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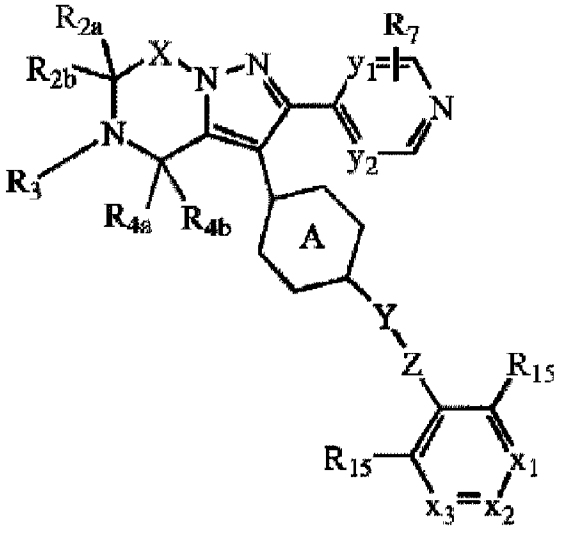
(54) **Titre : DERIVES 4,5,6,7-TETRAHYDRO-PYRAZOLO[1,5-α]PYRAZINE SUBSTITUES ET DERIVES 5,6,7,8-TETRAHYDRO-4H-PYRAZOLO[1,5-α][1,4]DIAZEPINE UTILISES COMME INHIBITEURS DE ROS1**

(54) **Title: SUBSTITUTED 4,5,6,7-TETRAHYDRO-PYRAZOLO[1,5-α]PYRAZINE DERIVATIVES AND 5,6,7,8-TETRAHYDRO-4H-PYRAZOLO[1,5-α][1,4]DIAZEPINE DERIVATIVES AS ROS1 INHIBITORS**



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(57) **Abrégé/Abstract:**
The present invention relates to substituted 4,5,6,7-tetrahydro-pyrazolo[1,5-α]pyrazine derivatives and 5,6,7,8-tetrahydro-4H-pyrazolo[1,5-α][1,4]diazepine derivatives of formula (I). The compounds according to the present invention are useful as ROS 1 inhibitors. The invention further relates to processes for preparing such novel compounds, pharmaceutical compositions comprising said compounds as an active ingredient as well as the use of said compounds as a medicament. (see formula I)

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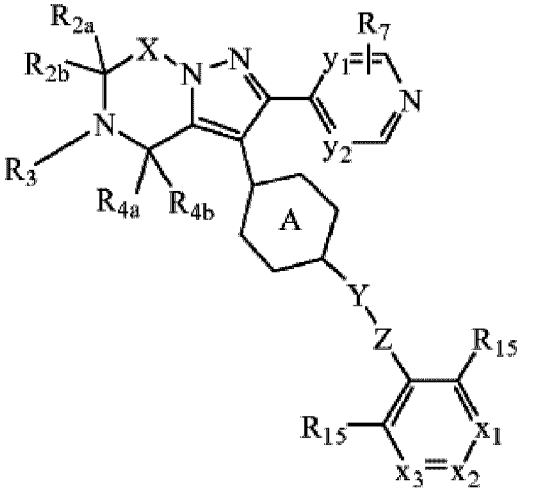
Abstract

The present invention relates to substituted 4,5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyrazine derivatives and 5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,4]diazepine derivatives of formula (I). The compounds according to the present invention are useful as ROS 1 inhibitors. The invention further relates to processes for preparing such novel compounds, pharmaceutical compositions comprising said compounds as an active ingredient as well as the use of said compounds as a medicament.



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SUBSTITUTED 4,5,6,7-TETRAHYDRO-PYRAZOLO[1,5-*a*]PYRAZINE DERIVATIVES AND 5,6,7,8-TETRAHYDRO-4*H*-PYRAZOLO[1,5-*a*][1,4]DIAZEPINE DERIVATIVES AS ROS1 INHIBITORS

Field of the Invention

The present invention relates to substituted 4,5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyrazine derivatives and 5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,4]diazepine derivatives useful as ROS1 inhibitors. The invention further relates to processes for preparing such compounds, pharmaceutical compositions comprising said compounds as an active ingredient as well as the use of said compounds as a medicament.

Background of the invention

Ros1 is a receptor tyrosine kinase closely related to the ALK and LTK kinases based on sequence similarity of their kinase domains. The Ros1 protein is composed of an extracellular domain containing several fibronectin-like repeats and a cytoplasmic kinase domain. The function of Ros1 has not been fully elucidated, but the presence of fibronectin domains suggests a role in cell adhesion or interactions with the extracellular matrix. However, endogenous Ros1 ligands have not yet been identified. Its expression in adult humans has been detected in several tissues, such as the kidney, cerebellum, and gastrointestinal tract, but appears to be low or absent in other tissues. Its expression in the developing kidney and intestine suggests that it may have a role in epithelial-mesenchymal transition. ROS1 deficient mice are healthy and viable, but males are infertile due to defects in the epididymis that result in incomplete spermatocyte maturation.

Several distinct genomic rearrangements involving ROS1 have been detected in a variety of cancers including non-small cell lung cancer (NSCLC), glioblastoma, cholangiocarcinoma, colorectal cancer, gastric adenocarcinoma, ovarian cancer, angiosarcoma, epithelioid hemangioendothelioma, melanoma, and inflammatory myofibroblastic tumors. These rearrangements result in proteins that contain the C-terminal kinase domain of Ros1 fused to the N-terminal domains of a number of different unrelated proteins. Several of these fusion proteins have been shown to be oncogenic. Expression in fibroblasts promotes their proliferation, growth in soft agar, and ability to form tumors in mice. Expression in murine Ba/F3 cells renders them independent of IL-3 for growth and promotes their ability to form tumors in mice (Takeuchi K, et al., Nat Med. 2012, 18:378-81; Gu TL, et al., PLoS One 2011, 6:e15640). The rate of oncogenic Ros1 fusions is generally low, ranging from 1-2% in NSCLC (Kim MH, et al., Lung Cancer 2014, 83:389-95; Takeuchi K, et al., Nat Med.

2012, 18:378-81; Davies KD, et al., Clin Cancer Res. 2012, 18:4570-9; Li C, et al., PLoS One 2011, 6:e28204; Rimkunas VM, et al., Clin Cancer Res. 2012, 18:4449-57), but may be relatively high in other cancers, up to 9% in cholangiocarcinoma (Gu TL, et al., PLoS One 2011, 6(1):e15640) and 17% in spitzoid (melanoma) tumors (Wiesner T, et al., Nat Commun. 2014, 5:3116).

Because of the similarity between ALK and Ros1 kinase domains, many ALK inhibitors also inhibit Ros1. Ros1 inhibition negatively affects proliferation of engineered Ba/F3 cells expressing Ros1 fusion proteins as well as the proliferation of NSCLC patient derived HCC78 cells that harbor a SLC34A2-ROS1 fusion. Ros1 inhibition also negatively affects growth of engineered Ba/F3 and HEK293 tumors containing Ros1 fusion proteins in mice.

Recently, a number of inhibitors described to have activity on Ros1 have entered clinical testing. The first, crizotinib (Xalkori®), has been shown to reduce tumors and significantly prolong survival in patients with ROS1 rearrangements. However, following an initial response, resistance is seen and in one report this has been linked to a G2032R mutation in the Ros1 kinase domain that is expected to affect crizotinib binding.

WO-2004/058176 discloses acyclic pyrazole compounds for the inhibition of mitogen activated protein kinase-activated protein kinase-2.

J. Med. Chem., 2011, 54, 5820-5835 discloses pyrazolo derivatives as phosphodiesterase subtype-10 inhibitors.

There is thus a strong need for novel Ros1 kinase inhibitors thereby opening new avenues for the treatment or prevention of cancer, in particular non-small cell lung cancer (specifically adenocarcinoma), cholangiocarcinoma, glioblastoma, colorectal cancer, gastric adenocarcinoma, ovarian cancer, angiosarcoma, epithelioid hemangioendothelioma, inflammatory myofibroblastic tumors, breast cancer and chronic myelogenous leukemia. In a particular embodiment, there is a need for Ros1 kinase inhibitors that are not affected by mutations that abrogate inhibition of the first wave of Ros1 inhibitors.

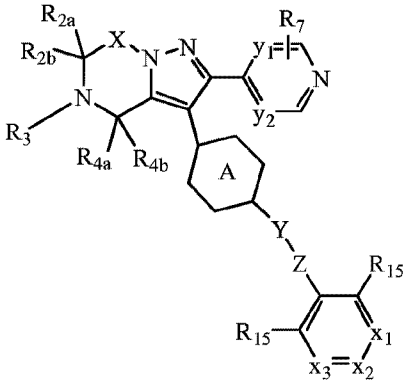
It is accordingly an object of the present invention to provide such compounds.

Summary of the invention

It has been found that the compounds of the present invention are useful as ROS1 inhibitors. The compounds according to the invention and compositions thereof, may be useful for the treatment or prevention, in particular for the treatment, of cancer, in particular non-small cell lung cancer (specifically adenocarcinoma),

cholangiocarcinoma, glioblastoma, colorectal cancer, gastric adenocarcinoma, ovarian cancer, angiosarcoma, epithelioid hemangioendothelioma, inflammatory myofibroblastic tumors, breast cancer and chronic myelogenous leukemia, and the like.

This invention concerns compounds of formula (I)



(I)

tautomers and stereoisomeric forms thereof, wherein

y_1 is CR_{7a} or N;

y_2 is CH or N;

R_{7a} is hydrogen, halo, trifluoromethyl or cyano;

R_7 is hydrogen, $-NH_2$, $-NHCH_3$, $-NH(CH_2CH_3)$, methyl, $-CH_2OH$, halo or cyano; or when y_1 represents CR_{7a}, this R_{7a} can be taken together with a R_7 on an adjacent carbon atom to form –CH=CH-NH- or -N=CH-NH-;

X is $-CR_1R_{1a}-$, $-CH_2-CHR_1-$;

R_1 is hydrogen or C_{1-6}alkyl;

R_{1a} is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$; or $-C(=O)-NR_{9a}R_{9b}$;

R_{2a} is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; or C_{1-6}alkyl substituted with one substituent selected from the group consisting of $-NR_{9a}R_{9b}$, cyano and C_{1-4}alkyloxy;

R_{2b} is hydrogen or C_{1-6}alkyl; or

R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2-$, $-CH_2-NR_{2c}-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-NR_{2c}-CH_2-$ or =O;

R_{2c} is hydrogen; C_{1-4}alkyl optionally substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyl substituted with one cyano group; or C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$;

R_3 is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one or two hydroxyl groups and one C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl- optionally substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkylcarbonyl-; $R_{10a}R_{10b}N$-C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-

O-carbonyl-; C_{1-6}alkylcarbonyloxy-; C_{1-6}alkyl substituted with one R_{11}; C_{1-6}alkyloxy optionally substituted with one -$NR_{10a}R_{10b}$; C_{2-6}alkenyl; C_{2-6}alkynyl; hydroxyC_{2-6}alkenyl; hydroxyC_{2-6}alkynyl; C_{1-6}alkyloxyC_{2-6}alkenyl; C_{1-6}alkyloxyC_{2-6}alkynyl; C_{2-6}alkenyl substituted with one –$NR_{10a}R_{10b}$; C_{2-6}alkynyl substituted with one –$NR_{10a}R_{10b}$; C_{1-6}alkyl substituted with one or two hydroxyl groups and one –$NR_{10}R_{10b}$; -C_{1-6}alkyl-$C(R_{13})$=N-O-R_{13}; -$S(=O)_2$-C_{1-6}alkyl; -$S(=O)_2$-$NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one –(C=O)-R_{14}; C_{1-6}alkyl substituted with one or two hydroxyl groups and one R_{14}; C_{1-6}alkyl substituted with one R_{14}; C_{2-6}alkenyl substituted with one R_{14}; C_{2-6}alkynyl substituted with one R_{14}; or R_{14};

R_{4a} is hydrogen;

R_{4b} is hydrogen; or

R_{4a} and R_{4b} are taken together to form =O;

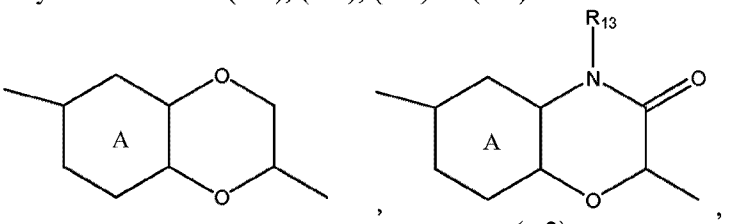
Y is –O- or -C(=O)-;

Z is –CHR_6- or –CH_2-C≡C-;

R_6 is hydrogen; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{1-4}alkyl substituted with one -$NR_{9a}R_{9b}$; or -C(=O)-$NR_{9a}R_{9b}$;

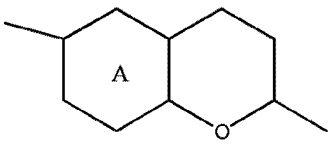
Ring A is phenyl or a 6-membered saturated, partially saturated or aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; C_{1-4}alkyl or halo; or a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1), (a-2), (a-3) or (a-4):



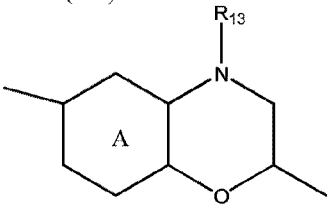
(a-1)

(a-2)



(a-3)

or



(a-4)

R_{9a} and R_{9b} each independently represent hydrogen; mono-or polyhaloC_{1-4}alkyl; C_{1-4}alkylcarbonyl-; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl substituted with one or two

hydroxyl groups; or C_{1-4}alkyl optionally substituted with one substituent selected from the group consisting of C_{1-4}alkyloxy, cyano, amino and mono-or di(C_{1-4}alkyl)amino;
R_{10a} and R_{10b} each independently represent hydrogen; C_{1-4}alkyl; cyanoC_{1-6}alkyl; C_{1-6}alkyl substituted with one $NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one –C(=O)-$NR_{9a}R_{9b}$; C_{1-6}alkyloxy optionally substituted with one or two hydroxyl groups; C_{1-6}alkyloxyC_{1-6}alkyl wherein each C_{1-6}alkyl is optionally substituted with one or two hydroxyl groups; R_{14}; C_{1-6}alkyl substituted with one R_{14}; -(C=O)-R_{14}; C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; mono-or polyhaloC_{1-6}alkylcarbonyl-substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkylcarbonyl-; C_{1-6}alkyl substituted with one –$Si(CH_3)_3$; -$S(=O)_2$-C_{1-6}alkyl optionally substituted with one or more halo substituents; -$S(=O)_2$-$NR_{9a}R_{9b}$;
C_{1-6}alkyl substituted with one -$S(=O)_2$-C_{1-6}alkyl wherein -$S(=O)_2$-C_{1-6}alkyl is optionally substituted with one or more halo substituents;
C_{1-6}alkyl substituted with one -$S(=O)_2$-$NR_{9a}R_{9b}$;
C_{1-6}alkyl substituted with one –NH-$S(=O)_2$-C_{1-6}alkyl wherein –NH-$S(=O)_2$-C_{1-6}alkyl is optionally substituted on a carbon atom with one or more halo substituents;
C_{1-6}alkyl substituted with one -NH-$S(=O)_2$-$NR_{9a}R_{9b}$;
mono-or polyhaloC_{1-4}alkyl; or C_{1-4}alkyl substituted with one or two hydroxyl groups;
R_{11} is cyano; -$NR_{10a}R_{10b}$; C_{1-6}alkyloxy optionally substituted with one or two hydroxyl groups; -$S(=O)_2$-C_{1-6}alkyl; -$S(=O)_2$-$NR_{9a}R_{9b}$; -NR_{13}-$S(=O)_2$-C_{1-6}alkyl; -NR_{13}-$S(=O)_2$-$NR_{9a}R_{9b}$; C_{1-6}alkylcarbonyloxy-; -C(=O)-$NR_{10a}R_{10b}$; -O-C(=O)-$NR_{10a}R_{10b}$; -COOH; –$P(=O)(OH)_2$; or –$P(=O)(O\text{-}C_{1-4}alkyl)_2$;
R_{12} is –$NR_{9a}R_{9b}$, C_{1-6}alkyloxy, or cyano;
R_{13} is hydrogen or C_{1-4}alkyl;
R_{14} is a C_{3-8}cycloalkyl; or a 4, 5 or 6 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents selected from the group consisting of oxo, C_{1-4}alkyl, halogen, cyano, hydroxyl, C_{1-6}alkyloxy and $NR_{9a}R_{9b}$;
x_1 is CR_{5a} or N;
x_2 is CR_{5b} or N;
x_3 is CR_{5c} or N;
each R_{15} is independently selected from the group consisting of hydrogen, methyl, halo, C_{1-4}alkyloxy and hydroxyl;
R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen; hydroxyl; cyano; halo; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyloxy; C_{1-6}alkyl substituted with one –$NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one cyano; C_{1-6}alkyloxyC_{1-6}alkyl wherein

each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkyloxy; C_{1-6}alkyloxy substituted with one or two hydroxyl groups; C_{1-6}alkyloxyC_{1-6}alkyloxy wherein each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups; C_{1-6}alkyloxy substituted with one cyano; and C_{1-6}alkyloxy substituted with one $-NR_{9a}R_{9b}$;
R_{5b} is hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; hydroxyl; cyano; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-4}alkyloxy; $-Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; C_{1-6}alkyl-O-carbonyl-; or C_{1-6}alkyloxy substituted with one R_{12};
and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention also concerns methods for the preparation of compounds of the present invention and pharmaceutical compositions comprising them.

The compounds of the present invention were found to inhibit ROS1, and therefore may be useful in the treatment or prevention, in particular in the treatment, of cancer, in particular non-small cell lung cancer (specifically adenocarcinoma), cholangiocarcinoma, glioblastoma, colorectal cancer, gastric adenocarcinoma, ovarian cancer, angiosarcoma, epithelioid hemangioendothelioma, inflammatory myofibroblastic tumors, breast cancer and chronic myelogenous leukemia, and the like. The compounds of the present invention may also have utility in male contraception.

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 ROS1, 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.

When any variable occurs more than one time in any constituent or in any formula (e.g. formula (I)), its definition in each occurence 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.

Whenever a radical or group is defined as "optionally substituted" in the present invention, it is meant that said radical or group is unsubstituted or is substituted.

Lines drawn from substituents into ring systems indicate that the bond may be attached to any of the suitable ring atoms.

The prefix "C_{x-y}" (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C_{1-6}alkyl group contains from 1 to 6 carbon atoms, a C_{3-6}cycloalkyl group contains from 3 to 6 carbon atoms, a C_{1-4}alkoxy group contains from 1 to 4 carbon atoms, and so on.

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 'mono- or polyhaloC_{1-4}alkyl' or 'mono- or polyhaloC_{1-6}alkyl' as used herein as a group or part of a group refers to a C_{1-4}alkyl or C_{1-6}alkyl group as defined herein wherein one or more than one hydrogen atom is replaced with a halogen. There may be one, two, three or more hydrogen atoms replaced with a halogen, so the 'mono- or polyhaloC_{1-4}alkyl' or 'mono- or polyhaloC_{1-6}alkyl' may have one, two, three or more halogens. Examples of such groups include fluoroethyl, fluoromethyl, trifluoromethyl or trifluoroethyl and the like.

The term "C_{1-6}alkyl" as a group or part of a group refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number ranging from 1 to 6. C_{1-6}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_{1-6}alkyl includes all linear, or 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, *iso*butyl and *tert*-butyl), pentyl and its isomers, hexyl and its isomers, and the like.

The term "C_{1-4}alkyl" as a group or part of a group refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number ranging from 1 to 4. C_{1-4}alkyl groups comprise from 1 to 4 carbon atoms, preferably from 1 to 3 carbon atoms, more preferably 1 to 2 carbon atoms. C_{1-4}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. C_{1-4}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, *iso*butyl and *tert*-butyl), and the like.

The term "C_{1-6}alkyloxy" as a group or part of a group refers to a radical having the Formula $-OR^b$ wherein R^b is C_{1-6}alkyl. Non-limiting examples of suitable alkyloxy include methyloxy, ethyloxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, *sec*-butyloxy, *tert*-butyloxy, pentyloxy, and hexyloxy.

The term "C_{1-4}alkyloxy" as a group or part of a group refers to a radical having the Formula $-OR^c$ wherein R^c is C_{1-4}alkyl. Non-limiting examples of suitable C_{1-4}alkyloxy include methyloxy (also methoxy), ethyloxy (also ethoxy), propyloxy, isopropyloxy, butyloxy, isobutyloxy, *sec*-butyloxy and *tert*-butyloxy.

The term "C_{1-6}alkylcarbonyl" as a group or part of a group refers to a radical $-C(=O)-C_{1-6}$alkyl. The term "C_{1-4}alkylcarbonyl" as a group or part of a group refers to a radical $-C(=O)-C_{1-4}$alkyl.

The term "C_{3-8}cycloalkyl" alone or in combination, refers to a cyclic saturated hydrocarbon radical having from 3 to 8 carbon atoms. Non-limiting examples of suitable C_{3-8}cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term "C_{3-6}cycloalkyl" alone or in combination, refers to a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms. Non-limiting examples of suitable C_{3-6}cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "C_{2-4}alkenyl" or "C_{2-6}alkenyl" as used herein as a group or part of a group refers to a linear or branched hydrocarbon group containing from 2 to 4 or 2 to 6 carbon atoms and containing a carbon carbon double bond such as, but not limited to, ethenyl, propenyl, butenyl, pentenyl, 1-propen-2-yl, hexenyl and the like.

The term "C_{2-4}alkynyl" or "C_{2-6}alkynyl" as used herein as a group or part of a group refers to a linear or branched hydrocarbon group having from 2 to 4 or 2 to 6 carbon atoms and containing a carbon carbon triple bond.

The term "cyanoC_{1-6}alkyl" means C_{1-6}alkyl substituted with one cyano.

The term "hydroxyC_{2-6}alkenyl" means C_{2-6}alkenyl substuted with one hydroxy.

The term "hydroxyC_{2-6}alkynyl" means C_{2-6}alkynyl substituted with one hydroxy.

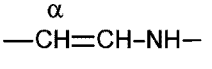
In particular, the 4, 5 or 6 membered saturated heterocyclyls (e.g. in the definition of R_{14}), contain 1, 2 or 3 heteroatoms selected from O, S and N, in particular 1 or 2 heteroatoms, in particular selected from O and N.

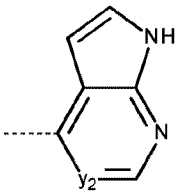
Examples of 4, 5 or 6 membered saturated heterocyclyls include, but are not limited to, pyrrolidinyl, dioxolanyl, oxazolidinyl, oxetanyl, tetrahydrofuranyl, and the like.

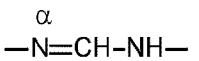
Examples of 6-membered aromatic heterocyclyls containing one or two nitrogen atoms (e.g. in the definition of ring A), include, but are not limited to, pyrimidinyl, pyridinyl, pyrazinyl and the like.

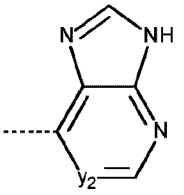
Examples of 6-membered partially saturated heterocyclyls containing one or two nitrogen atoms (e.g. in the definition of ring A), include, but are not limited to, 1,2,3,6-tetrahydro-pyridinyl and the like. In a particular embodiment, the 1,2,3,6-tetrahydro-pyridinyl is attached with its nitrogen atom to variable Y.

Examples of 6-membered saturated heterocyclyls containing one or two nitrogen atoms (e.g. in the definition of ring A), include, but are not limited to, piperidinyl and the like. In a particular embodiment, the piperidinyl is attached with its nitrogen atom to the pyrazolyl ring.

In case R_{7a} is taken together with a R_7 on an adjacent carbon atom to form –CH=CH-NH-, it is intended that the CH in position alpha  is attached to the carbon atom in the position of y1 as clearly shown below:



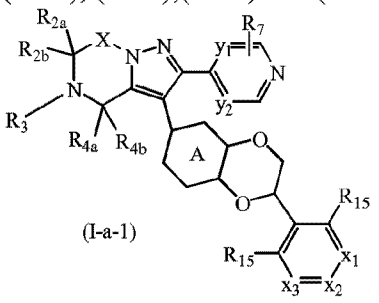
In case R_{7a} is taken together with a R_7 on an adjacent carbon atom to form –N=CH-NH-, it is intended that the nitrogen in position alpha  is attached to the carbon atom in the position of y1 as clearly shown below:



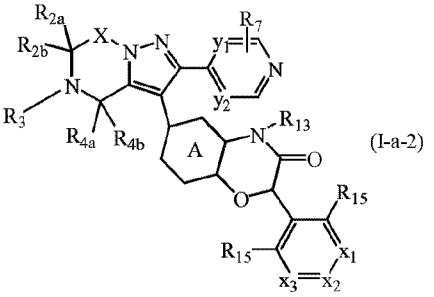
In case X is $–CH_2-CHR_1–$, it is intended that the carbon atom with the R_1 substituent is attached to the nitrogen atom of the pyrazole ring.

In case Z is $–CH_2-C\equiv C–$, it is intended that the CH_2 group is attached to variable Y.

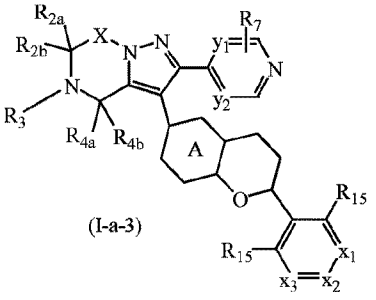
It will be clear that when a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent is taken together with the R_6 substituent of Z, compounds of formula (I-a-1), (I-a-2),(I-a-3) and (I-a-4) are formed:



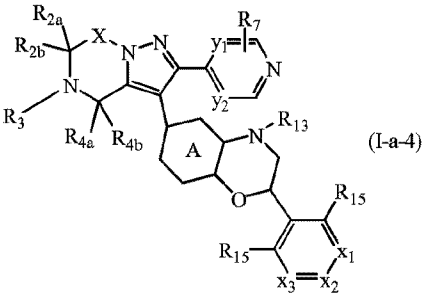
(I-a-1)



(I-a-2)



(I-a-3)



(I-a-4)

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 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 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 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.

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

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.

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.

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, diastereomers, racemates, E isomers, Z isomers, cis isomers, trans isomers and mixtures thereof, whenever chemically possible.

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

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 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}H, ^{3}H, ^{11}C, ^{18}F, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br. Preferably, the radioactive isotope is selected from the group of ^{2}H, ^{3}H, ^{11}C and ^{18}F. More preferably, the radioactive isotope is ^{2}H. In particular, deuterated compounds are intended to be included within the scope of the present invention

As used in the specification and the appended claims, the singular forms "a", "an," and "the" also include plural referents unless the context clearly dictates otherwise. For example, "a compound" means 1 compound or more than 1 compound.

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

y_1 is CR_{7a} or N;

y_2 is CH;

R_{7a} is hydrogen;

R_7 is hydrogen, $-NH_2$, $-NHCH_3$, $-NH(CH_2CH_3)$, methyl, $-CH_2OH$, halo or cyano;

or when y_1 represents CR_{7a}, this R_{7a} can be taken together with a R_7 on an adjacent carbon atom to form –CH=CH-NH- or -N=CH-NH-;

X is $-CR_1R_{1a}-$, $-CH_2-CHR_1-$;

R_1 is hydrogen or C_{1-6}alkyl;

R_{1a} is hydrogen;

R_{2a} is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; or C_{1-6}alkyl substituted with one substituent selected from the group consisting of $-NR_{9a}R_{9b}$, cyano and C_{1-4}alkyloxy;

R_{2b} is hydrogen; or

R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2-$, $-CH_2-NR_{2c}-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-NR_{2c}-CH_2-$ or =O;

R_{2c} is hydrogen; C_{1-4}alkyl optionally substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyl substituted with one cyano group; or C_{1-6}alkyl substituted with one -$NR_{9a}R_{9b}$;

R_3 is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one or two hydroxyl groups and one C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl- optionally substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkylcarbonyl-; $R_{10a}R_{10b}N$-C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkylcarbonyloxy-; C_{1-6}alkyl substituted with one R_{11}; C_{1-6}alkyloxy optionally substituted with one -$NR_{10a}R_{10b}$; C_{1-6}alkyl substituted with one or two hydroxyl groups and one –$NR_{10}R_{10b}$; -$S(=O)_2$-C_{1-6}alkyl; -$S(=O)_2$-$NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one –(C=O)-R_{14}; C_{1-6}alkyl substituted with one or two hydroxyl groups and one R_{14}; C_{1-6}alkyl substituted with one R_{14}; or R_{14};

R_{4a} is hydrogen;

R_{4b} is hydrogen; or

R_{4a} and R_{4b} are taken together to form =O;

Y is –O- or -C(=O)-; in particular Y is –O-;

Z is –CHR_6- or –CH_2-C≡C-;

R_6 is hydrogen; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{1-4}alkyl substituted with one -$NR_{9a}R_{9b}$; or -C(=O)-$NR_{9a}R_{9b}$;

Ring A is phenyl or a 6-membered saturated, partially saturated or aromatic heterocyclyl, in particular phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; C_{1-4}alkyl or halo; or a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1), (a-2), (a-3) or (a-4);

R_{9a} and R_{9b} each independently represent hydrogen; mono-or polyhaloC_{1-4}alkyl; C_{1-4}alkylcarbonyl-; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl substituted with one or two hydroxyl groups; or C_{1-4}alkyl optionally substituted with one substituent selected from the group consisting of C_{1-4}alkyloxy, cyano, amino and mono-or di(C_{1-4}alkyl)amino;

R_{10a} and R_{10b} each independently represent hydrogen; C_{1-4}alkyl; cyanoC_{1-6}alkyl; C_{1-6}alkyl substituted with one $NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one –C(=O)-$NR_{9a}R_{9b}$; C_{1-6}alkyloxy optionally substituted with one or two hydroxyl groups;

C_{1-6}alkyloxyC_{1-6}alkyl wherein each C_{1-6}alkyl is optionally substituted with one or two hydroxyl groups; C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-;

mono-or polyhaloC_{1-6}alkylcarbonyl- substituted with one or two hydroxyl groups;

mono-or polyhaloC_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkylcarbonyl-; mono-or polyhaloC_{1-4}alkyl; or C_{1-4}alkyl substituted with one or two hydroxyl groups;

R_{11} is cyano; -$NR_{10a}R_{10b}$; C_{1-6}alkyloxy optionally substituted with one or two hydroxyl groups; -$S(=O)_2$-C_{1-6}alkyl; -$S(=O)_2$-$NR_{9a}R_{9b}$; -NR_{13}-$S(=O)_2$-C_{1-6}alkyl; -NR_{13}-$S(=O)_2$-$NR_{9a}R_{9b}$; C_{1-6}alkylcarbonyloxy-; -C(=O)-$NR_{10a}R_{10b}$; -O-C(=O)-$NR_{10a}R_{10b}$; -COOH; –$P(=O)(OH)_2$; or –$P(=O)(O\text{-}C_{1-4}alkyl)_2$;

R_{12} is –$NR_{9a}R_{9b}$, C_{1-6}alkyloxy, or cyano;

R_{13} is hydrogen or C_{1-4}alkyl;

R_{14} is a 4, 5 or 6 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents selected from the group consisting of oxo, C_{1-4}alkyl, halogen, cyano, hydroxyl, C_{1-6}alkyloxy and $NR_{9a}R_{9b}$;

x_1 is CR_{5a} or N;

x_2 is CR_{5b};

x_3 is CR_{5c} or N;

each R_{15} is independently selected from the group consisting of hydrogen, methyl, halo, C_{1-4}alkyloxy and hydroxyl;

R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen; hydroxyl; cyano; halo; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyloxy; C_{1-6}alkyl substituted with one –$NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one cyano; C_{1-6}alkyloxyC_{1-6}alkyl wherein each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkyloxy; C_{1-6}alkyloxy substituted with one or two hydroxyl groups; C_{1-6}alkyloxyC_{1-6}alkyloxy wherein each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups; C_{1-6}alkyloxy substituted with one cyano; and C_{1-6}alkyloxy substituted with one –$NR_{9a}R_{9b}$;

R_{5b} is hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; hydroxyl; cyano; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-4}alkyloxy; -$Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; C_{1-6}alkyl-O-carbonyl-; or C_{1-6}alkyloxy substituted with one R_{12};

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_1 is CR_{7a} or N;

y_2 is CH;
R_{7a} is hydrogen;
R_7 is hydrogen, $-NH_2$, $-NHCH_3$, $-NH(CH_2CH_3)$, methyl, $-CH_2OH$, halo or cyano;
or when y_1 represents CR_{7a}, this R_{7a} can be taken together with a R_7 on an adjacent carbon atom to form –CH=CH-NH- or -N=CH-NH-;
X is $-CR_1R_{1a}-$, $-CH_2-CHR_1-$;
R_1 is hydrogen or C_{1-6}alkyl;
R_{1a} is hydrogen;
R_{2a} is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; or C_{1-6}alkyl substituted with one substituent selected from the group consisting of $-NR_{9a}R_{9b}$, cyano and C_{1-4}alkyloxy;
R_{2b} is hydrogen; or
R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2-$, $-CH_2-NR_{2c}-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-NR_{2c}-CH_2-$ or =O;
R_{2c} is hydrogen; C_{1-4}alkyl optionally substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyl substituted with one cyano group; or C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$;
R_3 is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one or two hydroxyl groups and one C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl- optionally substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkylcarbonyl-; $R_{10a}R_{10b}N$-C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkylcarbonyloxy-; C_{1-6}alkyl substituted with one R_{11}; C_{1-6}alkyloxy optionally substituted with one $-NR_{10a}R_{10b}$; C_{1-6}alkyl substituted with one or two hydroxyl groups and one $-NR_{10}R_{10b}$; $-S(=O)_2-C_{1-6}$alkyl; $-S(=O)_2-NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one $-(C=O)-R_{14}$; C_{1-6}alkyl substituted with one or two hydroxyl groups and one R_{14}; C_{1-6}alkyl substituted with one R_{14}; or R_{14};
R_{4a} is hydrogen;
R_{4b} is hydrogen; or
R_{4a} and R_{4b} are taken together to form =O;
Y is –O- or -C(=O)-; in particular Y is –O-;
Z is $-CHR_6-$ or $-CH_2-C\equiv C-$;
R_6 is hydrogen; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{1-4}alkyl substituted with one $-NR_{9a}R_{9b}$; or $-C(=O)-NR_{9a}R_{9b}$;
Ring A is phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;
each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; or halo;

or a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1), (a-2), (a-3) or (a-4);

R_{9a} and R_{9b} each independently represent hydrogen; mono-or polyhaloC_{1-4}alkyl; C_{1-4}alkylcarbonyl-; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl substituted with one or two hydroxyl groups; or C_{1-4}alkyl optionally substituted with one substituent selected from the group consisting of C_{1-4}alkyloxy, cyano, amino and mono-or di(C_{1-4}alkyl)amino;

R_{10a} and R_{10b} each independently represent hydrogen; C_{1-4}alkyl; cyanoC_{1-6}alkyl; C_{1-6}alkyl substituted with one $NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one –C(=O)-$NR_{9a}R_{9b}$; C_{1-6}alkyloxy optionally substituted with one or two hydroxyl groups; C_{1-6}alkyloxyC_{1-6}alkyl wherein each C_{1-6}alkyl is optionally substituted with one or two hydroxyl groups; C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; mono-or polyhaloC_{1-6}alkylcarbonyl- substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkylcarbonyl-; mono-or polyhaloC_{1-4}alkyl; or C_{1-4}alkyl substituted with one or two hydroxyl groups;

R_{11} is cyano; -$NR_{10a}R_{10b}$; C_{1-6}alkyloxy optionally substituted with one or two hydroxyl groups; -$S(=O)_2$-C_{1-6}alkyl; -$S(=O)_2$-$NR_{9a}R_{9b}$; -NR_{13}-$S(=O)_2$-C_{1-6}alkyl; -NR_{13}-$S(=O)_2$-$NR_{9a}R_{9b}$; C_{1-6}alkylcarbonyloxy-; -C(=O)-$NR_{10a}R_{10b}$; -O-C(=O)-$NR_{10a}R_{10b}$; -COOH; –$P(=O)(OH)_2$; or –$P(=O)(O\text{-}C_{1-4}alkyl)_2$;

R_{12} is –$NR_{9a}R_{9b}$, C_{1-6}alkyloxy, or cyano;

R_{13} is hydrogen or C_{1-4}alkyl;

R_{14} is a 4, 5 or 6 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents selected from the group consisting of oxo, C_{1-4}alkyl, halogen, cyano, hydroxyl, C_{1-6}alkyloxy and $NR_{9a}R_{9b}$;

x_1 is CR_{5a} or N;

x_2 is CR_{5b};

x_3 is CR_{5c} or N;

each R_{15} is independently selected from the group consisting of hydrogen, methyl, halo, C_{1-4}alkyloxy and hydroxyl;

R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen; hydroxyl; cyano; halo; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyloxy; C_{1-6}alkyl substituted with one –$NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one cyano; C_{1-6}alkyloxyC_{1-6}alkyl wherein each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkyloxy; C_{1-6}alkyloxy substituted with one or two hydroxyl groups; C_{1-6}alkyloxyC_{1-6}alkyloxy wherein each of the C_{1-6}alkyl groups

are optionally substituted with one or two hydroxyl groups; C_{1-6}alkyloxy substituted with one cyano; and C_{1-6}alkyloxy substituted with one $-NR_{9a}R_{9b}$;
R_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one hydroxyl group; C_{2-6}alkenyl; $-Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; or C_{1-6}alkyl-O-carbonyl-;
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_1 is CR_{7a} or N;
y_2 is CH or N;
R_{7a} is hydrogen, halo, trifluoromethyl or cyano;
R_7 is hydrogen, $-NH_2$, $-NHCH_3$, $-NH(CH_2CH_3)$, methyl, $-CH_2OH$, halo or cyano;
or when y_1 represents CR_{7a}, this R_{7a} can be taken together with a R_7 on an adjacent carbon atom to form –CH=CH-NH- or -N=CH-NH-;
X is $-CR_1R_{1a}-$, $-CH_2-CHR_1-$;
R_1 is hydrogen or C_{1-6}alkyl;
R_{1a} is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$; or $-C(=O)-NR_{9a}R_{9b}$;
R_{2a} is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; or C_{1-6}alkyl substituted with one substituent selected from the group consisting of $-NR_{9a}R_{9b}$, cyano and C_{1-4}alkyloxy;
R_{2b} is hydrogen or C_{1-6}alkyl; or
R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2-$, $-CH_2-NR_{2c}-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-NR_{2c}-CH_2-$ or =O;
R_{2c} is hydrogen; C_{1-4}alkyl optionally substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyl substituted with one cyano group; or C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$;
R_3 is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one or two hydroxyl groups and one C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl- optionally substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkylcarbonyl-; $R_{10a}R_{10b}N$-C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkylcarbonyloxy-; C_{1-6}alkyl substituted with one R_{11}; C_{1-6}alkyloxy optionally substituted with one $-NR_{10a}R_{10b}$; C_{2-6}alkenyl; C_{2-6}alkynyl; hydroxyC_{2-6}alkenyl; hydroxyC_{2-6}alkynyl; C_{1-6}alkyloxyC_{2-6}alkenyl;

C_{1-6}alkyloxyC_{2-6}alkynyl; C_{2-6}alkenyl substituted with one $-NR_{10a}R_{10b}$; C_{2-6}alkynyl substituted with one $-NR_{10a}R_{10b}$; C_{1-6}alkyl substituted with one or two hydroxyl groups and one $-NR_{10}R_{10b}$; $-C_{1-6}$alkyl-$C(R_{13})$=N-O-R_{13}; $-S(=O)_2-C_{1-6}$alkyl; $-S(=O)_2-NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one $-(C=O)-R_{14}$; C_{1-6}alkyl substituted with one or two hydroxyl groups and one R_{14}; C_{1-6}alkyl substituted with one R_{14}; C_{2-6}alkenyl substituted with one R_{14}; C_{2-6}alkynyl substituted with one R_{14}; or R_{14};

R_{4a} is hydrogen;

R_{4b} is hydrogen; or

R_{4a} and R_{4b} are taken together to form =O;

Y is –O- or -C(=O)-; in particular Y is –O-;

Z is $-CHR_6-$ or $-CH_2-C\equiv C-$;

R_6 is hydrogen; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{1-4}alkyl substituted with one $-NR_{9a}R_{9b}$; or $-C(=O)-NR_{9a}R_{9b}$;

Ring A is phenyl or a 6-membered saturated, partially saturated or aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents; in particular ring A is phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; or halo;

R_{9a} and R_{9b} each independently represent hydrogen; mono-or polyhaloC_{1-4}alkyl; C_{1-4}alkylcarbonyl-; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl substituted with one or two hydroxyl groups; or C_{1-4}alkyl optionally substituted with one substituent selected from the group consisting of C_{1-4}alkyloxy, cyano, amino and mono-or di(C_{1-4}alkyl)amino;

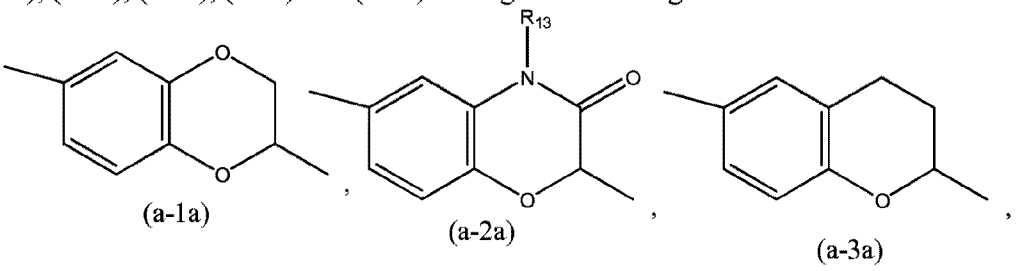
R_{10a} and R_{10b} each independently represent hydrogen; C_{1-4}alkyl; cyanoC_{1-6}alkyl; C_{1-6}alkyl substituted with one $NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one $-C(=O)-NR_{9a}R_{9b}$; C_{1-6}alkyloxy optionally substituted with one or two hydroxyl groups; C_{1-6}alkyloxyC_{1-6}alkyl wherein each C_{1-6}alkyl is optionally substituted with one or two hydroxyl groups; R_{14}; C_{1-6}alkyl substituted with one R_{14}; $-(C=O)-R_{14}$; C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; mono-or polyhaloC_{1-6}alkylcarbonyl-substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkylcarbonyl-; C_{1-6}alkyl substituted with one $-Si(CH_3)_3$; $-S(=O)_2-C_{1-6}$alkyl optionally substituted with one or more halo substituents; $-S(=O)_2-NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one $-S(=O)_2-C_{1-6}$alkyl wherein $-S(=O)_2-C_{1-6}$alkyl is optionally substituted with one or more halo substituents;

C_{1-6}alkyl substituted with one $-S(=O)_2-NR_{9a}R_{9b}$;

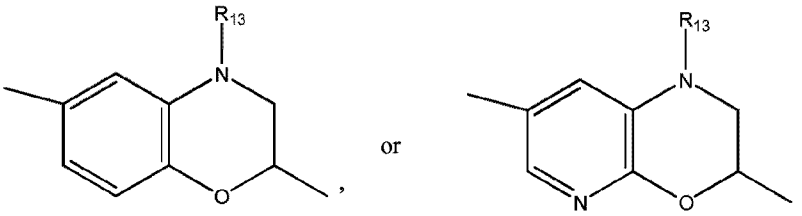
C_{1-6}alkyl substituted with one –NH-S(=O)$_2$-C_{1-6}alkyl wherein –NH-S(=O)$_2$-C_{1-6}alkyl is optionally substituted on a carbon atom with one or more halo substituents;
C_{1-6}alkyl substituted with one -NH-S(=O)$_2$-$NR_{9a}R_{9b}$;
mono-or polyhaloC_{1-4}alkyl; or C_{1-4}alkyl substituted with one or two hydroxyl groups;
R_{11} is cyano; -$NR_{10a}R_{10b}$; C_{1-6}alkyloxy optionally substituted with one or two hydroxyl groups; -S(=O)$_2$-C_{1-6}alkyl; -S(=O)$_2$-$NR_{9a}R_{9b}$; -NR_{13}-S(=O)$_2$-C_{1-6}alkyl; -NR_{13}-S(=O)$_2$-$NR_{9a}R_{9b}$; C_{1-6}alkylcarbonyloxy-; -C(=O)-$NR_{10a}R_{10b}$; -O-C(=O)-$NR_{10a}R_{10b}$; -COOH; –P(=O)(OH)$_2$; or –P(=O)(O-C_{1-4}alkyl)$_2$;
R_{12} is –$NR_{9a}R_{9b}$, C_{1-6}alkyloxy, or cyano;
R_{13} is hydrogen or C_{1-4}alkyl;
R_{14} is a C_{3-8}cycloalkyl; or a 4, 5 or 6 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents selected from the group consisting of oxo, C_{1-4}alkyl, halogen, cyano, hydroxyl, C_{1-6}alkyloxy and $NR_{9a}R_{9b}$;
x_1 is CR_{5a} or N;
x_2 is CR_{5b} or N;
x_3 is CR_{5c} or N;
each R_{15} is independently selected from the group consisting of hydrogen, methyl, halo, C_{1-4}alkyloxy and hydroxyl;
R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen; hydroxyl; cyano; halo; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyloxy; C_{1-6}alkyl substituted with one –$NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one cyano; C_{1-6}alkyloxyC_{1-6}alkyl wherein each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkyloxy; C_{1-6}alkyloxy substituted with one or two hydroxyl groups; C_{1-6}alkyloxyC_{1-6}alkyloxy wherein each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups; C_{1-6}alkyloxy substituted with one cyano; and C_{1-6}alkyloxy substituted with one –$NR_{9a}R_{9b}$;
R_{5b} is hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; hydroxyl; cyano; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-4}alkyloxy; -Si$(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; C_{1-6}alkyl-O-carbonyl-; or C_{1-6}alkyloxy substituted with one R_{12};
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 the bicycles of formula (a-1), (a-2), (a-3) and (a-4) are limited to bicycles of formula (a-1a), (a-2a), (a-3a), (a-4a) and (a-4b) having the following structures:



(a-1a), (a-2a), (a-3a)



(a-4a) or (a-4b).

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

y_1 is CR_{7a} or N;

y_2 is CH;

R_{7a} is hydrogen;

R_7 is hydrogen, $-NH_2$, $-CH_2OH$, halo or cyano;

or when y_1 represents CR_{7a}, this R_{7a} can be taken together with a R_7 on an adjacent carbon atom to form –CH=CH-NH-;

X is $-CR_1R_{1a}-$, $-CH_2-CHR_1-$;

R_1 is hydrogen or C_{1-6}alkyl;

R_{1a} is hydrogen;

R_{2a} is hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one hydroxyl group; or C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$ substituent;

R_{2b} is hydrogen; or

R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2-$, $-CH_2-NR_{2c}-CH_2-$ or =O;

R_{2c} is hydrogen; or C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$;

R_3 is hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one or two hydroxyl groups and one C_{1-6}alkyloxy; $R_{10a}R_{10b}N$-C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkyl substituted with one R_{11}; C_{1-6}alkyl substituted with one $-(C=O)-R_{14}$; or C_{1-6}alkyl substituted with one R_{14};

R_{4a} is hydrogen;

R_{4b} is hydrogen; or

R_{4a} and R_{4b} are taken together to form =O;

Y is –O- or -C(=O)-;

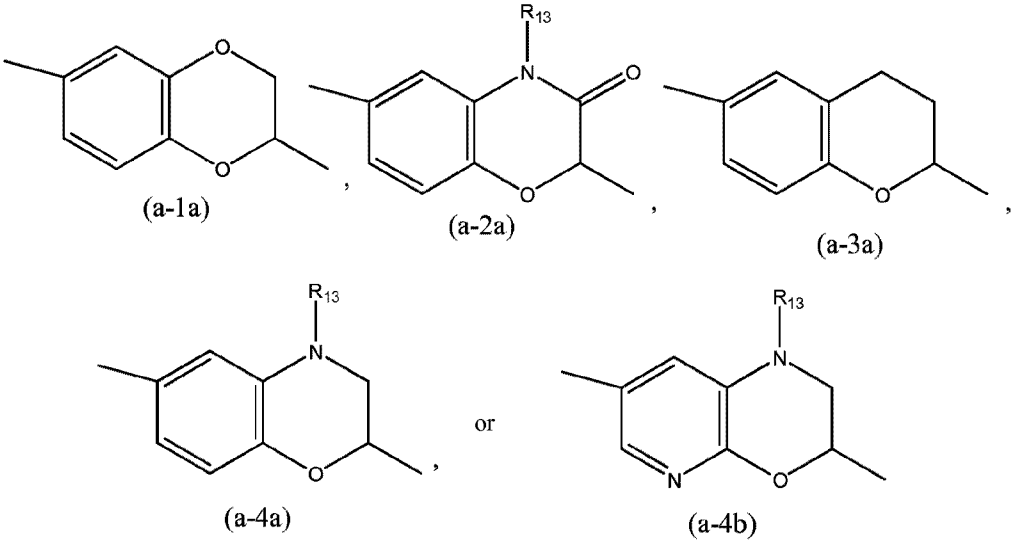
Z is $–CHR_6-$ or $–CH_2-C\equiv C-$;

R_6 is hydrogen; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl; C_{1-4}alkyl substituted with one hydroxyl group; C_{1-4}alkyl substituted with one $-NR_{9a}R_{9b}$; or $-C(=O)-NR_{9a}R_{9b}$;

Ring A is phenyl or a 6-membered saturated, partially saturated or aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; C_{1-4}alkyl or halo;

or a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1a), (a-2a), (a-3a), (a-4a) or (a-4b):



(a-1a) (a-2a) (a-3a)

(a-4a) or (a-4b)

R_{9a} and R_{9b} each independently represent hydrogen; C_{1-4}alkyl substituted with one hydroxyl group; or C_{1-4}alkyl;

R_{10a} and R_{10b} each independently represent hydrogen; C_{1-4}alkyl; C_{1-6}alkyl-O-carbonyl-; mono-or polyhaloC_{1-4}alkyl; or C_{1-4}alkyl substituted with one hydroxyl group;

R_{11} is cyano; $-NR_{10a}R_{10b}$; C_{1-6}alkyloxy optionally substituted with one hydroxyl group;

$-S(=O)_2-C_{1-6}$alkyl; C_{1-6}alkylcarbonyloxy-; $-C(=O)-NR_{10a}R_{10b}$; -COOH; or $–P(=O)(O-C_{1-4}alkyl)_2$;

R_{12} is $–NR_{9a}R_{9b}$, C_{1-6}alkyloxy, or cyano;

R_{13} is hydrogen or C_{1-4}alkyl;

R_{14} is a 5 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents selected from the group consisting of oxo and C_{1-4}alkyl;

x_1 is CR_{5a} or N;

x_2 is CR_{5b};

x_3 is CR_{5c} or N;

each R_{15} is independently selected from the group consisting of hydrogen, methyl, halo, and C_{1-4}alkyloxy;

R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen; hydroxyl; cyano; halo; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxy substituted with one hydroxyl group; C_{1-6}alkyloxyC_{1-6}alkyloxy;

R_{5b} is hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; cyano; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one hydroxyl group; C_{2-6}alkenyl; C_{1-4}alkyloxy; $-Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; or C_{1-6}alkyl-O-carbonyl-;

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_1 is CH or N;

y_2 is CH;

R_7 is hydrogen or $-NH_2$;

X is CH_2;

R_{2a} is hydrogen;

R_{2b} is hydrogen; or

R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2-$ or $-CH_2-NH-CH_2-$;

R_3 is hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one R_{11}; or C_{1-6}alkyl substituted with one R_{14};

R_{4a} is hydrogen;

R_{4b} is hydrogen; or

R_{4a} and R_{4b} are taken together to form =O;

Y is –O-;

Z is $-CHR_6$-;

R_6 is hydrogen;

Ring A is phenyl or pyridinyl; wherein the phenyl or pyridinyl is optionally substituted with one or two R_8 substituents;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; or halo;

or a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-3a);

R_{11} is C_{1-6}alkyloxy optionally substituted with one hydroxyl group; or -C(=O)-$NR_{10a}R_{10b}$;

R_{10a} and R_{10b} each independently represent hydrogen or C_{1-4}alkyl;

R_{14} is a 5 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents selected from the group consisting of C_{1-4}alkyl;

x_1 is CR_{5a} or N;

x_2 is CR_{5b};

x_3 is CR_{5c};

each R_{15} is hydrogen;

R_{5a} is hydrogen or C_{1-6}alkyloxyC_{1-6}alkyl;

R_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl; mono-or polyhaloC_{1-6}alkyloxy; C_{2-6}alkenyl; C_{1-6}alkyl substituted with one cyano; C_{1-4}alkyloxy; or C_{1-6}alkyl-O-carbonyl-;

R_{5c} is hydrogen;

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_1 is CH;

y_2 is CH;

R_7 is hydrogen;

X is CH_2;

R_{2a} is hydrogen;

R_{2b} is hydrogen;

R_3 is hydrogen; or C_{1-6}alkyl substituted with one or two hydroxyl groups;

R_{4a} and R_{4b} are taken together to form =O;

Y is –O-;

Z is $–CH_2$-;

Ring A is phenyl optionally substituted with one or two R_8 substituents;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; or F;

x_1 is CH;

x_2 is CR_{5b};

x_3 is CH;

each R_{15} is hydrogen;

R_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl; mono-or polyhaloC_{1-6}alkyloxy; C_{2-6}alkenyl; C_{1-6}alkyl substituted with one cyano; or C_{1-6}alkyl-O-carbonyl-; in particular R_{5b} is isopropyl or cyclopropyl;

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) y_2 is CH;

(ii) R_{7a} is hydrogen;

(iii) R_7 is hydrogen, $-NH_2$, $-CH_2OH$, halo or cyano;

or when y_1 represents CR_{7a}, this R_{7a} can be taken together with a R_7 on an adjacent carbon atom to form –CH=CH-NH-;

(iv) R_{1a} is hydrogen;

(v) R_{2a} is hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one hydroxyl group; or C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$ substituent;

R_{2b} is hydrogen; or

R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2-$, $-CH_2-NR_{2c}-CH_2-$ or =O;

(vi) R_{2c} is hydrogen; or C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$;

(vii) R_3 is hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one or two hydroxyl groups and one C_{1-6}alkyloxy; $R_{10a}R_{10b}N$-C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkyl substituted with one R_{11}; C_{1-6}alkyl substituted with one $-(C=O)-R_{14}$; or C_{1-6}alkyl substituted with one R_{14};

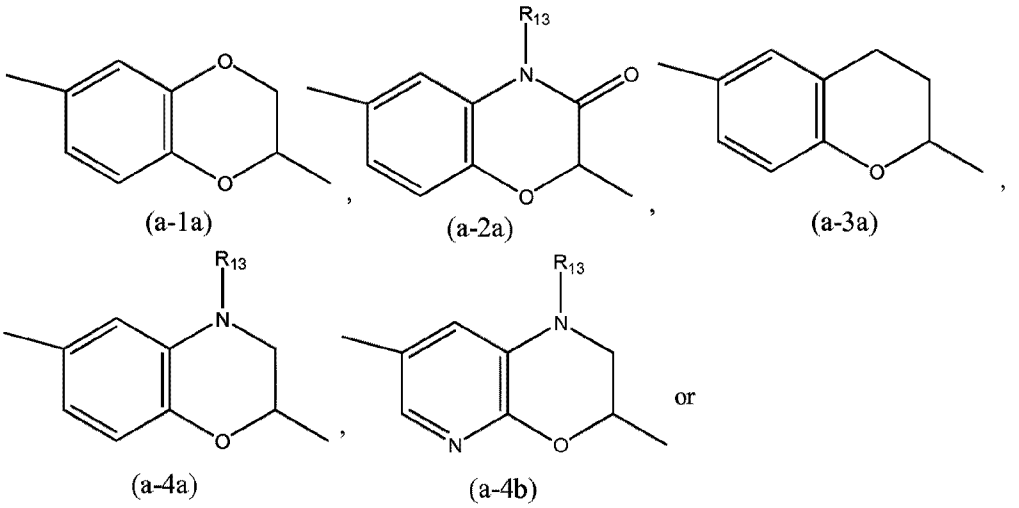
(viii) Y is –O- or -C(=O)-;

Z is $-CHR_6-$ or $-CH_2-C\equiv C-$;

R_6 is hydrogen; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl; C_{1-4}alkyl substituted with one hydroxyl group; C_{1-4}alkyl substituted with one $-NR_{9a}R_{9b}$; or $-C(=O)-NR_{9a}R_{9b}$;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; C_{1-4}alkyl or halo;

or a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1a), (a-2a), (a-3a), (a-4a) or (a-4b):



(a-1a) (a-2a) (a-3a)

(a-4a) (a-4b)

(ix) R_{9a} and R_{9b} each independently represent hydrogen; C_{1-4}alkyl substituted with one hydroxyl group; or C_{1-4}alkyl;

(x) R_{10a} and R_{10b} each independently represent hydrogen; C_{1-4}alkyl; C_{1-6}alkyl-O-carbonyl-; mono-or polyhaloC_{1-4}alkyl; or C_{1-4}alkyl substituted with one hydroxyl group;

(xi) R_{11} is cyano; $-NR_{10a}R_{10b}$; C_{1-6}alkyloxy optionally substituted with one hydroxyl group; $-S(=O)_2-C_{1-6}$alkyl; C_{1-6}alkylcarbonyloxy-; $-C(=O)-NR_{10a}R_{10b}$; -COOH; or $-P(=O)(O-C_{1-4}alkyl)_2$;

(xii) R_{14} is a 5 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents selected from the group consisting of oxo and C_{1-4}alkyl;

(xiii) R_6 is hydrogen; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl; C_{1-4}alkyl substituted with one hydroxyl group; C_{1-4}alkyl substituted with one $-NR_{9a}R_{9b}$; or $-C(=O)-NR_{9a}R_{9b}$;

(xiv) x_2 is CR_{5b};

(xv) each R_{15} is independently selected from the group consisting of hydrogen, methyl, halo,

and C_{1-4}alkyloxy;

(xvi) R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen; hydroxyl; cyano; halo; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxy substituted with one hydroxyl group; C_{1-6}alkyloxyC_{1-6}alkyloxy;

(xvii) R_{5b} is hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; cyano; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one hydroxyl group; C_{2-6}alkenyl; C_{1-4}alkyloxy; $-Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; or C_{1-6}alkyl-O-carbonyl-.

