: irregular bare silica 40g, Mobile phase: 90% DCM, 10% MeOH (+10% NH<sub>4</sub>OH)). The pure fractions were collected and the solvent was evaporated until dryness and the resulting residue was crystallized from DIPE. The precipitate was filtered off and dried in vacuo to give 107mg (23%) of compound 317. M.P: 167°C (DSC).

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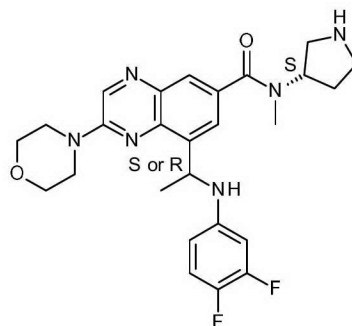
## Preparation of compound 318

Compound 318 was prepared according to an analogous procedure as described for the synthesis of compound 317 using intermediate 203 as starting material (75 mg, 30%).



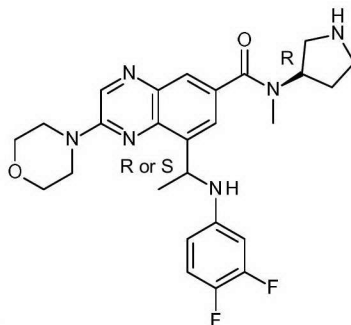
Preparation of compound 322a:

- 5 Compound 322a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 206a as starting material (152 mg, 39%, MP : 122°C, K).



Preparation of compound 322b:

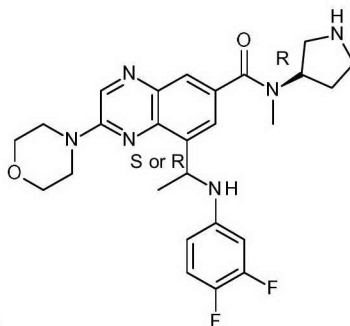
- 10 Compound 322b was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 206b as starting material (228 mg, 55%, MP : 80°C, K).



Preparation of compound 323a:

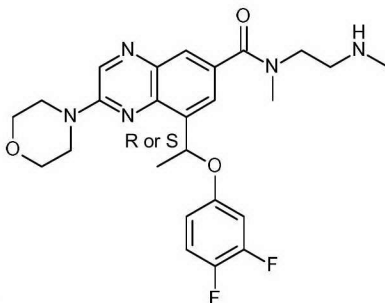
- 15 Compound 323a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 207a as starting material (246 mg, 62%, MP : 126°C, K).





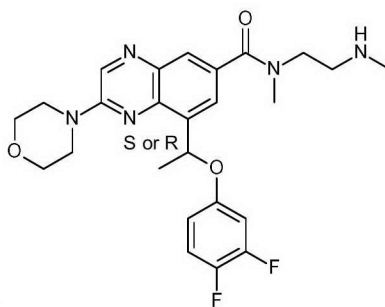
Preparation of compound 323b:

Compound 323b was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 207b as starting material (267 mg, 5 64%, MP : 130°C, K).



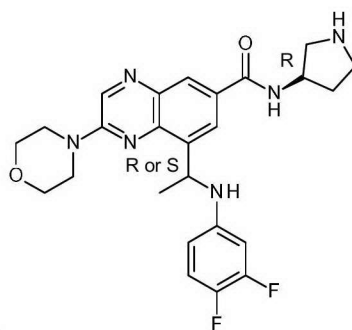
Preparation of compound 324a:

Compound 324a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 208a as starting material (158 mg, 10 37%, MP : 60°C, K).



Preparation of compound 324b:

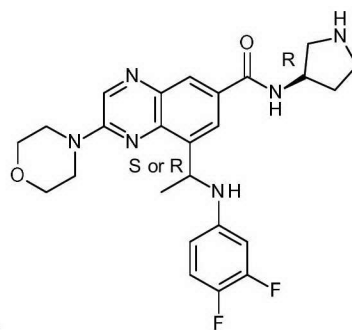
Compound 324b was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 208b as starting material (100 mg, 15 23%, MP : 60°C, K).



Preparation of compound 325a:

Compound 325a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 209a as starting material (123 mg, 37%, MP : 144°C, K).

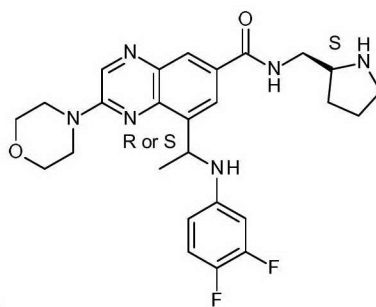
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Preparation of compound 325b:

Compound 325b was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 209b as starting material (162 mg, 47%, MP : 138°C, K).

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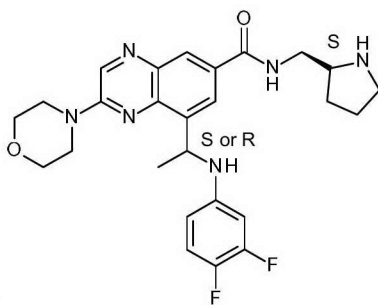


Preparation of compound 329a:

Compound 329a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 213a as starting material (175 mg, 50%, MP : 121°C, K).

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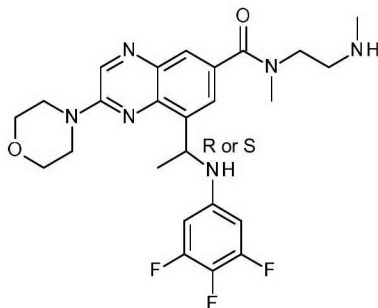
209



Preparation of compound 329b:

Compound 329b was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 213b as starting material (139 mg, 38%, MP : 124°C, K).

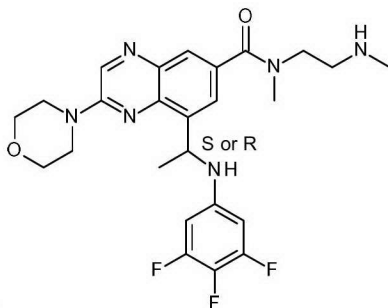
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Preparation of compound 335a:

Compound 335a was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 215a as starting material (75mg, 45%).

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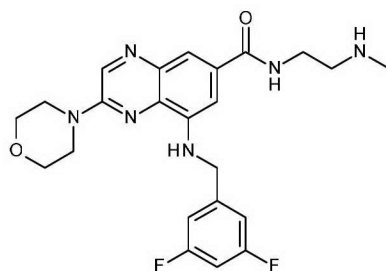


Preparation of compound 335b:

Compound 335b was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 315b (69 mg, 35%). M.P.: 80°C (gum, K).

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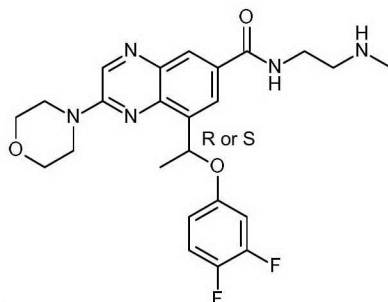
210



Preparation of compound 340:

Compound 340 was prepared according to an analogous procedure as described for the synthesis of compound 165, using intermediate 218 as starting material (133 mg, 52%).

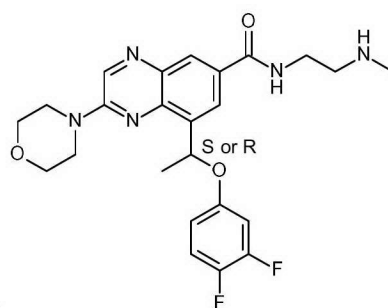
5 M.P.: 180°C, DSC).



Preparation of compound 344a:

Compound 344a was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 220a as starting material (234 mg,

10 39%). M.P.: 75°C, gum K).



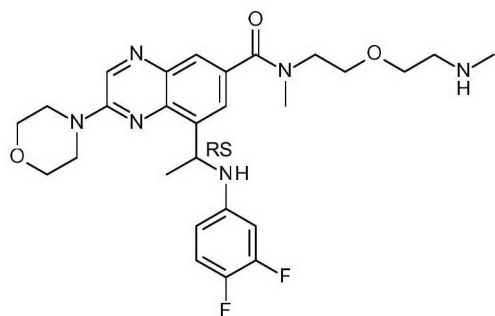
Preparation of compound 344b:

Compound 344b were prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 220b as starting material (258mg,

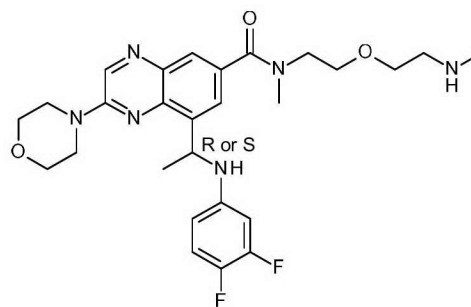
15

44%). M.P.: 75°C, gum K.

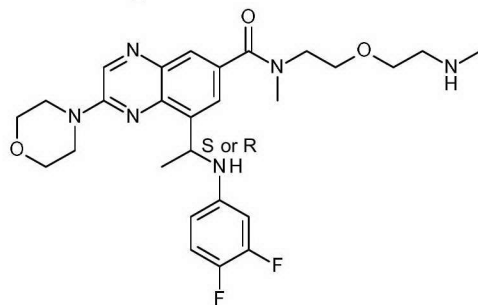
Preparation of compound 345, compound 345a and compound 345b



compound 345



compound 345a

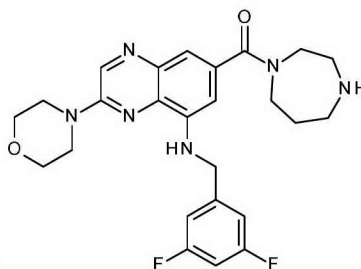


compound 345b

Compound 345 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 221 as starting material (590 mg; 82%).

The separation of the enantiomers from 590mg compound 345 was performed via  
 5 chiral SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu$ m 250x20mm, Mobile phase:  
 70% CO<sub>2</sub>, 30% EtOH). The pure fractions were collected and the solvent was  
 evaporated affording 2 fractions which were respectively crystallized from pentane to  
 give 153 mg (21%) compound 345a (M.P.: 80°C (K)) and 127 mg (21%) of compound  
 345b (M.P.: 80°C (K)).

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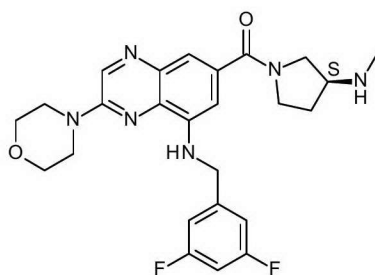


Preparation of compound 351:

Compound 351 was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 222 as starting material (209mg g; 29%).

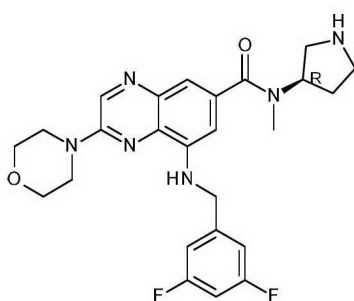
15

212



Preparation of compound 352:

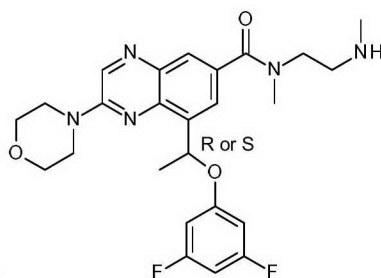
Compound 352 was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 223 as starting material (103mg g; 32%).



5 Preparation of compound 355:

Compound 355 was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 224 as starting material (179 mg, 28%).  
M.P.: gum (K).

10

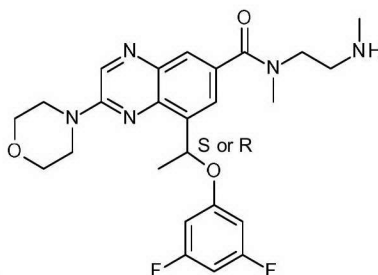


Preparation of compound 356a:

Compound 356a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 225a as starting material (24mg, 67%).

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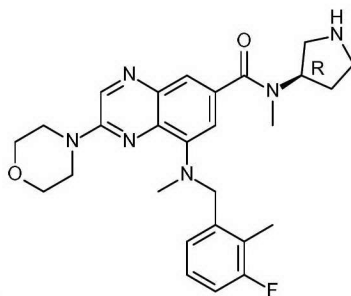
213



Preparation of compound 356b:

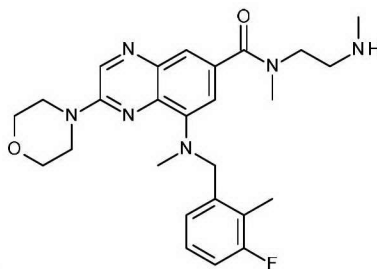
Compound 356b was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 225b as starting material (26mg, 70%).

5



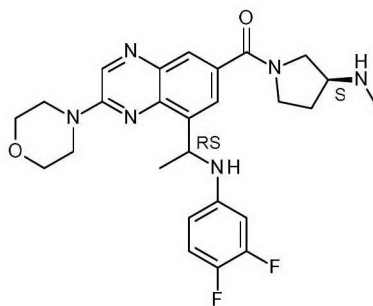
Preparation of compound 359:

Compound 359 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 226 as starting material (85mg, 33%).



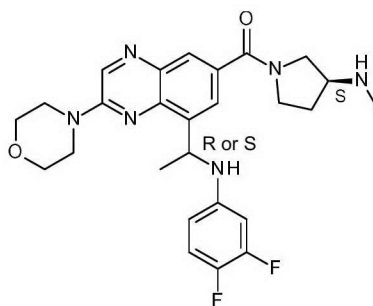
10 Preparation of compound 362:

Compound 362 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 227 as starting material (138mg, 48%).



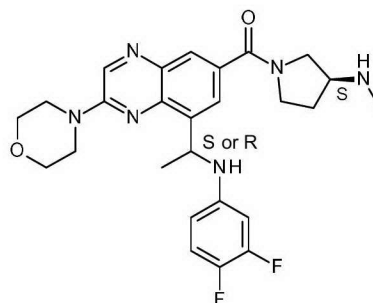
Preparation of compound 365:

Compound 365 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 228 as starting material (110mg; 66%, M.P: 80°C gum (K)).



5 Preparation of compound 365a:

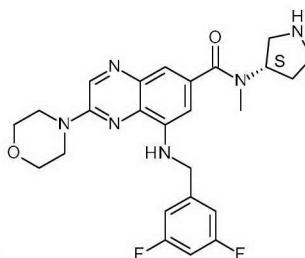
Compound 365a was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 228a as starting material (155mg; 95%, M.P: 80°C gum (K)).



10 Preparation of compound 365b:

Compound 365b was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 228b as starting material (106mg; 67%, M.P: 80°C gum (K)).

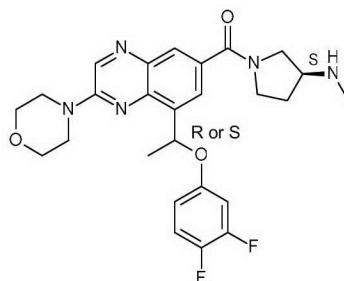
15



Preparation of compound 368:

Compound 368 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 229 as starting materials. (249 mg, 29%).

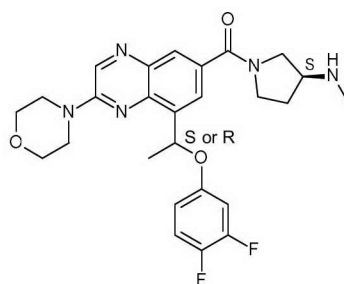




Preparation of compound 370a:

Compound 370a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 230a as starting material ( 55 mg, 14%, M.P.: 128°C (DSC).

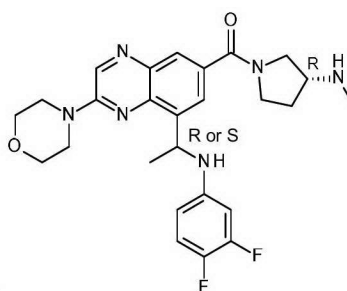
5



Preparation of compound 370b:

Compound 370b was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 270b as starting material (75 mg, 18%, M.P.: 80°C (gum, K).

10

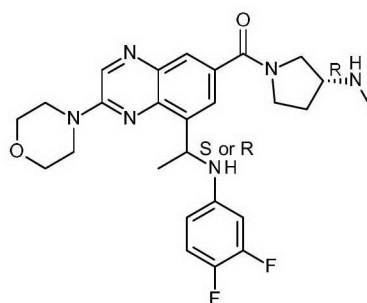


Preparation of compound 371a:

Compound 371a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 231a as starting material (174 mg, 43%, M.P.: 114°C, (K)).

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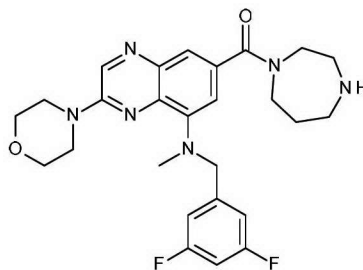
216



Preparation of compound 371b:

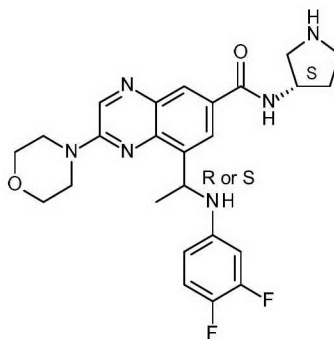
Compound 371b was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 271b as starting material (114 mg, 31%, M.P.: 107°C, (K)).

5



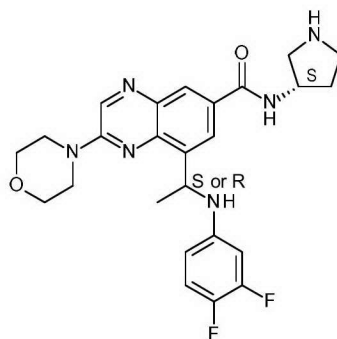
Preparation of intermediate 372:

Compound 372 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 232 as starting material (130mg; 68%).



10 Preparation of compound 374a:

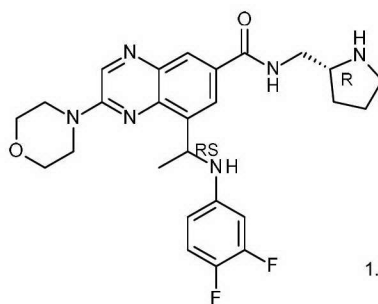
Compound 374a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 233a as starting material (180 mg, 61%, M.P.: 132°C (K)).



Preparation of compound 374b:

Compound 374b was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 233b as starting material (132mg, 52%, M.P.: 130°C (K)).

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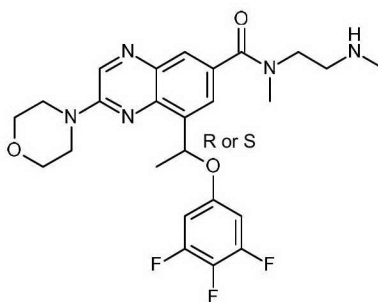


1.37HCl, 1.45 H<sub>2</sub>O

Preparation of compound 376:

Compound 376 was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 234 as starting material. (26mg, 4%, M.P.: gum at 130°C, (K))

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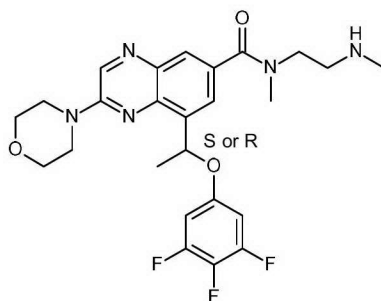


Preparation of compound 379a:

Compound 379a according to an analogous procedure as described for the synthesis of compound 17 using intermediate 235a as starting material (41mg, 31%).

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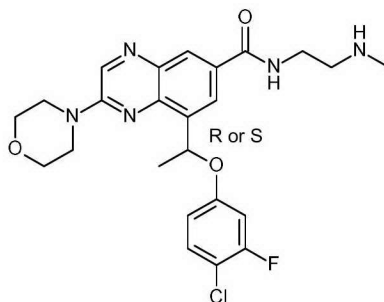
218



Preparation compound 379b:

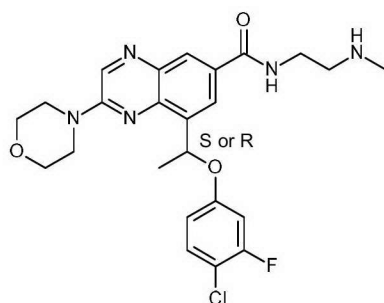
Compound 379b was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 235b as starting material (33mg, 26%).

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Preparation of compound 380a:

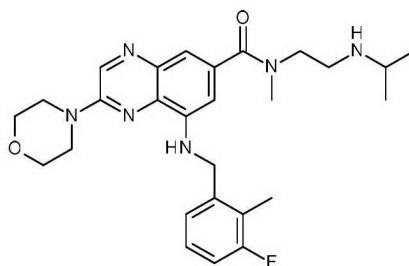
To a solution of intermediate 236a (105 mg; 0.179 mmol) in MeTHF (1.80 mL) was added HCl (357  $\mu$ L; 1.07 mmol, 3M in cyclopentylmethyl ether). The solution was stirred at rt over the weekend then slowly basified with a saturated aqueous solution of NaHCO<sub>3</sub> and DCM was added. The organic layer was separated and the aqueous layer was extracted with DCM (2x). The combined organic layers were dried over MgSO<sub>4</sub>, filtered off and evaporated. The crude (69 mg) was purified by silica gel chromatography (Irregular SiOH, 15-40  $\mu$ m, 4 g, Grace, liquid loading (DCM), mobile phase gradient: from DCM 100% to DCM 90%, MeOH/aq. NH<sub>3</sub> (95:5) 10%) to give 40 mg of a pale yellow oil which was solubilized in ACN (1 mL), extended with water (9 mL) and freeze-dried to give 38 mg (44%) of compound 380a as a yellow fluffy solid.



Preparation of compound 380b:

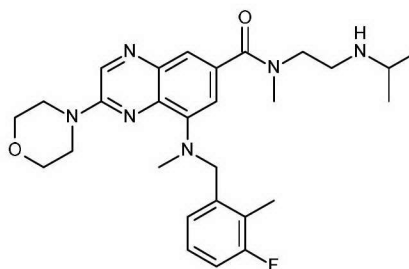
Compound 380b was prepared according to an analogous procedure as described for the synthesis of compound 380a using intermediate 236b as starting material. (26mg, 27%).

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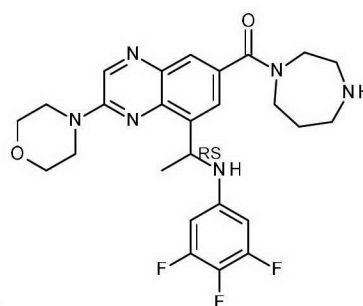
Preparation of compound 385:

Compound 385 was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 240 as starting material (148mg, 78%).



10 Preparation of compound 386:

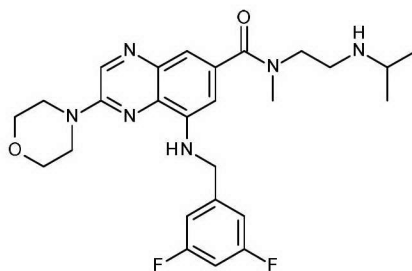
Compound 386 was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 241 as starting material (11 mg, 62%)



Preparation of intermediate 387:

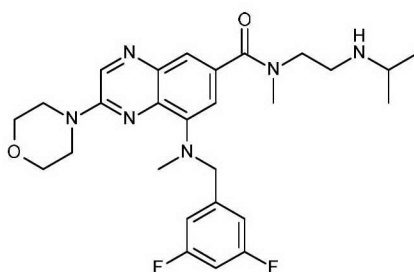
15 Compound 387 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 242 as starting material (300mg; 77%).

220



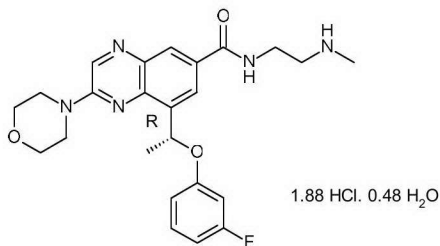
Preparation of compound 389:

Compound 389 was prepared according to an analogous procedure as described for the synthesis of compound 17, using intermediate 243 as starting material (90mg, 71%).



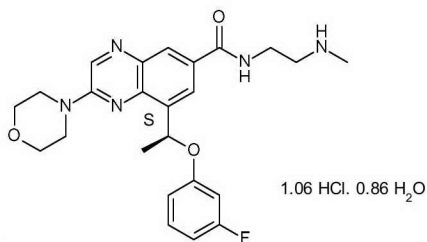
5 Preparation of compound 390 :

Compound 390 was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 244 as starting material (21 mg, 60%).



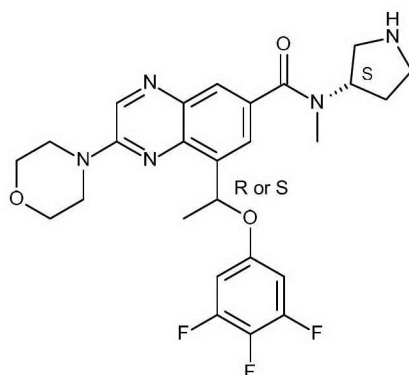
Preparation of compound 122a:

- 10 Compound 122a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 118a as starting material (3.85 g, 34%, MP : 116°C (DSC)).



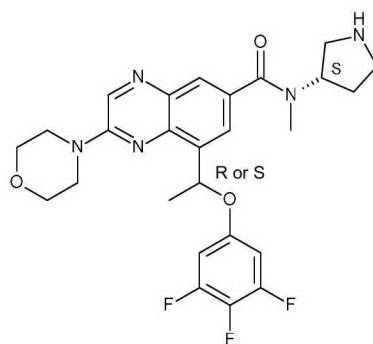
Preparation of compound 123a:

- 15 Compound 123a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 118b as starting material (73 mg, 9%, MP : 130°C (DSC)).



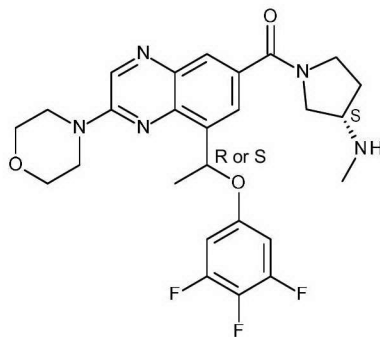
Preparation of compound 404a:

Compound 404a was prepared according to an analogous procedure as described for the synthesis of compound 317 using intermediate 346a as starting material (99 mg, 66%).



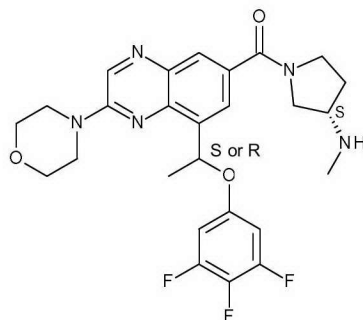
Preparation of compound 404b:

Compound 404b was prepared according to an analogous procedure as described for the synthesis of compound 317 using intermediate 346b as starting material (122 mg, 65%).



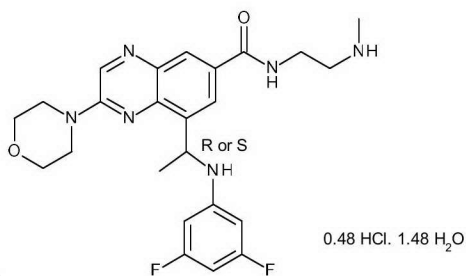
Preparation of compound 405a:

was prepared according to an analogous procedure as described for the synthesis of compound 317 using intermediate 347a as starting material (110 mg, 70%).



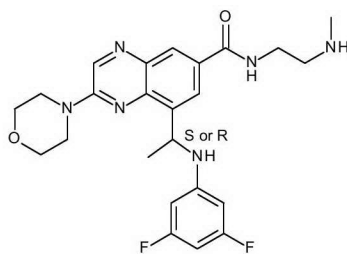
Preparation of compound 405b:

Compound 405b was prepared according to an analogous procedure as described for the synthesis of compound 317 using intermediate 347b as starting material (126 mg, 72%).



Preparation of compound 406a:

Compound 406a was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 348a as starting material (115 mg, 23%, gums at 80°C (K)).

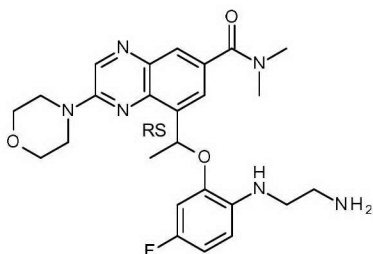


Preparation of compound 406b:

Compound 406b was prepared according to an analogous procedure as described for the synthesis of compound 17 using intermediate 348b as starting material (213 mg, 47%, gums at 80°C (K)).

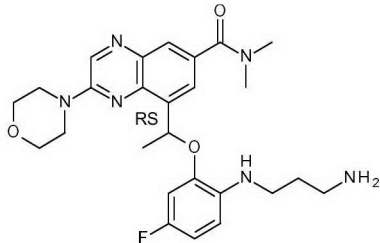
### Example B5





Preparation compound 79:

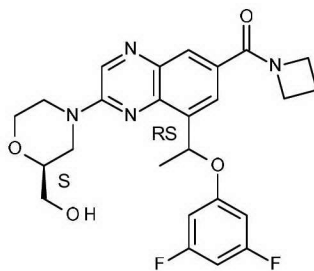
- TFA (1.0 mL; 13.07 mmol) was added to a solution of intermediate 86 (180 mg; 0.31 mmol) in DCM (2 mL). The reaction mixture was stirred at rt for 4h. The mixture was slowly quenched with a saturated solution of NaHCO<sub>3</sub>. The mixture was then diluted with DCM and water. The layers were separated and the aqueous layer was basified with K<sub>2</sub>CO<sub>3</sub> (pH 11). The aqueous layer was extracted with DCM. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under vacuum. The residue (170 mg, greenish oil) was purified by chromatography over silica gel (irregular SiOH; 15-40 μm; 4 g; gradient: from 99% DCM, 1% (MeOH/NH<sub>4</sub>OH: 95/5) to 88% DCM, 12% (MeOH//NH<sub>4</sub>OH: 95:5)). The pure fractions were collected and the solvent was evaporated. The resulting residue was freeze-dried with water/ACN to give 104 mg (70%, pale yellow fluffy solid) of compound 79.



Preparation of compound 82:

- Compound 82 was prepared according to an analogous procedure as described for the synthesis of compound 79, using intermediate 97 as starting materials (freeze-dried: 125 mg, 42%).

Example B6

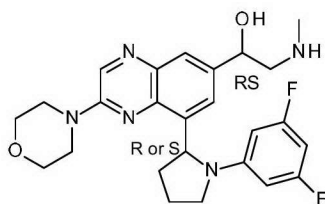


- Preparation of compound 81:

HCl (1M in H<sub>2</sub>O) (404 μL; 404 μmol) was added to a solution of intermediate 94 (46 mg; 80.9 μmol) in acetone (1 mL). The reaction mixture was stirred at rt overnight. The

mixture was quenched with a saturated aqueous solution of  $\text{NaHCO}_3$ . The mixture was evaporated in vacuum and the residue was taken up in DCM and water. The layers were separated and the organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated under vacuum. The residue (73 mg, yellow oil) was purified by reverse phase (X-  
 5 Bridge-C18; 5  $\mu\text{m}$  30\*150 mm; gradient: from 50% (aq.  $\text{NH}_4\text{HCO}_3$  0.5%), 50% MeOH to 100% MeOH). The pure fractions were collected and the solvent was evaporated. The residue was freeze-dried and the product (20.5 mg) was purified by achiral SFC (2 ETHYLPYRIDINE; 6  $\mu\text{m}$  150x21.2 mm; mobile phase: 85%  $\text{CO}_2$ , 15% MeOH). The pure fractions were collected and the solvent was evaporated. The residue was freeze-  
 10 dried with water/ACN (8/2) to give 14 mg (36%) of compound 81.

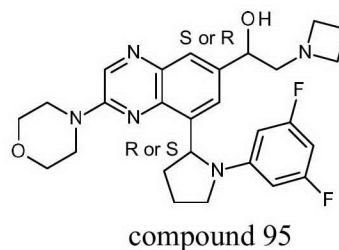
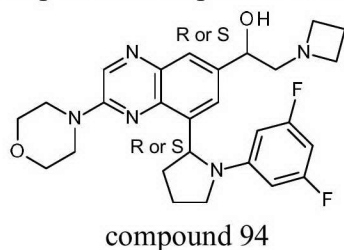
#### Example B7:



#### Preparation compound 19:

In a sealed glass, intermediate 51 (200 mg; 0.46 mmol) and methylamine (2M in THF)  
 15 (2.28 mL; 4.56 mmol) in THF (4 mL) were stirred at 100°C overnight. The resulting solution was poured into water and extracted with EtOAc. The organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated until dryness. The residue (245 mg) was purified by chromatography over silica gel (irregular 15-40  $\mu\text{m}$ ; 24 g; mobile phase: 90% DCM, 10% MeOH, 0.1%  $\text{NH}_4\text{OH}$ ). The pure fractions were collected and the solvent was  
 20 evaporated. The residue (79 mg) was purified by chromatography over silica gel (irregular 15-40  $\mu\text{m}$ ; 24 g; mobile phase: 90% DCM, 10% MeOH, 0.1%  $\text{NH}_4\text{OH}$ ). The pure fractions were collected and the solvent was evaporated to give 41 mg (19%) of compound 19. M.P.: 80°C (gum, K).

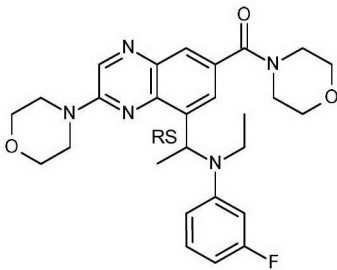
#### 25 Preparation compound 94 and compound 95



Compound 94 and compound 95 were prepared according to an analogous procedure as described for the synthesis of compound 19, using intermediate 51 and azetidine as

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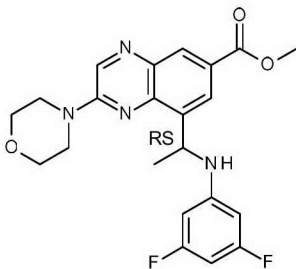
Example B8:



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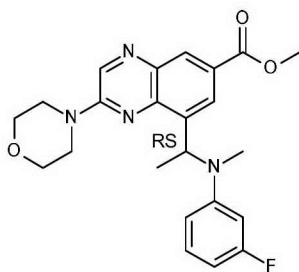
15

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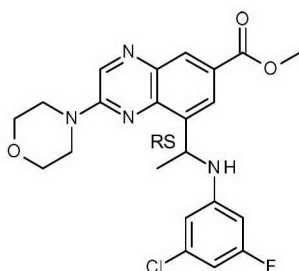
### Preparation compound 80:

25



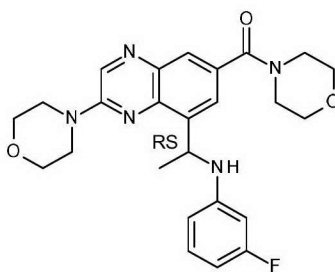
Preparation compound 97:

Compound 97 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 105 and 3-fluoro-N-methylaniline as starting materials (405 mg, 22%). M.P.: 146°C (DSC).



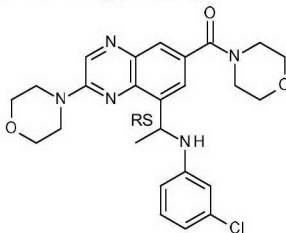
Preparation compound 99:

Compound 99 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 87 and 3-chloro-5-fluoroaniline as starting materials (400 mg, 22%). M.P.: 189°C (DSC).



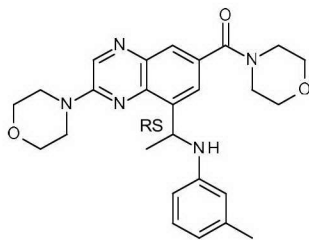
Preparation compound 104:

Compound 104 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 45 and 3-fluoroaniline as starting materials (20 mg, 11%). M.P.: 80°C (gum, K).



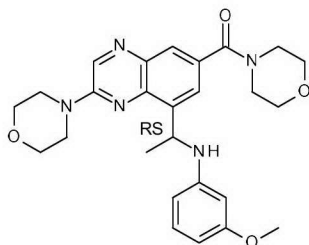
Preparation compound 119:

Compound 119 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 52 and 3-chloroaniline as starting materials (23 mg, 19%). M.P.: 80°C (K).



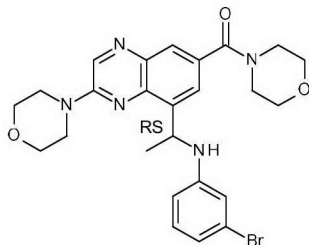
5 Preparation compound 120:

Compound 120 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 52 and m-toluidine as starting materials (28 mg, 25%). M.P.: 80°C (K).



10 Preparation compound 121:

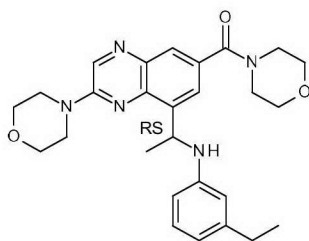
Compound 121 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 52 and m-anisidine as starting materials (24 mg, 20%). M.P.: 80°C (K).



Preparation compound 124:

- 15 Compound 124 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 52 and 3-bromoaniline as starting materials (50 mg, 31%). M.P.: 80°C (gum, K).

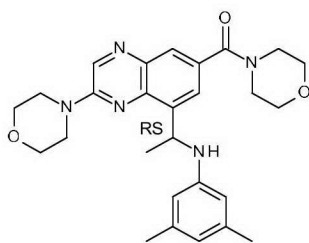
228



Preparation compound 125:

Compound 125 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 52 and 3-ethylaniline as starting materials (50 mg, 34%). M.P.: 80°C (gum, K).

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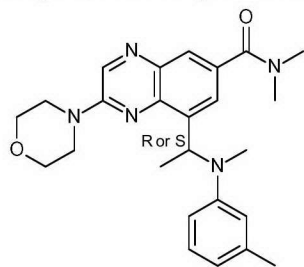


Preparation compound 126:

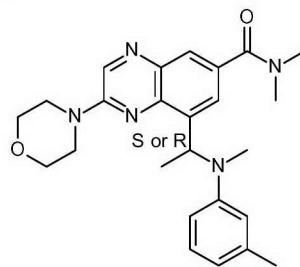
Compound 126 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 52 and 3,5-dimethylaniline as starting materials (50 mg, 34%). M.P.: 80°C (gum, K).

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Preparation compound 127 and compound 128



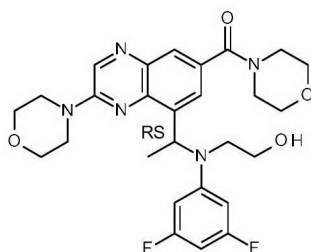
compound 127



compound 128

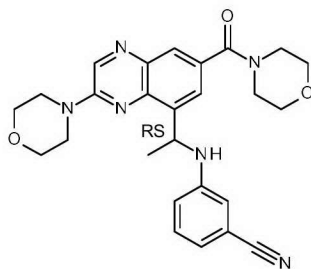
Compound 127 and compound 128 were prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 119 and N-methyl-m-toluidine as starting materials. 80 mg (26%) of compound 127; M.P.: 80°C (gum, K) and 85 mg (27%) of compound 128; M.P.: 80°C (gum, K) were obtained after chiral SFC (Stationary phase: Chiralpak IA 5 $\mu$ m 250\*20mm, Mobile phase: 70% CO<sub>2</sub>, 30% iPrOH(0.3% iPrNH<sub>2</sub>)) purification.

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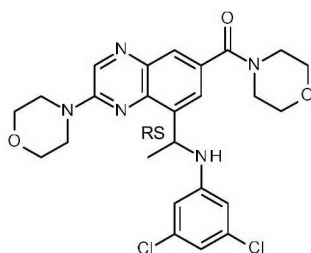
Preparation compound 129:

The solution of intermediate 52 (0.2 g; 0.51 mmol) and intermediate 121 (0.74 g; 2.6 mmol) in DMF (5 mL) was heated at 60°C for 24h in a sealed glassware. The solution was cooled down to rt and poured into cooled water. The mixture was basified with K<sub>2</sub>CO<sub>3</sub> and the product was extracted with EtOAc. The organic layer was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (677 mg) was taken-up with THF (20 mL) and tetrabutylammonium fluoride (3 mL; 10.2 mmol) was added. The reaction mixture was stirred at rt overnight. The solution was poured into cooled water and the product was extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (590 mg) was purified by chromatography over silica gel (irregular bare silica 40 g; mobile phase: 43% heptane, 7% MeOH (+10% NH<sub>4</sub>OH), 50% EtOAc). The pure fractions were collected and the solvent was evaporated to give 39 mg (14%) of compound 129. M.P.: 80°C (K).



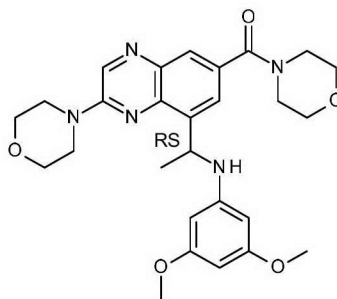
Preparation compound 131:

Compound 131 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 52 and 3-aminobenzonitrile as starting materials (49 mg, 34%). M.P.: 80°C (K).



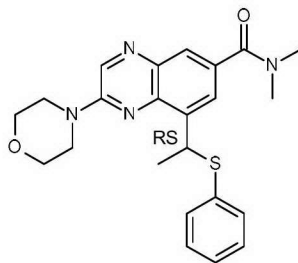
Preparation compound 133:

Compound 133 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 52 and 3,5-dichloroaniline as starting materials (25 mg, 16%). M.P.: 80°C (gum, K).



5 Preparation compound 134:

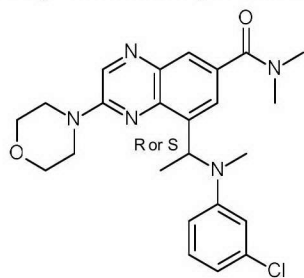
Compound 134 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 52 and 3,5-dimethoxyaniline as starting materials (26 mg, 17%). M.P.: 80°C (gum, K).



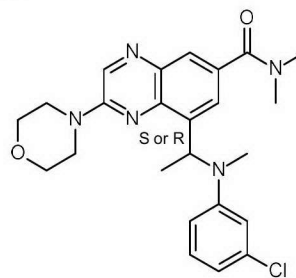
10 Preparation compound 135:

Compound 135 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 119 and sodium thiophenolate as starting materials (148 mg, 58%, pale yellow solid). M.P.: 144°C (DSC).

15 Preparation compound 140 and compound 141



compound 140

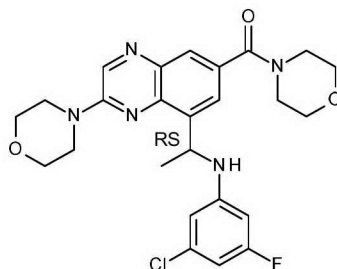


compound 141

Compound 140 and compound 141 were prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 119 and 3-chloro-N-methylaniline as starting materials. 69 mg (21%) of compound 140; M.P.: 80°C (gum,

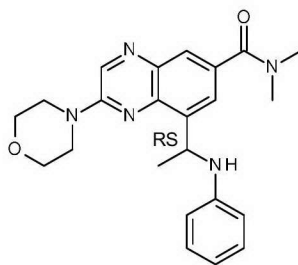


K) and 69 mg (21%) of compound 141; M.P.: 80°C (gum, K) were obtained after chiral SFC (Stationary phase: CHIRALCEL OJ-H 5µm 250x20mm, Mobile phase: 75% CO<sub>2</sub>, 25% MeOH(0.3% iPrNH<sub>2</sub>)) purification.



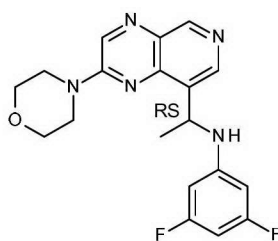
5 Preparation compound 146:

Compound 146 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 52 and 3-chloro-5-fluoroaniline as starting materials (29 mg, 19%). M.P.: 80°C (gum, K).



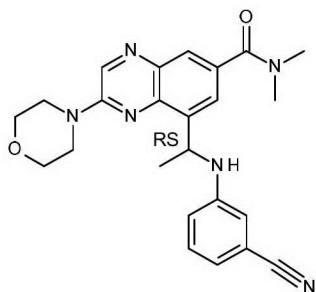
10 Preparation compound 150:

Compound 150 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 119 and aniline as starting materials (75 mg, 26%). M.P.: 110°C (K).



15 Preparation compound 153:

Compound 153 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 139 and 3,5-difluoroaniline as starting materials (90 mg, 23%, pale yellow foam). M.P.: 90°C (gum, K).

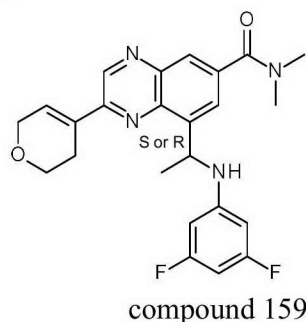
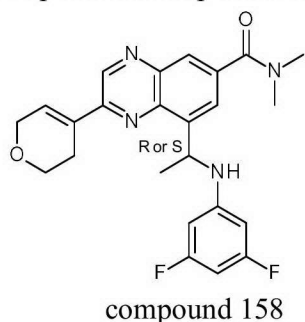


Preparation compound 155:

Compound 155 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 119 and 3-aminobenzonitrile as starting materials (57 mg, 18%). M.P.: 186°C (DSC).

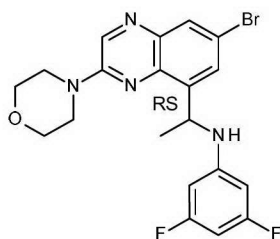
5

Preparation compound 158 and compound 159



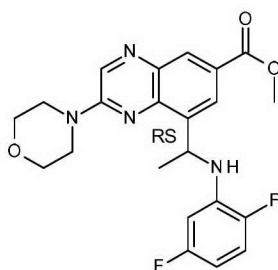
3-Difluoroaniline (1.36g; 10.55mmol) was added to a solution of intermediate 20 ((730mg; 2.11mmol) in DMF (19mL) under N<sub>2</sub>. The solution was stirred at 60°C for 7 days in a sealed tube. The solution was cooled, poured out into cooled water, basified with K<sub>2</sub>CO<sub>3</sub>. EtOAc was added. The product was extracted with EtOAc and the organic layer was concentrated. Et<sub>2</sub>O was added and a precipitate was filtered off. The precipitate was purified via silica gel chromatography (SiO<sub>2</sub>: 80g, Mobile phase: 45% heptane 5% MeOH 50% EtOAc 0.5% NH<sub>4</sub>OH). The pure fractions were collected and evaporated until dryness to give 450mg of an impure fraction of the racemic compound. This residue was purified via silica gel chromatography (SiO<sub>2</sub>: 80g, Mobile phase: 67% heptane 3% MeOH 30%EtOAc 0.5%NH<sub>4</sub>OH). The pure fractions were collected and evaporated until dryness to give of 322 mg (35%) of the racemic compound. Separation of the enantiomers was performed via chiral SFC (Stationary phase: CHIRALCEL OJ-H 5μm 250x20mm, Mobile phase: 85% CO<sub>2</sub>, 15% MeOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and evaporated until dryness to give 134 mg (14%) of compound 158 and 120 mg (13%) of compound 159.

233



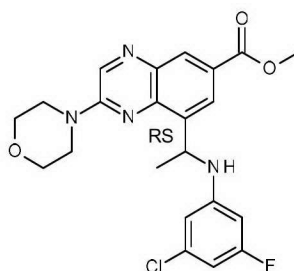
Preparation compound 167:

- Compound 167 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 145 and 3,5-difluoroaniline as starting materials (15 mg, 6%). M.P.: 80°C (gum, K). The reaction mixture was stirred at 50°C for 36h.



Preparation of compound 260:

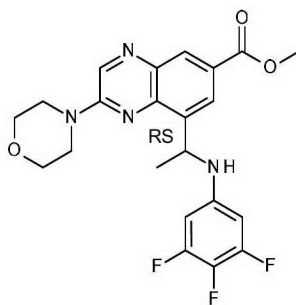
- A mixture of intermediate 87 (1 g; 2.17 mmol), 2,5-difluoroaniline (1.1 mL; 10.84 mmol) in DMF (10 mL) was stirred at 50°C for 48h in a sealed tube. The solution was poured into cooled water. EtOAc was added and the mixture was filtered through a pad of celite®. The product was extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (1.2 g) was crystallized from Et<sub>2</sub>O and dried to give 0.32 g (34%, yellow solid) of compound 260.