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) y_1 is CH or N;

(ii) y_2 is CH;

(iii) R_7 is hydrogen or $-NH_2$;

(iv) X is CH_2;

(v) R_{2a} is hydrogen;

R_{2b} is hydrogen; or

R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2-$ or $-CH_2-NH-CH_2-$;

(vi) R_3 is hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one R_{11}; or C_{1-6}alkyl substituted with one R_{14};

(vii) R_{4a} is hydrogen;

R_{4b} is hydrogen; or

R_{4a} and R_{4b} are taken together to form =O;

(viii) Y is –O-;

Z is $-CHR_6-$;

R_6 is hydrogen;

Ring A is phenyl or pyridinyl; wherein the phenyl or pyridinyl is optionally substituted with one or two R_8 substituents;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; or halo;

or a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-3a);

(ix) R_{11} is C_{1-6}alkyloxy optionally substituted with one hydroxyl group; or $-C(=O)-NR_{10a}R_{10b}$;

R_{10a} and R_{10b} each independently represent hydrogen or C_{1-4}alkyl;

(x) R_{14} is a 5 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents selected from the group consisting of C_{1-4}alkyl;

(xi) x_1 is CR_{5a} or N;

x_2 is CR_{5b};

x_3 is CR_{5c};

(xiii) each R_{15} is hydrogen;

(xiv) R_{5a} is hydrogen or C_{1-6}alkyloxyC_{1-6}alkyl;

(xv) R_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl; mono-or polyhaloC_{1-6}alkyloxy; C_{2-6}alkenyl; C_{1-6}alkyl substituted with one cyano; C_{1-4}alkyloxy; or C_{1-6}alkyl-O-carbonyl-;

(xvi) R_{5c} is hydrogen.

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) y_1 is CH;
(ii) y_2 is CH;
(iii) R_7 is hydrogen;
(iv) X is CH_2;
(v) R_{2a} is hydrogen;
(vi) R_{2b} is hydrogen;
(vii) R_3 is hydrogen; or C_{1-6}alkyl substituted with one or two hydroxyl groups;
(viii) R_{4a} and R_{4b} are taken together to form =O;
(ix) Ring A is phenyl optionally substituted with one or two R_8 substituents; each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; or F;
(x) Y is –O-;
(xi) Z is $-CH_2-$;
(xii) x_1 is CH;
x_2 is CR_{5b};
x_3 is CH;
(xiii) each R_{15} is hydrogen;
(xiv) R_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl; mono-or polyhaloC_{1-6}alkyloxy; C_{2-6}alkenyl; C_{1-6}alkyl substituted with one cyano; or C_{1-6}alkyl-O-carbonyl-; in particular R_{5b} is isopropyl or cyclopropyl.

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 is O.

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 each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; or halo; or a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1), (a-2), (a-3) or (a-4).

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 ring A is phenyl or a 6-membered saturated, partially saturated or aromatic heterocyclyl, in particular phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;
each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; C_{1-4}alkyl or halo.

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 ring A is phenyl or a 6-membered saturated, partially saturated or aromatic heterocyclyl, in particular phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;
each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; or halo.

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 ring A is phenyl or a 6-membered saturated, partially saturated or aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is substituted with one R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent, and said R_8 substituent is taken together with the R_6 substituent of Z (Z is $-CHR_6-$), by which ring A together with Y-Z forms a bicycle of formula (a-1), (a-2), (a-3) or (a-4).

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 ring A is phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is substituted with one R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent, and said R_8 substituent is taken together with the R_6 substituent of Z (Z is $-CHR_6-$), by which ring A together with Y-Z forms a bicycle of formula (a-1a), (a-2a), (a-3a), (a-4a) or (a-4b).

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 ring A is phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms, in particular ring A is phenyl; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 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 ring A is phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms.

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 ring A is phenyl.

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 each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; or halo.

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 each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; or halo; or a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1a), (a-2a), (a-3a), (a-4a), or (a-4b).

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 Z is $-CHR_6-$ and Y is O.

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_8 is other than C_{1-4}alkyl.

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 ring A is phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; or halo; or a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1), (a-2), (a-3) or (a-4); and

Y is –O-.

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 when ring A together with Y-Z forms a bicycle, this bicycle is of formula (a-1), (a-2), (a-3) or (a-4); in particular (a-1a), (a-2a), (a-3a), (a-4a), or (a-4b).

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_{14} is a 5-membered saturated heterocycle which is optionally substituted with one, two or three substituents selected from the group consisting of oxo, C_{1-4}alkyl, halogen, cyano, hydroxyl, C_{1-6}alkyloxy and $NR_{9a}R_{9b}$; in particular wherein R_{14} is a 5-membered saturated heterocycle which is substituted with one or two substituents selected from the group consisting of oxo or C_{1-4}alkyl.

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_{14} is a 5-membered saturated heterocycle selected from 1-pyrolidinyl, 1,3-dioxolan-4-yl, 5-oxazolidinyl, 3-oxetanyl and tetrahydro-2-furanyl, each optionally substituted with one, two or three substituents selected from the group consisting of oxo, C_{1-4}alkyl, halogen, cyano, hydroxyl, C_{1-6}alkyloxy and $NR_{9a}R_{9b}$; in particular wherein R_{14} is a 5-membered saturated heterocycle selected from 1-pyrolidinyl, 1,3-dioxolan-4-yl, 5-oxazolidinyl, 3-oxetanyl and tetrahydro-2-furanyl, each substituted with one or two substituents selected from the group consisting of oxo and C_{1-4}alkyl.

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} is

hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; or C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$.

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_{2a} is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; or C_{1-6}alkyl substituted with one substituent selected from the group consisting of $-NR_{9a}R_{9b}$, cyano and C_{1-4}alkyloxy;
R_{2b} is hydrogen or C_{1-6}alkyl; or
R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2-$, $-CH_2-NR_{2c}-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-NR_{2c}-CH_2-$.

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_{5b} is hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; hydroxyl; cyano; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-4}alkyloxy; $-Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; or C_{1-6}alkyloxy substituted with one R_{12}.

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_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one hydroxyl group; C_{2-6}alkenyl; $-Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; or C_{1-6}alkyl-O-carbonyl-.

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_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one hydroxyl group; C_{2-6}alkenyl; $-Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; or C_{1-6}alkyl-O-carbonyl-; and wherein R_8 is other than C_{1-4}alkyl.

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

ring A is phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;
each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; or halo; or
a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1), (a-2), (a-3) or (a-4);
x_2 is CR_{5b}; R_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; mono- or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one hydroxyl group; C_{2-6}alkenyl; $-Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; or C_{1-6}alkyl-O-carbonyl-.

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
ring A is phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;
each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; or halo; or
a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1a), (a-2a), (a-3a), (a-4a) or (a-4b);
x_2 is CR_{5b}; R_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; mono- or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one hydroxyl group; C_{2-6}alkenyl; $-Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; or C_{1-6}alkyl-O-carbonyl-.

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
ring A is phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;
each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; or halo; in particular each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; or halo;
x_2 is CR_{5b}; R_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; mono- or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one

hydroxyl group; C_{2-6}alkenyl; -$Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; or C_{1-6}alkyl-O-carbonyl-.

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 X is -CR_1R_{1a}-; in particular CH_2.

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_1 and R_{1a} are hydrogen.

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-Z- is –O-CH_2-.

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 Z is CHR_6, in particular CH_2.

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_6 is H.

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 is hydrogen or C_{1-6}alkyl substituted with one or two, in particular one, hydroxyl groups.

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_{2a} and R_{2b} are hydrogen.

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_{4a} is hydrogen; R_{4b} is hydrogen; or R_{4a} and R_{4b} are taken together to form =O.

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_{4a} and R_{4b} are hydrogen.

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_{4a} and R_{4b} are taken together to form =O.

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 x_1 and x_3 are CH; and x_2 is CR_{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 x_2 is CR_{5b}; R_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; hydroxyl; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{2-6}alkenyl; -$Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkyloxy substituted with one R_{12}.

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_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; hydroxyl; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{2-6}alkenyl; -$Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkyloxy substituted with one R_{12}.

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_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen; hydroxyl; cyano; halo; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyl wherein each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-6}alkyloxy; C_{1-6}alkyloxy substituted with one or two

hydroxyl groups; C_{1-6}alkyloxyC_{1-6}alkyloxy wherein each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups.

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 is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one or two hydroxyl groups and one C_{1-6}alkyloxy; C_{1-6}alkylcarbonyloxy-; C_{1-6}alkyl substituted with one R_{11}; C_{1-6}alkyloxy optionally substituted with one -$NR_{10a}R_{10b}$; C_{2-6}alkenyl; C_{2-6}alkynyl; hydroxyC_{2-6}alkenyl; hydroxyC_{2-6}alkynyl; C_{1-6}alkyloxyC_{2-6}alkenyl; C_{1-6}alkyloxyC_{2-6}alkynyl; C_{2-6}alkenyl substituted with one –$NR_{10a}R_{10b}$; C_{2-6}alkynyl substituted with one –$NR_{10a}R_{10b}$; C_{1-6}alkyl substituted with one or two hydroxyl groups and one –$NR_{10}R_{10b}$; -C_{1-6}alkyl-$C(R_{13})$=N-O-R_{13}; -$S(=O)_2$-C_{1-6}alkyl; -$S(=O)_2$-$NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one –(C=O)-R_{14}; C_{1-6}alkyl substituted with one or two hydroxyl groups and one R_{14}; C_{1-6}alkyl substituted with one R_{14}; C_{2-6}alkenyl substituted with one R_{14}; C_{2-6}alkynyl substituted with one R_{14}; or R_{14}.

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_{15} is hydrogen.

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_{15} is hydrogen or F, in particular F.

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_{7a} is hydrogen, halo, trifluoromethyl or cyano;
R_7 is hydrogen, -NH_2, -$NHCH_3$, -$NH(CH_2CH_3)$, methyl, -CH_2OH, halo or cyano.

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_{7a} is hydrogen; R_7 is hydrogen, -NH_2, -CH_2OH, halo or cyano.

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 ring A is phenyl optionally substituted with one or two R_8 substituents;
each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; or halo;
Y is –O-; Z is $–CH_2$-; R_{15} is H; x_1 and x_3 are CH; x_2 is CR_{5b}; R_{5b} is isopropyl.

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_1 and y_2 are CH; R_7 is H; X is CH_2; R_{2a} and R_{2b} are H;
R_{4a} and R_{4b} are taken together to form =O;
ring A is phenyl optionally substituted with one or two R_8 substituents;
each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; or halo;
Y is –O-; Z is $–CH_2$-; R_{15} is H; x_1 and x_3 are CH; x_2 is CR_{5b}; R_{5b} is isopropyl.

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_1 and y_2 are CH; R_7 is H; X is CH_2; R_{2a} and R_{2b} are H;
R_{4a} and R_{4b} are taken together to form =O;
ring A is phenyl; Y is –O-; Z is $–CH_2$-; R_{15} is H; x_1 and x_3 are CH; x_2 is CR_{5b}; R_{5b} is isopropyl.

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 x_1 and x_3 are CH; x_2 is CR_{5b}; R_{5b} is isopropyl.

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_1 and y_2 are CH.

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) y_1 and y_2 are CH;
(ii) R_7 is H;
(iii) X is CH_2;
(iv) R_{2a} and R_{2b} are H;

(v) R_{4a} and R_{4b} are taken together to form =O;
(vi) ring A is phenyl optionally substituted with one or two R_8 substituents;
each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; or halo;
(vii) Y is –O-;
(viii) Z is $–CH_2$-;
(ix) R_{15} is H;
(x) x_1 and x_3 are CH;
(xi) x_2 is CR_{5b}; R_{5b} is isopropyl.

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 x_2 is CR_{5b}; R_{5b} is isopropyl.

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 C_{1-6}alkyl is limited to C_{1-4}alkyl.

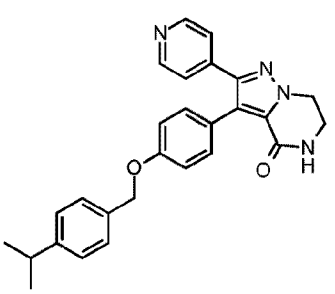
In an embodiment, the present invention relates to those compounds of formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R_{7a} is hydrogen, halo, trifluoromethyl or cyano;
R_7 is hydrogen, $-NH_2$, $-NHCH_3$, $-NH(CH_2CH_3)$, methyl, $-CH_2OH$, halo or cyano.

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_8 is not taken together with the R_6 substituent of Z to form a bicycle.

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_{14} is a 4, 5 or 6 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents selected from the group consisting of oxo, C_{1-4}alkyl, halogen, cyano, hydroxyl, C_{1-6}alkyloxy and $NR_{9a}R_{9b}$.

In an embodiment, the present invention relates to a subgroup of formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, as defined in the general reaction schemes.

In an embodiment the compound of Formula (I) is selected from the group consisting of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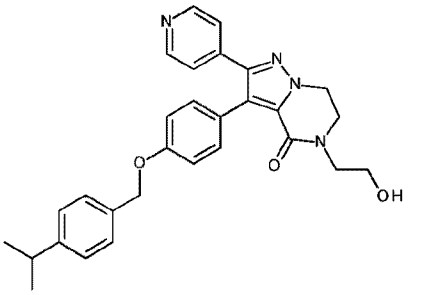
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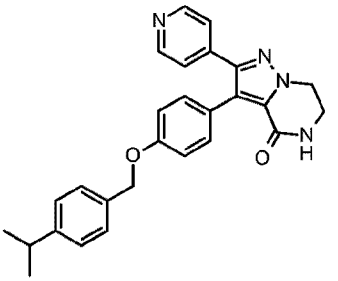
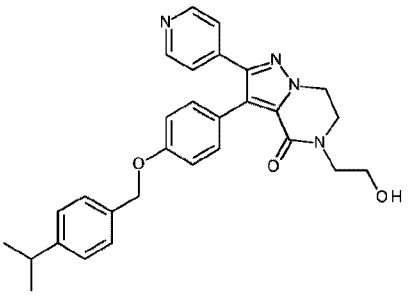
tautomers and stereoisomeric forms thereof,

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

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

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

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.

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 limit of the invention.

Alternatively, compounds of the present invention may also be prepared by analogous reaction protocols as described in the general schemes below, combined with standard 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, 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 protecting groups can be used in accordance with standard practice.

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_2-gas atmosphere, for example when NaH is used in the reaction.
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).
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 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.

All variables are defined as mentioned hereabove unless otherwise is indicated or is clear from the context.

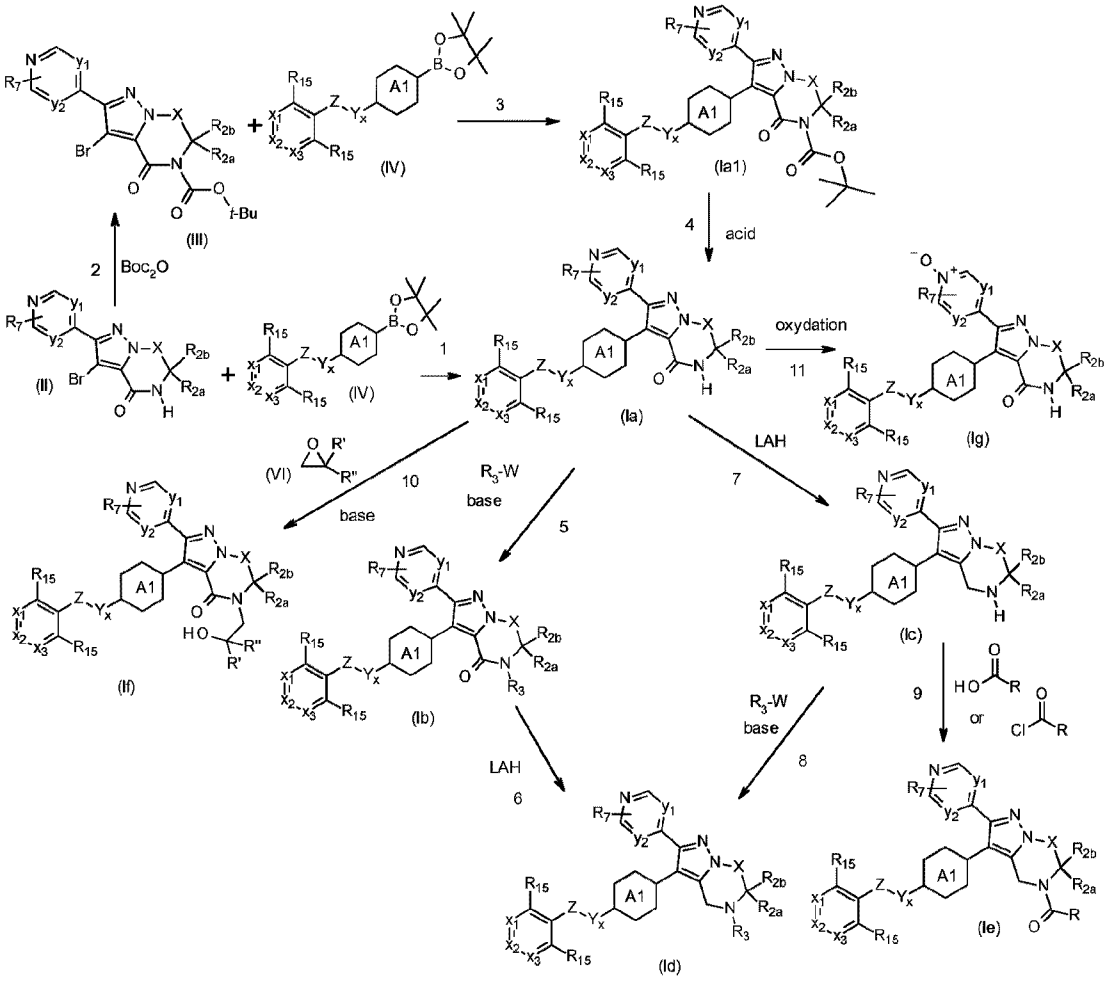
1) Scheme 1 :

In general, compounds of formula (Ia1), (Ia), (Ib), (Ic), (Id), (Ie) (If) and (Ig) can be prepared according to reaction Scheme 1. In scheme 1 the following definitions apply:
Y_x is defined as O;
ring A1 is phenyl or a 6-membered aromatic heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;
each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; C_{1-4}alkyl or halo; or a R_8 substituent of ring A1 on an atom adjacent to the atom carrying the Y_x-Z

substituent is taken together with the R_6 substituent of Z, by which ring A1 together with Y_x-Z forms a bicycle;

R, R' and R'' are functional groups within the limits of the scope;

and all other variables in Scheme 1 are defined according to the scope of the present invention.



1 : an intermediate of formula (II) can be reacted with an intermediate of formula (IV) in the presence of suitable catalyst, such as for example palladium (II) acetate or [1,1'-bis(diphenylphosphino-kP)ferrocene]dichloropalladium ($PdCl_2dppf$), a suitable base, such as for example potassium phosphate (K_3PO_4) or cesium carbonate (Cs_2CO_3), and a suitable solvent or solvent mixture, such as for example dimethylformamide or dioxane and water, resulting in a compound of formula (Ia). This type of reaction can also be performed in the presence of a suitable ligand, such as for example tricyclohexylphosphine.

2 : an intermediate of formula (II) can be reacted with *tert*-butoxycarbonyl anhydride (Boc_2O) in the presence of a suitable base, such as for example triethylamine (Et_3N), a suitable catalyst, such as for example 4-dimethylaminopyridine (DMAP) and a suitable solvent, such as for example tetrahydrofuran, resulting in an intermediate of formula (III).

3 : an intermediate of formula (III) can be reacted with an intermediate of formula (IV) in the presence of suitable catalyst, such as for example [1,1'-bis(diphenylphosphino-kP)ferrocene]dichloropalladium ($PdCl_2dppf$), a suitable base, such as potassium phosphate (K_3PO_4), and a suitable solvent or solvent mixture, such as for example dioxane and water, resulting in a compound of formula (Ia1).

4 : a compound of formula (Ia1) can be deprotected to a compound of formula (Ia) with a suitable acid, such as for example HCl and a suitable solvent, such as for example acetonitrile or an acohol, e.g. methanol.

5 : a compound of formula (Ia) can be reacted with an intermediate of formula R_3-W, wherein W represents a suitable leaving group, such as for example iodide, bromide, chloride or tosylate, in the presence of suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide or dimethylsulfoxide, resulting in a compound of formula (Ib).

6 : a compound of formula (Ib) can be converted into a compound of formula (Id) by reaction with lithiumaluminiumhydride in the presence of a suitable solvent, such as for example tetrahydrofuran.

7 : a compound of formula (Ia) can be converted into a compound of formula (Ic) by reaction with lithiumaluminiumhydride in the presence of a suitable solvent, such as for example tetrahydrofuran.

8 : a compound of formula (Ic) can be reacted with an intermediate of formula R_3-W, wherein W represents a suitable leaving group, such as for example iodide, bromide, chloride or tosylate, in the presence of suitable base, such as for example sodium hydride, Et_3N or K_2CO_3, and a suitable solvent, such as for example N,N-dimethylformamide or dimethylsulfoxide, resulting in a compound of formula (Id).

9 : a compound of formula (Ic) can be reacted with an intermediate of formula R-COOH, in the presence of a suitable peptide coupling agent, such as for example 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) or carbonyldiimidazole (CDI), a suitable base, such as for example, diisopropylethylamine (DIPEA), and a suitable solvent, such as for example dichloromethane or tetrahydrofuran, resulting in a compound of formula (Ie).

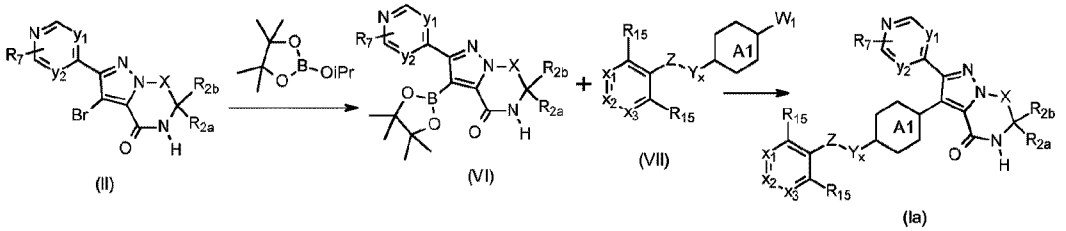
Or alternatively a compound of formula (Ic) can be reacted with an intermediate of formula R-CO-Cl, in the presence of a suitable base, such as for example DIPEA, and a suitable solvent, such as for example dichloromethane.

10 : a compound of formula (If) can be prepared by reacting a compound of formula (Ia) and an intermediate of formula (V) in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example dimethylformamide.

11 : a compound of formula (Ia) can be converted into a compound of formula (Ig) in the presence of a suitable oxidizing agent, such as for example meta-chloroperbenzoic acid (mCpBA), and a suitable solvent, such as for example dichloromethane.

2) Scheme 1a : second way final compounds (Ia)

Compounds of formula (Ia), wherein all variables are as defined before, can also be prepared according to the following reaction scheme 1a.

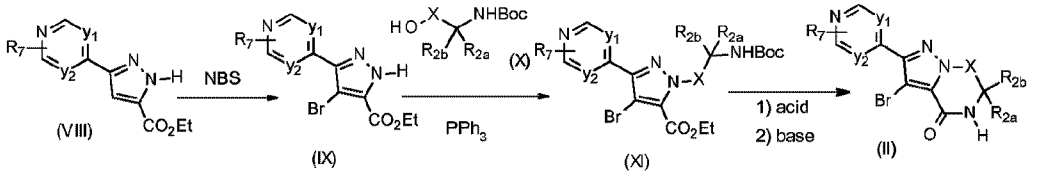


In Scheme 1a, an intermediate of formula (II) can be reacted with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxoborolane in the presence of isopropylmagnesium chloride and a suitable solvent, such as for example tetrahydrofuran (THF), resulting in an intermediate of formula (VI).

An intermediate of formula (VI) can be reacted with an intermediate of formula (VII), wherein W1 represents a suitable halogen, such as for exemple bromide, in the presence of suitable pre-catalyst, such as for example (*SP*-4-4)-[2'-(amino-κ*N*)[1,1'-biphenyl]-2-yl-κ*C*]chloro[dicyclohexyl[2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine]-palladium (X-Phos aminobiphenyl palladium chloride precatalyst; X-Phos Pd G2), a suitable base, such as potassium phosphate (K_3PO_4), and a suitable solvent or solvent mixture, such as for example THF and water, resulting in a compound of formula (Ia).

3) Scheme 1b : intermediate (II)

Intermediates of formula (II), wherein all variables are as defined before, can be prepared according to the following reaction scheme 1b.

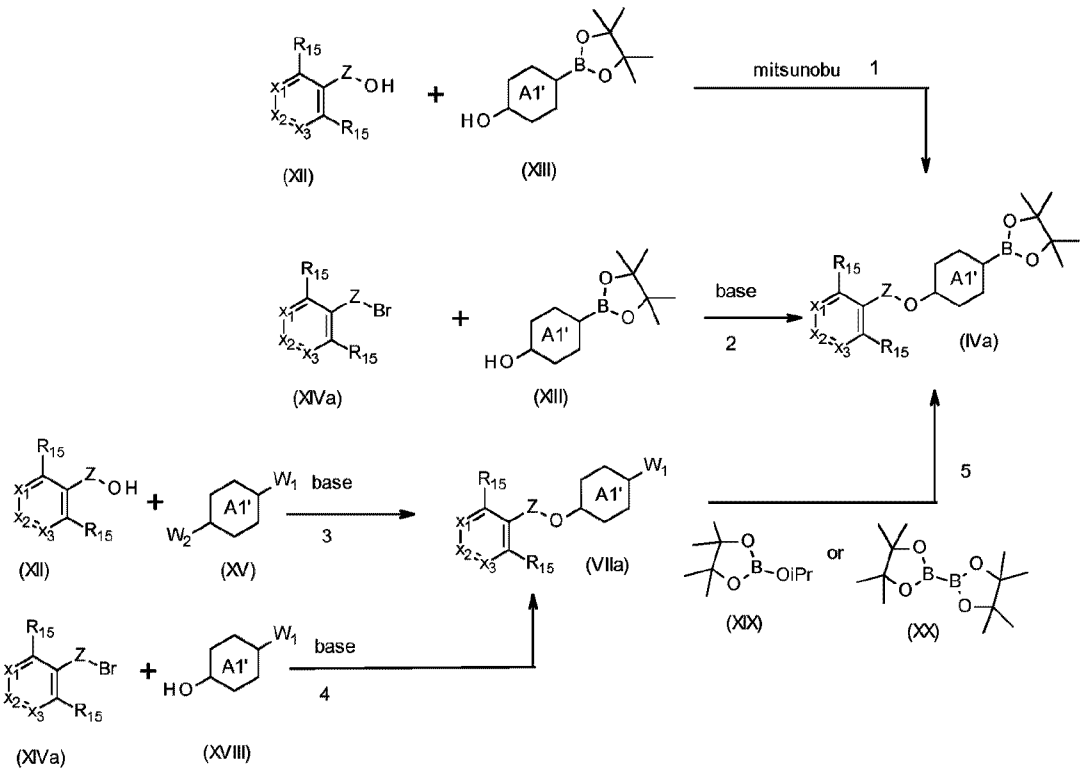


In Scheme 1b, an intermediate of formula (VIII) can be reacted with N-Bromosuccinimide (NBS) in the presence of a suitable solvent, such as for example DCM or DMF, resulting in an intermediate of formula (IX) which can be reacted in a next step with an intermediate of formula (X) in the presence of Triphenylphosphine (PPh_3), a suitable Mitsunobu reagent, such as for example Di-*tert*-butylazodicarboxylate (DBAD) and a suitable solvent, such as for example THF, resulting in an intermediate of formula (XI).

An intermediate of formula (XI) can then be deprotected in the presence of a suitable acid, such as for exemple Trifluoroacetic acid (TFA) and a suitable solvent, such as for exemple DCM. The resulting intermediate can be converted into an intermediate of formula (II) in the presence of a suitable base, such as for exemple cesium carbonate (Cs_2CO_3) or sodium bicarbonate ($NaHCO_3$) and a suitable solvent, such as for exemple MeOH or water.

4) Scheme 1c : intermediate (IVa)

Intermediates of formula (IV), wherein ring A1 is limited to A1' (no bicycles formed with Y_x-Z), hereby named an intermediate of formula (IVa), can be prepared according to the following reaction scheme 1c. Ring A1' is optionally substituted phenyl or an optionally substituted 6-membered aromatic heterocyclyl containing one or two nitrogen atoms (thus does not form a bicyclic ring with Y_x-Z), and all other variables are as defined before.



1 : an intermediate of formula (XII) can be reacted with an intermediate of formula (XIII) in the presence of triphenylphosphine (PPh_3), a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example Dichloromethane (DCM) or THF, resulting in an intermediate of formula (IV).

2 : an intermediate of formula (XIVa) can be reacted with an intermediate of formula (XIII) in the presence of a suitable base, such as for example K_2CO_3 or Ag_2CO_3, and a suitable solvent, such as for example CH_3CN or DMF, resulting in an intermediate of formula (IVa)

3 : an intermediate of formula (XII) can be reacted with an intermediate of formula (XV), wherein W1 represents a suitable halogen, such as for example iodide or bromide, and wherein W2 represents a suitable leaving group, such as for example chloride, fluoride or bromide, in the presence of a suitable base, such as for example Sodium hydride (NaH) and a suitable solvent, such as for example DMF, resulting in an intermediate of formula (VIIa).

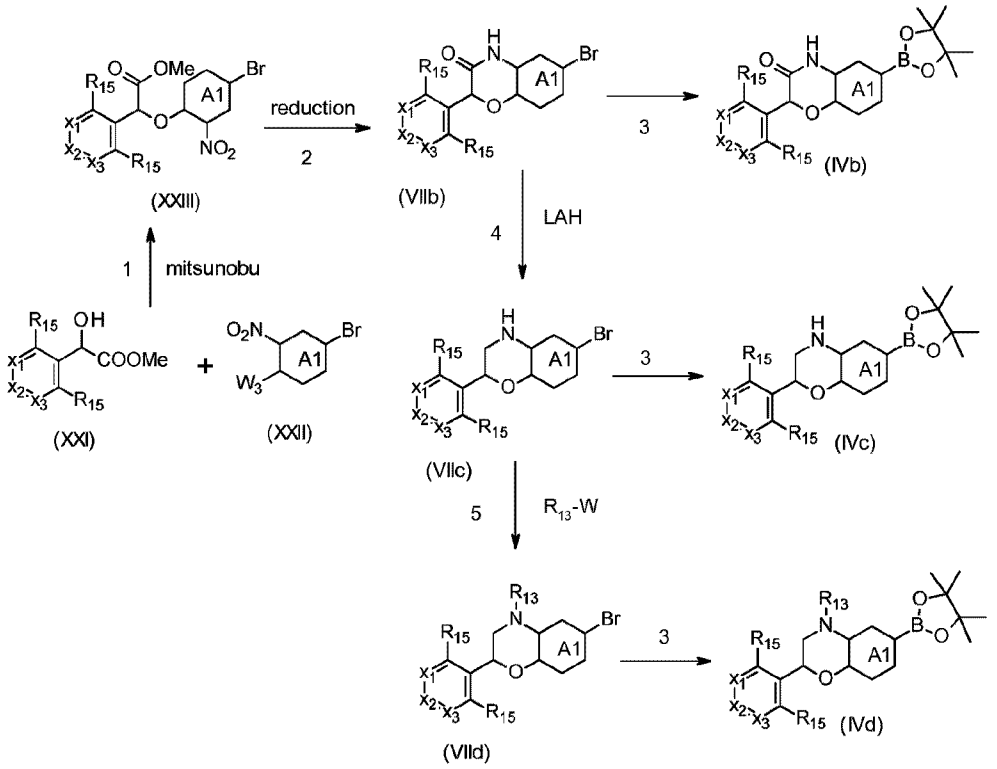
4 : an intermediate of formula (XIVa) can be reacted with an intermediate of formula (XVIII), wherein W1 represents a suitable halogen, such as for example iodide or bromide, in the presence of a suitable base, such as for example K_2CO_3 or Ag_2CO_3, and

a suitable solvent, such as for example CH_3CN or DMF, resulting in an intermediate of formula (VIIa).

5 : an intermediate of formula (VIIa) can be reacted with intermediates of formula (XIX) or (XX) in the presence of a suitable base, such as for example *n*BuLi or Potassium acetate (AcOK), and a suitable solvent, such as for example THF or dioxane resulting in an intermediate of formula (IVa).

5) Scheme 1d : intermediates of formula (IV) (bicycles)

Intermediates of formula (IV) wherein Y_x-Z forms a bicycle with ring A1 as shown in intermediates of formula (IVb), (IVc) and (IVd), can be prepared according to the following reaction scheme 1d-1. In scheme 1d-1, all variables are as defined before:



1 : an intermediate of formula (XXI) can be reacted with an intermediate of formula (XXII), wherein W_3 represents an hydroxyl, in the presence of PPh_3, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example THF resulting in an intermediate of formula (XXIII).

An intermediate of formula (XXI) can also be reacted with an intermediate of formula (XXII), wherein W_3 represents a bromide, in the presence of a suitable base, such as for example NaH and a suitable solvent, such as for example THF resulting in an intermediate of formula (XXIII).

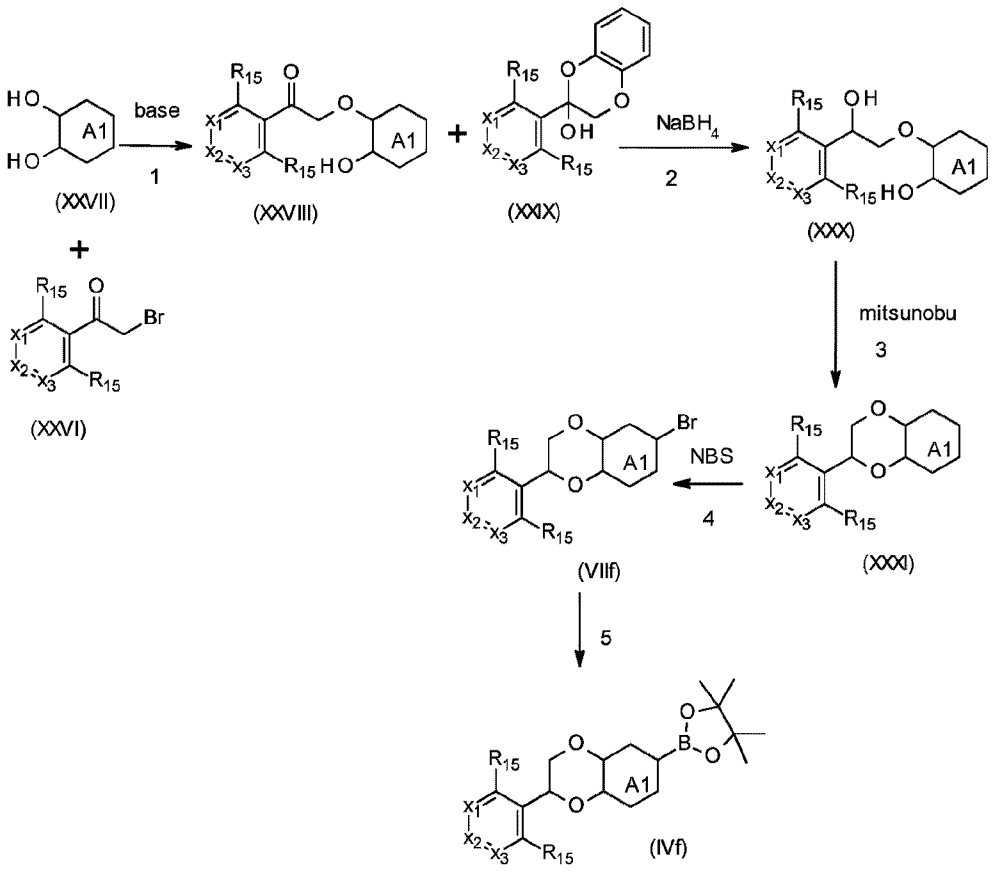
2 : An intermediate of formula (XXIII) can be converted into an intermediate of formula (VIIb) by reaction with Fe in the presence of a suitable solvent, such as for example acetic acid (AcOH).

3 : An intermediate of formula (VIIb), (VIIc) or (VIId) can be reacted with Bis(pinacolato)diboron in the presence of a suitable base, such as for example potassium acetate (AcOK), a suitable catalyst, such as for example $PdCl_2$(dppf) and a suitable solvent, such as for example 1,2-dimethoxyethane (DME) resulting in an intermediate of formula (IVb), (IVc) or (IVd) respectively.

4 : an intermediate of formula (VIIb) can be reduced in an intermediate of formula (VIIc) by reaction with LAH in the presence of a suitable solvent, such as for example THF.

5 : an intermediate of formula (VIIc) can be reacted with an intermediate of formula R_{13}-W, wherein W represents a suitable leaving group, such as for example iodide, in the presence of a suitable base, such as for example K_2CO_3 and a suitable solvent, such as for example DMF, resulting in an intermediate of formula (VIId).

Intermediates of formula (IV) wherein Y_x-Z forms a bicycle with ring A1 as shown in intermediate (IVf), can be prepared according to the following reaction scheme 1d-2. In scheme 1d-2, all variables are as defined before:



1 : an intermediate of formula (XXVI) can be reacted with an intermediate of formula (XXVII) in the presence of a suitable base, such as for example Et_3N, and a suitable solvent, such as for example 2-propanol (iPrOH), resulting in a mixture of intermediate of formula (XXVIII) and intermediate of formula (XXIX).

2 : a mixture of intermediate of formula (XXVIII) and an intermediate of formula (XXIX) can be converted into an intermediate of formula (XXX) by reaction with $NaBH_4$ in the presence of a suitable solvent or solvent mixture, such as for example THF and MeOH.

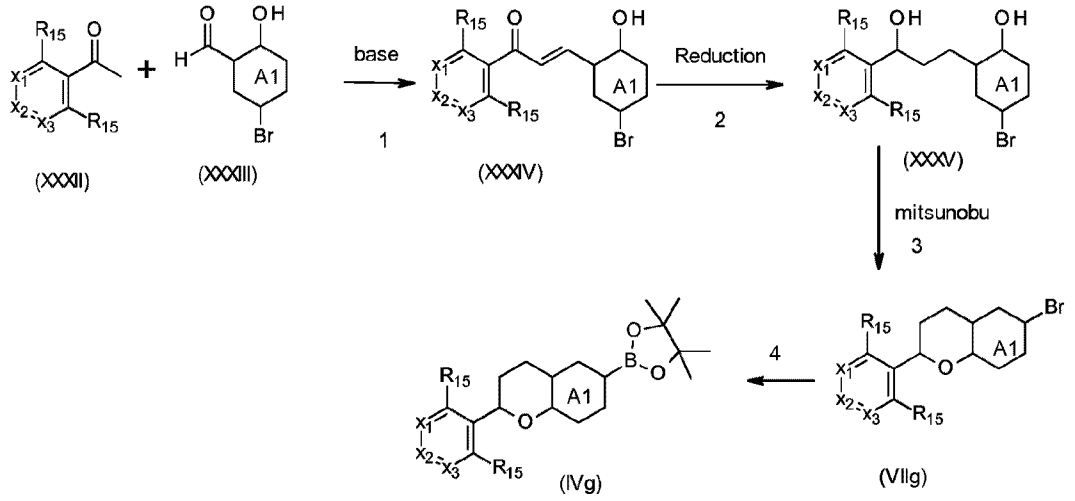
3 : an intermediate of formula (XXX) can be converted into an intermediate of formula (XXXI) by reaction with PPh_3, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example DCM.

4 : an intermediate of formula (XXXI) can be reacted with NBS in the presence of a suitable solvent, such as for example AcOH, resulting in an intermediate of formula (VIIf).

5 : An intermediate of formula (VIIf) can be reacted with Bis(pinacolato)diboron in the presence of a suitable base, such as for example AcOK, a suitable catalyst, such as for

example $PdCl_2(dppf)$ and a suitable solvent, such as for example DME resulting in an intermediate of formula (IVf).

Intermediates of formula (IV) wherein Y_x-Z forms a bicycle with ring A1, as shown in an intermediate of formula (IVg), can be prepared according to the following reaction scheme 1d-3. In scheme 1d-3, all variables are as defined before:



1 : an intermediate of formula (XXXII) can be reacted with an intermediate of formula (XXXIII) in the presence of a suitable base, such as for example KOH, and a suitable solvent, such as for example EtOH, resulting in an intermediate of formula (XXXIV).

2 : an intermediate of formula (XXXIV) can be converted into an intermediate of formula (XXXV) by reaction with $NaBH_4$ in the presence of Indium Chloride and a suitable solvent, such as for example acetonitrile.

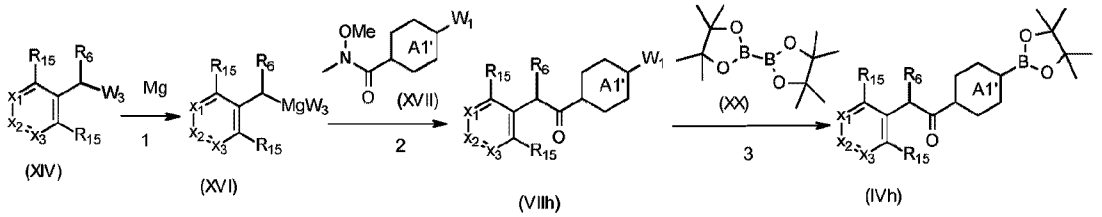
3 : an intermediate of formula (XXXV) can be converted into an intermediate of formula (VIIg) by reaction with PPh_3, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example DCM.

4 : An intermediate of formula (VIIg) can be reacted with Bis(pinacolato)diboron in the presence of a suitable base, such as for example AcOK, a suitable catalyst, such as for example $PdCl_2(dppf)$ and a suitable solvent, such as for example DME resulting in an intermediate of formula (IVg).

6) Scheme 1e : intermediates of formula (IVh) (Y is carbonyl)

By preparing derivatives of intermediates of formula (IV) wherein the general Y definition is carbonyl and wherein Z is CHR_6, hereby named an intermediate of formula (IVh), more compounds of formula (I) can be prepared by using analogous reaction protocols as described above or below and/or reaction protocols known by the skilled person.

Such an intermediate of formula (IVh) can be prepared according to the following reaction scheme 1e, wherein ring A1' is optionally substituted phenyl or an optionally substituted 6-membered aromatic heterocyclyl containing one or two nitrogen atoms, and wherein all other variables are as defined before:



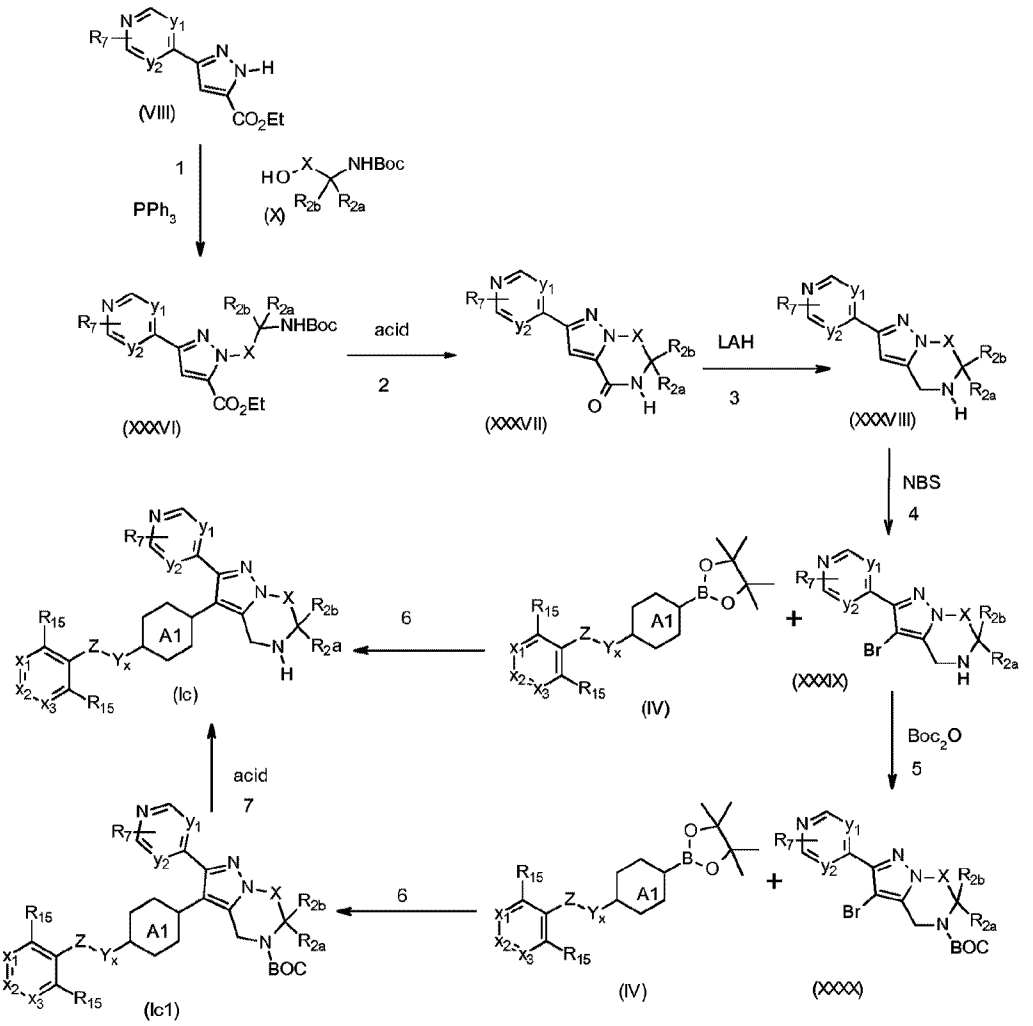
1 : an intermediate of formula (XIV) can be converted into an intermediate of formula (XVI) by reaction with magnesium and a suitable solvent, such as for example THF or diethyl ether (Et_2O). This type of reaction can also be performed in the presence of a suitable reagent, such as for example 1,2-dibromoethane.

2 : an intermediate of formula (XVI) can be reacted with an intermediate of formula (XVII) in the presence of a suitable solvent, such as for example methyltetrahydrofuran (Methyl-THF) or THF, resulting in an intermediate of formula (VIIh)

3 : an intermediate of formula (VIIh) can be reacted with an intermediate of formula (XX) in the presence of a suitable base, such as for example AcOK, and a suitable solvent, such as for example dioxane resulting in an intermediate of formula (IVh).

7) Scheme 2 : alternative for a compound of formula (Ic)

Compounds of formula (Ic) and (Ic1), wherein all variables are as defined before, can also be prepared according to the following reaction scheme 2.



1 : an intermediate of formula (VIII) can be reacted with an intermediate of formula (X), in the presence of PPh_3, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example THF resulting in an intermediate of formula (XXXVI).

2 : an intermediate of formula (XXXVI) or (II) can be converted into an intermediate of formula (XXXVII) in the presence of a suitable acid, such as for example TFA, and a suitable solvent, such as for example DCM.

3 : an intermediate of formula (XXXVII) can be converted into an intermediate of formula (XXXVIII) by reaction with lithium aluminium hydride in the presence of a suitable solvent, such as for example THF.

4 : an intermediate of formula (XXXVIII) can be reacted with NBS in the presence of a suitable solvent or solvent mixture, such as for example AcOH or AcOH and DCM, resulting in an intermediate of formula (XXXIX).

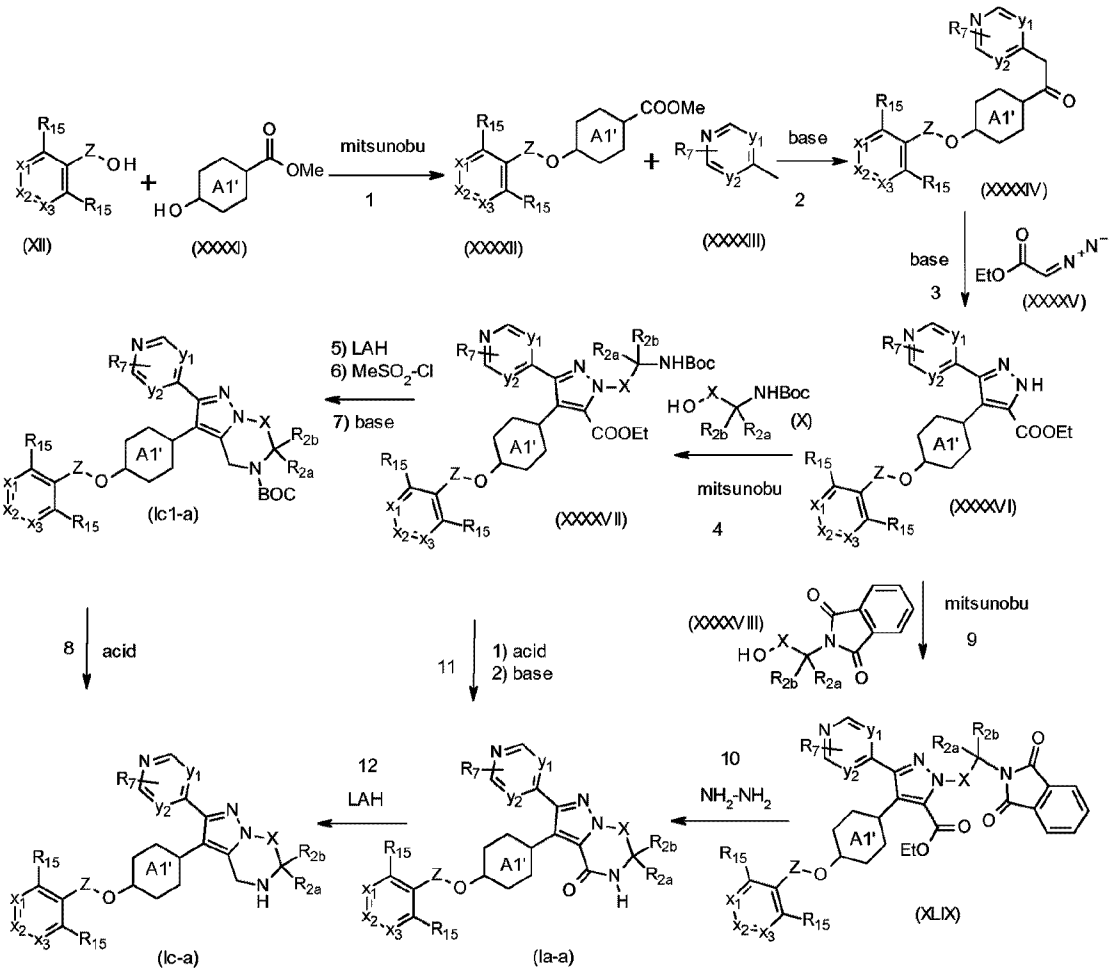
5 : an intermediate of formula (XXXIX) can be reacted with Boc_2O in the presence of a suitable base, such as for example Et_3N, and a suitable solvent, such as for example DCM, resulting in an intermediate of formula (XXXX).

6 : an intermediate of formula (IV) can be reacted with an intermediate of formula (XXXVIII) or (XXXIX) in the presence of suitable catalyst, such as for example [1,1'-bis(diphenylphosphino-kP)ferrocene]dichloropalladium ($PdCl_2$dppf), a suitable base, such as for example potassium phosphate (K_3PO_4) and a suitable solvent or solvent mixture, such as for example dioxane and water, resulting in a compound of formula (Ic).

7 : a compound of formula (Ic1) can be converted in a compound of formula (Ic) in a presence of a suitable acid, such as for example HCl, and a suitable solvent, such as for example MeOH.

8) Scheme 3a : third way final compound

Compounds of formula (Ia) and (Ic) wherein ring A1 is limited to A1' (no bicycles) hereby named compounds of formula (Ia-a) and (Ic-a), can also be prepared by the synthesis protocol described in Scheme 3a wherein ring A1' and all other variables are as defined before,



1 : an intermediate of formula (XII) can be reacted with an intermediate of formula (XXXXI), in the presence of PPh_3, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example THF resulting in an intermediate of formula (XXXXII).

2 : an intermediate of formula (XXXXII) can be reacted with an intermediate of formula (XXXXIII), in the presence of a suitable base, such as for example LiHMDS, and a suitable solvent, such as for example THF, resulting in an intermediate of formula (XXXXIV).

3 : an intermediate of formula (XXXXIV) can be reacted with an intermediate of formula (XXXXV), in the presence of a suitable base, such as for example DBU, and a suitable solvent, such as for example CH_3CN, resulting in an intermediate of formula (XXXXVI).

4 : an intermediate of formula (XXXXVI) can be reacted with an intermediate of formula (X), in the presence of PPh_3, a suitable Mitsunobu reagent, such as for example

DBAD and a suitable solvent, such as for example THF or DCE resulting in an intermediate of formula (XXXXVII).

5-6-7 : an intermediate of formula (XXXXVII) can be reacted with lithium aluminium hydride in the presence of a suitable solvent, such as for example THF. The resulting intermediate can be reacted with methanesulfonyl chloride in the presence of a suitable base, such as for example Et_3N, and a suitable solvent, such as for example DCM. The resulting intermediate can be reacted with a suitable base, such as for example NaH, and a suitable solvent, such as for example DMF, resulting in a compound of formula (Ic1-a).

8 : a compound of formula (Ic1-a) can be reacted into a compound of formula (Ic-a) in the presence of a suitable acid, such as for example HCl, an d a suitable solvent, such as for example CH_3CN.

9 : an intermediate of formula (XXXXVI) can be reacted with an intermediate of formula (XXXXVIII), in the presence of PPh_3, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example THF, resulting in an intermediate of formula (XLIX).

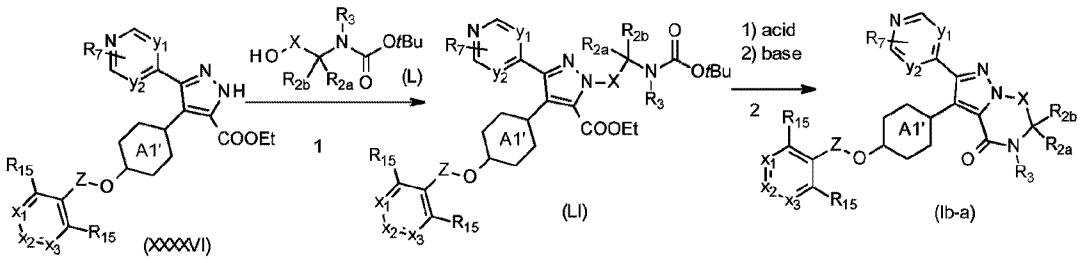
10 : an intermediate of formula (XLIX) can be deprotected to a compound of formula (Ia-a) with hydrazine hydrate and a suitable solvent, such as for example EtOH.

11 : an intermediate of formula (XXXXVII) can be deprotected with a suitable acid, such as for example HCl, and a suitable solvent, such as for example dioxane or ACN. The resulting intermediate can be converted into a compound of formula (Ia) in the presence of a suitable base, such as for example Cs_2CO_3 or K_2CO_3, and a suitable solvent, such as for example DCM or MeOH.

12 : a compound of formula (Ia-a) can be converted into a compound of formula (Ic-a) by reaction with lithiumaluminiumhydride in the presence of a suitable solvent, such as for example tetrahydrofuran or DME.

9) Scheme 3b : alternative method alkylated final compound

A compound of formula (Ib-a) wherein ring A1' is as defined before (no bicycles), and wherein all other variables are as defined before, can be prepared by the synthesis protocol described in Scheme 3b:

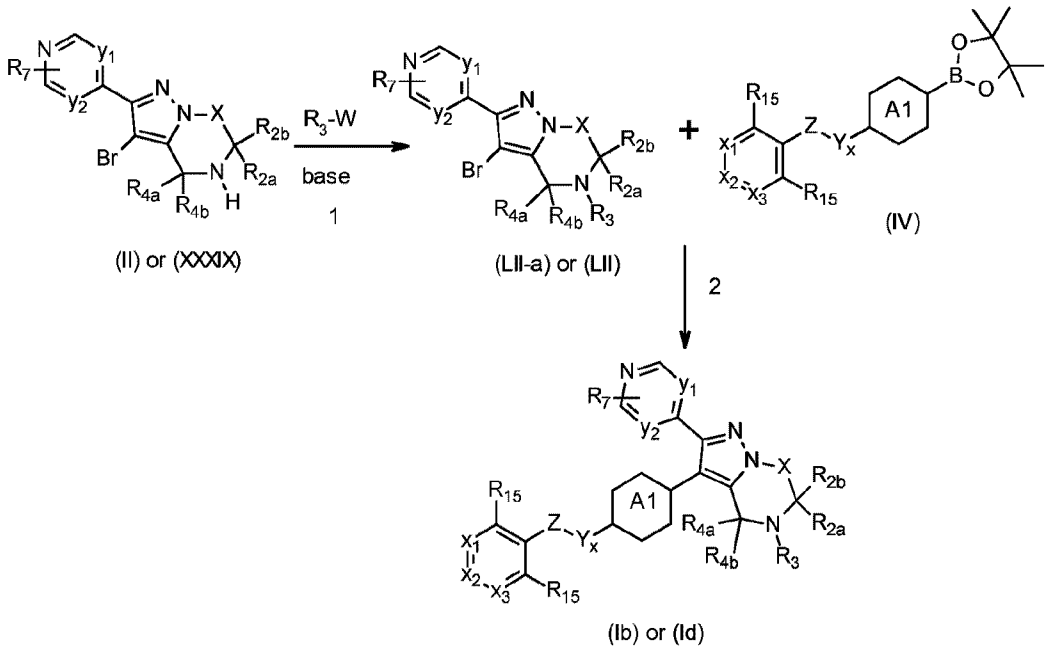


1 : an intermediate of formula (XXXXVI) can be reacted with an intermediate of formula (L) (*t*Bu is *tert*-butyl), in the presence of PPh_3, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example THF resulting in an intermediate of formula (LI).

2 : an intermediate of formula (LI) can be deprotected with a suitable acid, such as for example HCl, and a suitable solvent, such as for example dioxane or ACN. The resulting intermediate can be converted into a compound of formula (Ib-a) in the presence of a suitable base, such as for example Cs_2CO_3, and a suitable solvent, such as for example DCM or MeOH.

10) Scheme 4 :

Compounds of formula (Ib), wherein R_{4a} and R_{4b} are taken together to form =O, and (Id), wherein R_{4a} and R_{4b} are hydrogen, can also be prepared according to the following reaction scheme 4.

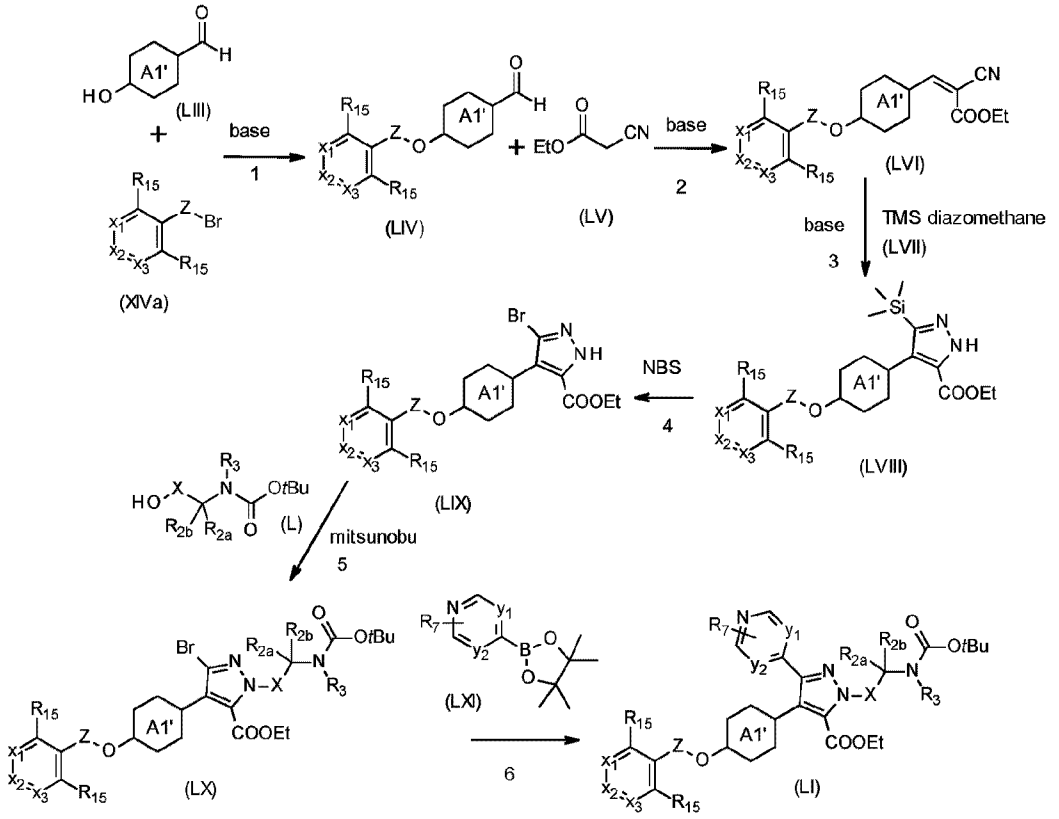


1 : an intermediate of formula (II), wherein R_{4a} and R_{4b} are taken together to form =O, or (XXXIX), wherein R_{4a} and R_{4b} are hydrogen, can be reacted with an intermediate of formula R_3-W, wherein W represents a suitable leaving group, such as for example iodide, bromide, chloride or tosylate, in the presence of suitable base, such as for example sodium hydride, Et_3N or K_2CO_3, and a suitable solvent, such as for example N,N-dimethylformamide or dimethylsulfoxide, resulting in an intermediate of formula (LII-a), wherein R_{4a} and R_{4b} are taken together to form =O or (LII), wherein R_{4a} and R_{4b} are hydrogen.

2 : an intermediate of formula (LII-a) or (LII) can be reacted with an intermediate of formula (IV) in the presence of suitable catalyst, such as for example [1,1'-bis(diphenylphosphino-kP)ferrocene]dichloropalladium ($PdCl_2dppf$), a suitable base, such as potassium phosphate (K_3PO_4), and a suitable solvent or solvent mixture, such as for example dioxane and water, resulting in a compound of formula (Ib), wherein R_{4a} and R_{4b} are taken together to form =O or (Id), wherein R_{4a} and R_{4b} are hydrogen.

11) Scheme 5 : alternative synthesis pyrazole-ester

Intermediates of formula (LI) wherein all variables are as defined before (Et means ethyl) can also be prepared according to the following reaction scheme 5:



1 : an intermediate of formula (XIVa) can be reacted with an intermediate of formula (LIII) in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example CH_3CN, resulting in an intermediate of formula (LIV).

2 : an intermediate of formula ((LIV) can be reacted with an intermediate of formula (LV) in the presence of a suitable base, such as for example piperidine, and a suitable solvent, such as for example EtOH, resulting in an intermediate of formula (LVI).

3 : an intermediate of formula (LVI) can be converted into an intermediate of formula (LVIII) by reaction with an intermediate of formula (LVII) (= trimethylsilyldiazomethane) in the presence of a suitable base, such as for example *n*BuLi and a suitable solvent, such as for example THF.

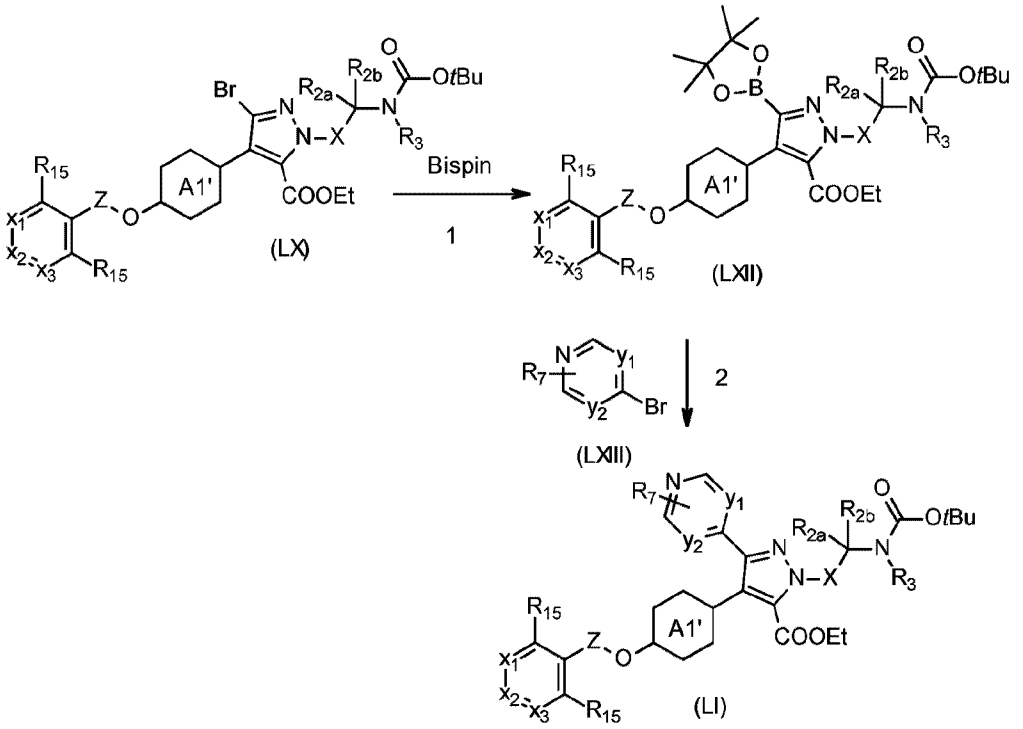
4 : an intermediate of formula (LVIII)) can be reacted with NBS in the presence of a suitable solvent, such as for example ACN, resulting in an intermediate of formula (LIX).

5 : an intermediate of formula (LIX) can be reacted with an intermediate of formula (L) in the presence of PPh_3, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example THF, resulting in an intermediate of formula (LX).

6 : an intermediate of formula (LX) can be reacted with an intermediate of formula (LXI) in the presence of suitable catalyst, such as for example Palladium acetate ($Pd(OAc)_2$), a suitable ligand, such as for example PCy_3 a suitable base, such as potassium phosphate (K_3PO_4), and a suitable solvent or solvent mixture, such as for example dioxane and water, resulting in an intermediate of formula (LI).

12) Scheme 5a : alternative II synthesis pyrazole-ester

Intermediates of formula (LI) can also be prepared according to the following reaction scheme 5a:

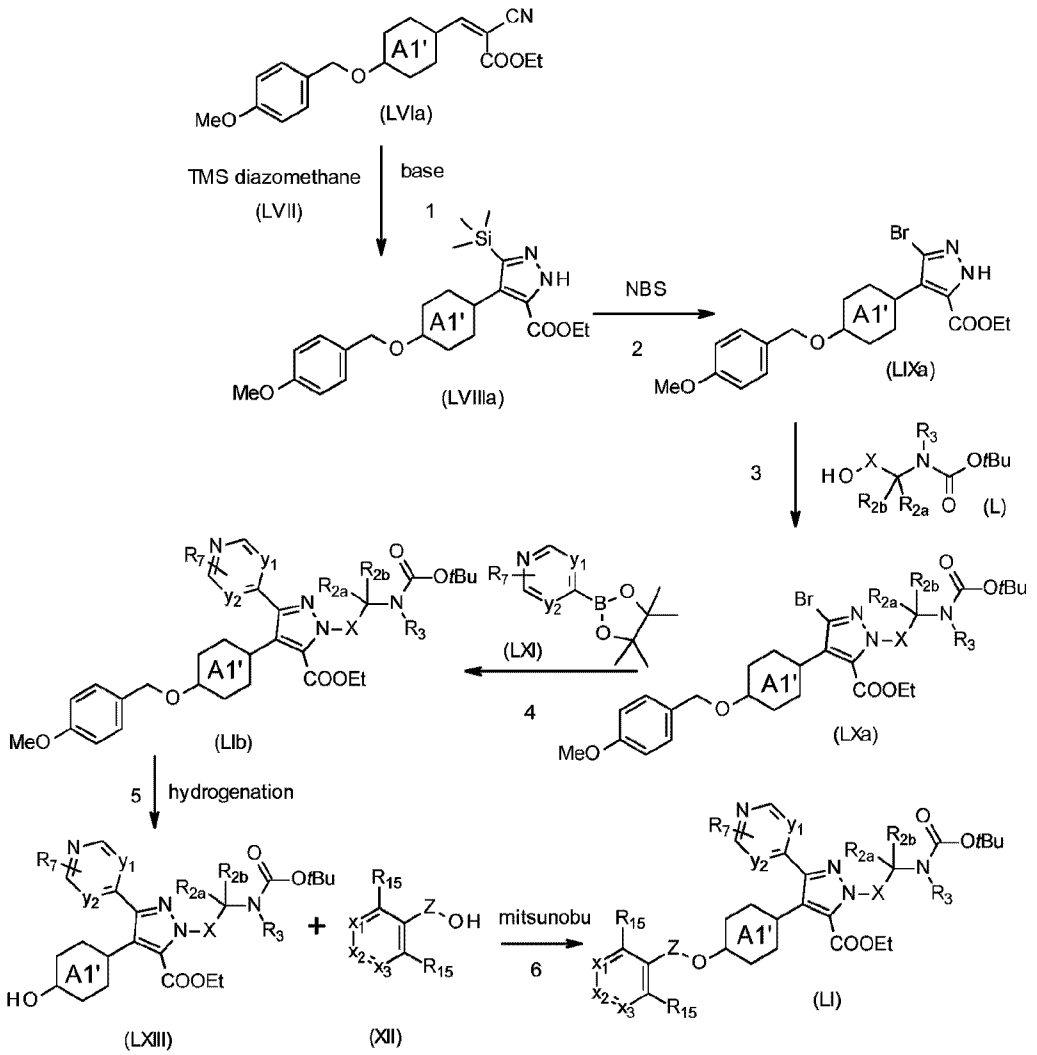


1 : an intermediate of formula (LX) can be reacted with bis(pinacolato)diboron (Bispin) in the presence of a suitable catalyst, such as for example $PdCl_2(dppf)$, a suitable base, such as for example AcOK and a suitable solvent, such as for example DME, resulting in an intermediate of formula (LXII).

2 : an intermediate of formula (LXII) can be reacted with an intermediate of formula (LXIII) in the presence of suitable catalyst, such as for example Palladium acetate ($Pd(OAc)_2$), a suitable ligand, such as for example tricyclohexylphosphine (PCy_3) a suitable base, such as potassium phosphate (K_3PO_4), and a suitable solvent or solvent mixture, such as for example dioxane and water, resulting in an intermediate of formula (LI).

13) Scheme 5b : alternative III synthesis pyrazoleester

Intermediates of formula (LI) can also be prepared according to the following reaction scheme 5b.



1 : an intermediate of formula (LVIa) can be converted into an intermediate of formula (LVIIIa) by reaction with an intermediate of formula (LVII) in the presence of a suitable base, such as for example *n*BuLi and a suitable solvent, such as for example THF

2 : an intermediate of formula (LVIIIa) can be reacted with NBS in the presence of a suitable solvent, such as for example ACN, resulting in an intermediate of formula (LIXa).

3 : an intermediate of formula (LIXa) can be reacted with an intermediate of formula (L) in the presence of PPh_3, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example THF, resulting in an intermediate of formula (LXa).

4 : an intermediate of formula (LXa) can be reacted with an intermediate of formula (LXI) in the presence of suitable catalyst, such as for example Palladium acetate

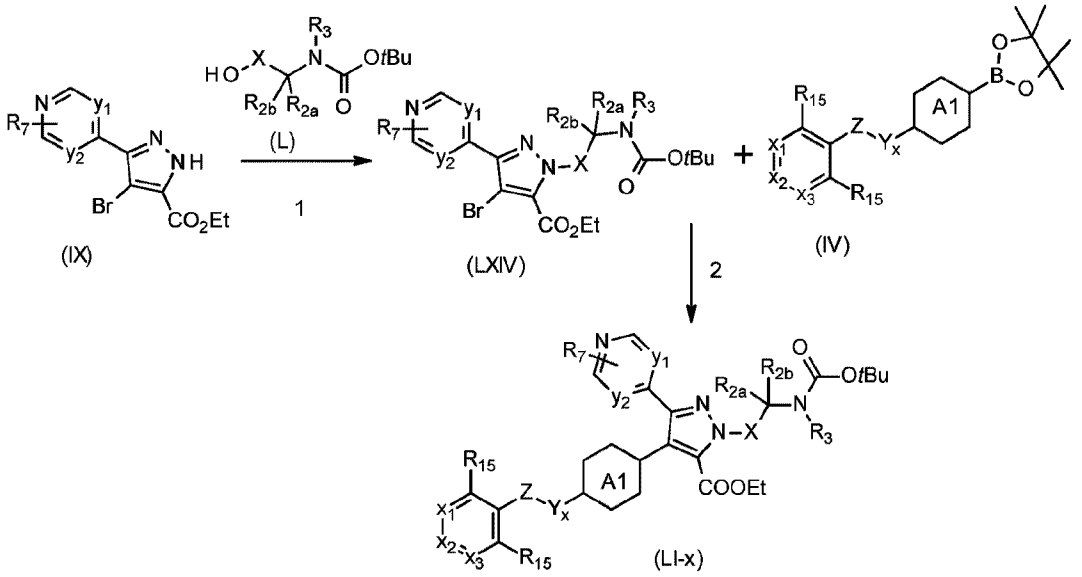
($Pd(OAc)_2$), a suitable ligand, such as for example PCy_3 a suitable base, such as potassium phosphate (K_3PO_4), and a suitable solvent or solvent mixture, such as for example dioxane and water, resulting in an intermediate of formula (LIb).

5 : an intermediate of formula (LIb) can be converted into a compound of formula (LXIII) by hydrogenation in the presence of a suitable catalyst, such as for example Pd/C 10%, and a suitable solvent, such as for example EtOH.

6 : an intermediate of formula (LXIII) can be reacted with an intermediate of formula (XII) in the presence of PPh_3, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example THF, resulting in an intermediate of formula (LI).

14) Scheme 5c : alternative IV synthesis pyrazole-ester

With the synthesis method in Scheme 5c, intermediates of formula (LI-x) can be prepared, which also includes the possibility that ring A1 forms a bicyclic ring with Z-Y_x. All variables in Scheme 5c are defined as mentioned before.



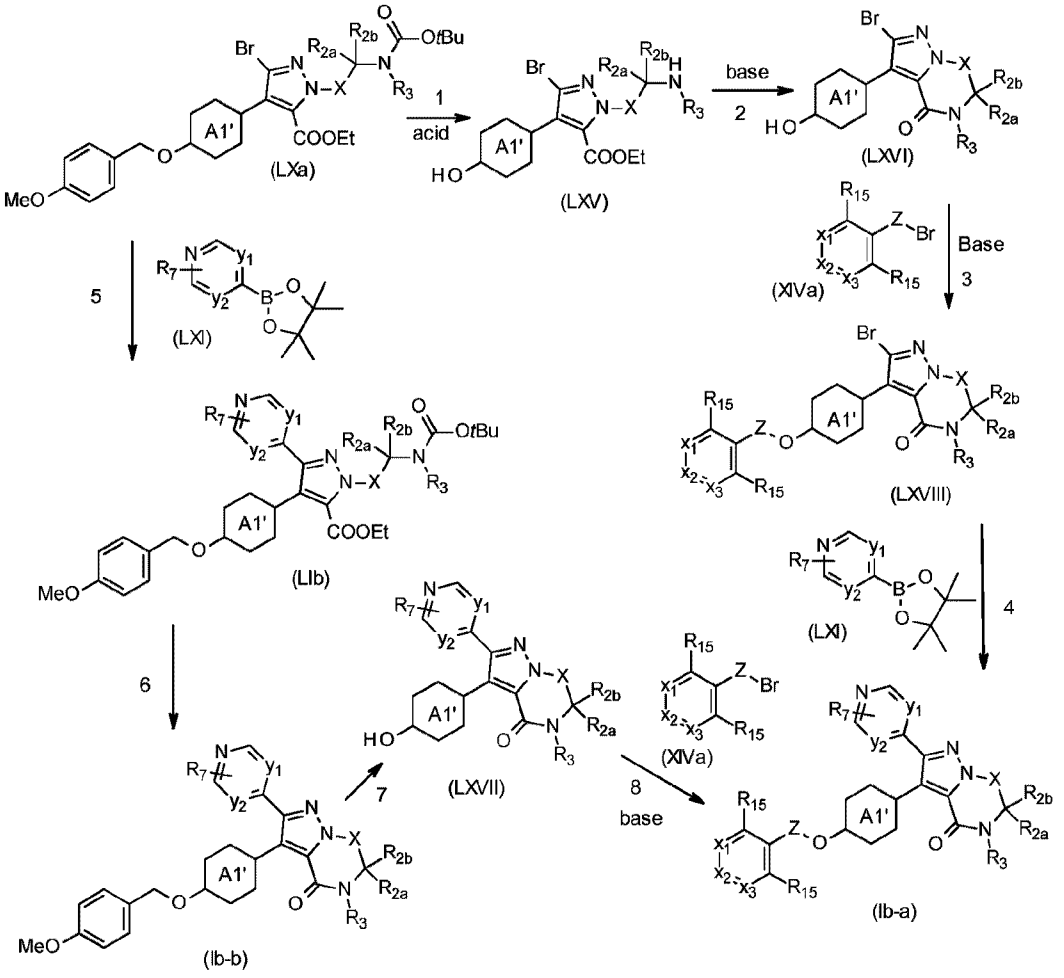
1 : an intermediate of formula (IX) can be reacted with an intermediate of formula (L), in the presence of PPh_3, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example THF resulting in an intermediate of formula (LXIV).

2 : an intermediate of formula (IV) can be reacted with an intermediate of formula (LXIV) in the presence of a suitable catalyst, such as for example $PdCl_2dppf$, a suitable base, such as for example potassium phosphate (K_3PO_4) and a suitable solvent or

solvent mixture, such as for example dioxane and water, resulting in an intermediate of formula (LI-x).

15) Scheme 6 : Fourth way final compound

Compounds of formula (Ib-a) and (Ib-b) wherein all variables are defined as before, can be prepared according to the following reaction scheme 6.



1 : an intermediate of formula (LXa) can be converted into an intermediate of formula (LXV) by reaction with a suitable acid, such as for example HCl, and a suitable solvent, such as for example dioxane.

2 : an intermediate of formula (LXV) can be converted into an intermediate of formula (LXVI) by reaction with a suitable base, such as for example Cs_2CO_3, and a suitable solvent, such as for example MeOH.

3 : an intermediate of formula (LXVI) can be reacted with an intermediate of formula (XIVa) in the presence of a suitable base, such as for example K_2CO_3, and a suitable

solvent, such as for example DMF, resulting in an intermediate of formula (LXVIII). This type of reaction can also be performed in the presence of a suitable reagent, such as for example NaI.

4 : an intermediate of formula (LXVIII) can be reacted with an intermediate of formula (LXI) in the presence of suitable catalyst, such as for example Palladium acetate ($Pd(OAc)_2$), a suitable ligand, such as for example PCy_3 a suitable base, such as potassium phosphate (K_3PO_4), and a suitable solvent or solvent mixture, such as for example dioxane and water, resulting in a compound of formula (Ib-a).

5 : an intermediate of formula (LXa) can be reacted with an intermediate of formula (LXI) in the presence of suitable catalyst, such as for example Palladium acetate ($Pd(OAc)_2$), a suitable ligand, such as for example PCy_3 a suitable base, such as potassium phosphate (K_3PO_4), and a suitable solvent or solvent mixture, such as for example dioxane and water, resulting in an intermediate of formula (LIb).

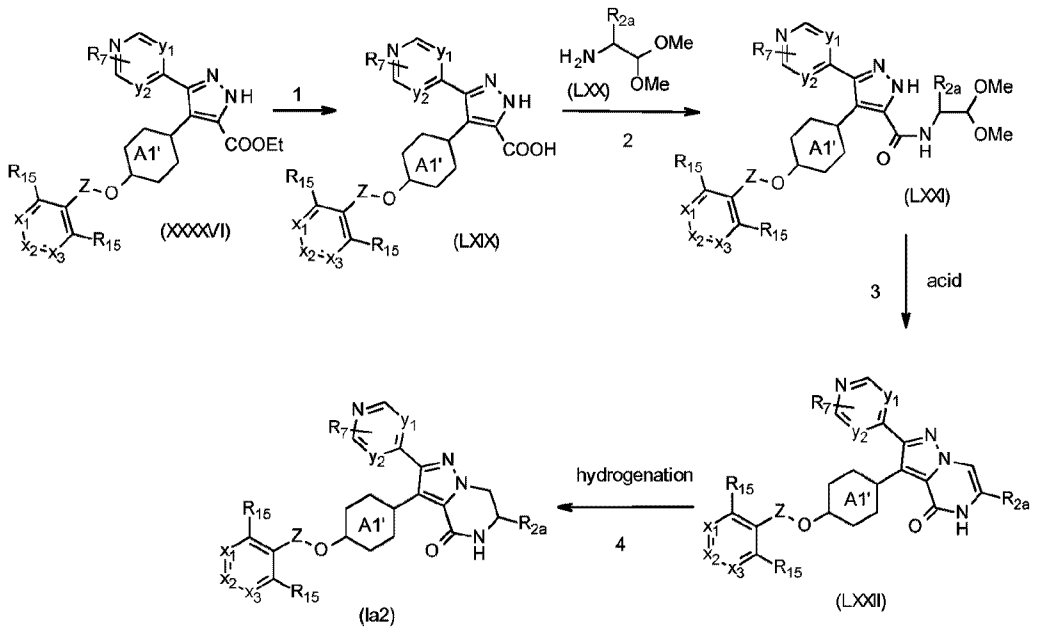
6 : an intermediate of formula (LIb) can be deprotected with a suitable acid, such as for example HCl, and a suitable solvent, such as for example dioxane or ACN. The resulting intermediate can be converted into a compound of formula (Ib-b) in the presence of a suitable base, such as for example Cs_2CO_3 or K_2CO_3, and a suitable solvent, such as for example DCM or MeOH.

7 : a compound of formula (Ib-b) can be converted into an intermediate of formula (LXVII) by reaction with a suitable acid, such as for example TFA, and a suitable solvent, such as for example toluene.

8 : an intermediate of formula (LXVII) can be reacted with an intermediate of formula (XIVa) in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example DMF, resulting in a compound of formula (Ib-a).

16) Scheme 7 : Fifth way final compound

A compound of formula (Ia) wherein ring A1 is limited to A1' (no bicycles), wherein R_{2b} is hydrogen and X is CH_2, hereby named a compound of formula (Ia2) can also be prepared according to the following reaction scheme 7.



1 : an intermediate of formula (XXXXVI) can be converted into an intermediate of formula (LXIX) by reaction with a suitable base, such as for example KOH, and a suitable solvent or solvent mixture, such as for example EtOH and water.

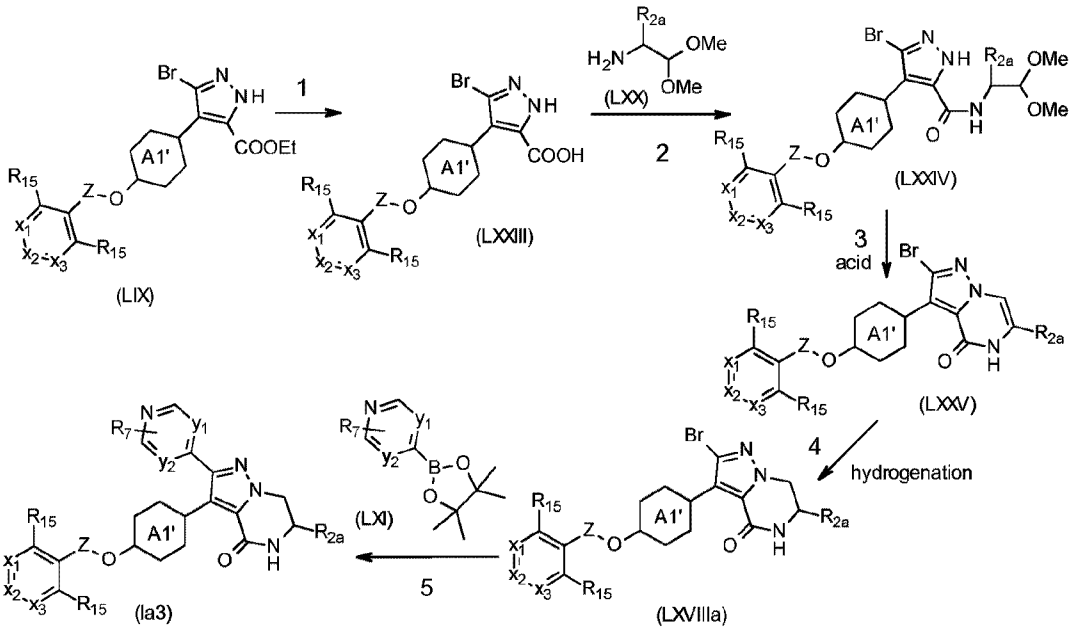
2 : an intermediate of formula (LXIX) can be reacted with an intermediate of formula (LXX) in the presence of a suitable peptide coupling agent, such as for example HATU, a suitable base, such as for example, DIPEA, and a suitable solvent, such as for example DMF, resulting in an intermediate of formula (LXXI).

3 : an intermediate of formula (LXXI) can be converted into an intermediate of formula (LXXII) by reaction with a suitable acid, such as for example methanesulfonic acid, HCl or TFA, and a suitable solvent, such as for example acetone or DCM.

4 : an intermediate of formula (LXXII) can be converted into a compound of formula (Ia2) by hydrogenation in the presence of a suitable catalyst, such as for example Pd/C 10% or PtO_2, and a suitable solvent, such as for example EtOH or MeOH.

17) Scheme 8 : Another alternative

Compounds of formula (Ia3), wherein all variables are defined as described before, can also be prepared according to the following reaction scheme 8.



1 : an intermediate of formula (LIX) can be converted into an intermediate of formula (LXXIII) by reaction with a suitable base, such as for example KOH, and a suitable solvent or solvent mixture, such as for example EtOH and water.

2 : an intermediate of formula (LXXIII) can be reacted with an intermediate of formula (LXX) in the presence of a suitable peptide coupling agent, such as for example HATU, a suitable base, such as for example, DIPEA, and a suitable solvent, such as for example DMF, resulting in an intermediate of formula (LXXIV).

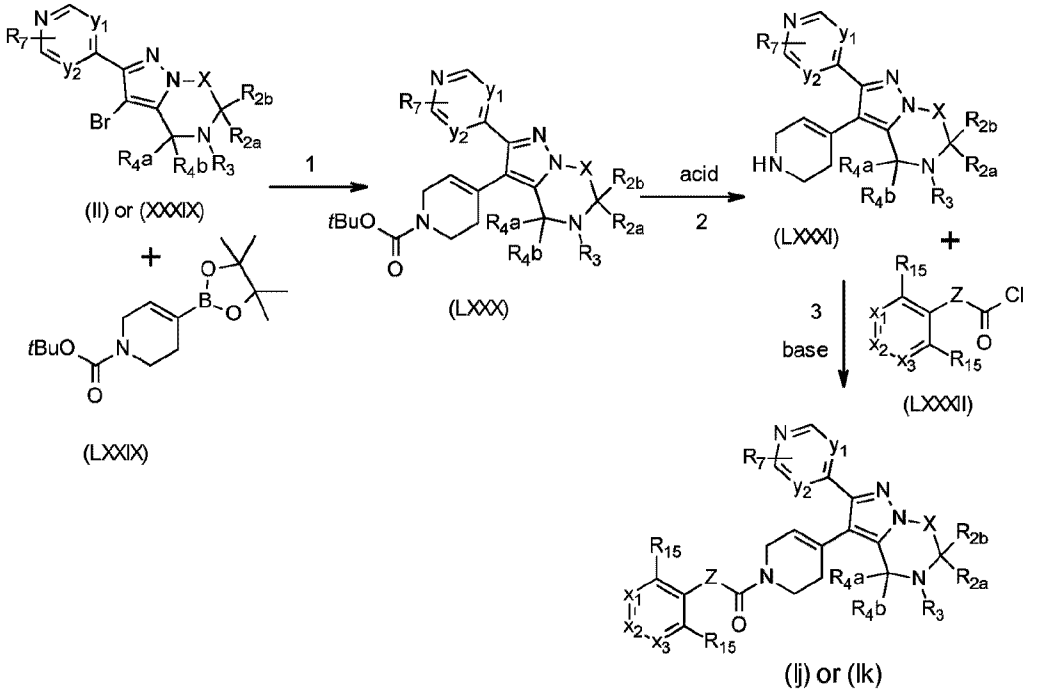
3 : an intermediate of formula (LXXIV) can be converted into an intermediate of formula (LXXV) by reaction with a suitable acid, such as for example methanesulfonic acid, HCl or TFA, and a suitable solvent, such as for example acetone or DCM.

4 : an intermediate of formula (LXXV) can be converted into a compound of formula (LXVIIIa) by hydrogenation in the presence of a suitable catalyst, such as for example Pd/C 10% or PtO_2, and a suitable solvent, such as for example EtOH or MeOH.

5 : an intermediate of formula (LXVIII) can be reacted with an intermediate of formula (LXI) in the presence of suitable catalyst, such as for example Palladium acetate ($Pd(OAc)_2$), a suitable ligand, such as for example PCy_3 a suitable base, such as potassium phosphate (K_3PO_4), and a suitable solvent or solvent mixture, such as for example dioxane and water, resulting in a compound of formula (Ia3).

18) Scheme 9 : Synthesis of final compounds when Ring A is partially saturated:

A compound of formula (I), wherein Y is C=O and Ring A is partially saturated, and wherein all other variables are as defined before, hereby named a compound of formula (I-j) or (I-k), can be prepared according to the following reaction scheme 9:



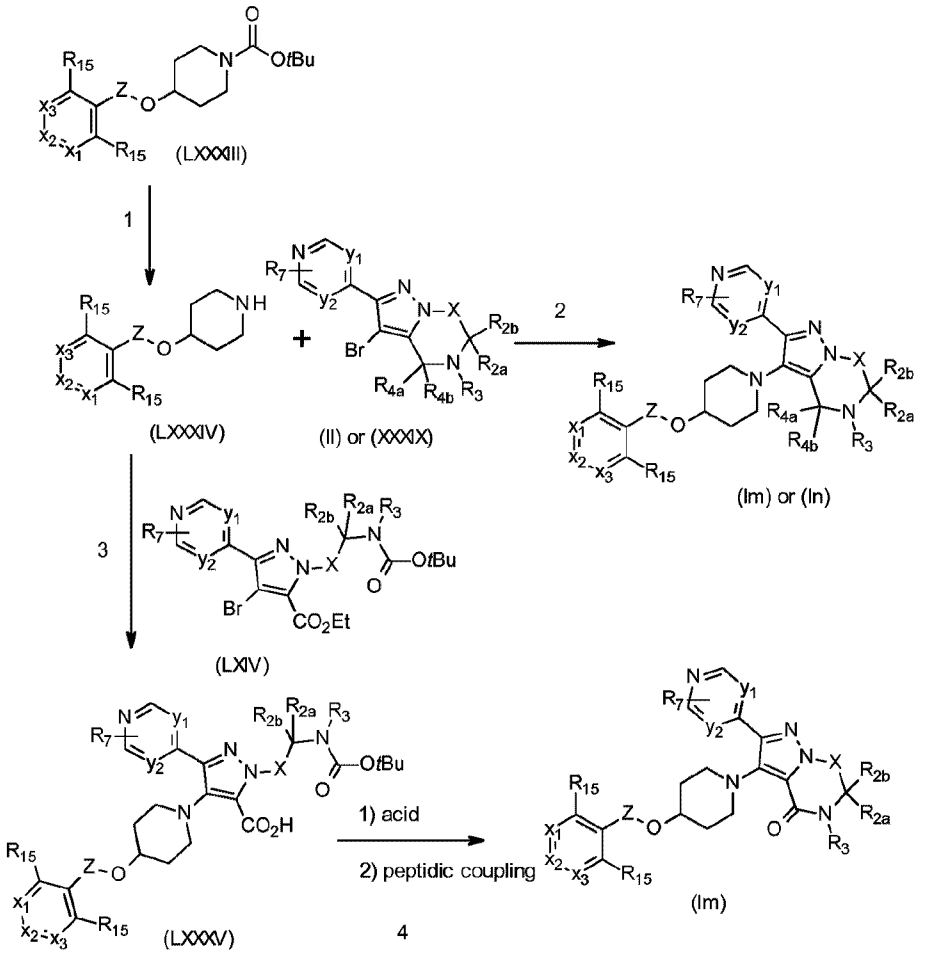
1 : an intermediate of formula (II) or (XXXIX) can be reacted with an intermediate of formula (LXXIX) in the presence of suitable catalyst, such as for example Palladium acetate ($PdCl_2dppf$), a suitable base, such as Na_2CO_3, and a suitable solvent, such as for example dioxane, resulting in an intermediate of formula (LXXX).

2 : an intermediate of formula (LXXX) can be deprotected to an intermediate of formula (LXXXI) by reaction with a suitable acid, such as for example HCl, and a suitable solvent, such as for example ACN.

3 : an intermediate of formula(LXXXI) can be reacted with an intermediate of formula (LXXXII) in the presence of a suitable base, such as for example Et_3N, and a suitable solvent, such as for example DCM, resulting in a compound of formula (Ij), wherein R_{4a} and R_{4b} are taken together to form =O, or a compound of formula (Ik), wherein R_{4a} and R_{4b} are hydrogen.

19) Scheme 10 : Synthesis of final compounds when Ring A is saturated :

A compound of formula (I), wherein Y is O and Ring A is saturated, and wherein all other variables are as defined before, hereby named a compound of formula (Im) or (In) can be prepared according to the following reaction scheme 10:



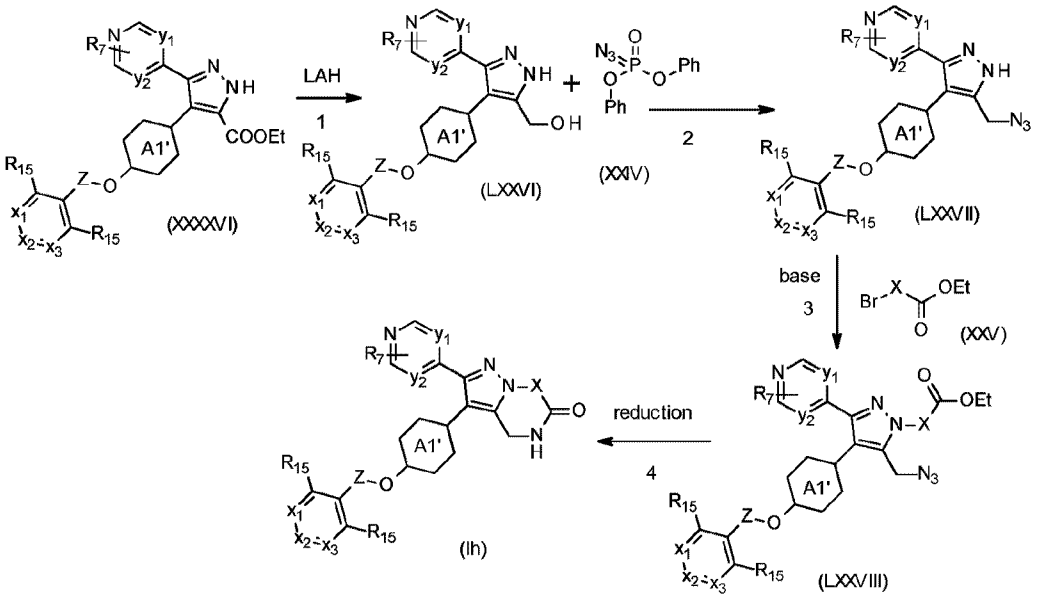
1 : an intermediate of formula (LXXXIII) can be deprotected to an intermediate of formula (LXXXIV) by reaction with a suitable acid, such as for example HCl, in the presence of a suitable solvent, such as for example ACN.

2 : an intermediate of formula (II) or (XXXIX) can be reacted with an intermediate of formula (LXXXIV) in the presence of suitable catalyst, such as for example (*SP*-4-4)-[2-[2-(amino-κ*N*)ethyl]phenyl-κ*C*]chloro[dicyclohexyl[3,6-dimethoxy-2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine-κ*P*]-palladium (BrettPhos Palladacycle), a suitable base, such as NaOtBu, and a suitable solvent, such as for example toluene, resulting in a compound of formula (Im), wherein R_{4a} and R_{4b} are taken together to form =O, and a compound of formula (In), wherein R_{4a} and R_{4b} are hydrogen.

3 : an intermediate of formula (LXXXIV) can be reacted with an intermediate of formula (LXIV) in the presence of a suitable base, such as for example Cs_2CO_3, suitable catalysts, such as for example CuI and 2-acetylcyclohexanone, and a suitable solvent, such as for example DMF, resulting in an intermediate of formula (LXXXV).

4 : an intermediate of formula (LXXXV) can be deprotected by reaction with a suitable acid, such as for example HCl, in the presence of a suitable solvent, such as for example ACN. The resulting intermediate can be converted into a compound of formula (Im), wherein R_{4a} and R_{4b} are taken together to form =O, by reaction with suitable peptide coupling reagents, such as for example 1-hydroxy-benzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl, a suitable base, such as for example, Et_3N, and a suitable solvent, such as for example DCM.

Scheme 11 : A compound of formula (Ih), wherein all variables are as defined before, can be prepared according to the following reaction scheme 11:



1 : an intermediate of formula (XXXXVI) can be converted into an intermediate of formula (LXXVI) by reaction with LAH in the presence of a suitable solvent, such as for example THF.

2 : an intermediate of formula (LXXVI) can be reacted with an intermediate of formula (XXIV) in the presence of a suitable base, such as for example DBU, and a suitable solvent, such as for example THF, resulting in an intermediate of formula (LXXVII).

3 : an intermediate of formula (LXXVII) can be reacted with an intermediate of formula (XXV) in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example DMF, resulting in an intermediate of formula (LXXVIII).

4 : an intermediate of formula (LXXVIII) can be converted into a compound of formula (Ih) by hydrogenation in the presence of a suitable catalyst, such as for example Nickel of Raney, and a suitable solvent, such as for example EtOH.

In all these preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration and chromatography. In particular, stereoisomers can be isolated chromatographically by Supercritical fluid chromatography using polysaccharide-based chiral stationary.

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 ROS1 kinase activity. In particular, the compounds of the present invention are potent and selective Ros1 inhibitors.

As a consequence of their activity in inhibiting ROS kinases, the compounds and compositions thereof will be useful in providing a means of preventing the growth or inducing apoptosis of neoplasias. It is therefore anticipated that the compounds or compositions thereof will prove useful in treating or preventing, in particular treating, proliferative disorders such as cancers. In addition, the compounds of the invention could be useful in the treatment of diseases in which there is a disorder of proliferation, apoptosis or differentiation.

Examples of cancers which may be treated (or inhibited) include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, urothelial, uterus, epidermis, liver, lung (for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, squamous lung cancer), oesophagus, head and neck, gall bladder, ovary, pancreas (e.g. exocrine pancreatic carcinoma), stomach, gastrointestinal (also known as gastric) cancer (e.g. gastrointestinal stromal tumours), cervix, endometrium, thyroid, prostate, or skin (for example squamous cell carcinoma or dermatofibrosarcoma protuberans); pituitary cancer, a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, B-cell lymphoma (e.g. diffuse large B-cell lymphoma), T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumour of myeloid lineage, for example leukemias, acute and chronic myelogenous leukemias, chronic myelomonocytic

leukemia (CMML), myeloproliferative disorder, myeloproliferative syndrome, myelodysplastic syndrome, or promyelocytic leukemia; multiple myeloma; thyroid follicular cancer; hepatocellular cancer, a tumour of mesenchymal origin (e.g. Ewing's sarcoma), for example fibrosarcoma or rhabdomyosarcoma; a tumour of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma (such as glioblastoma multiforme) or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

In particular examples of cancers which may be treated (or inhibited) include non-small cell lung cancer (specifically adenocarcinoma), cholangiocarcinoma, glioblastoma, colorectal cancer, gastric adenocarcinoma, ovarian cancer, angiosarcoma, epithelioid hemangioendothelioma, inflammatory myofibroblastic tumors, breast cancer and chronic myelogenous leukemia.

In an embodiment, the compounds of the invention and compositions thereof may be useful for use in the treatment or prevention, in particular in the treatment, of non–small-cell lung cancer, cholangiocarcinoma, and glioblastoma multiforme.

In an embodiment, all or some of the compounds of the invention and compositions thereof may be useful for use in reducing tumors or prolonging survival in patients with a G2032R mutation in the Ros1 kinase domain.

In an embodiment, all or some the compounds of the invention and compositions thereof may be useful for use in reducing tumors or prolonging survival in patients with a L2026M mutation in the Ros1 kinase domain.

The compounds of the invention can also be used in the treatment of hematopoetic diseases of abnormal cell proliferation whether pre-malignant or stable such as myeloproliferative diseases. Myeloproliferative diseases ("MPD"s) are a group of diseases of the bone marrow in which excess cells are produced. They are related to, and may evolve into, myelodysplastic syndrome. Myeloproliferative diseases include polycythemia vera, essential thrombocythemia and primary myelofibrosis. A further haematological disorder is hypereosinophilic syndrome. T-cell lymphoproliferative diseases include those derived from natural Killer cells.

Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

The compounds of the invention and compositions thereof may be useful in treating other conditions which result from disorders in proliferation such as type II or non-insulin dependent diabetes mellitus, autoimmune diseases, head trauma, stroke, epilepsy, neurodegenerative diseases such as Alzheimer's, motor neurone disease, progressive supranuclear palsy, corticobasal degeneration and Pick's disease for example autoimmune diseases and neurodegenerative diseases.

ROS is also known to play a role in apoptosis, proliferation, differentiation and transcription and therefore the compounds of the invention could also be useful in the treatment of the following diseases other than cancer; chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, autoimmune diabetes mellitus, Eczema hypersensitivity reactions, asthma, COPD, rhinitis, and upper respiratory tract disease; cardiovascular diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotropic lateral sclerosis, retinitis pigmentosa, spinal muscular atropy and cerebellar degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, haematological diseases, for example, chronic anemia and aplastic anemia; degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

The compounds of the present invention and compositions thereof may also have utility in male contraception.

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 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 analogoues 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 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, 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 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.

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; 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; 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.

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 ROS, in particular ROS1, kinase activity.

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.

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 ROS, in particular ROS1, mediated diseases or conditions.

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 ROS, in particular ROS1.

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.

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.

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 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-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 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 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 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 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 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 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 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 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 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 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, 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

pharmaceutical compositions, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives, in particular hydroxyalkyl substituted cyclodextrins, e.g. 2-hydroxypropyl-β-cyclodextrin or sulfobutyl-β-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.

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 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.

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:

- platinum coordination compounds for example cisplatin optionally combined with amifostine, carboplatin or oxaliplatin;
- taxane compounds for example paclitaxel, paclitaxel protein bound particles (Abraxane™) or docetaxel;
- topoisomerase I inhibitors such as camptothecin compounds for example 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;
- 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;
- glucocorticoïds 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, letrazole, 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;
- androgen receptor antagonist drugs, e.g. enzalutamide or ARN-509;
- 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).

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

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 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 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.
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 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 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.

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

The taxane compound is advantageously administered in a dosage of 50 to 400 mg per square meter (mg/m^2) of body surface area, for example 75 to 250 mg/m^2, particularly

for paclitaxel in a dosage of about 175 to 250 mg/m^2 and for docetaxel in about 75 to 150 mg/m^2 per course of treatment.

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

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

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

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

The alkylating agents such as nitrogen mustard or nitrosourea is advantageously administered in a dosage of 100 to 500 mg per square meter (mg/m^2) of body surface area, for example 120 to 200 mg/m^2, particularly for cyclophosphamide in a dosage of about 100 to 500 mg/m^2 , 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^2 , and for lomustine in a dosage of about 100 to 150 mg/m^2 per course of treatment.

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

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.

Antibodies are advantageously administered in a dosage of about 1 to 5 mg per square meter (mg/m^2) 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^2) of body surface area, particularly 2 to $4mg/m^2$ 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.

The following examples illustrate the present invention. In case no specific stereochemistry is indicated for a stereocenter of a compound, this means that the compound was obtained as a mixture of the R and the S enantiomers.
For a number of compounds, melting points (m.p.) were determined with a DSC 1 STAR^e System from Mettler Toledo. Melting points were measured with a temperature gradient of 10°C/minute up to 350 °C. Melting points are given by peak values.

Examples

Hereinafter, the term "NaH" means sodium hydride (60% in mineral oil); "DCM" means dichloromethane; "TBAF" means tetrabutylammonium fluoride; "$Pd(tBu_3P)_2$" means bis[tris(1,1-dimethylethyl)phosphine]-palladium; "quant." means quantitative; "Ac" means acetyl; "MeI" means iodomethane; "sat." means saturated; "DBU" means 1,8-diazabicyclo[5.4.0]undecene-7; "LAH" means lithium aluminium hydride; "NBS" means *N*-bromosuccinimide; "sol." means solution; "prep." means preparative; "MeMgCl" means Methylmagnesium chloride; "nBuLi" means n-butyllithium; "aq." means aqueous; "Int." Means Intermediate; "Co." means compound; "r.t." means room temperature; "r.m." means reaction mixture; "KOAc" means potassium acetate; "$AcONH_4$" means ammonium acetate; "BisPin" means bis(pinacolato)diboron; "DCE"

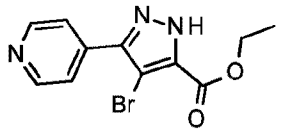
means 1,2-dichloroethane; "DIPE" means diisopropyl ether; "Boc" or "BOC" means *tert*-butoxycarbonyl; "CDI" means 1,1'-carbonyldiimidazole; "N-Boc sarcosine" means *N*-[(1,1-dimethylethoxy)carbonyl]-*N*-methyl-Glycine; "Boc-glycinol" means N-(*tert*-Butoxycarbonyl)ethanolamine; "$(BOC)_2O$" means di-*tert*-butyl dicarbonate; "ACN" means acetonitrile; "EDCI" means *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine monohydrochloride; ; "HOBT" means 1-hydroxy-1H-benzotriazole; "TBDPS" means *tert*-butyldiphenylsilyl; "OTBDPS" means *tert*-butyldiphenylsilyloxy; "TBDMS" means *tert*-butyldimethylsilyl; "TBDMSO" or "OTBDMS" means *tert*-butyldimethylsilyloxy; "S-Phos" means 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl; "LiHMDS" means lithium hexamethyldisilazane; "DMAP" means 4-(dimethylamino)pyridine; "MeOH" means methanol; "PCy_3" means tricyclohexylphosphine; "LC" means liquid chromatography; "LCMS" means Liquid Chromatography/Mass spectrometry; "HATU" means 1-[bis(dimethylamino)methylene]-1H-[1,2,3]triazolo[4,5-b]pyridin-1-ium 3-oxide hexafluorophosphate; "HPLC" means high-performance liquid chromatography; "TFA" means trifluoroacetic acid; "m.p." means melting point; "N_2" means nitrogen; "DBAD" means di-tert-butyl azodicarboxylate; "RP" means reversed phase; "min" means minute(s); "EtOAc" means ethyl acetate; "Et_3N" means triethylamine; "EtOH" means ethanol; "THF" means tetrahydrofuran; "Celite®" means diatomaceous earth; "DMF" means *N,N*-dimethyl formamide; "DMSO" means dimethyl sulfoxide; 'iPrOH" means 2-propanol; "$iPrNH_2$" means isopropylamine; "SFC" means Supercritical Fluid Chromatography; "DIPEA" means N,N-diisopropylethylamine; "$Pd(PPh_3)_4$" means tetrakis(triphenylphosphine)palladium; "w/v" means weight/volume; "PPh_3" means triphenylphosphine ; "PPh_3 supp." means triphenylphosphine supported (polymer bound); "Et_2O" means diethyl ether; "Pd/C" means palladium on carbon; "Pt/C" means platina on carbon; "$Pd(OAc)_2$" means palladium(II) acetate ; "Et" means ethyl; "Me" means methyl; "h" means hours; "precatalyst" means (*SP*-4-4)-[2'-(amino-κ*N*)[1,1'-biphenyl]-2-yl-κ*C*]chloro[dicyclohexyl[2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine]-palladium (CAS registry number [1310584-14-5]); and "$PdCl_2(dppf)$" means [1,1'-bis(diphenylphosphino-κP)ferrocene]dichloropalladium.