Preparation of compound 264:

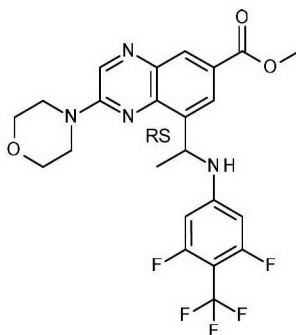
- Compound 264 was prepared according to an analogous procedure as described for the synthesis of compound 262 (alternative pathway), using intermediate 87 and 3-chloro-5-fluoroaniline as starting materials (400 mg, 42%). The reaction mixture was stirred at 50°C for 48h. M.P.: 189°C (DSC).

234



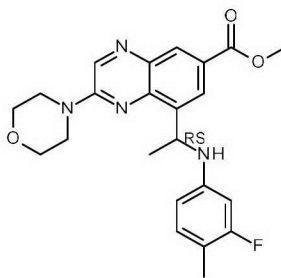
Preparation of compound 266:

Compound 266 was prepared according to an analogous procedure as described for the synthesis of compound 260, using intermediate 105 and 3,4,5-trifluoroaniline as starting materials (2.72 g, 64%, M.P.: 220°C (K)). The reaction mixture was stirred at 60°C for 4 days.



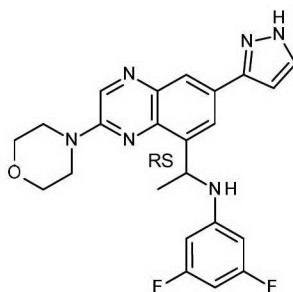
Preparation of compound 269:

Compound 269 was prepared according to an analogous procedure as described for the synthesis of compound 262, using intermediate 105 and 3,5-difluoro-4-(trifluoromethyl)aniline as starting materials (crystallized from Et<sub>2</sub>O; 865 mg; 34%).



Preparation of compound 293:

Compound 293 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 105 and 4-methyl-3-fluoroaniline as starting material (4.12g, 65%). M.P.: 186°C, K).



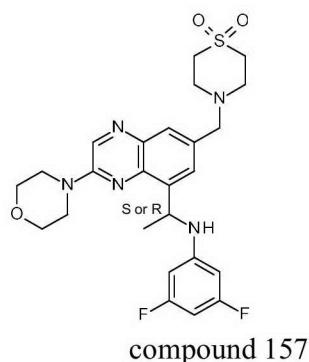
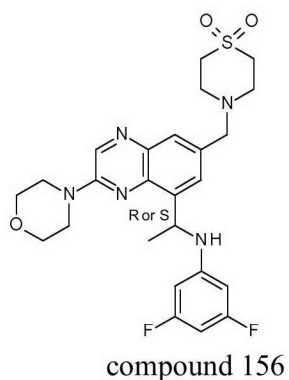
Preparation of compound 304:

Compound 304 was prepared according to an analogous procedure as described for the synthesis of compound 20 using intermediate 194 and 3,5-difluoroaniline as starting materials (10mg, 5%).

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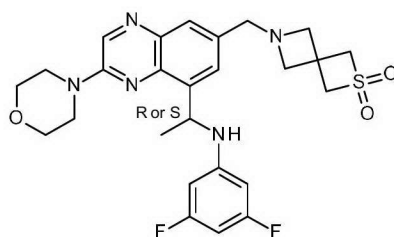
Example B9

Preparation compound 156 and compound 157



Thiomorpholine 1,1-dioxide (86 mg; 0.63 mmol) and  $K_2CO_3$  (117 mg; 0.85 mmol) were added to a mixture of intermediate 140 (177 mg; 0.42 mmol) in ACN (4 mL). The reaction mixture was stirred at 80°C overnight. The mixture was cooling down to rt, combined with another batch coming from a reaction performed on 63 mg of intermediate 140 and poured into water. The organic layer was extracted with EtOAc, washed with brine, dried over  $MgSO_4$ , filtered and evaporated until dryness. The residue (420 mg) was purified by chromatography over silica gel (40 g; mobile phase: from 100% DCM to 98% DCM, 2% MeOH). The pure fractions were collected and the solvent was evaporated until dryness. The residue (racemic, 220 mg) was purified by chiral SFC (CHIRALPAK IC 5  $\mu m$ ; 250x20 mm; mobile phase: 60%  $CO_2$ , 40% EtOH). The pure fractions were collected and the solvent was evaporated to give 101 mg (34%) of compound 156 and 98 mg (33%) of compound 157.

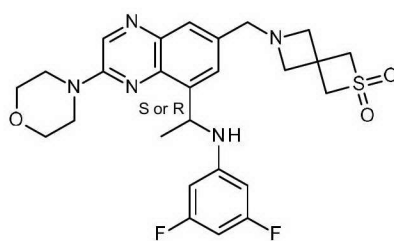
236



Preparation compound 160:

Compound 160 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 142 and 2-thia-6-aza-spiro[3.3]heptane 2,2-dioxide as starting materials (98 mg, 28%). M.P.: 229°C (DSC).

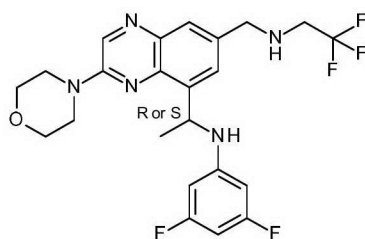
5



Preparation compound 161:

Compound 161 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 143 and 2-thia-6-aza-spiro[3.3]heptane 2,2-dioxide as starting materials (109 mg, 31%). M.P.: 228°C (DSC).

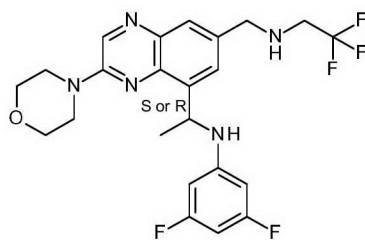
10



Preparation compound 162:

Compound 162 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 142 and 2,2,2-trifluoroethylamine as starting materials (60 mg, 25%). M.P.: 80°C (gum, K).

15

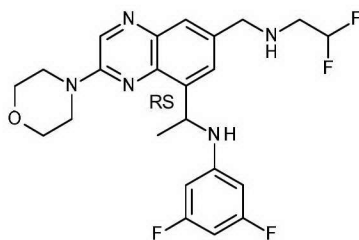


Preparation compound 163:

2.07 HCl 1.40 H<sub>2</sub>O

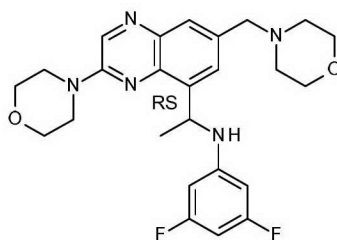
Compound 163 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 143 and 2,2,2-trifluoroethylamine as

starting materials. After the purification, the residue (140 mg) was dissolved in ACN, converted into hydrochloric acid salt ([HCl/iPrOH 5M ]; 3 eq. / V=0.17mL]). The salt was filtered to give 150 mg (51%) of compound 163 (2.07 HCl 1.40 H<sub>2</sub>O). M.P.: 239°C (DSC).



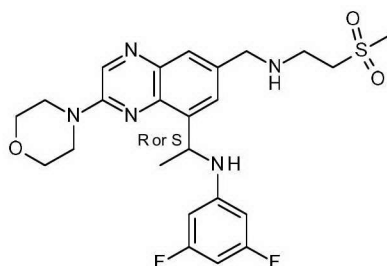
5 Preparation compound 164:

Compound 164 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 140 and 2,2-difluoroethylamine as starting materials (76 mg, 23%). M.P.: 116°C (DSC).



10 Preparation compound 168:

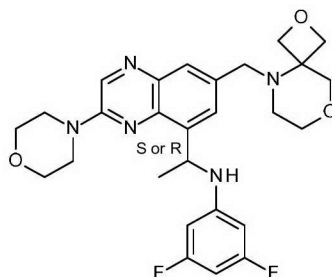
Compound 168 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 140 and morpholine as starting materials (121 mg, 31%). M.P.: 165°C (DSC).



15 Preparation compound 173:

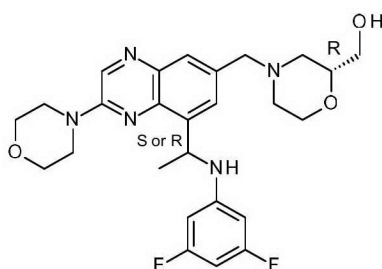
Compound 173 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 142 and 2-(methylsulfonyl)-ethanamine hydrochloride as starting materials (65 mg, 21%). M.P.: 80°C (gum, K).

238



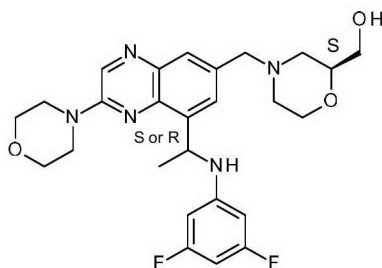
Preparation compound 192:

Compound 192 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 143 and 2,8-Dioxa-5-azaspiro[3.5]nonane oxalate salt as starting materials (34 mg, 11%). M.P.: 229°C (DSC).



Preparation compound 193:

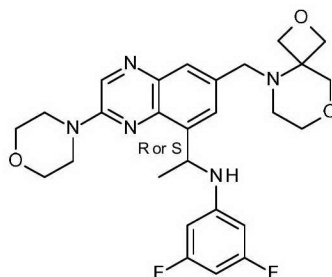
Compound 193 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 143 and (R)-(2-Hydroxymethyl)morpholine HCl as starting materials (105 mg, 35%). M.P.: 80°C (gum, K).



Preparation compound 194:

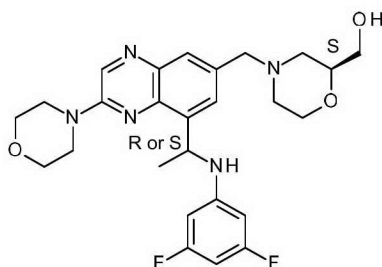
Compound 194 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 143 and (S)-(2-Hydroxymethyl)morpholine HCl as starting materials (152 mg, 51%). M.P.: 80°C (gum, K).





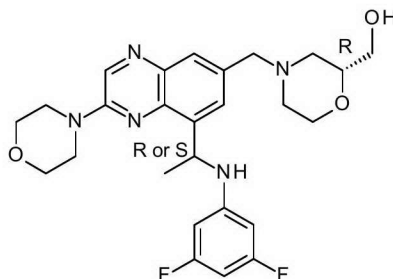
Preparation compound 195:

Compound 195 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 142 and 2,8-Dioxa-5-azaspiro[3.5]nonane oxalate salt as starting materials (110 mg, 43%). M.P.: 228°C (DSC).



Preparation compound 196:

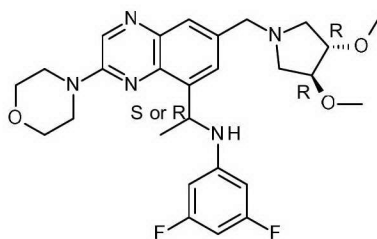
Compound 196 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 142 and (S)-(2-Hydroxymethyl)morpholine HCl as starting materials (freeze-dried: 158 mg, 63%). M.P.: 80°C (gum, K).



Preparation compound 197:

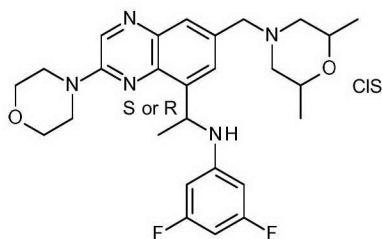
Compound 197 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 142 and (R)-(2-Hydroxymethyl)morpholine HCl as starting materials (freeze-dried: 170 mg, 68%). M.P.: 80°C (gum, K).

240



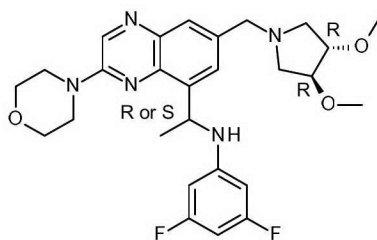
Preparation compound 205:

Compound 205 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 143 and (3R,4R)-3,4-Dimethoxypyrrolidine hydrochloride as starting materials (85 mg, 35%). M.P.: 80°C (gum, K).



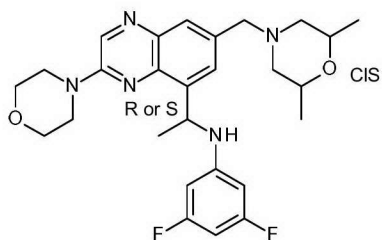
Preparation compound 206:

Compound 206 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 143 and cis-2,6-dimethylmorpholine as starting materials (97 mg, 41%). M.P.: 80°C (gum, K).



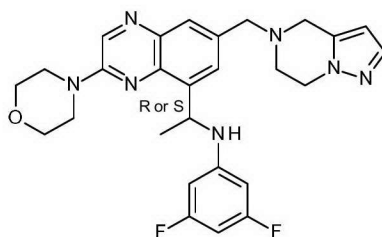
Preparation compound 207:

Compound 207 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 142 and (3R,4R)-3,4-Dimethoxypyrrolidine hydrochloride as starting materials (freeze-dried: 94 mg, 35%). M.P.: 80°C (gum, K).



Preparation compound 208:

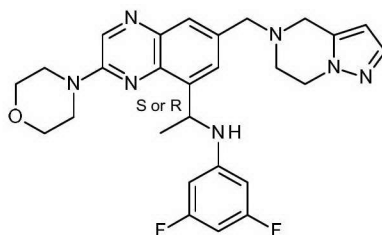
Compound 208 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 142 and *cis*-2,6-dimethylmorpholine as starting materials (133 mg, 52%). M.P.: 80°C (K).



#### 5 Preparation compound 210:

Compound 210 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 142 and 4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazine hydrochloride as starting materials (91 mg, 45%). M.P.: 80°C (K).

10



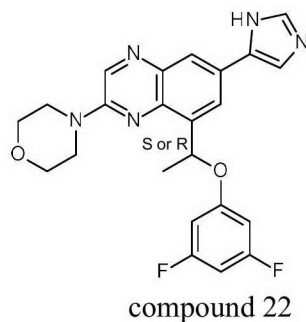
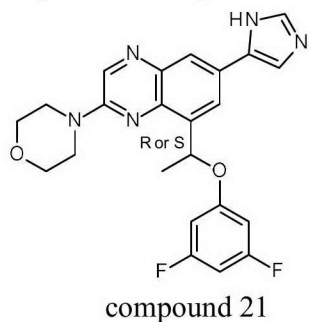
#### Preparation compound 222:

Compound 222 was prepared according to an analogous procedure as described for the synthesis of compound 156, using intermediate 143 and 4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazine hydrochloride as starting materials (17 mg, 7%). M.P.: 163°C (DSC).

15

#### Example B10

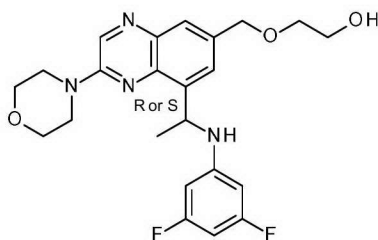
##### Preparation compound 21 and compound 22



20

A solution of intermediate 58 (76 mg; 0.15 mmol) and p-toluenesulfonic acid monohydrate (6 mg; 29  $\mu$ mol) in MeOH (6.38 mL) was heated at 50°C for 3 days. The resulting solution was evaporated under reduced pressure. The residue was dissolved in EtOAc (10 mL) and washed with a saturated aqueous solution of NaHCO<sub>3</sub> (5 mL). The aqueous layer was extracted with EtOAc (2x10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and evaporated under reduced pressure. The residue was combined with another batch from 127 mg of intermediate 58 and purified by chromatography over silica gel (irregular SiOH; 15-40  $\mu$ m; 24 g; gradient: from 100% EtOAc to 85% EtOAc, 15% MeOH (+5% NH<sub>4</sub>OH)). The pure fractions were collected and the solvent was evaporated. The residue (105 mg, brown powder) was combined with another batch coming from a reaction performed on 165 mg of intermediate 58 and purified by reverse phase (X-Bridge-C18 5  $\mu$ m 30\*150 mm; gradient: from 65% aq. NH<sub>4</sub>HCO<sub>3</sub> 0.5%, 35% ACN to 25% aq. NH<sub>4</sub>HCO<sub>3</sub> 0.5%, 75% ACN). The pure fractions were collected and the solvent was evaporated. The residue (158 mg) was purified by chiral SFC (Lux cellulose 4; 5  $\mu$ m 250\*21.2 mm; mobile phase: 75% CO<sub>2</sub>, 25% MeOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 59 mg (19%, yellow powder) of compound 21 (M.P.: 184°C (DSC)) and 54 mg (17%, yellow powder) of compound 22 (M.P.: 183°C (DSC)).

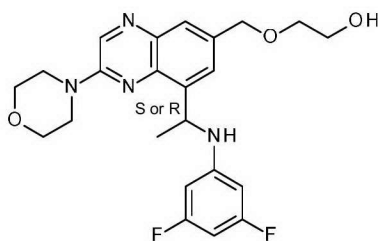
## Example B11



### Preparation of compound 177:

TFA (0.8 mL; 10.27 mmol) was added at 10°C to a solution of intermediate 150 (0.18 g; 0.34 mmol) in MeOH (20 mL). The reaction mixture was stirred at rt for 24h. The solution was cooled and the mixture was poured into cooled water, basified with K<sub>2</sub>CO<sub>3</sub> and the product was extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (130 mg) was purified by chromatography over silica gel (irregular bare silica 10 g; mobile phase: 97% DCM, 3% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated. The residue (73 mg) was freeze-dried with ACN/water 20/80 to give 69 mg (45%, yellow powder) of compound 177. M.P.: 80°C (gum, K)).

243

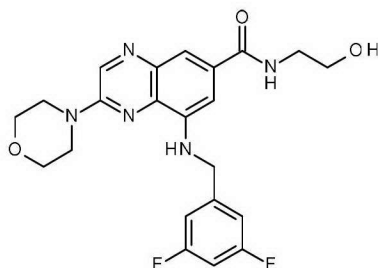


Preparation of compound 178:

Compound 178 was prepared according to an analogous procedure as described for the synthesis of compound 177, using intermediate 151 as starting materials (freeze-dried: 122 mg, 61%, yellow powder of compound 178; M.P.: 80°C (gum, K).

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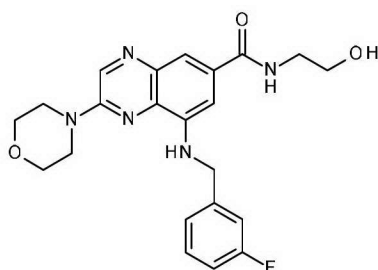
Example B12



Preparation of compound 229:

TBAF (0.69 mL; 0.69 mmol) was added to a mixture of intermediate 163 (350 mg; 0.63 mmol) in THF (9 mL) and the reaction mixture was stirred at rt for 2 h. The mixture was concentrated and the residue was purified by chromatography over silica gel (SiOH 15  $\mu$ m; 25 g mobile phase: 100% DCM to 90% DCM, 10% MeOH, 1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated. The residue was crystallized with diisopropylether/ACN (drops) under sonicated. The precipitate was filtered and dried to give 195 mg (63%) of compound 229.

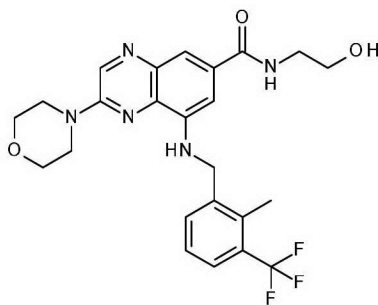
15



Preparation of compound 230:

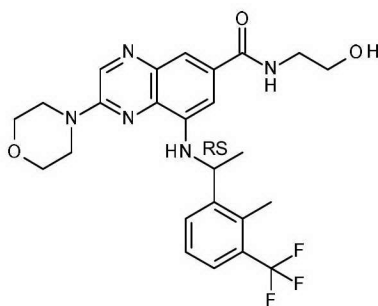
Compound 230 was prepared according to an analogous procedure as described for the synthesis of compound 229, using intermediate 165 as starting material (186 mg, 79%, M.P.: 218°C (DSC)).

244



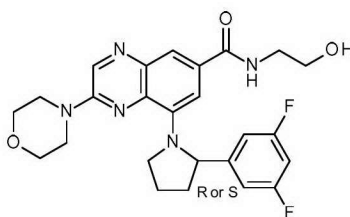
Preparation of compound 231:

Compound 231 was prepared according to an analogous procedure as described for the synthesis of compound 229, using intermediate 164 as starting material (102 mg, 42%)



5 Preparation of compound 232:

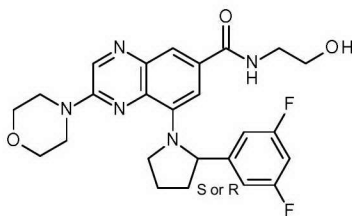
Compound 232 was prepared according to an analogous procedure as described for the synthesis of compound 229, using intermediate 166 as starting material (197 mg, 82%, M.P.: 181°C (DSC)).



10 Preparation of compound 244 :

TBAF (0.37 mL, 1 M, 0.37 mmol) was added to a mixture of intermediate 174 (200 mg, 0.34 mmol) in THF (4.9 mL) and the reaction mixture was stirred at rt for 2 hours. The mixture was concentrated and the residue (420 mg) was purified by chromatography over silica gel (SiOH 15µm, 25g mobile phase: gradient from 98% DCM 2% MeOH 0.2% NH<sub>4</sub>OH to 90% DCM 10% MeOH 0.1% NH<sub>4</sub>OH). The pure fractions were collected. The solvent was evaporated and crystallized from DIPE/ACN to give 78 mg (48%) of compound 244

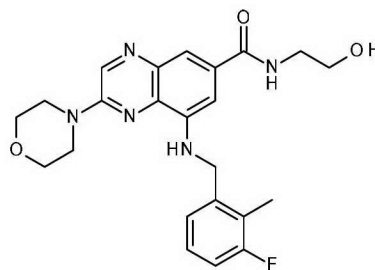
245



Preparation of compound 245 :

Compound 245 was prepared according to an analogous procedure as described for the synthesis of compound 244, using intermediate 175 as starting material, (87 mg; 41%) of compound 245.

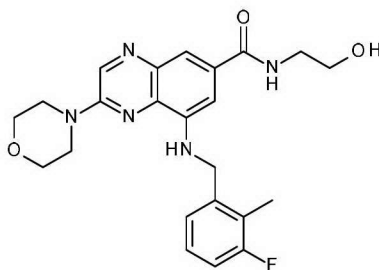
5



Preparation of compound 276:

Tetrabutylammoniumfluoride (0.6 mL, 1 M in THF, 0.6 mmol) was added to a mixture of intermediate 180 (300 mg, 0.542 mmol) in THF (8mL) and the reaction mixture was stirred at rt for 2 hours. The mixture was concentrated and the residue was purified by silica gel chromatography (SiO<sub>2</sub> 15μm, 25g, mobile phase: 98%DCM 2%MeOH 0.2%NH<sub>4</sub>OH to 90%DCM 10%MeOH 1.1%NH<sub>4</sub>OH). The pure fractions were concentrated and the resulting residue was crystallized from DIPE/ACN(drop) under sonication. The precipitate was filtered to give 155 mg (65%) of compound 276 (M.P.: 194°C (DSC)).

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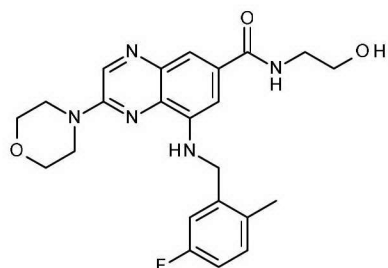


Preparation of compound 336:

Compound 336 was prepared according to an analogous procedure as described for the synthesis of compound 229, using intermediate 216 as starting material (155mg, 65%). M.P.: 195°C (DSC).

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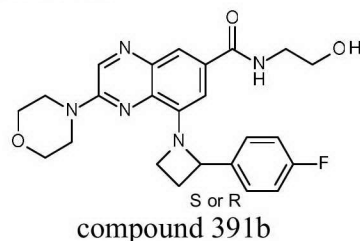
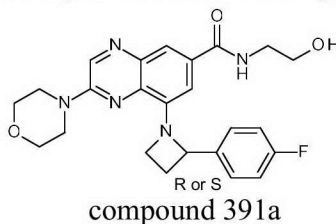
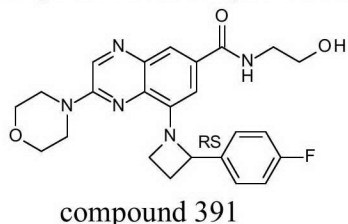
Preparation of compound 343:



Compound 343 was prepared according to an analogous procedure as described for the synthesis of compound 229, using intermediate 219 as starting material (955mg, 57%).

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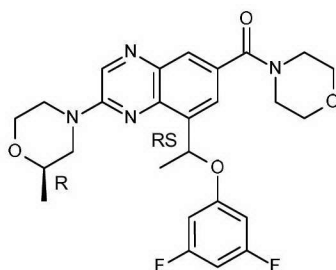
Preparation of compound 391, compound 391a and compound 391b



Compound 391 was prepared according to an analogous procedure as described for the synthesis of compound 229 using intermediate 245 as starting material (390 mg; 70%).

The separation of the enantiomers was performed by chiral SFC (CHIRALPAK DIACEL OJ 250x20 mm; mobile phase: CO<sub>2</sub>, EtOH-iPrOH (50-50) + 0.4% iPrNH<sub>2</sub>). The pure fractions were collected and the solvent was evaporated to give, after freeze-drying, 26 mg (5%) of compound 391a and 29 mg (5%) of compound 391b.

#### Example B13

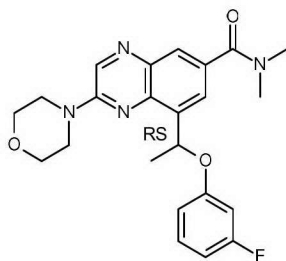


15 Preparation of compound 56:

In a microwave vial, 3,5-difluorophenol (31 mg; 0.24 mmol) and PPh<sub>3</sub> (62 mg; 0.24 mmol) were added to a solution of intermediate 76 (61 mg; 0.16 mmol) in THF (1.6 mL). Then, di-tert-butyl azodicarboxylate (55 mg; 0.24 mmol) was added and the mixture was stirred at rt for 18h. Then, more 3,5-difluorophenol (31 mg; 0.24 mmol), PPh<sub>3</sub> (62 mg; 0.24 mmol) and di-tert-butyl azodicarboxylate (55 mg; 0.24 mmol) were added successively and the mixture was stirred at 40°C for 18h. The mixture was



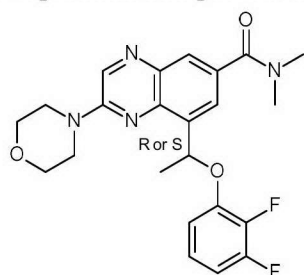
combined with another batch coming from a reaction performed on 20 mg of intermediate 76. The mixture was evaporated under vacuum and taken-up in DCM. The organic layer was washed with a saturated solution of  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$ , filtered and evaporated in vacuum. The residue (400 mg, yellow oil) was purified by chromatography over silica gel (irregular  $\text{SiOH}$ ; 15-40  $\mu\text{m}$ ; 10 g; gradient: from 100% DCM to 96.5% DCM, 3.5% MeOH). The pure fractions were collected and the solvent was evaporated. The residue (160 mg, yellow solid) was purified by achiral SFC (CYANO 6  $\mu\text{m}$  150x21.2 mm; mobile phase: 92%  $\text{CO}_2$ , 8% MeOH). The pure fractions were collected and the solvent was evaporated. The residue was freeze-dried with water-ACN (80/20) to give 32 mg (31%, white fluffy solid) of 56. M.P.: 55°C (DSC).



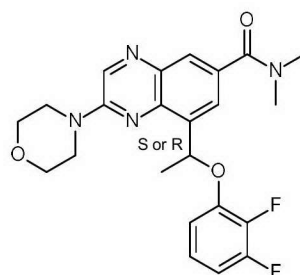
Preparation of compound 68:

Compound 68 was prepared according to an analogous procedure as described for the synthesis of compound 56, using intermediate 17 and 3-fluorophenol as starting materials (freeze-dried: 58 mg, 23%, yellow fluffy solid). M.P.: 49°C (DSC).

Preparation compound 73 and compound 74



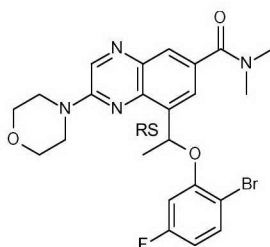
compound 73



compound 74

Compound 73 and compound 74 were prepared according to an analogous procedure as described for the synthesis of compound 56, using intermediate 17 and 2,3-difluorophenol as starting materials. 63 mg (24%, yellow fluffy solid) of compound 73 and 64 mg (24%, pale fluffy solid) of compound 74 were obtained after chiral SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu\text{m}$  250x20mm, Mobile phase: 70%  $\text{CO}_2$ , 30% EtOH) purification.

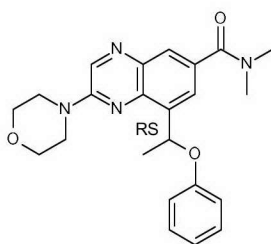
248



Preparation of compound 78:

Compound 78 was prepared according to an analogous procedure as described for the synthesis of compound 56, using intermediate 17 and 2-bromo-5-fluorophenol as starting materials (freeze-dried: 24 mg, 3%, yellow fluffy solid). M.P.: 235°C (DSC).

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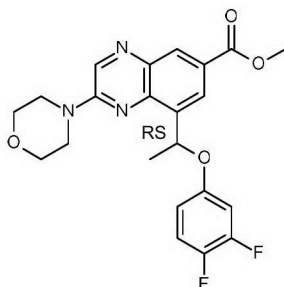


Preparation of compound 151:

In a sealed glassware, phenol (41 mg; 0.43 mmol) and cyanomethylenetriethylphosphorane (0.15 mL; 0.58 mmol) were added to a solution of intermediate 17 (100 mg; 0.29 mmol) in toluene (3 mL). The reaction mixture was stirred at 60°C overnight. The mixture was evaporated under vacuum to dryness. The residue (350 mg, brown oil) was purified by chromatography over silica gel (40 g; mobile phase: 40% heptane, 10% MeOH, 50% EtOAc, 0.5% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated until dryness. The residue (120 mg) was purified by chromatography over silica gel (40 g; mobile phase: 45% heptane, 5% MeOH, 50% EtOAc, 0.5% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated to give 17 mg (14%) of compound 151. M.P.: 80°C (gum, K).

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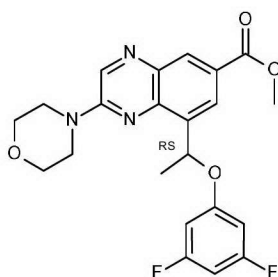


Preparation of compound 209:

Compound 209 was prepared according to an analogous procedure as described for the synthesis of compound 151, using intermediate 15 and 3,4-difluorophenol as starting materials (crystallized from diethylether: 1.4 g, 52%). M.P.: 183°C (DSC).

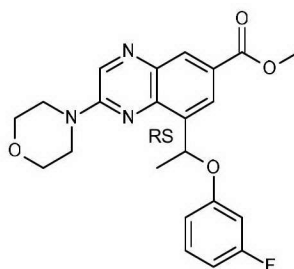
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249



Preparation of compound 247:

- 3,5-difluorophenol (480 mg; 3.69 mmol), di-tert-butyl azodicarboxylate (849 mg; 3.69 mmol) and PPh<sub>3</sub> (967 mg; 3.69 mmol) were added to a solution of intermediate 15 (1 g; 2.46 mmol) in THF (24 mL). The reaction mixture was stirred at rt overnight. Then, additionnal 3,5-difluorophenol (480 mg; 3.69 mmol), di-tert-butyl azodicarboxylate (849 mg; 3.69 mmol) and PPh<sub>3</sub> (967 mg; 3.69 mmol) were added and the mixture was stirred at 60°C for 4h. The mixture was filtered through a pad of celite® and the filtrate was evaporated under vacuum. The residue was triturated in Et<sub>2</sub>O, filtered and the filtrate was evaporated under vacuum. The resulting residue (2.5 g, orange oil) was purified chromatography over silica gel (regular SiOH 30 µm; 80 g; mobile phase: from 100% DCM to 70% DCM, 30% EtOAc). The pure fractions were collected and the solvent was evaporated to give 1.36 g (84%, yellow oil) of compound 247.



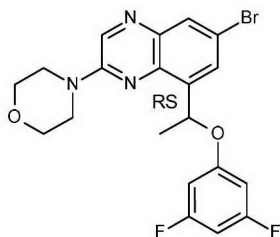
Preparation of compound 256:

- Compound 256 was prepared according to an analogous procedure as described for the synthesis of compound 247, using intermediate 15 and 3-fluorophenol as starting materials (1.44 g, 46%, yellow oil).

Alternative pathway:

- Compound 256 was prepared according to an analogous procedure as described for the synthesis of compound 277, using intermediate 15 and 3-fluorophenol as starting materials (1.57 g, 62%, yellow powder).

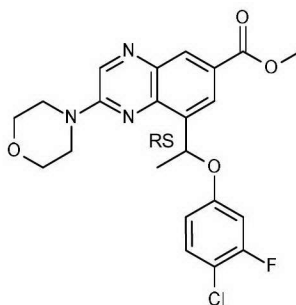
250



Preparation of compound 277:

3,5-difluorophenol (228 mg; 1.76 mmol) and cyanomethylenetriethylphosphorane (614  $\mu$ L; 2.34 mmol) were successively added to a solution of intermediate 56 (396 mg; 1.17 mmol) in toluene (11.9 mL). The reaction mixture was heated at 60°C overnight. The resulting solution was concentrated under reduced pressure. The residue was purified by chromatography over silica gel (irregular SiOH; 15-40  $\mu$ m; 24 g; gradient: from 90% heptane, 9% EtOAc, 1% MeOH to 60% heptane, 36% EtOAc, 4% MeOH). The pure fractions were collected and the solvent was evaporated 330 mg (63%, pale orange powder) of compound 277.

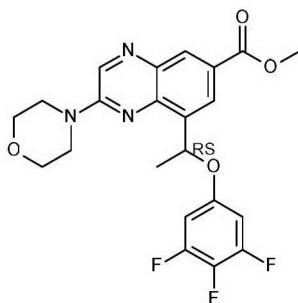
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Preparation of compound 310 :

Compound 310 was prepared according to an analogous procedure as described for the synthesis of compound 151 using intermediate 15 and 4-chloro-3-fluorophenol as starting materials (1.75 g, 100%).

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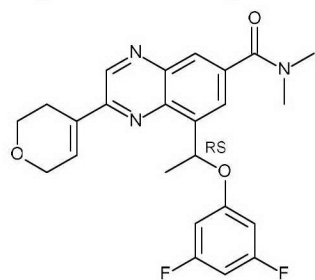


Preparation of compound 377

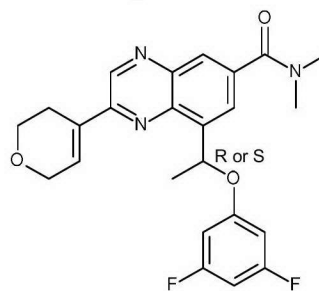
Compound 377 was prepared according to an analogous procedure as described for the synthesis of compound 151, using intermediate 15 and 3,4,5-Trifluorophenol as starting material (2.13g, 62%).

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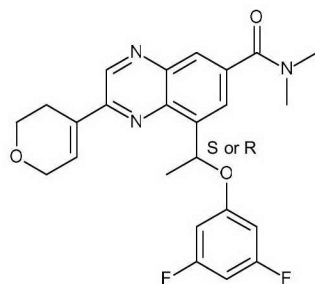
## Preparation of compound 403, compound 403a and compound 403b



compound 403



compound 403a



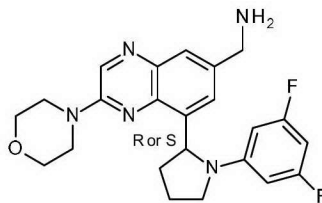
compound 403b

Compound 403 was prepared according to an analogous procedure as described for the synthesis of compound 247, using intermediate 17 and 3,5-difluorophenol as starting materials (233mg, 99%).

- 5 The separation of the enantiomers was performed by chiral SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu$ m 250x20mm, Mobile phase: 75% CO<sub>2</sub>, 25% iPrOH). The pure fractions were mixed and the solvent was evaporated to afford respectively, after freeze-drying, 32 mg (15%) of compound 403a (MP: 53°C, DSC) and 31 mg (14 %) of compound 403b (MP: 54°C, DSC).

10

## Example B14



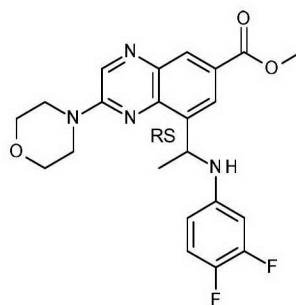
## Preparation of compound 96:

- Hydrazine hydrate (132 mg; 1.35 mmol) was added to a solution of intermediate 104 (750 mg; 1.35 mmol) in MeOH (20 mL). The solution was heated at reflux (70°C) for 20h. The solution was poured into cooled water and the organic layer was extracted with DCM, dried over MgSO<sub>4</sub>, filtered and evaporated until dryness. The residue (425 mg) was purified by chromatography over silica gel (irregular 15-40  $\mu$ m; 24 g; mobile phase: 90% DCM, 10% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and

evaporated. The residue (97 mg) was purified by chromatography over silica gel (irregular 15-40  $\mu$ m; 24 g; mobile phase: 90% DCM, 10% MeOH, 0.1%  $\text{NH}_4\text{OH}$ ). The pure fractions were collected and evaporated until dryness to give 45 mg (8%) of compound 96. M.P.: 80°C (gum, K).

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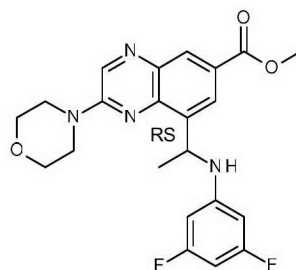
#### Example B15



Preparation of compound 233:

Compound 233 was prepared according to an analogous procedure as described for the synthesis of compound 262, using intermediate 105 and 3,4-difluoroaniline as starting material (7 g; 52%) M.P.: 210°C (K).

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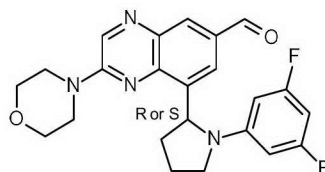


Preparation of compound 235:

3,5-difluoroaniline (16.4g; 0.13mmol) was added to a solution of intermediate 105 (8.5 g; 0.025 mol) in DMF (200 mL) under  $\text{N}_2$ . The solution was stirred at 60°C for 48 hours in a sealed tube. The solution was cooled, poured out into cooled water, basified with  $\text{K}_2\text{CO}_3$  and EtOAc was added. The mixture was extracted with EtOAc and the organic layer was concentrated. The residue was taken up  $\text{Et}_2\text{O}$  and a precipitate was filtered and dried given 7.2g (66%) of compound 235.

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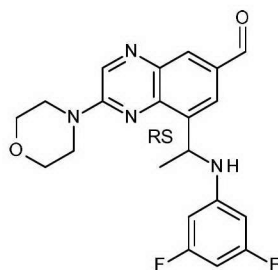
#### 20 Example B16



Preparation compound 250:

MnO<sub>2</sub> (2.08 g; 24 mmol) was added portionwise to a solution of compound 10 (1.7 g; 3.99 mmol) in DCM (77 mL). The reaction mixture was stirred at rt overnight. The mixture was filtered through a pad of celite® and the filtrate was evaporated to give 1.65 g (97%) of compound 250. M.P: 120°C (K).

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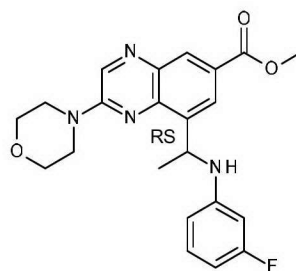


Preparation of compound 271:

Manganese oxide (782 mg; 8.99 mmol) was added portionwise to a solution of compound 84 (600 mg; 1.5 mmol) in DCM (30 mL). The mixture was stirred at rt overnight. The mixture was filtered through a pad of celite® and evaporated until dryness. Then, the residue was taken-up with diisopropylether to give 500 mg (83%) of compound 271. In case this compound was used in a conversion to another compound, it was used as such without further purification.

10

Example B17



15 Preparation of compound 262:

Thioglycolic acid (234 µL; 3.36 mmol) was added to a solution of intermediate 107( (1 g; 1.68 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (1 mL; 6.72 mmol) in ACN (16 mL). The solution was stirred at rt for 1h. Then DCM and 10% aqueous solution of Na<sub>2</sub>CO<sub>3</sub> were added. The organic layer was separated and the aqueous layer was extracted with DCM (2x). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and evaporated under vacuum. The residue was purified by chromatography over silica gel (Irregular SiOH 15-40 µm; 30 g; gradient: from 100% DCM to 95% DCM, 5% MeOH/NH<sub>4</sub>OH (95/5)). The pure fractions were collected and the solvent was evaporated to give 2 fractions of compound 262 respectively 242 mg (35%, yellow solid) and 382 mg (55%, pale brown solid). Global yield: 90%

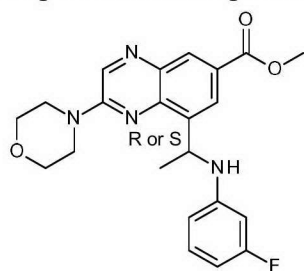
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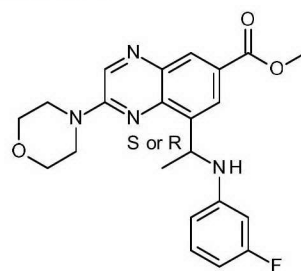
Alternative pathway:

3-fluoroaniline (1.75 mL; 18.17 mmol) was added to a solution of intermediate 105 (1.05 g; 3.13 mmol) in DMF (12 mL) under N<sub>2</sub>. The solution was stirred at 60°C for 48h in a sealed tube. The solution was cooling down to rt, then poured into cooled water and basified with K<sub>2</sub>CO<sub>3</sub>. EtOAc was added. The organic layer was extracted, washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and evaporated to dryness. The residue (3.4 g) was taken-up with DCM, MeOH and Et<sub>2</sub>O. A precipitate was filtered, washed with a mixture of MeOH and Et<sub>2</sub>O and dried to give 0.66 g (51%) of compound 262. M.P.: 222°C (DSC).

Preparation of compound 262a and compound 262b

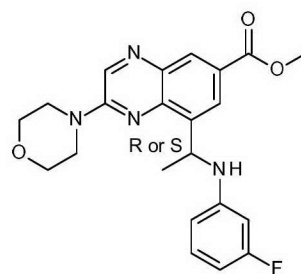


compound 262a



compound 262b

Compound 262a and 262b were obtained after separation of compound 262 by SFC (Stationary phase: Chiralpak AD-H 5μm 250\*30mm, Mobile phase: 70% CO<sub>2</sub>, 25% iPrOH(0.3% iPrNH<sub>2</sub>)). After concentration of the solvent, each fraction was crystallized from Et<sub>2</sub>O yielding, after filtration, 747mg (37%) of compound 262a (M.P: 199.7°C (DSC)) and 775mg (39%) of compound 262b, (M.P: 199.5°C (DSC)).

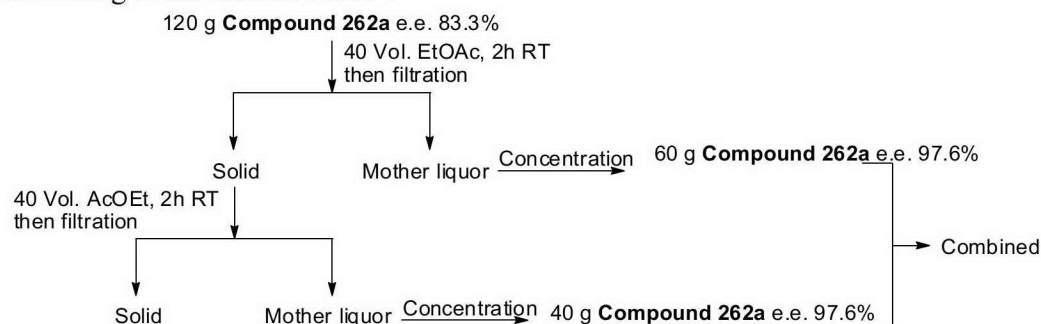


Alternative preparation of compound 262a:

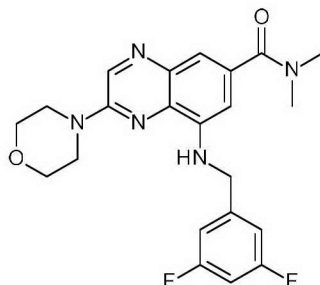
Intermediate 182 was dissolved in acetonitrile (10 volumes) and 1,8-diazabicyclo[5.4.0]undec-7-ene (4.0 eq.) and 2-mercaptoacetic acid (2.0 eq.) were added. The reaction mixture was stirred for 16 hours at room temperature. After concentration to about 2 volumes, water (7 volumes) was added. Compound 262a was isolated and dried in 92% yield (e.e.: 83.3%).



To improve the e.e., the solid obtained as described above was slurried twice in EtOAc according to the scheme below :



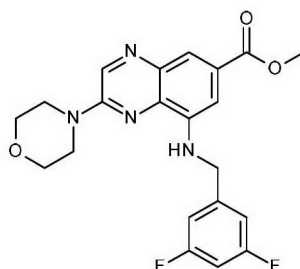
## 5 Example B18



Preparation of compound 278:

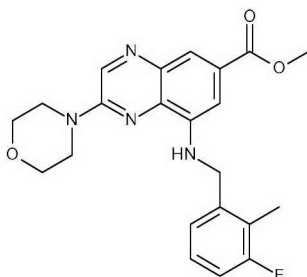
A mixture of intermediate 5 (200 mg; 0.55 mmol), 3,5-difluorobenzylamine (117.5 mg; 0.82 mmol) and cesium carbonate (535.2 mg; 1.64 mmol) in toluene (3 mL) was purged with nitrogen. Then, BrettPhos Precatalyst First Gen (4.4 mg; 0.0055 mmol) was added. The tube was sealed and the reaction was heated at 100°C for 72 hours. Then, the reaction was cooled down to rt, poured onto water and filtered through a pad of celite®. The aqueous layer was extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated.

The residue (420 mg) was purified by silica gel chromatography (irregular SiOH, 30g, mobile phase: 97% DCM 3% MeOH 0.1% NH<sub>4</sub>OH). The fractions containing the product were mixed and concentrated to afford 225mg of an intermediate fraction which was taken up with Et<sub>2</sub>O. The resulting precipitate was filtered, washed with Et<sub>2</sub>O twice then dried to afford 80mg (34%) of compound 278. M.P. 158°C (K).



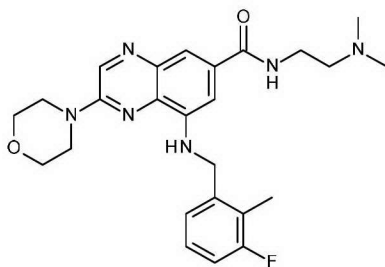
## 20 Preparation of compound 288

Compound 288 was prepared according to an analogous procedure as described for the synthesis of intermediate 163, using intermediate 3a as starting material and 3,5-difluorobenzylamine. (7.67g; 66%)



#### 5 Preparation of compound 305

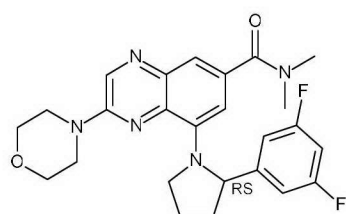
In a schlenk round flask, a mixture of intermediate 3a (10 g, 28.394 mmol), 3-Fluoro-2-methylbenzylamine 4.428 mL, 34.073 mmol) and cesium carbonate (18.503 g, 56.788 mmol) in *tert*-amylalcohol (130mL) was degazed with N<sub>2</sub>. 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (0.662 g, 1.42 mmol) and BrettPhos Precatalyst First Gen (1.134 g, 1.42 mmol) were added, The reaction mixture was purged with N<sub>2</sub> and heated at 100°C for 18h. The reaction mixture was poured into water and EtOAc. The organic layer was separated, washed with brine, dried over MgSO<sub>4</sub> and evaporated till dryness. The residue was taken up with DIPE. Then, the solid was filtered to give (7.8 g, 67%) of compound 305.