Hereinafter, "Int. 1 or **1**" is '3-(4-pyridinyl)-1*H*-pyrazole-5-carboxylic acid, ethyl ester'; "Int. 6 or **6**" is '4-(1-methylethyl)-benzenemethanol'; "Int. 7 or **7**" is '4-hydroxybenzeneboronic acid pinacol ester'; "Int. 8 or **8**" is '(1-(bromomethyl)-4-(1-methylethyl)-benzene)'; "Int. 9 or **9**" is '4-[[4-(1-methylethyl)phenyl]methoxy]-benzoic acid, methyl ester'; "Int. 13 or **13**" is '4-[[4-(1-methylethyl)phenyl]methoxy]-benzaldehyde'; "Int. 19 or **19**" is '2-cyano-3-[4-[(4-methoxyphenyl)-methoxy]phenyl]-

2-propenoic acid, ethyl ester'; "Int. 29 or **29**" is '6-cyclopropyl-3-pyridinemethanol'; "Int. 31 or **31**" is '4-cyclopropyl-benzenemethanol'; "Int. 33 or **33**" is '4-hydroxy-benzoic acid, methyl ester'; "Int. 39 or **39**" is '4-hydroxy-2-fluorophenylboronic acid pinacol ester'.

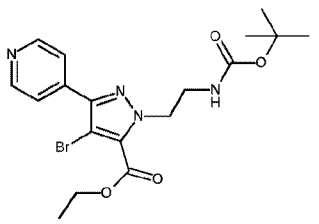
Preparation of the Intermediates and the final Compounds

Example A1 : Preparation of Co. 1 (1st approach)



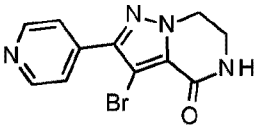
a- Synthesis of Int. 2 :

A sol. of **1** (3-(4-pyridinyl)-1*H*-pyrazole-5-carboxylic acid, ethyl ester) (34.7g; 160mmol) in DCM (464mL) was treated with NBS (31.3g; 176mmol) and stirred at r.t. for 20 h. The crude mixture was concentrated *in vacuo* and then taken up in Et_2O (200mL) and filtered on a glass frit. The solid was washed with Et_2O (100mL) and twice with MeOH and Et_2O (10mL/40mL). The solid was collected and dried *in vacuo* to give 43.57g of the Int. **2** (92%).



b- Synthesis of Int. 3 :

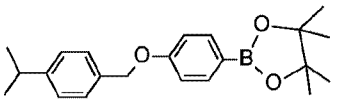
To a mixture of **2** (Int. 2) (25 g, 84.4 mmol), tert-butyl N-(2-hydroxyethyl)carbamate (20.4 g, 126 mmol) and PPh_3 supp. (39.6 g, 127 mmol) in dry THF (700 mL) was added DBAD (29.2 g, 126.6 mmol). The mixture was stirred for 4 h at r.t. then filtered through a glass frit. The filtrate was evaporated *in vacuo* to give 79.8 g of a residue which was purified by chromatography over silica gel (Irregular SiOH 35-40µm; 330g; mobile phase from 100% DCM to 97% DCM, 3% MeOH, 0.1% NH_4OH). The pure fractions were collected and evaporated to give 33.2 g of Int. **3** (90%).



c- Synthesis of Int. 4 :

TFA (49.5 mL, 646 mmol) was added to a sol. of **3** (35.5 g, 80.8 mmol) in DCM (320 mL) and the r.m. was stirred at r.t. for 17 h. The r.m. was quenched with a sat. sol. of $NaHCO_3$ (2000 mL) and stirred for 10 min. The precipitate was filtered on a glass frit and washed with Et_2O and dried *in vacuo* to give 23 g of a residue as a white solid. The residue was put in suspension in MeOH (150 mL) and treated with Cs_2CO_3 (5.27 g,

16.2 mmol). The r.m. was stirred at r.t. for 17 h. The crude mixture was filtered through a glass frit. The white precipitate was washed with water (2x 50mL), with MeOH (2x 10mL) and with Et_2O (4x 50mL). The white precipitate was collected and dried *in vacuo* to afford 17.8 g of Int. **4** as a white solid (75%).

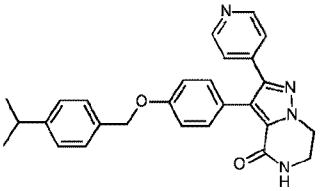


d- Synthesis of Int. 5 :

To a suspension of 7 (4-hydroxybenzeneboronic acid pinacol ester) (5.00 g, 22.7 mmol), **6** (4-(1-methylethyl)-benzenemethanol) (5.12 g, 34.1 mmol), PPh_3 supp. (8.94 g, 34.1 mmol) in dry DCM (150 mL) was added DBAD (7.85 g, 34.1 mmol) and the r.m. was stirred at r.t. for 18 h. The r.m. was then filtered through a glass frit and washed with EtOAc. The filtrate was evaporated *in vacuo* to give a residue (27g) as a yellow oil. The residue was purified by chromatography over silica gel (irregular SiOH 15-40µm, 150g, mobile phase: 90% Heptane, 10% EtOAc). The pure fractions were collected and the solvent evaporated to give 8.00 g of **5** as a white gum (Quant.).

Alternative method for the synthesis of Int. 5:

A sol. of 7 (7.00 g, 31.8 mmol) in ACN (75 mL) was treated with K_2CO_3 (5.28 g, 38.2 mmol) and **8** (1-(bromomethyl)-4-(1-methylethyl)-benzene) (6.03 mL, 35.0 mmol) at r.t. The r.m. was stirred at r.t. overnight. Then, the r.m. was filtered on a pad of Celite® and washed with DCM. The solvents were evaporated to a volume of 100 mL and Et_2O and heptane were added. The solvents were evaporated *in vacuo* to afford 12.36 g of a residue as a yellow solid. This residue was purified by prep. LC (Regular SiOH 50 µm, 220 g Grace, mobile phase gradient from Heptane 100% to Heptane 80%, EtOAc 20%). The fractions were collected and the solvent was evaporated to give 9.88 g of the Int. **5** as a white sticky solid (88%).

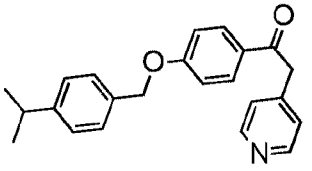


e- Synthesis of Co. 1 :

A mixture of **4** (9.5 g, 32.4 mmol), **5** (22.8 g, 64.7 mmol), K_3PO_4 (27.5 g, 0.13 mol) in 1,4-dioxane (165 mL) and H_2O (60 mL) was carefully purged with N_2. PCy_3 (1.8 g, 6.5 mmol) and $Pd(OAc)_2$ (0.73 g, 3.2 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 18 h at 80°C. The crude material was poured in water and EtOAc was added. This mixture was filtered through a pad of Celite®. The pad of Celite® was washed twice with a hot sol. of DCM+MeOH and the filtrate was evaporated until dryness, then diluted in DCM (500 mL) and purified by

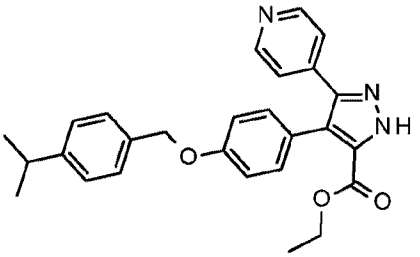
chromatography over silica gel (irregular SiOH 15-40 µm, 400 g, mobile phase gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH_4OH). The pure fractions were collected and evaporated until dryness to give 6.4 g of a first residue and 2.25 g of a second residue. The first residue was washed with MeOH, filtered and dried to yield 6.07 g of **Co. 1** (43%). m.p.: 264°C (DSC). The second residue was washed with MeOH, filtered and dried to yield 2.02 g of **Co. 1** (95% pure) (14%).

Example A2 : Preparation of Co. 1 (2nd approach)



a- Synthesis of Int. 10 :

In a dry flask under N_2, a sol. of **9** (4-[[4-(1-methylethyl)phenyl]methoxy]-benzoic acid, methyl ester) (45 g, 0.158 mol) and 4-picoline (16.9 mL, 0.174 mol) in THF (350 mL) was cooled to 0°C and treated with LiHMDS (316.5 mL, 0.317 mol) (slow addition). The r.m. was stirred at r.t. for 20 h and quenched with a sat. aq. sol. of NH_4Cl. EtOAc was added and the insoluble was filtered, washed with H_2O then Et_2O and dried to yield 33.7 g of a first batch of **10** (62%). The organic layer was extracted and evaporated. The residue was crystallized from Et_2O and H_2O, filtered and dried to give 17.22 g of a 2nd batch of Int. **10** (31%). The organic layer was extracted and evaporated to give 5.8 g of a residue. The residue was purified by chromatography over silica gel (SiOH 35-40µm, 80g, mobile phase gradient from 100% DCM to 98% DCM, 2% MeOH). The pure fractions were collected and evaporated to yield 1.14 g of the third batch of Int. **10** (2%) (Global yield 95%)

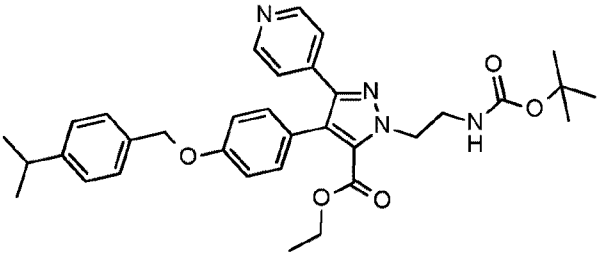


b- Synthesis of Int. 11 :

Quantities were divided into four parts of **10**.

To a suspension of **10** (93 g, 0.269 mol) in ACN (837 mL) was added DBU (68.5 mL, 0.458 mol) and ethyldiazoacetate (45.3 mL, 0.431mol). The mixture was stirred at r.t. for 1h. The mixture was poured into a sat. aq. sol. of $NaHCO_3$ and extracted with EtOAc. The aq. mixture was filtered, the filter was washed with EtOAc and the filter residue was dried to yield 66.44 g of the first batch of Int. **11** (56%). The organic layer was dried ($MgSO_4$), filtered and evaporated to give 75g of a residue. The residue was

purified by chromatography over silica gel (irregular SiOH 35-40µm, 2x330g, mobile phase gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH_4OH). The pure fractions were collected and evaporated to give 28.95 g of the second batch of Int. **11** (24%). Global yield: 80%.



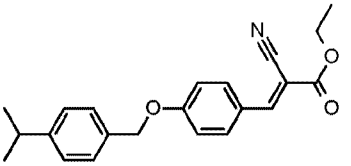
c- Synthesis of Int. 12 :

DBAD (31.9 g, 0.139 mol) was added portionwise to a sol. of **11** (51 g, 0.116 mol), Boc-glycinol (27.9 g, 0.173 mol), PPh_3 (36.4 g, 0.139 mol) in THF (960 mL) at r.t. under N_2 flow. The mixture was stirred for 2h at r.t., poured into H_2O and K_2CO_3 and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered and evaporated until dryness to give 154 g of a residue. The residue was purified by chromatography over silica gel (irregular SiOH 35-40µm, 330g, mobile phase gradient from 100% DCM to 97% DCM, 3% CH_3OH, 0.1% NH_4OH). The pure fractions were collected and evaporated until dryness to give 126.1 g of a residue. The residue was purified by achiral SFC on (2-ethylpyridine 6µm 150x21.2m, mobile phase 90% CO_2, 10% MeOH). The pure fractions were collected and evaporated until dryness to give 59.6 g of Int. **12** (88%).

d- Synthesis of Co. 1 :

A solution of **12** (54.6 g, 0.093 mol) and HCl 3N (155 mL, 0.465 mol) in ACN (1600 mL) was stirred at 80°C for 2h. The solvent was evaporated, a sat. aq. sol. of $NaHCO_3$ was added and the mixture was stirred at r.t. The organic layer was extracted with DCM, dried ($MgSO_4$) and concentrated. The residue was stirred for 3 days with Cs_2CO_3 (61 g, 0.187 mol) in MeOH (2700 mL) at r.t. The mixture was filtered, the filter was washed with MeOH and the filter residue was dried to give 37.4 g of Co. 1 (88%).

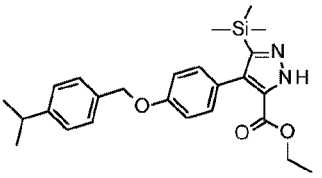
Example A3: Preparation of Co. 1 (3rd approach)



a- Synthesis of Int. 14 :

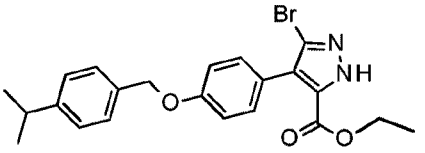
To a sol. of ethylcyanoacetate (2.6 mL, 24 mmol) in EtOH (15 mL) was added **13** (4-[[4-(1-methylethyl)phenyl]methoxy]-benzaldehyde) (5.9 g, 23mmol) and piperidine

(46.0 µL; 0.46 mmol). The mixture was refluxed for 2h then allowed to cool down to r.t. overnight. The precipitate formed was filtered on a glass frit and was dried *in vacuo* to give 6.8 g of Int. **14** as white needles (84%).



b- Synthesis of Int. 15 :

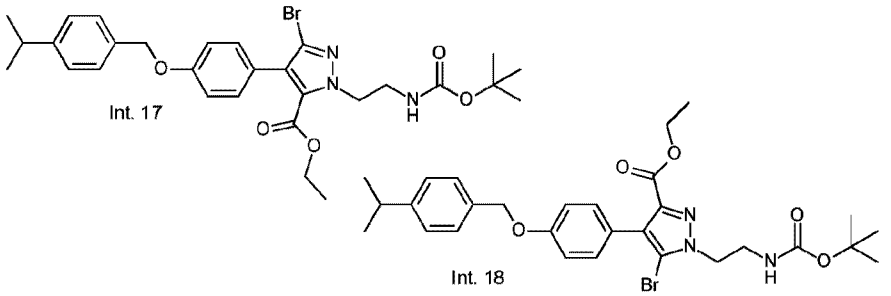
To a sol. of trimethylsilyldiazomethane (40 mL, 80 mmol) in dry THF (100 mL) at -78°C under N_2 was added *n*BuLi (50 mL, 80mmol) dropwise. The sol. was stirred for 30 min at -78°C and a sol. of **14** (18.6 g, 53.33 mmol) in dry THF (100 mL) was added dropwise at -78°C. The sol. was stirred for 1h at -78°C then at r.t. for 16h. EtOAc was added and the organic layer was washed twice with a sat. aq. sol. of $NaHCO_3$, dried ($MgSO_4$), filtered off and evaporated *in vacuo* to give a brown residue. The residue was purified by filtration on silica with a mixture of 97% DCM 3% MeOH to give 16.6 g of Int. **15** as a brown residue (71%).



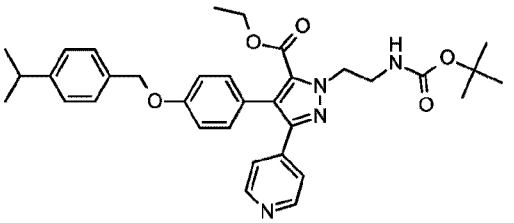
c- Synthesis of Int. 16 :

To a sol. of **15** (3.8 g, 8.7 mmol) in ACN (80 mL) was added NBS (1.63 g, 9.1 mmol) in ACN (40 mL) and the pale brown mixture was stirred at r.t. for 18h. The solvent was removed *in vacuo* and EtOAc and a sat. aq. sol. of K_2CO_3 were added to the residue. The organic layer was separated, dried over $MgSO_4$, filtered off and evaporated *in vacuo* to give 4.04 g of a brown oil. The residue was purified by prep. LC (Irregular SiOH 15-40µm, 80g GraceResolv™, mobile phase gradient from 80% heptane, 20% EtOAc to 70% heptanes, 30% EtOAc). The pure fractions were collected and evaporated until dryness to give 2.5 g of Int. **16** as a beige foam (65%).

d- Synthesis of Int. 17 and Int. 18



To a mixture of **16** (1.4 g, 3.2 mmol), Boc-Glycinol (0.76 g, 4.7 mmol) and PPh_3 supp. (1.5 g, 4.7 mmol) in dry THF (51 mL) was added DBAD (1.1 g, 4.7 mmol). The mixture was stirred at r.t. for 4 h. The mixture was filtered through a pad of Celite®, concentrated and purified by chromatography over silica gel (irregular SiOH 30µm; 80g; mobile phase 70% Heptane, 30% EtOAc). The fractions were collected and evaporated until dryness to give 2.35 g of Int. **17** (used like this in the next step) and 0.24 g of Int. **18**.



e- Synthesis of Int. 12 :

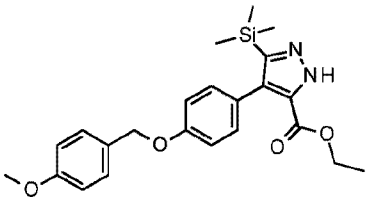
In a schlenk tube, a mixture of **17** (0.3 g, 0.51 mmol), 4-(4,4,5,5-tetramethylL-1,3,2-dioxaborolan-2-yl)pyridine (314 mg, 1.5 mmol), K_3PO_4 (0.43 g, 2.0 mmol) in 1,4-dioxane (1.4 mL) and H_2O (0.5 mL) was carefully degassed with N_2. PCy_3 (30 mg, 0.11 mmol) and $Pd(OAc)_2$ (12 mg, 0.054 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred overnight at 80°C. The crude material was dissolved in water (50mL) and extracted with DCM. The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. This residue was purified by chromatography over silica gel (irregular SiOH 15-40µm, 24g Interchim, mobile phase gradient from 98% DCM, 2% MeOH, 0.1% NH_4OH to 96% DCM, 4% MeOH, 0.1% NH_4OH). The pure fractions were collected and evaporated to give 0.166 g of Int. **12** as a colorless oil (56%).

f- Synthesis of Co. 1:

A mixture of **12** (166 mg, 0.28 mmol) and an aq. sol. of HCl 3N (0.47 mL, 1.4 mmol) in ACN (5 mL) was heated at 80°C for 2h. The solvent was evaporated and an aq. sol. of K_2CO_3 10% (20 mL) was added. The mixture was extracted with DCM, dried and concentrated. The residue was taken up in MeOH and the white solid formed was filtered and dried to give 27 mg of the first batch of Co. 1 (22%). The filtrate was

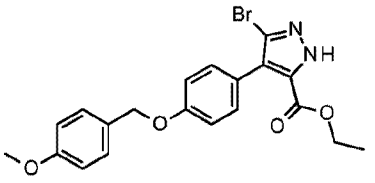
concentrated and the residue was washed with water. The white solid in suspension was filtrated and dried to yield 74 mg of a 2nd batch of Co. 1 as a beige powder (59%).

Example A4: Preparation of Co. 1 (4th approach)



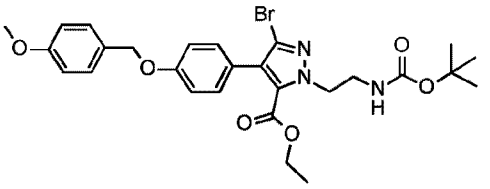
a- Synthesis of Int. 20 :

To a sol. of Trimethylsilyldiazomethane (17.1mL, 34.2 mmol) in dry THF (40 mL) at -78°C under N_2 was added dropwise *n*BuLi (21.4 mL, 34.2 mmol). The sol. was stirred for 30 min at -78°C and a suspension of **19** (2-cyano-3-[4-[(4-methoxyphenyl)methoxy]phenyl]-2-propenoic acid, ethyl ester) (7.7g, 22.8 mmol) in dry THF (60 mL) was added dropwise at -78°C. The sol. was stirred for 1h at -78°C then at r.t. for 16h. EtOAc was added and the organic layer was washed twice with a sat. aq. sol. of $NaHCO_3$, dried ($MgSO_4$), filtered off and evaporated *in vacuo* to give a brown solid. The residue was triturated in Et_2O and filtered on a glass frit to give 4.59 g of Int. **20** as a pale brown solid (47%).



b- Synthesis of Int. 21 :

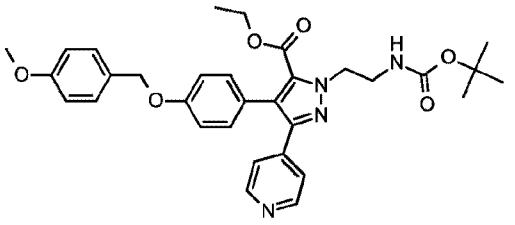
To a suspension of **20** (9.2 g, 21.67 mmol) in ACN (190 mL) was added NBS (3.86 g, 21.67 mmol) in ACN (95 mL) and the pale brown mixture was stirred at r.t. for 18h. The solvent was removed *in vacuo*. DCM and a sat. aq. sol. of $NaHCO_3$ were added to the residue. The organic layer was separated, washed 2x with a aq. sol. of K_2CO_3 10%, dried ($MgSO_4$), filtered off and evaporated *in vacuo* to give 9.07 g of Int. **21** as a brown solid (97%).



c- Synthesis of Int. 22 :

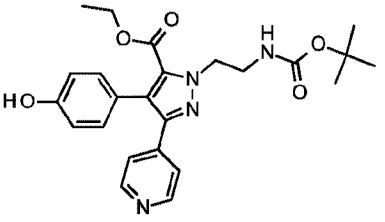
To a suspension of **21** (2.0 g, 4.6 mmol), Boc-Glycinol (1.1 mL, 7.0 mmol) and diphenylphosphinopolystyrene (2.2 g, 7.0 mmol) in dry THF (60 mL) was added DBAD (1.6 g, 7.0 mmol). The mixture was stirred at r.t. for 4 h. The sol. was filtered through a pad of Celite®, the polymer was washed with EtOAc and the filtrate was

evaporated *in vacuo*. The residue was purified by chromatography over silica gel (Regular SiOH, 30µm, 80g GraceResolv™, mobile phase gradient from 75% Heptane, 25% EtOAc to 70% Heptane, 30% EtOAc). The fractions were collected and evaporated until dryness to give 2.58 g of Int. **22** as a yellow solid used without further purification for the next step.



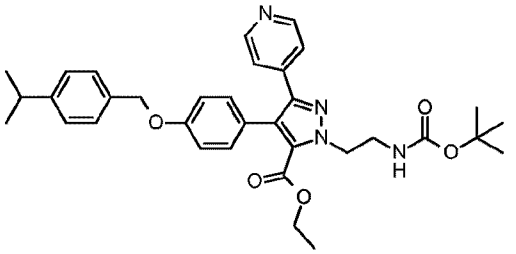
d- Synthesis of Int. 23 :

A mixture of **22** (2.5 g, 4.4 mmol), 4-(4,4,5,5-tetramethylL-1,3,2-dioxaborolan-2-yl)pyridine (2.7 g, 13 mmol), K_3PO_4 (3.7 g, 17 mmol) in 1,4-dioxane (11 mL) and distilled water (4.) was carefully degassed with N_2. PCy_3 (256 mg, 0.91 mmol) and $Pd(OAc)_2$ (103 mg, 0.46 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred overnight at 80°C. The crude material was dissolved in water (100 mL) and extracted with DCM. The organic phase was dried over $MgSO_4$, filtered through a pad of Celite® and evaporated *in vacuo*. This residue was purified by chromatography over silica gel (irregular SiOH 30µm, 80g, mobile phase from 40% Heptane, 60% EtOAc to 20% Heptane, 80% EtOAc). The pure fractions were collected and evaporated until dryness to give 1.49 g of Int. **23** as a beige powder (60%).



e- Synthesis of Int. 24 :

Pd/C (10%) (520 mg, 0.49 mmol) was added to a N_2 degassed sol. of **23** (1.4 g, 2.4 mmol) in EtOH (28 mL). The mixture was hydrogenated under 4 bars of H_2 pressure overnight at r.t. The mixture was filtered through a pad of Celite® which was washed with EtOAc, MeOH and DCM. The combined filtrates were concentrated. The residue (863 mg) was purified by chromatography over silica gel (Regular SiOH ; 30µm, 40g, mobile phase gradient from 98% DCM, 2% MeOH, 0.1% NH_4OH to 96% DCM, 4% MeOH, 0.1% NH_4OH). The pure fractions were collected and evaporated until dryness to give 160 mg of Int. **24** as a colorless oil (14%).

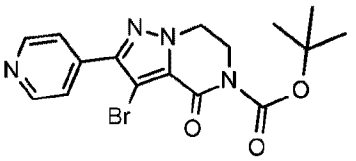


f- Synthesis of Int. 12 :

To a mixture of **24** (158 mg, 0.35 mmol), **6** (79 mg, 0.53 mmol) and PPh_3 (164 mg, 0.53 mmol) in dry THF (11 mL) was added DBAD (121 mg, 0.53 mmol). The mixture was stirred at r.t. overnight. The mixture was filtered through a pad of Celite®, washed with DCM and the solvent was concentratred. The residue was purified by chromatography over silica gel (irregular SiOH 15-40µm, 12g, mobile phase gradient from 98% DCM, 2% MeOH, 0.1% NH_4OH to 94% DCM, 6% MeOH, 0.1% NH_4OH) to give 140 mg of the Int. **12** (69%).

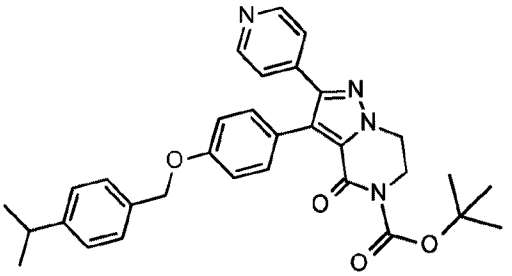
Finally, Int. 12 was reacted to Co. 1 by analogous methods as described in Example A2.d or A3.e.

Example A5: Preparation of Co. 70 and Co. 1 (5th approach)



a- Synthesis of Int. 25 :

To a suspension of **4** (7.5 g, 34.1 mmol), DMAP (0.83 g, 6.8 mmol), Et_3N (14.3 mL, 102 mmol) in THF (170 mL), $(Boc)_2O$ was added portionwise at r.t. The r.m. was stirred at r.t. for 3 h. H_2O and DCM were added. The organic layer was extracted, dried over $MgSO_4$, filtered and evaporated. The residue was purified by prep. LC (Irregular SiOH 35-40µm, 120g GraceResolv™, mobile phase gradient from 100% DCM to 95% DCM 5% MeOH 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 12.4 g of Int. **25** (92%).



b- Synthesis of Co. 70 :

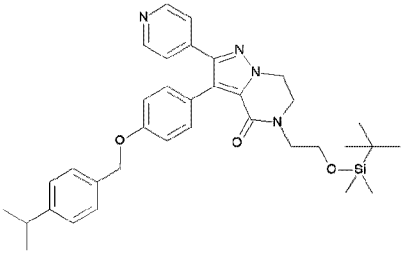
A mixture of **25** (29.4 g, 74.8 mmol), **5** (34.2 g, 97.2 mmol), K_3PO_4 (63.5 g, 300 mmol) in 1,4-dioxane (380 mL) and H_2O (120 mL) was purged with N_2 for 10min. Then

$PdCl_2(dppf)$ (6.1 g, 7.5 mmol) was added and purged with N_2 for 10min. The reaction was heated to 72°C for 3h. The mixture was poured into a aq. sol. of K_2CO_3 and extrated with EtOAc . The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness. The residue was purified by prep. LC (irregular SiOH 220g 35-40µm GraceResolv™ + 300g 30µm Interchim, mobile phase gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give two fractions : 28 g of impure Co.70 and 20.6 g of the Co. 70. The impure fraction (28g) was purified by prep. LC (irregular SiOH 220g + 330g 35-40µm GraceResolv™, mobile phase gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH_4OH). The pure fractions were collected and evaporated until dryness to give 11.14 g of Co. 70. Global yield : 31.7g of Co. 70 (79%).

c- Synthesis of Co. 1:

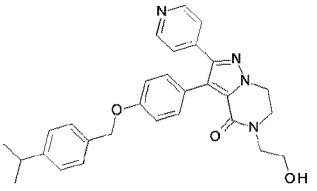
A sol. of **Co. 70** (34.6 g, 64.2 mmol) and HCl 3N (215 mL) in ACN (1700 mL) was heated to 80°C for 1h. Ice was added and the mixture was basified with K_2CO_3 and stirred for 10min. The mixture was filtered off, washed with H_2O then ACN and dried to give 24.55 g of Co. 1 (87%). m.p.: 262°C (DSC).

Example A6: Preparation of Co. 2 (1st approach)



a- Synthesis of Int. 27 :

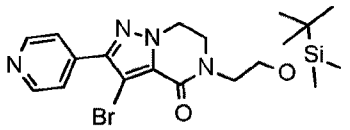
NaH (60%) (1.64 g, 41mmol) was slowly added to a suspension of Co. 1 (12g , 27.4 mmol) in DMF (180 mL) at r.t. under N_2. The mixture was stirred for 2h. Then (2-bromomethoxy)-tert-butyldimethylsilane (7mL, 32.8 mmol) was added and the r.m. was stirred for 15h. The reaction was poured into water and K_2CO_3 and extracted with EtOAc. The organic layer was evaporated until dryness. The residue was taken up with DCM, dried over $MgSO_4$, filtered and evaporated until dryness. The residue was purified by prep. LC (Irregular silica gel 35-40µm, 330g GraceResolv™, mobile phase gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH_4OH). The fractions were collected and evaporated to give 15.52 g of Int. **27** (95%).



b- Synthesis of Co. 2:

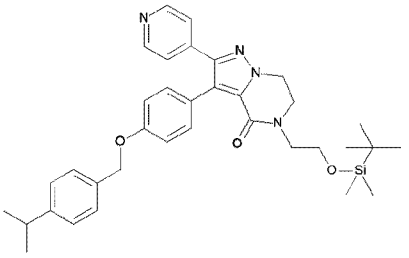
TBAF (1M in THF) (30.6 mL, 30.6 mmol) was added dropwise to a sol. of **27** (15.2 g, 25.5 mmol) in THF (150 mL) at room temperature. The mixture was stirred for 2 days. The mixture was evaporated. The residue was purified by prep. LC (Irregular silica gel SiOH 35-40µm, 330g GraceResolv™, mobile phase gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 11.9 g of Co. 2 (97%).

Example A7: Preparation of Co. 2 (2nd approach)



a- Synthesis of Int. 28 :

NaH (60%) (4.9 g, 123 mmol) was added to a suspension of **4** (30 g, 102 mmol) in DMSO (450 mL) at r.t. under N_2. The mixture was stirred for 2h. (2-Bromomethoxy)-tert-butyldimethylsilane (26.35 mL, 123mmol) was added and stirred for 24h. The mixture was poured into a sat. aq. sol. of K_2CO_3 and extracted with EtOAc. The organic layer was evaporated until dryness. The residue was taken up with DCM, filtered and the filtrate was evaporated until dryness. The residue was purified by prep. LC (Irregular silica gel 35-40µm, 330gGraceResolv™, gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 37.3 g of the Int. **28** (81%).



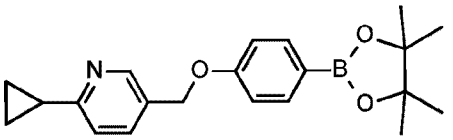
b- Synthesis of Int. 27 :

28 (26 g, 57.6 mmol), **5** (26.4 g, 74.9 mmol) and K_3PO_4 (47 g, 230 mmol) in 1,4-dioxane (270 mL) and H_2O (91 mL) in a sealed reactor were purged with N_2 for 10min. $PdCl_2(dppf)$ (4.7 g, 5.8 mmol) was added and purged with N_2 for 10min. The mixture was heated to 82°C for 20h. The r.m. was poured into a sat. aq. sol. of K_2CO_3 and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness. The residue was purified by prep. LC (irregular SiOH 35-

40µm, 330g GraceResolv™, gradient from 100% DCM to 97% DCM, 3% MeOH, 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 32 g of Int. **27** (97%).

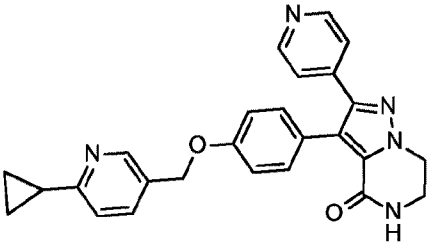
c- **Synthesis of Co. 2:** same procedure as A6b

Example A8: Preparation of Co. 3



a- **Synthesis of Int. 30 :**

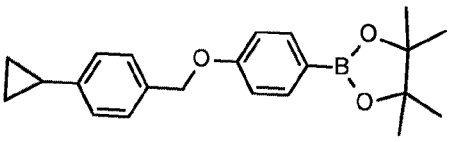
DBAD (2.01 g, 8.71 mmol) was added to a mixture of **7** (1.48 g, 6.70 mmol), **29** (6-cyclopropyl-3-pyridinemethanol) (1.3 g, 8.71 mmol) and PPh_3 supp. (2.91 g, 8.71 mmol) in DCM (30 mL). The r.m. was stirred under N_2 for 17h at r.t. The sol. was filtered and the residual polymer was washed with DCM. Then, the filtrate was evaporated *in vacuo* to give 4.80 g of a residue. This residue was purified by prep. LC (irregular SiOH 15-40 µm, 50 g Merck, mobile phase gradient: from Heptane 100% to EtOAc 20%, Heptane 80%). The pure fractions were collected and solvent was evaporated until dryness to give 2.22 g of the Int. **30** as a white solid (94%).



b- **Synthesis of Co. 3:**

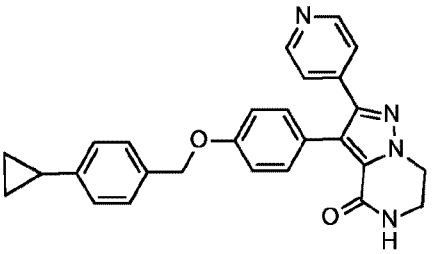
In a Schlenk tube, a mixture of **4** (0.3 g, 1.02 mmol), **30** (1.08 g, 3.07 mmol), K_3PO_4 (0.869 g, 4.09 mmol) in 1,4-dioxane (4.5 mL) and H_2O (1.5 mL) was carefully purged with N_2. PCy_3 (57 mg, 0.205 mmol) and $Pd(OAc)_2$ (23 mg, 102µmol) were added and the r.m. was purged again with N_2. The Schlenk tube was then sealed and the r.m. was stirred for 17 h at 80°C. The crude material was dissolved in water (7 mL) and filtered on glass frit. The grey precipitate was washed with water (2x 20mL) and with Et_2O (2x 40mL). The solid was collected to afford 360 mg of a residue as a grey solid. This residue was purified by prep. LC (irregular SiOH 15-40 µm, 30 g Merck, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%) to give 260 mg of **Co. 3** as a white solid (58%). m.p.: 276°C (DSC).

Example A9: Preparation of Co. 4



a- **Synthesis of Int. 32 :**

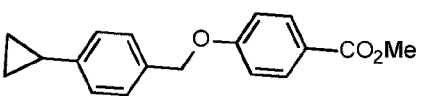
Under N_2, DBAD (15.5 g, 67 mmol) was added portionwise to a sol. of **31** (4-cyclopropyl-benzenemethanol) (10 g, 67 mmol), **7** (15 g, 67 mmol), PPh_3 (17.7 g, 67 mmol) in dry THF (500 mL). The r.m. was stirred at r.t. overnight. THF was evaporated to give 64 g of a residue as a yellow oil. The crude residue was purified by prep. LC (irregular SiOH 30 µm 220 + 330 g GraceResolv™, mobile phase: 90% Heptane, 10% EtOAc). The pure fractions were collected and solvent evaporated to give 19.7 g of Int. **32** as white solid (83%).



b- **Synthesis of Co. 4:**

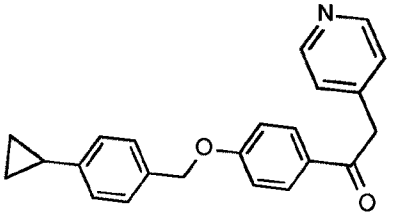
A mixture of **4** (1 g, 3.4 mmol), **32** (2.39g, 6.8 mmol), K_3PO_4 (2.9 g, 13.6 mmol) in 1,4-dioxane (17 mL) and H_2O (6.2 mL) was carefully purged with N_2. $Pd(OAc)_2$ (0.077 g, 0.34 mmol) and PCy_3 (0.19 g, 0.68 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 20h at 80°C. The mixture was poured into water and EtOAc was added. The mixture was filtered off and washed with DCM and MeOH. The different organic layers were put together, dried over $MgSO_4$, filtered and evaporated until dryness to give 2.5g of a residue. This residue was purified by prep. LC (regular of SiOH 30µm, 40g Interchim, mobile phase gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give a residue which was crystallized from MeOH, filtered and dried to give 0.708 g. The product was purified by prep. LC on (irregular SiOH 15-40µm 30g MERCK, mobile phase 0.1% NH_4OH, 98% DCM, 2% MeOH). The pure fractions were collected and the solvent was evaporated until dryness to give 600 mg which was crystallized from Et_2O, filtered and dried to give 587 mg of **Co. 4** (39%). m.p.: 262°C (dsc).

Example A10: Preparation of Co. 5



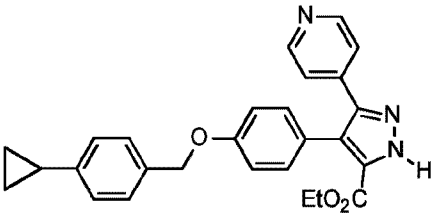
a- **Synthesis of Int. 34 :**

To a mixture of **33** (3.94 g, 25.9 mmol), **31** (4.60 g, 31.0 mmol) and diphenylphosphinopolystyrene (10.3 g, 31.0 mmol) in dry THF (40 mL) was added DBAD (7.15 g, 31.0 mmol). The mixture was stirred at r.t. for 18 h, then filtered on a glass frit and the solid was washed with EtOAc. The filtrate was evaporated *in vacuo* to give a residue as a yellow solid. The residue was triturated with Et_2O to give 4.50 g of Int. **34** as an off-white solid (62%).



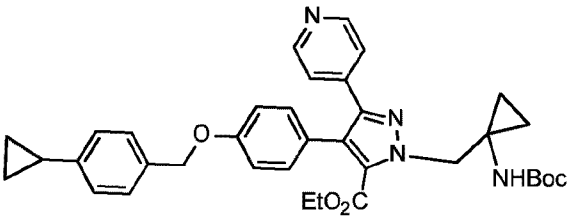
b- Synthesis of Int. 35 :

In a dry flask under N_2, a sol. of **34** (4.50 g, 15.9 mmol) and 4-picoline (1.71 mL, 17.5 mmol) in THF (30 mL) was cooled to 0°C and treated with LiHMDS (47.8 mL, 47.8 mmol) (slow addition over 10 min). The r.m. was stirred at r.t. for 17 h and quenched with a sat. aq. sol. of NH_4Cl. The insoluble was filtered off, washed with Et_2O and dried *in vacuo* to give 4.52 g of Int. **35** as a yellow solid (83%).



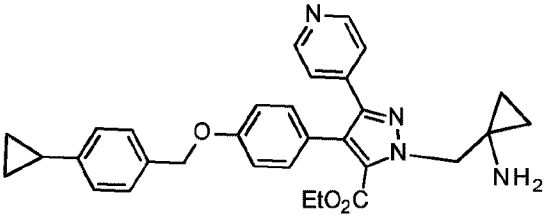
c- Synthesis of Int. 36 :

To a suspension of **35** (4.50 g, 13.1 mmol) in ACN (45 mL) in a sealed tube was added DBU (1.96 mL, 13.1 mmol) and ethyl diazoacetate (2.34 mL, 22.3 mmol). The mixture was heated at 100°C for 2h then cooled down to r.t. The solvent was removed *in vacuo* and the residue was diluted with DCM. The organic layer was successively washed with a sat. aq. sol. of $NaHCO_3$ and water, dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a brown residue. The residue was dissolved in DCM and a precipitate was filtered to give 2.84 g of Int. **36** as a pale yellow solid (49%). The filtrate was purified by prep. LC (Irregular SiOH 15-40 µm, 50 g Merck, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%). The pure fractions were collected and solvent was evaporated to give 754 mg of Int. **36** as yellow solid (13%). Global yield: 62%.



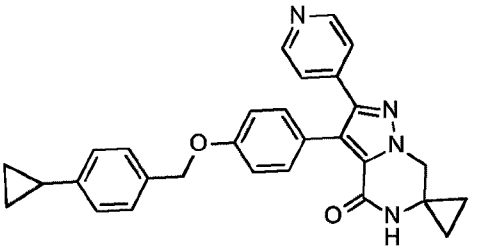
d- Synthesis of Int. 37 :

To a mixture of **36** (0.615 g, 1.40 mmol), 1-(boc-amino)cyclopropylmethanol (0.275 g, 1.47 mmol) and diphenylphosphinopolystyrene (0.933 g, 2.80 mmol) in dry THF (12 mL) was added DBAD (0.644 g, 2.80 mmol). The mixture was stirred for 72 h at r.t. then filtered through a glass frit and washed with EtOAc. The filtrate was evaporated *in vacuo* to give 1.54 g of yellow oil. The residue was purified by prep. LC (Irregular SiOH, 15-40 µm, 50 g Merck, mobile phase gradient: from DCM 100% to DCM 60%, EtOAc 40%) to give 636 mg of Int. **37** as a white foam (75%).



e- Synthesis of Int. 38 :

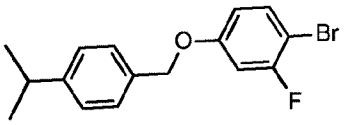
To a sol. of **37** (0.636 g, 1.05 mmol) in 1,4-dioxane (8 mL) was added HCl 4M in dioxane (2.10 mL, 8.36 mmol). The sol. was stirred at r.t. for 18h and was then poured out into Et_2O. The precipitate was filtered through a glass frit to give 584 mg of Int. **38** as a white solid (100%).



f- Synthesis of Co. 5 :

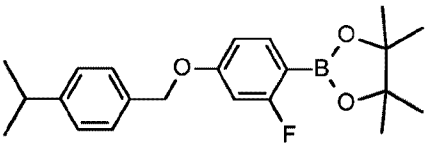
To a sol. of **38** (0.584 g, 1.07 mmol) in MeOH (10 mL) was added Cs_2CO_3 (1.75 g, 5.36 mmol) and the mixture was stirred at r.t. for 4 h. The solvent was removed *in vacuo* and water (25 mL) and DCM (25 mL) were added to the residue. The layers were separated and the aq. layer was extracted with DCM (25 mL). The organic layers were combined, dried over MgSO4, filtered off and evaporated *in vacuo* to give 419 mg of **Co. 5** as a white solid (85%). m.p.: 239°C (DSC).

Example A11: Preparation of Co. 6



a- Synthesis of Int. 41 :

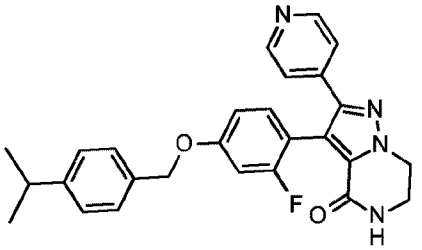
Under N_2, a sol. of **40** (4-bromo-3-fluorophenol) (11g, 58mmol) in ACN (150mL) was treated with K_2CO_3 (16g, 117mmol) and **8** (4-isopropylbenzyl bromide) (9.7mL, 58mmol) and the r.m. was stirred under reflux for 2h. The sol. was filtrated and concentrated to give 18.9 g of Int. **41**, colorless oil (100%) which was used like this in the next step.



b- Synthesis of Int. 42 :

First method: In a sealed tube, a mixture of **41** (1.00 g, 3.09 mmol), KOAc (0.911 g, 9.28 mmol), BisPin (0.943 g, 3.71 mmol) in DME (9 mL) was carefully purged with N_2. $PdCl_2$(dppf) (0.253 g, 0.309 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred for 17 h at 100°C. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3x). The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 2.00 g of a brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 50 g, MERCK, Mobile phase gradient from 100% Heptane to 80% Heptane, 20% EtOAc). The pure fractions were collected and solvent evaporated to give 903 mg of Int. **42**, colorless oil (79%).

Second method: To a sol. of **39** (4-hydroxy-2-fluorophenylboronic acid pinacol ester) (1.10 g, 4.62 mmol) in ACN (45mL) were added **8** (0.985 g, 4.62 mmol) and K_2CO_3 (1.28 g, 9.24 mmol). The reaction was heated at 80°C for 2h and cooled down to r.t. The mixture was filtered on a glass frit and evaporated *in vacuo* to give 1.78 g of Int. **42**, colorless oil which crystallized as a white solid (100%). Int. **42** was used without purification in the next step.

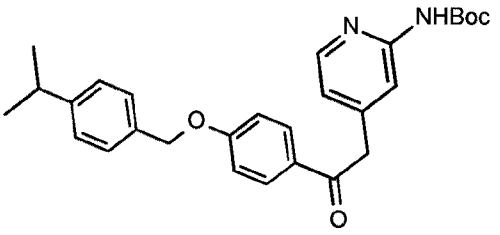


c- Synthesis of Co. 6

In a microwave vial, a mixture of **4** (0.594 g, 2.0 mmol), **42** (1.5 g, 4.0 mmol), K_3PO_4 (1.72 g, 8.1 mmol) in 1,4-dioxane (9.0 mL) and H_2O (3.2 mL) was carefully purged with N_2. $PdCl_2$(dppf) (0.166 g, 202 µmol) was added and the r.m. was purged again

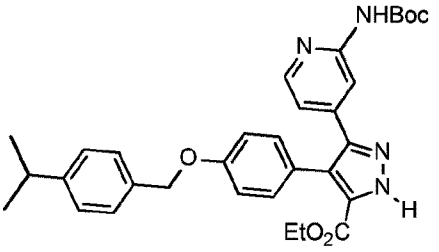
with N_2. The r.m. was heated at 80°C overnight. The crude material was diluted in DCM and washed with a sat. sol. of $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford brown oil. The oil was purified by prep. LC (irregular SiOH 15-40 µm, 40 g GraceResolv™, mobile phase gradient: from DCM 100% to DCM 97%, MeOH 3%). The pure fractions were collected and solvent was evaporated until dryness to give 905 mg of a beige solide which was crystallized from MeOH, washed with Et_2O, filtrated and dried to give 560 mg of Co. 6 as a white powder (61%). m.p. 271°C (dsc).

Example A12: Preparation of Co. 7



a- Synthesis of Int. 43 :

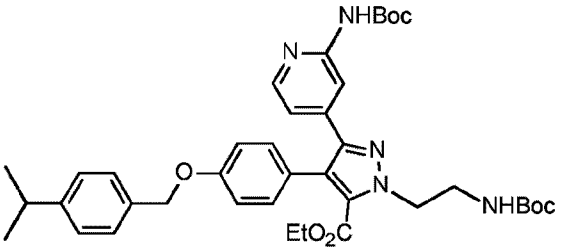
A sol. of **9** (2.0 g, 7.0 mmol) and 2-(4-methyl-2-pyridinyl)-imidodicarbonic acid, 1,3-bis(1,1-dimethylethyl) ester (2.17 g, 7.0 mmol) in dry THF (20 mL) was treated with LiHMDS (14 mL, 14 mmol) at 0°C (addition over 10 min). After stirring for 1h at 0°C, the reaction was allowed to warm to r.t. and was stirred for 17h. The reaction was quenched with a 10% aq. sol. of NH_4Cl (50 mL). The mixture was extracted with DCM. The organic layers were collected and evaporated *in vacuo* and the residue was purified by prep. LC (Irregular SiOH 15-40 µm, 80 g GraceResolv™, mobile phase gradient: heptane/EtOAc from 80/20 to 60/40). The pure fractions were collected and evaporated to give 1.98 g of Int. **43**, white solid (61%).



b- Synthesis of Int. 44 :

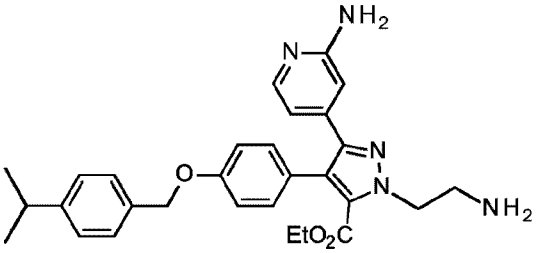
To a suspension of **43** (1.0 g, 2.1 mmol) in ACN (7.7 mL) in a sealed tube was added DBU (0.33 mL, 2.2 mmol) and ethyl diazoacetate (0.39 mL, 3.7 mmol). The mixture was heated at 100°C for 2h then cooled down to r.t. The solvent was removed *in vacuo* and the residue was diluted in EtOAc. The organic layer was washed with a sat. aq. sol. of $NaHCO_3$, water, dried over $MgSO_4$, filtered off and evaporated *in vacuo*. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 40 g GraceResolv™,

mobile phase gradient, from 70% Heptane, 30% EtOAc to 60% Heptane, 40% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 504 mg of Int. **44**, beige powder (42%).



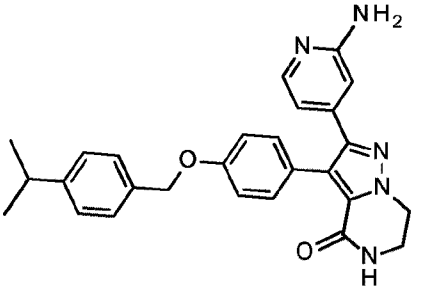
c- Synthesis of Int. 45 :

To a mixture of **44** (0.428 g, 0.77 mmol), Boc-Glycinol (0.149 g, 0.92 mmol) and PPh_3 (0.242 g, 0.92 mmol) in dry THF (20 mL) was added DBAD (0.212 g, 0.92 mmol). The mixture was stirred for 4h at r.t. The mixture was concentrated and the residue was purified by prep. LC (irregular SiOH 15-40 µm, 40 g GraceResolv™, Mobile phase: 70%heptane, 30% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 0.55g of Int. **45** as a white solid (100%).



d- Synthesis of Int. 46 :

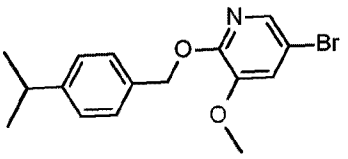
A solution of **45** (0.75 g, 1.1 mmol), HCl (3N) (1.8 mL, 5.4 mmol), in ACN (19 mL) was stirred at 80°C for 3 h. ACN was concentrated, K_2CO_3 10% aq was added and the mixture was extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 0.49 g of Int. **46**, white solid (92%).



e- Synthesis of Co. 7:

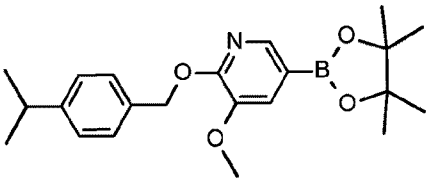
To a sol. of **46** (0.49 g, 0.98 mol) in MeOH (28 mL) was added Cs_2CO_3 (1.6 g, 4.9 mmol) and the mixture was stirred at r.t. overnight. The mixture was filtered, the white solid was collected and dried to give 0.28 g of **Co. 7**, white solid (63%). m.p.: 267°C (dsc).

Example A13: Preparation of Co. 8



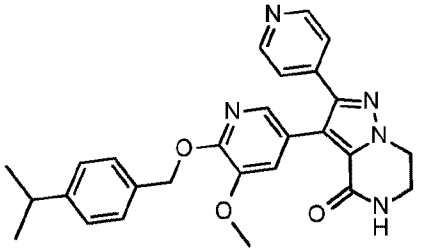
a- Synthesis of Int. 47 :

NaH 60% (0.275 g, 6.87 mmol) was added to a stirred suspension of **6** (0.967 g, 6.44 mmol) and 5-bromo-2-chloro-3-methoxypyridine (0.955 g, 4.29 mmol) in dry THF (16 mL) at 0°C under N_2. The mixture was stirred 10 min at 0°C under N_2, and the vial was sealed. Then the r.m. was stirred at 110 °C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 140 min. [fixed hold time]. The crude mixture was quenched with water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The solid residue was purified by trituration with MeOH, filtration and washing with MeOH, to give 0.785g of Int. **47**, white solid (54%).



b- Synthesis of Int. 48 :

In a sealed tube, a mixture of **47** (751 mg, 2.23 mmol), BisPin (681 mg, 2.68 mmol) and KOAc (658 mg, 6.70 mmol) in DME (12.5 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (183 mg, 0.223 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred for 17 h at 100°C. The r.m. was diluted with EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 572 mg of a solid. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 50 g, Merck, Mobile phase gradient: from 100% Heptane to 60% Heptane, 40% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 335 mg of Int. **48**, solid (39%).

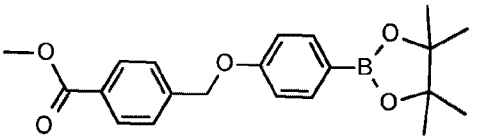


c- Synthesis of Co. 8:

A mixture of **4** (128 mg, 0.437mmol), **48** (335 mg, 0.874 mmol), K_3PO_4 (371 mg, 1.75 mmol) in 1,4-dioxane (3 mL) and H_2O (1 mL) was carefully purged with N_2. PCy_3 (25

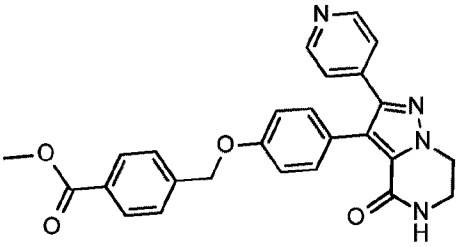
mg, 87 µmol) and $Pd(OAc)_2$ (10 mg, 43.7 µmol) were added, and the r.m. was purged again with N_2, and stirred for 15h at 80°C. The crude material was treated with water and extracted with DCM. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give a black solid. The solid was purified by prep. LC on (irregular SiOH 15-40µm 24g Grace, Mobile phase gradient: from 100% DCM to 8% MeOH, 92% DCM). The fractions were combined and the solvent was removed *in vacuo* to give 146 mg of a white solid. The solid was purified by Reverse phase on (X-Bridge-C18 5µm 30*150mm, Mobile phase: Gradient from 40% formic acid 0.1%, 60% MeOH to 100% MeOH). The pure fractions were isolated and concentrated *in vacuo* to yield 110 mg of **Co. 8**, white solid (54%). m.p. 135°C (dsc).

Example A14: Preparation of Co. 9a and 9



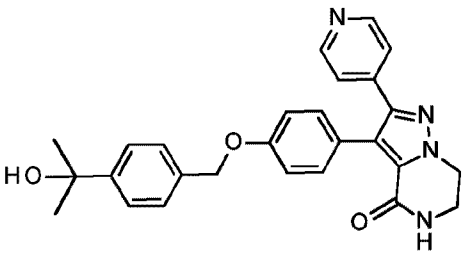
a- Synthesis of Int. 49 :

7 (1.1 g, 4.85 mmol), methyl 4-(bromomethyl)benzoate (1.1 g, 4.8 mmol), K_2CO_3 (1g, 7.2 mmol) in ACN (20 mL) were stirred at r.t. for 8 h. Then, the mixture treated with water and extracted with EtOAc. The organic phase was dried over MgSO4, filtered and evaporated *in vacuo* to give a solid. The solid was purified by prep. LC (irregular SiOH 15-40 µm, 40 g Grace, mobile phase: 70% heptanes, 30% EtOAc). The pure fractions were collected and solvent was evaporated to give 1.5g of Int. **49** (87%).



b- Synthesis of Co. 9a:

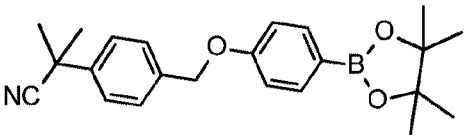
In a sealed tube, a mixture of **4** (438 mg, 1.5 mmol), **49** (0.5 g, 1.3 mmol), K_3PO_4 (1.1 g, 5.4 mmol) in 1,4-dioxane (8 mL) and H_2O (2mL) was carefully purged with N_2. PCy_3 (80 mg, 0.28 mmol) and $Pd(OAc)_2$ (32 mg, 0.1 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 8h at 80°C. Water and DCM were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated until dryness to give 0.8g of a residue. The residue was purified by prep. LC on (irregular SiOH 15-40µm 30g Merck, Mobile phase: 0.1% NH_4OH, 96% DCM, 4% MeOH). The pure fractions were collected and the solvent evaporated until dryness to give 250 mg of **Co. 9a**. (41%, dsc m.p.: 254°C).



c- **Synthesis of Co. 9 :**

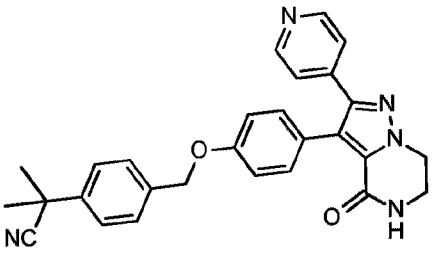
MeMgCl (0.567 mL, 1.68 mmol) was added to a stirred suspension of **Co. 9a** (153 mg, 0.337 mmol) in THF (5mL) under N2 at 0 °C. The mixture was stirred at 0° C for 5 min, and then it was warmed to r.t. and stirred for 2h. The r.m. was quenched with 10% NH_4Cl sol., and treated with EtOAc and a mixture of MeOH/DCM (90:10). The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 143 mg of a white solid. The solid was purified by trituration with DCM, filtration and washing with DCM, to give a solid that was dried *in vacuo*. The residue (100 mg) was purified by achiral SFC (diethylaminopropyl 5µm 150x21.2mm; Mobile phase gradient: from 0.3% $iPrNH_2$, 80% CO_2, 20% MeOH to 0.3% $iPrNH_2$, 60% CO_2, 40% MeOH). The fractions were collected and concentrated *in vacuo* to yield 74 mg which was purified by Reverse phase (X-Bridge-C18 5µm 30*150mm; Mobile phase gradient: from 80% (NH_4HCO_3 0.5% aq. sol.), 20% ACN to 100% ACN). The fractions were collected and concentrated *in vacuo* to give 28 mg of a solid residue. The resulting solid was suspended in ACN and water (20/80), freezed and dried *in vacuo* to afford 20 mg of **Co. 9**, white solid (13%). m.p.: 290°C (dsc).

Example A15: Preparation of Co. 10



a- **Synthesis of Int. 51 :**

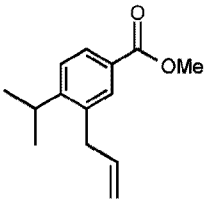
To a suspension of **7** (2.5 g, 11.3 mmol), 2-[4-(hydroxymethyl)phenyl]-2-methylpropanenitrile (1.8 g, 10.3 mmol), PPh_3 supp (3.8 g, 12.3 mmol) in dry DCM (50 mL) was added DBAD (2.8 g, 12.3 mmol) and the r.m. was stirred at r.t. for 18 h. The mixture was filtered through Celite®, washed with DCM and the filtrate was evaporated until dryness. The residue (7g) was purified by prep. LC (irregular SiOH 35-40µm, 90g GraceResolv™, gradient from 95% heptanes, 5% EtOAc to 80% heptanes, 20% EtOAc). The fractions were collected and evaporated until dryness to give 2.1g of Int. **51** (54%).



b- **Synthesis of Co. 10 :**

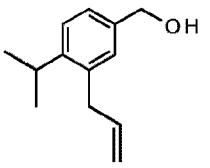
A mixture of **4** (400 mg, 1.36 mmol), **51** (0.77 g, 2 mmol), K_3PO_4 (1.16 g, 5.46 mmol) in 1,4-dioxane (7 mL) and H_2O (3mL) was carefully purged with N_2. PCy_3 (80.4 mg, 0.29 mmol) and $Pd(OAc)_2$ (32 mg, 0.14 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 8h at 80°C. The crude material was poured in water and EtOAc was added. The mixture was filtered through Celite®. The organic phase was dried over MgSO4, filtered and evaporated *in vacuo* to give 1.5g of a pale yellow solid. The solid was taken up in Et_2O, the precipitate was filtered off and dried *in vacuo* to give 700 mg of a residue. The residue was purified by prep. LC on (Stability Silica 5µm 150x30.0mm, mobile phase Gradient: from NH_4OH/DCM/MeOH 0.2/98/2 to NH_4OH/DCM/MeOH 0.8/92/8). The pure fractions were collected and solvent was evaporated until dryness to give 250 mg which was crystallized from Et_2O, filtered and dried to give 210 mg of **Co. 10** (33%). m.p.: 280°C (dsc).

Example A16: Preparation of Co. 11



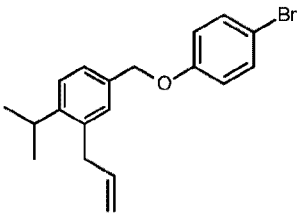
a- **Synthesis of Int. 52 :**

To a sol. of 3-bromo-4-(1-methylethyl)-benzoic acid, methyl ester (1.2 g, 4.7 mmol) in dry DMF (36 mL) degazed under N_2 were added $Pd(PPh_3)_4$ (270 mg, 0.23 mmol) and allyltri-N-butyltin (1.85 g, 5.6 mmol). The mixture was flushed again with N_2 for 5 min and heated at 80 °C overnight. After cooling, the mixture was partitioned between EtOAc and brine, and the organic layer was washed twice with brine, dried and concentrated to give 3.5 g of yellow oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 80 g, GraceResolv™, Mobile phase gradient: from 95% heptane, 5% EtOAc to 90% heptane, 10% EtOAc). The pure fractions were collected and solvent was evaporated to give 900 mg of Int. **52**, colorless oil (88%).



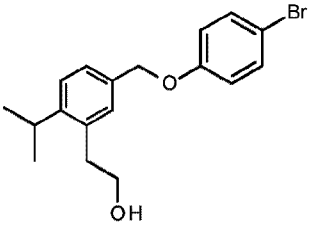
b- **Synthesis of Int. 53:**

52 (900 mg, 4.1 mmol) in dry THF (6.5 mL) was added dropwise to a suspension of LAH (188 mg, 4.9 mmol) in dry THF (6.5 mL) at 0°C under N2. The mixture was stirred for 30min. H_2O (1 mL) then DCM were added very slowly and stirred for 20min. The mixture was filtered on a pad of Celite® and the filtrate was dried over $MgSO_4$, filtered and evaporated until dryness to give 845 mg of Int. **53**, colorless oil (100%).



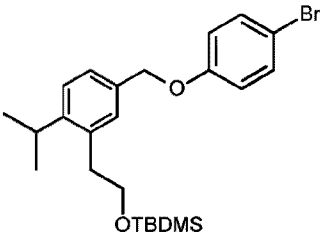
c- **Synthesis of Int. 54:**

To a suspension of **53** (6.52 g, 34 mmol), 4-bromophenol (5.9 g, 34 mmol) and PPh_3 (9.0 g, 34 mmol) in dry THF (210 mL) was added DBAD (7.9 g, 34 mmol). The mixture was stirred at r.t. overnight. The sol. was evaporated *in vacuo* to give 35 g of yellow oil. The residue was purified by prep. LC (Regular SiOH, 30 µm, 330 g GraceResolv™, mobile phase gradient: from 95% heptanes, 5% EtOAc to 90% heptane, 10% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 9.6 g of Int. **54**, pale yellow oil (81%).



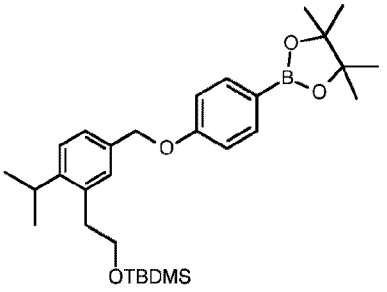
d- **Synthesis of Int. 55:**

A sol. of **54** (2.0 g, 5.8 mmol) in MeOH (23 mL) was cooled to -78 °C. Ozone was bubbled through the sol. until a red color developed (15 min). The excess of ozone was removed with a N_2 purge and the residue was partitioned between EtOAc and NH_4Cl 10% aq. The organic layer was washed with brine twice, dried over $MgSO_4$ and concentrated to give 2.2 g of colorless oil. The crude product was purified by prep. LC (irregular SiOH 30 µm, 40 g Interchim, mobile phase gradient from 80% heptane, 20% EtOAc to 70% heptanes, 30% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 1.21 g of Int. **55** (60%, colorless oil).



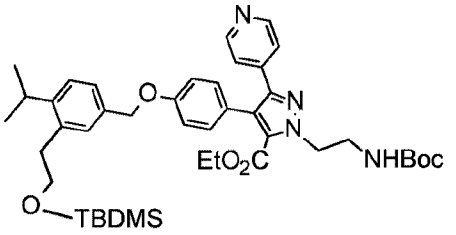
e- **Synthesis of Int. 56:**

Under N_2, TBDMS-Cl (0.77 g, 5.1 mmol) was added to a sol. of **55** (1.2 g, 3.4 mmol) and imidazole (0.70 g, 10 mmol) in dry DCM (33 mL) at r.t. The mixture was stirred at r.t. for 75 min. The r.m. was quenched with water and extracted with DCM. The organic layer was decanted, washed with water then brine, dried over $MgSO_4$, filtered and evaporated to dryness to give 1.69 g of Int. **56** (100%, colorless oil). The product was used like this for the next step.



f- **Synthesis of Int. 57:**

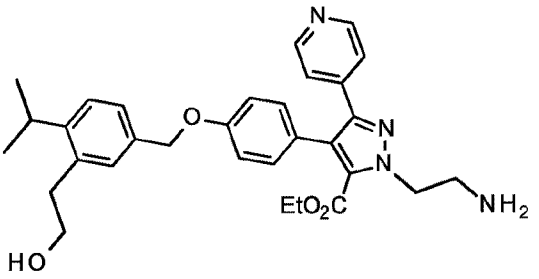
In a microwave vial, a mixture of **56** (1.69 g, 3.6 mmol), KOAc (1.1 g, 11 mmol), BisPin (1.4 g, 5.5 mmol) in DME (11 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (0.30 g, 0.36 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred overnight at 100°C. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 3.3 g of a brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 80 g, Interchim, Mobile phase gradient: from 95% Heptane, 5% EtOAc, to 90% Heptane, 10% EtOAc). The pure fractions were collected and solvent was evaporated to give 1.2 g of Int. **57** (65%, colorless oil).



g- **Synthesis of Int. 58:**

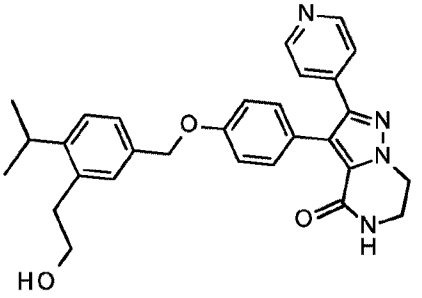
In a microwave vial, a mixture of **3** (0.86 g, 2.0 mmol), **57** (1.2 g, 2.35 mmol), K_3PO_4 (1.2 g, 5.9 mmol) in 1,4-dioxane (8.6 mL) and H_2O (3.1 mL) was carefully purged with

N_2. $PdCl_2(dppf)$ (0.16 g, 0.20 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic layer was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give a residue. The residue was purified by prep. LC (irregular SiOH 30 µm, 40 g, Interchim, Mobile phase: 60%heptane, 40% EtOAc). The pure fractions were collected and the solvent was evaporated until dryness to give 1.1g of Int. **58** (76%).



h- Synthesis of Int. 59:

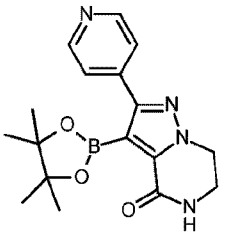
A solution of **58** (1.1 g, 1.5 mmol), HCl 3N (2.5 mL, 7.4 mmol), in ACN (26 mL) was stirred at 80°C for 2h. The mixture was concentrated, and $NaHCO_3$ sat aq (25 mL) was added and the mixture was stirred at r.t. 15 min and extracted with DCM. The organic layer was separated, dried and concentrated to give 780 mg of Int. **59** (100%). This residue was used like this for the next step.



i- Synthesis of Co. 11:

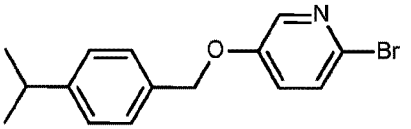
To a sol. of **59** (780 mg, 1.5 mmol) in MeOH (42 mL) was added Cs_2CO_3 (2.4 g, 7.4 mmol) and the mixture was stirred at r.t. overnight. The mixture was filtered and the white solid was collected and dried to give 180 mg. The filtrate was concentrated and taken in DCM and washed once with brine, dried over MgSO4 and concentrated. The crude product was purified by prep. LC (irregular SiOH 30 µm, 25 g Interchim, mobile phase gradient from DCM/MeOH/NH_4OH 97/3/0.1 to 96/4/0.1). The pure fractions were collected and solvent was evaporated to give 460 mg of white solid. The solid was washed in Et_2O, dried and added to the first solid to give 500 mg. This solid was crystallized from isopropanol, filtrated and dried to give 470 mg of **Co. 11**, white solid (66%). m.p.: 195°C (dsc).

Example A17: Preparation of Co. 12



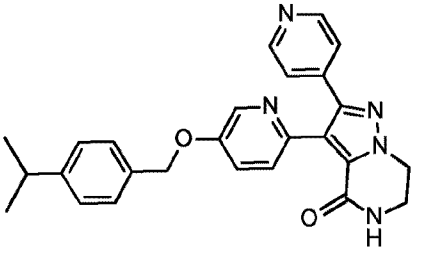
a- **Synthesis of Int. 60 :**

A mixture of **4** (800 mg, 2.73 mmol) in THF (16 mL) was carefully purged with N_2. Isopropylmagnesium chloride 2M in THF (5.5 mL, 10.9 mmol) was added at 0°C and then the r.m. was stirred 4h at r.t. Isopropoxyboronic acid pinacol ester (2.3 mL, 10.9 mmol) was added at 0°C and the r.m. was stirred at r.t. for 90 min. The sol. was diluted in DCM and water and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 915 mg of Int. **60**, white solid (99%).



b- **Synthesis of Int. 61:**

A sol. of 2-bromo-5-hydroxypyridine (800 mg, 4.60 mmol) in ACN (6 mL) and DMF (2 mL) was treated with K_2CO_3 (763 mg, 5.52 mmol) and **8** (0.833 mL, 4.83 mmol) at r.t. The r.m. was stirred for 16 h at r.t. Then water and EtOAc were added, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford a solid. The solid was purified by prep. LC (Irregular SiOH 15-40 µm, 80 g Grace, mobile phase gradient: from Heptane 100% to Heptane 50%, EtOAc 50%). The pure fractions were collected and solvent was evaporated until dryness to give 840 mg of Int. **61** (60%).

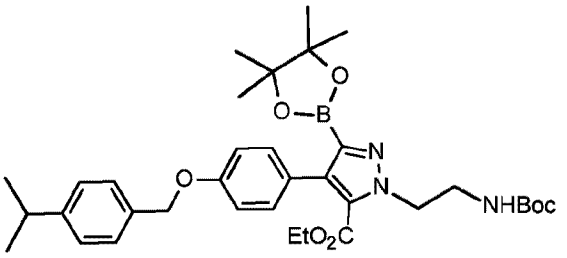


c- **Synthesis of Co. 12:**

A mixture of **60** (417 mg, 1.23 mmol), **61** (751 mg, 2.45 mmol), K_3PO_4 (781 mg, 3.68 mmol) in THF (5 mL) and H_2O (5 mL) was carefully purged with N_2. Precatalyst (96 mg, 123 µmol) was added and the r.m. was purged again with N_2. The r.m. was stirred at r.t. for 18h. The crude material was dissolved in water (20 mL) and extracted with EtOAc (2x 40mL). The organic layer was separated and evaporated *in vacuo*. The residue (500 mg yellow oil) was purified by prep. LC (irregular SiOH 15-40 µm, 30 g

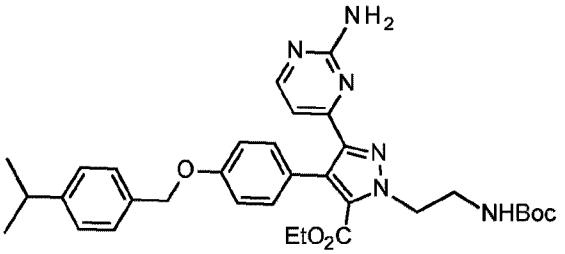
Merck, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%) to give 290 mg of **Co. 12**, white solid (54%). m.p.: 84 °C (DSC).

Example A18: Preparation of Co. 13



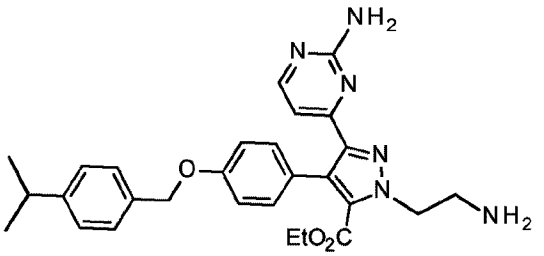
a- Synthesis of Int. 62 :

In a 20 mL microwave tube, a mixture of **17** (1.67 g, 2.85 mmol), KOAc (0.84 g, 8.5 mmol), BisPin (1.1 g, 4.3 mmol) in DME (8 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (233 mg, 0.29 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred overnight at 100°C. The r.m. was diluted with EtOAc and washed with water (once) and with brine (twice). The organic layer was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give a brown oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 40 g, GraceResolv™, Mobile phase gradient: from 70% Heptane, 30% EtOAc to 50% Heptane, 50% EtOAc). The fractions were collected and solvent was evaporated to give 630 mg of a mixture of Int. **62** and another product (initial **17** without Br). This mixture was used as such for the next step.



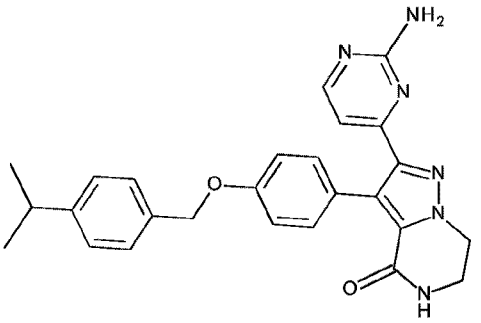
b- Synthesis of Int. 63:

A mixture of **62** (impure) (630 mg, 0.99 mmol), 2-amino-4-bromopyrimidine (173 mg, 0.99 mmol), K_3PO_4 (633 mg, 2.98 mmol) in 1,4-dioxane (2.5 mL) and H_2O (1.1 mL) was carefully degassed with N_2. $Pd(OAc)_2$ (47 mg, 0.21 mmol) and PCy_3 (29 mg, 0.10 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred overnight at 80°C. The crude material was dissolved in water (30 mL) and extracted with DCM (2x). The organic layer was dried over $MgSO_4$, filtered throught a pad of Celite® and evaporated *in vacuo* to give 800 mg of yellow oil. This residue was purified by prep. LC (irregular SiOH 30 µm, 40g Interchim, mobile phase gradient from 98% DCM, 2% MeOH, 0.1% NH_4OH to 95% DCM, 5% MeOH, 0.1% NH_4OH). The pure fractions were collected and solvent was evaporated to give 170 mg of Int. **63**, yellow oil (28%).



c- Synthesis of Int. 64:

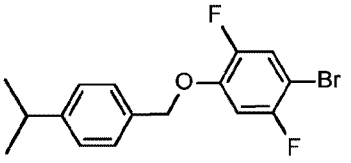
A solution of **63** (0.2 g, 0.33 mmol), HCl 3N (0.55 mL, 1.7 mmol), in ACN (6 mL) was heated at 80°C for 2h. ACN was concentrated, and $NaHCO_3$ sat aq (50 mL) was slowly added and the mixture was extracted with DCM, dried over $MgSO_4$ and concentrated until dryness to give 135 mg of Int. **64** (81%). This residue was used like this in the next step.



d- Synthesis of Co 13:

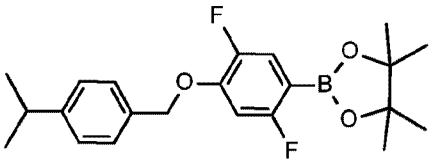
To a sol. of **64** (0.14 g, 0.28 mmol) in MeOH (8 mL) was added Cs_2CO_3 (0.46 g, 1.4 mmol) and the mixture was stirred at r.t. for 3 days. The mixture was concentrated and taken in DCM, the solid was filtered and the filtrate was concentrated to give 162 mg of a residue. The residue was purified by prep. LC on (Stability Silica 5µm 150x30.0mm), mobile phase (Gradient from NH_4OH/DCM/MeOH 0.2/98/2 to NH_4OH/DCM/MeOH 1/90/10). The pure fractions were collected and solvent was evaporated until dryness to give 9 mg of **Co 13**, white solid (7%).

Example A19: Preparation of Co. 14



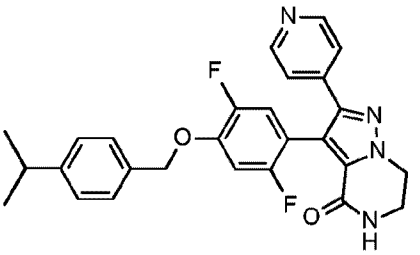
a- Synthesis of Int. 65 :

Under N_2, a sol. of 4-bromo-2,5-difluorophenol (12 g, 58 mmol) in ACN (150 mL) was treated with K_2CO_3 (16 g, 117 mmol) and **8** (9.7 mL, 58 mmol) and the r.m. was stirred under reflux for 2h. The sol. was filtered and concentrated to give 20 g of Int. **65**, colorless oil (100%). The product was used like this in the next step.



b- **Synthesis of Int. 66:**

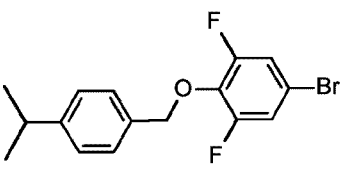
In a Schlenk tube, a mixture of **65** (10.0 g, 29 mmol), KOAc (8.6 g, 88 mmol), BisPin (11 g, 44 mmol) in dry DME (150 mL) was carefully purged with N_2. $PdCl_2$(dppf) (2.4 g, 2.9 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred overnight at 100°C. The r.m. was diluted with EtOAc and washed with water (1x) and with brine (2x). The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give brown oil. The oil was purified by prep. LC (irregular SiOH 15-40 µm, 330 g, GraceResolv™, Mobile phase: Heptane 90%, EtOAc 10%). The pure fractions were collected and solvent was evaporated until dryness to give 10.9 g of Int. **66**, yellow oil (96%).



c- **Synthesis of Co. 14:**

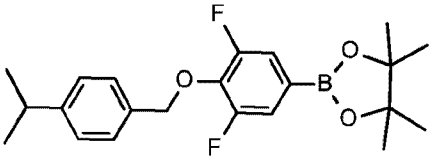
A sol. of **4** (660 mg, 2.25 mmol) and **66** (1.74 g, 4.50 mmol) in 1,4-dioxane (10 mL) and H_2O (8 mL) was treated with K_3PO_4 (1.43 g, 6.76 mmol) and purged with N_2. $PdCl_2$(dppf) (184 mg, 0.225 mmol) was then added and the r.m. was carefully purged with N_2. The mixture was heated at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 25 min [fixed hold time]. The crude mixture was diluted with DCM and washed with water. The organic layer was dried over $MgSO_4$ and evaporated to afford a brown residue. The residue was purified by prep. LC (Irregular SiOH 15-40 µm, 80 g Grace, mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The fractions containing pure Co. were combined and evaporated *in vacuo* to afford of **Co. 14**, white solid (13%). m.p.: 226°C and 231°C (DSC). The fractions containing impure Co. 14 were combined and evaporated *in vacuo* to afford 221mg of **Co. 14**, brown solid (global yield: 33%).

Example A20: Preparation of Co. 15



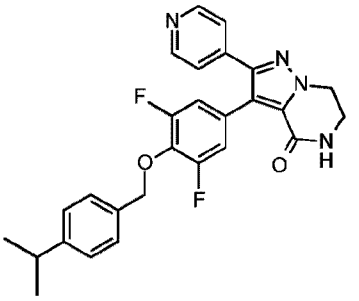
a- **Synthesis of Int. 67:**

To a sol. of 4-bromo-2,6-difluorophenol (1 g, 4.79 mmol), **8** (0.84 mL, 5.02 mmol) in DMF (10 mL) was added K_2CO_3 (0.727 g, 5.26 mmol). The mixture was stirred at r.t. for 2h. Water and DCM were added and the product was extracted with DCM. The organic layer was separated, dried, filtered and evaporated until dryness. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, mobile phase: 80/20 Heptane/EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 1.62g of Int. **67** (99%).



b- Synthesis of Int. 68:

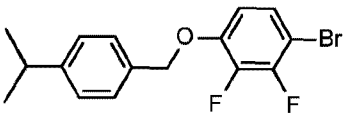
In a sealed tube, a mixture of **67** (1.62 g, 4.75 mmol), BisPin (2.41 g, 9.5 mmol), KOAc (1.4 g, 14.2 mmol) in DME (15 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (0.117 g, 0.142 mmol) was added and the r.m. was purged again with N_2. The mixture was heated at 100°C overnight. EtOAc and water were added and the mixture was extracted with EtOAc. The organic layer was separated, dried, filtered and evaporated until dryness to give 3.29 g of a residue. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, mobile phase (90/10 Heptane/EtOAc). The pure fractions were collected and evaporated until dryness to give and 1.03 g of Int. **68** (56%).



c- Synthesis of Co. 15:

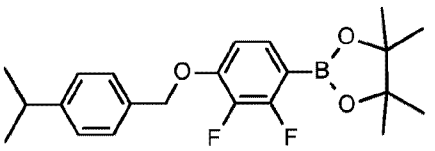
In a microwave vial, a mixture of **4** (0.3 g, 1.02 mmol), **68** (0.516 g, 1.33 mmol), K_3PO_4 (0.911 g, 4.29 mmol) in 1,4-dioxane (4.8 mL) and H_2O (1.6 mL) was carefully purged with N_2. PCy_3 (60 mg, 0.214 mmol) and $Pd(OAc)_2$ (24 mg, 0.11 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 16 h at 80°C. The crude material was put in water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 756 mg of a residue. The residue was purified by prep. LC on (Stability Silica 5µm 150x30.0mm, mobile phase gradient from NH_4OH/DCM/MeOH 0.2/98/2 to NH_4OH/DCM/MeOH 0.8/92/8). The pure fractions were collected and evaporated to give 212 mg of a residue which was crystallized from DIPE, filtered and dried to give 189 mg of **Co. 15** (39%).

Example A21: Preparation of Co. 16



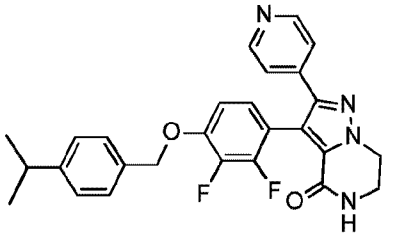
a- **Synthesis of Int. 69:**

Under N_2, a sol. of 4-bromo-2,3-difluorophenol (5.00 g, 23.9 mmol) in DMF (25 mL) was treated with K_2CO_3 (3.97 g, 28.7 mmol) and **8** (4.80 mL, 28.7 mmol) and the r.m. was stirred for 18 h at rt, then extracted with water and EtOAc. The organic layer was washed with brine (twice), dried over $MgSO_4$, filtered off and evaporated *in vacuo* to give 9.49 g of Int. **69**, colorless oil (100%).



b- **Synthesis of Int. 70:**

A mixture of **69** (7.30 g, 19.3 mmol), BisPin (7.34g, 28.9 mmol) and KOAc (5.67 g, 57.8 mmol) in DME (90 mL) was carefully purged with N_2. $PdCl_2$(dppf) (1.58 g, 1.93 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred at 18h at 100°C. The r.m. was diluted with EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 15.0 g of a brown solid. The solid was purified by prep. LC (irregular SiOH 15-40 µm, 150 g, Merck, mobile phase gradient: fomr Heptane 100% to Heptane 60%, EtOAc 40%). The pure fractions were collected and solvent was evaporated to give 6.60 g of Int. **70**, colorless oil (88%).

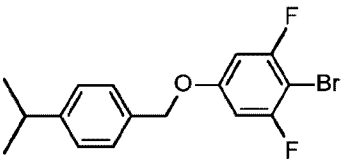


c- **Synthesis of Co. 16:**

A stirred sol. of **4** (551 mg, 1.88 mmol), **70** (1.54 g, 3.97 mmol) and K_3PO_4 (1.2 g, 5.64 mmol) in 1,4-dioxane (8 mL) and H_2O (7.5 mL) was purged with N_2, and then $PdCl_2$(dppf) (84 mg, 0.102 mmol) was added at rt. The resulting mixture was purged again with N_2, and stirred at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 30min. [fixed hold time]. DCM and water were added, the organic layer was separated, dried over MgSO4, filtered off and evaporated *in vacuo* to afford 2.07 g of a viscous black oil. This oil was purified by prep. LC (Irregular SiOH 50 µm, 120 g Grace, mobile phase gradient: from

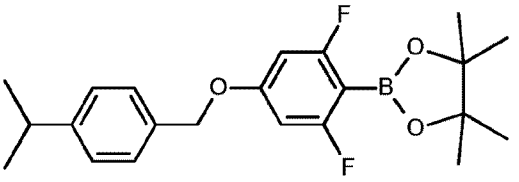
DCM 100% to DCM 92%, MeOH 8%). The fractions were collected and evaporated *in vacuo*. The solid (273 mg, pale grey solid) was crystallized from MeOH, filtered off and dried *in vacuo* to yield 111 mg of **Co. 16**, white solid (12%). m.p.: 214 °C (DSC).

Example A22: Preparation of Co. 17



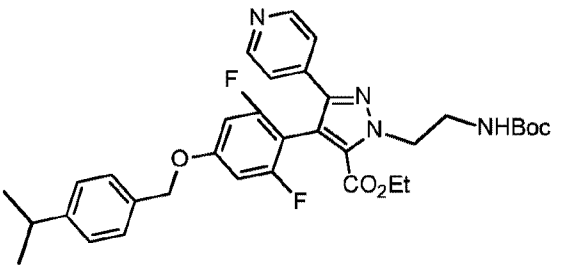
a- Synthesis of Int. 71:

Under N_2, a sol. of 4-bromo-3,5-difluorophenol (3.0 g, 14.4 mmol) in ACN (37 mL) was treated with K_2CO_3 (4.0 g, 29 mmol) and **8** (2.4 mL, 14.4 mmol) and the r.m. was stirred under reflux for 2h. The sol. was filtered and concentrated to give 4.9 g of Int. **71**, colorless oil (100%). The product was used like this in the next step.



b- Synthesis of Int. 72:

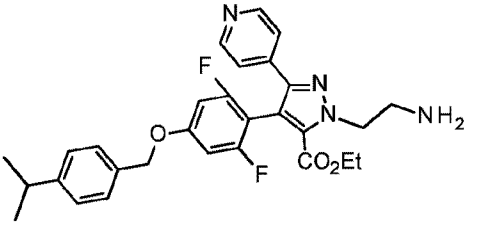
In a sealed tube, a mixture of **71** (1.34 g, 3.92 mmol), BisPin (1.15 g, 11.7 mmol), KOAc (1.19 g, 4.70 mmol) in DME (13 mL) was carefully purged with N_2. $PdCl_2$(dppf) (321 mg, 0.392 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred for 17 h at 100°C. The r.m. was diluted with EtOAc and washed with water (once) and with brine (thrice). The organic phase was dried over MgSO4, filtered and evaporated *in vacuo* to give 2.50 g of brown oil. The oil was purified by prep. LC (irregular SiOH 15-40 µm, 50 g, MERCK, Mobile phase gradient: from 100% Heptane to 90% Heptane, 10% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 1.10 g of Int. **72**, colorless oil (72%).



c- Synthesis of Int. 73:

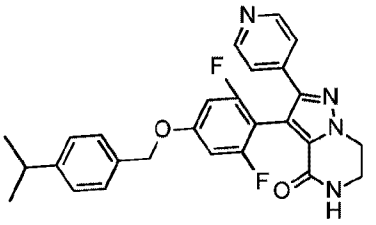
In a microwave vial, a mixture of **3** (570 mg, 1.3 mmol), **72** (1.0 g, 2.6 mmol), K_3PO_4 (1.1 g, 5.2 mmol) in 1,4-dioxane (5.7 mL) and H_2O (2.0 mL) was carefully purged with N_2. Precatalyst (100 mg, 130 µmol) was added and the r.m. was purged again with N_2.

The resulting mixture was stirred at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 1h. [fixed hold time]. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3x). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 1.4 g of a yellow oil. The oil was purified by prep. LC (irregular SiOH 15-40 µm, 40 g, Interchim, Mobile phase: DCM/MeOH/NH_4OH, gradient from 98/2/0.1 to 96/4/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 65 mg of Int. **73** (8%).



d- Synthesis of Int. 74:

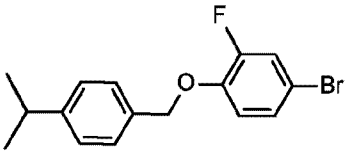
A solution of **73** (65 mg, 0.11 mmol), HCl 3N (0.18 mL, 0.53 mmol), in ACN (2 mL) was stirred at 80°C for 2h. ACN was concentrated, and $NaHCO_3$ sat aq (25mL) was added and the mixture was stirred at r.t. 15 min, extracted with DCM, dried and concentrated to give 63 mg of Int. **74** (quant.). This residue was used like this in the next step.



e- Synthesis of Co. 17:

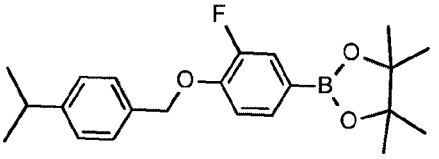
To a sol. of **74** (63 mg, 0.12 mmol) in MeOH (3.5 mL) was added Cs_2CO_3 (0.20 g, 0.61 mmol) and the mixture was stirred at r.t. overnight. The mixture was concentrated and taken in DCM and washed once with water, dried over $MgSO_4$ and concentrated. The crude product was purified by prep. LC (irregular SiOH 30 µm, 12 g GraceResolv™, mobile phase gradient from DCM/MeOH/NH_4OH 98:2:0.1 to 96/4/0.1). The fractions were collected and solvent was evaporated until dryness to give 37 mg, white solide. This solid was purified again by prep. LC on (irregular 15-40µm 30g Merck, mobile phase: 0.1% NH_4OH, 97% DCM, 3% MeOH. The pure fractions were collected and solvent was evaporated until dryness to give 22 mg of **Co. 17,** white solid (38%). m.p.: 235°C (dsc)

Example A23: Preparation of Co. 18



a- **Synthesis of Int. 75:**

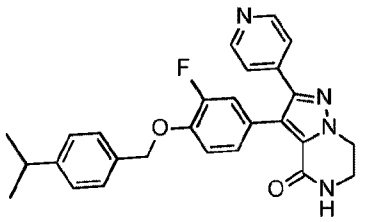
To a sol. of 4-bromo-2-fluorophenol (5 g, 26.1 mmol), **8** (4.6 mL; 27.5 mmol) in ACN (50 mL) was added K_2CO_3 (3.98 g, 28.8 mmol). The mixture was stirred at r.t. overnight. Water and DCM were added and the product was extracted with DCM. The organic layer was separated, dried, filtered and evaporated until dryness. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, mobile phase: 80/20 Heptane/EtOAc). The pure fractions were collected and evaporated until dryness to give 8.2 g of Int. **75** (97%).



b- **Synthesis of Int. 76:**

First method: In a sealed tube, a mixture of **75** (3 g, 9.3 mmol), BisPin (4.7 g, 18.6 mmol), KOAc (2.73 g, 27.8 mmol) in DME (30 mL) was purged with N_2. $PdCl_2(dppf)$ (0.228 g, 0.278 mmol) was added and the r.m. was purged again with N_2. The mixture was heated at 100°C overnight. EtOAc and water were added and the mixture was extracted with EtOAc. The organic layer was separated, dried, filtered and evaporated until dryness to give 6.7g of a residue. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 90g Merck, mobile phase: 90/10 Heptane/EtOAc). The pure fractions were collected and evaporated until dryness to 3.56 g of Int. **76**, 100%.

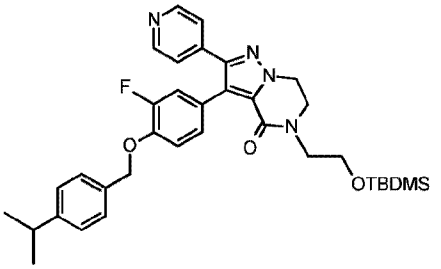
Second method: A sol. of 3-fluoro-4-hydroxyphenylboronic acid pinacol ester (0.91 g, 3.82 mmol) in ACN (10 mL) was treated with K_2CO_3 (0.634 g, 4.56 mmol) and **8** (0.725 mL, 4.2 mmol) at r.t. The r.m. was stirred for 18 h at r.t. Then water and DCM were added, and the organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 1.46 g of a residue. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, mobile phase: 90/10 Heptane/EtOAc). The pure fractions were collected and evaporated until dryness to give 677 mg of Int. **76**, 48%.



c- **Synthesis of Co. 18:**

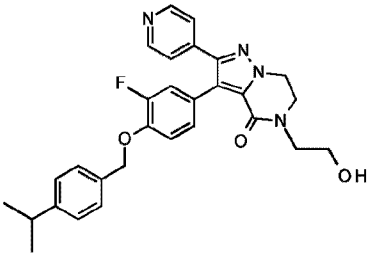
In a microwave vial, a mixture of **4** (0.3 g, 1.02 mmol), **76** (0.53 g, 1.43 mmol), K_3PO_4 (0.91 g, 4.29 mmol) in 1,4-dioxane (4.8 mL) and H_2O (1.6 mL) was carefully purged with N_2. PCy_3 (60 mg, 0.214 mmol) and $Pd(OAc)_2$ (24 mg, 0.107 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 16 h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 881 mg of a residue. The residue was purified by prep. LC on (irregular 15-40µm 30g Merck, mobile phase: NH_4OH/DCM/MeOH 0.3/97/3). The pure fractions were collected and the solvent was evaporated until dryness to give 330 mg which was crystallized from DIPE, filtered and dried to give 317 mg of **Co. 18** (68%). m.p.: 241°C (dsc).

Example A24: Preparation of Co. 19



a- Synthesis of Int. 77:

In a microwave vial, a mixture of **28** (0.4 g, 0.886 mmol), **76** (0.427 g, 1.15 mmol), K_3PO_4 (0.788 g, 3.7 mmol) in 1,4-dioxane (4.2 mL) and H_2O (1.4 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (73 mg, 0.09 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred for 16 h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 838 mg of a residue. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, mobile phase gradient: from DCM 100% to DCM 97%, MeOH 3%). The pure fractions were collected and evaporated until dryness to give 370 mg of Int. **77**, 68%.

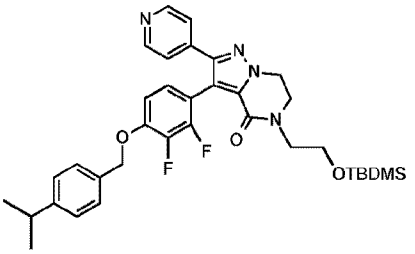


b- Synthesis of Co. 19:

TBAF (0.86 mL, 0.86 mmol) was added dropwise to a sol. of **77** (0.442 g, 0.72 mmol) in THF (4 mL) at r.t.. The mixture was stirred for 3h at rt. The mixture was poured into water and basified with K_2CO_3, extrated with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness to give 422 mg of a residue. The residue

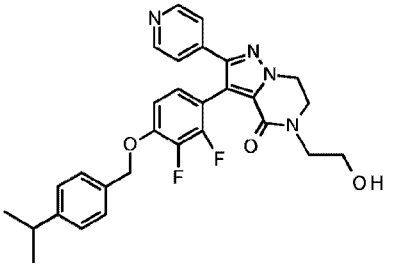
was purified by prep. LC (Stationary phase: Stability Silica 5µm 150x30.0mm), Mobile phase: Gradient from NH_4OH/DCM/MeOH 0.2/98/2 to NH_4OH/DCM/MeOH 0.9/90/9). The pure fractions were collected and evaporated until dryness to give 230 mg which was crystallized from Et_2O, filtered and dried to give 196 mg of **Co. 19** (54%) m.p.: 172°C (dsc).

Example A25: Preparation of Co. 20



a- Synthesis of Int. 78:

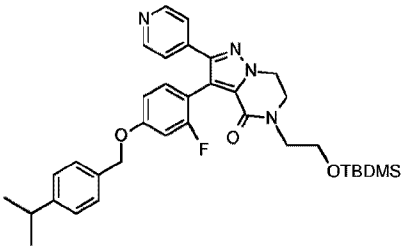
Under N_2, a sol. of **Co. 16** (915 mg, 1.93 mmol) in dry DMSO (17 mL) was treated with NaH (60%) (116 mg, 2.89 mmol). The r.m. was stirred at r.t. for 2h. Then, (2-bromomethoxy)-tert-butyldimethylsilane (496 µL, 2.31 mmol) was added and the reaction was stirred at r.t. for 17 h. The crude mixture was poured in EtOAc and washed with brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to afford 1.00 g of a crude mixture containing 29% of Int. **78** (brown residue). The residue was used as such for the next reaction step.



b- Synthesis of Co. 20:

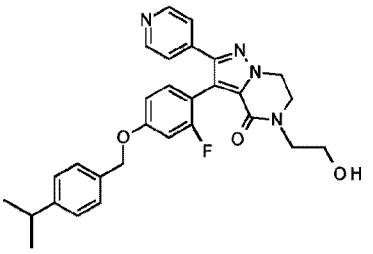
A sol. of mixture with **78** (1.00 g) in THF (35 mL) was treated with TBAF (790 µL, 790 µmol) and stirred at r.t. for 4 h. The crude mixture was then diluted in DCM, washed with water and brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to afford a brown residue. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 30 g, GraceResolv™, Mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The pure fractions were collected and solvent was evaporated to give 162 mg of **Co. 20**, white solid. m.p.: 138°C (DSC).

Example A26: Preparation of Co. 21



a- Synthesis of Int. 79:

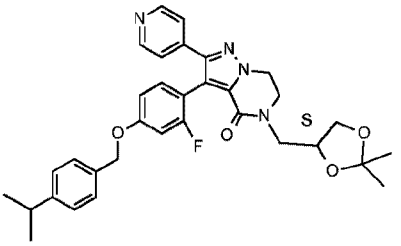
NaH (60%) (0.50 g, 12 mmol) was added slowly to a suspension of **Co. 6** (3.8 g, 8.3 mmol) in dry DMF (49 mL) at r.t. under N_2. The mixture was stirred for 2h then (2-bromomethoxy)-tert-butyldimethylsilane (2.1 mL, 10 mmol) was added and the resulting mixture was stirred overnight. Water was added and the mixture was concentrated under reduced pressure. The residue was taken up in EtOAc and washed five times with brine. The organic layer was dried on $MgSO_4$, filtered and concentrated to give 4.7 g of a mixture of **79** (50%) and the deprotected product (35%) as a yellow oil. This crude mixture was used like this in the next step.



b- Synthesis of Co. 21:

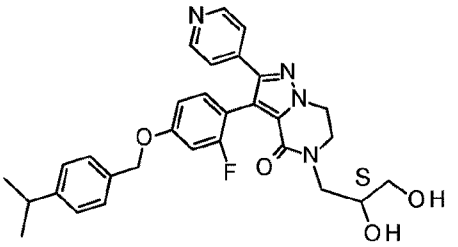
TBAF (9.2 mL, 9.2 mmol) was added dropwise to a sol. of the mixture with **79** (4.7 g, 7.6 mmol) in THF (75 mL) at r.t. The mixture was stirred overnight at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 µm, 120 g GraceResolv™, mobile phase: DCM/MeOH/NH_4OH 98/2/0.1). The fractions were collected and solvent was evaporated until dryness to give 2.5g of a residue. The residue was purified by achiral SFC (Stationary phase: diethylaminopropyl 5µm 150x21.2mm, Mobile phase: 90% CO_2, 10% MeOH). The pure fractions were collected and solvent was evaporated to give 2.1 g which was crystallized from Et_2O, filtrated and dried to give 1.9 g of **Co. 21,** white solid (50%). m.p.: 141°C (dsc).

Example A27: Preparation of Co. 22a and Co. 22



a- Synthesis of Co. 22a:

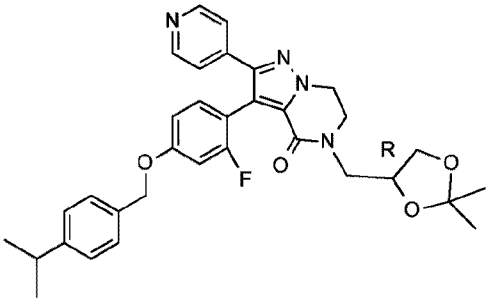
NaH (60%) (79 mg, 2.0 mmol) was added to **Co. 6** (0.60 g, 1.3 mmol) in DMF (8 mL) at r.t. under N_2. The mixture was stirred for 2h then (R)-(-)-2,2-dimethyl-1,3-dioxolane-4-ylmethyl P-toluenesulfonate (0.57 g, 2.0 mmol) was added and the mixture was stirred overnight. Water was added and the mixture was diluted with 150 mL of EtOAc and washed 4x with brine. The organic layer was dried on $MgSO_4$ and evaporated until dryness to give a white solid. The solid was purified by prep. LC (irregular SiOH 15-40 µm, 12g, GraceResolv™, Mobile phase: DCM/MeOH/NH_4OH, 98/2/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 200 mg of **Co. 22a** (S), colorless oil (27%).



b- Synthesis of Co. 22:

A sol. of **Co. 22a** (0.2 g, 0.35 mmol) and HCl 3N (0.58 mL, 1.7 mmol) in 1,4-dioxane (7.8 mL) was heated to reflux for 3 h. The mixture was cooled to r.t., poured into sat. $NaHCO_3$ and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 4 g, GraceResolv™, Mobile phase: DCM/MeOH/NH_4OH, from 97/3/0.1 to 95/5/0.1). The pure fractions were collected and the solvent was evaporated until dryness to give 150 mg of colorless oil. This oil was taken in Et_2O and triturated and the white solid formed was progressively solubilized in Et_2O. The sol. was left standing at r.t. overnight. Then, the solid was filtrated and dried to give 110 mg of **Co. 22** (S), white powder (59%). m.p.: 188°C (dsc); $[\alpha]_d$: -18.42 ° (589 nm, c 0.2715 w/v %, DMF, 20 °C).

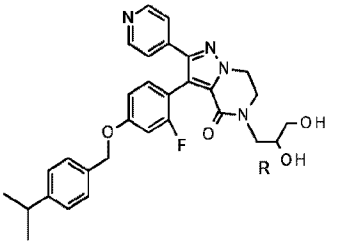
Example A28: Preparation of Co. 23a and Co. 23



a- Synthesis of Co. 23a:

NaH (60%) (79 mg, 2.0 mmol) was added to **Co. 6** (0.60 g, 1.3 mmol) in DMF (8 mL) at r.t. under N_2. The mixture was stirred for 2h then (S)-(-)-2,2-dimethyl-1,3-dioxolane-

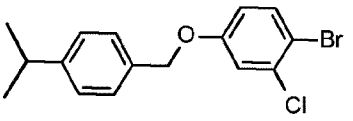
4-ylmethyl P-toluenesulfonate (0.57 g, 2.0 mmol) was added and the mixture was stirred overnight. Water was added and the mixture was diluted with 200 mL of EtOAc and washed four times with brine. The organic layer was dried on $MgSO_4$ and evaporated until dryness to give 0.80 g, white solid. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 12 g, GraceResolv™, Mobile phase: DCM/MeOH/NH_4OH, 98/2/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 165 mg of **Co. 23a** (R), colorless oil (22%).



b- Synthesis of Co. 23:

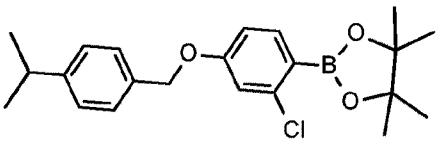
A sol. of **Co. 23a** (0.165 g, 0.29 mmol) and HCl 3N (0.4 8mL, 1.5 mmol) in 1,4-dioxane (6.4 mL) was heated to reflux for 2h. The mixture was cooled to r.t., poured into sat. $NaHCO_3$ and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and evaporated until dryness. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 4 g, GraceResolv™, Mobile phase: DCM/MeOH/NH_4OH from 97/3/0.1 to 95/5/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 114 mg of colorless oil. This oil was crystallized from Et_2O and the white solid formed was filtrated and dried to give 92 mg of **Co. 23** (R), white powder (60%). m.p.: 192°C (dsc); $[\alpha]_d$: +18.59 ° (589 nm, c 0.2475 w/v %, DMF, 20 °C).

Example A29: Preparation of Co. 24



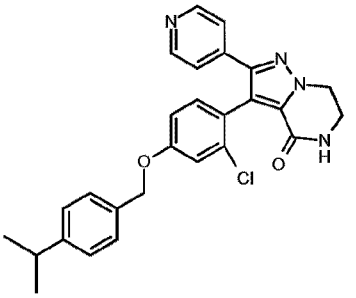
a- Synthesis of Int. 82:

A sol. of 4-bromo-3-chlorophenol (2.00 g, 9.64 mmol) in ACN (25 mL) was treated with K_2CO_3 (1.6 g, 11.6 mmol) and **8** (1.83 mL, 10.6 mmol) at r.t. The r.m. was stirred for 17h at r.t. Then, water and DCM were added, and the organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 3.43 g of a residue. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 120 g Grace, mobile phase gradient: from Heptane 100% to Heptane 85%, EtOAc 15%). The pure fractions were collected and solvent was evaporated until dryness to give 3.07 g of Int. **82**, white solid (88%).



b- **Synthesis of Int. 83:**

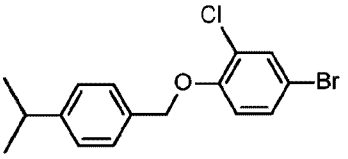
nBuLi 1.6N in hexane (4.25 mL, 6.8 mmol) was added to a stirred sol. of **82** (2.34 g, 6.48 mmol) in anhydrous THF (30 mL) at -78°C under N_2. The mixture was stirred at -78 °C for 30 min, and then isopropoxyboronic acid pinacol ester (1.36 mL, 6.67 mmol) was added at -78 °C under N_2. The r.m. was stirred at -78 °C for 75 min. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 2.37 g of a residue. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 120 g Grace, mobile phase gradient: from Heptane 100% to EtOAc 20%, Heptane 80%). The pure fractions were collected and solvent was evaporated to give 1.91 g of a solid. The solid was purified by prep. LC (irregular SiOH 15-40 µm, 50 g Grace, mobile phase gradient: from Heptane 100% to EtOAc 20%, Heptane 80%). The pure fractions were collected and solvent was evaporated until dryness to give 1.12 g of Int. **83** (45%).



c- **Synthesis of Co. 24:**

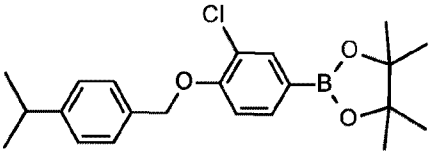
A sol. of **4** (258 mg, 0.882 mmol), **83** (750 mg, 1.94 mmol) and K_3PO_4 (655 mg, 3.09 mmol) in 1,4-dioxane (3.8 mL) and H_2O (1.2 mL) in a sealed tube was purged with N_2. Precatalyst (69 mg, 88.2 µmol) was added, the mixture was purged again with N_2 and stirred at 130°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 15 min [fixed hold time]. The r.m. was treated with DCM and water, and the organic layer was separated, washed with brine and evaporated *in vacuo* to yield 1.5 g of a yellow solid. The solid was purified by prep. LC (irregular SiOH 15-40µm 300g Merck, mobile phase: 0.1% NH_4OH, 97% DCM, 3% MeOH). The pure fractions were collected and the solvent was removed *in vacuo* to give 98 mg of a pale yellow solid which was triturated with pentane, and the solvent was removed *in vacuo* to yield 69 mg of **Co. 24**, white solid (17%). m.p.: 267°C (DSC).

Example A30: Preparation of Co. 25



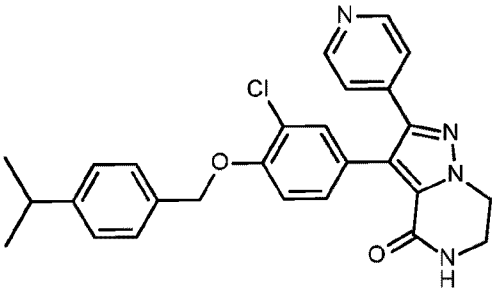
a- **Synthesis of Int. 84:**

To a sol. of 4-bromo-2-chlorophenol (0.6 g, 2.89 mmol), **8** (0.508 mL, 3.04 mmol) in DMF (6 mL) was added K_2CO_3 (0.44 g, 3.18 mmol). The mixture was stirred at r.t. for 2h. Water and DCM were added and the product was extracted with DCM. The organic layer was separated, dried, filtered and evaporated until dryness to give 933mg of Int. **84** (95%).



b- **Synthesis of Int. 85:**

In a sealed tube, a mixture of **84** (0.5 g, 1.47 mmol), BisPin (0.486 g, 1.91 mmol), KOAc (0.433 g, 4.42 mmol) in DME (7 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (36 mg, 0.044 mmol) was added and the r.m. was purged again with N_2. The mixture was heated at 100°C overnight. EtOAc and water were added and the mixture was extracted with EtOAc. The organic layer was separated, dried, filtered and evaporated to give 89 2mg of a residue. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, mobile phase: 80/20 Heptane/EtOAc. The pure fractions were collected and evaporated to give 437 mg of Int. **85** (77%).