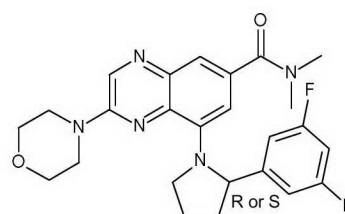
#### Preparation of compound 383

Compound 383 was prepared according to an analogous procedure as described for the synthesis of compound 305 using intermediate 237 and 3-fluoro-2-methylbenzylamine as starting materials (204mg, 43%, M.P: 172 °C(DSC)).

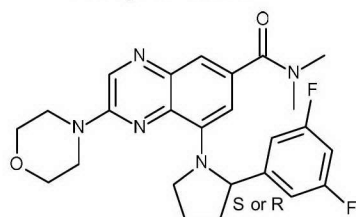
Preparation of compound 395, compound 395a and compound 395b



compound 395



compound 395a

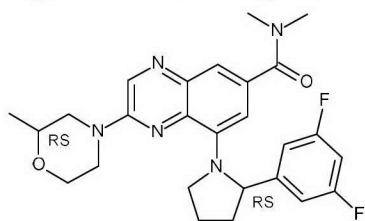


compound 395b

Compound 395 was prepared according to an analogous procedure as described for the synthesis of compound 1 using intermediate 5 and 2-(3,5-difluorophenyl)pyrrolidine as starting materials (133mg, 42%, M.P: 80 °C, gum (K)).

- The separation of the enantiomers was performed by chiral SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu$ m 250x20mm, Mobile phase: 75% CO<sub>2</sub>, 25% iPrOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were mixed and the solvent was evaporated to afford, after freeze-drying, respectively 47 mg (15%) of compound 395a (MP: 90°C, gum, K) and 45 mg (14%) of compound 395b (MP: 102°C, K).

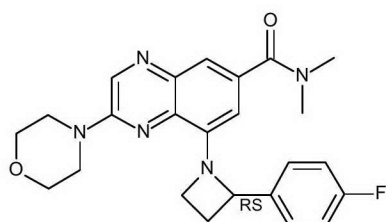
- 10 Preparation of compound 396 (mixture of 4 unseparable diastereoisomers)



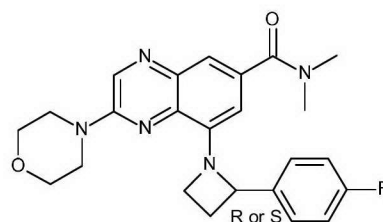
Compound 396 was prepared according to an analogous procedure as described for the synthesis of compound 1 using intermediate 5 and 2-(3,5-difluorophenyl)pyrrolidine as starting materials (89mg, 50%).

- 15

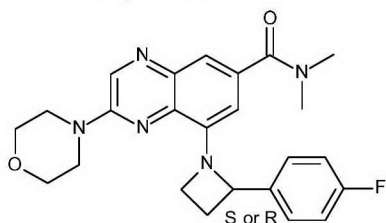
Preparation of compound 397, compound 397a and compound 397b



compound 397



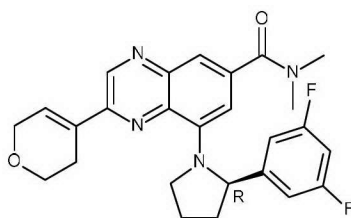
compound 397a



compound 397b

Compound 397 was prepared according to an analogous procedure as described for the synthesis of compound 1 using intermediate 5 and 2-(4-fluorophenyl)azetidine as starting materials (450mg, 75%).

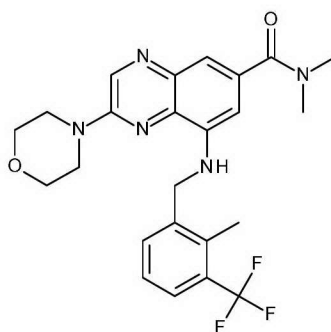
- 5 The separation of the enantiomers was performed by chiral SFC (Stationary phase: CHIRALCEL OJ-H 5 $\mu$ m 250x20mm, Mobile phase: 73% CO<sub>2</sub>, 27% iPrOH). The pure fractions were mixed and the solvent was evaporated to afford, respectively, 60 mg of compound 397a (MP: 80°C, gum, K) and 92 mg of compound 397b (MP: 80°C, gum, K).



#### 10 Preparation of compound 398

Compound 398 was prepared according to an analogous procedure as described for the synthesis of compound 1 using intermediate 28a and (2R)-2-(3,5-difluorophenyl)pyrrolidine as starting materials (32mg, 28%).

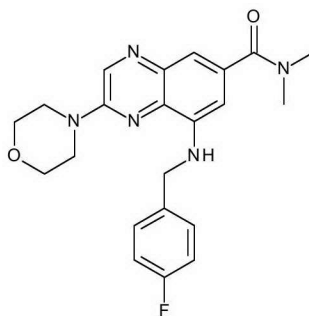
259



## Preparation of compound 399

Compound 399 was prepared according to an analogous procedure as described for the synthesis of compound 278 using intermediate 5 and 2-Methyl-3-(trifluoromethyl)benzylamine as starting materials (55mg, 21%, MP: 202°C (K)).

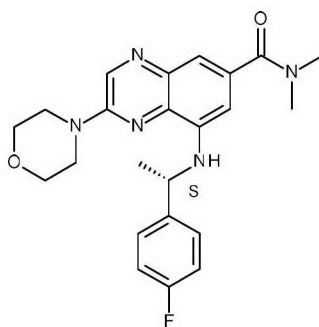
5



## Preparation of compound 400

Compound 400 was prepared according to an analogous procedure as described for the synthesis of compound 278 using intermediate 5 and 4-fluorobenzylamine as starting materials (92mg, 41%, MP: 80°C, gum (K)).

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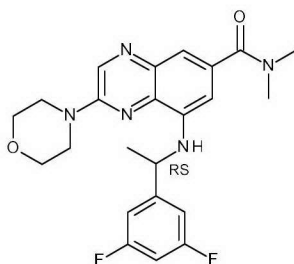


## Preparation of compound 401

Compound 401 was prepared according to an analogous procedure as described for the synthesis of compound 278 using intermediate 5 and (*S*)-4-Fluoro- $\alpha$ -methylbenzylamine as starting materials (6mg, 3%, MP: 80°C, gum (K)).

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260

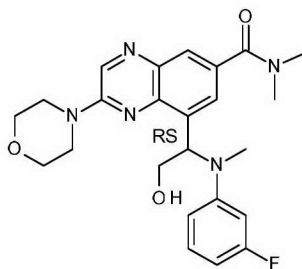


## Preparation of compound 402

Compound 402 was prepared according to an analogous procedure as described for the synthesis of compound 278 using intermediate 5 and (RS)-1-(3,5-Difluorophenyl)ethylamine as starting materials (25mg, 5%, MP: 80°C, gum (K)).

5

## Example B19

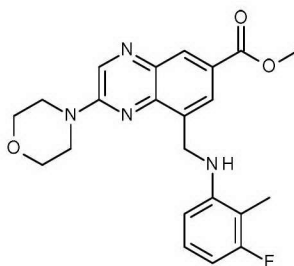


## Preparation of compound 301

In a sealed tube, 3-fluoro-1-methylaniline (60.4  $\mu$ L, 0.536 mmol) was added to a solution of intermediate 191 (177 mg, 0.536 mmol) and glycolaldehyde dimer (32.2 mg, 0.268 mmol) in hexafluoroisopropanol (1.07 mL). The mixture was stirred at room temperature for 14 days. The resulting solution was concentrated under reduced pressure. The crude product was purified by reverse phase (Stationary phase: X-Bridge-C18 5 $\mu$ m 30\*150mm, Mobile phase: Gradient from 85% aq.  $\text{NH}_4\text{HCO}_3$  0.2% , 15% ACN to 45% aq.  $\text{NH}_4\text{HCO}_3$  0.2% , 55% ACN) to give compound 301 (18.6 mg, 8%, MP : 315°C, DSC) as a yellow powder

15

## Example B20

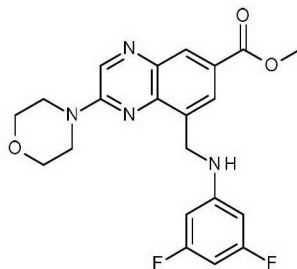


## Preparation of compound 326

To a solution of intermediate 212 (949 mg, 2.32 mmol) in DCM (23 mL) was added sodium triacetoxybororohydride (1.48 g, 6.97 mmol). The mixture was stirred at rt overnight then DCM and water were added. The organic layer was separated, dried

20

over  $\text{MgSO}_4$ , filtered off and evaporated in vacuo to give 1.52 g of compound 326 as a yellow solid directly used in the next step without any further purification.

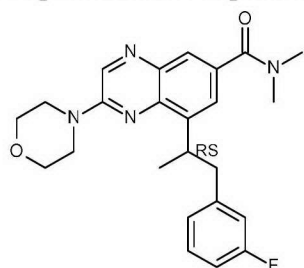


Preparation of compound 330:

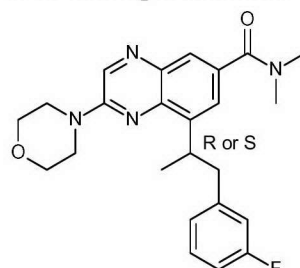
- 5 Compound 330 was prepared according to an analogous procedure as described for the synthesis of compound 326 using intermediate 214 as starting material (504 mg, used without purification in the next step).

Example B21

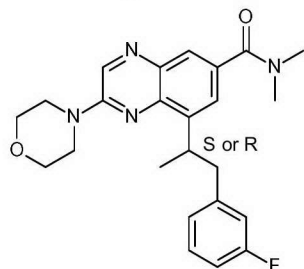
- 10 Preparation of compound 339, compound 339a and compound 339b



compound 397



compound 339a



compound 339b

- 15 A solution of 3-fluorophenylacetone (110 mg, 0.723 mmol) and *N*-tosylhydrazine (135 mg, 0.723 mmol) in 1,4-dioxane (2.89 mL) was stirred at 80 °C for 1.5h.  $\text{K}_2\text{CO}_3$  (150 mg, 1.08 mmol) and intermediate 191 (386 mg, 1.08 mmol) were successively added and the reaction mixture was heated to 110 °C for 3 days. The resulting solution was cooled down to room temperature and concentrated under reduced pressure. The residue was taken up in a saturated aqueous  $\text{NaHCO}_3$  solution (10 mL) and extracted with DCM (3x20 mL). The combined organic layers were washed with a saturated

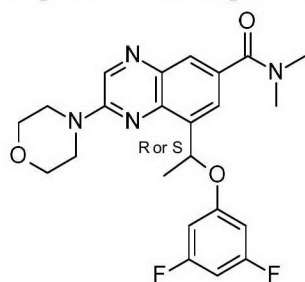
aqueous  $\text{NaHCO}_3$  solution (2x20 mL) and brine (20 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure.

- The residue was purified by silica gel chromatography (irregular  $\text{SiOH}$ , 15-40  $\mu\text{m}$ , 24g, mobile phase gradient: from DCM 100% to DCM 80%, MeOH 20%) to give of an impure fraction of compound **339** as an orange foam This residue was purified by reverse phase (Stationary phase: X-Bridge-C18 5 $\mu\text{m}$  30\*150mm, Mobile phase: Gradient from 65% aq.  $\text{NH}_4\text{HCO}_3$  0.2% , 35% ACN to 25% aq.  $\text{NH}_4\text{HCO}_3$  0.2% , 75% ACN) to give 105 mg (34%) of compound **339** as a yellow powder. M: 117°C (DSC).
- Compound **339** was purified by chiral SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu\text{m}$  250x20mm, Mobile phase: 70%  $\text{CO}_2$ , 30% iPrOH) to give 2 fractions which were triturated in a mixture of pentane/Et<sub>2</sub>O (5:1, 6 mL). The precipitates were filtered on glass frit to give 16.1 mg (5%) of compound **339a** as a light yellow powder (M.P: 131°C(DSC) and 16.7 mg, (5%) of compound **339b** as a light yellow powder (M.P: 128°C(DSC).

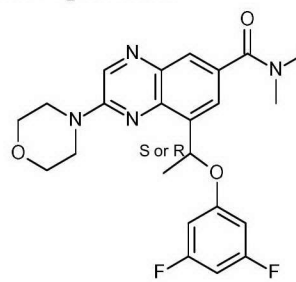
### C. Conversion of the final compounds

#### Conversion C1

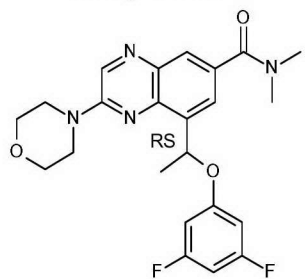
Preparation of compound 5, compound 6 and compound 53



compound 5



compound 6

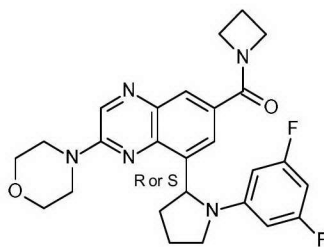


compound 53

- DIPEA (0.42 mL; 2.41 mmol) and HBTU (365 mg; 0.963 mmol) were added to a solution of compound 248 (400 mg; 0.96 mmol) in dry DMF (9.5 mL). The reaction mixture was stirred at rt for 30min. Then, dimethylamine (2M in THF) (0.72 mL; 1.44

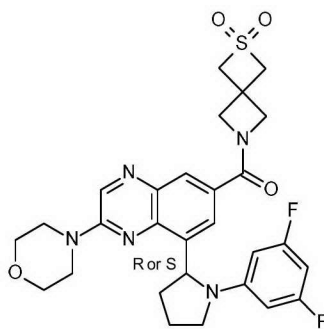


- mmol) was added and the reaction mixture was stirred at rt overnight. The mixture was evaporated in vacuum and the residue was taken-up with EtOAc. The organic layer was washed with a saturated aqueous solution of NaHCO<sub>3</sub>, brine (2x), dried over MgSO<sub>4</sub>, filtered and evaporated under vacuum. The residue (520 mg, beige foam) was purified by chromatography over silica gel (irregular SiOH 15-40  $\mu$ m; 25 g; mobile phase: from 100% DCM to 40% DCM, 60% EtOAc). The pure fractions were collected and the solvent was evaporated to give 393 mg (92%) of compound 53. The residue (393 mg) was purified by chiral SFC (CHIRALPAK AD-H; 5  $\mu$ m 250x20 mm; mobile phase: 75% CO<sub>2</sub>, 25% EtOH). The pure fractions were collected and the solvent was evaporated to give two fractions which were freeze-dried with water-ACN to give 186 mg (44%, pale yellow fluffy solid) of compound 5 and 182 mg (43%, pale yellow fluffy solid) of compound 6.



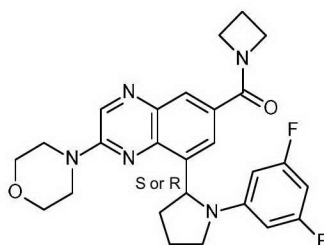
Preparation of compound 33:

- Compound 33 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 251 and azetidine hydrochloride as starting materials (83 mg, 38%). M.P.: 280°C (DSC).



Preparation of compound 34:

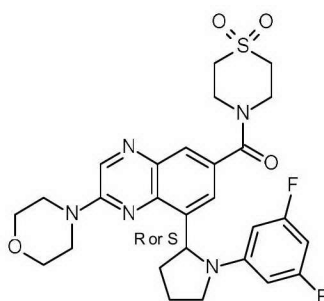
- Compound 34 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 251 and 2-thia-6-azaspiro[3.3]heptane,2,2-dioxide,2,2,2-trifluoroacetate as starting materials (68 mg, 48%). M.P.: 160°C (K).



Preparation of compound 37:

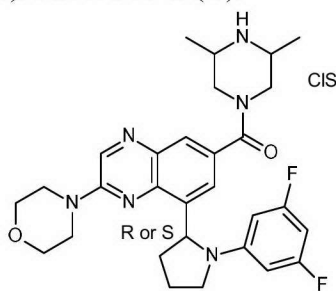
Compound 37 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 253 and azetidine hydrochloride as starting materials (61 mg, 43%). M.P.: 276°C (DSC).

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Preparation of compound 38:

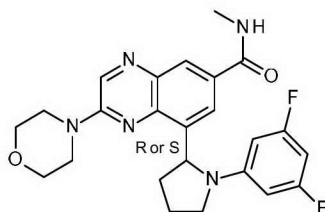
Compound 38 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 251 and thiomorpholine 1,1-dioxide as starting materials (67 mg, 48%). M.P.: 146°C (K).



10 Preparation of compound 39:

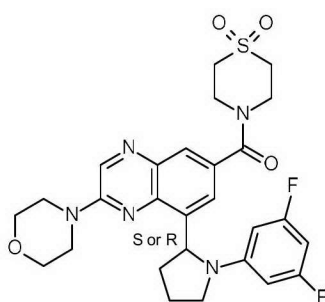
Under N<sub>2</sub>, at rt, 2,6-Dimethylpiperazine (44mg; 0.38mmol) was added to a solution of compound 251 (110 mg; 0.25 mmol), HBTU (142 mg; 0.38 mmol), and DIPEA (0.13 mL; 0.75 mmol) in DMF(3mL). The solution was stirred at rt for 64 hours. The solution was poured into cooled water. The product was extracted with DCM and the organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (180 mg) was purified by silica gel chromatography (Spherical bare silica 5μm 150x30.0mm, Mobile phase: Gradient from 98% DCM, 2% MeOH (+10% NH<sub>4</sub>OH) to 88% DCM, 12% MeOH (+10% NH<sub>4</sub>OH)). The fractions were collected and evaporated until dryness and freeze-dried with CH<sub>3</sub>CN/water to afford 81 mg (60%) of compound 39. M.P.: 80°C (gummed, K).

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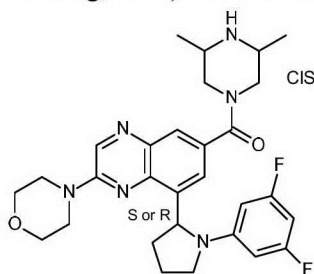
Preparation of compound 40:

Compound 40 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 251 and methylamine (2M in THF) as starting materials (freeze-dried: 51 mg, 35%, yellow powder). M.P.: 80°C (gum, K).



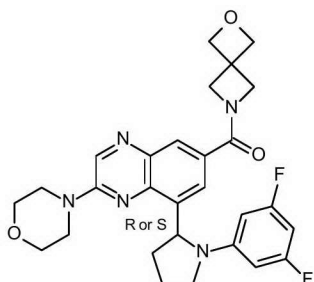
Preparation of compound 43:

Compound 43 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 253 and thiomorpholine 1,1-dioxide as starting materials (freeze-dried: 46 mg, 45%). M.P.: 80°C (gum, K).



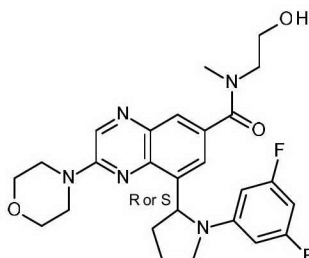
Preparation of compound 46:

Compound 46 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 253 and 2,6-dimethylpiperazine as starting materials (freeze-dried: 30 mg, 31%). M.P.: 80°C (gum, K).



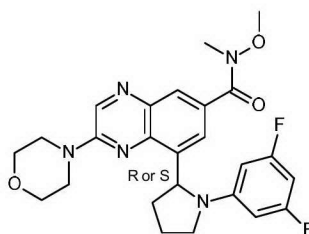
Preparation of compound 47:

Compound 47 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 251 and 2-oaxa-6aza-spiro(3,3)heptane as starting materials (freeze-dried: 32 mg, 25%). M.P.: 80°C (gum, K).



5 Preparation of compound 50:

Compound 50 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 251 and 2-(methylamino)ethanol as starting materials (freeze-dried: 35 mg, 28%). M.P.: 80°C (gum, K).

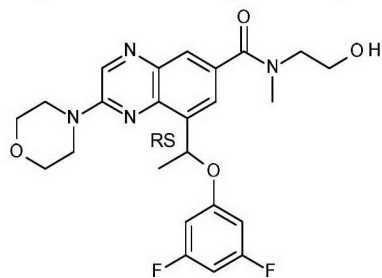


10 Preparation of compound 51:

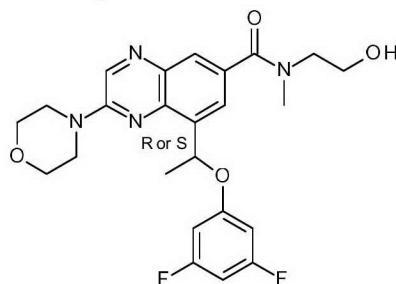
Compound 51 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 251 and N,O-dimethylhydroxylamine hydrochloride as starting materials (freeze-dried: 14 mg, 32%, yellow powder). M.P.: 80°C (gum, K).

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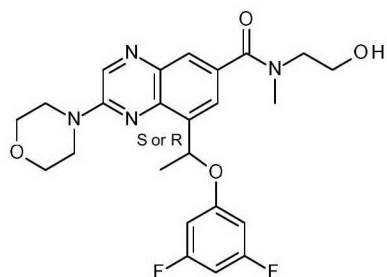
Preparation of compound 59, compound 60 and compound 61



compound 59

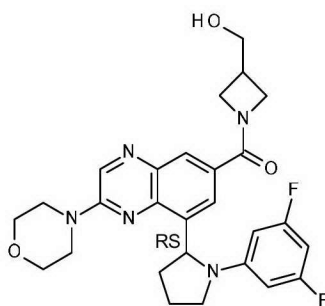


compound 60



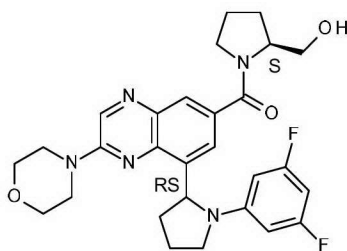
compound 61

- Compound 59, compound 60 and compound 61 were prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 248 and 2-(methylamino)ethanol as starting material (388 mg, 85%, pale yellow solid of compound 59. Separation of the enantiomers by chiral SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu$ m 250x20mm, Mobile phase: 80% CO<sub>2</sub>, 20% iPrOH(0.3% iPrNH<sub>2</sub>)) of 355 mg of racemic compound 59 gave respectively 145 mg (32%, yellow fluffy solid) of compound 60 and 125 mg (27%, pale fluffy solid) of compound 61.



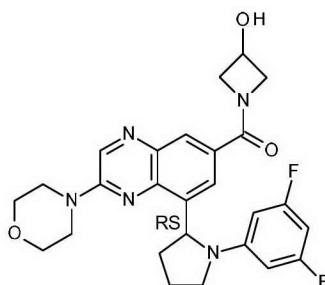
Preparation of compound 63:

- Compound 63 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 62 and (azetidin-3-yl)methanol as starting materials (freeze-dried: 29 mg, 25%). M.P.: 100°C (gum, K).



Preparation of compound 64:

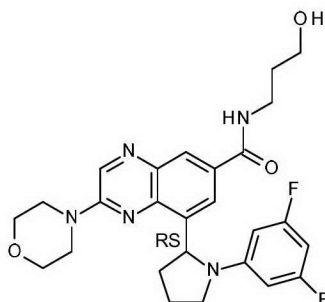
- Compound 64 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 62 and (S)-(+)-2-pyrrolidinemethanol as starting materials (freeze-dried: 51 mg, 43%). M.P.: 80°C (gum, K).



Preparation of compound 65:

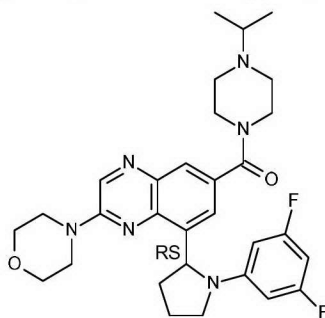
Compound 65 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 62 and 3-hydroxyazetidine hydrochloride as starting materials (freeze-dried: 51 mg, 45%). M.P.: 80°C (gum, K).

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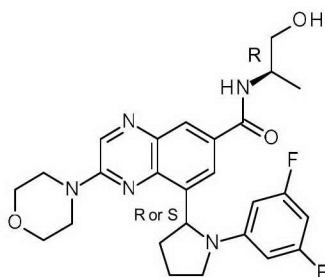
Preparation of compound 66:

Compound 66 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 62 and 3-amino-1-propanol as starting materials (freeze-dried: 46 mg, 41%). M.P.: 80°C (gum, K).



10 Preparation of compound 69:

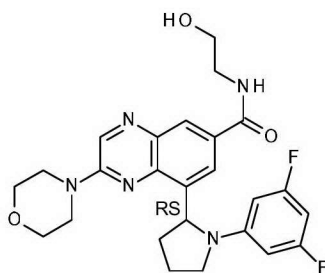
Compound 69 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 62 and 1-isopropylpiperazine as starting materials (freeze-dried: 44 mg, 35%, white powder). M.P.: 80°C (gum, K).



Preparation of compound 70:

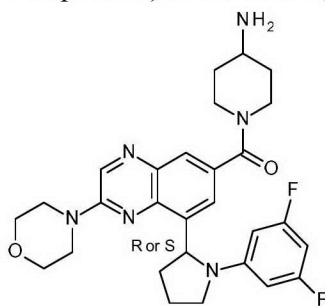
Compound 70 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 251 and (2R)-aminopropan-1-ol as starting materials (freeze-dried: 77 mg, 57%, white powder). M.P.: 80°C (gum, K).

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Preparation of compound 71:

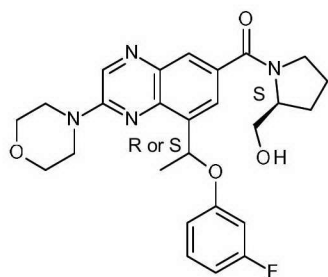
Compound 71 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 62 and ethanolamine as starting materials (freeze-dried: 79 mg, 36%, yellow powder). M.P.: 80°C (gum, K).



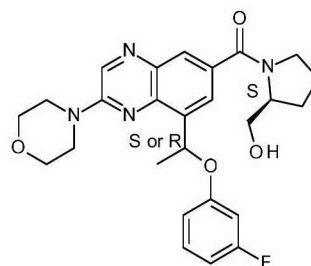
10 Preparation of compound 75:

Compound 75 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 251 and 4-aminopiperidine as starting material (freeze-dried: 14 mg, 12%). M.P.: 80°C (gum, K).

15 Preparation of compound 86 and compound 87



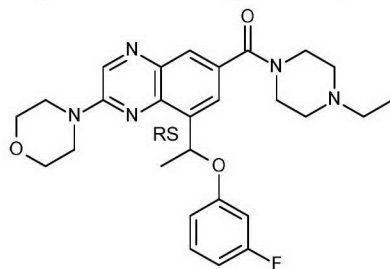
compound 86



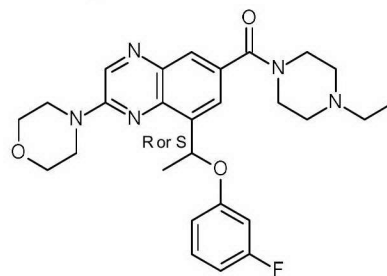
compound 87

Compound 86 and compound 87 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 257a and (S)-(+)-2-(pyrrolidinemethanol) as starting material. The residue (680 mg, orange oil) was purified by chromatography over silica gel (regular SiOH; 30  $\mu$ m; 40 g; gradient: from 99.5% DCM, 0.5% MeOH to 95% DCM, 5% MeOH). The pure fractions were collected and the solvent was evaporated. The residue (340 mg, pale yellow foam) was purified by achiral SFC (CHIRALPAK AD-H; 5  $\mu$ m; 250x20 mm; mobile phase: 65% CO<sub>2</sub>, 35% EtOH). The pure fractions were collected and the solvent was evaporated to give two fractions which were solubilized in DCM, evaporated and dried under vacuum (50°C, 24h) to give 115 mg (25%, pale yellow foam) of compound 86 (M.P.: 76°C, DSC) and 125 mg (28%, pale yellow foam) of compound 87 (M.P.: 74°C, DSC)

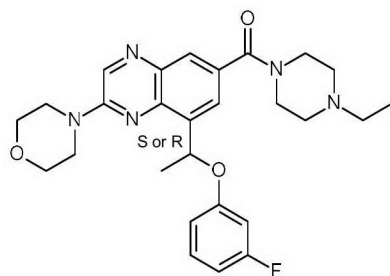
#### Preparation of compound 90, compound 91 and compound 92



compound 90



compound 91



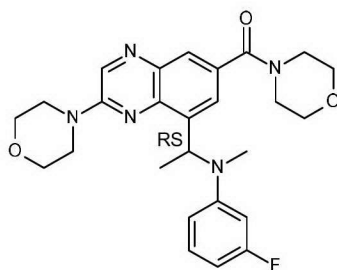
compound 92

Compound 90, compound 91 and compound 92 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound



257a and 1-ethylpiperazine as starting material. The residue (420 mg, brown oil) was purified by chromatography over silica (irregular SiOH; 15-40  $\mu$ m; 12 g; gradient: from 98% DCM, 2% MeOH to 94% DCM, 6% MeOH). The pure fractions were collected and the solvent was evaporated to give 2 fractions of compound 90 respectively:

- 5        - Fraction A: 72 mg of compound 90. 30mg of this fraction were solubilized in MeCN and washed with pentane. The MeCN layer was evaporated under vacuo and the solid was triturated in Et<sub>2</sub>O to give, after filtration, 21 mg of compound 90 (6%, off-white foam).
- 10       - Fraction B: 270 mg of compound 90 which were combined with the residual 42mg of fraction A. The resulting residue (312 mg) was purified by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x20 mm; mobile phase: 70% CO<sub>2</sub>, 30% EtOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give two fractions which were separately co-evaporated in DCM (2x) and dried under reduced pressure (16h, 50°C) to give respectively 92 mg (27%, pale yellow foam) of compound 91 and 101 mg (30%, pale yellow foam) of compound 92.
- 15

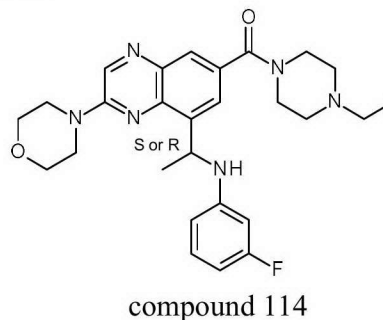
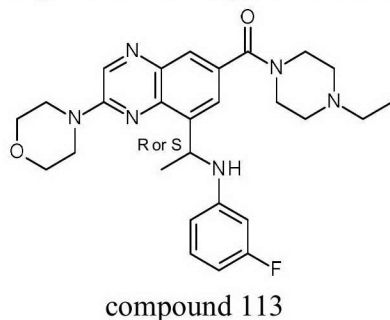


Preparation of compound 105:

Compound 105 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 98 and morpholine as starting materials (96 mg, 52%). M.P.: 161°C (DSC).

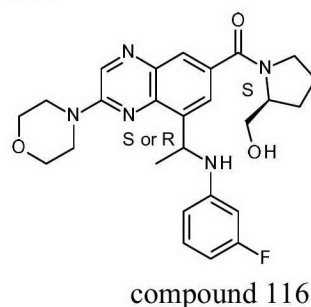
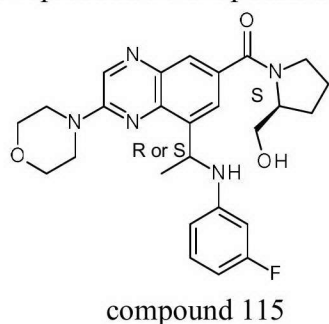
20

Preparation of compound 113 and compound 114



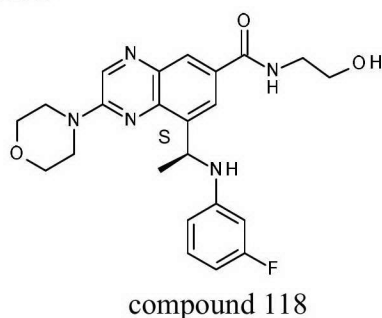
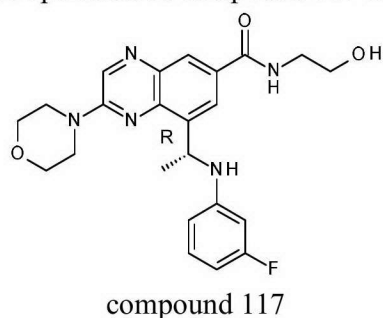
Compound 113 and compound 114 were prepared according to an analogous procedure as described for the synthesis of compound 5, using intermediate 117 and 1-ethylpiperazine as starting material (74 mg, 40%, pale yellow solid of compound 113; M.P.: 307°C (DSC) and 74 mg, 40%, pale yellow solid of compound 114; M.P.: 303°C (DSC) were obtained after chiral SFC (Stationary phase: Chiralpak AS-H 5 $\mu$ m 250\*20mm, Mobile phase: 60% CO<sub>2</sub>, 40% MeOH(0.3% iPrNH<sub>2</sub>)) purification).

#### Preparation of compound 115 and compound 116



Compound 115 and compound 116 were prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 263 and L-prolinol as starting materials (67 mg, 33%, pale yellow solid of compound 115; M.P.: 327°C (DSC) and 77 mg, 37%, pale yellow solid of compound 116; M.P.: 332°C (DSC) were obtained after chiral SFC (Stationary phase: CHIRALCEL OJ-H 5 $\mu$ m 250x20mm, Mobile phase: 80% CO<sub>2</sub>, 20% EtOH(0.3% iPrNH<sub>2</sub>)) purification).

#### Preparation of compound 117 and compound 118

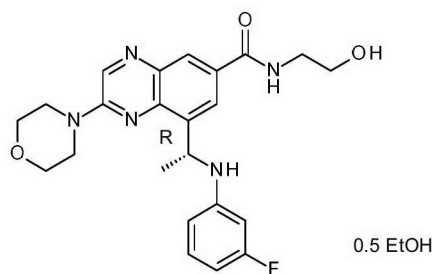


To a solution of compound 263 (120.0 mg; 303  $\mu$ mol), HBTU (230 mg; 0.605 mmol), and DIPEA (313  $\mu$ L; 1.82 mmol) in DMF (3 mL) was added 2-aminoethanol (36.3  $\mu$ L; 0.605 mmol). The solution was stirred at room temperature for 1 h. Then, water and DCM were added. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered off, evaporated under vacuum and purified by silica gel chromatography (Irregular SiOH 15-40  $\mu$ m, 24 g, liquid injection (DCM), mobile phase gradient: from DCM 100% to

DCM 90%, iPrOH/aq NH<sub>3</sub> (95:5) 10%) to give 144 mg (yellow foam) of racemic compound. The separation of the enantiomers was performed by chiral SFC (CHIRALCEL OJ-H 5  $\mu$ m 250x20 mm; Mobile phase: 70% CO<sub>2</sub>, 30% EtOH(0.3% iPrNH<sub>2</sub>)) The pure fractions were collected and the solvent was evaporated to give 63 mg (41%, pale yellow solid) of compound 117 and 67 mg (43%) of compound 118 (M.P.: 237°C, DSC).

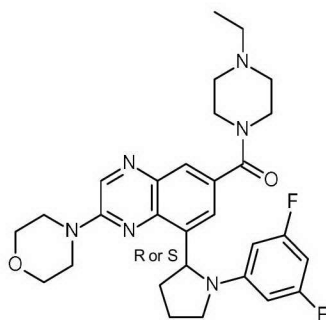
Alternative preparation of compound 117:

To a solution of compound 274 (94 mg, 0.237 mmol), HBTU (0.179 g, 0.474 mmol), and DIPEA (0.245 mL, 1.423 mmol) in DMF (3 mL) was added 2-aminoethanol (0.028 mL, 0.474 mmol) under N<sub>2</sub>. The solution was stirred at rt for 15h. The solution was cooled and the mixture was poured into cooled water, the product was extracted with EtOAc. The organic layer was washed with H<sub>2</sub>O, separated, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue 120mg was purified by chromatography over silica gel (Irregular SiOH 15-40  $\mu$ m 24g : gradient from 98% DCM, 2% MeOH to 90% DCM, 10% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated until dryness to give 32 g (31%) of compound 117 (ee=91.8%)



Preparation of compound 117:

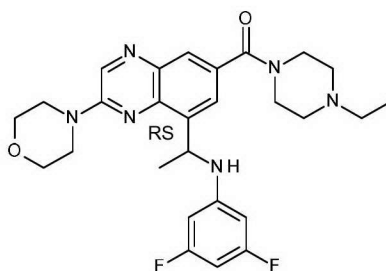
Compound 274 was coupled with ethanolamine (2.0 eq.) in DMF (3 volumes) using DIPEA (6.0 eq.) and HBTU (*N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate) (2.0 eq) at room temperature. After complete reaction the mixture was diluted with EtOAc, washed with 5% NaHCO<sub>3</sub> and concentrated to a residue. The solid was then slurried in THF (10 volumes) to improve the purity and the e.e. The procedure was executed respectively on 20 and 95 g scale of compound 274 and gave compound 117 in an average yield of 77% (e.e: 99.4%). The batches were then combined and for removing the THF, the resulting solid was dissolved in ethanol. The solvent was evaporated to a residue twice, and the resulting solid was then dried at 50 °C under reduced pressure overnight to obtain 90 g of compound 174a as a hemi-ethanolate solvate (e.e: 99.4%).



Preparation of compound 142:

Compound 142 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 251 and 1-ethylpiperazine as starting materials (107 mg, 80%). M.P.: 80°C (gum, K).

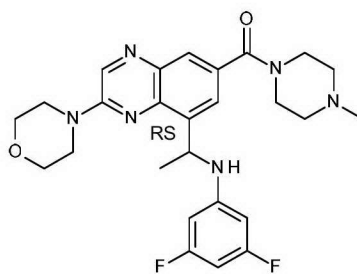
5



Preparation of compound 143:

Compound 143 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 83a and 1-ethylpiperazine as starting materials (136 mg, 74%). M.P.: 80°C (gum, K).

10

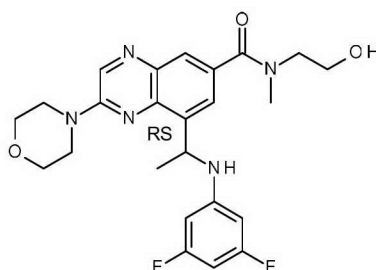


Preparation of compound 144:

Compound 144 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 83a and 1-methylpiperazine as starting materials (156 mg, 87%). M.P.: 80°C (gum, K).

15

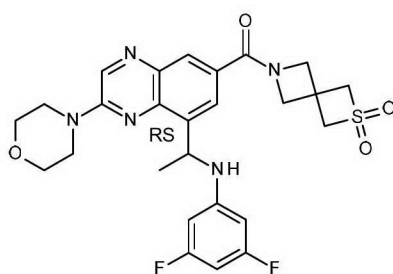
275



Preparation of compound 145:

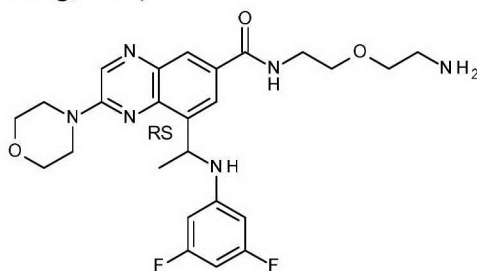
Compound 145 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 83a and 2-(methoxycarbonyl)-2-methylpropan-1-ol as starting materials (134 mg, 79%). M.P.: 80°C (gum, K).

5



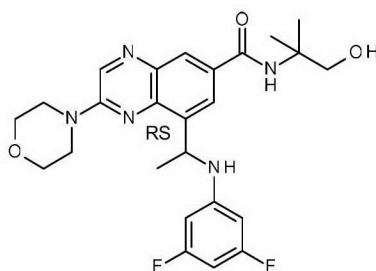
Preparation of compound 148:

Compound 148 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 83a and 2-thia-6-aza-spiro[3.3]heptane 2,2-dioxide as starting materials (124 mg, 47%).



10 Preparation of compound 149:

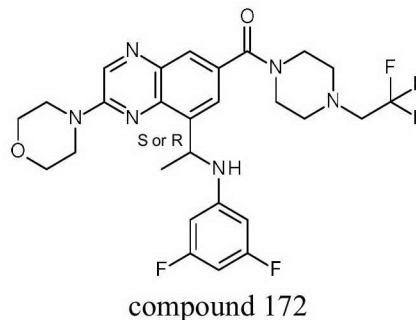
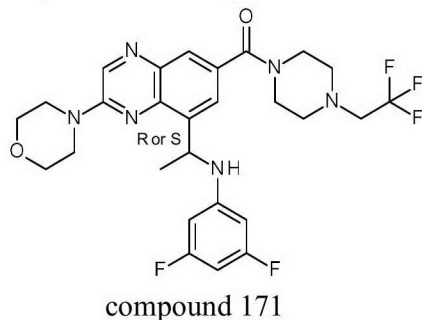
Compound 149 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 83a and 2,2'-oxybis(ethylamine) as starting materials (48 mg, 26%). M.P.: 80°C (gum, K).



15 Preparation of compound 169:

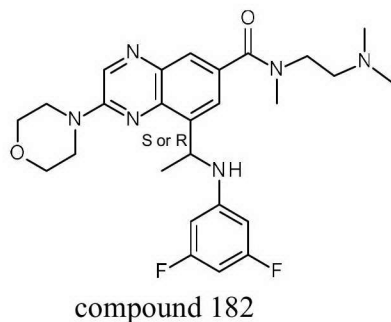
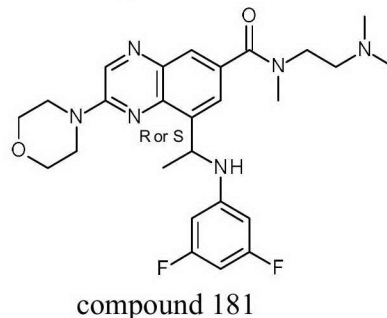
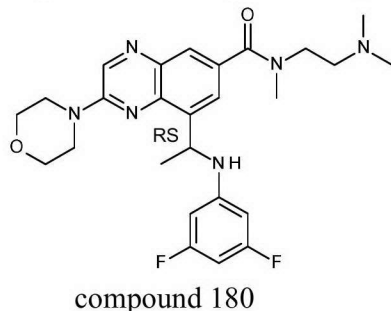
Compound 169 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 83a and 2-amino-2-methyl-1-propanol as starting materials (89 mg, 25%). M.P.: 217°C (DSC).

#### 5 Preparation of compound 171 and compound 172



Compound 171 and compound 172 were prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 83a and 1-(2,2,2-trifluoroethyl)piperazine as starting materials (104 mg, 38%, compound 171 (M.P.: 125°C (gum, K)) and 100 mg, 37%, compound 172 (M.P.: 130°C (gum, K)) were obtained after chiral SFC (Stationary phase: CHIRALCEL OJ-H 5 $\mu$ m 250x20mm, Mobile phase: 85% CO<sub>2</sub>, 15% MeOH(0.3% iPrNH<sub>2</sub>)) purification).

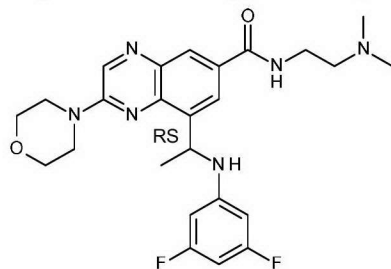
#### Preparation of compound 180, compound 181 and compound 182



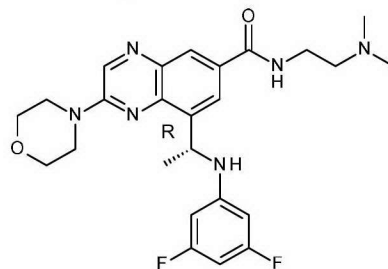
N,N,N'-trimethylethylenediamine (185  $\mu$ L; 1.45 mmol) was added to a solution of compound 83a (300 mg; 0.72 mmol), HBTU (549 mg; 1.45 mmol) and DIPEA (0.75

mL; 4.34 mmol) in Me-THF (10 mL). The reaction mixture was stirred at rt for 16h. The mixture was poured into water, extracted with EtOAc and washed with brine (2x). The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated. The residue (520 mg) was purified by column chromatography over silica gel (40 g; mobile phase: from 100% DCM to 97% DCM, 3% MeOH, 0.3% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated to give 295 mg (82%) of compound 180. M.P.: 148°C (K). Compound 180 was purified by chiral SFC (AS-H 5 µm 250\*20 mm; mobile phase: 80% CO<sub>2</sub>, 20% EtOH). The pure fractions were collected and the solvent was evaporated to give two fractions which were crystallized in diethylether, filtered and dried under vacuum to give 38 mg (11%) of compound 181 (M.P.: 134°C, DSC) and 60 mg (16%) of compound 182 (M.P.: 134°C, DSC).

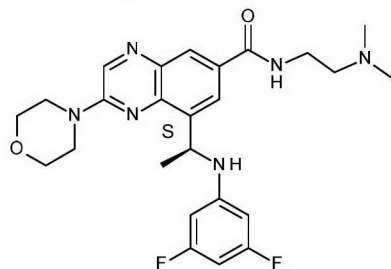
#### Preparation of compound 183, compound 184 and compound 185



compound 183



compound 184

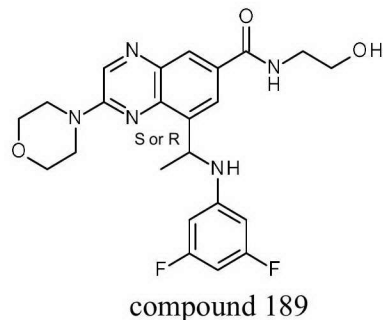
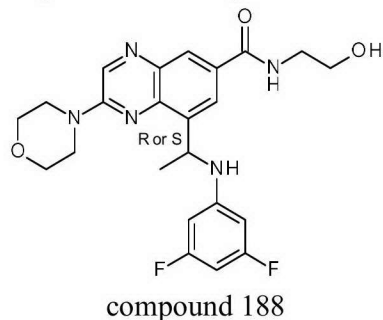


compound 185

To a solution of compound 83a (300 mg; 0.72 mol), HBTU (550 mg; 1.45 mmol) and DIPEA (0.75 mL; 4.34 mmol) in DMF (6 mL) was added N,N-dimethylethylenediamine (0.16mL; 1.45mmol) and the mixture was stirred at rt for 16h. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with brines (x2), dried over MgSO<sub>4</sub>, filtrated and evaporated until dryness. The residue was purified via silica gel chromatography (Stationary phase: 40g, Mobile phase from: 100% DCM to 97% DCM 3% MeOH 0.3% NH<sub>4</sub>OH). The pure fractions were collected and evaporated until dryness to give 290 mg (83%) of compound 183. Separation of the enantiomers was performed via chiral SFC (Stationary phase: CHIRALCEL OJ-H 5µm 250x20mm, Mobile phase: 85% CO<sub>2</sub>, 15% MeOH (0.3%

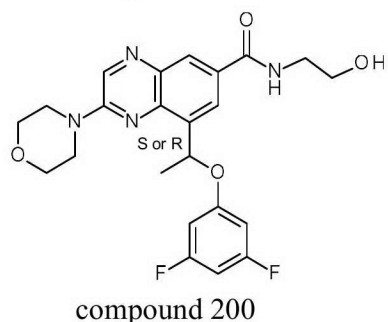
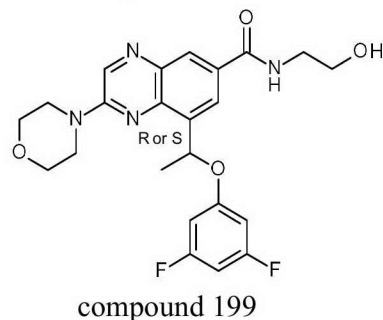
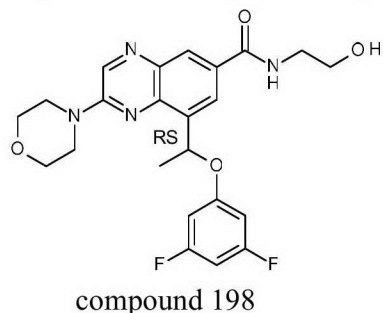
iPrNH<sub>2</sub>)). The pure fractions were collected and evaporated until dryness. Each fractions were crystallized from Et<sub>2</sub>O to give 70mg (20%) of compound 184 (M.P.: 157°C (DSC)), and 58 mg (20%) of compound 185 (M.P.: 152°C(DSC)).