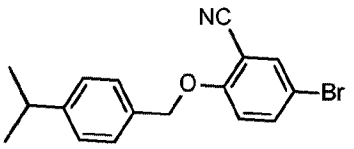


c- **Synthesis of Co. 25:**

In a microwave vial, a mixture of **4** (251 mg, 0.86 mmol), **85** (430 mg, 1.11 mmol), K_3PO_4 (761 mg, 3.59 mmol) in 1,4-dioxane (1.6 mL) and H_2O (0.53 mL) was carefully purged with N_2. PCy_3 (50 mg, 0.18 mmol) and $Pd(OAc)_2$ (20 mg ; 0.09 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 16 h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 765 mg of a residue. The residue was purified by prep. LC on (irregular 15-40µm 30g Merck, mobile phase: NH_4OH/DCM/MeOH 0.3/97/3). The pure fractions were collected and

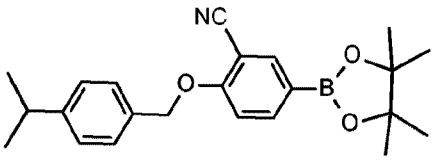
the solvent was evaporated until dryness to give 250 mg which was crystallized from DIPE, filtered and dried to give 188 mg of **Co. 25** (46%). m.p.: 251°C (dsc).

Example A31: Preparation of Co. 26



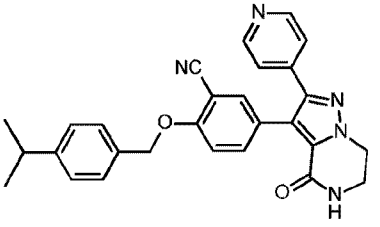
a- Synthesis of Int. 86:

To a sol. of 5-bromo-2-hydroxybenzonitrile (0.6g, 3.03mmol), **8** (0.532mL, 3.18mmol) in DMF (6mL) was added K_2CO_3 (0.46g, 3.33mmol). The mixture was stirred at r.t. for 2h. Water and DCM were added and the product was extracted with DCM. The organic layer was separated, dried, filtered and evaporated until dryness to give 1g of Int. **86** (100%).



b- Synthesis of Int. 87:

In a sealed tube, a mixture of **86** (0.296 g, 0.896 mmol), BisPin (0.455 g, 1.79 mmol), KOAc (0.264 g, 2.69 mmol) in DME (5 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (22 mg, 0.027mmol) was added and the r.m. was purged again with N_2. The mixture was heated at 100°C overnight. EtOAc and water were added and the mixture was extracted with EtOAc. The organic layer was separated, dried, filtered and evaporated. The residue (644 mg) was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, mobile phase: 80/20 Heptane/EtOAc). The pure fractions were collected and evaporated to give 370 mg of Int. **87** (100%).

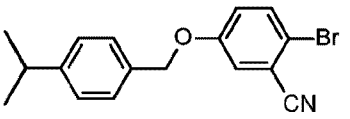


c- Synthesis of Co. 26:

In a microwave vial, a mixture of **4** (0.17 g, 0.58 mmol), **87** (0.371 g, 0.86 mmol), K_3PO_4 (0.516 g, 2.43 mmol) in 1,4-dioxane (2.72 mL) and H_2O (0.91 mL) was carefully purged with N_2. PCy_3 (34 mg, 0.122 mmol) and $Pd(OAc)_2$ (14 mg, 0.061 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 16 h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 332 mg of a residue. The residue was purified by prep. LC on (irregular 15-40µm 50g Merck,

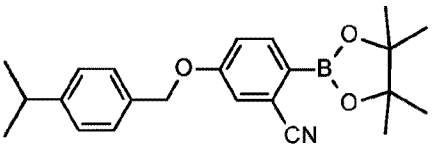
mobile phase: NH_4OH/DCM/MeOH 0.2/96/4). The pure fractions were collected and the solvent was evaporated until dryness to give 85 mg which was crystallized from DIPE, filtered and dried to give 84 mg of **Co. 26** (31%). m.p.: 235°C (dsc).

Example A32: Preparation of Co. 27



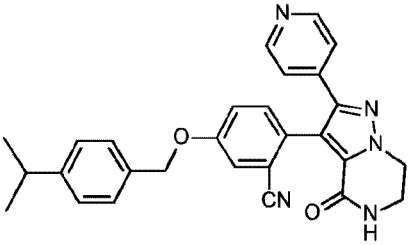
a- Synthesis of Int. 88:

A sol. of 2-bromo-5-hydroxybenzonitrile (6.29 g, 31.8 mmol) in ACN (90 mL) and DMF (10 mL) was treated with K_2CO_3 (4.83 g, 34.9 mmol) and **8** (7.11 g, 33.4 mmol) at rt. The r.m. was stirred for 18 h at r.t. Then, water and EtOAc were added, and the organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 11.4 g of Int. **88**, white solid (quant.).



b- Synthesis of Int. 89:

A mixture of **88** (4.72 g, 14.3 mmol), BisPin (5.45 g, 21.4 mmol) and KOAc (4.21 g, 42.9 mmol) in DME (90 mL) was carefully purged with N_2. $PdCl_2$(dppf) (1.17 g, 1.43 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred at 100°C for 18 h. The r.m. was diluted with EtOAc and water. The organic layer was washed with brine and sat $NaHCO_3$ sol., dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 9.09 g of a black solid. The solid was purified by prep. LC (irregular SiOH 15-40 µm, 220 g, Grace, mobile phase gradient: Heptane 100% to EtOAc 30%, Heptane 70%). The pure fractions were collected and solvent was evaporated until dryness to give 3.26 g of Int. **89**, white solid (60%).

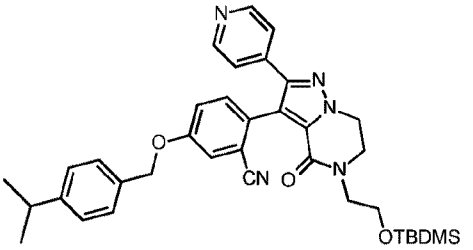


c- Synthesis of Co. 27:

A sol. of **4** (0.8 g, 2.73 mmol), **89** (1.85 g, 4.91 mmol) and Cs_2CO_3 (2.22 g, 6.82 mmol) in DMF (16 mL) in a sealed tube was purged with N_2. $Pd(PPh_3)_4$ (0.315 g, 0.273 mmol) was added, and the mixture was purged again with N_2 and stirred at 150°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min [fixed hold time]. The crude mixture was diluted with a

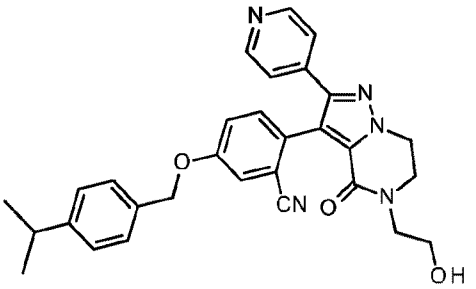
DCM/MeOH sol. (95/5) and brine. The organic layer was separated, dried over $MgSO_4$, filtered off and evaporated *in vacuo* to yield 1.85 g of a sticky brown solid. The solid was purified by prep. LC (Irregular SiOH 50 µm, 80 g Grace, mobile phase gradient: from DCM 100% to DCM 85%, MeOH 15%). The fractions were collected and evaporated *in vacuo* to give 333 mg of a yellow solid. This solid was triturated with pentane. The solvent was removed *in vacuo* and the remaining solid was purified by prep. LC (Irregular SiOH 50 µm, 40 g Grace, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%). The fractions were combined and evaporated *in vacuo* to give 180 mg of a pale yellow solid which was crystallized from a mixture of Et_2O/EtOH (3/1). The solvents were removed, and the remaining solid was triturated with Et_2O. The solid was filtered and dried to give 135 mg of **Co. 27**, pale yellow solid (11%). m.p.: 268 °C (DSC)

Example A33: Preparation of Co. 28



a- Synthesis of Int. 90:

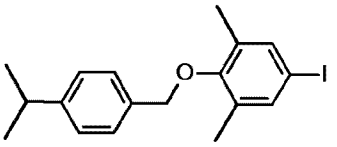
A sol. of **28** (1.20 g, 2.66 mmol), **89** (1.81 g, 4.79 mmol) and Cs_2CO_3 (2.17 g, 6.65 mmol) in DMF (16 mL) in a sealed tube was purged with N_2. $Pd(PPh_3)_4$ (0.307 g, 0.266 mmol) was added, and the mixture was purged again with N_2 and stirred at 150°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min [fixed hold time]. Then, additional **89** (1.00 g, 2.66 mmol), Cs_2CO_3 (0.866 g, 2.66 mmol) and $Pd(PPh_3)_4$ (0.154 g, 0.133 mmol) were added, and the mixture was purged again with N_2 and stirred at 150°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 15 min [fixed hold time]. The crude mixture was concentrated *in vacuo*, and then diluted with a DCM/MeOH sol. (95/5) and water. The organic layer was separated, washed with brine, dried over MgSO4, filtered off and evaporated *in vacuo* to yield 3.69 g of a sticky brown solid. The solid was purified by prep. LC (Irregular SiOH 50 µm, 120 g Grace, mobile phase gradient: from DCM 100% to DCM 97%, MeOH 3%). The fractions were collected and evaporated *in vacuo* to give 510 mg of Int. **90**, yellow oil with a purety of 70%. The product was used as such as for the next step.



b- **Synthesis of Co. 28:**

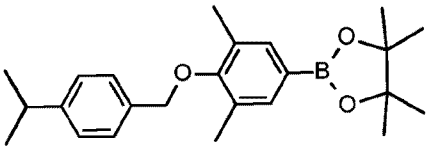
TBAF (0.580 mL, 0.580 mmol) was added to a stirred sol. of **90** (510 mg, 0.574 mmol) in THF (5 mL) at 0°C, and the r.m. was stirred at r.t. for 18 h. The crude mixture was diluted with water and a sol. of DCM/MeOH (96:4). The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue (790 mg) was purified by prep. LC (Irregular SiOH 50 µm, 30 g Grace, mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The fractions were collected and evaporated *in vacuo* to give 231 mg of a white solid. This solid was solubilized in MeOH (1 mL). The solvent was allowed to evaporate slowly to give 230 mg of **Co. 28**, crystalline white solid (79%). m.p.: 185 °C (DSC).

Example A34: Preparation of Co. 29 :



a- **Synthesis of Int. 91:**

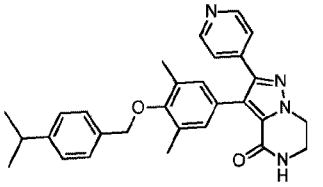
To a sol. of 2,6-dimethyl-4-iodophenol (2.48 g, 10 mmol), **8** (1.76 mL, 10.5 mmol) in ACN (25 mL) was added K_2CO_3 (1.52 g, 11 mmol). The mixture was stirred at r.t. overnight. Water and DCM were added and the product was extracted with DCM. The organic layer was separated, dried, filtered and evaporated until dryness to give 3.43 g of a residue. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, mobile phase: 90/10 Heptane/EtOAc). The pure fractions were collected and evaporated until dryness to give 2.5 g of Int. **91** (66%).



b- **Synthesis of Int. 92:**

In a sealed tube, a mixture of **91** (2.45 g, 6.44 mmol), BisPin (2.45 g, 9.66 mmol), KOAc (1.89 g, 19.3 mmol) in DME (25 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (0.158 g, 0.193 mmol) was added and the r.m. was purged again with N_2. The mixture was heated at 100°C overnight. EtOAc and water were added and the

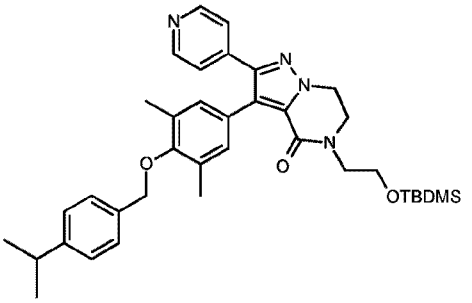
mixture was extracted with EtOAc. The organic layer was separated, dried, filtered and evaporated until dryness to give 4.09 g of a residue. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 90g Merck, mobile phase: 90/10 Heptane/EtOAc). The pure fractions were collected and evaporated until dryness to 2.43g of Int. **92** (yield 99%; purity 75%). The product was used as such for the next reaction step.



c- Synthesis of Co. 29:

In a microwave vial, a mixture of **4** (0.4 g, 1.37 mmol), **92** (0.843 g, 1.77 mmol), K_3PO_4 (1.21 g, 5.72 mmol) in 1,4-dioxane (6.4 mL) and H_2O (2.13 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (112 mg, 0.14 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred for 16 h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 1.16 g of a residue. The residue was purified by prep. LC (Stationary phase: irregular SiOH 15-40µm 300g Merck, Mobile phase: NH_4OH/DCM/MeOH 0.2/97/3). The pure fractions were collected and evaporated until dryness to give 475 mg which was crystallized from Et_2O, filtered and dried to give 443mg of **Co. 29** (70%). m.p.: 260°C (dsc)

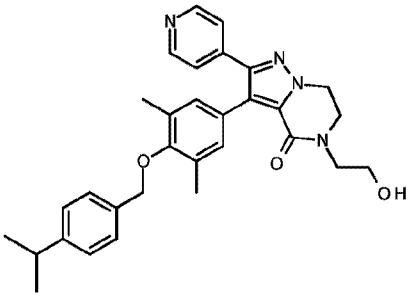
Example A35: Preparation of Co. 30



a- Synthesis of Int. 93:

In a microwave vial, a mixture of **28** (0.6 g, 1.33 mmol), **92** (0.758 g, 1.6 mmol), K_3PO_4 (1.13 g, 5.3 mmol) in 1,4-dioxane (5.84 mL) and H_2O (2 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (109 mg, 0.13 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (twice). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 1.39 g of an oil. This oil was purified by prep. LC (irregular SiOH 30 µm, 40 g Interchim, mobile phase: DCM/MeOH/NH_4OH 98/2/0.1.) The pure fractions were collected and evaporated until dryness to give 111 mg of **93** and 648mg of a 2nd residue. The 2nd

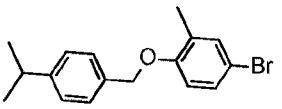
residue was purified by prep. LC (irregular SiOH 30µm, 40g Interchim, mobile phase: DCM/MeOH/NH_4OH 98/2/0.1). The pure fractions were collected and evaporated until dryness to give 588 mg of **93**. Both fractions were combined to yield 699mg of Int. **93** (84%).



b- Synthesis of Co. 30:

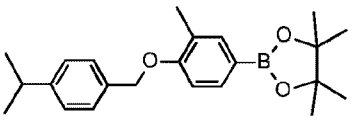
TBAF (1.44 mL, 1.44 mmol) was added dropwise to a sol. of **93** (0.752 g, 1.2 mmol) in THF (12 mL) at r.t. The mixture was stirred for 3h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 626 mg of a residue. The residue was purified by prep. LC (Regular SiOH, 30 µm, 12g GraceResolv™, mobile phase gradient: DCM/MeOH/NH_4OH from 98/2/0.1 to 96/4/0.1). The pure fractions were collected and evaporated until dryness to give 317 mg which was crystallized from Et_2O, filtered and dried to give 218 mg of **Co. 30** (35%). m.p.: 170°C (dsc).

Example A36: Preparation of Co. 31



a- Synthesis of Int. 94:

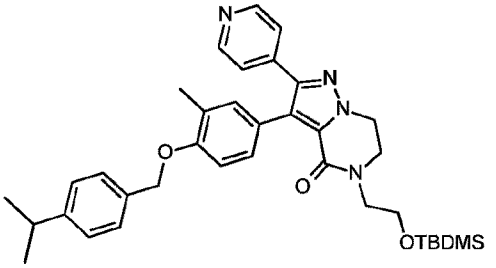
To a sol. of 4-bromo-2-methylphenol (2.5g, 13.4mmol), **8** (2.35mL, 14mmol) in ACN (25mL) was added K_2CO_3 (2.03g, 14.7mmol). The mixture was stirred at r.t. overnight. Water and DCM were added and the product was extracted with DCM. The organic layer was separated, dried, filtered and evaporated until dryness to give 4.33g of Int. **94** (100%).



b- Synthesis of Int. 95:

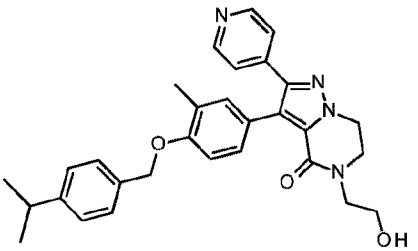
In a sealed tube, a mixture of **94** (3 g, 9.4 mmol), BisPin (3.58 g, 14 mmol), KOAc (2.77 g, 28.2 mmol) in DME (30 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (0.230 g , 0.282 mmol) was added and the r.m. was purged again with N_2. The mixture was

heated at 100°C overnight. EtOAc and water were added and the mixture was extracted with EtOAc. The organic layer was separated, dried, filtered and evaporated until dryness to give 6g of a residue. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 90g Merck, mobile phase: 90/10 Heptane/EtOAc). The fractions were collected and evaporated until dryness to give 1.34 g of a first fraction and 1.11 g of a second fraction.Both fractions were purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, mobile phase: from 98/2 Heptane/EtOAc to 95/5 Heptane/EtOAc). The pure fractions were collected and evaporated to give 1.46 g of Int. **95** (42%).



c- **Synthesis of Int. 96:**

In a microwave vial, a mixture of **28** (0.7 g, 1.55 mmol), **95** (0.738 g, 2.02 mmol), K_3PO_4 (1.32 g, 6.2 mmol) in 1,4-dioxane (6.8 mL) and H_2O (2.42 mL) was carefully purged with N_2. $PdCl_2$(dppf) (127 mg, 0.16 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3x). The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 1.73 g of a residue. The residue was purified by prep. LC (irregular SiOH 30 µm, 40 g Interchim, mobile phase: from DCM 100% to DCM/MeOH/NH_4OH 97/3/0.1). The pure fractions were collected and evaporated until dryness to give 1.2 g of Int. **96** (100%).

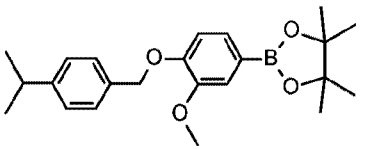


d- **Synthesis of Co. 31:**

TBAF (2.36 mL, 2.36 mmol) was added dropwise to a sol. of **96** (1.2 g, 1.96 mmol) in THF (20 mL) at r.t.. The mixture was stirred for 3h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 980 mg of a residue. The residue was purified by prep. LC (Regular SiOH, 30 µm, 24g GraceResolv™, mobile phase gradient: from DCM 100% to DCM/MeOH/NH_4OH, 95/5/0.1). The pure fractions were collected and evaporated until dryness to give 780

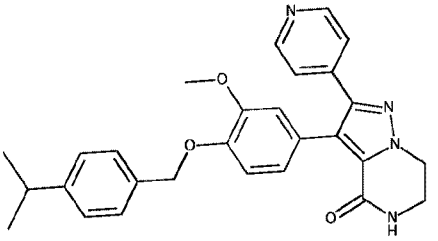
mg which was crystallized from DIPE, filtered and dried to give 491 mg of **Co. 31** (50%).

Example A37: Preparation of Co. 32



a- Synthesis of Int. 97:

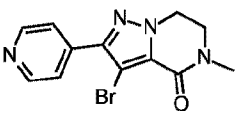
A flask was charged with 4-hydroxy-3-methoxyphenyl boronic acid pinacol ester (1.50 g, 6.00 mmol), **6** (1.35 g, 9.00 mmol), diphenylphosphinopolystyrene (3.00 g, 9.00 mmol) and DCM (40 mL). DBAD (2.07 g, 9.00 mmol) was then added and the r.m. was stirred at r.t. for 17 h. After filtration on a glass frit, the residual polymer was washed with DCM. The filtrate was evaporated *in vacuo* to afford yelow oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 80 g Grace, dry loading, mobile phase gradient: from 100% heptane to heptane 90%, EtOAc 10%). The pure fractions were collected and solvent was evaporated until dryness to give 1.61 g of Int. **97**, white solid (70%).



b- Synthesis of Co. 32:

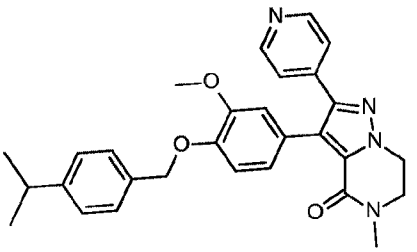
In a Schlenk tube, a mixture of **4** (250 mg, 0.853 mmol), **97** (815 mg, 2.13 mmol), K_3PO_4 (724 mg, 3.41 mmol) in 1,4-dioxane (6 mL) and H_2O (2 mL) was carefully purged with N_2. $Pd(OAc)_2$ (19 mg, 85.3 µmol) and PCy_3 (48 mg, 171 µmol) were added and the r.m. was purged again with N_2. The Schlenk tube was then sealed and the r.m. was stirred for 17 h at 80°C. The crude mixture was then diluted in DCM and washed with water (2x 20mL). The organic layer was collected, dried over $MgSO_4$ and evaporated *in vacuo* to afford brown oil. The oil was purified by prep. LC (irregular SiOH 15-40 µm, 40 g Merck, Mobile phase gradient: from 100% DCM to DCM 95%, MeOH 5%) to give 330 mg of **Co. 32**, white solid (83%). m.p.: 187 °C (DSC).

Example A38: Preparation of Co. 33



a- Synthesis of Int. 98:

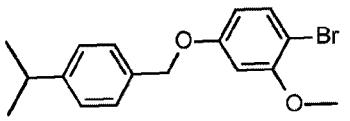
NaH (60%) (655 mg, 216.4 mmol) was added to a suspension of **4** (4.00 g, 13.6 mmol) in DMSO (50 mL) at r.t. under N_2. The mixture was stirred for 2h. MeI (1020 µL, 16.4 mmol) was added and the mixture was stirred for 2h. The mixture was poured into water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness to give 5.00 g of Int. **98**, yellow solid (quant.).



b- Synthesis of Co. 33:

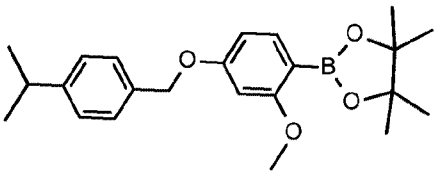
In a sealed tube, a mixture of **98** (154 mg, 501 µmol), **97** (766 mg, 2.00 mmol), K_3PO_4 (425 mg, 2.00 mmol) in 1,4-dioxane (3 mL) and H_2O (1 mL) was carefully purged with N_2. PCy_3 (28 mg, 100 µmol) and $Pd(OAc)_2$ (11 mg, 50.1 µmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 17 h at 100°C. The crude material was dissolved in water (20 mL) and extracted with EtOAc (2x 40mL). The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 874 mg of black oil. The black oil was purified by prep. LC (irregular SiOH 15-40 µm, 30 g Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and evaporated until dryness to give 200 mg of a white solid which was tritured with Et_2O, filtered off and dried to give 196 mg of **Co. 33**, white solid (83%). m.p.: 151°C (DSC).

Example A39: Preparation of Co. 34



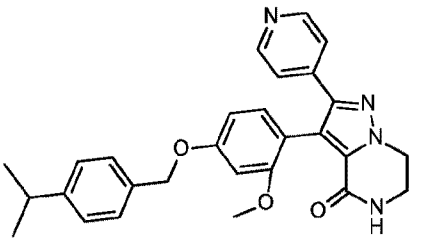
a- Synthesis of Int. 99:

Under N_2, a sol. of 4-bromo-3-methoxyphenol (4.00 g, 19.7 mmol) in ACN (19 mL) was treated with K_2CO_3 (3.00 g, 21.7 mmol) and **8** (3.63 mL, 21.7 mmol) and the r.m. was stirred for 18 h at r.t., then extracted with water and EtOAc. The organic layer was washed with brine (twice), dried over $MgSO_4$, filtered off and evaporated *in vacuo* to give 7.99 g of yellow oil. This oil was diluted in Et_2O and washed with brine (3x50mL), the organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 6.8 g of Int. **99**, yellow oil (quant.).



b- **Synthesis of Int. 100:**

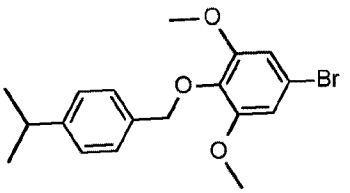
A mixture of **99** (5.57 g, 16.6 mmol) in dry THF (70 mL) was carefully purged with N_2. nBuLi 1.6N in hexane (11.4 mL, 18.3 mmol) was added at -78°C and the r.m. was stirred 2h at -78°C. Isopropoxyboronic acid pinacol ester (3.8 mL, 18.3 mmol) was added at -78°C and the r.m. was stirred for 3h at -78°C. The sol. was diluted in DCM and water. The organic layer was washed with HCl 1N, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 7.7g of colorless oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 30 g Merck, mobile phase: Heptane 50%, EtOAc 50%). The pure fractions were collected and solvent was evaporated to give 6.6 g of Int. **100** (quant.).



c- **Synthesis of Co. 34:**

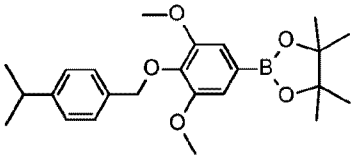
In a sealed tube, a mixture of **4** (500 mg, 1.71 mmol), **100** (1.63 g, 4.26 mmol), K_3PO_4 (1.45 g, 6.82 mmol) in 1,4-dioxane (8 mL) and H_2O (2.6 mL) was carefully purged with N_2. PCy_3 (96 mg, 341 µmol) and $Pd(OAc)_2$ (38 mg, 171 µmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 18h at 100°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 1.20 g of brown oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 30 g Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent was evaporated to give 205 mg of a white solid. The solid was triturated in pentane and evaporated *in vacuo* to give 175 mg of **Co. 34**, white solid (16%). m.p.: 276°C (DSC).

Example A40: Preparation of Co. 35



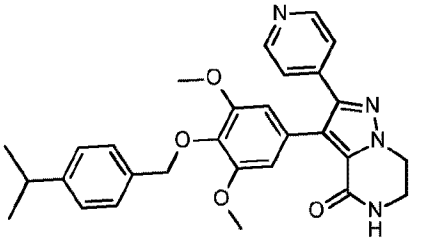
a- **Synthesis of Int. 101:**

To a sol. of 4-bromo-2,6-dimethoxyphenol (2 g, 8.6 mmol), **8** (1.5 mL, 9 mmol) in ACN (25 mL) was added K_2CO_3 (1.31 g, 9.4 mmol). The mixture was stirred at r.t. overnight. Water and DCM were added and the product was extracted with DCM. The organic layer was separated, dried, filtered and evaporated until dryness to give 3.37 g of a residue. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, mobile phase: 90/10 Heptane/EtOAc). The fraction was collected and evaporated until dryness to give 2.82 g which was purified again by prep. LC on (Irregular SiOH 15-40µm 50g Merck, mobile phase: 95/5 Heptane/EtOAc). The pure fractions were collected and evaporated until dryness to give 1.82 g of Int. **101** (58%).



b- **Synthesis of Int. 102:**

In a sealed tube, a mixture of **101** (1.82 g, 4.98 mmol), BisPin (1.9 g, 7.47 mmol), KOAc (1.47 g, 14.9 mmol) in DME (20 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (0.122 g, 0.15 mmol) was added and the r.m. was purged again with N_2. The mixture was heated at 100°C overnight. EtOAc and water were added and the mixture was extracted with EtOAc. The organic layer was separated, dried, filtered and evaporated until dryness to give 3.05 g of a residue. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, mobile phase: 90/10 Heptane/EtOAc). The pure fraction was collected and evaporated until dryness to give 1.79 g of Int. **102** (87%; 80% purity). The product was used like that for the next step.

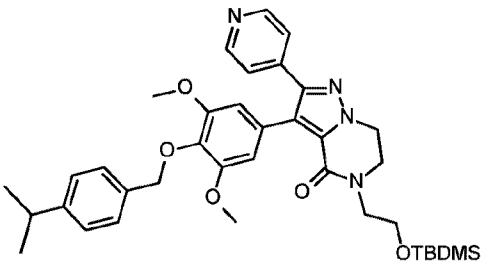


c- **Synthesis of Co. 35:**

In a microwave vial, a mixture of **4** (0.3 g, 1.02 mmol), **102** (0.686 g, 1.33 mmol), K_3PO_4 (0.911 g, 4.29 mmol) in 1,4-dioxane (4.8 mL) and H_2O (1.6 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (84 mg, 0.1 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred for 16 h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 759 mg of a residue. The residue was purified by prep. LC (Stationary phase: irregular 15-40µm 24g Grace, mobile phase gradient: from DCM 100% to 0.1% NH_4OH, 95% DCM, 5% MeOH). The pure fractions were collected and

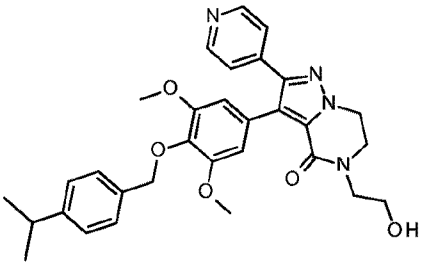
evaporated until dryness to give 290 mg which was crystallized in Et_2O, filtered and dried to give 255 mg of **Co. 35** (50%). m.p.: 192°C (dsc).

Example A41: Preparation of Co. 36



a- Synthesis of Int. 103:

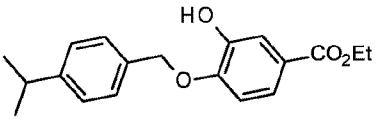
In a microwave vial, a mixture of **28** (0.7 g, 1.55 mmol), **102** (0.96 g, 1.86 mmol), K_3PO_4 (1.32 g, 6.2 mmol) in 1,4-dioxane (6.8 mL) and H_2O (2.42 mL) was carefully purged with N_2. $PdCl_2$(dppf) (127 mg, 0.16 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3x). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 1.3 g of a residue. The residue was purified by prep. LC (irregular SiOH 30 µm, 40 g Interchim, mobile phase: from DCM 100% to DCM/MeOH/NH_4OH 97/3/0.1). The pure fractions were collected and evaporated until dryness to give 0.538 g of Int. **103** (53%).



b- Synthesis of Co. 36:

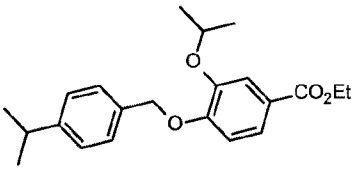
TBAF (0.93 mL, 0.93 mmol) was added dropwise to a sol. of **103** (509 mg, 0.775 mmol) in THF (8 mL) at r.t. The mixture was stirred for 3h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 463 mg of a residue. The residue was purified by prep. LC (Regular SiOH, 30 µm, 12g GraceResolv™, mobile phase gradient: from DCM 100% to DCM/MeOH/NH_4OH 95/5/0.1). The pure fractions were collected and evaporated until dryness. The residue (330 mg) was crystallized from DIPE, filtered and dried to give 303 mg of **Co. 36** (72%). m.p.: 176°C (dsc).

Example A42: Preparation of Co. 37



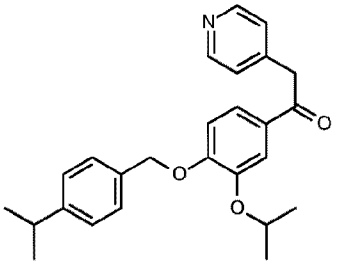
a- Synthesis of Int. 104:

DBAD (7.6 g, 33 mmol) was added to a sol. of ethyl-3,4-dihydroxybenzoate (4 g, 22 mmol), PPh_3 supp. (10.3 g, 33 mmol), **6** (4 mL, 26.3 mmol) in THF (100 mL). The mixture was stirred at r.t. for 5 h. Water and EtOAc were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated until dryness to give 14.2 g of a residue. The residue was purified by prep. LC on (Irregular SiOH 20-45µm 450g MATREX, mobile phase: 85% Heptane, 15% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 2.2g of Int. **104** (32%).



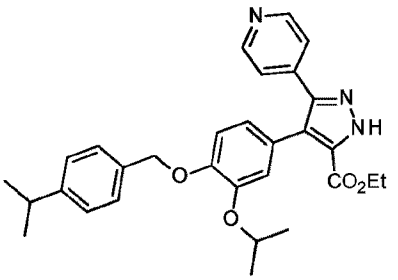
b- Synthesis of Int. 105:

A solution of **104** (1.5 g, 4.8 mmol), 2-bromopropane (0.5 ml, 5.2 mmol), K_2CO_3 (1 g, 7.1 mmol) in ACN (20ml) was stirred at 80°C for 18h. Water and EtOAc were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The residue was purified by prep. LC on (Irregular SiOH 20-45µm 450g MATREX, mobile phase: 85% Heptane, 15% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 1.1g of Int. **105** (65%).



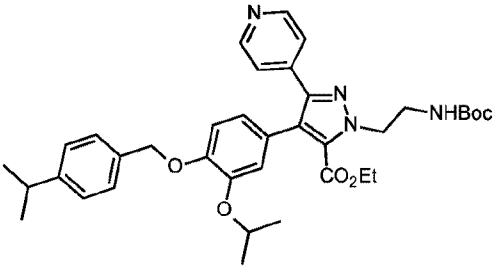
c- Synthesis of Int. 106:

A sol. of **105** (1 g, 2.8 mmol) and 4-picoline (0.3 ml, 3.1 mmol) in dry THF (30 mL) was treated with LiHMDS (5.6 ml, 5.6 mmol) at 0°C (addition over 10 min). After stirring for 1h at 0°C, the reaction was allowed to warm to r.t. and was stirred for a weekend. The reaction was quenched with a 10% aq. sol. of NH_4Cl (50mL). The mixture was extracted with DCM. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The residue was purified by prep. LC (Irregular SiOH 20-45µm 80g MATREX, mobile phase: 95/5/0.1 DCM/MeOH/NH_4OH). The pure fractions were collected and the solvent was evaporated to give 900 mg of Int. **106** (80%).



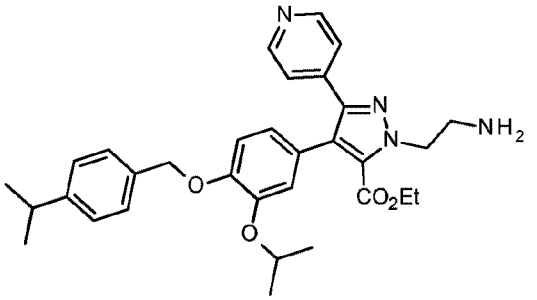
d- Synthesis of Int. 107:

To a suspension of **106** (900 mg, 2.23 mmol) in ACN (5 mL) was added DBU (0.33 mL, 2.23 mmol) and ethyl diazoacetate (0.4 mL, 3.8 mmol). The mixture was stirred at r.t. for 2h. The solvent was removed *in vacuo* and the residue was diluted in EtOAc. The organic layer was washed with a sat. aq. sol. of $NaHCO_3$, dried over $MgSO_4$, filtered off and evaporated *in vacuo*. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 40 g Grace, mobile phase: 97/3 DCM/MeOH). The pure fractions were collected and the solvent was evaporated until dryness to give 460 mg of Int. **107** (41%, beige powder).



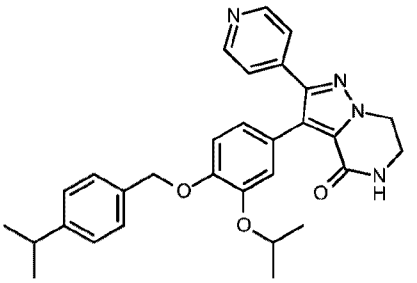
e- Synthesis of Int. 108:

To a mixture of **107** (460 mg, 0.921 mmol), Boc-Glycinol (222 mg, 1.4 mmol) and PPh_3 supp. (362 mg, 1.4 mmol) in dry THF (10 mL) was added DBAD (318 mg, 1.4 mmol). The mixture was stirred for 4h at r.t. The mixture was filtered and the filtrate was evaporated until dryness to give 1.4 g of a residue. The residue was purified by prep. LC on (irregular SiOH 15-40µm 300g Merck, mobile phase: 59% Heptane, 6% MeOH, 35% EtOAc). The pure fractions were collected and the solvent was evaporated until dryness to give 320 mg of Int. **108** (54%).



f- Synthesis of Int. 109:

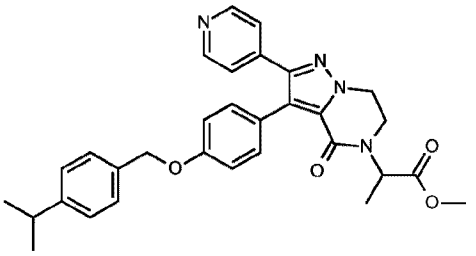
A solution of **108** (250 mg, 0.39 mmol) and HCl 3N (0.65 mL, 1.9 mmol) in ACN (5mL) was stirred at 80°C for 2h. K_2CO_3 10% and EtOAc were added and the mixture was extracted. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated to give 250 mg of Int. **109** (100%).



g- Synthesis of Co. 37:

To a sol. of **109** (250 mg, 0.46 mmol) in MeOH (10 mL) was added Cs_2CO_3 (750 mg, 2.3 mmol) and the mixture was stirred at r.t. overnight. The mixture was filtered, the white solid was collected, washed with Et_2O and dried to give 138 mg. The solid was taken up in H_2O and DCM and extracted. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The residue was taken up in Et_2O, the precipitate was filtered off and dried to give 97 mg of **Co. 37** (42%). m.p.: 206°C (dsc).

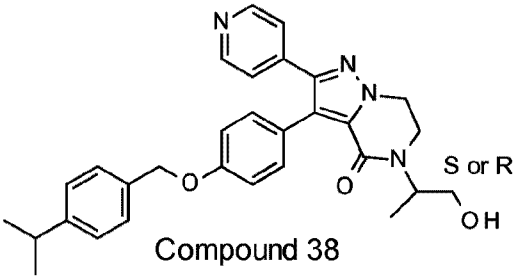
Example A43: Preparation of Co. 38 and Co. 39



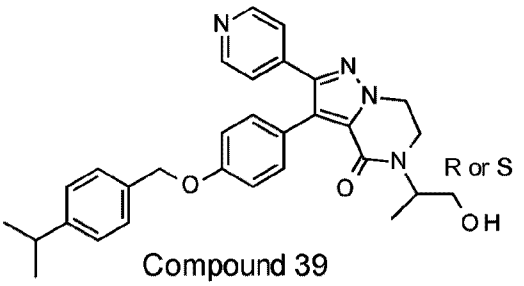
a- Synthesis of Int. 120:

NaH 60% (274 mg, 6.8 mmol) was added slowly to a suspension of Co. 1 (2 g, 4.6 mmol) in dry DMSO (40 mL) at r.t. under N2. The mixture was stirred for 2h. Then, methyl-2-bromopropionate (1.02 mL, 9.1 mmol) was added and the final mixture was stirred for 20h. The mixture was poured into water and K_2CO_3, and extracted with EtOAc. The organic layer was evaporated until dryness. The residue was taken up with DCM, dried over $MgSO_4$, filtered and evaporated until dryness to give 2.6 g. The residue was purified by prep. LC (80g of SiOH 30µm Interchim, mobile phase gradient: from 100% DCM to 95% DCM 5% MeOH 0.1% NH_4OH). The pure fractions were collected and evaporated until dryness to give 2.47 g of Int. **120** (100%).

b- Synthesis of Co. 38 and Co. 39:



Compound 38



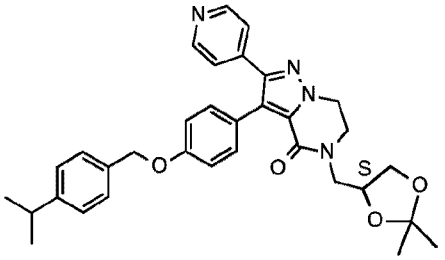
Compound 39

120 (2.47 g, 4.7 mmol) in THF (20 mL) was added dropwise to a suspension of LAH (268 mg, 7.06 mmol) in THF (30 mL) at 0°C under N2. The mixture was stirred for 1.5h. Ice water was added dropwise then DCM was added. The mixture was filtered and the filtrate was dried over $MgSO_4$, filtered and evaporated until dryness to give 2.6 g which was purified by prep. LC (80g of irregular SiOH 30µm Interchim, graduent from 100% DCM to 95% DCM 5% CH_3OH 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 0.467g of a residue. This residue was purified by achiral SFC (Stationary phase: AMINO 6µm 150x21.2mm), Mobile phase: 80% CO_2, 20% MeOH). The fractions were collected and evaporated until dryness to give 290 mg which was purified by chiral SFC (Stationary phase: Chiralpak IC 5µm 250x20mm), Mobile phase: 60% CO_2, 40% iPrOH). The pure fractions were collected and evaporated until dryness to give 130 mg of a first residue and 130 mg of a second residue. The first residue was crystallized from Et_2O, filtered and dried to give 97 mg of **Co. 39** (4%). m.p.: 144°C (dsc). The second residue was crystallized from Et_2O, filtered and dried to give 100 mg of **Co. 38** (4%). m.p.: 144°C (dsc).

Co. 39: $[\alpha]_d$: +19.74 ° (589 nm, c 0.309 w/v %, DMF, 20 °C);

Co. 38: $[\alpha]_d$: -18.36 ° (589 nm, c 0.305 w/v %, DMF, 20 °C).

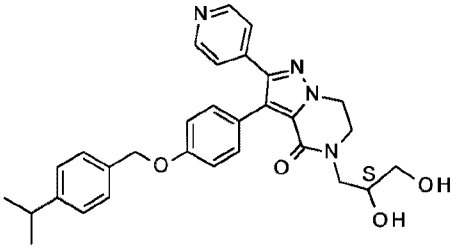
Example A44: Preparation of Co. 40



NaH 60% (0.82 g, 20.5 mmol) was added to Co. 1 (6 g, 13.7 mmol) in DMF (160 mL) at r.t. under N_2. The mixture was stirred for 2h then (R)-(-)-2,2-dimethyl-1,3-dioxolane-4-ylmethyl P-toluenesulfonate (5.9 g, 20.5 mmol) was added portionwise and stirred

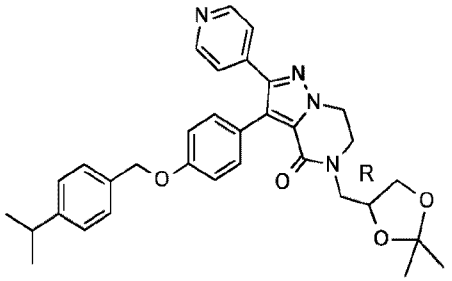
for 15h. The mixture was poured into water and K_2CO_3 and extracted with EtOAc. The organic layer was evaporated until dryness. The residue was taken up with DCM, dried over $MgSO_4$, filtered and evaporated until dryness to give 14g which was purified by prep. LC (Stationary phase: Irregular SiOH 20-45µm 450g MATREX, Mobile phase: 0.1% NH_4OH, 98% DCM, 2% MeOH). The pure fractions were collected and evaporated until dryness to give 4.4 g of a residue (58%). A part of the residue was crystallized from Et_2O, filtered and dried to give 258 mg of **Co. 40** (S).
m.p.: 113°C (dsc); $[\alpha]_d$: -16.95 ° (589 nm, c 0.295 w/v %, meOH, 20 °C).

Example A45: Preparation of Co. 41



Co. 40 (3.7 g, 6.7 mmol), HCl 3N (11.1 mL, 33.5 mmol) in 1,4-dioxane (140 mL) were heated to 80°C for 0.5h. The mixture was cooled to r.t., poured into water and K_2CO_3 and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness. The residue was purified by prep. LC (80g of SiOH 30 µm Interchim, mobile phase gradient: from 100% DCM to 90% DCM 10% CH_3OH 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give a residue which was crystallized from Et_2O, filtered and dried to give 2.97 g of **Co. 41** (S) (87%).
m.p.: 191°C (dsc); $[\alpha]_d$: -18.85 ° (589 nm, c 0.2705 w/v %, DMF, 20 °C)

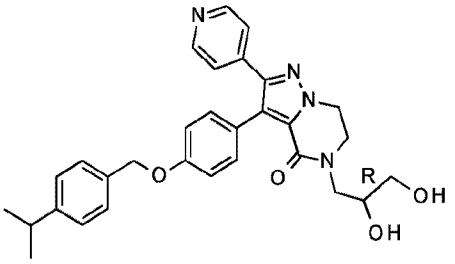
Example A46: Preparation of Co. 42



NaH 60% (0.684 g, 17.1 mmol) was added to Co. 1 (5 g, 11.4 mmol) in DMF (125 mL) at r.t. under N_2. The mixture was stirred for 2h then (S)-(-)-2,2-dimethyl-1,3-dioxolane-4-ylmethyl P-toluenesulfonate (4.9 g, 17.1 mmol) in DMF (10 mL) was added dropwise and stirred for 15 h at rt. The mixture was poured into water and K_2CO_3 and extracted with EtOAc. The organic layer was evaporated until dryness. The residue was

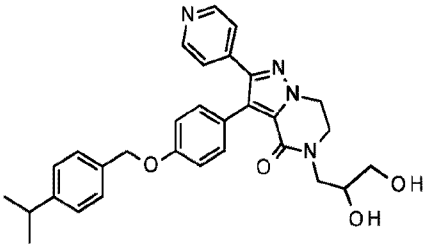
taken up with DCM, dried over $MgSO_4$, filtered and evaporated until dryness to give 9.7g which was purified by prep. LC (120 g of silica gel 30μm Interchim, mobile phase gradient: from 100% DCM to 95% DCM 5% CH_3OH 0.1% NH_4OH). The desired fractions were collected and evaporated until dryness to give 2.12 g of a first residue and 2.1 g of a second residue. The second residue was purified by prep. LC (80g of silica gel 30μm Interchim, mobile phase gradient: from 100% DCM to 95% DCM 5% CH_3OH 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 1.58 g a residue. The first residue and the last one were brought together to give 3.7g of Co. 42 (59%). A part of Co. 42 was crystallized from Et_2O, filtered and dried to give 250 mg of **Co. 42** (R). m.p.: 114°C (dsc); $[\alpha]_d$: +9.98 ° (589 nm, c 0.2405 w/v %, meOH, 20 °C).

Example A47: Preparation of Co. 43



Co. 42 (3.17 g, 5.7 mmol), HCl 3N (9.6 mL, 28.7 mmol) in 1,4-dioxane (120 mL) were heated to 80°C for 1h. The mixture was cooled to r.t., poured into water and K_2CO_3 and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness to give 3.36 g. The residue was purified by prep. LC (80g of SiOH 30 μm Interchim, mobile phase gradient: from 100% DCM to 90% DCM 10% CH_3OH 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 2.76 g of a residue which was crystallized from Et_2O, filtered and dried to give 2.56 g of **Co. 43** (R) (87%). m.p.: 190 °C (dsc); $[\alpha]_d$: +17.39 ° (589 nm, c 0.2875 w/v %, DMF, 20 °C).

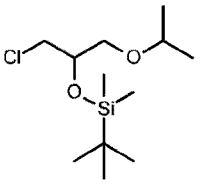
Example A48: Preparation of Co. 44



NaH 60% (55 mg, 1.4 mmol) was added slowly to a suspension of **Co. 1** (0.4 g, 0.91 mmol) in dry DMSO (5 mL) at r.t. under N_2. The mixture was stirred for 2h then 3-

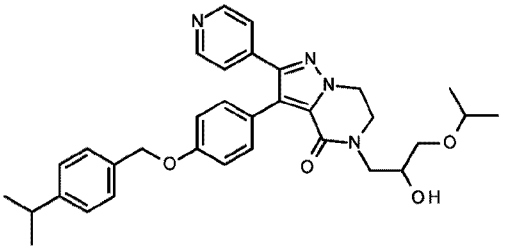
bromo-1,2-propanediol (88 µL, 1.0 mmol) was added and stirred overnight. Water was added and the mixture was filtered, dissolved in DCM with CH_3OH. The organic layer was separated, dried on $MgSO_4$ and evaporated until dryness to give 530 mg of a residue. This residue was purified by prep. LC (irregular SiOH 30 µm, 25g, Interchim, mobile phase gradient: DCM/MeOH/NH_4OH from 96/4/0.1 to 92/8/0.1). The pure fractions were collected and solvent was evaporated until dryness to give colorless oil. This oil was taken up in Et_2O and triturated. The white solid formed was filtrated and dried to give 294 mg of **Co. 44**, white solid (63%). m.p.: 192°C (dsc).

Example A49: Preparation of Co. 45



a- Synthesis of Int. 121:

Tert-butyldimethylsilyl chloride (0.44 g, 2.9 mmol) was added to a sol. of 1-chloro-3-isopropoxy-2-propanol (0.3 g, 1.9 mmol) and imidazole (0.4 g, 5.8 mmol) in DCM (19 mL) at r.t. The r.m. was stirred at r.t. overnight. The mixture was quenched with water and extracted with DCM. The organic layer was decanted, washed with H_2O then brine, dried ($MgSO_4$), filtered and evaporated to dryness to give 0.5 g of Int. **121**, colorless oil (purity 70%), used as such for the next step.

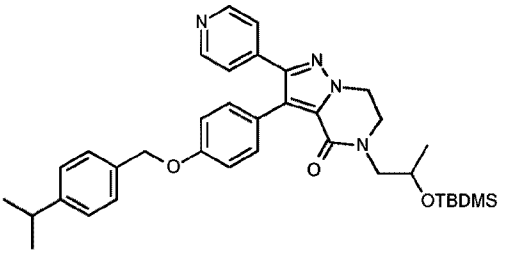


b- Synthesis of Co. 45:

NaH 60% (71 mg, 1.8 mmol) was added slowly to a suspension of **Co. 1** (0.52 g, 1.2 mmol) in dry DMF (7.1 mL) at r.t. under N_2. The mixture was stirred for 2h then **121** (500 mg, 1.3 mmol) in dry DMF (4 mL) was added and the r.m. was stirred overnight. Water was added and the mixture was concentrated under reduced pressure. The residue was taken in EtOAc and washed (5x) with brine. The organic layer was dried on $MgSO_4$, filtered and concentrated to give 0.4 g of a residue. The residue was purified by prep. LC (Stationary phase: Sunfire Silica 5µm 150x30.0mm, mobile phase gradient: from 71% Heptane, 1% MeOH (+10% NH_4OH), 28% EtOAc to 20% MeOH (+10% NH_4OH), 80% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 72 mg which was taken in Et_2O and triturated. The

white solid formed was filtrated and dried to give 45 mg of **Co. 45**, white solid (7%). m.p.: 148°C (dsc).

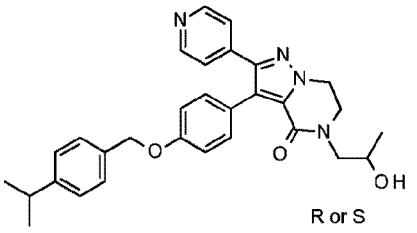
Example A50: Preparation of Co. 46 and Co. 47



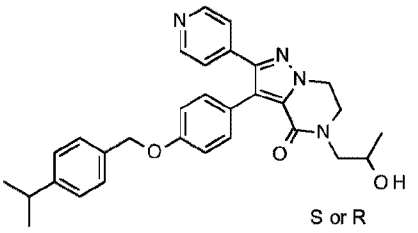
a- Synthesis of Int. 122:

NaH 60% (137 mg, 3.4 mmol) was added to a sol. of Co. 1 (1 g, 2.28 mmol) in DMSO (20 mL) at r.t. under N_2. The mixture was stirred for 2h. (2-Bromo-1-methylethoxy)(1,1-dimethylethyl)dimethyl silane (0.87 g, 3.4 mmol) was added and the r.m. was stirred for 3 days. The mixture was poured into water, K_2CO_3 and extracted with EtOAc. The organic layer was evaporated until dryness to give 1.21 g. The residue was taken up in DCM, dried over $MgSO_4$, filtered and evaporated until dryness to give 1.1 g. The residue was purified by prep. LC on (25g of SiOH 30µm Interchim, mobile phase: DCM 100% to 0.1% NH_4OH, 95% DCM, 5% CH_3OH). The pure fractions were collected and solvent was evaporated until dryness to give 0.68 g of Int. **122** (49%).

b- Synthesis of Co. 46 and Co. 47:



Compound 46



Compound 47

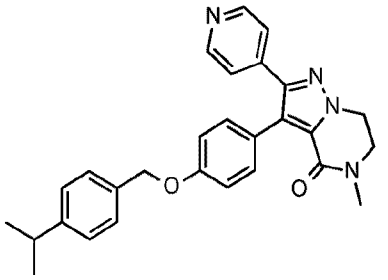
TBAF (1.49 mL, 1.49 mmol) was added dropwise to a sol. of **122** (0.76 g, 1.24 mmol) in THF (7 mL) at r.t.. The mixture was stirred for 15h. The mixture was evaporated until dryness. The residue was purified by prep. LC (25g of SiOH 30µm Interchim, mobile phase gradient from 100% DCM to 95% DCM 5% MeOH 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 0.47 g of racemic Co. This racemic Co. and 0.53g of another batch were put together to give 1g of racemic Co. which was purified by chiral SFC on (Chiralpak IC 5µm 250x20mm), mobile phase (50% CO_2, 50% iPrOH). The fractions were collected and solvent was evaporated until dryness to give 485 mg of a first enantiomer and 467 mg of a second enantiomer. The first one was purified again by achiral SFC on (Amino 6µm

150x21.2mm), mobile phase (80% CO_2, 20% MeOH). The fractions were collected and solvent was evaporated until dryness to give 340 mg of the first enantiomer which was crystallized in Et_2O, filtered and dried to give 288 mg of **Co. 46** (global yield: 13%). m.p.: 177°C (dsc). The second enantiomer (467 mg) was crystallized in Et_2O, filtered and dried to give 395 mg of **Co. 47** (global yield: 17%). m.p.: 177°C (dsc).

Co. 46: $[\alpha]_d$: -27.34 ° (589 nm, c 0.256 w/v %, DMF, 20 °C);

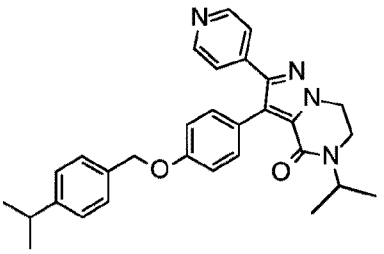
Co. 47: $[\alpha]_d$: +27.06 ° (589 nm, c 0.3585 w/v %, DMF, 20 °C).

Example A51: Preparation of Co. 48



In a sealed tube, a mixture of **98** (250 mg, 0.81 mmol), **5** (1.15 g, 3.26 mmol), K_3PO_4 (724 mg, 3.41 mmol) in 1,4-dioxane (3.8 mL) and H_2O (1.3 mL) was carefully purged with N_2. PCy_3 (48 mg, 0.171 mmol) and $Pd(OAc)_2$ (19 mg, 0.085 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 17h at 100°C. The crude material was dissolved in water (10 mL) and extracted with Et_2O (2x 40mL). The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 1.10 g of yellow oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 30 g Merck, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%). The pure fractions were collected and solvent was evaporated until dryness to give 270 mg of **Co. 48**, white solid (73%). m.p.: 155°C (dsc).