#### 5 Preparation of compound 188 and compound 189



Compound 188 and compound 189 were prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 83a and 2-aminoethanol as starting materials (82 mg, 25%, compound 188 (M.P.: 80°C (gum, K)) and 94 mg, 87%, compound 189 (M.P.: 80°C (gum, K)) were obtained after chiral SFC (Stationary phase: CHIRALCEL OJ-H 5μm 250x20mm, Mobile phase: 75% CO<sub>2</sub>, 25% EtOH(0.3% iPrNH<sub>2</sub>)) purification).

#### Preparation of compound 198, compound 199 and compound 200

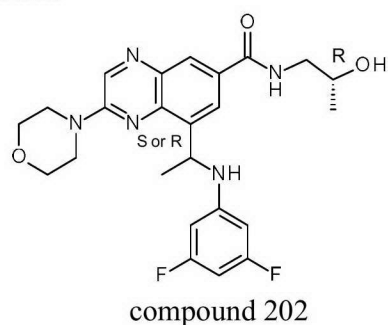
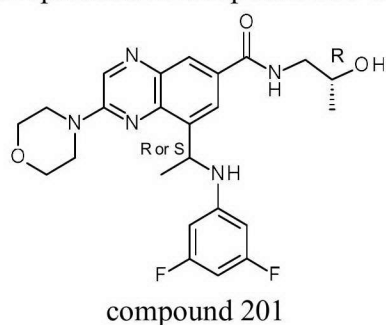


Compounds 198, 199 and 200 were prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 39 and 2-aminoethanol as



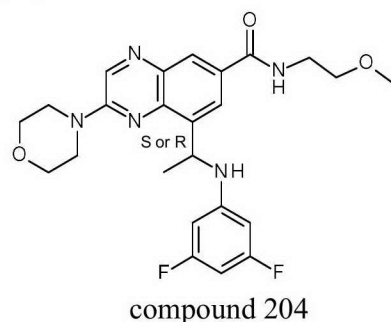
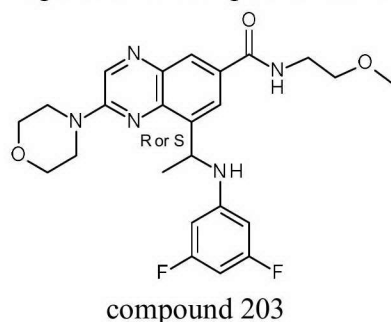
starting materials. 130 mg (24%) of compound 198 were obtained after crystallization in a mixture of Et<sub>2</sub>O/DCM. M.P.: 171°C (DSC). Compound 198 was purified by chiral SFC (CHIRALCEL OJ-H 5 µm 250x20 mm; mobile phase: 90% CO<sub>2</sub>, 10% MeOH). The pure fractions were collected and the solvent was evaporated. Each residue was  
 5 crystallized from DCM/diethylether. Each precipitate was filtered and dried under vacuum to give 68 mg (12%) of compound 199 (M.P.: 140°C, K) and 57 mg (10%) of compound 200 (M.P.: 115°C, gum, K).

#### Preparation of compound 201 and compound 202



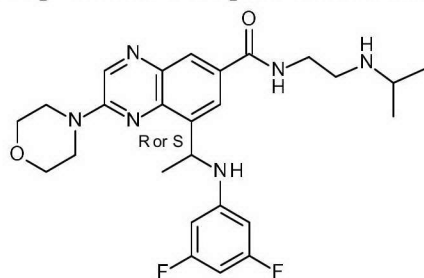
Compound 201 and compound 202 were prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 83a and (2R)-(-)-1-aminopropan-2-ol as starting materials. 253 mg (22%) of compound 201 (M.P.: 70°C, DSC) and 276 mg (24%) of compound 202 were obtained after chiral SFC (Stationary phase: CHIRALCEL OJ-H 5µm 250x20 mm, Mobile phase: 83% CO<sub>2</sub>, 17% MeOH (0.3% iPrNH<sub>2</sub>)) purification.  
 15

#### Preparation of compound 203 and compound 204

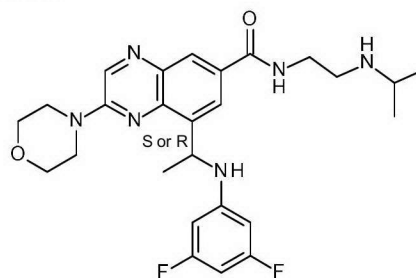


Compound 203 and compound 204 were prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 83a and 2-methoxyethylamine as starting material (after purification to separate the enantiomers from 280 mg of racemic compound and crystallization from diethylether; 28 mg (8%) of compound 203 (M.P.: 118°C, DSC) and 76 mg (22%) of compound 204 (M.P.: 80°C, gum, K).  
 20

## Preparation of compound 211 and compound 212



compound 211



compound 212

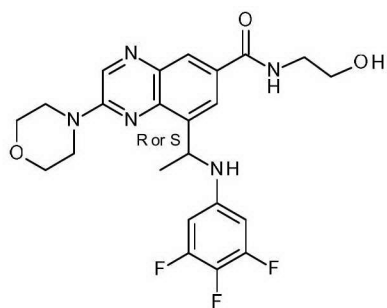
A solution of compound 83a (1g; 2.41mmol), HBTU (1.37g; 3.62mmol) and DIPEA (1.25mL; 7.24mmol) in DMF (25 mL) was stirred at rt for 15min. Then, *N*-isopropylethylenediamine (0.46mL; 3.62mmol) was added and the solution was stirred at rt for 15h. The product was poured in ice water and extracted with EtOAc. The organic layer was washed with brine (x 2), dried over MgSO<sub>4</sub>, filtered and evaporated until dryness. The residue was purified by silica gel chromatography (Stationary phase: irregular SiOH 15-40μm 300g MERCK, Mobile phase: 0.1% NH<sub>4</sub>OH, 95% DCM, 0.5% MeOH). The fractions containing the product were mixed and concentrated to afford 720 mg of the racemate.

This racemate was purified by chiral SFC (Stationary phase: CHIRALCEL OJ-H 5μm 250x20mm, Mobile phase: 90% CO<sub>2</sub>, 10% MeOH(0.3% iPrNH<sub>2</sub>)). The fractions containing the products were mixed and concentrated to afford 320 mg of fraction A and 315 mg of fraction B.

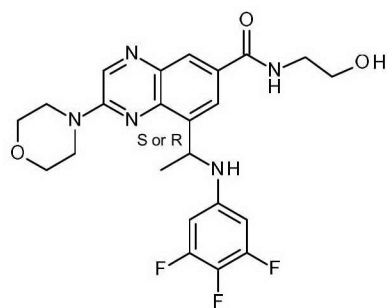
Fraction A was crystallized from a mixture of DCM/Et<sub>2</sub>O. The precipitate was filtered off and dried under vacuum to give 280mg (23%) of compound 211 (M.P.: 206°C (DSC)).

Fraction B was crystallized from a mixture of DCM/Et<sub>2</sub>O. The precipitate was filtered off and dried under vacuum to give 250mg (21%) of compound 212 (M.P.: 204 °C (DSC)).

## Preparation of compound 213 and compound 214

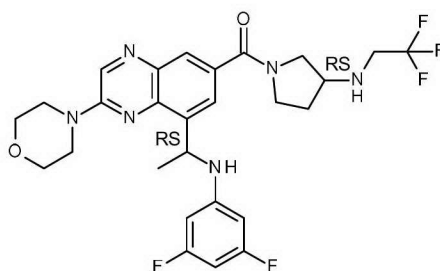


compound 213



compound 214

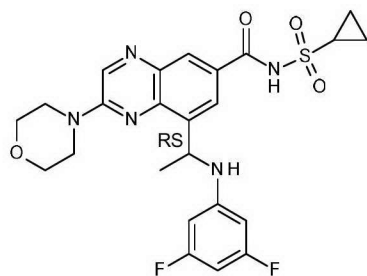
Compound 213 and compound 214 were prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 170 and 2-aminoethanol as starting materials. 117 mg (27%) of compound 213 (M.P.: 80°C, gum, K) and 136 mg (31%) of compound 214 (M.P.: 80°C, gum, K) were obtained after chiral SFC (Stationary phase: CHIRALCEL OJ-H 5 $\mu$ m 250x20mm, Mobile phase: 80% CO<sub>2</sub>, 20% MeOH (0.3% iPrNH<sub>2</sub>)) purification.



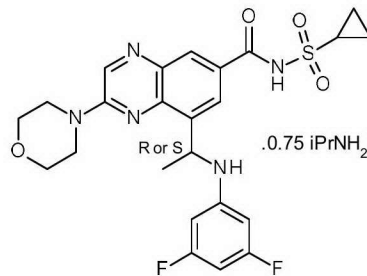
Preparation of compound 217:

Compound 217 (undefined mixture of 4 diastereoisomers) was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 83a and 3-(trifluoroacetamido)pyrrolidine as starting materials (crystallized from diisopropylether; 120 mg, 29%).

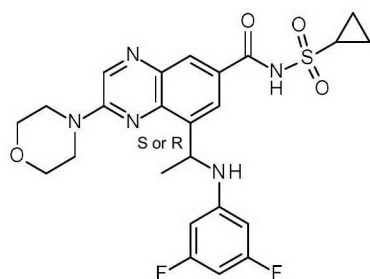
Preparation of compound 218, compound 219 and compound 220



compound 218

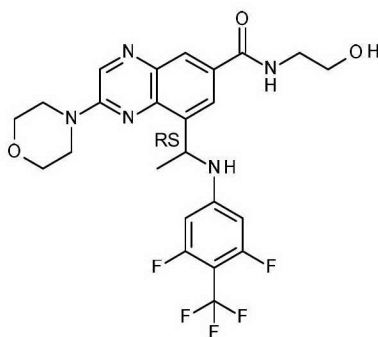


compound 219



compound 220

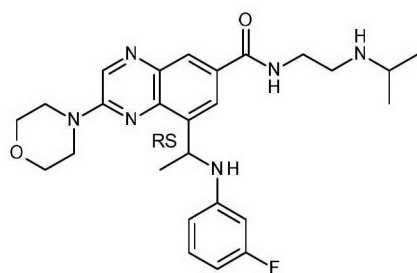
1,1'-Carbonyldiimidazole (324 mg; 2.0 mmol) was added to a solution of compound 83a (690 mg; 1.67 mmol) in Me-THF (14 mL) and the mixture was heated at reflux for 2 h. The mixture was cooled down to rt and cyclopropanesulphonamide (202 mg; 1.67 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (370  $\mu$ L; 2.50 mmol) were added. The mixture was stirred at rt overnight. The mixture was poured into water. The organic layer was extracted with DCM, separated, dried over  $\text{MgSO}_4$ , filtered and evaporated. The residue was purified by chromatography over silica gel (Irregular SiOH 15-40  $\mu$ m; 40 g; gradient: from 100% DCM to 90% DCM, 10% MeOH, 0.1%  $\text{NH}_4\text{OH}$ ). The pure fractions were collected and the solvent was evaporated until dryness to give 970 mg of compound 218. A part (106 mg) was crystallized from DIPE. The precipitate was filtered off and dried under vacuum to give 59 mg of compound 218. The rest of the compound 218 was purified by chiral SFC (CHIRALCEL OJ-H 5  $\mu$ m; 250x20 mm; mobile phase: 60%  $\text{CO}_2$ , 40% MeOH (0.3%  $\text{iPrNH}_2$ )). The pure fractions were collected and the solvent was evaporated to give two fractions which were crystallized from diisopropylether. Each precipitate was filtered off and dried under vacuum to give 312 mg (33%) of compound 219 and 248 mg (29%) of compound 220.



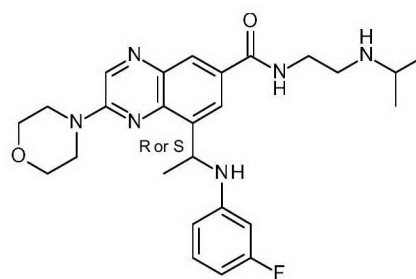
#### Preparation of compound 223:

Compound 223 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 159 and 2-aminoethanol as starting materials (crystallized from DCM; 195 mg, 60%). M.P.: 200°C (DSC).

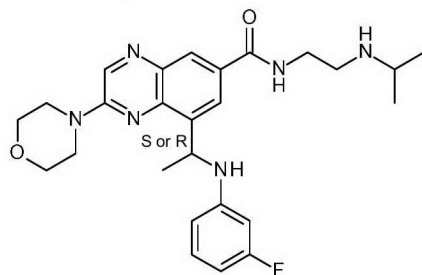
#### Preparation of compound 226, compound 227 and compound 228



compound 226



compound 227



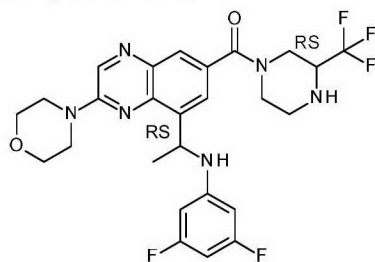
compound 228

Compounds 226, 227 and 228 were prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 263 and *N*-isopropylethylenediamine as starting materials. After crystallization from diethylether 192 mg (49%) of compound were obtained. M.P.: 158°C (DSC).

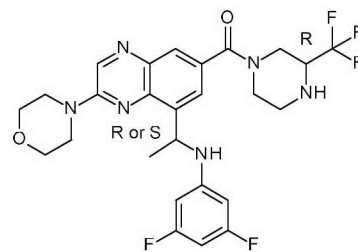
- 5 Compound 226 was purified by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m; 250x20 mm; mobile phase: 60% CO<sub>2</sub>, 40% EtOH). The pure fractions were collected and the solvent was evaporated. Each residue was freeze-dried with ACN/water (20/80) to give 74 mg (19%, yellow powder) of compound 227 (M.P.: 80°C, gum, K) and 76 mg (20%, yellow powder) of compound 228 (M.P.: 80°C, gum, K).

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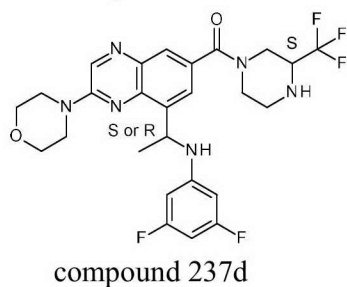
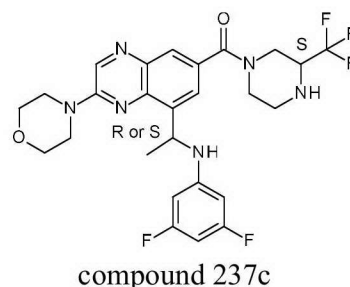
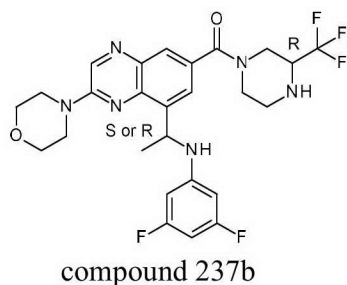
Preparation of compound 237, compound 237a, compound 237b, compound 237c and compound 237d



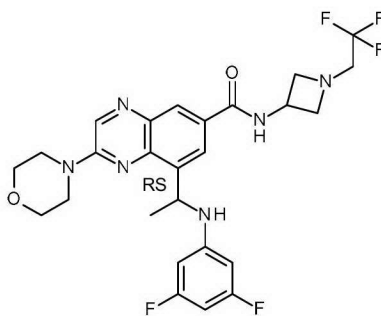
compound 237



compound 237a



Compound 237 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 236 and 2-Trifluoromethylpiperazine (R/S: 80/20) as starting materials. The residue (700 mg,) was purified by chromatography over silica gel (irregular 15-40 $\mu$ m; mobile phase : 97% DCM, 3% MeOH (+10% NH<sub>4</sub>OH)). The pure fractions were collected and the solvent was evaporated. The residue (500 mg) was crystallized from Heptane and Et<sub>2</sub>O. The precipitate was filtered and dried to give (0.45 g, 67% of compound 237 (M.P: 105°C (Kofler). Compound 237 was further purified by chiral SFC (CHIRALCEL OJ-H; 5  $\mu$ m 250x20 mm; mobile phase: 80% CO<sub>2</sub>, 20% MeOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 2 fractions of diastereoisomers. The first fraction of diastereoisomers was purified by chiral SFC (CHIRALPAK AD-H, 5  $\mu$ \* 250\*20 mm; mobile phase 85% CO<sub>2</sub>, 15% EtOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 2 fractions. The first one (122 mg) was crystallized from Et<sub>2</sub>O to give after filtration 94 mg of compound 237b (M.P : 120°C (Kofler)) and the second one (38 mg) was freeze-dried with water-ACN to give 33 mg (5%) of compound 237d (M.P.: 80°C (Kofler). The second fraction was purified by chiral SFC (CHIRALPAK AD-H, 5  $\mu$ \* 250\*20 mm; mobile phase 82% CO<sub>2</sub>, 18% EtOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 2 fractions. The first one (120 mg) was crystallized from Et<sub>2</sub>O to give after filtration 66 mg (10%) of compound 237a (M.P.:120°C (Kofler) and the second one (43 mg) was freeze-dried with water-ACN to give 40 mg (6%) of compound 237c (M.P.:80°C (Kofler)).

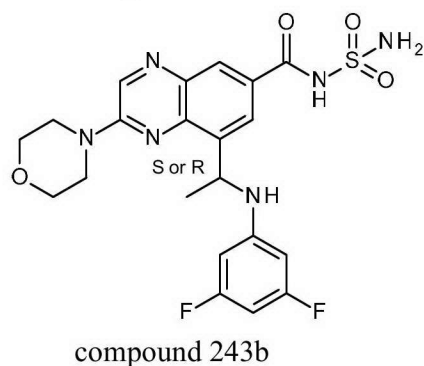
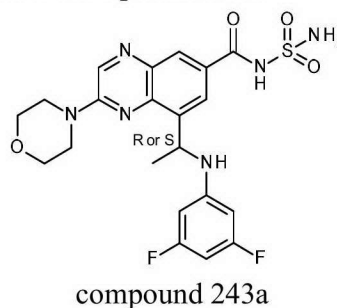
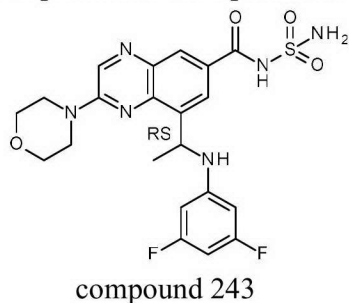


Preparation of compound 238:

Compound 238 ( was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 236 and 1-(2,2,2-trifluoroethyl)-3-azetidinamine as starting materials (Heptane/Et<sub>2</sub>O, 350mg, 45%).M.P: 110°C (gum, K).

5

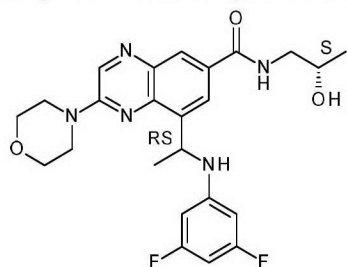
Preparation of compound 243, compound 243a and compound 243b



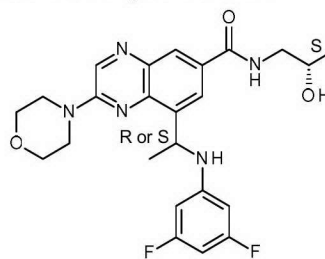
Compound 243 ( was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 236 and sulfamide as starting materials. The residue (480 mg) was purified by chromatography over silica gel (irregular 15-40μm; 40g, mobile phase : 100% DCM). The pure fractions were collected; The solvent was evaporated and a part of product was crystallized from DIPE. The precipitate was filtered and dried to give (41 mg) of compound 243. The residue was purified by chiral SFC (CHIRALPAK AD-H, 5 μ\* 250\*20 mm; mobile phase 60% CO<sub>2</sub>, 40% MeOH). The pure fractions were collected and the solvent was evaporated to give 2 fractions which were taken up DCM and evaporated to give 98 mg (20%) of

compound 243a (M.P.:160°C (Kofler)) and 96 mg (20%) of compound 243b (M.P : 200°C (Kofler))

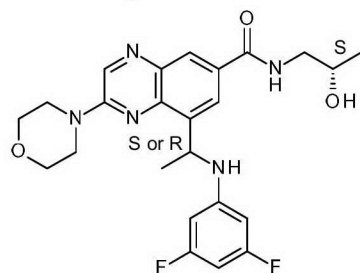
Preparation of compound 246, compound 246a and compound 246b



compound 246



compound 246a



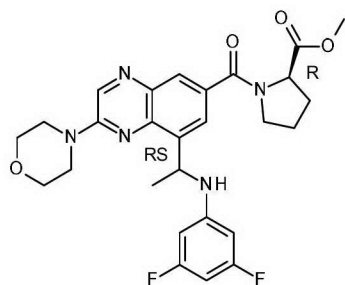
compound 246b

- 5 Compound 246 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 236 and (2S)-1-amino-2-propanol as starting materials. The residue (580 mg.) was purified by chromatography over silica gel (irregular 15-40 $\mu$ m; 40g, mobile phase: gradient from 100% DCM to 97% DCM 3% MeOH 0.3% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was
- 10 evaporated to give 345 mg of compound 246. This compound was purified by chiral SFC (CHIRALCEL OJ-H, 5  $\mu$ \* 250\*20 mm; mobile phase 75% CO<sub>2</sub>, 25% MeOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 2 fractions which were crystallized from Et<sub>2</sub>O and dried to give 123 mg (36%) of compound 246a and 118 mg (34 %) of compound 246b (M.P : 75°C (DSC)).

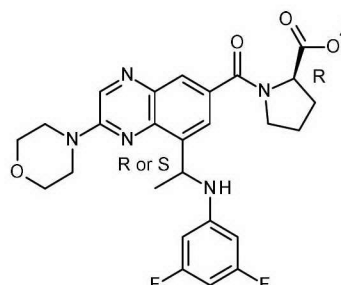
15

Preparation of compound 272, compound 272a and compound 272b

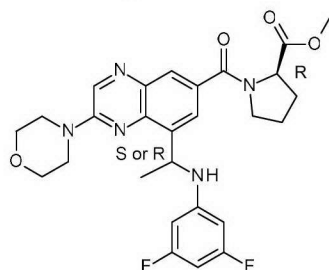




compound 272



compound 272a

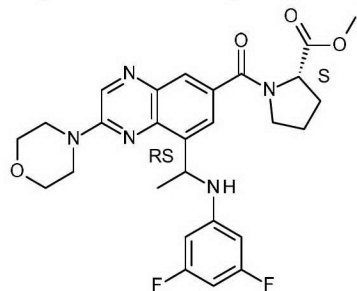


compound 272b

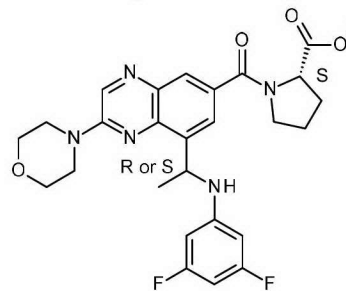
Compound 272 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 236 and D-proline methylester hydrochloride as starting materials. The residue was purified by chromatography over silica gel (irregular bare silica 40 g; mobile phase: gradient from 100% DCM to 0.1% NH<sub>4</sub>OH, 90% DCM, 10% MeOH). The pure fractions were collected and the solvent was evaporated to give 250mg (78%) of compound 272. Compound 272 was purified by chiral SFC (CHIRALCEL OJ-H; 5  $\mu$ m 250x20 mm; mobile phase: 75% CO<sub>2</sub>, 25% MeOH). The pure fractions were collected and the solvent was evaporated to give respectively 87 mg (27%) of compound 272a and 86 mg (27%) of compound 272b.

10

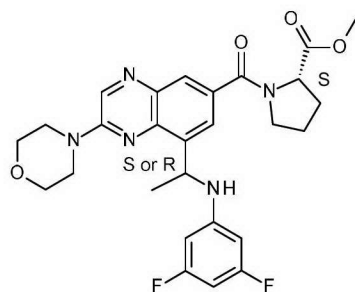
Preparation of compound 273, compound 273a and compound 273b



compound 273



compound 273a

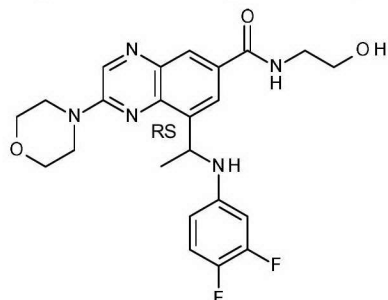


compound 2723b

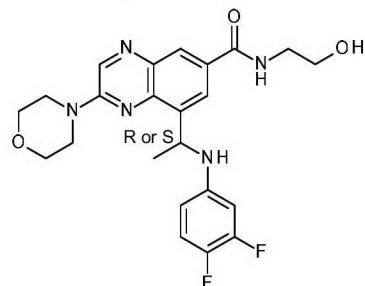
Compound 273 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 236 and L-proline methylester hydrochloride as starting material. The residue was purified by chromatography over silica gel (irregular bare silica 40 g; mobile phase: gradient from 100% DCM to 0.1% NH<sub>4</sub>OH, 90% DCM, 10% MeOH). The pure fractions were collected and the solvent was evaporated to give 320 mg of compound 273. Compound 273 was purified by chiral SFC (CHIRALCEL OJ-H; 5  $\mu$ m 250x20 mm; mobile phase: 80% CO<sub>2</sub>, 20% MeOH). The pure fractions were collected and the solvent was evaporated to give respectively 105 mg (33%) of compound 273a and 96 mg (32%) of compound 273b.

10

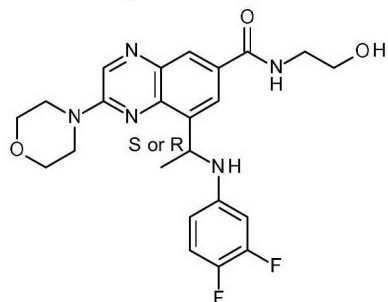
Preparation of compound 279, compound 279a and compound 279b



compound 279



compound 279a

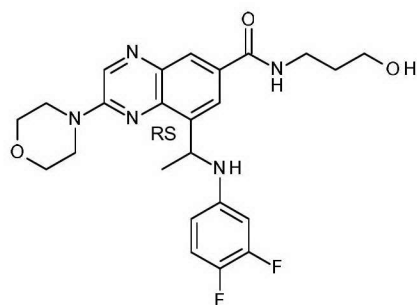


compound 279b

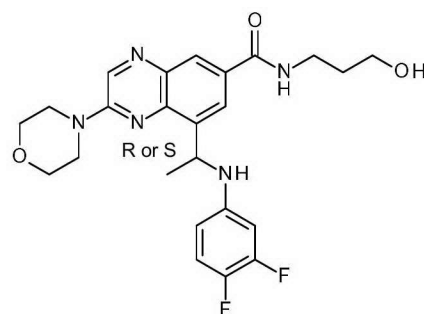
Compound 279 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 234 and 2-aminoethanol as starting materials (570 mg, 65%). M.P = 77°C DSC.

- 5 Compound 179 was purified by chiral SFC (Stationary phase: CHIRALPAK AD-H 5µm 250x20mm, Mobile phase: 55% CO<sub>2</sub>, 45% EtOH(0.3% iPrNH<sub>2</sub>)) to give 150 mg of each enantiomers which were freeze-dried with a mixture of ACN and water (1/3) giving 90 mg (10%) of compound 279a (M.P.: 80°C, gum, K) and 100 mg (11%) of compound 279b (M.P.: 80°C, gum, K).

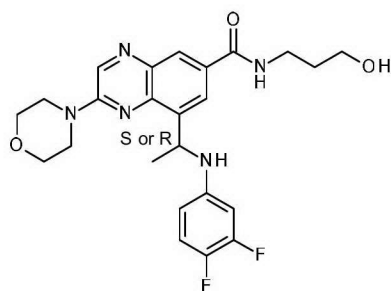
- 10 Preparation of compound 280, compound 280a and compound 280b



compound 280



compound 280a

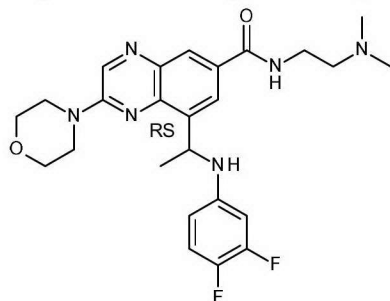


compound 280b

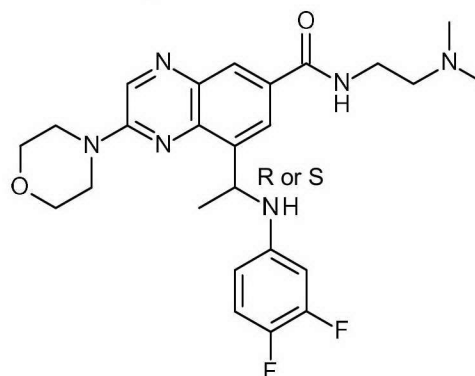
- 15 Compound 280 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 234 and 3-Amino-1-propanol as starting materials (330 mg, 72%, M.P : 164°C, DSC).

- 20 Compound 280 was purified by chiral SFC (CHIRALPAK AD-H 5 µm 250x20 mm; mobile phase: 60% CO<sub>2</sub>, 40% MeOH). The pure fractions were collected and the solvent was evaporated to give 140 mg of one compound which were freeze-dried with a mixture of ACN and water (1/3) giving 105mg (10%) of compound 280a: (MP : 80°C, gum, K) and 135 mg of another compound which were freeze-dried with a mixture of ACN and water (1/3) giving 120mg (26%) of compound 280b (MP : 80°C, gum, K).

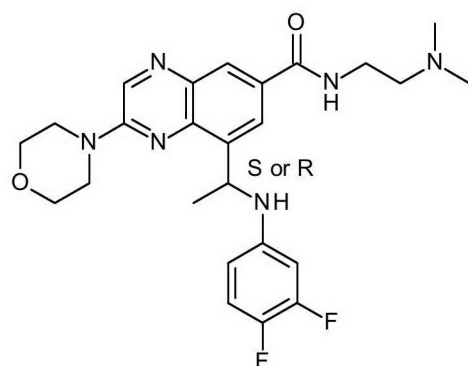
Preparation of compound 281, compound 281a and compound 281b



compound 281



compound 281a

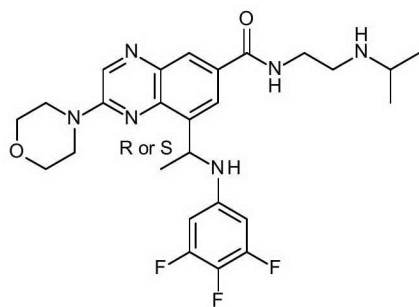


compound 281b

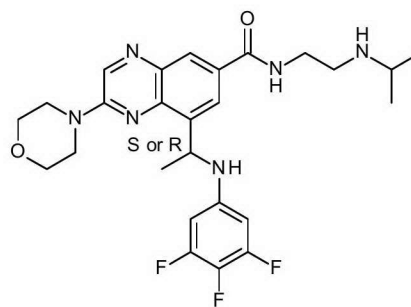
Compound 281 was prepared according to an analogous procedure as described for the  
 5 synthesis of compound 5, using compound 234 and *N,N*-dimethylethylenediamine as  
 starting materials (570 mg, 100%, M.P = 80°C, K)

Compound 281 was purified by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x20 mm;  
 mobile phase: 60% CO<sub>2</sub>, 40% MeOH). The pure fractions were collected and the  
 solvent was evaporated to give 253 mg of one compound which was crystallized from  
 10 pentane giving 136mg (23%) of compound 281a (MP : 102°C, K) and 234 mg of  
 another compound which was crystallized from pentane giving 164mg (28%) of  
 compound 281b (MP : 80°C, gum, K).

Preparation of compound 283a and compound 283b



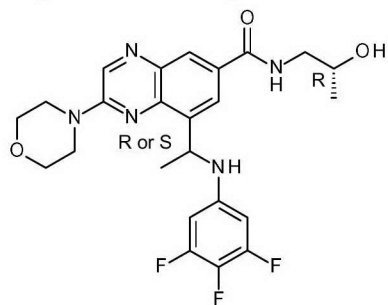
compound 283a



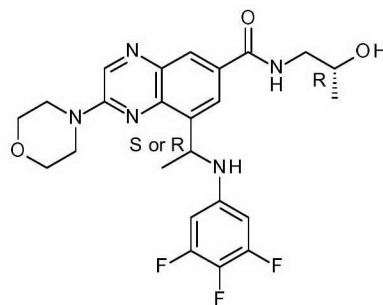
compound 283b

Compound 283a and compound 283b were prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 170 and *N*-isopropylethylenediamine as starting materials giving 290 mg (97%) of a racemic intermediate compound which was purified by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x20 mm; mobile phase: 60% CO<sub>2</sub>, 40% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 102 mg of one compound which was crystallized from Et<sub>2</sub>O giving 63mg (21%) of compound 283a: (MP : 173°C, DSC) and 105 mg of other compound which was crystallized from Et<sub>2</sub>O giving 60mg (20%) of compound 283b: (MP : 170°C, DSC).

#### Preparation of compound 284a and compound 284b



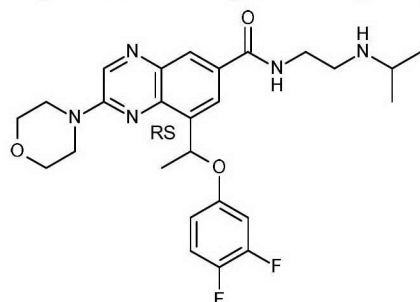
compound 284a



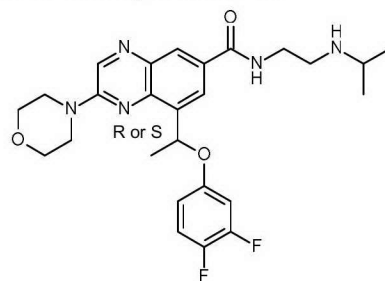
compound 284b

Compound 284a and compound 284b were prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 170 and (2R)-(-)-1-aminopropan-2-ol as starting materials giving 745 mg (84%) of a racemic compound, which was purified by chiral SFC (CHIRALCEL OJ-H 5  $\mu$ m 250x20 mm; mobile phase: 83% CO<sub>2</sub>, 17% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 323 mg of one compound which was crystallized from pentane giving 190mg (21%) of compound 284a (MP : 113°C, K) and 368 mg of another compound which was crystallized from pentane giving 240mg (27%) of compound 284b (MP : 112°C, K).

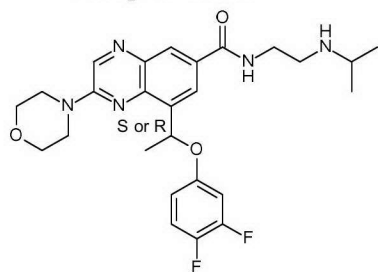
## Preparation of compound 286, compound 286a and compound 286b



compound 286



compound 286a

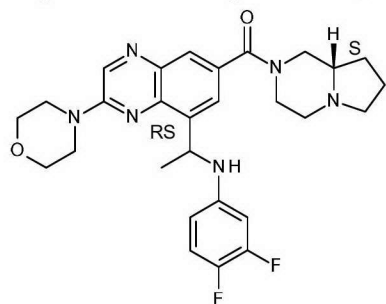


compound 286b

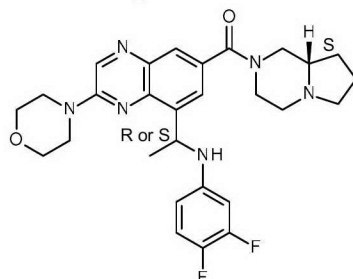
Compound 286 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 285 and *N*-isopropylethylenediamine, as starting materials (645 mg, 67%, MP : 85°C, gum, K).

Compound 286 (598 mg) was purified by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x30 mm; mobile phase: 65% CO<sub>2</sub>, 35% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 262 mg of one compound which was crystallized from Et<sub>2</sub>O giving 187mg (19%) of compound 286a (MP : 85°C, gum, K) and 231 mg of other compound which was crystallized from Et<sub>2</sub>O giving 220mg (23%) of compound 286b (MP : 85°C, gum, K).

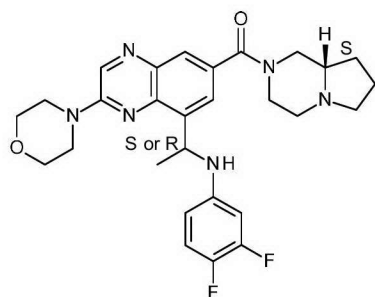
## Preparation of compound 287, compound 287a and compound 287b



compound 287



compound 287a



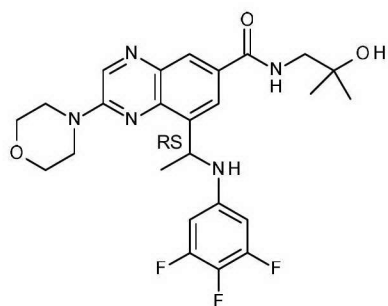
compound 287b

Compound 287 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 234 and (6S)-1,4-diazabicyclo[4,3,0]nonane as starting materials (1.03g, 82%, M.P = 80°C, gum, K).

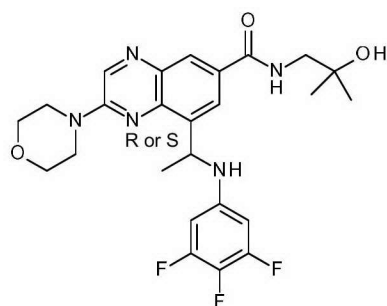
Compound 287 (980 mg) was purified by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x20 mm; mobile phase: 70% CO<sub>2</sub>, 30% MeOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 274 mg (22%) of one compound which was crystallized from DIPE giving 255mg (20%) of compound 287a (MP : 90°C, K) and 185 mg of other compound which was crystallized from Et<sub>2</sub>O giving 130mg (10%) of compound 287b (MP : 95°C, gum, K).

10

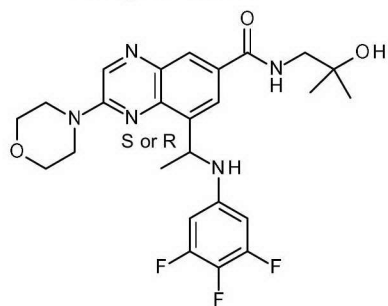
Preparation of compound 292, compound 292a and compound 292b



compound 292



compound 292a

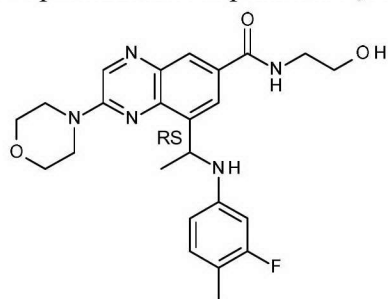


compound 292b

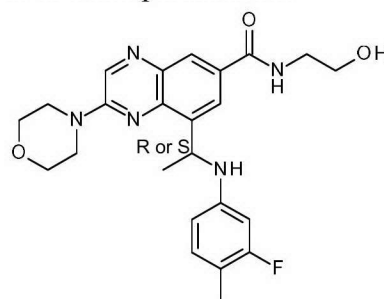
Compound 292 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 170 and 1-amino-2-methylpropan-2-ol as starting materials (650 mg, 93%, MP : 80°C, gum, K).

Compound 292 (650 mg) was purified by chiral SFC (CHIRALCEL OJ-H 5  $\mu$ m 250x20 mm; mobile phase: 80% CO<sub>2</sub>, 20% MeOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 310 mg of one compound which was crystallized from pentane and Et<sub>2</sub>O giving 186mg (27%) of compound 292a (MP : 110°C, gum, K) and 305 mg of other compound which was crystallized from pentane and Et<sub>2</sub>O giving 190mg (27%) of compound 292b (MP : 110°C, gum, K).

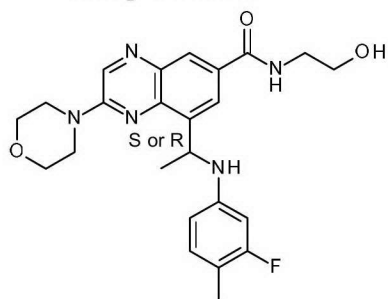
Preparation of compound 295, compound 295a and compound 295b:



compound 295



compound 295a



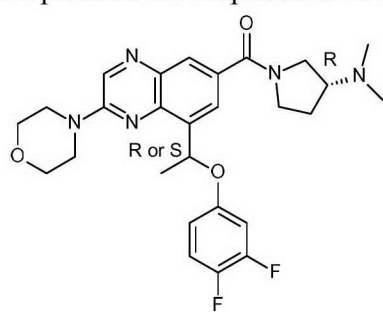
compound 295b

Compound 295 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 294 and ethanolamine as starting materials (700 mg, 79%, MP : 80°C, gum, (K)).

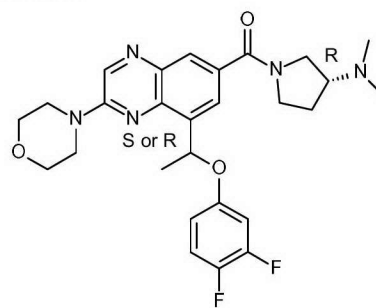
Compound 295 was purified by chiral SFC (CHIRALPAK IC-H 5  $\mu$ m 250x30 mm; mobile phase: 60% CO<sub>2</sub>, 40% iPrOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 276 mg of one compound which was crystallized from pentane giving 244mg (28%) of compound 295a(MP : 120°C, gum, K) and 291 mg of other compound which was crystallized from pentane giving 225mg (25%) of compound 295b(MP : 120°C, gum, K).



## Preparation of compound 298a and compound 298b



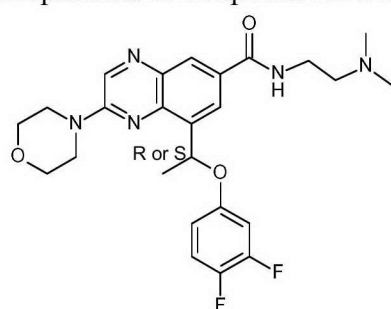
compound 298a



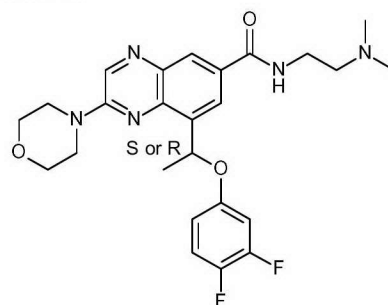
compound 298b

Compound 298a and compound 298b were prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 285 and (R)-  
 5 (+)-3-(Dimethylamino)pyrrolidine as starting materials. The separation of the enantiomers from 360 mg of racemic compound was performed by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x30 mm; mobile phase: 60% CO<sub>2</sub>, 40% EtOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give one compound which was crystallized from pentane and Et<sub>2</sub>O giving 74mg (20%) of  
 10 compound 298a (MP : 100°C, gum, K) and the other compound which was crystallized from pentane and Et<sub>2</sub>O giving 45mg (12%) of compound 298b (MP : 100°C, gum, K).

## Preparation of compound 299a and compound 299b



compound 299a

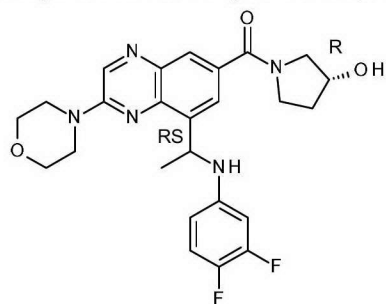


compound 299b

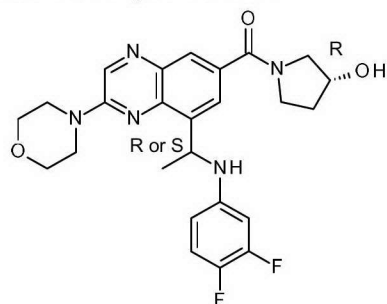
Compound 299a and compound 299b were prepared according to an analogous  
 15 procedure as described for the synthesis of compound 5 using compound 285 and N,N-dimethylethylenediamine as starting materials. The separation of the enantiomers from 440 mg of racemic compound was performed by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x20 mm; mobile phase: 78% CO<sub>2</sub>, 22% EtOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give one compound which  
 20 was crystallized from DCM and Et<sub>2</sub>O giving 98mg (17%) of compound 299a (MP :

100°C, gum, K) and the other compound which was crystallized from DCM and Et<sub>2</sub>O giving 86mg (15%) of compound 299b(MP : 100°C, gum, K).

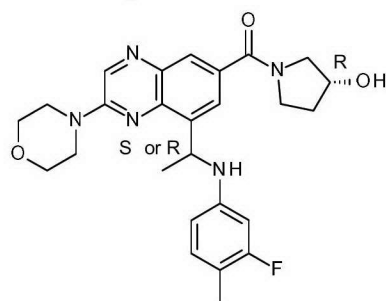
Preparation of compound 300, compound 300a and compound 300b



compound 300



compound 300a



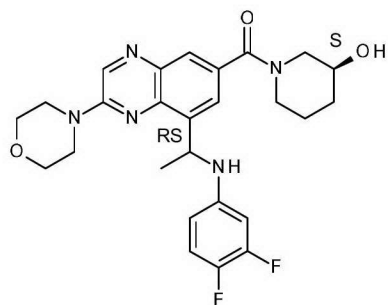
compound 300b

5

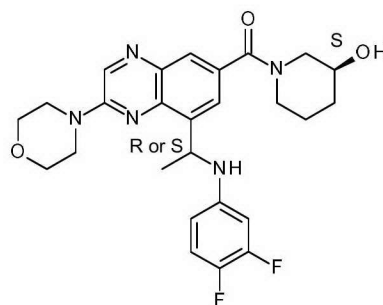
Compound 300 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 234 and (R)-(-)-3-pyrrolidinol as starting materials. (723 mg, 88%).

Compound 300 was purified by chiral SFC (CHIRALPAK DIACEL AD 250x30 mm; mobile phase: CO<sub>2</sub>, iPrOH(0.4% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give one compound which was crystallized from Et<sub>2</sub>O giving 152mg (19%) of compound 300a (MP : 140°C, K) and another compound which was crystallized from Et<sub>2</sub>O giving 130mg (16%) of compound 300b (MP : 135°C, K).

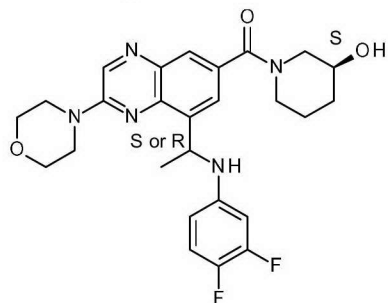
15 Preparation of compound 302, compound 302a and compound 302b



compound 302



compound 302a

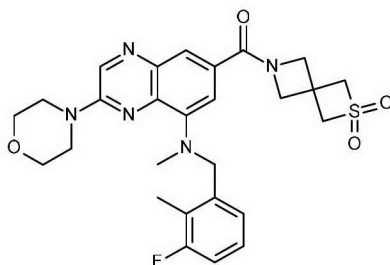


compound 302b

Compound 302 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 234 and (S)-3-hydroxypiperidine hydrochloride as starting materials. (637 mg, 100%, MP :80°C, K).

Compound 302 was purified by chiral SFC (CHIRALPAK AS-H 5 $\mu$ m 250x20 mm; mobile phase: 65%CO<sub>2</sub>, 35%EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 376 mg of one compound which was crystallized from pentane giving 90mg (15%) of compound 302a (MP : 135°C, K) and 245 mg of another compound which was crystallized from pentane giving 245mg (41%) of compound 302b (MP : 135°C, K).

10

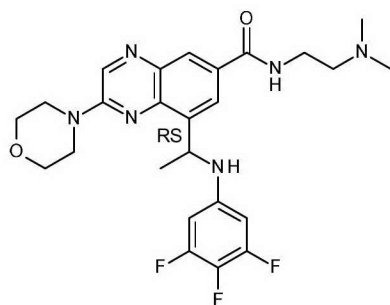


Preparation of compound 308:

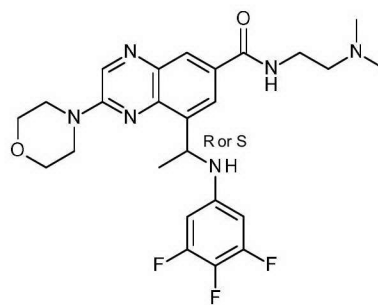
Compound 308 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 307 and 2-Thia-6-azaspiro[3.3]heptane, 2,2-dioxide as starting materials (156mg, 59%, MP : 195°C, DSC).

15

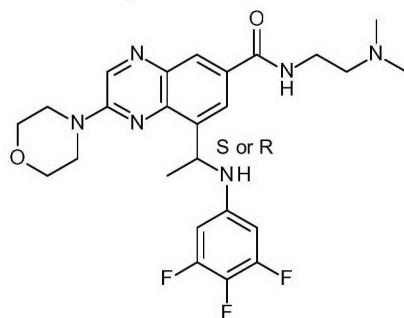
Preparation of compound 309, compound 309a and compound 309b



compound 309



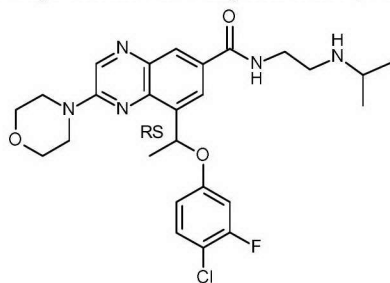
compound 309a



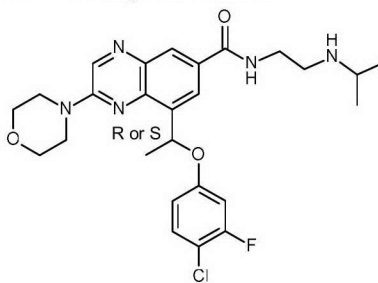
compound 309b

Compound 309 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 170 and *N,N*-dimethylethylenediamine as starting materials (610 mg, 100%). Compound 309 was purified by chiral SFC (CHIRALPAK AD-H 5 $\mu$ m 250x30 mm; mobile phase: 70%CO<sub>2</sub>, 30%EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 208 mg of one compound which was crystallized from Et<sub>2</sub>O giving 192mg (33%) of compound 309a and 192 mg of another compound which was crystallized from pentane giving 192mg (33%) of compound 309b.

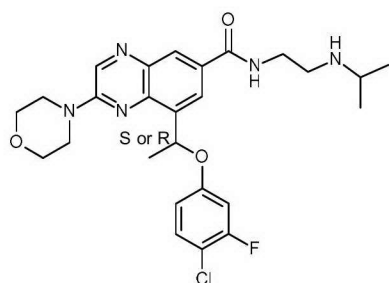
#### 10 Preparation of compound 312, compound 312a and compound 312b



compound 312



compound 312a



compound 312b

To a solution of compound 311 (150 mg; 0.347 mmol), N-diisopropylethylenediamine (52.6  $\mu$ L; 0.417 mmol) and DIPEA (120  $\mu$ L; 0.695 mmol) in DMF (3 mL) was added COMU (223 mg; 0.521 mmol). The solution was stirred at rt for 18h then combined with another reaction performed on 50 mg of compound 311. Water and EtOAc were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with a saturated aqueous solution of NaCl (3x), dried over  $\text{MgSO}_4$ , filtered off and evaporated in vacuo.

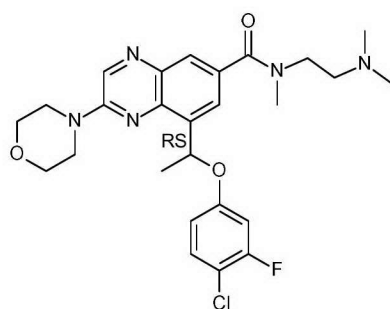
The crude (438 mg) was purified by silica gel chromatography (Stationary phase: irregular bare silica 40g, Mobile phase: 0.5% aq.  $\text{NH}_3$ , 94% DCM, 6% MeOH) to give 149 mg of compound 312 as a yellow oil.

Compound 312 was purified by chiral SFC (Stationary phase: CHIRALPAK AD-H  $5\mu\text{m}$  250x20mm, Mobile phase: 65%  $\text{CO}_2$ , 35% iPOH(0.3% iPr $\text{NH}_2$ )) to give 55 mg of impure compound 312a as a yellow oil and 58 mg of impure compound 312b as a yellow oil.

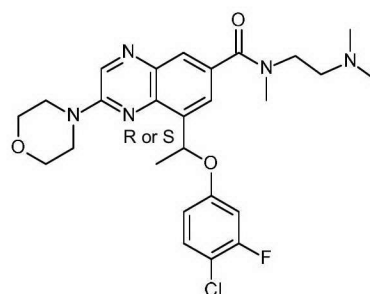
Impure compound 312a was purified by silica gel chromatography (Irregular SiOH 15-40  $\mu\text{m}$ , 4 g Grace, mobile phase gradient: from DCM 100% to DCM 95%, MeOH/aq  $\text{NH}_3$  (95:5) 5%) to give 49 mg of a yellow oil which were solubilized in ACN (1 mL), extended with water (9 mL) and freeze-dried to give 46 mg of compound 312a as a pale yellow fluffy solid.

Impure compound 312b was purified by silica gel chromatography (Irregular SiOH 15-40  $\mu\text{m}$ , 4 g Grace, mobile phase gradient: from DCM 100% to DCM 95%, MeOH/aq  $\text{NH}_3$  (95:5) 5%) to give 47 mg of a yellow oil which were solubilized in ACN (1 mL), extended with water (9 mL) and freeze-dried to give 45 mg of compound 312b as a pale yellow fluffy solid.

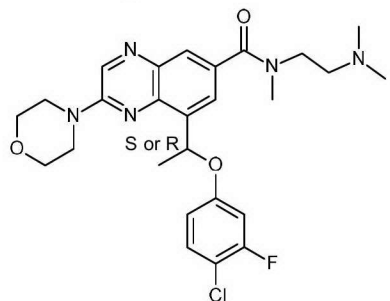
Preparation of of compound 313, compound 313a and compound 313b



compound 313



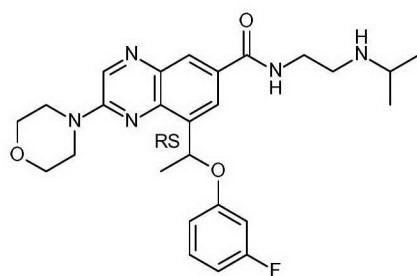
compound 313a



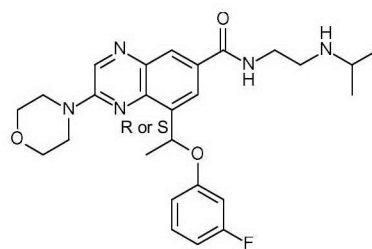
compound 313b

Compound 313 was prepared according to an analogous procedure as described for the synthesis of compound 312 using compound 311 and *N,N,N'*-trimethylethylenediamine as starting materials (197 mg). Compound 313 was purified by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x20 mm; mobile phase: 80% CO<sub>2</sub>, 20% EtOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and each enantiomer was again purified by silica gel chromatography. The fractions containing the products were mixed and the solvent was evaporated to give one compound (44mg) which was freeze-dried from pentane and H<sub>2</sub>O giving 42mg (23%) of compound 313a and the other compound (43 mg) which was freeze-dried from pentane and H<sub>2</sub>O giving 42mg (23%) of compound 313b.

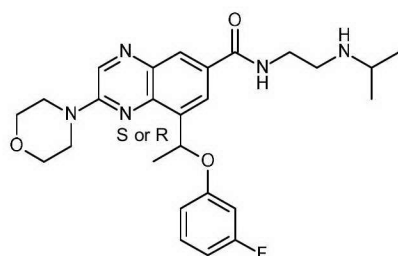
#### Preparation of compound 314 compound 314a and compound 314b



compound 314



compound 314a

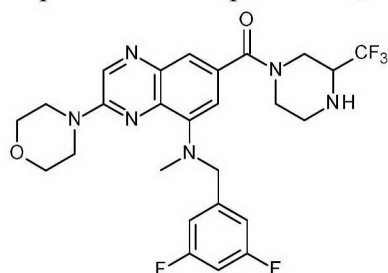


compound 314b

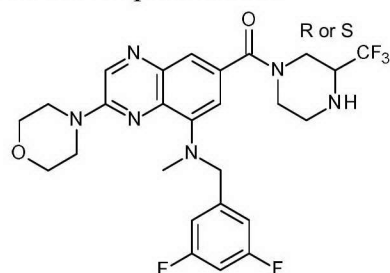
Compound 314 were prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 257a and *N*-isopropylethylenediamine as starting materials giving 250 mg (57%) of compound 314, which was purified by chiral SFC (CHIRALPAK DIACEL AD 250x20 mm; mobile phase: CO<sub>2</sub>, EtOH-*i*PrOH 50/50(0.4% *i*PrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 113 mg of one compound which was freeze-dried with pentane and H<sub>2</sub>O giving 86mg (20%) of compound 314a (MP : 80°C, gum, K) and 99 mg of other compound which was freeze-dried with pentane and H<sub>2</sub>O giving 79mg (18%) of compound 414b (MP : 80°C, gum, K).

10

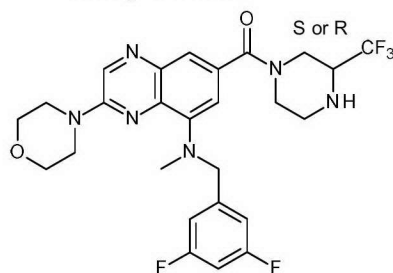
Preparation of compound 319, compound 319a and compound 319b



compound 319



compound 319a



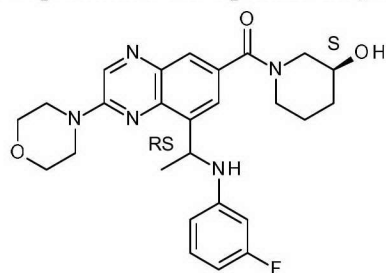
compound 319b

Compound 319 was prepared and compound 78IPIL were prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 291 and (±)-2-(Trifluoromethyl)piperazine as starting materials (517 mg; 97%).

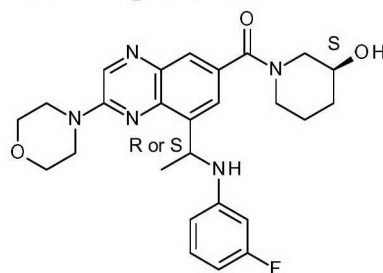
15

Compound 319 was separated by chiral SFC (CHIRALPAK AS-H 5  $\mu$ m 250x20 mm; mobile phase: 80% CO<sub>2</sub>, 20% EtOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give one compound (186mg) which was freeze-dried with pentane and H<sub>2</sub>O giving 182mg (34%) of compound 319a and second compound (184 mg) which was freeze-dried with pentane and H<sub>2</sub>O giving 166mg (31%) of compound 319b .

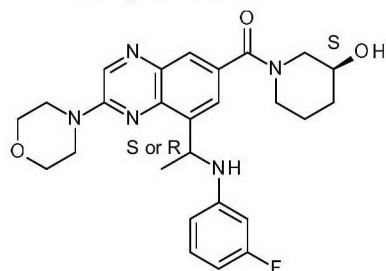
Preparation of compound 320, compound 320a and compound 320b



compound 320



compound 320a



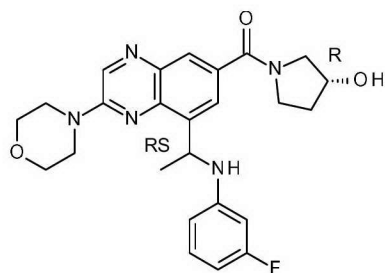
compound 320b

Compound 320 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 263 and (S)-3-hydroxypiperidine hydrochloride as starting materials (800 mg; 94%).

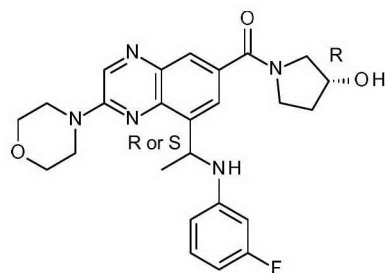
The separation of the enantiomers from 800 mg of compound 320 was performed by chiral SFC (CHIRALCEL OJ-H 5  $\mu$ m 250x20 mm; mobile phase: 82% CO<sub>2</sub>, 18% EtOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give one compound (354mg) which was crystallized from DCM and pentane giving 248mg (29%) of compound 320a (MP : 110°C, K) and a second compound (407 mg) which was crystallized from DCM and pentane giving 300mg (35%) of compound 320b (MP : 136°C, K).

Preparation of compound 321, compound 321a and compound 321b:

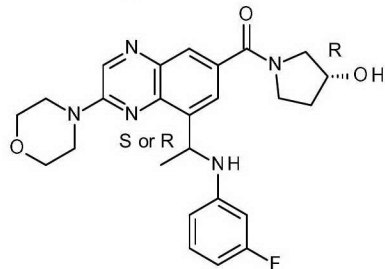




compound 321



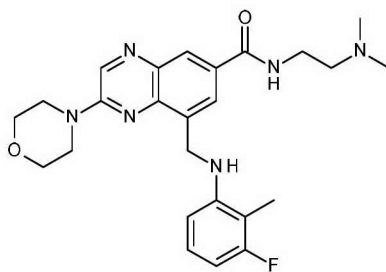
compound 321a



compound 321b

Compound 321 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 263 and (R)-(+)-3-hydroxypyrrolidine as starting materials (700; 85%).

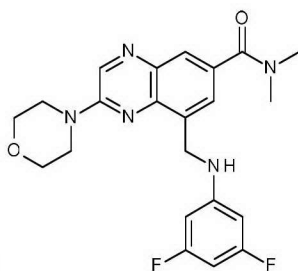
The separation of the enantiomers from 700 mg of compound 321 was made by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x30 mm; mobile phase: 70% CO<sub>2</sub>, 30% iPrOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give one compound (337mg) which was crystallized from DCM and pentane giving 262mg (32%) of compound 321a (MP : 118°C, K) and a second compound (367 mg) which was crystallized from DCM and pentane giving 265mg (32%) of compound 321b (MP : 128°C, K).



Preparation of compound 328:

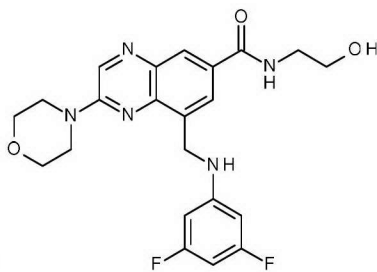
To a solution of compound 327 (200 mg; 0.505 mmol), *N,N*-dimethylethylenediamine (83  $\mu$ L; 0.76 mmol) and diisopropylethyl amine (174  $\mu$ L; 1.01 mmol) in DMF (5 mL) was added COMU (324 mg; 0.757 mmol). The solution was stirred at room temperature for 1h. Then, water and EtOAc were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic

- layers were washed with a saturated aqueous solution of NaCl (3x), dried over MgSO<sub>4</sub>, filtered off and evaporated in vacuo. The residue (brown oil) was purified by silica gel chromatography (Irregular SiOH 15-40 μm, 24g, mobile phase gradient: from DCM 100% to DCM 90%, MeOH/aq NH<sub>3</sub> (95:5) 10%) to give 252 mg of a yellow oil. This fraction was further purified by silica gel chromatography (Irregular SiOH 15-40 μm, 10 g, liquid loading (DCM), mobile phase gradient: from heptane 70%, EtOAc/(MeOH/aq. NH<sub>3</sub> (95:5)) (80:20) 30% to heptane 30%, EtOAc/(MeOH/aq. NH<sub>3</sub> (95:5)) (80:20) 70%) to give 206 mg of a yellow film which was again further purified by silica gel chromatography (Irregular SiOH, 15-40 μm, 10 g, dry loading, mobile phase: heptane 80%, EtOAc/(MeOH/aq. NH<sub>3</sub> (95:5)) (80:20) 20%) to give 138 mg of a yellow film. This fraction was triturated in Et<sub>2</sub>O. The solvent was evaporated in vacuo and the precipitate dried under high vacuum (50 °C, 18h) to give 136 mg (58%) of compound 328 as a yellow solid (MP : 98°C, DSC).



15 Preparation of compound 332

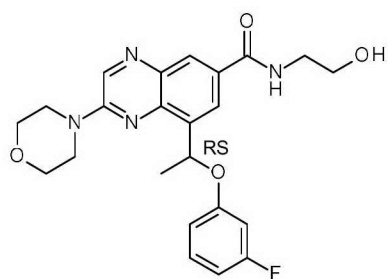
Compound 332 was prepared according to an analogous procedure as described for the synthesis of compound 312 using compound 331 and dimethylamine (solution 2M in THF) as starting materials (96 mg, 50%, MP : 169°C, DSC).



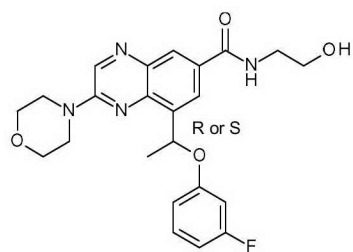
20 Preparation of compound 333

Compound 333 was prepared according to an analogous procedure as described for the synthesis of compound 312 using compound 331 and ethanolamine as starting materials (80 mg, 68%, MP : 265°C, DSC).

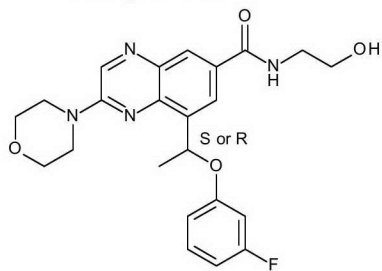
25 Preparation of compound 334, compound 334a and compound 334b



compound 334



compound 334a

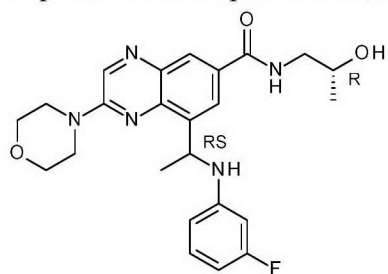


compound 334b

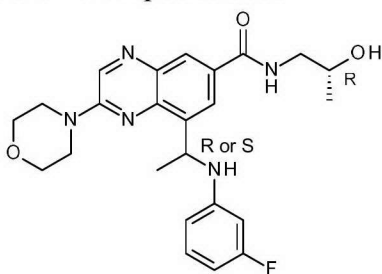
Compound 334 prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 257a and 2-aminoethanol as starting material. The residue (280 mg) was purified by chromatography over silica (irregular SiOH; 15-40  $\mu\text{m}$ ; 30 g; gradient: from 95% DCM, 5% MeOH to 93% DCM, 7% MeOH). The pure fractions were collected and the solvent was evaporated to give 150mg (54%) of compound 334.

The separation of the enantiomers from 150mg of compound 334 was performed by chiral SFC (CHIRALCEL OD-H 5  $\mu\text{m}$  250x20 mm; mobile phase: 70%  $\text{CO}_2$ , 30%  $\text{uPrOH}$ ). The pure fractions were collected and the solvent was evaporated to give two fractions which were crystallized from  $\text{Et}_2\text{O}$  to give respectively 70 mg (16%) of compound 334a (M.P.: 136°C, DSC) and 71 mg (11%) of compound 334b (M.P.: 134°C, DSC).

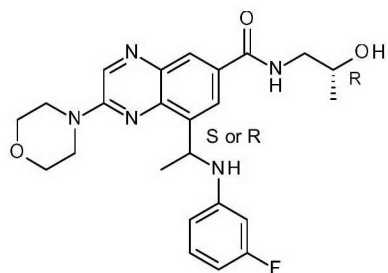
#### 15 Preparation of compound 338, compound 338a and compound 338b



compound 338

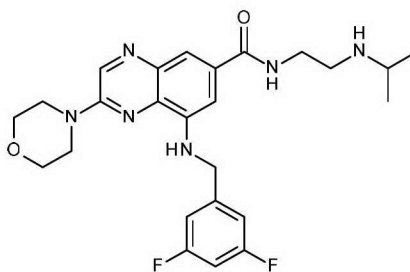


compound 338a



compound 338b

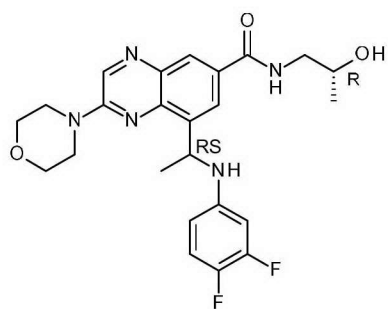
- Compound 338 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 263 and (2R)-(-)-1-Aminopropan-2-ol as starting material (Crystallization from DIPE; 360 mg, 72%). The separation of the enantiomers from 309 mg of compound 338 was performed by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m; 250x20 mm; mobile phase: 75% CO<sub>2</sub>, 25% EtOH). The pure fractions were collected and the solvent was evaporated. and each fraction was crystallized from DIPE to afford 112 mg (22%), of compound 338a (M.P.: 90°C (DSC)) and 108 mg (21%) of compound 338b (M.P.: 91°C (DSC))



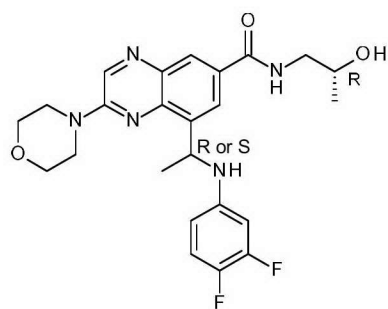
- 10 Preparation of compound 342:

A solution of compound 289 (100 mg, 0.25 mmol), HATU (142.45 mg, 0.375 mmol) and Et<sub>3</sub>N 0.104 mL, 0.749 mmol) in Me-THF (5mL) was stirred at rt for 15min. Then, *N*-isopropylethylenediamine (47.26  $\mu$ L, 0.375 mmol) was added and the solution was stirred at rt for 5h. The reaction mixture was poured in ice water and extracted with EtOAc. The organic layer was washed with brine (X2), dried over MgSO<sub>4</sub>, filtered and evaporated until dryness. The resulting residue was purified via silica gel chromatography (Stationary phase: irregular SiOH 15-40 $\mu$ m, 40g, Mobile phase: 95% DCM, 5% MeOH, 0.5% NH<sub>4</sub>OH) to afford 75 mg (62%) of compound 342.

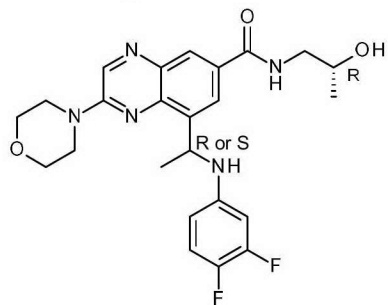
- 20 Preparation of compound 346, compound 346a , and compound 346b



compound 346



compound 346a

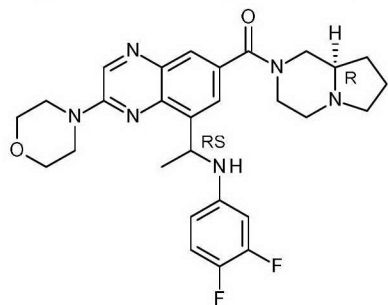


compound 346b

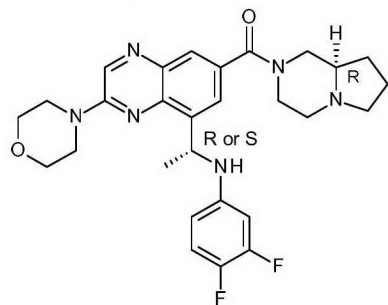
Compound 346 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 234 and (2R)-(-)-1-aminopropan-2-ol as starting material (460 mg; 81%).

- 5 The separation of the enantiomers from 460mg of compound 346 was performed via chiral SFC (Stationary phase: CHIRALPAK IC 5 $\mu$ m 250x20mm, Mobile phase: 83% CO<sub>2</sub>, 17% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and evaporated until dryness and crystallized from pentane to give 115 mg (20%) of compound 346a (M.P.: 107°C (K)) and 107 mg (19%) of compound 26 (M.P.: 106°C (K)).

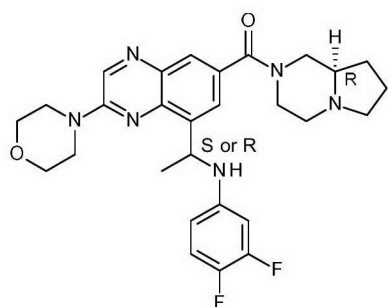
10 Preparation of compound 347, compound 347a and compound 347b



compound 347



compound 347a



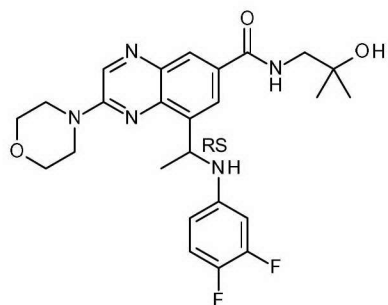
compound 347b

Compound 347 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 234 and (R)-1,4-diazabicyclo[4.3.0] nonane as starting material. (1g; 79%; M.P.: 170°C (DSC)).

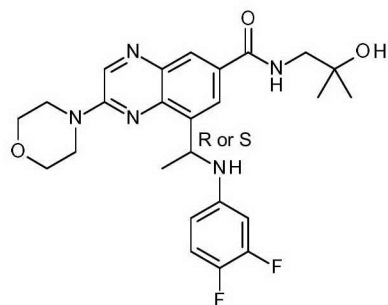
The separation of the enantiomers from 950 mg of compound 347 was performed via  
 5 chiral SFC (Stationary phase: Chiralpak AS-H 5 $\mu$ m 250\*20mm, Mobile phase: 50% CO<sub>2</sub>, 50% MeOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and evaporated until dryness and crystallized from a mixture of pentane/DCM (19/1) to give 400 mg (32%) of compound 347a (M.P.: 125°C (K)) and 317mg (30%) of compound 347b (M.P.: 125°C (K)).

10

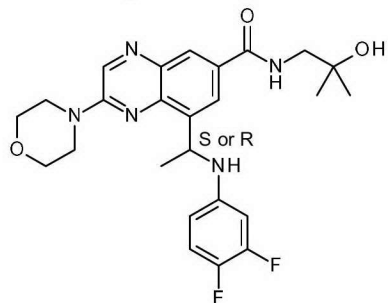
Preparation of compound 348, compound 348a and compound 348b



compound 348



compound 348a

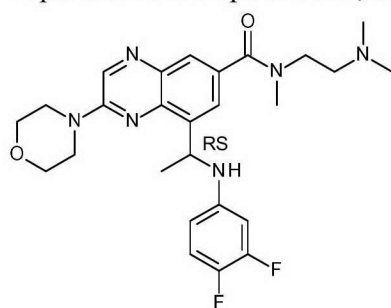


compound 348b

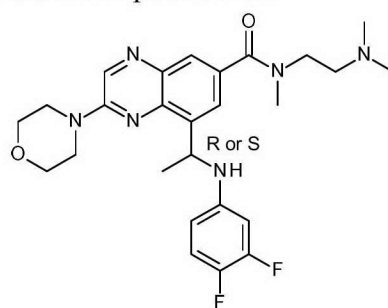
Compound 348 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 234 and 1-amino-2-methyl-2-propanol as starting materials (540 mg; 92%).

- 5 The separation of the enantiomers from 540 mg of compound 348 was performed via SFC (Stationary phase: CHIRALCEL OJ-H 5 $\mu$ m 250x20mm, Mobile phase: 86% CO<sub>2</sub>, 14% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and evaporated until dryness and crystallized from pentane to give 157mg (27) of compound 348a (M.P.: 102°C (K)) and 173mg (30%) of compound 348b (M.P.: 102°C (K)).

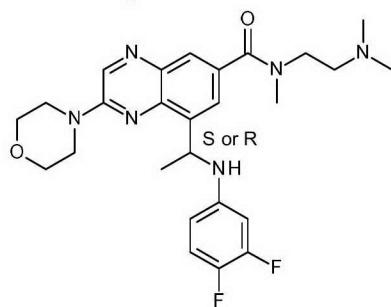
- 10 Preparation of compound 349, compound 349a and compound 349b



compound 349



compound 349a

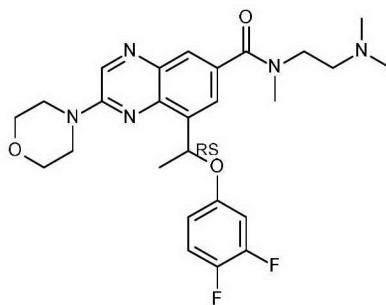


compound 349b

Compound 349 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 234 and *N,N,N'*-Trimethylenediamine as starting materials (480 mg; 80%).

- 15 The separation of the enantiomers from 480 mg of compound 349 was performed via chiral SFC (Stationary phase: CHIRALPAK AD-H 5 $\mu$ m 250x20mm, Mobile phase: 83% CO<sub>2</sub>, 17% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and evaporated until dryness and crystallized from pentane to give 131 mg (22%) of compound 349a (M.P.: 82°C (K)) and 131 mg (22%) of compound 349b (M.P.: 82°C (K)).

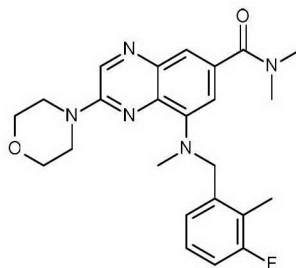
310



Preparation of compound 353:

Compound 353 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 285 and *N,N,N'*-trimethylethylene diamine as starting material (350mg, 58%, 80°C, (K)).

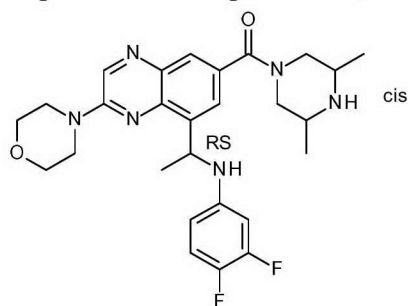
5



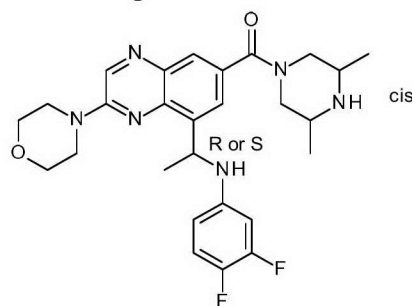
Preparation of compound 354:

Compound 354 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 307 as starting material (72 mg, 41%).

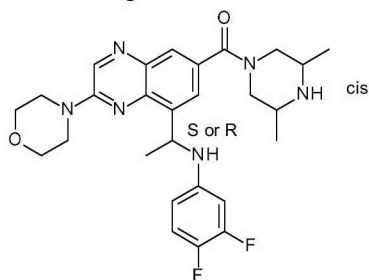
# 10 Preparation of compound 357, compound 357a and compound 357b



compound 357



compound 357a



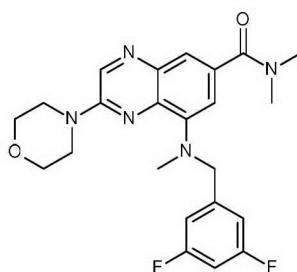
compound 357b



Compound 357 prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 234 and cis 2,6-dimethylpiperazine as starting materials (570 mg; 92%).

5 The separation of the enantiomers from 570 mg of compound 357 was performed via SFC (Chiralpak AS-H 5 $\mu$ m 250\*20mm, Mobile phase: 45% CO<sub>2</sub>, 55% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated. Each fraction was crystallized from pentane to give, after filtration, 191mg (31%) of compound 43 (M.P.: 116°C (K)) and 170 mg (38%) of compound 44 b (M.P.: 120°C (K))

10

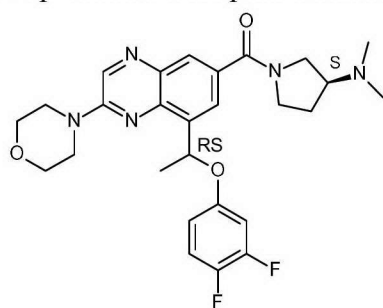


Preparation of compound 358:

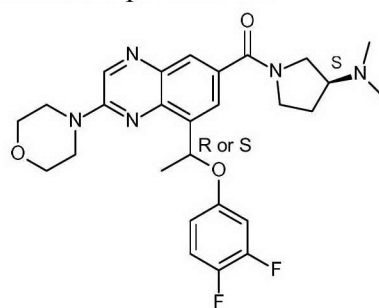
Compound 358 was prepared according to an analogous procedure as described for the preparation of compound 5, using compound 291 and dimethylamine as starting materials (126mg of 60%).

15

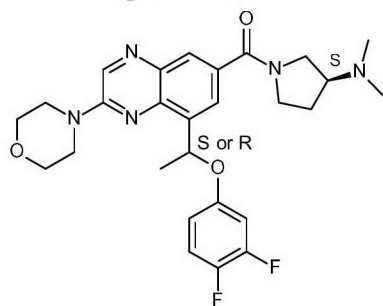
Preparation of compound 363 compound 363a and compound 363b



compound 363



compound 363a

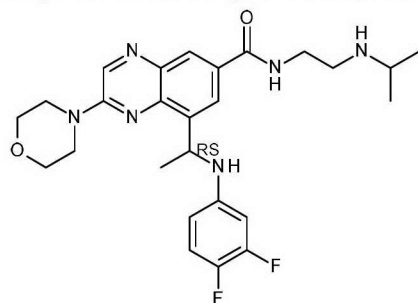


compound 363b

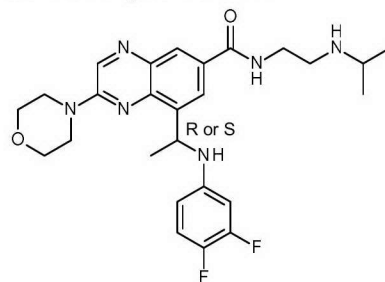
Compound 363 was prepared according to an analogous procedure as described for the synthesis of compound 5 starting from compound 285 and (S)-(+)-3-(dimethylamino)pyrrolidine

- 5 The separation of the enantiomers was performed by SFC (Stationary phase: Chiralpak Diacel AD 20 x 250 mm, Mobile phase: CO<sub>2</sub>, iPrOH + 0.4 iPrNH<sub>2</sub>). The pure fractions were mixed and concentrated to afford 20 mg (5%) of compound 363a (M.P.: 80°C, gum K) and 70mg (19%) of compound 363b (M.P.: 80°C, gum K)

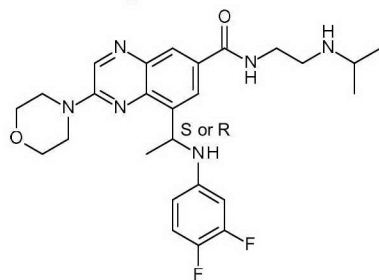
Preparation of compound 364, compound 364a and compound 364b



compound 364



compound 364a

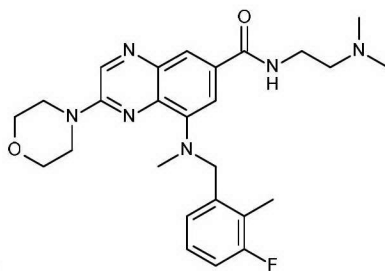


compound 364b

- 10 Compound 364 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 234 and *N*-isopropylethylenediamine as starting materials (280 mg, 58%, M.P.: 80°C gum (K)).

- The separation of the enantiomers was performed by chiral SFC (CHIRALPAK AD-H 5 μm; 250x20 mm; mobile phase: 60% CO<sub>2</sub>, 40% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated. Each fraction was crystallized from a mixture of DCM/Et<sub>2</sub>O and gave, after filtration, 90 mg (18%) of compound 364a (M.P.: 80°C, gum (K)) and 89mg (18%) of compound 364b (M.P.: 80°C, gum (K)).
- 15

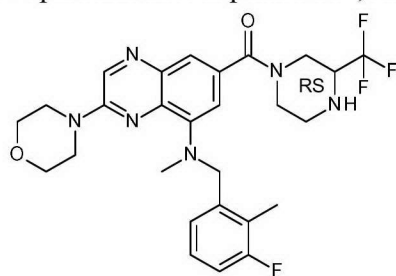
313



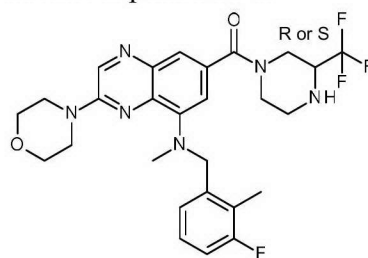
Preparation of compound 366:

Compound 366 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 307 as starting material (154 mg, 66%).

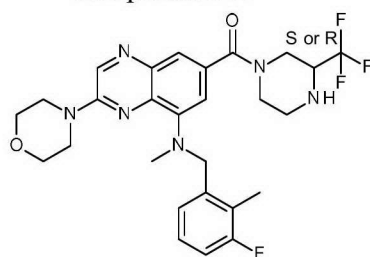
5 Preparation of compound 367, compound 367a and compound 367b



compound 367



compound 367a

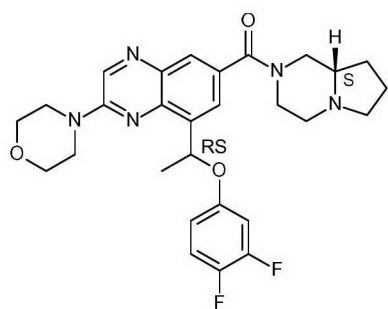


compound 367b

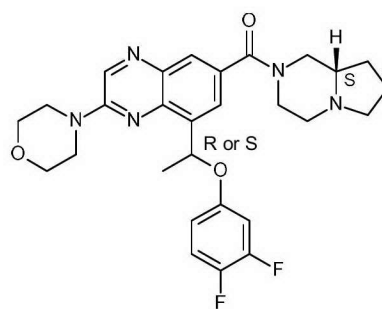
Compound 367 was prepared according to an analogous procedure as described for the synthesis of compound 5 using compound 307 and (+/-)-2-(Trifluoromethyl)piperazine as starting material (453 mg, 85%).

- 10 The separation of the enantiomers from 453 mg of compound 367 was performed chiral SFC (CHIRALPAK AD-H 5  $\mu$ m; 250x30 mm; mobile phase: 70% CO<sub>2</sub>, 30% EtOH(0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and each fraction was crystallized from a mixture of Pentane/Et<sub>2</sub>O to give, after filtration, 119 mg (22%) of compound 367a and 127 mg (24%) of compound 367b.

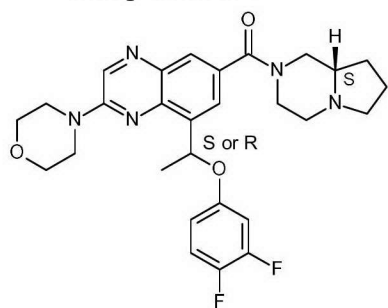
15 Preparation of compound 369, compound 369a and compound 369b



compound 369



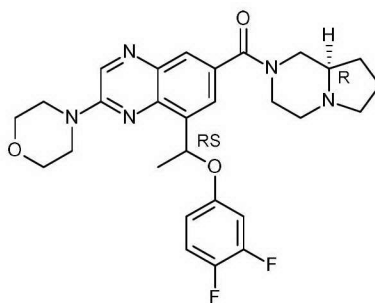
compound 369a



compound 369b

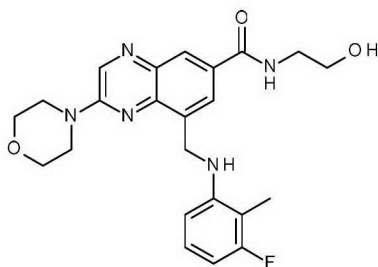
Compound 369 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 285 and (6S)-1,4-diazabicyclo[4.3.0]nonane as starting materials (800 mg; 96%).

- The separation of the enantiomers was performed by chiral SFC (Stationary phase: Chiralpak Diacel AD 20 x 250 mm, Mobile phase: CO<sub>2</sub>, EtOH + 0.4 iPrNH<sub>2</sub>). The pure fractions were mixed and concentrated to afford fraction A (470 mg) and fraction B (450 mg). Fraction A was taken up with a mixture of Et<sub>2</sub>O/pentane. The precipitate was filtered to afford 180mg (22%) of compound 369a (22%). Fraction B was taken up with a mixture of DCM/pentane. The precipitate was filtered to afford 140mg (17%) of compound 369b (M.P.: 147°C, (DSC K)).



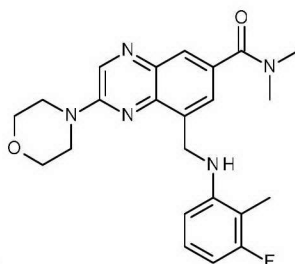
Preparation of compound 375:

- Compound 375 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 285 and (R)-1,4-Diazabicyclo[4.3.0]nonane as starting materials (250mg, 20%, M.P: 80° Gum (K)).



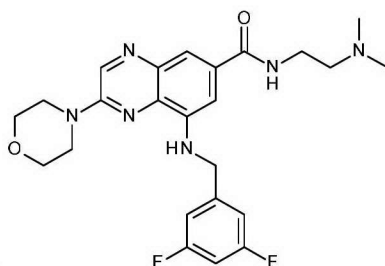
Preparation of compound 381:

Compound 381 was prepared according to an analogous procedure as described for the synthesis of compound 312 using compound 327 and 2-aminoethanol as starting materials. (162mg, 73%).



Preparation of compound 382:

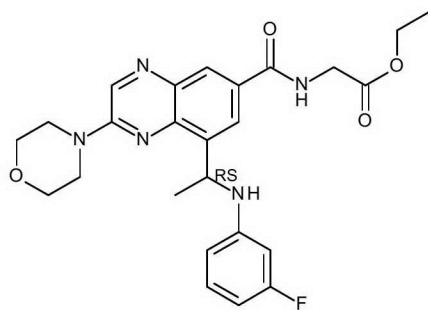
Compound 382 was prepared according to an analogous procedure as described for the synthesis of compound 312 broux using compound 327 and dimethyl amine (2M solution in THF) as starting materials (136mg, 64%, M.P: 150 °C(DSC)).



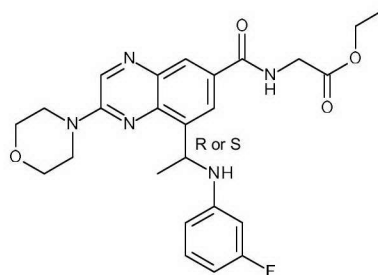
Preparation of compound 384:

Compound 384 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 289 and *N,N*-dimethylethylenediamine as starting materials (66mg, 19%).

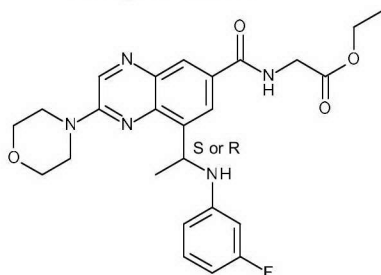
Preparation of compound 392, compound 392a and compound 392b



compound 392



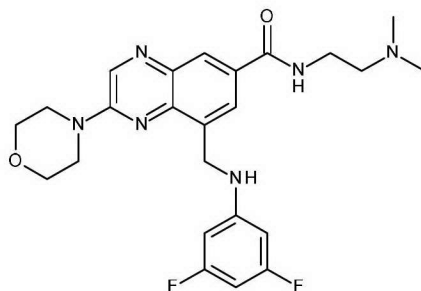
compound 392a



compound 392b

Compound 392 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 263 and glycine ethyl ester hydrochloride as starting materials (727mg, 66%).

- 5 The separation of the enantiomers was performed by chiral SFC (Stationary phase: Chiralpak AD-H 5 $\mu$ m 250\*30mm, Mobile phase: 60% CO<sub>2</sub>, 40% EtOH(0.3% iPrNH<sub>2</sub>)). The fractions containing the products were concentrated to afford, after freeze-drying in a mixture of ACN/water (20/80), 220 mg (20%) of compound 392a (MP: 80°C, gum, Kofler) and 215 mg (20%) of compound 392b.

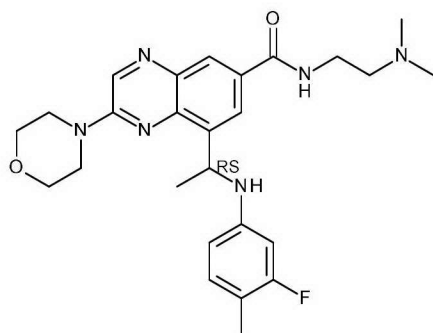


- 10 Preparation of compound 394:

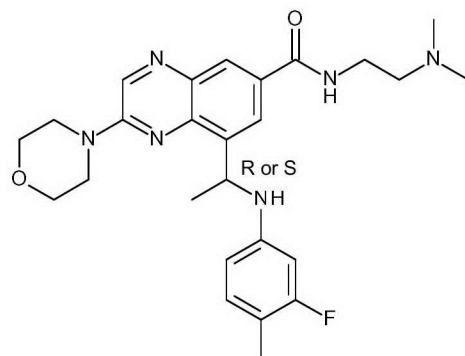
Compound 394 was prepared according to an analogous procedure as described for the synthesis of compound 312, using compound 331 and N,N-dimethylethylenediamine as starting materials (86mg, MP: 161°C (DSC)).

15

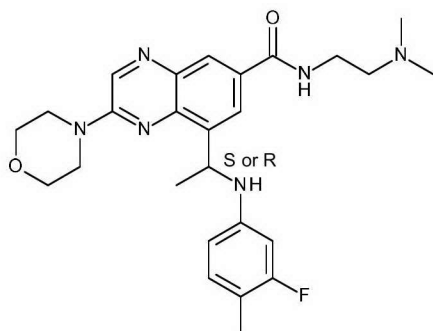
Preparation of compound 407, compound 407a, compound 407b



compound 407



compound 407a

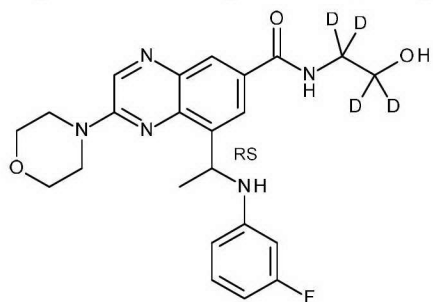


compound 407b

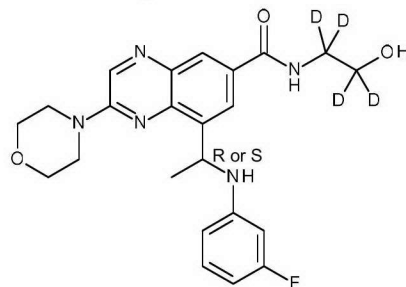
Compound 407 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 294 and N,N-dimethylethylenediamine as starting materials (588mg, 85%).

- The separation of the enantiomers was performed by chiral SFC (Stationary phase: 5 CHIRALPAK AD-H 5 $\mu$ m 250x20mm, Mobile phase: 60% CO<sub>2</sub>, 40% EtOH(0.3% iPrNH<sub>2</sub>)). The fractions containing the products were concentrated to afford, after freeze-drying in a mixture of ACN/water (20/80), 232 mg (34%) of compound 407a (MP: 115°C, Kofler) and 170 mg (25%) of compound 407b (MP: 105°C, Kofler).

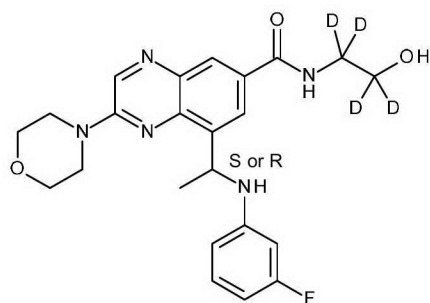
#### 10 Preparation of compound 408, compound 408a and compound 408b



compound 408



compound 408a

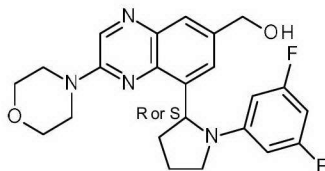


compound 408b

Compound 408 was prepared according to an analogous procedure as described for the synthesis of compound 5, using compound 263 and ethanol-1,1,2,2-d<sub>4</sub>-amine as starting materials (400mg, 71%).

- The separation of the enantiomers was performed by chiral SFC (Stationary phase: CHIRALPAK IC 5 $\mu$ m 250x30mm, Mobile phase: 55% CO<sub>2</sub>, 45% iPOH(0.3% iPrNH<sub>2</sub>)). The fractions containing the products were concentrated to afford, after crystallization from EtOH, 161 mg (28%) of compound 408a (MP: 127°C, DSC) and 131 mg (22%) of compound 408b (MP: 123°C, DSC).