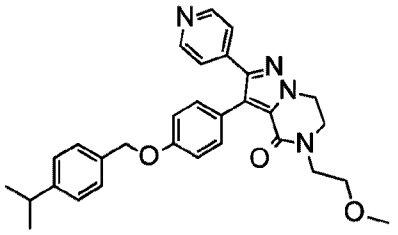
Example A52: Preparation of Co. 49



NaH 60% (41 mg, 1 mmol) was added slowly to a suspension of **Co. 1** (0.3 g, 0.68 mmol) in DMSO (4 mL) at r.t. under N_2. The mixture was stirred for 2h then 2-iodopropane (0.137 mL, 1.4 mmol) was added and stirred for 17 h. Water was added, the mixture was filtered and washed with water. The residue was dissolved in DCM,

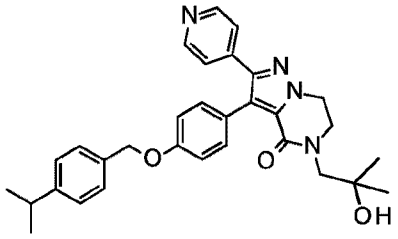
dried over $MgSO_4$, filtered and evaporated until dryness to give 0.34 g which was purified by prep. LC (irregular SiOH 12g 35-40µm GraceResolv™, mobile phase gradient from 100% DCM to 95% DCM 5% MeOH 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 203 mg of Co. 49 (62%). This batch was put together with another one (125mg) and crystallized from Et_2O, filtered and dried to give 289 mg of **Co. 49** (global yield 44%). m.p.: 168°C (dsc).

Example A53: Preparation of Co. 50



NaH 60% (55 mg, 1.4 mmol) was added slowly to a suspension of **Co. 1** (0.4 g, 0.91 mmol) in dry DMSO (5mL) at r.t. under N_2. The mixture was stirred for 2h then 2-bromo ethyl methyl ether (94 µL, 1.0 mmol) was added and the r.m. was stirred overnight. Water was added and the insoluble was filtered, then dissolved in DCM, dried over $MgSO_4$ and evaporated to give 580 mg. The residue was purified by prep. LC (Regular SiOH, 30 µm, 25 g Interchim, mobile phase gradient: DCM/MeOH/NH_4OH from 98/2/0.1 to 97/3/0.1). The pure fractions were collected and solvent was evaporated to give 390 mg of colorless oil. This oil was taken up in Et_2O and the solid formed was filtrated and dried to give 360 mg of **Co. 50**, white solid (79%). m.p.: 167°C (dsc).

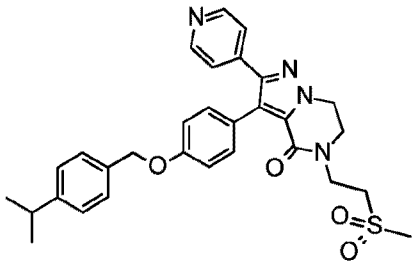
Example A54: Preparation of Co. 51



NaH 60% (0.34 g, 8.6 mmol) was added portionwise to a suspension of **Co. 1** (2.5 g, 5.7 mmol) in dry DMSO (31 mL) at r.t. under N_2. The mixture was stirred for 2h then 1-chloro-2-methyl-2-propanol (0.66 mL, 6.3 mmol) was added and the r.m. was stirred for overnight. Water was added and the insoluble was filtered, then dissolved in DCM, dried on $MgSO_4$ and evaporated until dryness to give 2.9 g, white solid. The solid was purified by prep. LC (Stationary phase: irregular SiOH 15-40µm, 300g MERCK,

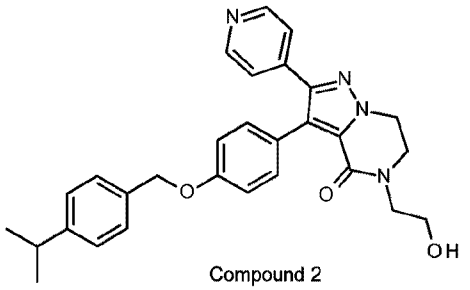
mobile phase): 0.1% NH_4OH, 98% DCM, 2% MeOH). The pure fractions were collected and the solvent was evaporated until dryness to give 290 mg of 2.1g of Co. 1 and **Co. 51**, white solid (10%). m.p. : 211°C (dsc).

Example A55: Preparation of Co. 52

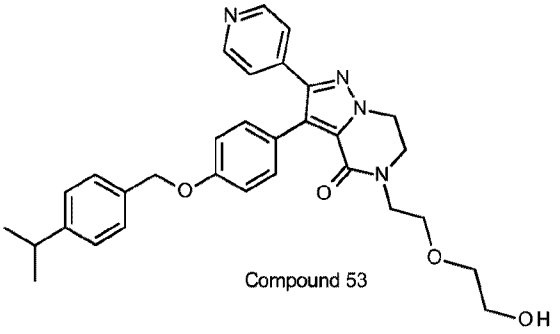


NaH 60% (53 mg, 1.3 mmol) was added slowly to a suspension of **Co. 1** (0.39 g, 0.89 mmol) in dry DMSO (5 mL) at r.t. under N_2. The mixture was stirred for 2h then 2-bromoethyl-methylsulfone (183 mg, 0.98 mmol) was added and the r.m. was stirred overnight. Water was added and the insoluble was filtered off, then dissolved in DCM and MeOH, dried on $MgSO_4$ and evaporated until dryness to give 780 mg, beige solid. The residue was purified by prep. LC (irregular SiOH 30 µm, 25 g, Interchim, Mobile phase: DCM 97%, MeOH 3%, NH_4OH 0.1%). The fractions were collected and the solvent was evaporated to give 450 mg of colorless oil. The residue was purified again by prep. LC on (Stability Silica 5µm 150x30.0mm, mobile phase gradient: from 100% DCM to NH_4OH/DCM/MeOH 0.8/92/8). The pure fractions were collected and solvent was evaporated. The white solid obtained was triturated in Et_2O, filtrated and dried to give 245 mg of **Co. 52**, white powder (51%). m.p.: 219°C (dsc).

Example A56: Preparation of Co. 2 and Co. 53



Compound 2

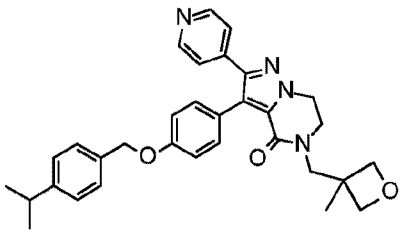


Compound 53

TBAF (23.3 mL, 23.3 mmol) was added dropwise to a sol. of **27** (11.58 g, 19.4 mmol) in THF (100 mL) at r.t.. The mixture was stirred for 15h. The mixture was evaporated until dryness to give 18 g. The residue was purified by prep. LC (330g of SiOH 35-40µm GraceResolv™, mobile phase gradient: from 100% DCM to 95% DCM 5%

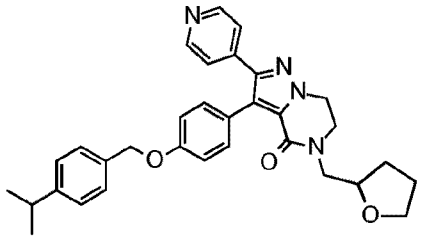
MeOH 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 8.76 g (94%). Another batch (4 g) was purified by prep. LC (120g of SiOH 35-40µm GraceResolv™, mobile phase gradient: from 100% DCM to 96% DCM 4% MeOH 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 3.11 g of a residue. Both residues (8.76 g and 3.11 g) were put together and gave 11.8 g which was crystallized from Et_2O, filtered and dried to give 10.64 g of a mixture (majority Co. 2 and 8% of Co. 53). This mixture was purified by achiral SFC (Stationary phase: Amino 6µm 150x21.2mm, mobile phase: 80% CO_2, 20% MeOH). The fractions were collected and evaporated until dryness to give 9.5 g of Co. 2 and 0.81 g of a residue. This residue was purified by achiral SFC (Stationary phase: Amino 6µm 150x21.2mm, mobile phase: 80% CO_2, 20% MeOH). The pure fractions were collected and solvent was evaporated to give 641 mg which was crystallized from Et_2O, filtered and dried to give 557 mg of **Co. 53**. m.p.: 121°C (dsc).

Example A57: Preparation of Co. 54



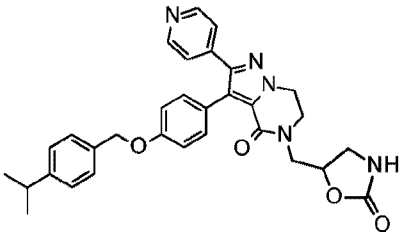
NaH 60% (54.7 mg, 1.4 mmol) was added slowly to a suspension of **Co. 1** (0.4 g, 0.9 mmol) in DMSO (5 mL) at r.t. under N_2. The mixture was stirred for 2h, then 2-(chloromethyl)-2-methyl-1,3-epoxypropane (0.12 mL, 1 mmol) was added and the r.m. was stirred for 24h. Water was added and the insoluble was filtered off. The insoluble was dissolved in DCM and MeOH, dried over $MgSO_4$ and evaporated until dryness to give 0.49 g of a residue. The residue was purified by prep. LC on (Stability Silica 5µm 150x30.0mm, mobile phase gradient from: NH_4OH/DCM/MeOH 0.2/98/2 to NH_4OH/DCM/MeOH 1/90/10). The pure fractions were collected and solvent was evaporated until dryness to give a residue (272 mg) which was crystallized from Et_2O, filtered and dried to give 256 mg of product (traces impurities). The product (256mg) was taken up with MeOH, filtered and dried to give 221mg of **Co. 54** (46%). m.p.: 204°C (dsc).

Example A58: Preparation of Co. 55



NaH 60% (55 mg, 1.4 mmol) was added portionwise to a suspension of **Co. 1** (0.4 g, 0.91 mmol) in dry DMF (5.5 mL) at r.t. under N_2. The mixture was stirred for 2h then tetrahydrofurfuryl bromide (0.18 g, 1.0 mmol) was added and the r.m. was stirred overnight. Water was added and the mixture was diluted with 150 mL of EtOAc and washed 4x with brine. The organic layer was dried on $MgSO_4$ and evaporated until dryness. The residue (0.55g) was purified by prep. LC (irregular SiOH 15-40 µm, 12 g, GraceResolv™, Mobile phase: DCM/MeOH/NH_4OH, 97/3/0.1). The fractions were collected and solvent was evaporated until dryness to give 195 mg of white solid. This fraction was purified again by prep. LC (Stationary phase: Sunfire Silica 5µm 150x30.0mm, mobile phase gradient: from 71% Heptane, 1% MeOH, 28% EtOAc to 20% MeOH, 80% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 150 mg which was crystallized from Et_2O, filtrated and dried to give 90 mg of **Co. 55**, white solid (19%). m.p.: 165°C (dsc).

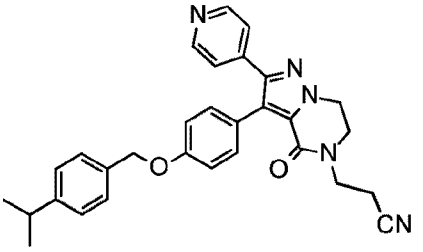
Example A59: Preparation of Co. 56



NaH 60% (82 mg, 0.21 mmol) was added slowly to a suspension of **Co. 1** (0.60 g, 1.4 mmol) in dry DMF (8.0 mL) at r.t. under N_2. The mixture was stirred for 2h then tert-butyl N-(2-oxiranyl-methyl) carbamate (355mg, 2.1mmol) was added and the r.m. was stirred overnight. Water was added and the mixture was concentrated under reduced pressure. The residue was taken up in EtOAc and washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to give 1.13g. The residue was purified by prep. LC (Stationary phase: irregular SiOH 15-40µm 300g Merck, mobile phase gradient: from 42% Heptane, 8% MeOH (+10% NH_4OH), 50% EtOAc to 40% Heptane, 10% MeOH (+10% NH_4OH), 50% EtOAc). The pure fractions were collected and the solvent was evaporated until dryness to give 390 mg of Co. 1 and 27 mg of a

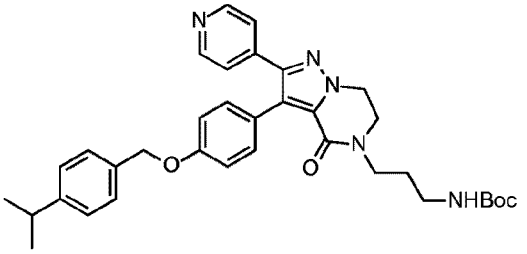
white powder residue. The residue was taken in Et_2O, triturated and the white solid formed was filtrated and dried to give 17 mg of **Co. 56** (2.3%).

Example A60: Preparation of Co. 57



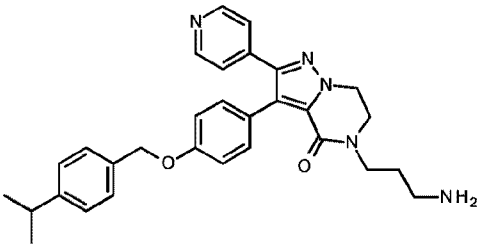
NaH 60% (55 mg, 1.4 mmol) was added portionwise to a suspension of **Co. 1** (0.40 g, 0.91 mmol) in dry DMF (5.5 mL) at r.t. under N_2. The mixture was stirred for 2h then 3-bromopropionitrile (0.13 g, 1.0 mmol) was added and the r.m. was stirred overnight at r.t. Water was added and the mixture was diluted with 150 mL of EtOAc and washed 4x with brine. The organic layer was dried on $MgSO_4$ and evaporated until dryness to give 0.62 g. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 12g, GraceResolv™, Mobile phase: DCM/MeOH/NH_4OH, 98/2/0.1). The pure fractions were collected and the solvent was evaporated until dryness to give 211 mg of colorless oil. This oil was triturated in Et_2O. The solid formed was filtered and dried to give 132 mg of **Co. 57**, white solid (29%). m.p.: 158°C (dsc).

Example A61: Preparation of Co. 58a and Co. 58



a- Synthesis of Co. 58a

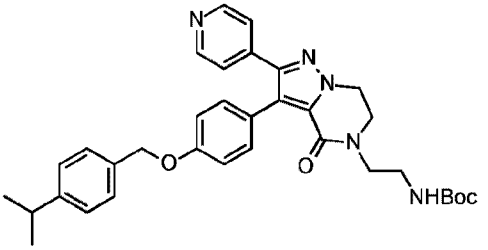
NaH 60% (68 mg, 1.7 mmol) was added slowly to a suspension of **Co. 1** (0.5 g, 1.1 mmol) in dry DMF (7.0mL) at r.t. under N_2. The mixture was stirred for 2h then tert-butyl N-(3-bromopropyl) carbamate (543 mg, 2.3 mmol) was added and the r.m. was stirred overnight. Water was added and the mixture was concentrated. The residue was taken in EtOAc and washed 3x with brine, dried and concentrated to give 680 mg of **Co. 58a**, white solid (100%). The product was used like this in the next step.



b- Synthesis of Co. 58:

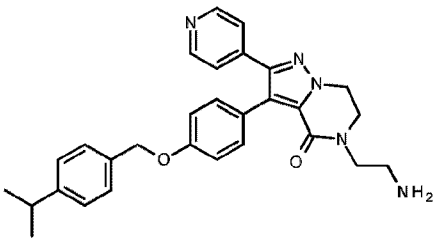
A solution of **Co. 58a** (680 mg, 1.1 mmol), HCl 3N (1.9 mL, 5.7mmol), in ACN (20mL) was stirred at 80°C for 2h. The mixture was concentrated, and $NaHCO_3$ sat aq (100 mL) was added and the mixture was stirred at r.t. for 15 min, extracted with DCM, dried and concentrated. The residue (550 mg) was purified by prep. LC (Regular SiOH, 30 µm, 12 g Interchim, mobile phase gradient: DCM/MeOH/NH_4OH from 88/12/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 340 mg as an oil. This oil was taken in Et_2O. The solid formed was filtered and dried to give 192 mg of **Co. 58**, white solid (34%).

Example A62: Preparation of Co. 238, Co. 59a and Co. 59



a- Synthesis of Co. 238

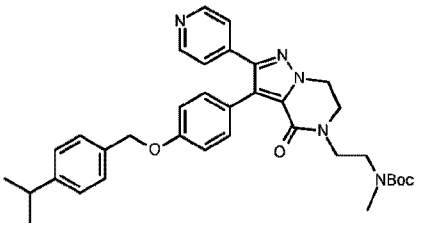
NaH 60% (0.41 g, 10.3 mmol) was added slowly to a suspension of **Co. 1** (3 g, 6.8 mmol) in dry DMSO (45 mL) at r.t. under N_2. The mixture was stirred for 2h then tert-butyl N-(2-bromoethyl) carbamate (2.3 g, 10.26 mmol) was added and the r.m. was stirred for 20h. The mixture was poured into water and EtOAc was added. The insoluble was filtered and washed with EtOAc. K_2CO_3 was added to the filtrate and the organic layer was extracted, separated and evaporated until dryness. The residue was taken up with DCM, dried over $MgSO_4$, filtered and evaporated until dryness to give 2.08 g of a residue. The residue was purified by prep. LC (Stationary phase: Irregular SiOH 20-45µm 450g MATREX, mobile phase: 40% Heptane, 10% MeOH, 50% EtOAc). The pure fractions were collected and the solvent was evaporated to give 1.2g of **Co. 238** (30%).



b- **Synthesis of Co. 59a and Co. 59:**

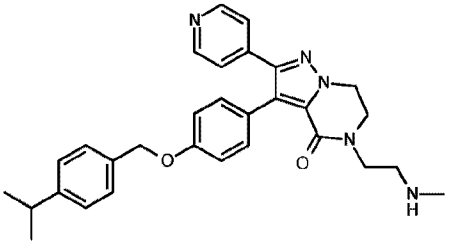
Co. 238 (650 mg, 1.12 mmol), HCl 3N (1.9mL, 5.6mmol) in ACN (20mL) was heated at 70°C for 1.5 h. The mixture was cooled to r.t. and the insoluble was filtered, washed with ACN and Et_2O and dried to give 379 mg of Co. 59a (HCl salt; .2 HCl .1.78 H_2O) (58%). Part of Co. 59a was converted to the free base (Co. 59).

Example A63: Preparation of Co. 60a and Co. 60



a- **Synthesis of Co. 60a**

NaH 60% (50.2 mg, 1.3 mmol) was added to **Co. 238** (487 mg, 0.84 mmol) in DMF (8 mL) at r.t. under N_2. The mixture was stirred for 2h, then MeI (62.5 µL, 1 mmol) was added dropwise and stirred for 2.5h. The mixture was poured into water and K_2CO_3 and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness. The residue (0.7 g) was purified by prep. LC (40g of SiOH 15µm Interchim, mobile phase gradient from 100% DCM to 96% DCM 4% MeOH 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 308 mg of **Co. 60a** (62%).

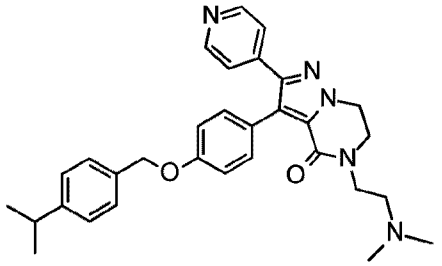


b- **Synthesis of Co. 60:**

Co. 60a (308 mg, 0.52 mmol) and HCl 3N (0.86 mL, 2.6 mmol) in ACN (10 mL) was heated at 70°C for 1.5 h, cooled to r.t. and the mixture was poured into water and K_2CO_3 and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness. The residue (0.22 g) was purified by achiral SFC (Stationary phase: Amino 6µm 150x21.2mm, mobile phase: 70% CO_2, 30% MeOH (0.3% $iPrNH_2$)). The pure fractions were collected and the solvent was evaporated until

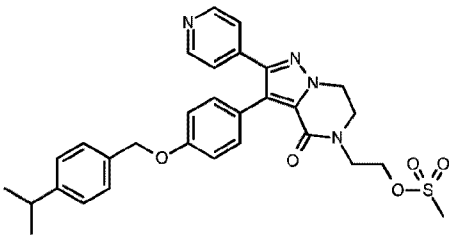
dryness to give 180 mg which was crystallized from Et_2O, filtered and dried to give 131 mg of **Co. 60** (51%).

Example A64: Preparation of Co. 61



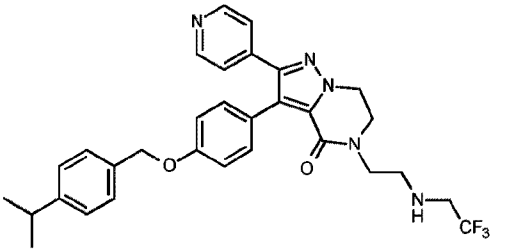
Formaldehyde (46.7 µL, 0.623 mmol) was added to a sol. of **Co. 59** (100 mg, 0.21 mmol) in DCM (2 mL) and THF (1 mL) at r.t. The mixture was stirred for 1h then sodium triacetoxyborohydride (88 mg, 0.415 mmol) was added and the r.m. was stirred for 15h. The mixture was poured into water and K_2CO_3 and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness. The residue (103 mg) was purified by prep. LC (Stationary phase: irregular 15-40µm 30g Merck, mobile phase: 1% NH_4OH, 69% toluene, 30% iPrOH). The pure fractions were collected and solvent was evaporated until dryness to give 30mg of **Co. 61** (28%).

Example A65: Preparation of Co. 62



a- Synthesis of Int. 126:

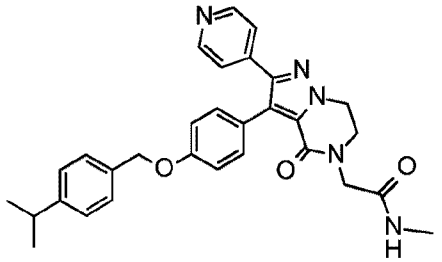
Methanesulfonyl chloride (49 µL, 0.64 mmol) was added dropwise to a sol. of **Co. 2** (205 mg, 0.43 mmol) and Et_3N (178 µL, 1.3 mmol) in dry DCM (5 mL) at 0°C under N_2 atmosphere. The r.m. was stirred at 0°C for 2h. Water was added and the mixture was extracted with DCM. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent was evaporated until dryness to give 280 mg of Int. mixture **126**, yellow solid. The solid was used in the next reaction step without further purification.



b- Synthesis of Co. 62:

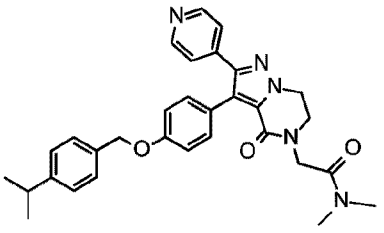
In a microwave vial, a sol. of **126** (225 mg, 0.43 mmol) in 2,2,2-trifluoroethylamine (6.3 mL, 80 mmol) was stirred at 80°C overnight. Water was added and the mixture was extracted with DCM. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent was concentrated to obtain a residue (120 mg). The aq. layer was basified with $NaHCO_3$ sat. and extracted 3x with DCM, dried and concentrated. This residue was combined with the earlier residue (120 mg) to give 220 mg of yellow oil. This oil was purified by prep. LC (Stationary phase: Stability Silica 5µm 150x30.0mm, mobile phase: Gradient from 100% DCM to NH_4OH/DCM/MeOH 0.9/91/9). The pure fractions were collected and evaporated until dryness to give 46 mg of **Co. 62**, beige solid (17%).

Example A66: Preparation of Co. 63



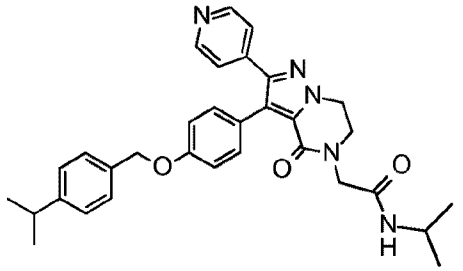
NaH 60% (27.4 mg, 0.68 mmol) was added to a sol. of **Co. 1** (200 mg, 0.46 mmol) in DMSO (4 mL) at r.t. under N_2. The mixture was stirred for 2h. 2-bromo-N-methylacetamide (104 mg, 0.68 mmol) was added and stirred for 15h. The mixture was poured into water and extracted with EtOAc (another batch with 102mg of initial reactant, Co. 1 was put together for work up). The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness to give 0.35g. The residue was purified by prep. LC on (Stability Silica 5µm 150x30.0mm, mobile phase gradient: from NH_4OH/DCM/MeOH 0.2/98/2 to NH_4OH/DCM/MeOH 0.8/92/8). The pure fractions were collected and solvent was evaporated to give 290 mg which was crystallized from Et_2O, filtered and dried to give 233 mg of **Co. 63**, (global yield : 66%). m.p.: 161°C (dsc).

Example A67: Preparation of Co. 64



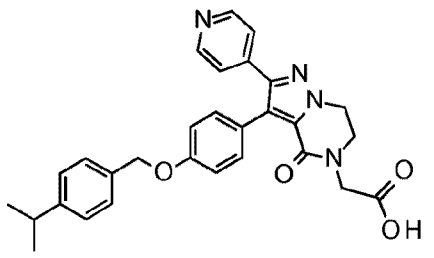
NaH 60% (72 mg, 1.8mmol) was added portionwise to a suspension of **Co. 1** (0.52 g, 1.2 mmol) in dry DMF (7.1 mL) at r.t. under N_2. The mixture was stirred for 2h then N,N-dimethylchloroacetamide (0.18 mL, 1.8 mmol) was added and the r.m. was stirred overnight at r.t. Water was added and the mixture was concentrated under reduced pressure. The residue was taken in EtOAc and washed 5x with brine. The organic layer was dried over $MgSO_4$, filtrated and concentrated. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 25 g, Interchim, mobile phase: DCM/MeOH/NH_4OH, 97/3/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 0.46 g of colorless oil. This oil was triturated in Et_2O. The solid formed was filtered and dried to give 390 mg of **Co. 64**, white solid (63%).

Example A68: Preparation of Co. 65



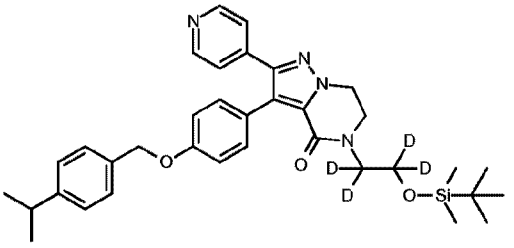
NaH 60% (72 mg, 1.8 mmol) was added portionwise to a suspension of **Co. 1** (0.52 g, 1.2 mmol) in dry DMF (7.1 mL) at r.t. under N_2. The mixture was stirred for 2h then N-isopropyl-2-chloroacetamide (0.24 g, 1.8 mmol) was added and stirred overnight at r.t. Water was added and the mixture was concentrated under reduced pressure. The residue was taken in EtOAc and washed 5x with brine. The organic layer was dried over $MgSO_4$, filtrated and concentrated to give 0.7 g. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 25 g, GraceResolv™, mobile phase: DCM/MeOH/NH_4OH, 97/3/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 500 mg of colorless oil. This oil was triturated in Et_2O. The solid formed was filtered and dried to give to give 312 mg of **Co. 65**, white solid (49%).

Example A69: Preparation of Co. 66



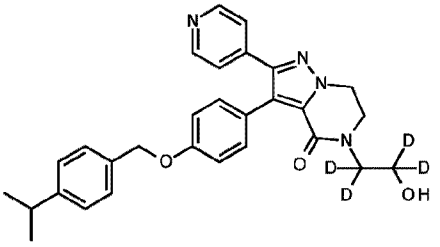
NaH 60% (68 mg, 1.7 mmol) was added slowly to a suspension of **Co. 1** (0.50 g, 1.1 mmol) in dry DMSO (6.3 mL) at r.t. under N_2. The mixture was stirred for 2h and then methylbromoacetate (0.12 mL, 1.25 mmol) was added and stirred overnight. Water was added and the mixture was concentrated under reduced pressure. The solid obtained was triturated in EtOAc and the white solid formed was filtered and dried to give 400 mg of beige solid (70%). 290 mg of solid was used in a next step, and the other 110 mg was taken in water, the aq. layer was acidified with HCl 3N and extracted with DCM. The organic layer was dried on $MgSO_4$, filtered and evaporated to give 75 mg of **Co. 66**, white solid.

Example A70: Preparation of Co. 67



a- Synthesis of Int. 127:

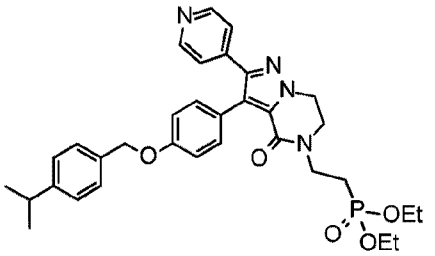
NaH 60% (68 mg, 1.7 mmol) was added slowly to a suspension of **Co. 1** (0.5 g, 1.1 mmol) in dry DMF (7.0 mL) at r.t. under N_2. The mixture was stirred for 2h then (2-bromoethoxy-1,1,2,2-d_4)(1,1-dimethylethyl)dimethyl-silane (554 mg, 2.3 mmol) was added and the r.m. was stirred overnight. Water was added and the mixture was concentrated. The residue was taken in EtOAc and washed 3x with brine, dried over $MgSO_4$, filtered and concentrated to give 750 mg of Int. **127**, yellow oil as a mixture which was used like this in the next step.



b- Synthesis of Co. 67:

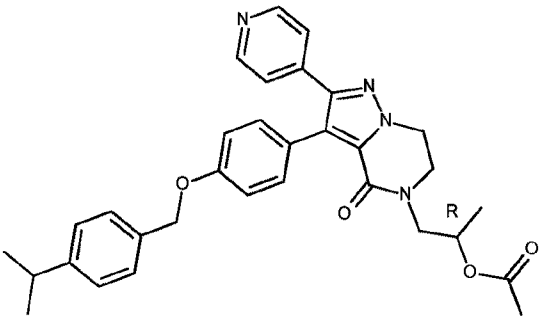
TBAF (1.0 mL, 1.0 mmol) was added dropwise to a sol. of **127** (0.75 g, 0.88 mmol) in THF (8.5 mL) at r.t. The mixture was stirred overnight at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 µm, 25 g GraceResolv™, mobile phase: DCM/MeOH/NH_4OH 96/4/0.1). The pure fractions were collected and the solvent was evaporated until dryness to give 360 mg of colorless oil which was triturated in Et_2O. The white solid formed was filtered, washed and dried to give 0.286 g of **Co. 67**, white solid (67%). m.p.: 179°C (dsc).

Example A71: Preparation of Co. 68



NaH 60% (27.4 mg, 0.68 mmol) was added to **Co. 1** (0.2 g, 0.46 mmol) in DMSO (2.8 mL) at r.t. under N_2. The mixture was stirred for 2h then diethyl-2-bromoethylphosphonate (0.13 mL, 0.68 mmol) was added and the r.m. was stirred for 20h. The mixture was poured into water, K_2CO_3 was added and extracted with EtOAc. The organic layer was evaporated until dryness. The residue was taken up with EtOAc and water. The organic layer was extracted, dried over $MgSO_4$, filtered and evaporated. The residue (0.27 g) was purified by prep. LC (25g of irregular SiOH 35-40µm GraceResolv™, mobile phase gradient from 100% DCM to 95% DCM 5% MeOH 0.1% NH_4OH). The pure fractions were collected and evaporated to give 0.2g which was crystallized from DIPE, filtered and dried to give 137 mg of **Co. 68** (50%). m.p.: 90°C (dsc).

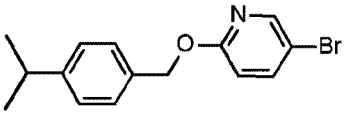
Example A72: Preparation of Co. 69



NaH 60% (480 mg, 12 mmol) was added slowly to a suspension of **Co. 1** (3.5 g, 8.0 mmol) in dry DMF (47 mL) at r.t. under N_2. The mixture was stirred for 2h then (R)-(+) propylene oxide (1.1 mL, 16 mmol) was added and stirred overnight. Water was added and the mixture was concentrated under reduced pressure. The residue was taken in EtOAc and washed 5x with brine. The organic layer was dried on $MgSO_4$, filtrated and concentrated to give 5.9 g. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 120 g GraceResolv™, mobile phase gradient: from 100% DCM to DCM 95%, MeOH 5%). The fractions were collected and evaporated until dryness to give 1.2g of initial reactant Co. 1 and a residue which was purified by prep. LC (Stationary phase: irregular SiOH 15-40µm 300g MERCK, mobile phase: 42% Heptane, 8%

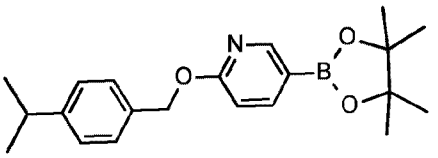
MeOH (+10% NH_4OH), 50% EtOAc). The pure fractions were collected and the solvent was evaporated to give 1.02 g which was triturated in Et_2O and the white solid formed was filtrated and dried to give 450 mg of **Co. 69** (R) (10%).

Example A73: Preparation of Co. 71



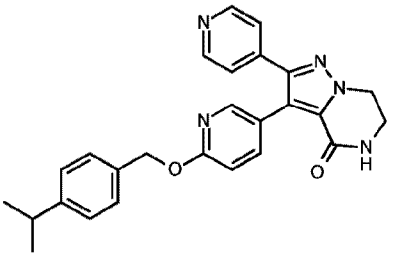
a- Synthesis of Int. 128:

A sol. of **6** (3.1 g, 20 mmol) in dry DMF (50 mL) was treated at 0°C with NaH 60% (818 mg, 20 mmol). After stirring for 1h at r.t., 5-bromo-2-fluoropyridine (3.0 g, 17 mmol) was added and the r.m. was stirred at r.t. for 3 days. The r.m. was quenched with water 200mL and the white solid formed was filtrated. This solid was solubilized in EtOAc and dried on $MgSO_4$, filtrated and concentrated to give 5.9 g of Int. **128**, white solid (100%).



b- Synthesis of Int. 129:

BisPin (5.2 g, 20 mmol) and KOAc (3.3 g, 34 mmol) were added to a sol. of **128** (5.2 g, 17 mmol) in 1,4-dioxane (57 mL). The sol. was purged with N_2 and charged with $PdCl_2(PPh_3)_2$ (0.60 g, 0.85 mmol). The resulting sol. was purged again with N_2 and stirred at 80°C for 17h. After dilution in EtOAc, the crude material was washed with water and brine. The organic layer was dried over $MgSO_4$ and evaporated to afford 12 g of brown oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 120 g GraceResolv™, mobile phase: heptane/EtOAc 80/20). The pure fractions were collected and solvent was evaporated to give 5.6 g of Int. **129**, brown solid (93%).

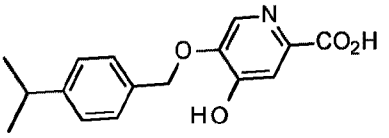


c- Synthesis of Co. 71:

In a Schlenk tube, a mixture of **4** (150 mg, 0.512 mmol), **129** (452 mg, 1.28 mmol), K_3PO_4 (434 mg, 2.05 mmol) in 1,4-dioxane (3.75 mL) and H_2O (1.5 mL) was carefully purged with N_2. $Pd(OAc)_2$ (11 mg, 51.2 µmol) and PCy_3 (29 mg, 102 µmol) were added and the r.m. was purged again with N_2. The Schlenk tube was then sealed and the

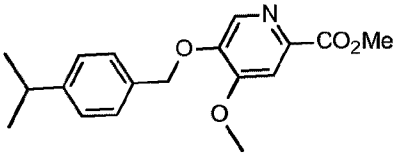
r.m. was stirred for 17 h at 80°C. The crude mixture was then diluted in DCM and washed with water (2 x 10mL). The organic layer was collected, dried over $MgSO_4$ and evaporated *in vacuo* to afford brown oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 50 g Merck, Mobile phase gradient: from 100% DCM to DCM 95%, MeOH 5%). The pure fractions were collected and solvent was evaporated until dryness to give 169 mg of **Co. 71**, white solid (75%). m.p.: 199 °C (dsc).

Example A74: Preparation of Co. 72



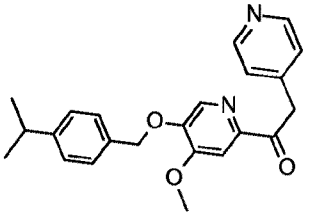
a- Synthesis of Int. 130:

A sol. of 5-[[4-(1-methylethyl)phenyl]methoxy]-4-oxo-4*H*-pyran-2-carboxylic acid (2.82 g, 9.78 mmol) in NH_3 (28% in water) (18 mL) was stirred at 90 °C for 4h. Then the solvent was evaporated *in vacuo* to afford 2.13 g of Int. **130**, brown solid (76%).



b- Synthesis of Int. 131:

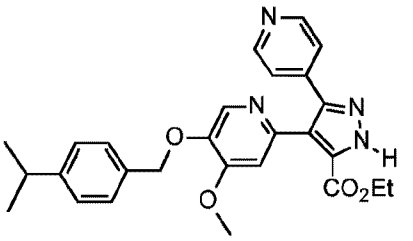
(Trimethylsilyl)diazomethane, 2M in hexane (10.4 mL, 20.8 mmol) was added to a stirred sol. of **130** (1.05 g, 3.66 mmol) in MeOH (5 mL) and toluene (20 mL) at 0°C under N_2. The crude mixture was stirred warming to r.t. for 1 h, and then water and EtOAc were added. The organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford 830 mg of a brown solid. Another batch, 400mg was combined to 830mg, and the mixture was purified by prep. LC (irregular SiOH 15-40 µm, 45 g Grace, mobile phase gradient: from EtOAc 10%, Heptane 90% to EtOAc 75%, Heptane 25%). The pure fractions were collected and solvent was evaporated until dryness to give 370 mg of Int. **131** (global yield: 22%).



c- Synthesis of Int. 132:

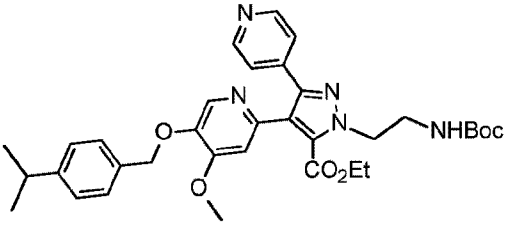
In a dry flask under N_2, a sol. of **131** (283 mg, 0.897 mmol) and 4-picoline (0.140 mL, 1.44 mmol) in THF (7 mL) was cooled to 0°C and treated with LiHMDS (1.80 mL, 1.80 mmol). The r.m. was stirred at r.t. for 20 h. The crude mixture was quenched with an aq. sol. of NH_4Cl, and EtOAc was added. The organic layer was washed with brine,

dried over $MgSO_4$, filtered and evaporated *in vacuo* to yield 295 mg of Int. **132**, a brown solid (66%) which was used as such in the next reaction step.



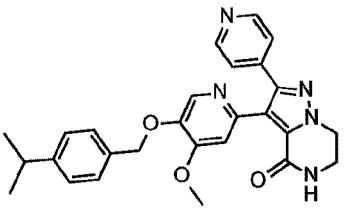
d- Synthesis of Int. 133:

A suspension of **132** (287 mg, 0.572 mmol) in ACN (5 mL) was treated with DBU (103 µL, 0.686 mmol) then with ethyl diazoacetate (96 µL, 0.915 mmol). The r.m. was stirred at r.t. for 20 h. Then, EtOAc and water were added, and the organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and evaporated *in vacuo* to yield 330 mg of a brown solid. The solid was purified by prep. LC (irregular SiOH 15-40 µm, 24 g, GraceResolv™, mobile phase gradient: from DCM 100% to DCM 93%, MeOH 7%). The pure fractions were collected and solvent was evaporated until dryness to give 169 mg of Int. **133**, pale yellow solid (63%).



e- Synthesis of Int. 134:

DBAD (123 mg, 0.533 mmol) was added to a stirred sol. of **133** (140 mg, 0.296 mmol), Boc-glycinol (86 mg, 0.533 mmol) and PPh_3 (140 mg, 0.533 mmol) in dry DCE (3 mL) at r.t. under N_2. The r.m. was stirred at r.t. for 20 h, and then water and EtOAc were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 490 mg of yellow oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 24 g, GraceResolv™, mobile phase gradient: from DCM 100% to EtOAc 100%). The pure fractions were collected and solvent was evaporated until dryness to give 203 mg of Int. **134**, viscous yellow solid (100%).

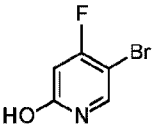


f- Synthesis of Co. 72:

A sol. of **134** (190 mg, 0.309 mmol) and HCl 3N (0.514 mL, 1.54 mmol) in ACN (5 mL) was stirred at 80°C for 90 min. Then, EtOAc and a sat. sol. of $NaHCO_3$ were

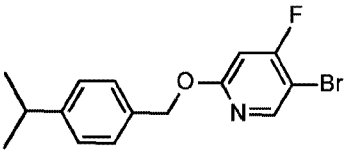
added, and the r.m. was stirred at r.t. for 20h. Water and more EtOAc were added, and the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue (114 mg) was purified by prep. LC (Irregular SiOH 50 µm, 10 g Grace, mobile phase gradient: from DCM 100% to DCM 92%, MeOH 8%). The fractions were collected and evaporated *in vacuo* to give 79 mg of a white solid. This solid was dissolved in MeOH, and the solvent was allowed to evaporate slowly. After crystallization, the remaining solvent was removed. The solid was dried for 4h, yielding 70 mg of **Co. 72**, white solid (48%). m.p.: 231 °C (DSC).

Example A75: Preparation of Co. 73



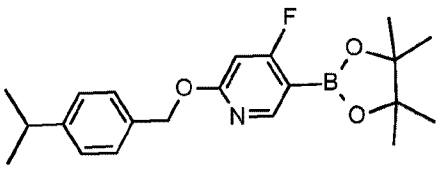
a- Synthesis of Int. 135:

To a sol. of 2-hydroxy-4-fluoropyridine (1.0 g, 8.8 mmol) in ACN (23 mL) was added dropwise N-bromosuccinimide (1.6 g, 8.8 mmol) in ACN (23 mL) at r.t. in darkness. The sol. was stirred at r.t. for 3 days. The solvent was removed *in vacuo*. EtOAc and a sat. aq. sol. of brine were added to the residue, the organic layer was washed, separated, dried on $MgSO_4$, filtered and evaporated *in vacuo* to give 1.44 g of a white solid. This solid was taken in DCM and the solid was filtered. The filtrate was concentrated and the purification was carried out by prep. LC (Interchim, 40 g, mobile phase: DCM/MeOH/NH_4OH, 96/4/0.1). The pure fractions were collected and the solvent was evaporated until dryness to give 540 mg of Int. **135**, white solid (32%).



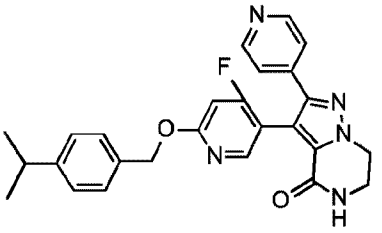
b- Synthesis of Int. 136:

8 (0.49 mL, 2.9 mmol) was added to a sol. of **135** (0.54 g, 2.0 mmol) and Ag_2CO_3 (2.3 g, 8.4 mmol) in ACN (15mL). The mixture was stirred overnight at 80 °C. The mixture was filtrated on celite® and the filtrate was concentrated to give 0.76 g, white oil. This oil was taken in DCM and the white solid was filtrated off. The filtrate was concentrated and it was purified by prep. LC (irregular SiOH 15-40 µm, 25 g GraceResolv™, mobile phase gradient: heptane/EtOAc from 100/0 to 93/7). The pure fractions were collected and solvent was evaporated until dryness to give 350 mg of Int. **136**, colorless oil (39%).



c- **Synthesis of Int. 137:**

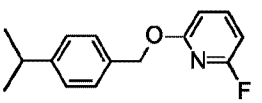
In a microwave vial, BisPin (0.33 g, 1.3 mmol) and KOAc (0.21 g, 2.2 mmol) were added to a sol. of **136** (0.35 g, 1.1 mmol) in 1,4-dioxane (3.6 mL). The sol. was purged with N_2 and charged with $PdCl_2$(dppf) (38 mg, 54 µmol). The resulting sol. was purged again with N_2 and stirred at 80°C for 17h. After dilution in EtOAc, the crude material was washed with water and brine. The organic layer was dried over $MgSO_4$ and evaporated to afford 680 mg of dark oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 12 g GraceResolv™, mobile phase: heptane/EtOAc 90/10). The pure fractions were collected and evaporated until dryness to give 390 mg of Int. **137**, colorless oil (97%).



d- **Synthesis of Co. 73:**

In a microwave vial, a mixture of **4** (0.26 g, 0.88 mmol), **137** (0.39 g, 1.1 mmol), K_3PO_4 (0.74 g, 3.5 mmol) in 1,4-dioxane (3.8 mL) and H_2O (1.4 mL) was carefully purged with N_2. $PdCl_2$(dppf) (72 mg, 88 µmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 550 mg, brown solid. The solid was purified by prep. LC (Stationary phase: Spherical bare silica 5µm 150x30.0mm, mobile phase gradient: from NH_4OH/DCM/MeOH 0.1/99/1 to NH_4OH/DCM/MeOH 0.7/93/7). The pure fractions were collected and solvent was evaporated until dryness to give 61 mg of colorless product which was crystallized from Et_2O. The solid was filtrated and dried to give 33 mg of **Co. 73**, white solid (8%). m.p.: 207°C (dsc).

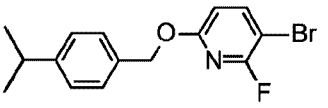
Example A76: Preparation of Co. 74



a- **Synthesis of Int. 138:**

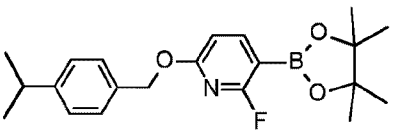
A sol. of **6** (3.1 g, 20 mmol) in dry DMF (60 mL) was treated at 0°C with NaH 60% (0.99 g, 25 mmol). After stirring for 1h at r.t., 2,6-difluoro-pyridine (2.4 g, 21 mmol)

was added and the r.m. was stirred at r.t. overnight. The r.m. was quenched with water 200 mL and the mixture was extracted with DCM 3x. The organic layer was dried and concentrated to give 5.7 g of Int. **138**, colorless oil (100%, purity 89%) which was used like this in the next step.



b- Synthesis of Int. 139:

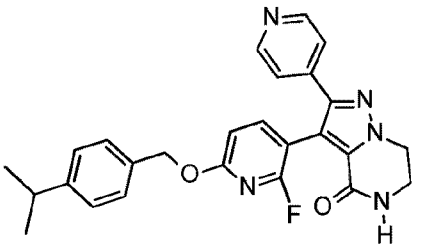
To a sol. of **138** (4.7 g, 17 mmol) in ACN (60 mL) was slowly added N-bromosuccinimide (3.0 g, 17 mmol) in ACN (60 mL) at r.t. The sol. was stirred at 80°C overnight. The solvent was removed *in vacuo* and the residue was taken in EtOAc and washed with NaCl sat, $NaHCO_3$, filtrated and dried. The residue and the mixture was purified by prep. LC (irregular SiOH 15-40 µm, 120 g Interchim, mobile phase: heptane/EtOAc, 98/2). The fractions were collected and solvent was evaporated to give 3.0 g. This fraction was purified by prep. LC (irregular SiOH 15-40 µm, 40 g Interchim, mobile phase: heptane/EtOAc, 98/2). The pure fractions were collected and solvent was evaporated until dryness to give 2.6 g Int. **139**, colorless oil (47%, purity: 80%) which was used such as for the next step.



c- Synthesis of Int. 140:

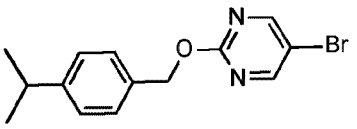
BisPin (0.94 g, 3.7 mmol) and KOAc (0.61 g, 6.2 mmol) were added to a sol. of **139** (1g, 3.1 mmol) in 1,4-dioxane (10 mL). The sol. was purged with N_2 and charged with $PdCl_2(dppf)$ (0.11 g, 0.15 mmol). The resulting sol. was purged again with N_2 and stirred at 80°C for 17h. After dilution in EtOAc, the crude material was washed with water and brine. The organic layer was dried over $MgSO_4$ and evaporated to afford dark oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 25 g GraceResolv™, mobile phase: heptane/EtOAc 90/10). The fractions were collected and solvent was evaporated until dryness to give 1.1 g of Int. **140**, yellow oil (48%, purity 50%) which was used like this in the next step.

d- Synthesis of Co. 74 :



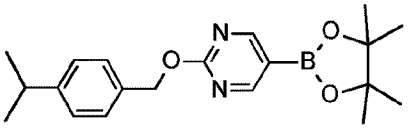
In a microwave vial, a mixture of **4** (0.72 g, 2.5 mmol), **140** (1.1 g, 3.0 mmol), K_3PO_4 (2.1 g, 10 mmol) in 1,4-dioxane (11 mL) and H_2O (4 mL) was carefully purged with N_2. $PdCl_2$(dppf) (200 mg, 0.25 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give a brown solid. It was purified by prep. LC (irregular SiOH 15-40 µm, 40 g GraceResolv™, mobile phase: DCM 96%, MeOH 4%). The fractions were collected and solvent was evaporated until dryness to give 610 mg of white solid. The solid was purified by prep. LC (Stationary phase: Spherical bare silica 5µm 150x30.0mm, mobile phase gradient: from NH_4OH/DCM/MeOH 0.2/98/2 to NH_4OH/DCM/MeOH 0.9/91/9). The pure fractions were collected and solvent was evaporated until dryness to give 152 mg of a white solid which was triturated with Et_2O. The solid was filtrated and dried to give 0.129 g of **Co. 74**, white solid (11%, mp: 275°C).

Example A77: Preparation of Co. 75



a- Synthesis of Int. 141:

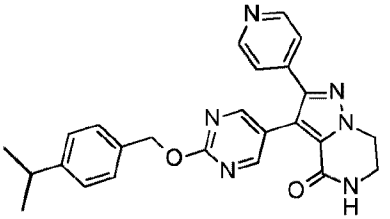
A sol. of **6** (4.66 g, 31.0 mmol) in dry THF (200 mL) was treated with NaH 60% (1.29 g, 32.3 mmol) and stirred at r.t. for 10 min. 5-bromo-2-chloropyrimidine (5.00 g, 25.8 mmol) was then added and the r.m. was stirred at r.t. for 17 h. The r.m. was then heated at 70°C for 5 extra h and concentrated *in vacuo*. The concentrate was taken up with EtOAc, washed with water and brine, dried over $MgSO_4$ and evaporated *in vacuo* to give yellow oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 80 g, Grace, dry loading, mobile phase: heptane 80% to EtOAc 20%). The pure fractions were collected and solvent was evaporated to give 5.92g of Int. **141**, white solid (75%).



b- Synthesis of Int. 142:

In a Schlenk tube, a sol. of **141** (3.0 g, 9.77 mmol), BisPin (4.96 g, 19.5 mmol) and KOAc (2.88 g, 29.3 mmol) in DME (60 mL) was purged with N_2. $PdCl_2$(dppf) (800 mg, 0.977 mmol) was added to the mixture and the mixture was purged with N_2 again. The reaction was heated at 110°C for 17 h then poured in EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and evaporated *in vacuo* to give a black residue. The residue was filtered through a short pad of silica gel (eluent: EtOAc

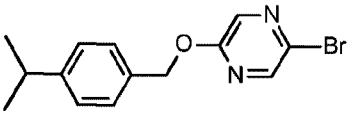
100%) and the filtrate was evaporated *in vacuo* to give a brown solid. This solid was purified by prep. LC (irregular SiOH 15-40 µm, 80 g, Grace, dry loading, mobile phase: heptane 80% to EtOAc 20%). The pure fractions were collected and solvent was evaporated to give 2.20g of Int. **142**, white solid (64%).



c- Synthesis of Co. 75:

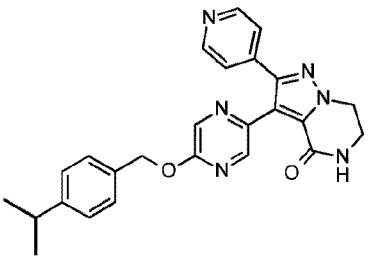
A sol. of **4** (400 mg, 1.37 mmol) and **142** (967 mg, 2.73 mmol) in 1,4-dioxane (8 mL) and H_2O (4 mL) was treated with K_3PO_4 (869 mg, 4.09 mmol) and purged with N_2. $PdCl_2(dppf)$ (112 mg, 137 µmol) was then added and the r.m. was carefully purged with N_2. The mixture was heated at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 20 min [fixed hold time]. The r.m. was poured in DCM/MeOH (95/5) and washed with water and brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a black residue which was purified by prep. LC (irregular SiOH 15-40µm, 45g, Merck, dry loading, mobile phase gradient: from DCM 100% to DCM 92%, MeOH 8%). The pure fractions were collected and solvent was evaporated until dryness to give 170mg of an off-white solid. The solid was crystallized from EtOH, filtered on a glass frit and washed with Et_2O. The solid was collected and dried *in vacuo* to give 145 mg of a white solid which was solubilized in MeOH. The solvent was allowed to evaporate slowly overnight. The solid was triturated in Et_2O, filtered and dried *in vacuo* to give 132 mg of **Co. 75** (white solid; 22%). m.p.: 126°C (dsc).

Example A78: Preparation of Co. 76



a- Synthesis of Int. 143:

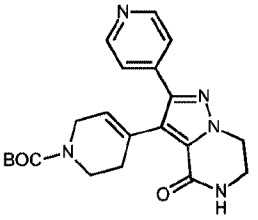
Under N_2, a sol. of 2,5-dibromopyrazine (1.97 g, 8.28 mmol) and **6** (1.57 mL, 9.94 mmol) in dry DMF (45 mL) was treated with NaH 60% (397 mg, 9.94 mmol) and stirred at r.t. for 18 h. The r.m. was poured in EtOAc and water, and the organic layer was washed with brine (twice), dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 2.83 g, brown oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 120 g, GraceResolv™, mobile phase gradient: from heptane 100% to heptane 50%, EtOAc 50%). The pure fractions were collected and solvent was evaporated until dryness to give 2.25 g of Int. **143**, yellow oil (88%).



b- Synthesis of Co. 76:

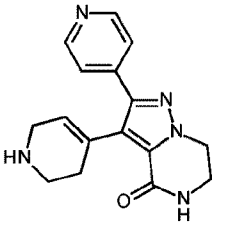
A mixture of **60** (304 mg, 0.894 mmol), **143** (549 mg, 1.79 mmol), K_3PO_4 (569 mg, 2.68 mmol) in THF (6 mL) and H_2O (3 mL) was carefully purged with N_2. Precatalyst (70 mg, 89.4 µmol) was added and the r.m. was purged again with N_2. The r.m. was stirred at r.t. for 66h, and then a sol. of DCM/MeOH 95:5 and water were added. The organic layer was washed with brine, separated and evaporated *in vacuo* to afford 3.00 g of a solid. The solid was diluted in a sol. of DCM/MeOH 50:50, and filtered off. The filtrate was evaporated *in vacuo* to yield 930 mg of a pale yellow solid. This solid was purified by prep. LC (Irregular SiOH 50 µm, 40 g Grace, mobile phase gradient: from DCM 100% to DCM 91%, MeOH 9%). The desired fractions were collected and evaporated *in vacuo* to give 188 mg of a white solid. The residue was purified by achiral SFC (Stationary phase: 2-ethylpyridine 6µm 150x30mm, mobile phase: 85% CO_2, 15% MeOH (0.3% $iPrNH_2$). The pure fractions were collected and solvent was evaporated until dryness to yield 126 mg which was crystallized from EtOH. The solid was filtered, washed with Et_2O, and dried *in vacuo* to yield 81 mg of **Co. 76**, white solid (21%). m.p.: 225 °C (dsc).