#### 10 Conversion C2

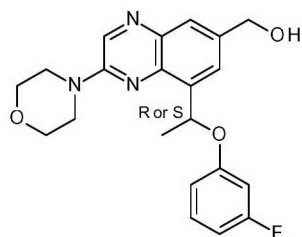


Preparation compound 10:

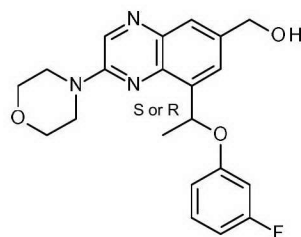
- Diisobutylaluminium hydride (solution 20% in toluene) (15.8 mL; 3.79 mmol) was added dropwise to a solution of compound 249 (860 mg; 1.89 mmol) in THF (50 mL) at -70°C under N<sub>2</sub>. The mixture was stirred at -70°C for 1h30. The solution was poured into ice-water. EtOAc was added and the mixture was filtered through a pad of celite<sup>®</sup>. The product was extracted with EtOAc. Then, the organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (820 mg) was purified by chromatography over silica gel (irregular bare silica 40 g; mobile phase: 97% DCM, 3% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated to give 594 mg which was recrystallized with diethylether. The precipitate was filtered and dried to give 425 mg (52%) of compound 10. M.P.: 189°C (DSC).

Preparation compound 88 and compound 89





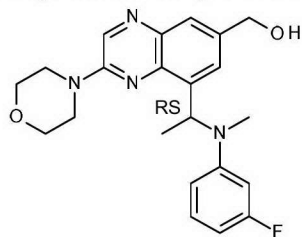
compound 88



compound 89

Compound 88 and compound 89 were prepared according to an analogous procedure as described for the synthesis of compound 10, using compound 257a as starting materials. After purification by chromatography over silica gel (irregular SiOH; 15-40  $\mu$ m; 30 g; gradient: from 65% heptane, 31.5% EtOAc, 3.5% MeOH to 30% heptane, 63% EtOAc, 7% MeOH), the resulting residue (409 mg, pale yellow foam) was purified by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x20 mm; mobile phase: 75% CO<sub>2</sub>, 25% MeOH). The pure fractions were collected and the solvent was evaporated to give two fractions which were separately co-evaporated in DCM (x2) and dried under reduced pressure (16h, 50°C) to give respectively 144 mg (28%, pale yellow foam) of compound 88 and 160 mg (30%, pale yellow foam) of compound 89.

## Preparation compound 111



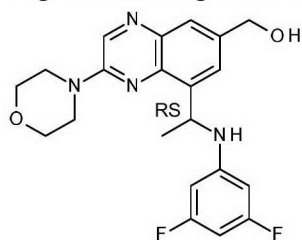
compound 111

Diisobutylaluminium hydride (solution 20% in toluene) (1.96 mL; 0.47 mmol) was added dropwise to a solution of compound 97 (100 mg; 0.24 mmol) in THF (7 mL) at -70°C under N<sub>2</sub>. The mixture was stirred at -70°C for 2h. The solution was poured into ice-water. EtOAc was added and the mixture was filtered through a pad of celite®. The product was extracted with EtOAc. Then the organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (100 mg) was purified by chromatography over silica gel (irregular bare silica 10 g; mobile phase: 97% DCM, 3% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated. The residue (59 mg; impure compound 111) was taken-up with DCM. Oxygen was bubbled in the solution for 30min and the solution was stirred at rt overnight. Then, the solution was evaporated to dryness. The residue (54 mg) was

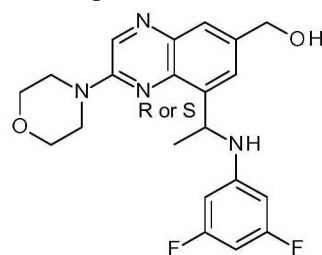
purified by reverse phase (X-Bridge-C18 5  $\mu$ m; 30\*150 mm; gradient: from 65%  $\text{NH}_4\text{HCO}_3$  0.5%, 35% ACN to 25%  $\text{NH}_4\text{HCO}_3$  0.5%, 75% ACN). The pure fractions were collected and the solvent was evaporated to give 30 mg (32%) of compound 111. M.P.: 80°C (K).

5

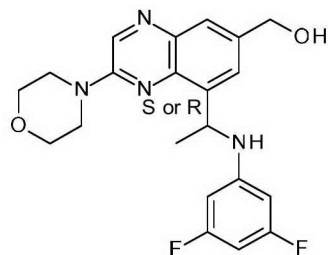
Preparation compound 84, compound 154a and compound 154b



compound 84



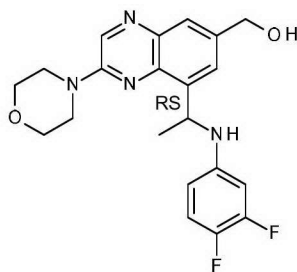
compound 154a



compound 154b

Compound 84, compound 154a and compound 154b were prepared according to an analogous procedure as described for the synthesis of compound 111, using compound 80 as starting material. Compound 84 (2.6 g) was purified by chiral SFC (CHIRALCEL OJ-H; 5  $\mu$ m 250x20 mm; mobile phase: 65%  $\text{CO}_2$ , 35% EtOH (0.3%  $\text{iPrNH}_2$ )). The pure fractions were collected and the solvent was evaporated to give two fractions, which were separately taken-up in diethylether and heptane, filtered and dry under vacuum to give respectively 220 mg (5%) of compound 154a and 210 mg (5%) of compound 154b. M.P.: 90°C (K).

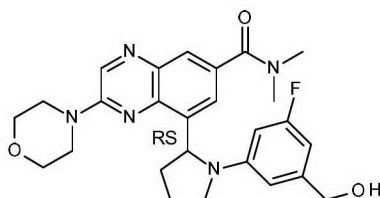
15



Preparation of compound 303:

Compound 303 was prepared according to an analogous procedure as described for the synthesis of compound 10 using compound 233 (as starting material. (100 mg, 33%, MP :138°C, DSC).

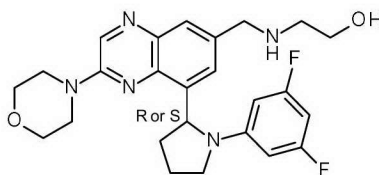
#### 5 Conversion C3



Preparation of compound 45:

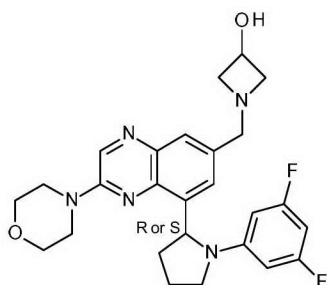
NaBH<sub>4</sub> (7 mg; 0.19 mmol) was added to a solution of compound 44 (90 mg; 0.19 mmol) in MeOH (2 mL) at 5°C. The reaction mixture was stirred at 5°C for 4h. The mixture was poured into H<sub>2</sub>O, filtered through a pad of celite<sup>®</sup> and extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated until dryness. The residue (110 mg) was purified by chromatography over silica gel (irregular 15-40 μm; 30 g; mobile phase: 97% DCM, 3% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and evaporated until dryness. The residue (65 mg) was freeze-dried with water/ACN 80/20 to give 62 mg (69%, yellow solid) of compound 45. M.P.: 80°C (gum, K).

#### Conversion C4



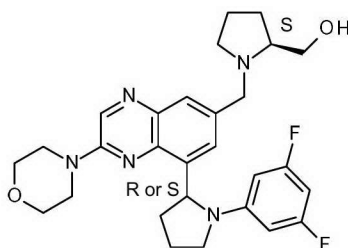
Preparation compound 14:

2-aminoethanol (0.21 mL; 3.53 mmol) was added to a solution of compound 250 (150 mg; 0.35 mmol) in MeOH (7 mL) and the reaction mixture was stirred at rt for 4h. Then sodium borohydride (20 mg; 0.53 mmol) was added portionwise at 0°C and the reaction mixture was stirred at rt for 1h30. Water was added and the product extracted with EtOAc. The organic layer was washed with brine (2x), dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (200 mg) was purified by chromatography over silica gel (irregular 15-40 μm; mobile phase: 90% DCM, 10% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated to give 145 mg (88%) of compound 14. M.P.: 140°C (K).



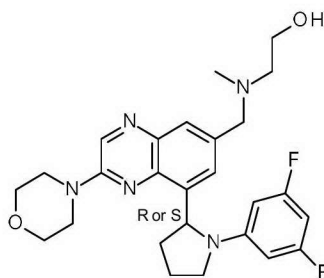
Preparation compound 76:

Compound 250 (100 mg; 0.24 mmol) was added to a solution of 3-hydroxyazetidine hydrochloride (258 mg; 2.36 mmol) and sodium acetate (193 mg; 2.36 mmol) in MeOH (3 mL). The reaction mixture was stirred at rt for 4h. Then, sodium borohydride (18 mg; 0.47 mmol) was added portionwise at 0°C and the reaction mixture was stirred at rt for 1h30. Water was added and the product extracted with EtOAc. The organic layer was washed with brine (2x), dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (210 mg) was purified by chromatography over silica gel (irregular 15-40 µm; 24 g; mobile phase: 90% DCM, 10% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated to give 115 mg (100%) of compound 76. M.P.: 90°C (DSC).



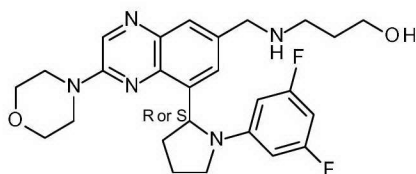
Preparation compound 77:

Compound 77 was prepared according to an analogous procedure as described for the synthesis of compound 76, using compound 250 and L-prolinol as starting materials (freeze-dried: 48 mg, 80%). M.P.: 80°C (gum, K).



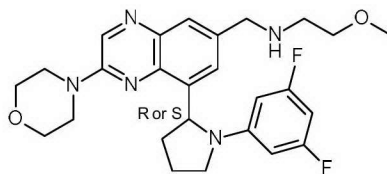
Preparation compound 101:

Compound 101 was prepared according to an analogous procedure as described for the synthesis of compound 76, using compound 250 and 2-(methylamino)ethanol as starting materials (72 mg, 63%). M.P.: 80°C (gum, K).



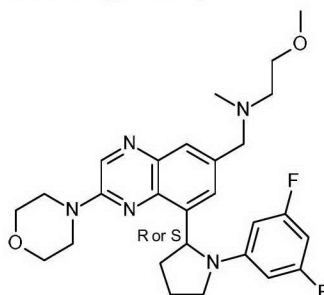
Preparation compound 102:

Compound 102 was prepared according to an analogous procedure as described for the synthesis of compound 14, using compound 250 and 3-amino-1-propanol as starting materials (55 mg, 48%). M.P.: 80°C (gum, K).



Preparation compound 103:

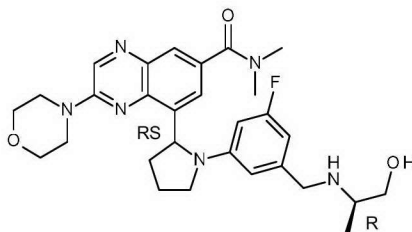
Compound 103 was prepared according to an analogous procedure as described for the synthesis of compound 14, using compound 250 and 2-methoxyethylamine as starting materials (83 mg, 73%). M.P.: 80°C (gum, K).



Preparation compound 112:

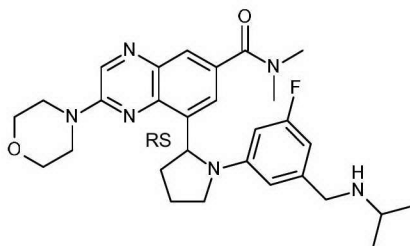
Compound 112 was prepared according to an analogous procedure as described for the synthesis of compound 76, using compound 250 and N-(2-(methoxyethyl)methylamine as starting materials (76 mg, 22%). M.P.: 80°C (gum, K).

Conversion C5



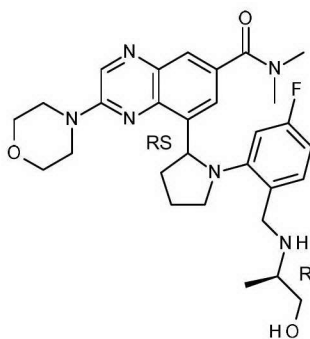
Preparation compound 48:

Compound 48 was prepared according to an analogous procedure as described for the synthesis of compound 14, using compound 44 and D-alaninol as starting materials (freeze-dried: 27 mg, 48%). M.P.: 80°C (gum, K).



Preparation compound 49:

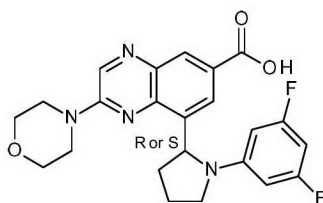
Compound 49 was prepared according to an analogous procedure as described for the synthesis of compound 14, using compound 44 and isopropylamine as starting materials (freeze-dried: 14 mg, 21%). M.P.: 80°C (gum, K).



Preparation compound 67:

Compound 67 was prepared according to an analogous procedure as described for the synthesis of compound 14, using compound 44 and D-alaninol as starting material (freeze-dried: 25 mg, 20%). M.P.: 80°C (gum, K).

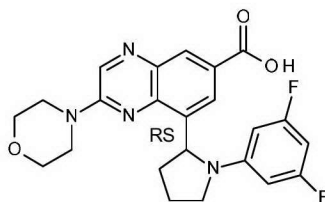
Conversion C6



Preparation of compound 251:

A solution of lithium hydroxide monohydrate (370 mg; 8.8 mmol) in water (3 mL) was added to a mixture of compound 249 (400 mg; 0.88 mmol) in THF (12 mL) at rt. The reaction mixture was heated at 50°C for 15h. The mixture was cooled down to rt. Ice-water was added and the solution was slowly acidified with a 3N aqueous solution of HCl. A precipitate was filtered, washed with Et<sub>2</sub>O and dried to give 226 mg of fraction 1. The filtrate was extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated. The residue (88 mg) was combined with fraction 1 (226 mg) and the resulting residue (314 mg) was purified by reverse phase (X-Bridge-C18 5 μm;

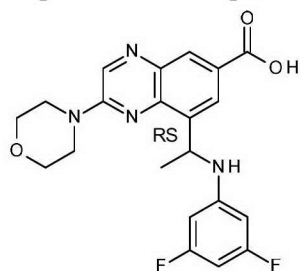
30\*150 mm; gradient: from 75%  $\text{NH}_4\text{HCO}_3$  0.5%, 25% ACN to 35%  $\text{NH}_4\text{HCO}_3$  0.5%, 65% ACN). The pure fractions were collected and the solvent was evaporated to give 196 mg (51%) of compound 251. M.P.: 299°C (DSC).



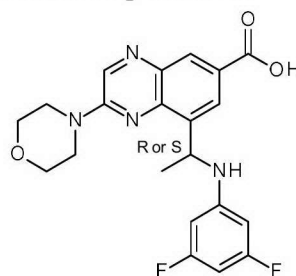
5 Preparation of compound 62:

Compound 62 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 254 as starting material (1.05 g, 86%; after recrystallization from 150 mg: 58 mg, 5% of compound 62. M.P.: >260°C (K).

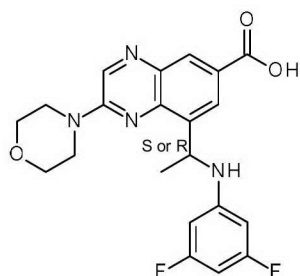
10 Preparation of compound 83a, compound 83b and compound 83c



compound 83a



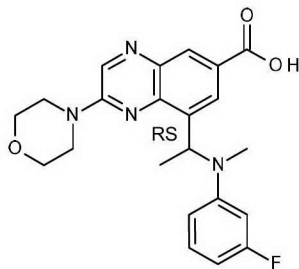
compound 83b



compound 83c

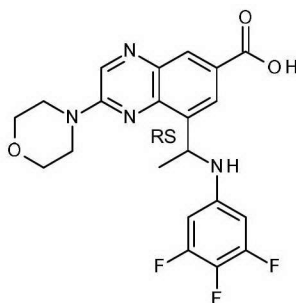
- Compound 83a, compound 83b and compound 83c were prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 80 as starting material. A first reaction gave 56 mg (41%) of compound 83a. M.P.: 240°C (DSC). A second reaction gave 1.3g of compound 83a was further purified by chiral SFC (Chiralpak IA 5  $\mu\text{m}$ ; 250\*20 mm; mobile phase: 60%  $\text{CO}_2$ , 40%  $\text{iPrOH}$  (0.3%  $\text{iPrNH}_2$ )). The pure fractions were collected and the solvent was evaporated to give two fractions which were separately taken-up with  $\text{H}_2\text{O}$ , acidified with 3N aqueous solution of  $\text{HCl}$ . The precipitate were filtered, washed with  $\text{H}_2\text{O}$  and

diethylether and dried to give respectively 287 mg (26%) of compound 83b (M.P.: 180°C, DSC) and 278 mg (25%) of compound 83c (M.P.: 157°C, DSC).



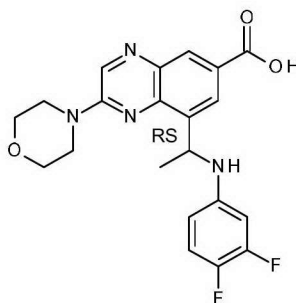
Preparation of compound 98:

- 5 Compound 98 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 97 as starting material (after recrystallization: 177 mg, 77%. M.P.: 240°C (DSC).



Preparation of compound 170:

- 10 Compound 170 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 266 as starting material (1.15 g, 88%. M.P.: 285°C (DSC).

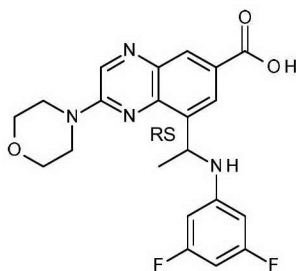


Preparation of compound 234:

- 15 Compound 234 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 233 as starting material (8.57 g, 95%).



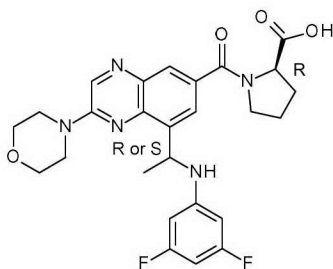
327



Preparation of compound 236 :

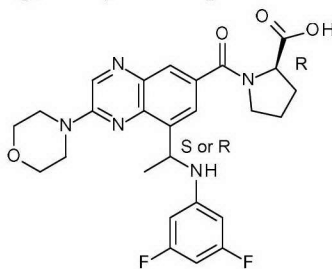
Compound 236 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 235 as starting material. (11 g; 96%) of compound 236. M.P : 240°C (DSC)

5



Preparation of compound 239 :

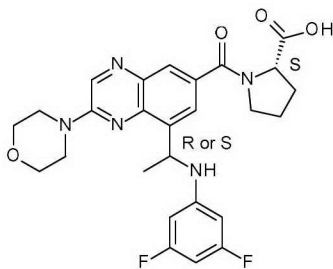
Compound 239 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 272a as starting material. The reaction was stirred at rt overnight. (44 mg; 52%) of compound 239.



10 Preparation of compound 240:

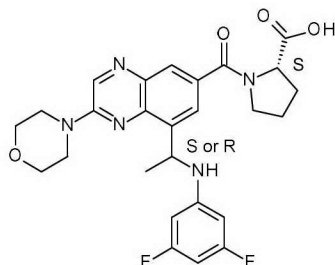
1.73 H<sub>2</sub>O 0.68 HCl

Compound 240 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 272b as starting material. The reaction was stirred at rt overnight. (42 mg; 50%) of compound 240 (1.73 H<sub>2</sub>O 0.68 HCl).



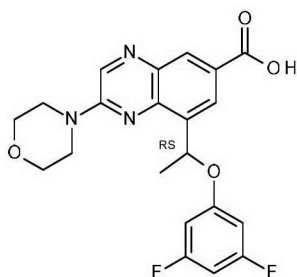
15 Preparation of compound 241 :

Compound 241 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 273a as starting material. The reaction was stirred at rt overnight. (76 mg; 73%) of compound 241.



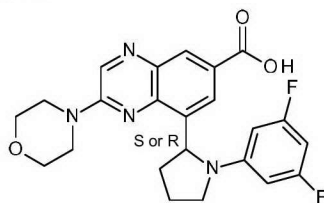
5 Preparation of compound 242 :

Compound 242 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 273b as starting material. The reaction was stirred at rt overnight. (76 mg; 73%) of compound 242.



10 Preparation compound 248:

To a solution of compound 248 (1.36 g, 2.05 mmol) in THF (10 mL) and MeOH (10 mL) was added an aqueous solution of NaOH (6.16 mL, 1 M, 6.16 mmol). The mixture was stirred at rt over the weekend. The mixture was evaporated and the resulting residue was slowly acidified with an aqueous solution of HCl (1N). The precipitate was filtered to give 797 mg (93%; yellow oil) of compound 248.

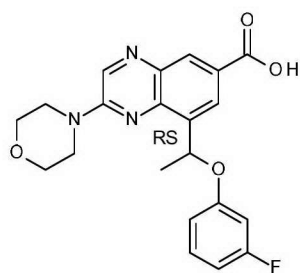


Preparation of compound 253:

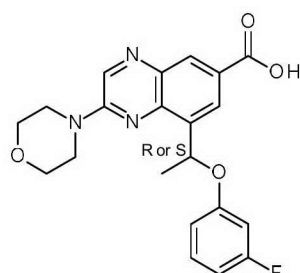
Compound 253 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 252 as starting material (200 mg, 88%). The product was used without purification in the next step.

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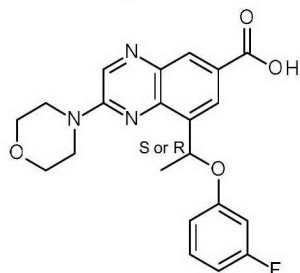
Preparation of compound 257a, compound 257b and compound 257c



compound 257a



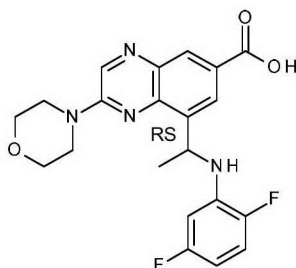
compound 257b



compound 257c

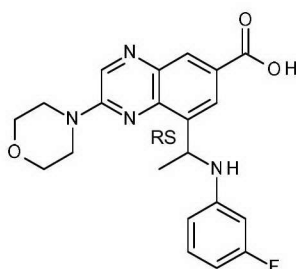
Compound 257a was prepared according to an analogous procedure as described for the synthesis of compound 248, using compound 256 as starting material. The reaction mixture was heated at 50°C for 1h. The mixture was cooled down to rt and evaporated in vacuum. The residue was slowly acidified with 1N aqueous solution of HCl, filtered and dried under vacuum. Compound 257a (994 mg, 98%, yellow solid) was purified by chiral SFC (Chiralpak AD-H 5  $\mu$ m 250\*30 mm; mobile phase: 80% CO<sub>2</sub>, 20% iPrOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give 196 mg (yellow oil) of fraction 1 and 145 mg (yellow oil) of fraction 2. Fraction 1 was purified by chromatography over silica gel (irregular SiOH; 15-40  $\mu$ m; 10 g; gradient: from 96% DCM, 4% MeOH/NH<sub>4</sub>OH (95/5) to 82% DCM, 18% MeOH/NH<sub>4</sub>OH (95/5)). The pure fractions were collected and the solvent was evaporated. The residue (109 mg, pale yellow oil) was purified by reverse phase (X-  
 5 Bridge-C18 5  $\mu$ m 30\*150 mm; gradient: from 85% (aq. NH<sub>4</sub>HCO<sub>3</sub> 0.5%), 15% ACN to 45% (aq. NH<sub>4</sub>HCO<sub>3</sub> 0.5%), 55% ACN). The pure fractions were collected and the solvent was evaporated. The residue was co-evaporated in DCM/pentane (1/4) and dried under vacuum (50°C, 16h) to give 66 mg (7%, pale yellow solid) of compound 257b. Fraction 2 was purified by chromatography over silica gel (irregular SiOH; 15-40  $\mu$ m; 10 g; gradient: from 96% DCM, 4% MeOH/NH<sub>4</sub>OH (95/5) to 80% DCM, 20% MeOH/NH<sub>4</sub>OH (95/5)). The pure fractions were collected and the solvent was evaporated. The residue was triturated in DCM/pentane (1/4), filtered and dried under vacuum (50°C, 16h) to give 119 mg (12%, pale yellow solid) of compound 257c.

330



Preparation of compound 261:

Compound 261 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 260 as starting material (280 mg, 90%, yellow solid).



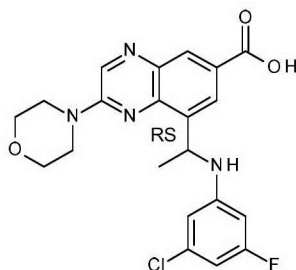
5 Preparation of compound 263:

Compound 263 was prepared according to an analogous procedure as described for the synthesis of compound 248, using compound 262 as starting material (577 mg, 96%, yellow solid).

10 Alternative pathway:

Compound 263 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 262 as starting material (217 mg, quant.). The reaction mixture was stirred at 50°C for 15h. The product was used without purification for the next step.

15

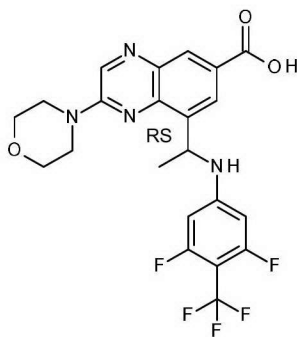


Preparation of compound 265:

Compound 265 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 264 as starting material (170 mg, 47%, yellow solid). The product was used without purification in the next step.

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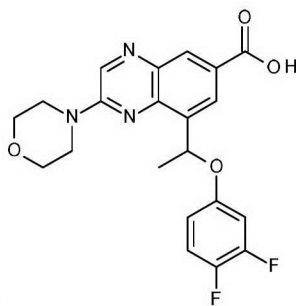
331



Preparation of compound 270:

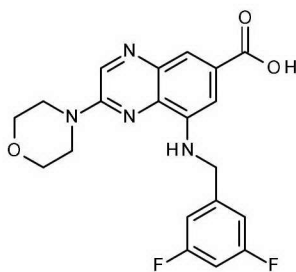
Compound 270 was prepared according to an analogous procedure as described for the synthesis of compound 251 using compound 269 as starting material (890 mg; 100%). The product was used without purification for the next step.

5



Preparation of compound 285:

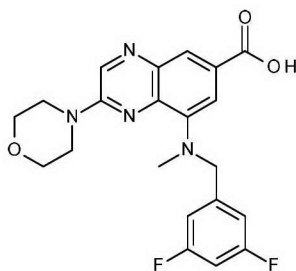
Compound 285 was prepared according to an analogous procedure as described for the synthesis of compound 251 using compound 209 as starting material (3.5 g, 90%).



10 Preparation of compound 289:

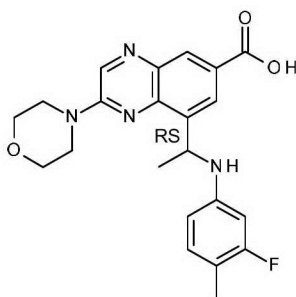
Compound 289 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 288 as starting material (3.98g, 84%).

332



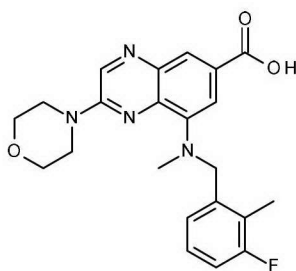
Preparation of compound 291 :

compound 291 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 290 as starting material (300 mg, 48%).



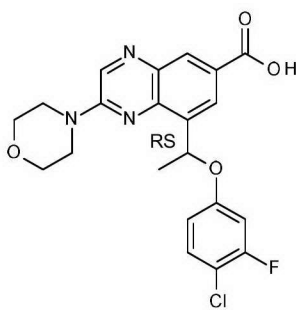
5 Preparation of compound 294 :

Compound 294 was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 293 as starting material (3.8g, 95%).



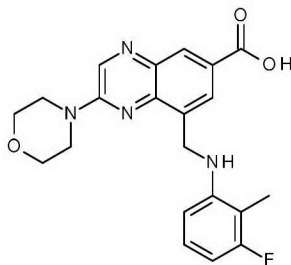
Preparation of compound 307:

10 Compound 307 was prepared according to an analogous procedure as described for the synthesis of compound 83a using compound 306 as starting material (2.8g; 113%).



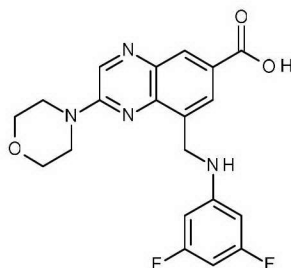
Preparation of compound 311 :

Compound 311 was prepared according to an analogous procedure as described for the synthesis of compound 248 using compound 310 as starting material (1 g, 59%).



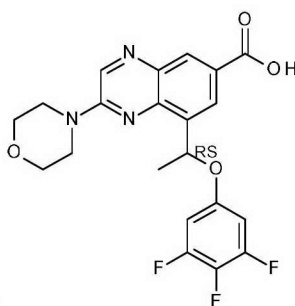
Preparation of compound 327 :

- 5 To a suspension of compound 326 (1.52 g; 3.70 mmol) in MeTHF (15 mL) and MeOH (15 mL) was added a 1M aqueous solution of sodium hydroxide (22.2 mL; 22.2 mmol). The mixture was heated at 40 °C for 1 h then at 50 °C for 1h. After cooling down to rt, the crude was concentrated in vacuo. The residue was slowly acidified with a 1N aqueous solution of HCl (until pH#4) and the precipitate formed was filtered on a glass frit. The solid was taken up in EtOH and evaporated in vacuo to give 900 mg (61%) of compound 327 as a yellow solid.
- 10



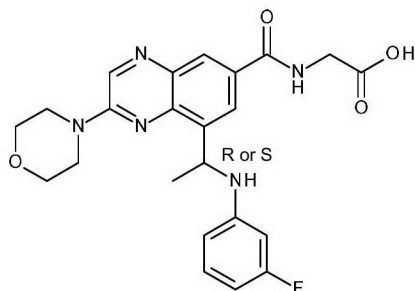
Preparation of compound 331:

- Compound 331 was prepared according to an analogous procedure as described for the synthesis of compound 327 using compound 330 as starting material (298 mg, 61%).
- 15



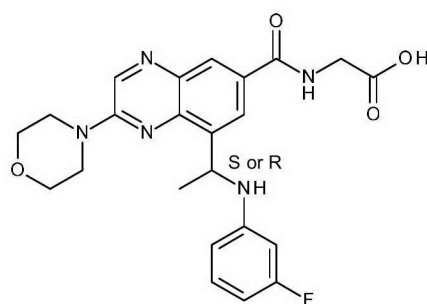
Preparation of compound 378:

- Compound 378 (was prepared according to an analogous procedure as described for the synthesis of compound 248, using compound 377 as starting material (1.67g, 99%).
- 20



Preparation of compound 393a:

Compound 393a was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 393a as starting material (108mg, 57%, MP: 115°C, gum, Kofler).

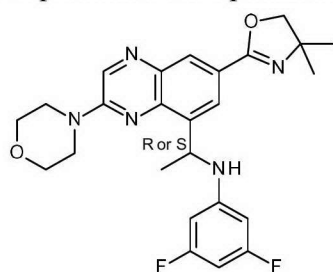


Preparation of compound 393b:

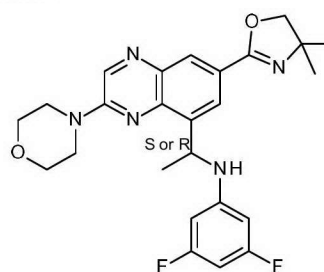
Compound 393b was prepared according to an analogous procedure as described for the synthesis of compound 251, using compound 393b as starting material (110mg, 51%, MP: 196°C, DSC).

#### Conversion C7

Preparation of compound 186 and compound 187



compound 186



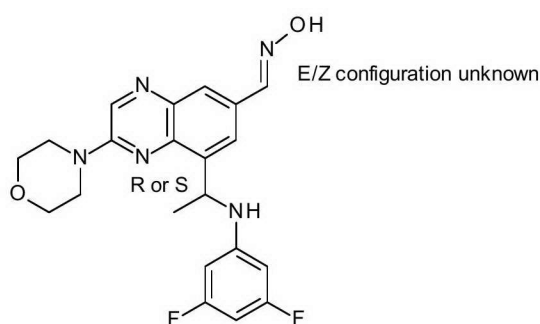
Intermediate 187

At 0°C, thionyl chloride (0.5 mL; 7.21 mmol) was added to a solution of compound 169 (350 mg; 0.72 mmol) in DCM (7 mL). The reaction mixture was stirred at rt overnight. The mixture was poured into ice and 10% aqueous solution of K<sub>2</sub>CO<sub>3</sub>, then extracted with EtOAc. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and evaporated until dryness. The residue (320 mg) was combined with another



batch coming from a reaction performed on 206 mg of compound 169. The two residues were purified together by column chromatography over silica gel (40 g, mobile phase; from 100% DCM to 97% DCM, 3% MeOH, 0.3% NH<sub>4</sub>OH). The pure fractions were collected and evaporated. The residue (333 mg) was purified by chiral SFC (CHIRALCEL OJ-H 5  $\mu$ m 250x20 mm; mobile phase: 80% CO<sub>2</sub>, 20% EtOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and evaporated to give 136 mg (25%) of compound 186 (M.P.: 80°C (gum, K)) and 139 mg (26%) of compound 187 (M.P.: 80°C (gum, K)).

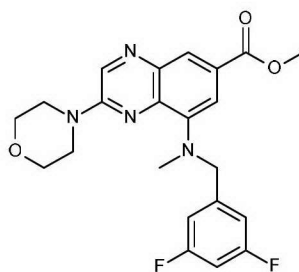
#### 10 Conversion C8



Preparation of compound 225:

A mixture of compound 271 (200 mg; 0.50 mmol), hydroxylamine hydrochloride (105 mg; 1.51 mmol) in EtOH (10 mL) and water (3 mL) was heated at 100°C for 5 h. The mixture was poured into water and extracted with DCM. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (200 mg) was purified by chromatography over silica gel (irregular SiOH 15-40  $\mu$ m; 300 g; mobile phase: 96% DCM, 4% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated. The residue (110 mg) was crystallized from diethylether. The yellow precipitate was filtered off and dried to give 75 mg (36%) of compound 225. M.P.: 80°C (gum, K).

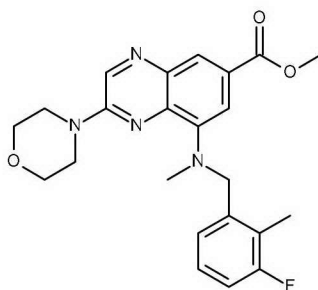
#### Conversion C9



Preparation of compound 290:

NaH (60% dispersion in mineral oil) (202.7 mg, 5.07 mmol) was added portion wise to a solution of compound 289 (1 g, 2.41 mmol) in DMF (10mL) under nitrogen at 0-5

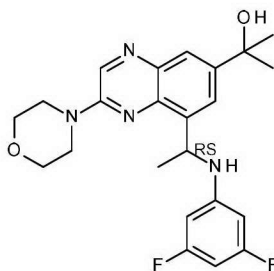
°C (ice bath cooling). The mixture was stirred at 0-5°C for 15mn then, iodomethane (300  $\mu$ L, 4.83 mmol) was added. The reaction mixture was stirred at room temperature for 16h, poured onto iced water and extracted with EtOAc, the organic layer was washed with water, dried over MgSO<sub>4</sub> and evaporated to dryness, The residue was  
 5 purified by silica gel chromatography to give 650 mg (63%) of compound 290 .



Preparation of compound 306:

NaH (60% dispersion in miral oil; 1.023 g, 25.582 mmol) was added portionwise to a solution of compound 305 (5 g, 12.18 mmol) in DMF (50mL) under nitrogen at 0-5 °C  
 10 (ice bath cooling).The mixture was stirred at 0-5°C for 15mn then, iodomethane (1.52 mL, 24.36 mmol) was added. The reaction mixture was stirred at room temperature for 16h. The reaction mixture was poured into cooled water.The product was extracted with AcOEt and the organic layer was evaporated to dryness. The residue (6.6g) was purified by silica gel chromatography (120g of SiOH 20-45 $\mu$ m, gradient from 40/60 to  
 15 10/90 Heptane/EtOAc).The fractions were collected and evaporated until dryness to afford 1.9 g (37%) of compound 306.

Conversion C10



20 Preparation of compound 341:

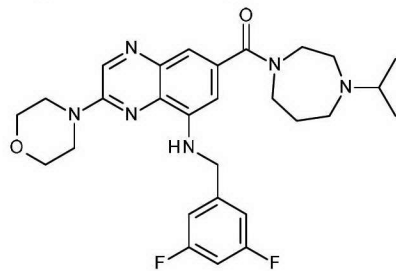
Under N<sub>2</sub> at 10°C, methylmagnesium bromide 3M in E<sub>2</sub>O (467 $\mu$ L; 1.4mmol) was added to a solution of compound 80 (300mg, 0.7mmol) in THF (12mL). The solution was stirred at 10°C for 2 hours. The solution was cooled and the mixture was poured into cooled water and a 10% NH<sub>4</sub>Cl solution. The product was extracted with EtOAc.  
 25 The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness.The residue (300mg) was purified via silica gel chromatography (Stationary

phase: irregular bare silica 40g, Mobile phase: 98% DCM, 2% MeOH, 0.1% NH<sub>4</sub>OH). The pure fractions were collected and the solvent was evaporated. The residue was freeze-dried with acetonitrile/water (20/80) to give 40mg (13%) of compound 341 as yellow powder. M.P.: 80°C, gum, K.

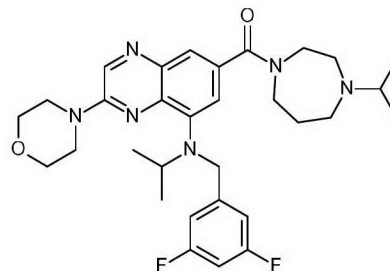
5

#### Conversion C11

Preparation of compound 360 and compound 361



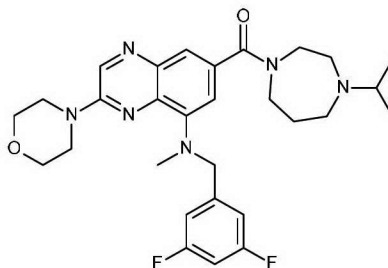
compound 360



Intermediate 361

Compound 351 (210 mg, 0.435 mmol), 2-iodopropane (47.87  $\mu$ L, 1.7 g/mL, 0.479 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (425.393 mg, 1.306 mmol) in ACN (10mL) were stirred at 80°C for 18h. Then, the mixture was poured into water and extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered off and evaporated in vacuo. The residue (325mg) was purified by silica gel chromatography (12g of SiOH 15 $\mu$ m, gradient from 98/2/0.2 to 90/10/1). The fractions were collected and evaporated until dryness to give 90 mg (39%) of compound 360 and 30 mg (12%) of compound 361.

15

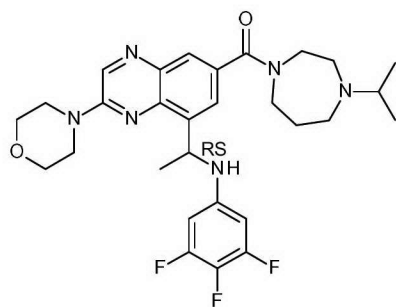


#### Preparation of compound 373:

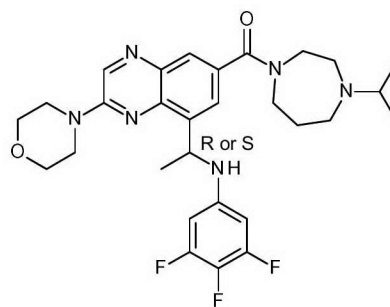
Compound 373 was prepared according to an analogous procedure as described for the synthesis of compound 360 using compound 372 as starting material (105mg; 92%).

20

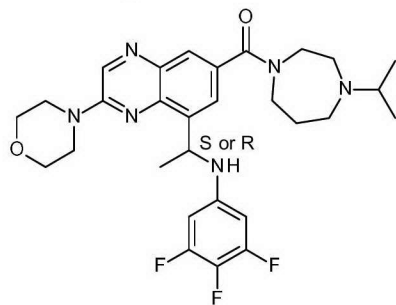
Preparation of compound 388, compound 388a and 388b



compound 388



compound 388a

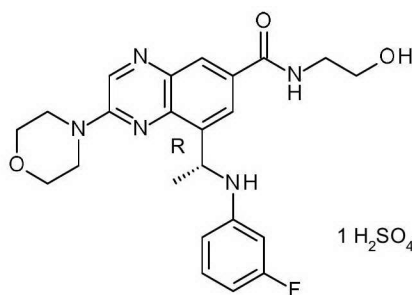


compound 388b

Compound 388 was prepared according to an analogous procedure as described for the synthesis of compound 360 using compound 387 as starting material (90 mg; 28%).

- The separation of the enantiomers from 90 mg of compound 388 was performed by chiral SFC (CHIRALPAK AD-H 5  $\mu$ m 250x20 mm; mobile phase: 70% CO<sub>2</sub>, 30% iPrOH (0.3% iPrNH<sub>2</sub>)). The pure fractions were collected and the solvent was evaporated to give, after freeze-drying, 46 mg (14%) of compound 388a and 47 mg (14%) of compound 388b.

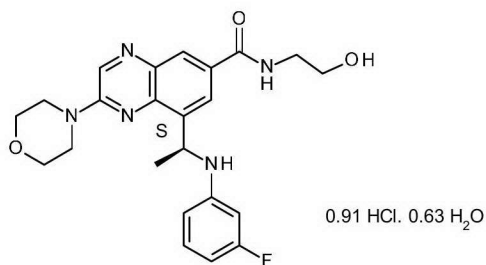
#### Conversion C12



1 H<sub>2</sub>SO<sub>4</sub>· 0.1 H<sub>2</sub>O. 0.18 lPrOH

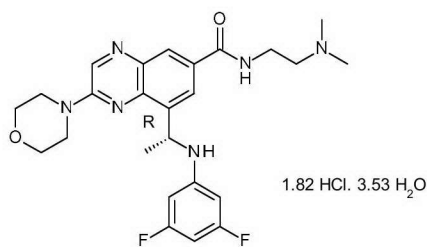
#### 10 Preparation of compound 117a

Compound 117 (1g; 2.17 mmol) was dissolved in isopropanol (32 mL) at room temperature. Then, a solution of sulfuric acid (58  $\mu$ L; 1.082mmol) was added dropwise. A precipitate appeared slowly and the mixture was stirred for 2 hours at room temperature. The precipitate was filtered and dried at 60°C under vacuum to give 693 mg (58%) of compound 117a (MP: 179°C, DSC).



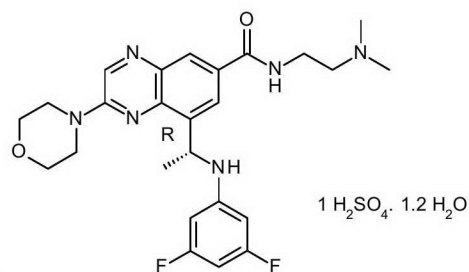
#### Preparation of compound 118a

Compound 118 (0.5g; 1.14 mmol) was dissolved in MeTHF (20 mL) at room temperature. Then, a solution of HCl, 4M in dioxane (284  $\mu$ L; 1.14mmol) was added dropwise. A precipitate appeared slowly and the mixture was stirred for overnight at room temperature. The precipitate was filtered and dried at 60°C under vacuum to give 411 mg (75%) of compound 118a.



#### Preparation of compound 184a

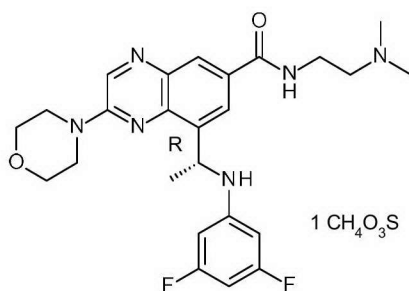
At 0°C, a solution of HCl, 4M in dioxane (516  $\mu$ L; 2.06mmol) was added to a solution of compound 184 (0.5g; 1.03 mmol) dissolved in MeOH (10 mL). The solution was allowed to reach slowly room temperature and stirred for several days. Et<sub>2</sub>O was added; the red precipitate was filtered and dried to give 554 mg (87%) of compound 184a (gum at 80°C, K).



#### Preparation of compound 184b

At 0°C, sulfuric acid (33  $\mu$ L; 0.619mmol) was added to a solution of compound 184 (0.3g; 0.619 mmol) dissolved in EtOH (3 mL). The solution was allowed to reach slowly room temperature and stirred overnight. Et<sub>2</sub>O was added; the precipitate was filtered and dried to give 360 mg (97%) of compound 184b (MP: 270 °C; DSC).

340



#### Preparation of compound 184c

At 0°C, methane sulfonic acid (40  $\mu$ L; 0.619mmol) was added to a solution of compound 184 (0.3g; 0.619 mmol) dissolved in EtOH (3 mL). The solution was allowed to reach slowly room temperature and stirred overnight. Et<sub>2</sub>O was added; the yellow precipitate was filtered and dried to give 320 mg (89%) of compound 184c (MP: 74°C, DSC).

#### Analytical Part

##### LCMS (Liquid chromatography/Mass spectrometry)

The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software. Compounds are described by their experimental retention times ( $R_t$ ) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the  $[M+H]^+$  (protonated molecule) and/or  $[M-H]^-$  (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e.  $[M+NH_4]^+$ ,  $[M+HCOO]^-$ , etc...). For molecules with multiple isotopic patterns (e.g. Br, Cl), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used. Hereinafter, "SQD" means Single Quadrupole Detector, "RT" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, "DAD" Diode Array Detector. Table: LCMS Method codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes).

Method code	Instrument	Column	Mobile phase	gradient	Flow Column T	Run time
Method 1	Waters: Acquity UPLC <sup>®</sup> - DAD and Quattro Micro <sup>™</sup>	Waters: BEH C18 (1.7µm, 2.1x100mm)	A: 95% CH <sub>3</sub> COONH <sub>4</sub> 7mM / 5% CH <sub>3</sub> CN, B: CH <sub>3</sub> CN	84.2% A for 0.49min, to 10.5% A in 2.18min, held for 1.94min, back to 84.2% A in 0.73min, held for 0.73min.	0.343 ----- 40	6.2
Method 2	Waters: Acquity UPLC <sup>®</sup> H-Class – DAD and SQD 2	Waters: BEH C18 (1.7µm, 2.1x100 mm)	A: 95% CH <sub>3</sub> COONH <sub>4</sub> 7mM / 5% CH <sub>3</sub> CN, B: CH <sub>3</sub> CN	From 84.2% A to 10.5% A in 2.18 min, held for 1.94min, back to 84.2% A in 0.73min, held for 0.73min.	0.343 ----- 40	6.1
Method 3	Waters: Alliance <sup>®</sup> - DAD and ZQ <sup>™</sup>	Waters Atlantis <sup>®</sup> C18 (5µm, 3.9x100mm)	A: CH <sub>3</sub> COONH <sub>4</sub> 7mM, B: CH <sub>3</sub> CN, C: 0.2% HCOOH	50% A/0% B for 1.5min, to 10% A/80% B in 3.5min, held for 4min, back to 50% A/0% B in 1.5min, held for 1.5min.	0.8 ----- 30	12

### DSC

For a number of compounds, melting points (MP) were determined with a DSC1 (Mettler-Toledo). Melting points were measured with a temperature gradient of 10 °C/minute. Maximum temperature was 350 °C. Values are peak values.”

- For a number of compounds, melting points were obtained with a Kofler hot bench, consisting of a heated plate with linear temperature gradient, a sliding pointer and a temperature scale in degrees Celsius.

### NMR

- The NMR experiments were carried out using a Bruker Avance 500 III using internal deuterium lock and equipped with reverse triple-resonance (<sup>1</sup>H, <sup>13</sup>C, <sup>15</sup>N TXI) probe head or using a Bruker Avance DRX 400 spectrometer at ambient temperature, using internal deuterium lock and equipped with reverse double-resonance (<sup>1</sup>H, <sup>13</sup>C, SEI) probe head with z gradients and operating at 400MHz for the proton and 100MHz for carbon. Chemical shifts (δ) are reported in parts per million (ppm).

**OR**

Optical Rotation (OR) is measured with a polarimeter 341 Perkin Elmer. The polarized light is passed through a sample with a path length of 1 decimeter and a sample concentration of 0.2 to 0.4 gram per 100 milliliters. 2 to 4 mg of the product in vial are weight, then dissolved with 1 to 1.2 ml of spectroscopy solvent (e.g. Dimethylformamide). The cell is filled with the solution and put into the polarimeter at a temperature of 20 °C. The OR is read with 0.004° precision.

Calculation of the concentration : weight in gram x 100/ volume in ml

$[\alpha]_D^{20}$  : (read rotation x 100) / (1.000 dm x concentration).

<sup>d</sup> is sodium D line (589 nanometer).

Table: Co. No. means compound number; Retention time ( $R_t$ ) in min; MP means melting point (°C); dec means decomposition; n.d. means not determined.

Co. No.	MP (°C)	Kofler (K) or DSC	$R_t$	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
1	100	K	3.10	468	1
2	80 (gum)	K	3.11	468	1
3	n.d.	-	3.27	482	1
4	n.d.	-	3.26	482	1
5	n.d.	-	2.98	443	1
6	n.d.	-	2.98	443	1
7	206	DSC	2.80	484	1
8	100 (gum)	K	2.80	484	1
9	n.d.	-	2.80	484	1
10	189	DSC	3.06	427	1
11	228	DSC	2.82	442	1
12	218	DSC	2.82	442	1
13	217	DSC	2.82	442	1
14	140	K	2.69	470	1
15	80 (gum)	K	3.18	441	1
16	80 (gum)	K	3.18	441	1
17	170	K	2.64	497	1
18	80 (gum)	K	2.69	511	1
19	80 (gum)	K	2.64	470	1
20	80 (gum)	K	3.04	494	1
21	184	DSC	2.78	438	1
22	183	DSC	2.78	438	1
23	n.d.	-	3.05	398	1
24	100	K	3.05	398	1

Co. No.	MP (°C)	Kofler (K) or DSC	$R_t$	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
	(gum)				
25	98 (gum)	K	3.05	398	1
26	80 (gum)	K	3.10	468	1
27	80 (gum)	K	3.06	432	1
28	80 (gum)	K	3.06	450	1
29	n.d.	-	3.22	464	1
30	n.d.	-	3.23	464	1
31	213	DSC	3.49	455	1
32	80 (gum)	K	3.03	480	1
33	280	DSC	3.12	480	1
34	160	K	2.92	570	1
35	80 (gum)	K	3.23	464	1
36	n.d.	-	3.28	482	1
37	276	DSC	3.12	480	1
38	146	K	2.95	558	1
39	80 (gum)	K	2.84	537	1
40	80 (gum)	K	2.96	454	1
41	80 (gum)	K	2.98	462	1
42	80 (gum)	K	3.07	450	1
43	80 (gum)	K	2.93	558	1



Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
44	80 (gum)	K	2.85	478	1
45	80 (gum)	K	2.57	480	1
46	80 (gum)	K	2.83	537	1
47	80 (gum)	K	2.92	522	1
48	80 (gum)	K	2.33	537	1
49	80 (gum)	K	2.40	521	1
50	80 (gum)	K	2.84	498	1
51	80 (gum)	K	3.22	484	1
52	80 (gum)	K	3.29	500	1
53	n.d.	-	2.99	443	1
54	80 (gum)	K	2.81	475	1
55	80 (gum)	K	3.45	514	1
56	55	DSC	3.10	499	1
57	80 (gum)	K	2.97	523	1
58	80 (gum)	K	2.97	523	1
59	n.d.	-	2.69	473	1
60	n.d.	-	2.69	473	1
61	n.d.	-	2.69	473	1
62	>260	K	2.30	441	1
63	100 (gum)	K	2.77	510	1
64	80 (gum)	K	3.02	524	1
65	80 (gum)	K	2.76	496	1
66	80 (gum)	K	2.81	498	1
67	80 (gum)	K	2.27	537	1
68	49	DSC	2.89	425	1
69	80 (gum)	K	3.28	551	1
70	80 (gum)	K	2.88	498	1
71	80 (gum)	K	2.77	484	1

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
72	80 (gum)	K	2.60	497	1
73	n.d.	-	2.89	483	1
74	n.d.	-	2.89	483	1
75	80 (gum)	K	2.50	523	1
76	90	DSC	2.81	482	1
77	80 (gum)	K	3.09	510	1
78	235	DSC	3.08	503	1
79	n.d.	-	2.14	483	1
80	244	DSC	3.18	429	1
81	n.d.	-	2.62	485	1
82	n.d.	-	5.81	511	3
83a	240	DSC	2.12	415	1
83b	180	DSC	2.10	Fragment m/z 286 (weak 414.9)	1
83c	157	DSC	2.10	Fragment m/z 286 (weak 415.0)	1
84	80 (gum)	K	2.76	401	1
85	n.d.	-	2.74	424	1
86	76	DSC	2.79	481	1
87	74	DSC	2.77	481	1
88	n.d.	-	2.83	384	1
89	n.d.	-	2.83	384	1
90	n.d.	-	2.88	494	1
91	n.d.	-	2.88	494	1
92	n.d.	-	2.88	494	1
93	80 (gum)	K	2.92	497	1
94	80 (gum)	K	2.71	496	1
95	80 (gum)	K	2.73	496	1
96	80 (gum)	K	2.71	426	1
97	146	DSC	3.46	425	1
98	240	DSC	2.15	411	1
99	189	DSC	3.33	445	1
100	n.d.	-	2.66	383	1
101	80 (gum)	K	2.99	484	1
102	80 (gum)	K	2.68	484	1

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
103	80 (gum)	K	3.04	484	1
104	80 (gum)	K	2.70	466	1
105	161	DSC	2.92	480	1
106	80 (gum)	K	3.74	411	1
107	80-90 (gum)	K	3.74	411	1
111	80	K	2.91	397	1
112	80 (gum)	K	3.46	498	1
113	307	DSC	2.70	493	1
114	303	DSC	2.70	493	1
115	327	DSC	2.65	480	1
116	332	DSC	2.64	480	1
117	n.d.	-	2.44	440	1
117a	179	DSC	2.46	440	1
118	237	DSC	2.44	440	1
118a	n.d.	-	2.45	440	1
119	80	K	2.84	482	1
120	80	K	2.76	462	1
121	80	K	2.59	478	1
122	n.d.	-	2.40	454	1
122a	116	DSC	2.31	454	1
123	n.d.	-	2.40	454	1
123a	130	DSC	2.34	454	1
124	80 (gum)	K	2.88	526	1
125	80 (gum)	K	2.91	476	1
126	80 (gum)	K	2.89	476	1
127	80 (gum)	K	3.09	434	1
128	80 (gum)	K	3.09	434	1
129	80	K	2.63	528	1
130	159	DSC	2.50	467	1
131	80	K	2.55	473	1
132	80 (gum)	K	2.39	471	1
133	80 (gum)	K	3.06	516	2
134	80 (gum)	K	2.28	508	2
135	144	DSC	2.90	423	1
136	184	DSC	2.67	438	2

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
137	80 (gum)	K	2.20	485	2
138	n.d.	-	2.11	453	2
139	n.d.	-	2.11	453	2
140	80 (gum)	K	2.86	454	2
141	80 (gum)	K	2.86	454	2
142	80 (gum)	K	2.84	537	2
143	80 (gum)	K	2.53	511	2
144	80 (gum)	K	2.40	497	2
145	80 (gum)	K	2.30	472	2
146	80 (gum)	K	2.92	Fragment m/z 355 (weak 500)	1
147	80 (gum)	K	2.56	487	1
148	n.d.	-	2.68	544	1
149	80 (gum)	K	2.40	501	1
150	110	K	2.67	406	1
151	80 (gum)	K	2.84	407	1
152	80 (gum)	K	2.47	485	1
153	90 (gum)	K	2.73	372	1
154a	n.d.	-	2.76	401	1
154b	90	K	2.76	401	1
155	186	DSC	2.58	431	1
156	n.d.	-	2.88	Fragment m/z 383 (weak 518)	1
157	n.d.	-	2.88	Fragment m/z 383 (weak 518)	1
158	n.d.	-	2.96	439	1
159	n.d.	-	2.96	439	1
160	229	DSC	2.79	Fragment m/z 383 (weak 530)	1
161	228	DSC	2.79	530	1
162	80 (gum)	K	3.22	Fragments m/z 353 and 383	1

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
163	239	DSC	3.21	Fragments m/z 353 and 383	1
164	116	DSC	3.05	Fragments m/z 335 and 383	1
165	80 (gum)	K	2.50	472	1
166	80 (gum)	K	2.51	472	1
167	80 (gum)	K	3.45	449	1
168	165	DSC	3.00	470	1
169	217	DSC	2.79	486	1
170	285	DSC	2.15	Fragment m/z 286 (weak 433)	1
171	125 gum	K	3.12	565+fragment m/z 436	1
172	130 gum	K	3.12	565	1
173	80 gum	K	2.71	506 + fragment m/z 383	1
174	80 gum	K	2.49	529	1
175	80 gum	K	2.48	529	1
176	n.d.	-	2.41	525 + fragment m/z 313	1
177	80 gum	K	2.77	467 [M+Na] <sup>+</sup> + fragment m/z 316	1
178	80 gum	K	2.77	467 [M+Na] <sup>+</sup> + fragment m/z 316	1
180	148	K	2.58	499	1
181	134	DSC	2.51	499	1
182	134	DSC	2.50	499	1
183	145	K	2.46	485	1
184	157	DSC	2.42	485	1
184a	80°C (gum)	K	2.54	485	1
184b	270	DSC	2.57	485	1
184c	74	DSC	2.57	485	1
185	152	DSC	2.40	485	1

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
186	80 (gum)	K	3.18	468	1
187	80 (gum)	K	3.18	468	1
188	80 (gum)	K	2.52	458 + fragment m/z 329	1
189	80 (gum)	K	2.52	458 + fragment m/z 329	1
192	229	DSC	3.00	512 + fragment m/z 383	1
193	80 (gum)	K	2.70	500 + 522 [M+Na] <sup>+</sup> + fragments m/z 371+383	1
194	80 (gum)	K	2.69	500 + 522 [M+Na] <sup>+</sup> + fragments m/z 371+383	1
195	228	DSC	2.99	411 + fragment m/z 383	1
196	80 (gum)	K	2.69	500 + fragment m/z 383	1
197	80 (gum)	K	2.68	500 + fragment m/z 383	1
198	171	DSC	2.61	459	1
199	140	K	2.50	459	1
200	115 gum	K	2.50	459	1
201			2.61	472	1
202	70	DSC	2.61	472	1
203	118	DSC	2.75	472	1
204	80 (gum)	K	2.75	472	1
205	80 (gum)	K	3.08	514	1
206	80 (gum)	K	3.27	498	1
207	80 (gum)	K	3.09	514	1

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
208	80	K	3.28	498	1
209	183	DSC	3.36	430	1
210	80	K	2.98	506	1
211	206	DSC	2.53	499	1
212	204	DSC	2.52	499	1
213	80 (gum)	K	2.58	476	1
214	80 (gum)	K	2.58	476	1
217	n.d.	-	2.94	565	1
218	n.d.	-	2.23	518	1
219	n.d.	-	2.20	389	1
220	n.d.	-	2.20	389	1
222	163	DSC	2.98	506	1
223	200	DSC	2.76	526	1
224	163	DSC	2.66	553	1
225	80 (gum)	K	2.85	414+ fragment m/z 285	1
226	158	DSC	2.39	481	1
227	80 (gum)	K	2.37	481	1
228	80 (gum)	K	2.35	481	1
229	n.d.	-	2.36	444	1
230	218	DSC	2.27	426	1
231	n.d.	-	2.61	490	1
232	181	DSC	2.46	458	1
233	192	Kofler	n.d.	n.d.	-
236	240	DSC	2.12	415	1
237	80	K	2.83	551	1
237a	120	DSC	2.85	551	1
237b	120	DSC	2.84	551	1
237c	80	K	2.85	551	1
237d	80	K	2.86	551	1
238	110	K	2.94	551	1
239	n.d.	-	2.11	512	1
240	n.d.	-	2.10	512	1
241	n.d.	-	2.10	512	1
242	n.d.	-	2.12	512	1
243	n.d.	-	2.13	493	1
243a	160	K	2.10	493	1
243b	200	K	2.10	493	1
244	n.d.	-	2.51	484	1
245	n.d.	-	2.50	484	1
246a	n.d.	-	2.56	472	1
246b	75	DSC	2.54	472	Method 1

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
249	211	DSC	n.d.	n.d.	-
250	120	K	n.d.	n.d.	-
251	299	DSC	n.d.	n.d.	-
262	222	DSC	n.d.	n.d.	-
262a	199.7	DSC	3.10	411	1
262b	199.5	DSC	3.10	411	1
264	189	DSC	n.d.	n.d.	-
266	220	K	n.d.	n.d.	-
276	194	DSC	2.39	440	1
278	158	K	2.65	428	1
279	77	DSC	2.41	457	1
279a	80 (gum)	K	2.48	457	1
279b	80 (gum)	K	2.48	457	1
280	164	DSC	2.44	471	1
280a	80 (gum)	K	2.51	471	1
280b	80 (gum)	K	2.51	471	1
281	80 (gum)	K	2.37	484	1
281a	102	K	2.45	484	1
281b	80 (gum)	K	2.44	484	1
282	100 (gum)	K	2.14	452	1
282a	100 (gum)	K	2.33	452	1
282b	100 (gum)	K	2.34	452	1
283a	173	DSC	2.51	516	1
283b	170	DSC	2.52	516	1
284a	113	K	2.66	489	1
284b	112	K	2.66	489	1
286	85 (gum)	K	2.61	499	1
286a	85 (gum)	K	2.59	499	1
286b	85 (gum)	K	2.59	499	1
287	80 (gum)	K	2.78	522	1
287a	90 (gum)	K	2.78	522	1
287b	95	K	2.78	522	1

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
292	80 (gum)	K	2.74	503	1
292a	110 (gum)	K	2.74	503	1
292b	110 (gum)	K	2.74	503	1
293	186	K	3.18	425	1
294	n.d.	-	n.d.	n.d.	-
295	80 (gum)	K	2.55	453	1
295a	120 (gum)	K	2.56	453	1
295b	120 (gum)	K	2.56	453	1
296	n.d.	-	2.51	514	1
296a	n.d.	-	2.50	514	1
296b	n.d.	-	2.52	514	1
297	n.d.	-	2.50	514	1
297a	n.d.	-	2.52	514	1
297b	n.d.	-	2.52	514	1
298a	100 (gum)	K	2.74	511	1
298b	100 (gum)	K	2.75	511	1
299a	100 (gum)	K	2.55	485	1
299b	100 (gum)	K	2.55	485	1
300	n.d.	n.d.	2.48	483	1
300a	140	K	2.49	483	1
300b	135	K	2.49	483	1
301	315	DSC	2.44	453	1
302	80 (GUM)	K	2.61	497	1
302a	135	K	2.62	497	1
302b	135	K	2.62	497	1
303	138	DSC	2.70	400	1
304	n.d.	-	2.87	436	1
308	195	DSC	2.78	539	1
309	n.d.	-	n.d.	n.d.	-
309a	n.d.	-	2.58	502	1
309b	n.d.	-	2.59	502	1
312a	n.d.	-	2.75	515	1
312b	n.d.	-	2.75	515	1
313a	n.d.	-	2.86	515	1
313b	n.d.	-	2.87	515	1

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
314a	80 (gum)	K	2.55	481	1
314b	80 (gum)	K	2.54	481	1
315a	86 (gum)	K	2.30	546	2
315b	90	K	2.29	547	1
317	167	DSC	1.92	509	1
318	n.d.	-	2.11	492	1
319a	n.d.	-	2.90	550	1
319b	n.d.	-	2.90	550	1
320a	110	K	2.57	479	1
320b	136	K	2.58	479	1
321a	118	K	2.44	465	1
321b	128	K	2.44	465	1
322a	122	K	2.40	496	1
322b	80	K	2.39	496	1
323a	126	K	2.39	496	1
323b	130	K	2.41	496	1
324a	60	K	2.45	485	1
324b	60	K	2.45	485	1
325a	144	K	2.39	482	1
325b	138	K	2.38	482	1
328	98	DSC	2.48	466	1
329a	121	K	2.46	496	1
329b	124	K	2.46	496	1
332	169	DSC	2.75	427	1
333	265	DSC	2.46	443	1
334a	136	DSC	2.50	441	1
334b	134	DSC	2.58	441	1
335a	n.d.	-	2.55	503	1
335b	80 (gum)	K	2.52	503	1
336	194	DSC	2.40	440	1
338	n.d.	-	2.43	454	1
338a	89.8	DSC	2.49	454	1
338b	90.8	DSC	2.49	454	1
339	117	DSC	2.89	423	1
339a	131	DSC	2.97	423	1
339b	129	DSC	2.96	423	1
340	180	DSC	2.19	457	1
341	80	K	2.89	429	1
342	n.d.	-	2.31	485	1
343	n.d.	-	2.32	440	1

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
344a	75	K	2.36	472	1
344b	75	K	2.37	472	1
345a	80	K	2.38	529	1
345b	80	K	2.38	529	1
346a	107	K	2.54	472	1
346b	106	K	2.54	472	1
347	170	DSC	2.78	523	1
347a	125	K	2.80	523	1
347b	125	K	2.80	523	1
348a	102	K	2.62	486	1
348b	102	K	2.62	486	1
349a	82	K	2.55	499	1
349b	82	K	2.55	499	1
351	n.d.	-	2.22	483	1
352	n.d.	-	2.25	483	1
353	80 (gum)	K	2.69	500	1
354	n.d.	-	2.97	438	1
355	80 (gum)	K	2.26	483	1
357a	116	K	2.55	511	1
357b	120	K	2.55	511	1
358	80 (gum)	K	2.86	442	1
359	n.d.	-	2.51	493	1
360	n.d.	-	2.58	525	1
362	n.d.	-	2.51	481	1
363a	80 (gum)	K	2.76	512	1
363b	80 (gum)	K	2.75	512	1
364	80 (gum)	K	2.50	499	1
364a	80 (gum)	K	2.47	499	1
364b	80 (gum)	K	2.48	499	1
365	80 (gum)	K	2.39	497	1

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
365a	80 (gum)	K	2.41	497	1
365b	80 (gum)	K	2.40	497	1
366	154	DSC	2.51	489	1
367a	n.d.	-	3.01	547	1
367b	n.d.	-	3.01	547	1
368	n.d.	-	2.26	483	1
369a	n.d.	-	2.99	524	1
369b	147	DSC	2.99	524	1
370a	128	DSC	2.48	498	1
370b	80 (gum)	K	2.50	498	1
371a	114	K	2.40	497	1
371b	107	K	2.40	497	1
373	n.d.	-	2.79	539	1
374a	132	K	2.36	483	1
374b	130	K	2.38	483	1
375	80	K	2.99	524	1
376	130 gum	K	2.48	497	1
379a	n.d.	-	2.60	504	1
379b	n.d.	-	2.59	504	1
380a	n.d.	-	2.59	488	1
380b	n.d.	-	2.60	488	1
381	n.d.	-	2.48	440	1
382	150	DSC	2.80	424	1
383	172	DSC	2.44	467	1
384	n.d.	-	2.36	471	1
385	n.d.	-	2.50	495	1
386	n.d.	-	2.65	509	1
388a	n.d.	-	2.88	557	1
388b	n.d.	-	2.88	557	1
389	n.d.	-	2.36	499	1
390	n.d.	-	2.53	513	1
391	n.d.	-	2.42	452	1

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
391a	n.d.	-	2.32	452	1
391b	n.d.	-	2.32	452	1
392a	80 (gum)	K	2.79	482	1
392b	n.d.	-	2.79	482	1
393a	115 (gum)	K	1.99	454	1
393b	196	DSC	1.99	454	1
394	161	DSC	2.41	471	1
395	80 (gum)	K	2.97	468	1
395a	90 (gum)	K	2.97	468	1
395b	102	K	2.97	468	1
396	n.d.	-	3.14	482	1
397	70 (gum)	K	2.82	436	1
397a	80 (gum)	K	2.83	436	1
397b	80 (gum)	K	2.83	436	1
398	n.d.	-	3.10	465	1

Co. No.	MP (°C)	Kofler (K) or DSC	Rt	[M+H] <sup>+</sup> or [M+Na] <sup>+</sup> or fragments	Method HPLC
399	202	K	2.96	474	1
400	80 (gum)	K	2.60	410	1
401	80 (gum)	K	2.78	424	1
402	80 (gum)	K	2.83	442	1
403a	53	DSC	3.13	440	1
403b	54	DSC	3.13	440	1
404a	n.d.	-	2.60	516	1
404b	n.d.	-	2.58	516	1
405a	n.d.	-	2.59	516	1
405b	n.d.	-	2.58	516	1
406a	80 (gum)	K	2.47	471	1
406b	80 (gum)	K	2.47	471	1
407a	115	K	2.58	481	1
407b	105	K	2.59	481	1
408a	127	DSC	2.47	444	1
408b	123	DSC	2.47	444	1

**OR data:** Solvent: DMF; temperature: 20°C; wavelength: 589 nm ('Co. No.' means Compound Number; 'OR' means optical rotation; 'Conc.' means concentration in g/100 mL)

Co. No.	OR (°)	Conc.
1	-292.75	0.392
2	+316.79	0.401
5	-412.51	0.331
6	+421.30	0.342
8	-382.23	0.266
9	+375.10	0.253
10	-402.40	0.258
12	-414.74	0.285
13	+416.86	0.261

Co. No.	OR (°)	Conc.
21	-320.83	0.264
22	+317.85	0.297
24	-498.40	0.281
25	+527.65	0.327
31	+352.63	0.244
33	-295.09	0.265
34	-239.57	0.278
37	+274.14	0.263
38	-238.83	0.291

Co. No.	OR (°)	Conc.
40	-301.03	0.290
43	+228.28	0.290
47	-243.13	0.276
51	-294.42	0.236
57	-213.58	0.202
58	+231.82	0.220
60	+341.54	0.321
61	+421.30	0.342
73	-348.84	0.301

Co. No.	OR (°)	Conc.
74	+343.7	0.270
83b	-513.10	0.229
83c	-496.67	0.330
85	-363.50	0.194
88	-459.09	0.264
89	+464.44	0.270
91	-348.27	0.245
92	+357.52	0.262
103	-309.92	0.259
106	-432.69	0.260
107	+391.95	0.236
113	+308.69	0.224
114	-337.35	0.191
117	-429.65	0.185
117a	-342.13	0.254
118	+404.14	0.198
118a	+359.47	0.338
122	-3145.76	0.197
122a	-314.81	0.216
123	+367.55	0.218
123a	+317.06	0.293
127	-105.60	0.250
128	+107.53	0.242
137	-365.95	0.173
138	-373.79	0.237
139	+395.19	0.270
140	+73.81	0.279
141	+76.81	0.292
152	+335.71	0.280
154a	-466.21	0.191
154b	+480.87	0.274
156	-317.47	0.256

Co. No.	OR (°)	Conc.
157	+307.31	0.260
158	-249.76	0.208
159	+259.50	0.203
160	-335.79	0.190
161	+318.44	0.242
162	-340.81	0.241
163	+292.77	0.188
165	-370.38	0.260
166	+366.30	0.270
171	-313.87	0.252
172	+311.51	0.304
174	+378.33	0.240
175	-335.27	0.258
177	-401.08	0.185
178	+427.32	0.194
181	+295.85	0.265
182	-324.34	0.189
184	-376.8	0.250
185	+301.82	0.275
186	-400.67	0.300
187	+402.33	0.314
188	-394.49	0.254
189	+420.35	0.226
192	+285.27	0.258
195	-339.85	0.266
199	-350.00	0.260
200	+343.06	0.288
203	-401.47	0.327
210	-334.15	0.244
211	-380.48	0.251
212	+360.74	0.298
213	-393.33	0.315

Co. No.	OR (°)	Conc.
214	+398.92	0.277
219	-341.38	0.290
220	+346.21	0.290
222	+265.31	0.245
227	-372.39	0.268
228	+372.09	0.258
237a	-335.17	0.290
237b	+319.70	0.264
243a	-341.33	0.354
243b	+375.76	0.445
244	+88.00	0.200
245	-67.62	0.245
249	-343.79	0.239
250	-374.62	0.231
251	-327.17	0.254
252	+352.63	0.244
257b	+413.08	0.193
257c	-367.10	0.207
262a	-494.03	0.268
262b	+483.66	0.257
279a	-387.27	0.267
279b	+401.56	0.256
280a	-358.62	0.290
280b	352.99	0.251
281a	-353.28	0.259
281b	+334.32	0.303
282a	-373.79	0.237
282b	+395.19	0.27
283a	-347.53	0.324
283b	+307.65	0.327
286a	+308.51	0.282
286b	-285.98	0.271



Co. No.	OR (°)	Conc.
292a	-342.13	0.224
292b	+354.32	0.238
295a	-409.09	0.253
295b	+409.72	0.288
296a	-299.27	0.275
296b	+264.91	0.285
297a	+292.92	0.24
297b	-303.53	0.238
298a	-255.68	0.273
298b	+391.81	0.293
299a	-336.73	0.245
299b	+316.61	0.289
309a	-344.58	0.249
309b	+347.21	0.269
312a	+400.77	0.26
312b	-362.14	0.28
313a	-316	0.25
313b	+407.69	0.26
314a	+346.67	0.255
314b	-342.01	0.269
315a	+285.04	0.274
315b	-304.43	0.271
319a	+6.84	0.263
319b	-8.3	0.277
324a	-303.6	0.25
324b	+346.84	0.269
325a	+334.04	0.285
325b	-376	0.25
329a	-315.38	0.26
329b	+321.85	0.27

Co. No.	OR (°)	Conc.
334a	-379.05	0.269
334b	+344.92	0.305
335a	-307.47	0.255
335b	+302.73	0.33
339a	-84.62	0.272
339b	+87.02	0.222
344a	-341.31	0.259
344b	+325.98	0.254
345a	-309.67	0.300
345b	+313.61	0.294
348a	-301.71	0.297
348b	+358.89	0.253
349a	-330.45	0.312
349b	+322.3	0.287
352	+18.94	0.396
355	+25.61	0.285
357a	+350.18	0.285
357b	-342.9	0.331
359	-16.73	0.269
363a	-376.21	0.269
363b	+260.7	0.57
367a	+5.62	0.267
367b	-9.6	0.267
368	-40.22	0.271
369a	-333.22	0.304
369b	+146.67	0.266
370a	-333.42	0.304
370b	+340.23	0.266
374a	-294.40	0.25
374b	+376.33	0.3

Co. No.	OR (°)	Conc.
379a	-353.65	0.274
379b	+316.25	0.277
380a	+381.39	0.274
380b	-401.88	0.266
388a	+279.3	0.256
388b	-273.06	0.271
391a	-287.94	0.257
391b	-301.54	0.260
392a	-384.21	0.248
393a	-381.05	0.281
393b	+315.51	0.245
395a	-142.92	0.365
395b	+171.98	0.335
397a	+33.21	0.268
397b	-35.66	0.258
398	-120.03	0.319
403a	-246.42	0.723
403b	+236.25	0.245
404a	+302.98	0.235
404b	-327.05	0.233
405a	+341.45	0.226
405b	-329.15	0.223
406a	-390.85	0.308
406b	+394.78	0.287
407a	-356	0.25
407b	+347.54	0.242
408a	-400.66	0.302
408b	+390.38	0.312

**SFC-MS Methods:**

General procedure for SFC-MS methods

The SFC measurement was performed using an Analytical Supercritical fluid chromatography (SFC) system composed by a binary pump for delivering carbon dioxide (CO<sub>2</sub>) and modifier, an autosampler, a column oven, a diode array detector  
 5 equipped with a high-pressure flow cell standing up to 400 bars. If configured with a Mass Spectrometer (MS) the flow from the column was brought to the (MS). It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was  
 10 performed with appropriate software.

Table: Analytical SFC-MS Methods (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes, Backpressure (BPR) in bars).

Method number	column	mobile phase	gradient	Flow ----- Col T	Run time ----- BPR
1	Daicel Chiralpak® AD-H column (5 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH(+0.3% iPrNH <sub>2</sub> )	25% B hold 7 min,	3 ----- 35	7 ----- 100
2	Daicel Chiralpak® AD-H column (5 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH(+0.3% iPrNH <sub>2</sub> )	30% B hold 7 min,	3 ----- 35	7 ----- 100
3	Daicel Chiralpak® AD-H column (5 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH(+0.3% iPrNH <sub>2</sub> )	40% B hold 7 min,	3 ----- 35	7 ----- 100
4	Daicel Chiralpakl® AS-3 column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH(+0.3% iPrNH <sub>2</sub> )	20% B hold 3 min,	3.5 ----- 35	3 ----- 103
5	Daicel Chiralpakl® AS-3 column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: MeOH(+0.3% iPrNH <sub>2</sub> )	25% B hold 3 min,	3.5 ----- 35	3 ----- 103
6	Daicel Chiralcel® OJ-H column (5 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH(+0.3% iPrNH <sub>2</sub> )	15% B hold 7 min,	3 ----- 35	7 ----- 100

Method number	column	mobile phase	gradient	Flow ----- Col T	Run time ----- BPR
7	Daicel Chiralcel® OJ-H column (5 μm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH(+0.3% iPrNH <sub>2</sub> )	25% B hold 7 min,	3 ----- 35	7 ----- 100
8	Daicel Chiralcel® OJ-H column (5 μm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: MeOH(+0.3% iPrNH <sub>2</sub> )	20% B hold 7 min,	3 ----- 35	7 ----- 100
9	Daicel Chiralcel® OJ-H column (5 μm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: MeOH(+0.3% iPrNH <sub>2</sub> )	25% B hold 7 min,	3 ----- 35	7 ----- 100
10	Daicel Chiralpakl® AD-3 column (3 μm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH(+0.3% iPrNH <sub>2</sub> )	25% B hold 3 min,	3.5 ----- 35	3 ----- 103
11	Daicel Chiralpakl® AD-3 column (3 μm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH(+0.3% iPrNH <sub>2</sub> )	40% B hold 3 min,	3.5 ----- 35	3 ----- 103

Table: Analytical SFC-MS data – R<sub>t</sub> means retention time (in minutes), method refers to the method used for (SFC)MS analysis of enantiomerically pure compounds.

\* Co. No. 207 is a mixture of 2 diastereoisomers

Co. No.	R <sub>t</sub>	Chiral purity UV Area%	Method number	Co. No.	R <sub>t</sub>	Chiral purity UV Area%	Method number
237c	1.43	100	9	371a	2.14	100	1
237d	1.78	99.69	9	371b	2.6	99.48	1
364a	0.79	100	11	322a	1.41	99.46	5
364b	2.00	100	11	322b	1.81	99.33	5
365a	5.31	100	2	323a	1.32	97.97	5
365b	6.44	100	2	323b	1.77	99.09	5
392b	3.96	100	3	201	1.87	100	8
207*	2.42	55	6	202	2.84	100	8
208	1.65	100	8	205	3.71	45	6

Co. No.	Rt	Chiral purity UV Area%	Method number
284a	1.56	100	7
284b	1.96	99.46	7
338a	2.16	100	7
338b	2.7	99.44	7
287a	1.61	100	10
287b	1.96	95.36	10
201	2.08	100	8

Co. No.	Rt	Chiral purity UV Area%	Method number
202	3.07	100	8
347a	5.02	100	1
347b	4.48	100	1
302a	1.43	100	4
302b	1.89	100	4
300a	3.24	100	2
300b	4.73	100	2

**<sup>1</sup>H NMR data:**

**Compound 117:** <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.93 (s, 1 H) 8.55 (t, *J*=5.5 Hz, 1 H) 8.27 (d, *J*=2.2 Hz, 1 H) 8.11 (d, *J*=2.2 Hz, 1 H) 6.88 - 6.98 (m, 1 H) 6.70 (d, *J*=7.3 Hz, 1 H) 6.24 - 6.32 (m, 1 H) 6.14 - 6.23 (m, 2 H) 5.44 (quin, *J*=6.8 Hz, 1 H) 4.72 (t, *J*=5.7 Hz, 1 H) 3.73 - 3.88 (m, 8 H) 3.51 (q, *J*=6.0 Hz, 2 H) 3.28 - 3.33 (m, 2 H) 1.49 (d, *J*=6.6 Hz, 3 H)

**Compound 184:** <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.93 (s, 1 H) 8.49 (t, *J*=5.5 Hz, 1 H) 8.25 (d, *J*=1.9 Hz, 1 H) 8.08 (d, *J*=1.9 Hz, 1 H) 7.02 (d, *J*=7.3 Hz, 1 H) 5.98 - 6.18 (m, 3 H) 5.44 (q, *J*=6.8 Hz, 1 H) 3.73 - 3.90 (m, 8 H) 3.36 (q, *J*=6.6 Hz, 2 H) 2.40 (t, *J*=6.8 Hz, 2 H) 2.17 (s, 6 H) 1.49 (d, *J*=6.9 Hz, 3 H)

**Compound 276:** <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.85 (s, 1 H) 8.38 (br t, *J*=5.4 Hz, 1 H) 7.61 (d, *J*=1.3 Hz, 1 H) 7.09 - 7.18 (m, 1 H) 6.96 - 7.08 (m, 2 H) 6.90 (d, *J*=0.9 Hz, 1 H) 6.76 (br t, *J*=6.1 Hz, 1 H) 4.70 (t, *J*=5.7 Hz, 1 H) 4.55 (br d, *J*=6.3 Hz, 2 H) 3.73 - 3.88 (m, 8 H) 3.48 (q, *J*=6.0 Hz, 2 H) 3.29 (q, *J*=6.2 Hz, 2 H) 2.29 (s, 3 H)

**Compound 158:** <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 9.44 (s, 1 H) 7.94 (d, *J*=1.9 Hz, 1 H) 7.75 (d, *J*=1.6 Hz, 1 H) 7.32 (br s, 1 H) 7.06 (d, *J*=7.9 Hz, 1 H) 6.12 - 6.24 (m, 1 H) 6.06 - 6.12 (m, 2 H) 5.66 (quin, *J*=6.9 Hz, 1 H) 4.40 (q, *J*=2.5 Hz, 2 H) 3.93 (t, *J*=5.5 Hz, 2 H) 3.01 (s, 3 H) 2.74 - 2.88 (m, 5 H) 1.56 (d, *J*=6.9 Hz, 3 H)

**Compound 14:** <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.86 (s, 1 H) 7.69 (s, 1 H) 7.23 (d, *J*=1.3 Hz, 1 H) 6.25 (br t, *J*=9.5 Hz, 1 H) 5.97 (br d, *J*=10.4 Hz, 2 H) 5.61 (br d, *J*=7.6 Hz, 1 H) 4.46 (br s, 1 H) 3.70 - 3.86 (m, 11 H) 3.36 - 3.46 (m, 3 H) 2.44 - 2.50 (m, 1 H) 1.81 - 2.09 (m, 3 H)

**Compound 12:** <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.91 (s, 1 H) 7.74 (d, *J*=1.9 Hz, 1 H) 7.59 (d, *J*=1.9 Hz, 1 H) 6.99 (d, *J*=7.6 Hz, 1 H) 6.14 (tt, *J*=9.5, 2.2 Hz, 1 H) 6.04 - 6.09 (m, 2 H) 5.44 (quin, *J*=6.9 Hz, 1 H) 3.75 - 3.89 (m, 8 H) 2.74 - 3.09 (m, 6 H) 1.50 (d, *J*=6.6 Hz, 3 H)

**Compound 39:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.92 (s, 1 H) 7.72 (s, 1 H) 7.06 (br s, 1 H) 6.26 (br t, *J*=9.6 Hz, 1 H) 5.97 (br d, *J*=10.1 Hz, 2 H) 5.58 (d, *J*=8.1 Hz, 1 H) 4.27 (br s, 1 H) 3.64 - 3.98 (m, 9 H) 3.40 (br q, *J*=7.6 Hz, 1 H) 3.15 (br s, 1 H) 2.60 (br s, 2 H) 2.10 - 2.44 (m, 4 H) 1.77 - 2.07 (m, 3 H) 0.39 - 1.10 (m, 6 H).

5 **Compound 211:** <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.94 (s, 1H) 8.55 (t, *J*=5.7 Hz, 1H) 8.27 (d, *J*=1.9 Hz, 1H) 8.08 (d, *J*=1.9 Hz, 1H) 7.07 (d, *J*=7.3 Hz, 1H) 6.12 (tt, *J*=9.5, 2.0 Hz, 1H) 6.06 (br d, *J*=11.0 Hz, 2H) 5.44 (quin, *J*=6.8 Hz, 1H) 3.72 - 3.92 (m, 8H) 3.28 - 3.32 (m, 2H, partially obscured by solvent peak) 2.61 - 2.78 (m, 3H) 1.61 (br s, 1H) 1.49 (d, *J*=6.6 Hz, 3H) 0.96 (d, *J*=6.0 Hz, 6H)

10 **Compound 328:** <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.93 (s, 1H) 8.50 (br t, *J*=5.5 Hz, 1H) 8.25 (s, 1H) 8.01 (s, 1H) 6.85 (q, *J*=7.9 Hz, 1H) 6.32 (t, *J*=9.0 Hz, 1H) 6.18 (d, *J*=8.2 Hz, 1H) 5.99 (br t, *J*=6.0 Hz, 1H) 4.80 (br d, *J*=5.7 Hz, 2H) 3.71 - 3.94 (m, 8H) 3.34 - 3.37 (m, 2H, partially obscured by solvent peak) 2.39 (br t, *J*=6.9 Hz, 2H) 2.16 (s, 6H) 2.09 (s, 3H)

15 Pharmacology update

Enzyme Binding Assays (KINOMEScan®)

Kinase enzyme binding affinities of compounds disclosed herein were determined using the KINOMEScan technology performed by DiscoverX Corporation, San Diego, California, USA (www.kinomescan.com). Table A reports the obtained K<sub>d</sub> values

20 (nM), with the K<sub>d</sub> being the inhibitor binding constant:

Co. No.	K <sub>d</sub> PIK3Cα_h (nM)	K <sub>d</sub> PIK3Cβ_h (nM)	K <sub>d</sub> PIK3Cδ_h (nM)	K <sub>d</sub> PIK3Cγ_h (nM)	K <sub>d</sub> MTOR_h (nM)
1	34	0.3	15	313	28184
2	12276	1086	16407	>30200	>30200
3	47	1	20	229	17783
4	23442	1698	22909	>30200	>30200
5	1587	2	225	7977	25119
6	26003	1894	16923	>30200	>30200
7	513	2	245	10000	>30200
8	396	1	109	3864	20893
9	27542	417	18197	>30200	>30200
10	142	0.5	74	336	>30200
11	631	1	275	2512	>30200
12	276	0.4	75	1137	26331
13	23855	182	5888	>30200	>30200
14	174	0.2	36	229	>10000
15	234	1	43	372	>30200
16	93	1	16	126	16982

Co. No.	Kd PIK3C $\alpha$ _h (nM)	Kd PIK3C $\beta$ _h (nM)	Kd PIK3C $\delta$ _h (nM)	Kd PIK3C $\gamma$ _h (nM)	Kd MTOR_h (nM)
17	25	0.1	3	107	12303
18	5	0.1	1	37	21878
19	363	0.2	29	309	18197
20	3631	17	1549	22387	21878
21	4786	63	2239	15849	19953
22	15136	5623	18621	>30200	21878
23	324	1	331	724	15136
24	302	1	245	372	18621
25	12303	37	4677	12883	>30200
26	174	2	117	1318	>30200
27	269	1	58	1622	>30200
28	107	1	29	832	>30200
29	10233	1660	21878	>30200	23442
30	39	1	18	407	21878
31	>32000	>32000	>32000	>32000	>32000
32	120	1	85	646	>30200
33	58	1	47	389	>30200
34	50	0.4	30	933	>30200
35	162	2	151	1905	>30200
36	224	2	107	1585	15849
37	6166	20	2884	>30200	>30200
38	3	0.4	6	933	>30200
39	14	0.2	7	214	>30200
40	56	1	35	309	17378
41	389	1	141	1380	>30200
42	331	1	56	1479	>30200
43	4677	316	7244	1096	>30200
44	234	1	174	631	23442
45	170	3	126	2089	31623
46	9333	85	9550	>30200	>30200
47	41	0.2	32	759	14791
48	2455	28	724	14791	>30200
49	2188	16	933	7586	>30200
50	11	0.2	8	87	8913
51	55	1	39	339	>30200
52	6166	38	4898	13804	>30200
53	2951	3	692	21380	>30200
54	16218	115	7079	>30200	26915
55	>30200	3981	>30200	>30200	>30200
56	6607	13	2630	>30200	>30200
57	49	0.4	31	525	25119
58	1995	9	912	18621	>30200
59	1202	3	331	10715	>30200

Co. No.	Kd PIK3C $\alpha$ _h (nM)	Kd PIK3C $\beta$ _h (nM)	Kd PIK3C $\delta$ _h (nM)	Kd PIK3C $\gamma$ _h (nM)	Kd MTOR_h (nM)
60	22909	490	15488	>30200	>30200
61	676	2	209	5248	>30200
62	25	1	51	234	2042
63	79	0.5	27	891	8128
64	224	1	58	1288	15136
65	38	1	17	200	10715
66	65	2	79	676	16982
67	2455	18	617	20893	>30200
68	3162	3	589	15136	22387
69	891	3	195	3090	>30200
70	339	2	148	1096	19055
71	251	1	138	794	22387
72	56	0.2	17	204	20417
73	2042	9	282	19498	>30200
74	8511	603	5623	>30200	23442
75	30	0.1	2	4	>30200
76	50	0.1	19	251	>30200
77	363	0.3	100	646	>30200
78	3715	15	1175	13490	>30200
79	2291	2	204	19953	>30200
80	>30200	50	7586	24547	>30200
81	19055	30	2630	29512	>30200
82	12303	15	166	>30200	>30200
84	692	1	96	1288	8511
85	257	0.3	41	1660	562
86	3467	15	537	21380	>30200
87	22909	1380	9550	>30200	>30200
88	2138	5	603	4677	14125
89	7244	832	11749	9550	13490
90	9120	17	741	22909	>30200
91	4467	10	1230	21380	>30200
92	16218	1023	16596	>30200	>30200
93	219	0.3	33	191	21878
94	79	0.1	29	178	21380
95	295	0.5	178	1096	>30200
96	363	0.4	83	302	17378
97	19055	214	>30200	>30200	>30200
98	479	47	955	437	2239
99	9772	52	4677	11482	>30200
100	1288	1	295	1738	14125
101	263	0.4	40	398	>30200
102	245	0.2	31	398	>30200
103	1134	3	1001	2995	24547

Co. No.	Kd PIK3C $\alpha$ _h (nM)	Kd PIK3C $\beta$ _h (nM)	Kd PIK3C $\delta$ _h (nM)	Kd PIK3C $\gamma$ _h (nM)	Kd MTOR_h (nM)
104	1349	3	263	17783	>30200
105	3890	8	871	28184	>30200
106	3162	6	1000	3311	>30200
107	>30200	363	23442	>30200	>30200
111	6026	16	1820	1479	10000
112	955	1	204	2399	>30200
113	>30200	1023	>30200	>10000	>30200
114	1622	1	186	6918	>30200
115	1660	2	324	10000	>30200
116	>30200	2884	30200	>30200	>30200
117	1105	3	324	3412	17128
118	14232	204	10192	2851	>30200
119	2239	2	490	11749	>30200
120	6761	14	2188	>30200	>30200
121	5370	10	1585	>30200	>30200
122	2884	0.3	151	5623	25704
123	9333	91	2239	12589	16596
124	1072	4	575	7762	8128
125	6457	68	5888	>30200	>30200
126	6918	13	1288	>30200	>30200
127	6457	32	2291	21878	25704
128	4898	1122	15136	12303	21380
129	1778	3	1072	8913	9772
130	363	0.5	135	240	6166
131	3162	11	2512	19953	>30200
132	832	0.5	115	2188	11482
133	5754	3	263	26303	>30200
134	>30200	87	6310	>30200	>30200
135	10000	195	3802	17378	11220
136	2344	3	355	5129	15136
137	138	0.1	9	501	>30200
138	398	0.1	56	2150	30903
139	3765	41	4423	3433	18621
140	14791	5129	15849	25119	>30200
141	6607	6	776	8128	>30200
142	209	0.5	59	741	>30200
143	2818	2	389	9550	>30200
144	1738	2	437	5623	>30200
145	537	1	102	1862	23442
146	1905	2	933	8128	>30200
147	776	0.4	129	1148	>30200
148	1072	1	316	8128	>30200
149	2951	2	398	2344	>30200



Co. No.	Kd PIK3C $\alpha$ _h (nM)	Kd PIK3C $\beta$ _h (nM)	Kd PIK3C $\delta$ _h (nM)	Kd PIK3C $\gamma$ _h (nM)	Kd MTOR_h (nM)
150	2884	3	501	3715	>30200
151	3631	8	813	8710	>30200
152	3981	10	1820	8710	>30200
153	5370	8	1175	2692	16218
155	2138	6	759	6607	>30200
156	398	2	363	>30200	>30200
157	13183	102	19953	>30200	>30200
158	339	0.4	120	2291	>30200
159	>30200	110	23442	>30200	>30200
160	813	2	575	9772	19498
161	>30200	776	>30200	>30200	>30200
162	3981	9	1230	24547	>30200
163	>30200	832	16218	>30200	>30200
164	2399	4	1096	13804	>30200
165	1778	0.3	182	5495	14125
166	16596	19	4074	14791	21878
167	17378	26	7762	12883	>30200
168	3631	17	1862	>30200	>30200
169	4074	8	1122	5370	18621
170	617	5	288	2239	4365
171	2188	3	575	>30200	>30200
172	>30200	1259	>30200	>30200	>30200
173	832	1	372	3548	24547
174	>30200	1202	26303	>30200	>30200
175	1698	0.4	112	2570	>30200
176	1995	1	102	3467	>30200
177	1380	2	170	6918	23988
178	>30200	1096	16596	>30200	>30200
180	891	0.1	49	2188	>30200
181	5012	117	20417	17783	>30200
182	126	0.3	32	912	>30200
183	2512	0.1	102	1738	>30200
184	599	0.2	57	994	18905
185	5754	29	5370	4266	>30200
186	6310	10	1778	27542	>30200
187	>30200	1047	>30200	>30200	>30200
188	851	1	182	2291	16218
189	>30200	2512	28184	4467	>30200
192	>30200	9120	>30200	>30200	>30200
193	>30200	158	17783	>30200	>30200
194	>30200	1820	>30200	>30200	>30200
195	1950	2	479	12883	>30200
196	2818	5	813	15849	>30200

Co. No.	Kd PIK3C $\alpha$ _h (nM)	Kd PIK3C $\beta$ _h (nM)	Kd PIK3C $\delta$ _h (nM)	Kd PIK3C $\gamma$ _h (nM)	Kd MTOR_h (nM)
197	692	3	302	13804	>30200
198	11220	22	3162	15488	>30200
199	4898	68	5495	11749	28840
200	>30200	2399	>30200	>30200	>30200
201	1455	2	710	4451	16549
202	>30200	3948	>30200	3325	6026
203	1660	5	912	6607	21380
204	>30200	1072	>30200	14454	>30200
205	>30200	204	17378	>30200	>30200
206	>30200	7079	>30200	>30200	>30200
207	5248	6	891	16218	7943
208	3467	8	1413	>30200	>30200
209	>30200	316	11482	16982	>30200
210	3162	12	1023	>30200	>30200
211	3369	1	190	3599	20198
212	7093	12	3291	5073	13804
213	2089	2	269	3236	7762
214	>30200	1230	>30200	4571	>30200
217	2138	4	1288	23988	>30200
218	537	5	1175	3090	3311
219	93	1	275	955	3311
220	25704	2754	>30200	25704	6457
222	>30200	759	>30200	>30200	>30200
223	>30200	4786	>30200	13804	>30200
224	27542	186	4467	>30200	>30200
225	4677	6	537	2512	>30200
226	2570	1	275	5623	28840
227	1778	1	339	3802	>30200
228	6166	603	15488	4074	>30200
229	3890	7	1738	20417	12589
230	7079	12	759	18197	12023
231	16982	52	>3311	>30200	>10000
232	16218	98	2818	>30200	13183
234	n.d.	n.d.	n.d.	n.d.	n.d.
235	>32000	50	7586	24547	>32000
236	112	2	158	813	1318
237	288	1	138	9333	>30200
238	5013	8	2211	12306	>30200
239	603	2	316	1288	10471
240	9333	2239	17378	18197	>30200
241	427	8	589	5370	22387
242	15849	4786	17783	>30200	>30200
243	66	1	71	145	1905

Co. No.	Kd PIK3C $\alpha$ _h (nM)	Kd PIK3C $\beta$ _h (nM)	Kd PIK3C $\delta$ _h (nM)	Kd PIK3C $\gamma$ _h (nM)	Kd MTOR_h (nM)
244	8318	741	4169	12589	19953
245	8710	72	1047	13183	21878
249	794	4	955	2399	>30200
250	339	1	219	955	14454
251	8	0.3	23	65	676
252	>30200	>30200	>30200	>30200	>30200
262	n.d.	n.d.	n.d.	n.d.	n.d.
264	9772	52	4677	11482	>30200
272	4898	5	1995	>30200	>30200
273	6310	8	2754	>10000	>30200
276	1950	4	871	9120	10965
278	2089	8	1738	15849	19498
279	5370	5	372	6457	19055
280	5129	6	427	11220	>30200
281	3162	0.3	91	3548	>30200
282	832	0.2	68	1820	23442
286	7413	18	2042	16982	>30200
287	2692	13	977	26303	>30200
291	550	407	2818	513	10233
292	6607	16	1698	27542	>30200
293	>30200	>30200	>30200	>30200	>30200
295	7244	309	7762	6310	30903
296	2951	1	166	6457	>30200
297	1862	0.3	110	1950	>30200
300	2692	4	513	16982	>30200
301	5370	43	3236	1514	15136
302	1950	5	380	15488	>30200
303	3548	9	457	3890	18621
304	7244	62	6761	19953	>30200
308	>30200	324	7244	>30200	>30200
309	n.d.	n.d.	n.d.	n.d.	n.d.
316	12883	21	1380	>30200	>30200
317	6166	13	708	20893	>30200
318	3467	6	288	>30200	>30200
328	1905	0.2	324	6607	17783
332	2951	15	4266	21380	>30200
333	5248	37	7413	17378	>30200
336	1950	4	871	9120	10965
337	3981	35	3802	7943	>30200
338	2344	12	2951	4365	>30200
339	5888	427	2455	9333	16218
340	1514	2	372	5012	12023
341	3388	17	1479	8128	21380

Co. No.	Kd PIK3C $\alpha$ _h (nM)	Kd PIK3C $\beta$ _h (nM)	Kd PIK3C $\delta$ _h (nM)	Kd PIK3C $\gamma$ _h (nM)	Kd MTOR_h (nM)
342	3802	9	1000	26915	16596
343	2188	22	3311	10000	>10000
347	3715	4	407	28840	>30200
350	n.d.	n.d.	n.d.	n.d.	n.d.
351	2512	21	1698	2138	>30200
352	2291	2	1000	9772	>30200
353	5012	4	692	>30200	>30200
354	8128	63	2399	28184	>30200
355	4786	13	2884	20893	13183
358	10000	148	2239	17783	>30200
359	11327	43	796	28840	6463
360	6761	42	11749	26915	>30200
361	2951	2	490	9772	19055
362	2951	2	490	9772	19055
364	7413	5	813	13804	>30200
365	2089	1	117	2884	>30200
366	1047	4	123	1318	4266
368	5370	7	1413	>30200	>30200
373	>30200	158	5248	>30200	>30200
375	18621	117	2188	>30200	>30200
376	4266	1	295	5129	>30200
381	3548	26	3802	8318	>30200
382	>30200	17	5012	>30200	>30200
383	1230	1	234	7943	7079
384	2692	1	575	15849	19953
385	933	1	347	6166	16596
386	3236	15	692	14791	24547
389	3162	5	2188	>30200	>30200
390	16596	78	3236	22387	>30200
391	5495	251	3388	12023	24547
394	3236	0.2	776	12589	23442
395	3467	33	2239	14125	18197
396	7762	120	2042	20893	>30200
397	2692	36	661	22909	>30200
398	10715	257	5754	>30200	>30200
399	2818	45	5248	9333	>30200
400	2344	24	1585	18621	26303
401	1862	550	12303	>30200	11482
402	4467	44	4074	>30200	>30200
117a	n.d.	n.d.	n.d.	n.d.	n.d.
118a	n.d.	n.d.	n.d.	n.d.	n.d.
122a	3702	3	660	7969	14125
123a	10233	107	5129	11482	16982

Co. No.	Kd PIK3C $\alpha$ _h (nM)	Kd PIK3C $\beta$ _h (nM)	Kd PIK3C $\delta$ _h (nM)	Kd PIK3C $\gamma$ _h (nM)	Kd MTOR_h (nM)
154a	437	1	98	741	8511
154b	20893	490	14791	7762	25119
184a	806	0.1	74	1483	21880
184b	589	0.1	66	1096	19953
184c	829	0.1	54	1268	23988
237a	105	1	204	5012	>30200
237b	8710	74	7762	>30200	>30200
237c	372	4	234	5495	>30200
237d	12589	240	19498	>30200	>30200
243a	39	0.5	69	100	1479
243b	1660	14	3388	1950	1349
246a	813	4	3890	6761	26915
246b	>30200	16596	>30200	6166	>30200
257b	851	22	468	3090	2818
257c	1698	603	3020	3162	1660
262a	>30200	1778	24547	>30200	>30200
262b	>30200	11482	>30200	>30200	>30200
279a	2188	7	513	5623	21380
279b	26303	1905	30200	6457	>30200
280a	1698	12	562	12023	20893
280b	22387	813	21380	24547	>30200
281a	1514	0.3	72	4074	23442
281b	6166	151	3467	7413	>30200
283a	12023	7	1549	19055	>30200
283b	>30200	1380	18197	29512	>30200
284a	2076	10	939	8137	19055
284b	>30200	2145	>30200	5070	>30200
286a	10233	182	5754	>30200	25704
286b	6026	2	355	16218	>30200
287a	1738	3	234	20893	>30200
287b	9333	27	2951	>30200	>30200
292a	2818	17	603	21878	32359
292b	>30200	14791	>30200	>30200	>30200
295a	6457	288	6761	>30200	14454
295b	>30200	19498	>30200	4571	>30200
296a	1380	1	170	3236	>30200
296b	>30200	14	9333	>30200	>30200
297a	16982	26	6310	15136	>30200
297b	1023	0.5	112	1479	>30200
298a	4786	4	724	24547	>30200
298b	23988	186	10233	>30200	>30200
299a	6310	1	269	10965	>30200
299b	13183	60	5248	19498	>30200

Co. No.	Kd PIK3C $\alpha$ _h (nM)	Kd PIK3C $\beta$ _h (nM)	Kd PIK3C $\delta$ _h (nM)	Kd PIK3C $\gamma$ _h (nM)	Kd MTOR_h (nM)
300a	1479	2	191	5495	>30200
300b	23988	537	23442	>30200	>30200
302a	>30200	1318	>30200	>30200	>30200
302b	1096	3	186	11749	>30200
309a	1096	0.1	59	1738	19953
309b	4898	18	2344	5623	>30200
312a	15488	1148	10000	>30200	>10000
312b	5129	26	1862	28184	19953
313a	5012	3	851	26303	>30200
313b	14454	302	5495	>30200	>30200
314a	17378	417	6026	30200	19055
314b	8913	2	1000	16596	>30200
315a	>30200	2239	>30200	>30200	>30200
315b	2754	1	162	5495	>30200
319a	9120	200	2818	>30200	>30200
319b	4365	59	1023	>30200	>30200
320a	513	2	182	4467	>30200
320b	11482	69	5129	>30200	>30200
321a	832	1	174	4677	>30200
321b	18621	166	7413	>30200	>30200
322a	29512	513	23988	>30200	>30200
322b	2188	0.3	68	6166	>30200
323a	>30200	1000	28840	>30200	>30200
323b	3802	1	182	3090	>30200
324a	1738	0.5	83	7244	>30200
324b	4898	229	3090	22387	>30200
325a	10715	1318	11482	14125	>30200
325b	3020	4	525	12023	9120
329a	339	0.1	26	2754	22909
329b	6026	42	1778	6310	22909
334a	5370	19	1072	12883	26915
334b	21380	457	7586	10965	17378
335a	466	0.2	33	1218	18621
335b	8315	11	3421	13490	>30200
338a	1514	11	1072	7244	25704
338b	22909	851	>30200	2344	19953
339a	4571	112	2089	10715	>30200
339b	759	316	1950	2188	6457
344a	2138	2	288	8318	>30200
344b	8128	166	3802	14125	>30200
345a	4365	2	282	14791	>30200
345b	>30200	724	22909	>30200	>30200
346a	2512	3	955	9550	30903

Co. No.	Kd PIK3C $\alpha$ _h (nM)	Kd PIK3C $\beta$ _h (nM)	Kd PIK3C $\delta$ _h (nM)	Kd PIK3C $\gamma$ _h (nM)	Kd MTOR_h (nM)
346b	23442	741	20893	2754	>30200
347a	>30200	2692	>30200	>30200	>30200
347b	3890	2	355	25704	>30200
348a	3020	10	912	29512	>30200
348b	>30200	1318	25704	>30200	>30200
349a	813	0.2	36	4266	>30200
349b	4677	14	2754	25704	>30200
356a	n.d.	n.d.	n.d.	n.d.	n.d.
356b	n.d.	n.d.	n.d.	n.d.	n.d.
357a	22909	3311	16218	>30200	>30200
357b	933	1	158	8128	>30200
363a	10965	10	417	26915	>30200
363b	31623	1288	16982	>30200	27542
364a	2455	1	204	6918	>30200
364b	7079	372	7762	8128	>30200
365a	5248	1	204	10233	>30200
365b	15488	251	4169	22909	>30200
367a	4074	63	1148	23442	29512
367b	2455	35	427	>30200	28184
369a	7244	20	525	>30200	25119
369b	>30200	3311	28840	>30200	>30200
370a	1230	0.3	107	2630	>30200
370b	>30200	550	15488	>30200	>30200
371a	1514	0.3	83	1047	>30200
371b	12589	20	5012	10965	>30200
374a	2455	0.3	141	5888	>30200
374b	13490	98	5754	21878	>30200
379a	9772	2	813	>30200	>30200
379b	>30200	1259	>30200	>30200	>30200
380a	9120	1047	7244	10000	19055
380b	3802	5	1202	8913	18621
388a	>30200	933	>30200	>30200	>30200
388b	2188	3	200	2399	>30200
391a	>30200	10715	>30200	>30200	16982
391b	>30200	19498	>30200	>30200	>30200
392a	3981	21	2818	14125	20417
392b	n.d.	n.d.	n.d.	n.d.	n.d.
393a	437	11	1230	1380	6761
393b	10965	2291	25704	6607	15849
395a	3467	33	1259	17783	>30200
395b	3981	631	3548	32359	18621
397a	3631	1413	10715	25119	15488
397b	1862	25	871	12303	>30200

Co. No.	Kd PIK3C $\alpha$ _h (nM)	Kd PIK3C $\beta$ _h (nM)	Kd PIK3C $\delta$ _h (nM)	Kd PIK3C $\gamma$ _h (nM)	Kd MTOR_h (nM)
403a	1479	3	331	8913	>30200
403b	>30200	3162	17378	>30200	>30200
404a	>30200	1514	>30200	>30200	>30200
404b	5248	1	1072	16596	>30200
405a	>30200	501	7413	>30200	>30200
405b	5012	1	219	4677	20893
406a	372	0.1	39	1047	22909
406b	7413	141	3467	3802	>30200
407a	2042	7	724	7943	10471
407b	4365	339	2951	3802	>30200
408a	1445	3	331	4266	26303
408b	23442	324	17378	8128	>30200
83a	112	2	158	813	1318
83b	170	1	129	562	1288
83c	3090	158	4898	2692	3090

#### Cellular assays:

Cellular activity of PI3K $\beta$  inhibitors was determined by quantifying the phosphorylation of Akt in PC-3 cells. Akt phosphorylated at Ser473 and Thr308 were measured using an enzyme-linked immunosorbent assay (ELISA; Meso Scale Discovery (MSD), Gaithersburg, MD) and specific primary antibodies from MSD.

On day 1, PC3 cells (ATCC # CRL-14351) were seeded into PerkinElmer MW96 plates at 25,000 cells per well, in 75  $\mu$ l complete culture medium (DMEM high glucose, AQmedia™, D0819, Sigma-Aldrich) containing 10% heat inactivated FCS and incubated at 37 °C, 5% CO<sub>2</sub> during 24 hours. On day 2, compound or DMSO (0.3%) was added and cells were further incubated for 60 min at 37 °C, 5% CO<sub>2</sub> in a total volume of 100  $\mu$ l of medium.

The phosphoprotein assay was executed according to vendor instructions in the Phospho-Akt (Ser473) Assay Whole Cell Lysate Kit (MSD # K15100D-3) and the Phospho-Akt (Thr308) Assay Whole Cell Lysate Kit (MSD # K151DYD-3 ) using the lysis, blocking and wash buffer provided.

Briefly, at the end of the cell treatment period, media were removed by aspiration and adherent cells were lysed in 50  $\mu$ l ice-cold lysis buffer. MSD plates are supplied pre-coated with capture antibodies for Phospho-Akt (Ser473 and Thr308). After blocking, lysates from tissue culture plates were added and plates were washed. Then, a solution containing the detection antibody (anti-total Akt conjugated with an



electrochemiluminescent compound-MSD Sulfo-tag label) was added. The signals were detected using an MSD SECTOR Imager 6000 and are proportional to the phospho-Akt titres.

Data were processed. The percentage of inhibition was plotted against the log concentration of test compounds, and the sigmoidal log concentration-effect curve of best fit was calculated by nonlinear regression analysis. From these concentration-response curves, the IC<sub>50</sub> values were calculated. Five concentrations were used for curve fitting.

10 Table B reports the obtained IC<sub>50</sub> values (nM):

Co. No.	IC <sub>50</sub> pAkt_S473 (nM)	IC <sub>50</sub> pAkt_Thr308 (nM)
1	2	3
2	>513	>513
3	3	~3
4	>513	>513
5	100	99
6	>513	>513
7	42	21
8	25	20
9	>513	>513
10	4	3
11	81	42
12	18	9
13	>513	>513
14	31	11
15	4	2
16	~5	2
17	~3	1
18	1	0,3
19	15	10
20	363	372
21	513	~501
22	>513	>513
23	~68	42
24	36	30
25	>513	>513
26	4	~1.35
27	22	14
28	5	6
29	>513	>513
30	5	~4

Co. No.	IC <sub>50</sub> pAkt_S473 (nM)	IC <sub>50</sub> pAkt_Thr308 (nM)
31	>513	>513
32	12	17
33	3	4
34	<0.8	3
35	~39	~26.92
36	10	5
37	200	126
38	~0.8	1
39	7	5
40	7	4
41	31	22
42	16	11
43	>513	331
44	74	66
45	166	72
46	>513	>513
47	3	4
48	>513	~457
49	>513	468
50	1	1
51	3	3
52	>513	240
53	214	148
54	>513	>513
55	>513	>513
56	>513	148
57	~5	4
58	>513	295
59	263	110
60	>513	>513

Co. No.	IC <sub>50</sub> pAkt_S473 (nM)	IC <sub>50</sub> pAkt_Thr308 (nM)
61	182	123
62	52	32
63	9	4
64	13	6
65	6	2
66	13	6
67	195	166
68	257	148
69	117	~32
70	~45	23
71	~15	13
72	2	1
73	>513	331
74	>513	>513
75	2	1
76	7	7
77	~76	~51
78	~219	~295
79	158	123
80	~214	~79
81	~490	219
82	>513	>513
84	56	32
85	48	78
86	513	263
87	>513	>513
88	178	89
89	>513	>513
90	>513	>513
91	>513	234
92	>513	>513
93	41	28
94	8	12
95	34	18
96	25	20
97	>513	>513
98	>513	>513
99	>513	355
100	145	68
101	21	14
102	22	23
103	65	28
104	110	55

Co. No.	IC <sub>50</sub> pAkt_S473 (nM)	IC <sub>50</sub> pAkt_Thr308 (nM)
105	302	138
106	105	62
107	>513	>513
111	389	162
112	174	~62
113	>513	>513
114	50	18
115	66	31
116	>513	>513
117	49	44
118	>513	>513
119	105	81
120	479	269
121	347	~331
122	40	26
123	>513	>513
124	151	93
125	>513	>513
126	427	275
127	~457	331
128	>513	>513
129	112	105
130	89	65
131	501	363
132	52	37
133	59	32
134	>513	>513
135	>513	>513
136	178	65
137	1	1
138	3	2
139	132	249
140	479	>513
141	182	102
142	10	7
143	102	30
144	59	28
145	~32	9
146	83	38
147	10	6
148	68	30
149	251	138
150	138	91

Co. No.	IC <sub>50</sub> pAkt_S473 (nM)	IC <sub>50</sub> pAkt_Thr308 (nM)
151	490	66
152	62	87
153	316	316
155	437	339
156	42	51
157	>513	417
158	23	20
159	>513	>513
160	58	23
161	>513	>513
162	209	91
163	>513	>513
164	145	71
165	45	11
166	>513	>513
167	>513	~427
168	214	112
169	200	102
170	>513	>513
171	155	102
172	>513	>513
173	78	52
174	>513	>513
175	9	11
176	16	15
177	60	42
178	>513	>513
180	3	1
181	~447	~398
182	1	0
183	6	3
184	2	2
185	~331	148
186	339	182
187	>513	>513
188	22	15
189	>513	>513
192	>513	>513
193	>513	>513
194	>513	>513
195	~102	47
196	182	91
197	65	43

Co. No.	IC <sub>50</sub> pAkt_S473 (nM)	IC <sub>50</sub> pAkt_Thr308 (nM)
198	>513	200
199	>513	309
200	n.d.	n.d.
201	42	26
202	>513	>513
203	98	44
204	>513	>513
205	>513	>513
206	>513	>513
207	372	105
208	186	83
209	>513	>513
210	245	151
211	36	22
212	398	328
213	33	25
214	>513	>513
217	79	49
218	>513	>513
219	>513	>513
220	>513	>513
222	>513	>513
223	>513	>513
224	468	>513
225	102	87
226	20	13
227	27	20
228	>513	347
229	186	96
230	145	141
231	~457	398
232	>513	>513
234	n.d.	n.d.
235	214	79
236	>513	>513
237	20	11
238	219	157
239	>513	>513
240	>513	>513
241	>513	>513
242	>513	>513
243	>513	>513
244	>513	>513

Co. No.	IC <sub>50</sub> pAkt_S473 (nM)	IC <sub>50</sub> pAkt_Thr308 (nM)
245	>513	>513
249	71	52
250	5	6
251	52	23
252	>513	>513
262	n.d.	n.d.
264	>513	355
272	151	~85
273	447	~257
276	85	46
278	295	178
279	145	115
280	~275	158
281	15	15
282	7	6
286	398	245
287	151	48
291	n.d.	n.d.
292	437	234
293	n.d.	n.d.
295	>513	>513
296	42	14
297		20
300	71	85
301	>513	427
302	76	76
303	87	79
304	>513	295
308	>513	>513
309	n.d.	n.d.
316	>513	>513
317	>513	>513
318	>513	~295
328	9	9
332	~316	112
333	>513	148
336	85	46
337	204	71
338	275	98
339	>513	>513
340	76	50
341	46	26
342	n.d.	n.d.

Co. No.	IC <sub>50</sub> pAkt_S473 (nM)	IC <sub>50</sub> pAkt_Thr308 (nM)
343	389	178
347	219	63
350	n.d.	n.d.
351	n.d.	n.d.
352	14	21
353	52	18
354	>513	>513
355	>513	437
358	>513	>513
359	>513	>513
360	>513	>513
361	229	263
362	229	263
364	49	43
365	20	13
366	102	91
368	120	~23
373	>513	>513
375	n.d.	n.d.
376	105	85
381	209	117
382	513	91
383	23	6
384	20	7
385	32	20
386	>513	>513
389	39	28
390	n.d.	n.d.
391	>513	>513
394	~26.3	18
395	>513	>513
396	>513	>513
397	>513	>513
398	>513	>513
399	>513	>513
400	457	~371.54
401	>513	>513
402	>513	>513
117a	n.d.	n.d.
118a	n.d.	n.d.
122a	12	9
123a	>513	380
154a	30	23

Co. No.	IC <sub>50</sub> pAkt_S473 (nM)	IC <sub>50</sub> pAkt_Thr308 (nM)
154b	>513	>513
184a	3	2
184b	3	2
184c	4	2
237a	6	4
237b	>513	>513
237c	26	11
237d	>513	>513
243a	>513	>513
243b	>513	>513
246a	44	24
246b	n.d.	n.d.
257b	>513	>513
257c	>513	>513
262a	n.d.	n.d.
262b	n.d.	n.d.
279a	58	41
279b	59	>513
280a	87	45
280b	>513	>513
281a	5	3
281b	>513	>513
283a	81	52
283b	n.d.	n.d.
284a	90	61
284b	>513	>513
286a	>513	>513
286b	n.d.	204
287a	31	34
287b	>513	417
292a	155	98
292b	>513	>513
295a	>513	>513
295b	>513	>513
296a	23	16
296b	468	339
297a	200	204
297b	7	3
298a	135	47
298b	501	>513
299a	~45	56
299b	>513	>513
300a	29	19

Co. No.	IC <sub>50</sub> pAkt_S473 (nM)	IC <sub>50</sub> pAkt_Thr308 (nM)
300b	n.d.	n.d.
302a	>513	>513
302b	54	39
309a	9	8
309b	363	282
312a	>513	>513
312b	>513	>513
313a	257	166
313b	>513	>513
314a	~407	>513
314b	191	n.d.
315a	195	>20.42
315b	~110	~85
319a	>513	>513
319b	>513	>513
320a	20	17
320b	n.d.	n.d.
321a	18	8
321b	n.d.	n.d.
322a	>513	>513
322b	42	26
323a	n.d.	n.d.
323b	209	100
324a	13	10
324b	n.d.	n.d.
325a	n.d.	n.d.
325b	>513	263
329a	14	6
329b	>513	>513
334a	339	219
334b	>513	>513
335a	5	2
335b	188	207
338a	115	68
338b	>513	>513
339a	>513	407
339b	>513	>513
344a	>102	56
344b	>513	~513
345a	79	28
345b	>513	>513
346a	178	68
346b	>513	>513

Co. No.	IC <sub>50</sub> pAkt_S473 (nM)	IC <sub>50</sub> pAkt_Thr308 (nM)
347a	>513	>513
347b	85	60
348a	288	138
348b	>513	>513
349a	4	2
349b	479	302
356a	n.d.	n.d.
356b	n.d.	n.d.
357a	>513	>513
357b	30	14
363a	~126	74
363b	n.d.	n.d.
364a	35	26
364b	>513	>513
365a	52	35
365b	n.d.	n.d.
367a	>513	>513
367b	>513	>513
369a	~363	251
369b	>513	>513
370a	107	40
370b	>513	>513
371a	10	2
371b	>513	251
374a	32	17
374b	>513	>513
379a	~29	22
379b	n.d.	n.d.
380a	n.d.	n.d.

Co. No.	IC <sub>50</sub> pAkt_S473 (nM)	IC <sub>50</sub> pAkt_Thr308 (nM)
380b	>513	>513
388a	n.d.	n.d.
388b	38	19
391a	n.d.	n.d.
391b	n.d.	n.d.
392a	n.d.	n.d.
392b	n.d.	n.d.
393a	>513	>513
393b	>513	>513
395a	>513	>513
395b	>513	>513
397a	>513	>513
397b	~513	>513
403a	~275	~132
403b	>513	>513
404a	>513	>513
404b	398	295
405a	>513	>513
405b	44	33
406a	8	4
406b	>513	>513
407a	n.d.	n.d.
407b	n.d.	n.d.
408a	n.d.	n.d.
408b	n.d.	n.d.
83a	>513	>513
83b	>513	>513
83c	>513	>513

#### Prophetic Composition examples

“Active ingredient” (a.i.) as used throughout these examples relates to a compound of Formula (I), including any tautomer or stereoisomeric form thereof, or a N-oxide, a pharmaceutically acceptable addition salt or a solvate thereof; in particular to any one of the exemplified compounds.

Typical examples of recipes for the formulation of the invention are as follows:

#### *1. Tablets*

Active ingredient	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg

Talcum	10 mg
Magnesium stearate	5 mg
Potato starch	ad 200 mg

#### 2. *Suspension*

- 5 An aqueous suspension is prepared for oral administration so that each milliliter contains 1 to 5 mg of active ingredient, 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

#### 3. *Injectable*

- 10 A parenteral composition is prepared by stirring 1.5 % (weight/volume) of active ingredient in 0.9 % NaCl solution or in 10 % by volume propylene glycol in water.

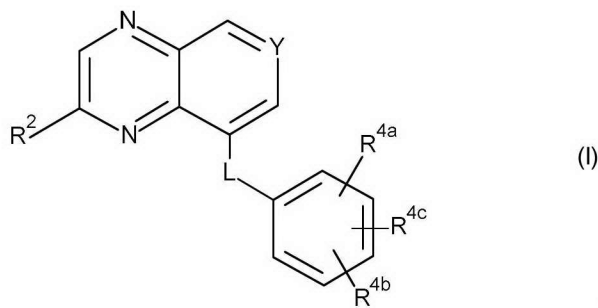
#### 4. *Ointment*

- |                    |              |
|--------------------|--------------|
| Active ingredient  | 5 to 1000 mg |
| Stearyl alcohol    | 3 g          |
| Lanoline           | 5 g          |
| 15 White petroleum | 15 g         |
| Water              | ad 100 g     |

In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

Claims

1. A compound of Formula (I)



a tautomer or a stereoisomeric form thereof, wherein

5 Y represents CR<sup>3</sup> or N;

L represents -CH(C<sub>1-4</sub>alkyl)-CH<sub>2</sub>-, -CH<sub>2</sub>-CH(C<sub>1-4</sub>alkyl)-, -CH(C<sub>1-4</sub>alkyl)-CH(C<sub>1-4</sub>alkyl)-, -CHR<sup>1a</sup>-X-, or -X-CHR<sup>1c</sup>-;

X represents O, S, or NR<sup>1b</sup>;

R<sup>1a</sup> represents hydrogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkyl substituted with one -OH;

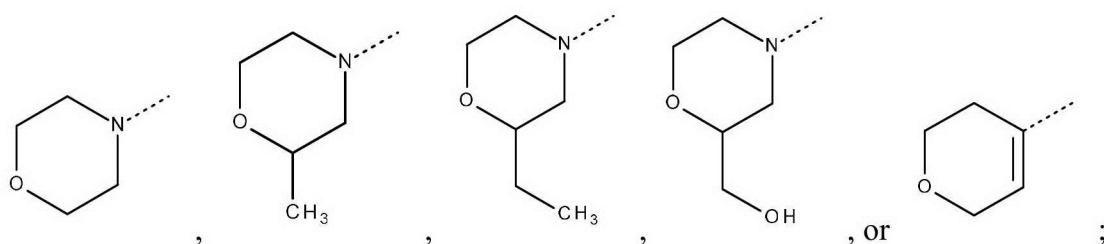
10 R<sup>1c</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

R<sup>1b</sup> represents hydrogen, C<sub>1-4</sub>alkyl, -CH<sub>2</sub>-C(=O)-NR<sup>6a</sup>R<sup>6b</sup>, or C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -O-C<sub>1-4</sub>alkyl, and -NR<sup>6c</sup>R<sup>6d</sup>;

or R<sup>1b</sup> is taken together with R<sup>1a</sup> or R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>3</sub>-;

15 or R<sup>1b</sup> is taken together with R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>2</sub>- or -(CH<sub>2</sub>)<sub>4</sub>-;

R<sup>2</sup> represents



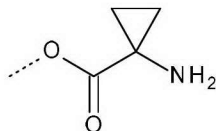
R<sup>6a</sup> and R<sup>6b</sup> each independently are selected from the group consisting of hydrogen and C<sub>1-4</sub>alkyl;

20 R<sup>6c</sup> and R<sup>6d</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl), and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>;

R<sup>3</sup> represents R<sup>7</sup>, -(C=O)H, -(C=O)-C<sub>1-4</sub>alkyl, -(C=O)-NR<sup>5a</sup>R<sup>5b</sup>, -(C=O)-OR<sup>5c</sup>, -C(=O)-Het<sup>1</sup>, -C(=O)-NH-Het<sup>2</sup>, -C(=O)-NH-C<sub>1-4</sub>alkyl-Het<sup>1</sup>,



-C(=O)-N(C<sub>1-4</sub>alkyl)-C<sub>1-4</sub>alkyl-Het<sup>1</sup>, -C(=O)-N(C<sub>1-4</sub>alkyl)-Het<sup>2</sup>, C<sub>1-4</sub>alkyl, -CH=N-OH, -CH(OH)-CH<sub>2</sub>-NR<sup>5d</sup>R<sup>5e</sup>, -CH(OH)-CH<sub>2</sub>-Het<sup>1</sup>, -CH(OH)-C<sub>1-4</sub>alkyl, -C(OH)(C<sub>1-4</sub>alkyl)<sub>2</sub>, halo, or R<sup>3</sup> represents C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, fluoro, -NR<sup>5f</sup>R<sup>5g</sup>, Het<sup>1</sup>, -O-(C=O)-CH(NH<sub>2</sub>)-C<sub>1-4</sub>alkyl,



- 5 -O-(C=O)-CH(NH<sub>2</sub>)-C<sub>1-4</sub>alkyl-Ar, , -O-C<sub>1-4</sub>alkyl-OH, and  
-O-C<sub>1-4</sub>alkyl-NH<sub>2</sub>;

R<sup>5a</sup> and R<sup>5b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, -O-C<sub>1-4</sub>alkyl, -S(=O)<sub>2</sub>-NH<sub>2</sub>, -S(=O)<sub>2</sub>-C<sub>1-4</sub>alkyl, -S(=O)<sub>2</sub>-C<sub>3-6</sub>cycloalkyl, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and

- 10 C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of hydroxyl, -O-C<sub>1-4</sub>alkyl, -S(=O)<sub>2</sub>-C<sub>1-4</sub>alkyl, -O-C<sub>1-4</sub>alkyl-NH<sub>2</sub>,  
-O-C<sub>1-4</sub>alkyl-NH(C<sub>1-4</sub>alkyl), -O-C<sub>1-4</sub>alkyl-N(C<sub>1-4</sub>alkyl)<sub>2</sub>, -(C=O)-O-C<sub>1-4</sub>alkyl,  
-(C=O)-OH, -(C=O)-C<sub>1-4</sub>alkyl, -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl) and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>;

R<sup>5c</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

- 15 R<sup>5d</sup> and R<sup>5e</sup> each independently are selected from the group consisting of hydrogen and C<sub>1-4</sub>alkyl;

R<sup>5f</sup> and R<sup>5g</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of

- 20 hydroxyl, -O-C<sub>1-4</sub>alkyl, -S(=O)<sub>2</sub>-C<sub>1-4</sub>alkyl, -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl), and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>;

R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> each independently are selected from the group consisting of hydrogen, cyano, C<sub>1-4</sub>alkyl, halo, -C(=O)H, -NR<sup>6e</sup>R<sup>6f</sup>, -O-C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, and -NR<sup>6g</sup>R<sup>6h</sup>;

- 25 R<sup>6e</sup> and R<sup>6f</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl), and hydroxyl;

R<sup>6g</sup> and R<sup>6h</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one substituent selected from the group

- 30 consisting of -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl), and hydroxyl;

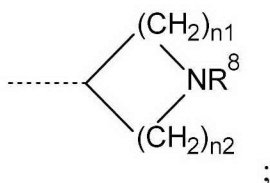
Het<sup>1</sup> represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N; or Het<sup>1</sup> represents a bicyclic 8-, 9- or 10-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected

5 from O, S, S(=O)<sub>p</sub> and N;

each optionally substituted with one or two substituents each independently selected from the group consisting of halo, -NR<sup>9a</sup>R<sup>9b</sup>, C<sub>1-4</sub>alkyl, -(C=O)-OR<sup>5h</sup>, -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -C<sub>1-4</sub>alkyl-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, hydroxyl, -O-C<sub>1-4</sub>alkyl, cyano, C<sub>1-4</sub>alkyl substituted with one or more halo atoms, and C<sub>1-4</sub>alkyl substituted with one substituent selected from  
 10 the group consisting of hydroxyl, -NH<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl) and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>; or two substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A;

R<sup>9a</sup> and R<sup>9b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

15 Het<sup>2</sup> represents



n1 represents 1 or 2;

n2 represents 1 or 2;

R<sup>8</sup> represents hydrogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

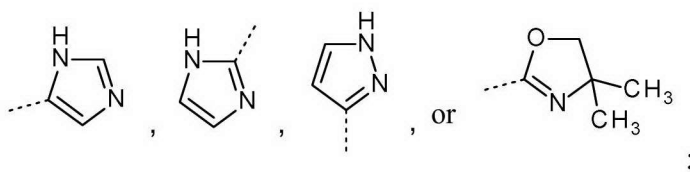
20 R<sup>5h</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

Ring A represents cyclobutyl, cyclopentyl, cyclohexyl, or a 4-, 5- or 6-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)<sub>p</sub> and N; said cyclobutyl, cyclopentyl, cyclohexyl, or 4-, 5- or 6-membered saturated heterocyclyl is optionally substituted with one or two C<sub>1-4</sub>alkyl  
 25 substituents, with one C<sub>1-4</sub>alkyl and one hydroxy substituent, or with one hydroxy substituent;

p represents 1 or 2;

Ar represents phenyl optionally substituted with one hydroxyl;

R<sup>7</sup> represents



or a N-oxide, a pharmaceutically acceptable addition salt or a solvate thereof.

2. The compound according to claim 1, wherein

5  $R^{1a}$  represents  $C_{1-4}$ alkyl;

$R^{5a}$  and  $R^{5b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl,  $-O-C_{1-4}$ alkyl,  $-S(=O)_2-NH_2$ ,  $-S(=O)_2-C_{1-4}$ alkyl,  $-S(=O)_2-C_{3-6}$ cycloalkyl,  $C_{1-4}$ alkyl substituted with one or more halo atoms, and

10  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}$ alkyl,  $-S(=O)_2-C_{1-4}$ alkyl,  $-O-C_{1-4}$ alkyl- $NH_2$ ,  $-O-C_{1-4}$ alkyl- $NH(C_{1-4}$ alkyl),  $-O-C_{1-4}$ alkyl- $N(C_{1-4}$ alkyl) $_2$ ,  $-NH_2$ ,  $-NH(C_{1-4}$ alkyl) and  $-N(C_{1-4}$ alkyl) $_2$ .

3. The compound according to claim 1, wherein

15  $R^{1a}$  represents  $C_{1-4}$ alkyl;

$R^{1c}$  represents hydrogen or  $C_{1-4}$ alkyl;

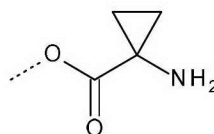
$R^{1b}$  represents hydrogen,  $C_{1-4}$ alkyl, or  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}$ alkyl, and  $-NR^{6c}R^{6d}$ ;

or  $R^{1b}$  is taken together with  $R^{1a}$  or  $R^{1c}$  to form  $-(CH_2)_3-$ ;

20 or  $R^{1b}$  is taken together with  $R^{1c}$  to form  $-(CH_2)_2-$  or  $-(CH_2)_4-$ ;

$R^3$  represents  $R^7$ ,  $-(C=O)H$ ,  $-(C=O)-C_{1-4}$ alkyl,  $-(C=O)-NR^{5a}R^{5b}$ ,  $-(C=O)-OR^{5c}$ ,  $-C(=O)-Het^1$ ,  $-C(=O)-NH-Het^2$ ,  $C_{1-4}$ alkyl,  $-CH=N-OH$ ,  $-CH(OH)-CH_2-NR^{5d}R^{5e}$ ,  $-CH(OH)-CH_2-Het^1$ ,  $-CH(OH)-C_{1-4}$ alkyl,  $-C(OH)(C_{1-4}alkyl)_2$ , halo, or  $R^3$  represents  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl, fluoro,

25  $-NR^{5f}R^{5g}$ ,  $Het^1$ ,  $-O-(C=O)-CH(NH_2)-C_{1-4}$ alkyl, and  $-O-C_{1-4}$ alkyl- $NH_2$ .



,  $-O-C_{1-4}$ alkyl-OH,

4. The compound according to claim 1, wherein

L represents  $-CH(C_{1-4}alkyl)-CH_2-$ ,  $-CHR^{1a}-X-$ , or  $-X-CHR^{1c}-$ ;

30  $R^{1a}$  represents hydrogen,  $C_{1-4}$ alkyl, or  $C_{1-4}$ alkyl substituted with one  $-OH$ ;

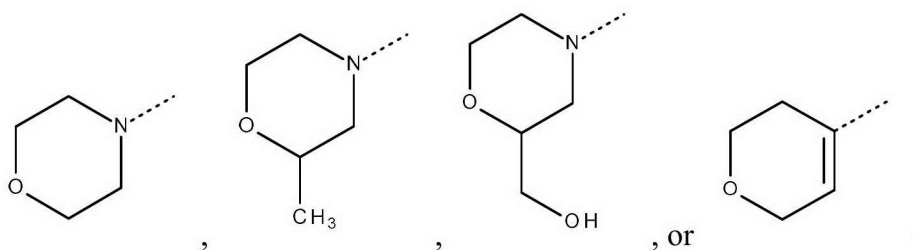
$R^{1c}$  represents hydrogen or  $C_{1-4}$ alkyl;

$R^{1b}$  represents hydrogen or  $C_{1-4}$ alkyl;

or  $R^{1b}$  is taken together with  $R^{1a}$  or  $R^{1c}$  to form  $-(CH_2)_3-$ ;

or  $R^{1b}$  is taken together with  $R^{1c}$  to form  $-(CH_2)_2-$ ;

- 5  $R^2$  represents



$R^3$  represents  $R^7$ ,  $-(C=O)H$ ,  $-(C=O)-NR^{5a}R^{5b}$ ,  $-(C=O)-OR^{5c}$ ,  $-(C=O)-Het^1$ ,  $-(C=O)-NH-Het^2$ ,  $-(C=O)-NH-C_{1-4}alkyl-Het^1$ ,  $-(C=O)-N(C_{1-4}alkyl)-Het^2$ ,  $C_{1-4}alkyl$ ,  $-CH=N-OH$ ,  $-CH(OH)-CH_2-NR^{5d}R^{5e}$ ,  $-CH(OH)-CH_2-Het^1$ ,  $-CH(OH)-C_{1-4}alkyl$ , halo, or  $R^3$

- 10 represents  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of hydroxyl, fluoro,  $-NR^{5f}R^{5g}$ ,  $Het^1$ , and  $-O-C_{1-4}alkyl-OH$ ;

$R^{5a}$  and  $R^{5b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}alkyl$ ,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-NH_2$ ,  $-S(=O)_2-C_{3-6}cycloalkyl$ ,

$C_{1-4}alkyl$  substituted with one or more halo atoms, and

- 15  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}alkyl$ ,  $-O-C_{1-4}alkyl-NH_2$ ,  $-O-C_{1-4}alkyl-NH(C_{1-4}alkyl)$ ,  $-(C=O)-O-C_{1-4}alkyl$ ,  $-(C=O)-OH$ ,  $-NH(C_{1-4}alkyl)$  and  $-N(C_{1-4}alkyl)_2$ ;

$R^{5f}$  and  $R^{5g}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}alkyl$ ,  $C_{1-4}alkyl$  substituted with one or more halo atoms, and

- 20  $C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}alkyl$ , and  $-S(=O)_2-C_{1-4}alkyl$ ;

$R^{6e}$  and  $R^{6f}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}alkyl$ , and  $C_{1-4}alkyl$  substituted with one hydroxyl substituent;

$Het^1$  represents a monocyclic 4-, 5-, 6- or 7-membered saturated heterocyclyl

- 25 containing at least one heteroatom each independently selected from O,  $S(=O)_p$  and N; or  $Het^1$  represents a bicyclic 9-membered saturated or partially saturated heterocyclyl containing at least one N-atom;

each optionally substituted with one or two substituents each independently selected from the group consisting of  $-NR^{9a}R^{9b}$ ,  $C_{1-4}alkyl$ ,  $-(C=O)-OR^{5h}$ , hydroxyl,  $-O-C_{1-4}alkyl$ ,

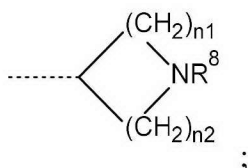
- 30  $C_{1-4}alkyl$  substituted with one or more halo atoms, and  $C_{1-4}alkyl$  substituted with one

substituent selected from the group consisting of hydroxyl and -NH(C<sub>1-4</sub>alkyl); or two substituents on the same carbon atom of said heterocyclyl are taken together to form together with the common carbon atom to which they are attached Ring A;

R<sup>9a</sup> and R<sup>9b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

5 R<sup>9a</sup> and R<sup>9b</sup> each independently are selected from the group consisting of hydrogen, C<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

Het<sup>2</sup> represents



n<sub>1</sub> represents 1;

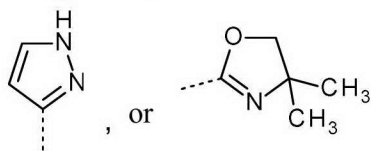
R<sup>8</sup> represents hydrogen, or C<sub>1-4</sub>alkyl substituted with one or more halo atoms;

10 R<sup>5h</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

Ring A represents a 4-membered saturated heterocyclyl containing at least one heteroatom each independently selected from O, and S(=O)<sub>p</sub>;

p represents 2;

R<sup>7</sup> represents



15

5. The compound according to claim 1, wherein

Y represents CR<sup>3</sup>;

L represents -CHR<sup>1a</sup>-X- or -X-CHR<sup>1c</sup>-;

20 X represents NR<sup>1b</sup>;

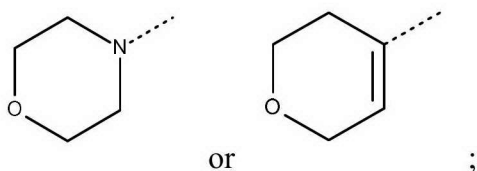
R<sup>1a</sup> represents C<sub>1-4</sub>alkyl;

R<sup>1c</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

R<sup>1b</sup> represents hydrogen;

or R<sup>1b</sup> is taken together with R<sup>1c</sup> to form -(CH<sub>2</sub>)<sub>3</sub>-;

25 R<sup>2</sup> represents



$R^3$  represents  $-(C=O)-NR^{5a}R^{5b}$ ,  $-(C=O)-Het^1$ , or  $R^3$  represents  $C_{1-4}$ alkyl substituted with one  $-NR^{5f}R^{5g}$  substituent;

$R^{5a}$  and  $R^{5b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of hydroxyl,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$  and  $-N(C_{1-4}alkyl)_2$ ;

$R^{5f}$  and  $R^{5g}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl, and  $C_{1-4}$ alkyl substituted with one hydroxyl substituent;

$R^{4a}$ ,  $R^{4b}$  and  $R^{4c}$  each independently are selected from the group consisting of hydrogen, cyano,  $C_{1-4}$ alkyl, and halo;

$Het^1$  represents a monocyclic 4-, 5-, 6- or 7-membered saturated or partially saturated heterocyclyl containing at least one heteroatom each independently selected from O, S,  $S(=O)_p$  and N; each optionally substituted with one or two substituents each independently selected from the group consisting of  $C_{1-4}$ alkyl.

15

**6.** The compound according to claim 1, wherein

Y represents  $CR^3$ ;

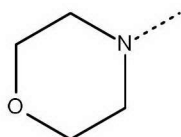
L represents  $-CHR^{1a}-X-$ ;

X represents O, S, or  $NR^{1b}$ ;

20  $R^{1a}$  represents  $C_{1-4}$ alkyl;

$R^{1b}$  represents hydrogen or  $C_{1-4}$ alkyl;

$R^2$  represents



;

$R^3$  represents  $-(C=O)H$ ,  $-(C=O)-C_{1-4}alkyl$ ,  $-(C=O)-NR^{5a}R^{5b}$ ;

25  $R^{5a}$  and  $R^{5b}$  each independently are selected from the group consisting of hydrogen,  $C_{1-4}$ alkyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-NH_2$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{3-6}cycloalkyl$ ,  $C_{1-4}alkyl$  substituted with one or more halo atoms, and

$C_{1-4}alkyl$  substituted with one substituent selected from the group consisting of hydroxyl,  $-O-C_{1-4}alkyl$ ,  $-S(=O)_2-C_{1-4}alkyl$ ,  $-O-C_{1-4}alkyl-NH_2$ ,  $-O-C_{1-4}alkyl-NH(C_{1-4}alkyl)$ ,  $-O-C_{1-4}alkyl-N(C_{1-4}alkyl)_2$ ,  $-NH_2$ ,  $-NH(C_{1-4}alkyl)$  and  $-N(C_{1-4}alkyl)_2$ ;

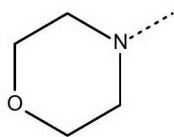
30

$R^{4a}$ ,  $R^{4b}$  and  $R^{4c}$  each independently are selected from the group consisting of hydrogen, cyano,  $C_{1-4}$ alkyl, halo, and  $-O-C_{1-4}$ alkyl.

7. The compound according to claim 1, wherein  
 5 Y represents  $CR^3$ ;  
 L represents  $-CHR^{1a}-X-$  or  $-X-CHR^{1c}-$ ;  
 X represents  $NR^{1b}$ ;  
 $R^{1a}$  represents  $C_{1-4}$ alkyl;  
 $R^{1c}$  represents hydrogen or  $C_{1-4}$ alkyl;  
 10  $R^{1b}$  represents hydrogen.

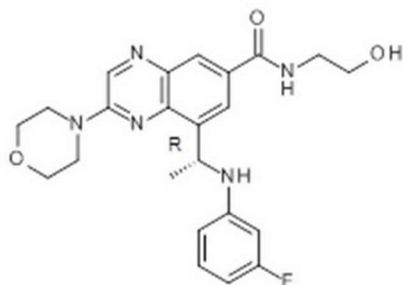
8. The compound according to claim 1, wherein  
 $R^{1b}$  is taken together with  $R^{1a}$  or  $R^{1c}$  to form  $-(CH_2)_3-$ .

- 15 9. The compound according to claim 1, wherein  
 $R^2$  represents



10. The compound according to claim 1, wherein Y represents  $CR^3$ .  
 20

11. The compound according to claim 1, wherein the compound is



or a N-oxide, a pharmaceutically acceptable addition salt or a solvate thereof.

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to any one of claims 1 to 11.
- 5 13. A compound as defined in any one of claims 1 to 11 for use as a medicament.
- 10 14. A compound as defined in any one of claims 1 to 11 for use in the treatment or prevention of a disease or condition selected from cancer, autoimmune disorders, cardiovascular diseases, inflammatory diseases, neurodegenerative diseases, allergy, pancreatitis, asthma, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, and lung injuries.
- 15 15. The compound according to claim 14 wherein the disease or condition is cancer.
- 16 16. The compound according to claim 15 wherein the disease or condition is prostate cancer.
- 20 17. A method of inhibition of PI3K $\beta$ , the method comprising administering to a subject in need thereof an effective amount of a compound as defined in any one of claims 1 to 11 or a pharmaceutical composition as defined in claim 12.
- 25 18. A method of treatment or prevention of a disease or condition modulated by PI3K $\beta$ , the method comprising administering to a subject in need thereof an effective amount of a compound as defined in any one of claims 1 to 11 or a pharmaceutical composition as defined in claim 12.
- 30 19. A method of treatment or prevention of a disease or condition according to claim 18, wherein the disease or condition is selected from cancer, autoimmune disorders, cardiovascular diseases, inflammatory diseases, neurodegenerative diseases, allergy, pancreatitis, asthma, multiorgan failure, kidney diseases,



platelet aggregation, sperm motility, transplantation rejection, graft rejection, and lung injuries.

- 5
20. The method according to claim 19 wherein the disease or condition is cancer.
21. The method according to claim 20 wherein the disease or condition is prostate cancer.
- 10
22. Use of a compound as defined in any one of claims 1 to 11, or a pharmaceutical composition as defined in claim 12, in the manufacture of a medicament for inhibition of PI3K $\beta$ .
- 15
23. Use of a compound as defined in any one of claims 1 to 11, or a pharmaceutical composition as defined in claim 12, in the manufacture of a medicament for treatment or prevention of a disease or condition modulated by PI3K $\beta$ .
- 20
24. Use of a compound or a pharmaceutical composition in the manufacture of a medicament according to claim 23, wherein the disease or condition is selected from cancer, autoimmune disorders, cardiovascular diseases, inflammatory diseases, neurodegenerative diseases, allergy, pancreatitis, asthma, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, and lung injuries.
- 25
25. Use of a compound or a pharmaceutical composition in the manufacture of a medicament according to claim 24 wherein the disease or condition is cancer.
26. Use of a compound or a pharmaceutical composition in the manufacture of a medicament according to claim 25 wherein the disease or condition is prostate cancer.