Example A79: Preparation of Co. 77



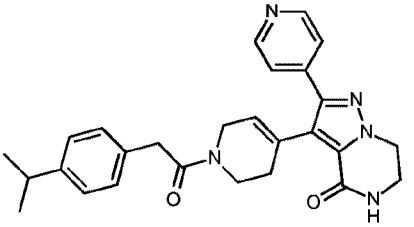
a- Synthesis of Int. 153:

4 (1.9 g, 6.5 mmol), N-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (2 g, 6.5 mmol), Na_2CO_3 (13 mL, 13 mmol) in 1,4-dioxane (21 mL) were degassed with N_2. $PdCl_2(dppf)$ (0.53 g, 0.65 mmol) was added and heated to 110°C in sealed tube for 20h. The mixture was poured into water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness to give 3.5g. The residue was purified by LC prep. (80g of SiOH 30µm Interchim, mobile phase gradient: from 100% DCM to 90/10/0.1 DCM/CH_3OH/NH_4OH). The pure fractions were collected and evaporated until dryness to give 2.3g of Int. **153** (89%).



b- Synthesis of Int. 154:

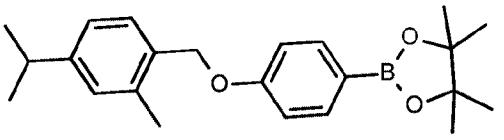
HCl 3N (9.7 mL, 29.08 mmol) was added to **153** (2.3 g, 5.8 mmol) in ACN (100 mL). The mixture was heated for 30min at 80°C and poured into water, basified with K_2CO_3 and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness to give 0.62 g of Int. **154** (36%).



c- Synthesis of Co. 77:

4-(1-methylethyl)-benzeneacetyl chloride (0.31 g, 1.56 mmol) in DCM (4 mL) was added dropwise to a sol. of **154** (384 mg, 1.3 mmol), Et_3N (0.27 mL, 1.95 mmol) in DCM (11 mL) at 5°C. The mixture was stirred for 15h and poured into water. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated to give a residue (0.63 g) which was purified by prep. LC (40g of SiOH 15µm Interchim, mobile phase gradient from 100% DCM to 90% DCM 10%, MeOH 0.1%, NH_4OH). The fractions were collected and evaporated until dryness to give 315mg which was crystallized from Et_2O, filtered and dried to give 246 mg of **Co. 77** (41%).

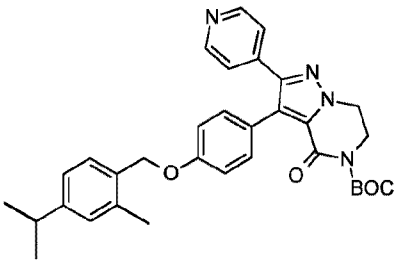
Example A80: Preparation of Co. 78a and Co. 78



a- Synthesis of Int. 155:

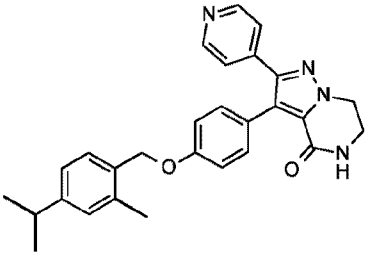
To a sol. of 2-methyl-4-(1-methylethyl)-benzenemethanol (0.97 g, 5.9 mmol), **7** (1.3 g, 5.9 mmol), PPh_3 (1.7 g, 6.5 mmol) in dry DCM (40 mL) was added DBAD (1.5 g, 6.5 mmol) and the r.m. was stirred at r.t. for 2 days. The mixture was poured into water and the organic layer was extracted, dried over $MgSO_4$, filtered and evaporated until dryness to give 6 g. The residue was tritured in heptane and the solid formed was filtered off. The filtrate was concentrated and injected to be purified by prep. LC (80g of irregular SiOH 35-40µm GraceResolv™, mobile phase gradient: from 100% heptane

to 80% heptane 20% EtOAc). The fractions were collected and evaporated until dryness to give 1.7g of Int. **155** (78%)



b- Synthesis of Co. 78a:

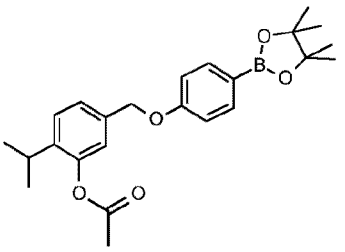
25 (0.97 g, 2.5 mmol), **155** (0.94 g, 2.5mmol), K_3PO_4 (2.1 g, 9.8 mmol) in 1,4-dioxane (13 mL) and H_2O (3.5 mL) were purged with N_2 for 10min. Then, $PdCl_2(dppf)$ (0.2 g, 0.25 mmol) was added and purged with N_2 for 10min. The mixture was heated to 75°C for 15h, cooled to r.t., poured into water and K_2CO_3 and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and dried to give 1.9 g. The residue was purified by prep. LC (40g of irregular SiOH 35-40µm GraceResolv™, mobile phase gradient: from 100% DCM to 90% DCM 10% MeOH 0.1% NH_4OH). The pure fractions were collected and solvent was evaporated until dryness to give 510 mg of **Co. 78a** (37%).



c- Synthesis of Co. 78:

Co. 78a (510 mg, 0.92 mmol), ACN (24 mL), HCl 3N (3 mL) were heated to 80°C for 1h. The mixture was cooled to r.t., poured into water and basified with K_2CO_3 and EtOAc was added. The insoluble was filtered and the organic layer was separated, dried over $MgSO_4$, filtered and evaporated until dryness. The residue was purified by prep. LC (40g of SiOH 30µm Interchim, mobile phase gradient: from 100% DCM to 90% DCM 10% MeOH 0.1% NH_4OH). The pure fractions were collected and evaporated until dryness to give 153 mg which was crystallized from Et_2O, filtered and dried to give 136 mg of **Co. 78** (33%). m.p.: 247°C (dsc).

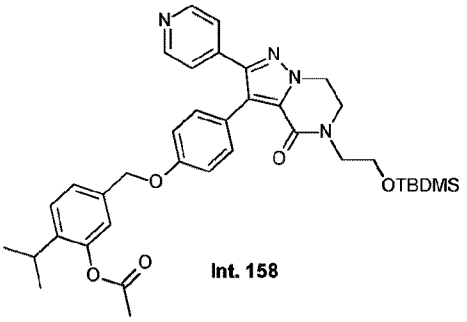
Example A81: Preparation of Co. 79



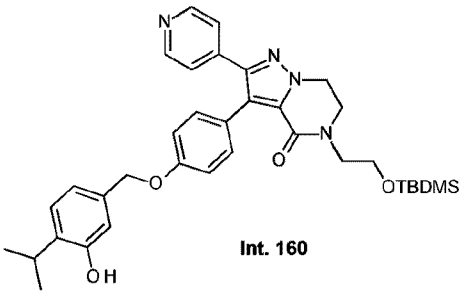
a- **Synthesis of Int. 157:**

To a suspension of 3-(acetoxy)-4-(1-methylethyl)-benzenemethanol (498 mg, 2.39 mmol), 7 (632 mg, 2.87 mmol), PPh_3 supp. (661 mg, 2.87 mmol) in dry DCM (10 mL) was added DBAD (897 mg, 2.87 mmol) and the r.m. was stirred at r.t. for 18 h. The insoluble was filtered through Celite®, washed with DCM. Water was added and the organic layer was separated, dried, filtered and concentrated to give 1.66 g. The residue was purified by prep. LC on (Irregular SiOH 30µm 40g Interchim, mobile phase gradient: from Heptane 95/EtOAc 5 to Heptane 90/EtOAc 10). The pure fractions were collected and evaporated until dryness to give 413 mg of Int. **157** (42%).

b- **Synthesis of Int. 158 and Int. 160:**



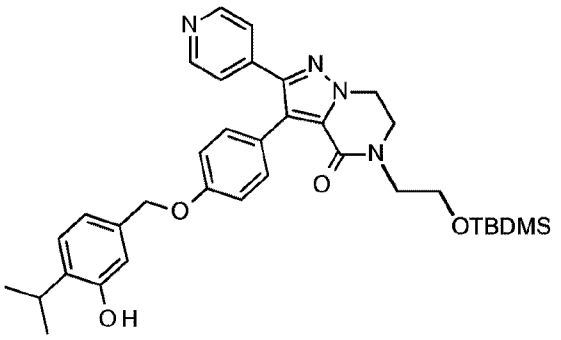
Int. 158



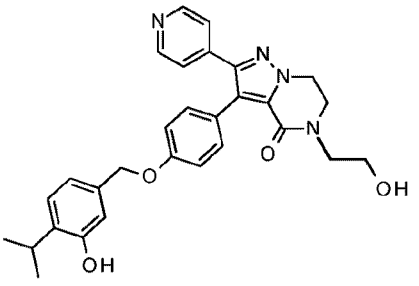
Int. 160

In a microwave vial, a mixture of **28** (0.413 g, 0.92 mmol), **157** (0.413 g, 1 mmol), K_3PO_4 (0.78 g, 3.7 mmol) in 1,4-dioxane (4 mL) and H_2O (1.43 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (75 mg, 0.09 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 792 mg. The residue was purified by prep. LC (irregular SiOH 30 µm, 40 g Interchim, mobile phase gradient: from DCM 100% to DCM/MeOH/NH_4OH 95/5/0.1). The fractions were collected and solvent was evaporated until dryness to give 270 mg of Int. **158** (purity 50%) and 271mg of Int. **160** (purity 79%). **158** and **160** were used as such for the next steps.

c- **Synthesis of Int. 160:**



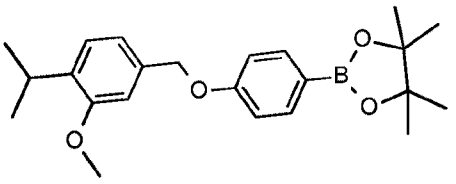
To a sol. of **158** (270 mg, 0.41 mmol) in MeOH (4 mL) was added KOH (69 mg, 1.24 mmol) and the mixture was heated at 50°C for 3h. Water and DCM were added and the organic layer was separated, dried, filtered and concentrated until dryness to give 235 mg of Int. **160** as a (crude) mixture which was used as such for the next step.



d- Synthesis of Co. 79:

TBAF (1.03 mL, 1.03 mmol) was added dropwise to a sol. of **160** (506 mg) in THF (8.5 mL) at r.t. The mixture was stirred for 3h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 395 mg. The residue was purified by prep. LC (Regular SiOH, 30 µm, 12g GraceResolv™, mobile phase gradient: from DCM 100% to DCM/MeOH/NH_4OH 95/5/0.1). The pure fractions were collected and evaporated until dryness to give 291 mg which was crystallized from DIPE, filtered and dried to give 265 mg of **Co. 79**. m.p.: 236°C (dsc).

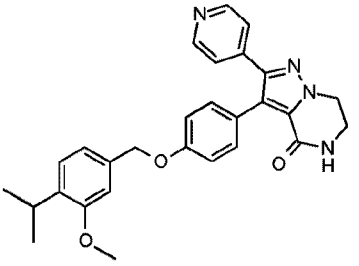
Example A82: Preparation of Co. 80



a- Synthesis of Int. 161:

To a suspension of 3-methoxy-4-isopropylbenzenemethanol (0.29 g, 1.6 mmol), **7** (0.425 g, 1.93 mmol), DBAD (0.45 g, 1.93 mmol) in dry DCM (5 mL) was added PPh_3 supp. (0.6 g, 1.93 mmol) and the r.m. was stirred at r.t. for 18 h. The insoluble was filtered through Celite®, washed with DCM. Water was added and the organic layer was separated, dried, filtered and concentrated until dryness to give 1.07 g. The residue

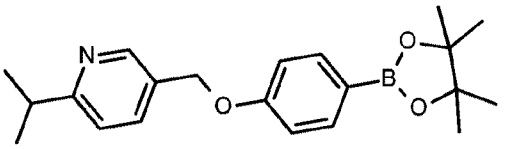
was purified by prep. LC on (Irregular SiOH 15-40µm 30g Merck, mobile phase: 90/10 Heptane/EtOAc). The pure fractions were collected and evaporated until dryness to give 411mg of Int. **161** (67%).



b- Synthesis of Co. 80:

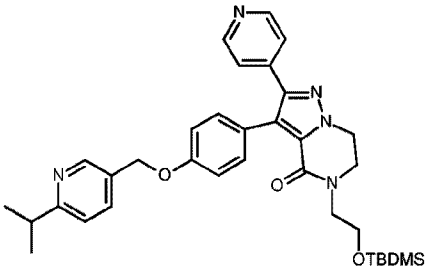
In a microwave vial, a mixture of **4** (0.25 g, 0.853 mmol), **161** (0.391 g, 1.023 mmol), K_3PO_4 (0.76 g, 3.58 mmol) in 1,4-dioxane (4 mL) and H_2O (1.33 mL) was carefully purged with N_2. PCy_3 (50 mg, 0.179 mmol) and $Pd(OAc)_2$ (20 mg, 0.089 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 16 h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 506 mg. The residue was purified by prep. LC on (irregular SiOH 15-40µm 300g Merck, mobile phase: 40% Heptane, 10% MeOH (+10% NH_4OH), 50% EtOAc). The desired fractions were combined and the solvent was removed *in vacuo* to give 80 mg which was crystallized from DIPE, filtered and dried to give 70 mg of **Co. 80** (18%). m.p.: 232°C (dsc).

Example A83: Preparation of Co. 81



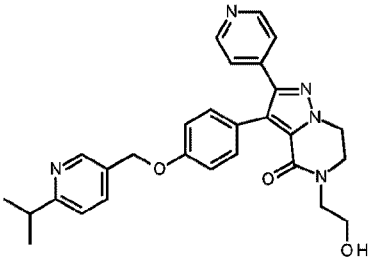
a- Synthesis of Int. 162:

A mixture of **7** (2.20 g, 10.0 mmol), 6-(1-methylethyl)-3-pyridinemethanol (1.97 g, 13.0 mmol) and PPh_3 (3.41 g, 13.0 mmol) in dry THF (30 mL) was treated with DBAD (2.99 g, 13.0 mmol) and stirred at r.t. for 2h. The r.m. was poured in water and DCM. The organic layer was separated, washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to afford yellow oil. The oil was purified by prep. LC (irregular SiOH 15-40 µm, 80 g Grace Resolv, solid loading, mobile phase gradient: from heptane 80%, EtOAc 20% to heptane 60%, EtOAc 40%). The pure fractions were collected and solvent evaporated until dryness to give 4.08 g of Int. **162**, colorless oil (Quant.).



b- Synthesis of Int. 163:

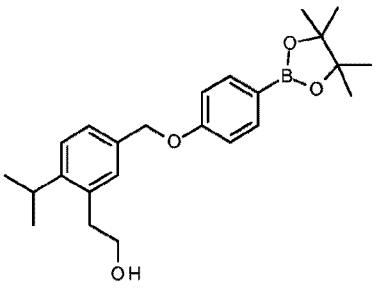
A sol. of **28** (800 mg, 1.77 mmol) and **162** (1.25 g, 3.54 mmol) in 1,4-dioxane (11 mL) and H_2O (5.5 mL) was treated with K_3PO_4 (1.13 g, 5.32 mmol) and purged with N_2. $PdCl_2$(dppf) (145 mg, 0.177 mmol) was then added and the r.m. was carefully purged with N_2. The mixture was heated at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min [fixed hold time]. The crude mixture was diluted with DCM and washed with water. The organic layer was dried over $MgSO_4$ and evaporated to afford a brown residue. The brown residue was purified by prep. LC (irregular SiOH 15-40 µm, 80 g, GraceResolv™, solid loading, Mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The pure fractions were collected and solvent evaporated to give 1.30 g of Int. **163**, yellow oil which was used such as for the next step.



c- Synthesis of Co. 81:

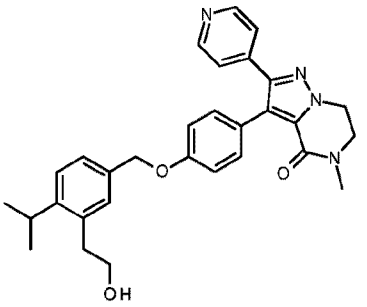
A sol. of **163** (1.30 g, 2.18 mmol) in THF (40 mL) was treated with TBAF (1.74 mL, 1.74 mmol) and stirred for 2h at r.t. The r.m. was poured in H_2O and extracted 2x with DCM. The organic layers were combined, dried over $MgSO_4$ and evaporated *in vacuo* to afford yellow oil. The oil was purified by prep. LC (irregular SiOH 15-40 µm, 80 g, GraceResolv™, solid loading, Mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The pure fractions were collected and solvent evaporated to give 540 mg of **Co. 81**, white solid (51%). m.p.: 93°C (DSC).

Example A84: Preparation of Co. 82



a- **Synthesis of Int. 164:**

A stirred sol. of **55** (1.02 g, 2.92 mmol), BisPin (1.11 g, 4.38 mmol) and KOAc (860 mg, 8.76 mmol) in E (15 mL) was carefully purged with N_2, and $PdCl_2(dppf)$ (239 mg, 292 µmol) was added. The r.m. was purged again with N_2, and stirred for 18 h at 100°C. The r.m. was diluted with EtOAc and washed with water and brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The black residue was purified by prep. LC (irregular SiOH 15-40 µm, 40 g, Merck, mobile phase gradient: from heptane 80%, EtOAc 20% to heptane 60%, EtOAc 40%). The pure fractions were collected and solvent was evaporated to give 1.10 g of Int. **164** (95%).

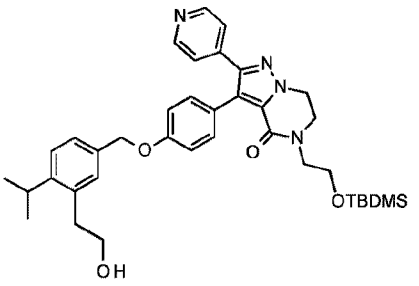


b- **Synthesis of Co. 82:**

A mixture of **98** (600 mg, 1.95 mmol), **164** (1.16 g, 2.93 mmol) and KOAc (1.04 g, 4.88 mmol) in 1,4-dioxane (12 mL) and H_2O (6 mL) was purged with N_2. $PdCl_2(dppf)$ (160 mg; 195 µmol) was then added. The mixture was purged again with N_2 and heated at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 25 min [fixed hold time]. The r.m. was then poured in DCM and water. The organic layer was separated. The aq. layer was extracted again with DCM. The organic layers were combined, dried over $MgSO_4$ and evaporated *in vacuo*. The brown residue was purified by prep. LC (irregular SiOH 15-40 µm, 80 g, GraceResolv™, dry loading, mobile phase gradient: from DCM 100% to DCM 96%, MeOH 4%). The pure fractions were collected and solvent was evaporated until dryness to give 744 mg of a residue, beige foam. This residue was purified by prep. LC (irregular SiOH 15-40 µm, 45 g, Merck, dry loading, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent was evaporated to give 460 mg of a residue which was purified again by Reverse phase (Stationary phase: X-Bridge-C18 5µm 30*150mm; Mobile phase Gradient: from 80%

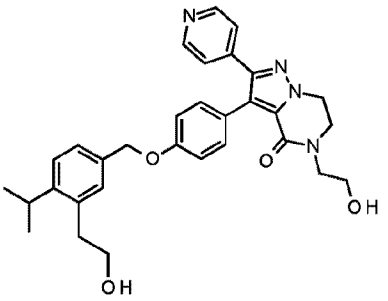
(NH_4HCO_3 0.5% aq. sol.), 20% ACN to 100% ACN). The fractions containing the pure product were combined and evaporated *in vacuo* to give 340 mg, a white foam. The residue was finally dissolved in a small amount of MeOH and triturated while Et_2O was added. The white solid was filtered on a glass frit and washed with Et_2O. The solid was collected and dried *in vacuo* to afford 225 mg of **Co. 82**, white solid (23%).

Example A85: Preparation of Co. 83



a- Synthesis of Int. 165:

A mixture of **28** (0.680 g, 1.51 mmol), **164** (0.963 g, 2.26 mmol) and K_3PO_4 (0.959 g, 4.52 mmol) in 1,4-dioxane (9 mL) and H_2O (4 mL) was purged with N_2. $PdCl_2$(dppf) (0.100 g, 0.122 mmol) was then added. The mixture was purged again with N_2 and stirred at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 25 min [fixed hold time]. Then, a sol. of DCM/MeOH (94:6) and water were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give a dark solid. The solid was purified by prep. LC (Irregular SiOH 50 µm, 80 g Grace, mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The desired fractions were evaporated *in vacuo* to yield 1.10 g of Int. **165**, oil (97 %, purity 85%) used as such for the next step.

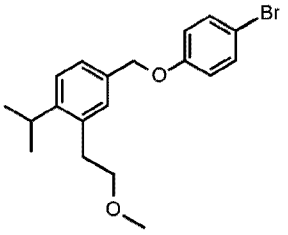


b- Synthesis of Co. 83:

TBAF (1.47 mL, 1.47 mmol) was added to a stirred sol. of **165** (1.10 g, 1.46 mmol) in 1,4-dioxane (14 mL) at 0°C, and the r.m. was stirred at r.t. for 18 h. The crude mixture was diluted with water and a sol. of DCM/MeOH (96/4). The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford 790 mg of a solid. This solid was purified by prep. LC (Irregular SiOH 50 µm, 50 g Grace, mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The desired fractions were collected and evaporated *in vacuo* to give 253 mg which was solubilized in

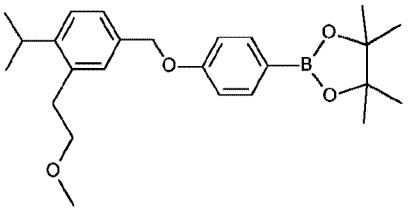
MeOH (1mL). The solvent was allowed to slowly evaporate, yielding 246 mg of **Co. 83**, crystalline white solid (32%). m.p.: 176 °C (DSC).

Example A86: Preparation of Co. 84



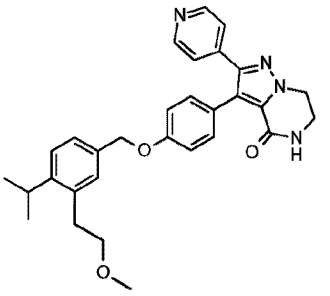
a- Synthesis of Int. 166:

NaH 60% (53 mg, 1.3 mmol) was added slowly to a suspension of **55** (0.30 g, 0.88 mmol) in THF (5.0 mL) at r.t. under N_2. The mixture was stirred for 2h then MeI (0.08 mL, 1.3 mmol) was added and stirred overnight. Water was added and the mixture was extracted with DCM (3x), dried on $MgSO_4$ and evaporated until dryness and give 334 mg of yellow oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 12 g, GraceResolv™, Mobile phase: Heptane/EtOAc, 95/5). The pure fractions were collected and solvent was evaporated to give 253 mg of Int. **166** (79%).



b- Synthesis of Int. 167:

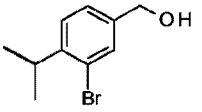
In a microwave vial, a mixture of **166** (0.25 g, 0.69 mmol), KOAc (0.20 g, 2.1 mmol), BisPin (0.26 g, 1.0 mmol) in DME (2 mL) was carefully purged with N_2. $PdCl_2$(dppf) (56 mg, 69 µmol) was added and the r.m. was purged again with N_2. The r.m. was stirred overnight at 100°C. The r.m. was diluted with EtOAc and washed with water (1x) and with brine (3x). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 530 mg of brown oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 12 g, GraceResolv™, Mobile phase: Heptane/EtOAc, gradient from 95/5 to 90/10). The pure fractions were collected and solvent was evaporated until dryness to give 307 mg of Int. **167**, colorless oil (100%).



c- **Synthesis of Co. 84:**

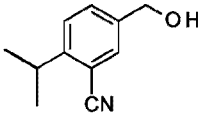
In a microwave vial, a mixture of **4** (167 mg, 0.57 mmol), **167** (0.28 g, 0.68 mmol), K_3PO_4 (0.36 g, 1.7 mmol) in 1,4-dioxane (2.5 mL) and H_2O (0.89 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (47 mg, 57 µmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic layer was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 295 mg of brown oil. This oil was purified by prep. LC (irregular SiOH 30 µm, 25 g, Interchim, Mobile phase: DCM/MeOH/NH_4OH 97/3/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 230 mg of white solid. This solid was washed with Et_2O, filtered and dried to give 210 mg of **Co. 84**, white solid (74%). m.p.: 208°C (dsc).

Example A87: Preparation of Co. 85 and Co. 86



a- **Synthesis of Int. 168:**

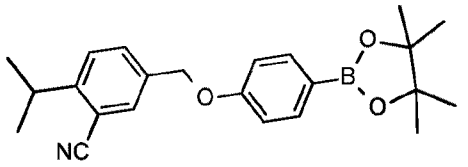
LAH (5.52g, 145mmol) was added to a stirred sol. of methyl-3-bromo-4-isopropylbenzoate (34.0g, 132mmol) in THF (600mL) at -20°C. The r.m. was stirred at -20°C for 2h. The r.m. was quenched with H_2O (5.26mL), NaOH 3N (5.52mL) and H_2O (16mL). The cake was filtered and washed (DCM). The filtrate was evaporated *in vacuo* to give 20.0g of Int. **168**, yellow oil (66%).



b- **Synthesis of Int. 169:**

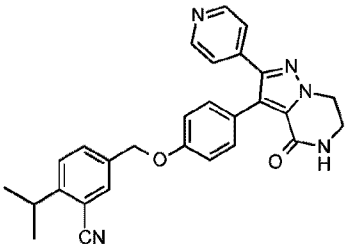
$Pd(PPh_3)_4$ (1.6g, 1.4mmol) was added to a mixture of **168** (3.2g, 14mmol) and $Zn(CN)_2$ (1.7g, 14mmol) in DMF (10mL) in a sealed tube. The mixture was heated at 120°C for 60 min using one single mode microwave (Biotage) with a power output ranging from 0 to 400 W. The r.m. was cooled to r.t., poured into ice water and extracted (DCM). The organic layer was separated, dried over $MgSO_4$, filtered and the solvent was evaporated until dryness to give 2.6g. The residue was purified by prep. LC on

(Irregular SiOH 15-40µm 50g Merck, mobile phase: 70/30 heptane/EtOAc). The pure fraction was collected and evaporated to give 1.4g of Int. **169** (57%).



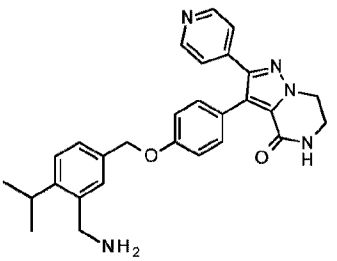
c- **Synthesis of Int. 170:**

DBAD (1.3 g, 5.5 mmol) was added portionwise to a sol. of **69** (0.8 g, 4.6 mmol), **7** (1.2 g, 5.5 mmol), PPh_3 supp. (1.7 g, 5.5 mmol) in dry THF (30 mL). The mixture was stirred at r.t. overnight. The mixture was filtered. The filtrate was evaporated to give 3.7 g yellow oil. The crude residue was purified by prep. LC (irregular SiOH 30µm 80g Interchim, mobile phase: heptane/EtOAc 90/10). The pure fractions were collected and solvent was evaporated until dryness to give 1.0 g of Int. **170**, colorless oil which crystallized in white solid (58%).



d- **Synthesis of Co. 85:**

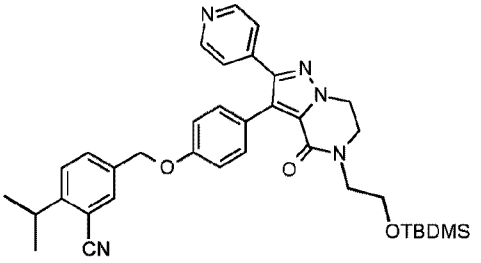
A mixture of **4** (867 mg, 2.96 mmol), **170** (0.93 g, 2.5 mmol), K_3PO_4 (1.57 g, 7.4 mmol) in 1,4-dioxane (11 mL) and H_2O (4 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (201.7 mg, 0.25 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 8h at 80°C in a sealed tube. Water and DCM were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The residue was purified by prep. LC on (irregular 15-40µm 30g Merck, mobile phase: 98% DCM, 2% MeOH). The pure fractions were collected and the solvent evaporated until dryness to give 570 mg which was crystallized from Et_2O, the precipitate was filtered off and dried to give 453mg of **Co. 85** (40%). m.p.: 240°C (dsc).



e- **Synthesis of Co. 86:**

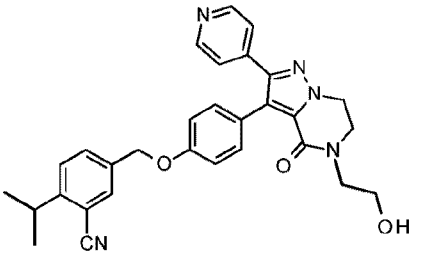
A solution of **Co. 85** (280 mg, 0.604 mmol), MeOH/NH_3 (10 mL), Ni Raney (300 mg), THF (5 mL), DCM (5 mL) was hydrogenated under a 3 bars pressure at r.t. overnight. The catalyst was filtered over a Celite® pad, the filtrate was evaporated and the residue was purified by prep. LC (irregular SiOH 30 µm, 25 g, Interchim, Mobile phase gradient: DCM/MeOH/NH_4OH from 96/4/0.1 to 92/8/0.1). The pure fractions were put together and evaporated. The residue was taken up in Et_2O, filtrated and dried to give 15 mg of **Co. 86** (5%).

Example A88: Preparation of Co. 87



a- Synthesis of Int. 171:

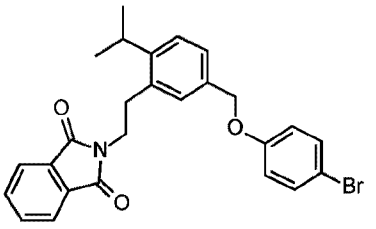
In a microwave vial, a mixture of **28** (0.5 g, 1.1 mmol), **170** (0.5 g, 1.3 mmol), K_3PO_4 (0.94 g, 4.4 mmol) in 1,4-dioxane (4.9 mL) and H_2O (1.7 mL) was carefully purged with N_2. $PdCl_2$(dppf) (90 mg, 0.11 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give a residue. The residue was purified by prep. LC (irregular SiOH 30 µm, 40 g Interchim, mobile phase: DCM/MeOH/NH_4OH 98/2/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 0.72 g of Int. **171**, beige solid (100%).



b- Synthesis of Co. 87:

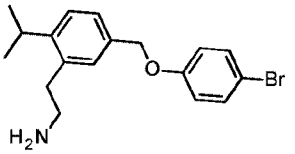
TBAF (1.4 mL, 1.4 mmol) was added dropwise to a sol. of **171** (0.72 g, 1.2 mmol) in THF (11 mL) at r.t.. The mixture was stirred overnight at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 µm, 25 g GraceResolv™, mobile phase: DCM/MeOH/NH_4OH 98/2/0.1). The pure fractions were collected and the solvent was evaporated until dryness to give 0.38 g which was triturated in Et_2O. The white solid formed was filtered and dried to give 0.32 g of **Co. 87** (55%). m.p.: 160°C (dsc).

Example A89: Preparation of Co. 88a and Co. 88



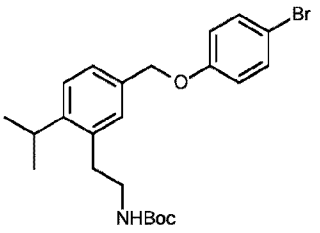
a- Synthesis of Int. 172:

DBAD (99 mg, 0.43 mmol) was added portionwise to a sol. of **55** (100 mg, 0.29 mmol), phthalimide (63 mg, 0.43 mmol), diphenylphosphinopolystyrene (134 mg, 0.43 mmol) in THF (3.3 mL) at r.t. under N_2. The mixture was stirred for 3 days. The mixture was filtrated through a pad of Celite®, washed with EtOAc and concentrated. The crude residue was purified by prep. LC (irregular SiOH 35-40 µm 12 g GraceResolv™, mobile phase gradient: heptane/EtOAc from 90/10 to 85/15). The pure fractions were collected and solvent was evaporated until dryness to give 63 mg of Int. **172** (46%).



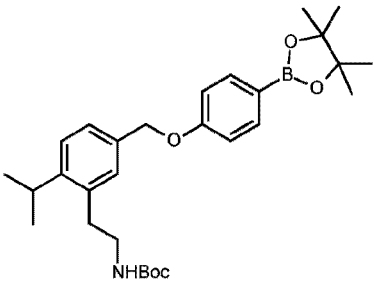
b- Synthesis of Int. 173:

In a microwave vial, hydrazine hydrate (230 µL, 2.4 mmol) was added to a suspension of **172** (380 mg, 0.79 mmol) in EtOH (5 mL) and the mixture was heated at 70°C for 1h. The white solid was filtered and washed with EtOH to give 295 mg of Int. **173** (used like this in the next step).



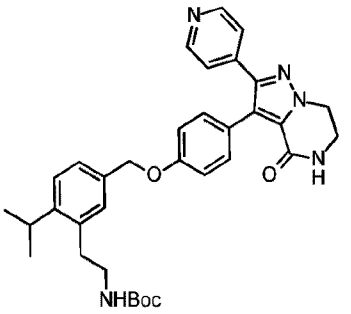
c- Synthesis of Int. 174:

Boc_2O (203 mg, 0.93 mmol) and Et_3N (0.35 mL, 2.5 mmol) were added to a suspension of **173** (295 mg, 0.85 mmol) in DCM (4.5 mL). The mixture was stirred at r.t. overnight. The mixture was diluted with DCM and quenched with water. The organic layer was decanted, washed with water, with $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated to give 300 mg of Int. **174**, colorless oil (79%).



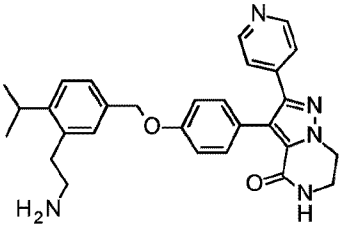
d- **Synthesis of Int. 175:**

In a microwave vial, a mixture of **174** (0.30 g, 0.67 mmol), KOAc (0.20 g, 2.0 mmol), BisPin (0.26 g, 1.0 mmol) in DME (5.1 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (55 mg, 67 µmol) was added and the r.m. was purged again with N_2. The r.m. was stirred overnight at 100°C. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 540 mg. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 12 g, GraceResolv™, mobile phase gradient: Heptane/EtOAc, from 85/15 to 80/20). The pure fractions were collected and solvent was evaporated until dryness to give 333 mg of Int. **175**, colorless oil (100%).



e- **Synthesis of Co. 88a**

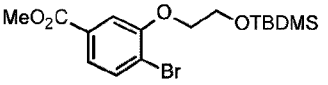
In a microwave vial, a mixture of **4** (164 mg, 0.56 mmol), **175** (333 mg, 0.67 mmol), K_3PO_4 (357 mg, 1.68 mmol) in 1,4-dioxane (2.5 mL) and H_2O (0.8 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (46 mg, 56 µmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of celite® and evaporated *in vacuo* to give 390 mg. The residue was purified by prep. LC (irregular SiOH 30 µm, 12 g, GraceResolv™, Mobile phase gradient: DCM/MeOH/NH_4OH from 98/2/0.1 to 97/3/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 220 mg of **Co. 88a**, white solid (68%).



f- Synthesis of Co. 88:

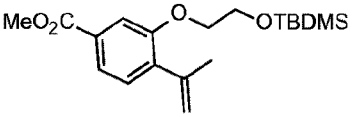
A solution of **Co. 88a** (220 mg, 0.38 mmol), HCl 3N (0.63 mL, 1.9 mmol), in ACN (6.7 mL) was stirred at 80°C for 2h. The mixture was concentrated, and $NaHCO_3$ sat aq was added and the mixture was stirred at r.t. 15 min. The mixture was extracted with DCM, dried, filtered and concentrated to give 213 mg of a solid. This solid was triturated in Et_2O, filtrated and dried to give 127 mg of **Co. 88**, beige powder (70%). m.p.: 181°C (dsc).

Example A90: Preparation of Co. 89



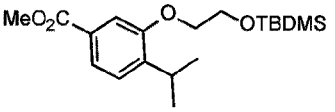
a- Synthesis of Int. 177:

A solution of Methyl 4-bromo-3-hydroxybenzoate (2.5 g, 10.8 mmol), (2-bromoethoxy)-tert-butyldimethylsilane (2.5 mL, 11.9 mmol), K_2CO_3 (2.2 g, 16.2 mmol) in ACN (50 mL) was stirred at 80°C overnight. Water and EtOAc were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The residue was purified by prep. LC (Regular SiOH, 30 µm, 120g Grace, mobile phase: 80/20 heptane/EtOAc). The pure fractions were collected and the solvent was evaporated until dryness to give 3.2g of Int. **177** (76%).



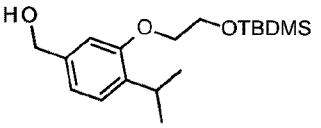
b- Synthesis of Int. 178:

A solution of **177** (3.2 g, 8.2 mmol), $Pd(tBu_3P)_2$ (210 mg, 0.4 mmol), CsF (2.7 g, 18 mmol), 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.5 g, 9 mmol) in THF (30 mL) was refluxed overnight. Water and EtOAc were added, the mixture was filtered over a Celite® pad, washed with EtOAc. The mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated until dryness to give 3.4 g. The residue was purified by prep. LC on (irregular SiOH 30 µm, 90g, GraceResolv™, Mobile phase: 80/20 heptane/EtOAc). The pure fractions were collected and evaporated till dryness yielding 2.5 g of Int. **178** (87%).



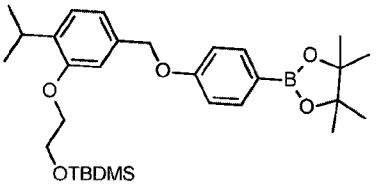
c- Synthesis of Int. 179:

A solution of **178** (2.5 g, 7.1 mmol), ammonium formate (2.6 g, 43 mmol), Pd/C 10% (379 mg, 0.3 mmol) in THF (10 mL) and MeOH (30 mL) were refluxed for 90 min. The mixture was filtered through Celite®, washed with EtOAc, and the filtrate was concentrated to give 3.8 g. Water and EtOAc were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and dried to give 2.2 g of Int. **179** (87%) used as such for the next step.



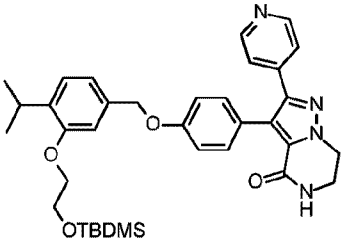
d- Synthesis of Int. 180:

LAH (310 mg, 8.2 mmol) was added carefully at 5°C to a sol. of **179** (2.4 g, 6.8 mmol) in THF (40 mL). The mixture was stirred at r.t. for 1h. Water was carefully added at 5°C and EtOAc were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated until dryness to give 2.4g of Int. **180** (quant.).



e- Synthesis of Int. 181:

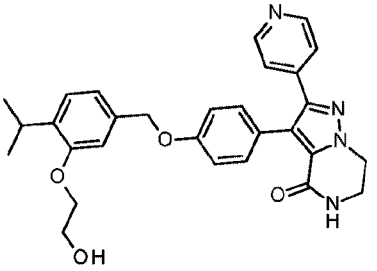
DBAD (0.7 g, 2.9 mmol) was added portionwise to **180** (640 mg, 2 mmol), **7** (520 mg, 2.4 mmol), PPh_3 supp. (0.9 g, 3 mmol) in THF (10 mL). The mixture was stirred at r.t. overnight. PPh_3 supp. was filtered and the filtrate was evaporated. The residue was purified by prep. LC on (Stability Silica 5µm 150x30.0mm, Mobile phase Gradient from 85% Heptane, 15% EtOAc to 100% EtOAc). The pure fractions were collected and the solvent was evaporated to give 260 mg of Int. **181** (25%).



f- Synthesis of Int. 182:

In a microwave vial, a mixture of **4** (768 mg, 2.6 mmol), **181** (1.15 g, 2.2 mmol), K_3PO_4 (1.4 g, 6.5 mmol) in 1,4-dioxane (10 mL) and H_2O (3 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (179 mg, 218 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3x). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo*. The residue was purified

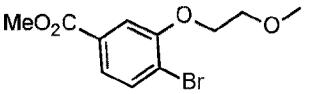
by prep. LC (Stationary phase: irregular SiOH 15-40µm 300g Merck, mobile phase: 43% Heptane, 7% MeOH, 50% EtOAc). The pure fractions were collected and evaporated till dryness to give 640 mg of Int. **182** (48%).



g- Synthesis of Co. 89:

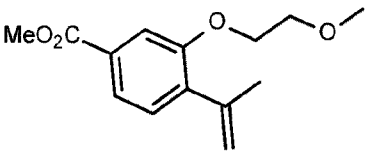
TBAF (0.45 mL, 0.45 mmol) was added dropwise to a sol. of **182** (230 mg, 0.375 mmol) in THF (5 mL) at r.t.. The mixture was stirred 90 min at r.t. The mixture was poured into water, extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness. The residue was purified by prep. LC (Regular SiOH, 30 µm, 25 g grace, mobile phase gradient: DCM/MeOH/NH4OH from 97/3/0.1 to 94/6/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 170 mg which was purified by achiral SFC on (Chiralpak IA 5µm 250*20mm, mobile phase: 50% CO_2, 50% MeOH). The pure fractions were collected and evaporated till dryness to give 105 mg. The product was crystallized from Et_2O. The solid was filtered off and dried to give 91 mg of **Co. 89** (49%).

Example A91: Preparation of Co. 90



a- Synthesis of Int. 183:

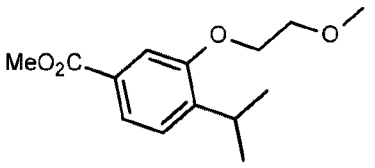
Methyl 4-bromo-3-hydroxybenzoate (2g, 8.6mmol), 2-bromo ethyl methylether (0.9mL, 9.5mmol), K_2CO_3 (1.8g, 13mmol) in ACN (40ml) at 80°C overnight. Water and EtOAc were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The residue was purified by prep. LC on (Irregular SiOH 20-45µm 450g MATREX, Mobile phase: 85% heptane, 15% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 2.1g of Int. **183** (84%).



b- Synthesis of Int. 184:

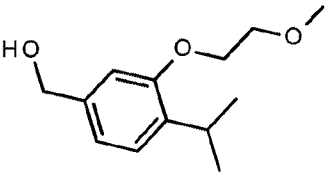
A solution of **183** (1.9 g, 6.6 mmol), CsF (2.2 g, 14.4 mmol), 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 g, 7.2 mmol), $Pd(tBu_3P)_2$ (168 mg, 0.3 mmol) in

THF (30 mL) was refluxed overnight. Water and EtOAc were added, the mixture was filtered over Celite®, washed with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The residue was purified by prep. LC on (Irregular SiOH 20-45µm 40g Grace, mobile phase: 85% heptane, 15% EtOAc). The pure fractions were collected and the solvent was evaporated until dryness to give 560 mg of Int. **184** (34%).



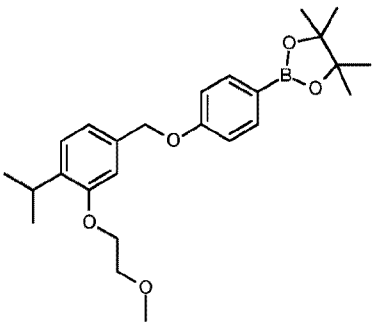
c- Synthesis of Int. 185:

A solution of **184** (450 mg, 1.8 mmol), ammonium formate (658 mg, 10.8 mmol), 10% Pd/C (95 mg, 0.09 mmol) in THF (3mL) and MeOH (10mL) was refluxed for 30 min. The mixture (combined with another batch) was filtered through Celite®, washed with EtOAc, and the filtrate was concentrated until dryness to give 590 mg of Int. **185** (global yield 100%).



d- Synthesis of Int. 186:

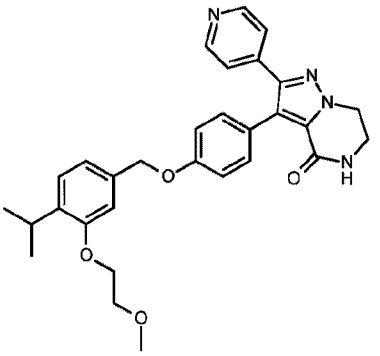
LAH (106 mg, 2.8 mmol) was added carefully at 5°C to a sol. of **185** (590 mg, 2.3 mmol) in THF (10 mL). The mixture was stirred at r.t. for 1h. Water was carefully added at 5°C and EtOAc was added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated until dryness to give 450 mg of Int. **186** (86%).



e- Synthesis of Int. 187:

DBAD (692 mg, 3 mmol) was added portionwise to **186** (450 mg, 2 mmol), **7** (529 mg, 2.4 mmol), PPh_3 supp. (0.94 g, 3 mmol) in THF (10 mL). The mixture was stirred at r.t. overnight. PPh_3 supp. was filtered and the filtrate was evaporated. The residue was

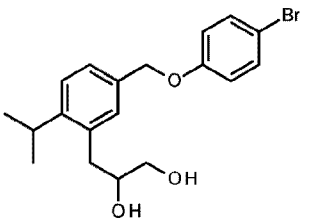
purified by prep. LC on (Stability Silica 5µm 150x30.0mm, mobile phase gradient: from 85% heptane, 15% EtOAc to 100% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 350 mg of a first residue and 300 mg of second residue. The last residue was purified by prep. LC on (Stability Silica 5µm 150x30.0mm, mobile phase Gradient: from 85% heptane, 15% EtOAc to 100% EtOAc). The pure fractions were collected and solvent was evaporated to give 160 mg of Int. 187. Both fractions (350 mg and 160 mg) were put together to give 510 mg of Int. **187** (60%).



f- Synthesis of Co. 90:

A mixture of **4** (265 mg, 0.9 mmol), **187** (0.35 g, 0.82 mmol), K_3PO_4 (0.7 g, 3.3 mmol) in 1,4-dioxane (5 mL) and H_2O (1.2 mL) was carefully purged with N_2. PCy_3 (48 mg, 0.17 mmol) and $Pd(OAc)_2$ (19 mg, 0.09 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 8h at 80°C in a sealed tube. Water and DCM were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated until dryness to give 530 mg. The residue was purified by prep. LC on (irregular 15-40µm 30g Merck, mobile phase: 0.1% NH_4OH, 98% DCM, 2% MeOH). The pure fractions were collected and the solvent evaporated until dryness to give 130 mg which was taken up in Et_2O. The solid was filtered off and dried to give 90 mg of **Co. 90** (21%). m.p.: 209°C (dsc).

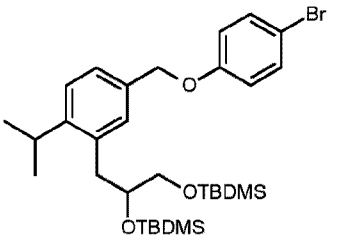
Example A92: Preparation of Co. 91



a- Synthesis of Int. 188:

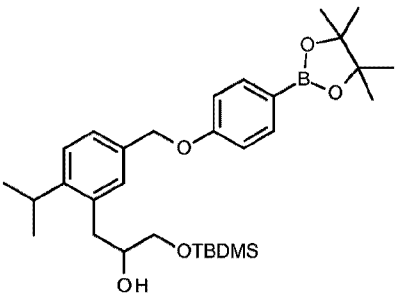
Under N_2 atmosphere, to a sol. of **54** (0.75 g, 2.2 mmol) in acetone (16 mL) and H_2O (2 mL), was successively added 4-methylmorpholine-4-oxide (305 mg, 2.6 mmol) and OsO_4 2.5% in butanol (1.5 mL, 0.11 mmol). The mixture was stirred at r.t. overnight. An aq. sol. of Na_2SO_3 sol. (7.5 mL, 10%) was added to the r.m. and the mixture was

stirred for 30 min at r.t. Then, the solvent was evaporated *in vacuo* and the residue was extracted with EtOAc (30 mL). The extract was washed with brine (3× 10mL) and the organic layer, after drying over $MgSO_4$ and filtration, was evaporated until dryness to give 1g, brown oil. This oil and another batch were purified by prep. LC (irregular SiOH 30 µm, 25 g, Interchim, Mobile phase: heptane/EtOAc 60/40). The pure fractions were collected and solvent was evaporated until dryness to give 820 mg of Int. **188**, white solid (global yield: 88%).



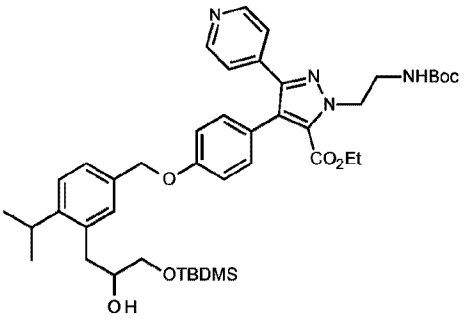
b- Synthesis of Int. 189:

Under N_2, tert-butyldimethylsilyl chloride (0.97 g, 6.4 mmol) was added to a sol. of **188** (0.82g, 2.1 mmol) and imidazole (0.87 g, 13 mmol) in dry DCM (21 mL) at r.t. The mixture was stirred at r.t. for 1h. The mixture was quenched with water and extracted with DCM. The organic layer was decanted, washed with water then brine, dried over $MgSO_4$, filtered and evaporated to dryness to give 1.29 g of Int. **189**, colorless oil (99%).



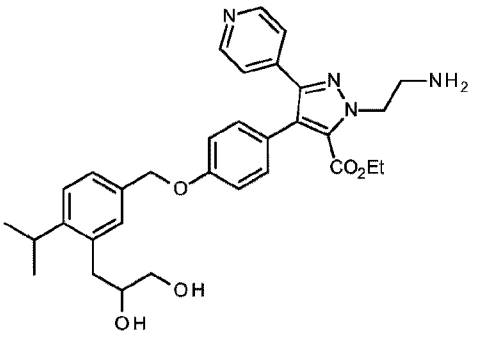
c- Synthesis of Int. 190:

In a microwave vial, a mixture of **189** (1.3 g, 2.1 mmol), KOAc (0.63 g, 6.4 mmol), BisPin (0.82 g, 3.2 mmol) in DME (6.2 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (0.18 g, 0.21 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred overnight at 100°C. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic layer was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give a brown oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 40 g, Interchim, Mobile phase gradient: Heptane/EtOAc, from 95/5 to 90/10). The pure fractions were collected and solvent was evaporated until dryness to give 0.6 g of Int. **190**, colorless oil (52%).



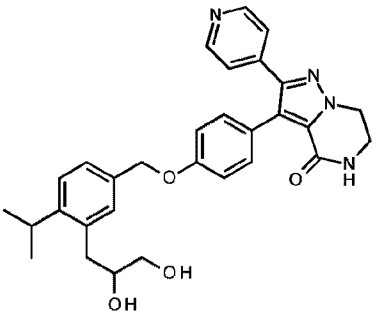
d- Synthesis of Int. 191:

In a microwave vial, a mixture of **3** (0.41 g, 0.93 mmol), **190** (0.60 g, 1.1 mmol), K_3PO_4 (0.59 g, 2.8 mmol) in 1,4-dioxane (4.1 mL) and H_2O (1.5 mL) was carefully purged with N_2. $PdCl_2$(dppf) (75 mg, 92 µmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C for 3 days. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 1.2 g, brown oil. This oil was purified by prep. LC (irregular SiOH 30 µm, 25 g, Interchim, Mobile phase gradient: heptane/EtOAc from 60/40 to 45/55). The pure fractions were collected and solvent was evaporated until dryness to give 0.5g of Int. **191**, colorless oil (70%).



e- Synthesis of Int. 192:

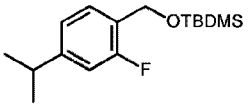
A solution of **191** (0.50 g, 0.65 mmol), HCl 3N (1.1 mL, 3.2 mmol), in ACN (11 mL) was stirred at 80°C for 2h. The mixture was concentrated, and $NaHCO_3$ sat. aq. (25mL) was added and the mixture was extracted with DCM, dried and evaporated until dryness to give 0.36 g of Int. **192** (quant.). This residue was used like this in the next step.



f- Synthesis of Co. 91:

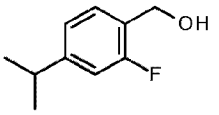
To a sol. of **192** (360 mg, 0.64 mmol) in MeOH (18 mL) was added Cs_2CO_3 (1.1 g, 3.2 mmol) and the mixture was stirred at r.t. overnight. The mixture was concentrated and taken in DCM and washed once with brine, dried of $MgSO_4$ and concentrated till dryness to give 520 mg, white solid. The crude product was purified by prep. LC (irregular SiOH 30 µm, 12 g graceResolv™, mobile phase gradient from DCM/MeOH/NH_4OH 97:3:0.1 to 95/5/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 190 mg of white solid which was purified by prep. LC (Stationary phase: Stability Silica 5µm 150x30.0mm, mobile phase gradient: from 47% EtOAc, 3% MeOH (+0.2%NH_4OH), 50% Heptane to 75% EtOAc, 25% MeOH(+0.2% NH_4OH)). The pure fractions were collected and solvent was evaporated until dryness to give 130 mg. This residue was purified by achiral SFC (Stationary phase: Diethylaminopropyl 5µm 150x21.2mm, mobile phase: CO_2, MeOH (0.3% $iPrNH_2$)) followed by prep. LC (Stationary phase: irregular 15-40µm 30g Merck, mobile phase: 0.5% NH_4OH, 95% DCM, 5% MeOH). 108 mg of white solid was collected and it was washed with Et_2O. The white solid was filtered and dried to give 90mg of **Co. 91** (27%).

Example A93: Preparation of Co. 92



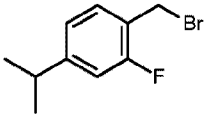
a- Synthesis of Int. 193:

Under N_2, a sol. of [(4-bromo-2-fluorobenzyl)oxy](tert-butyl)dimethylsilane (6.0 g, 18.8 mmol) in dry THF (50 mL) was treated with isopropylmagnesium chloride 2M in THF (47.0 mL, 94.0 mmol) at r.t. The r.m. was then purged with N_2 and $PdCl_2$(dppf) (1.54 g, 1.88 mmol) was added. The r.m. was purged again with N_2 and stirred at 50°C for 5h. After being quenched with water, the r.m. was diluted with Et_2O, washed with water (1x) and brine (2x). The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to afford a brown residue. The residue was supported on silica gel and purified through a short pad of silica (mobile phase: heptane 90%, Et_2O 10%). The filtrate was collected and evaporated *in vacuo* to give 5.0 g of Int. **193**, yellow oil (94%).



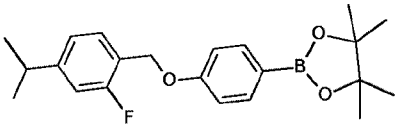
b- Synthesis of Int. 194:

A sol. of **193** (5.0 g, 17.7 mmol) in THF (150 mL) was cooled to 0°C and treated with TBAF (21.2 mL, 21.2 mmol). The r.m. was stirred for 90 min at 0°C, concentrated and poured in Et_2O. The organic layer was washed with water (3x 50mL), dried over $MgSO_4$ and evaporated *in vacuo* to afford a yellow oil (3.3 g) which was purified by prep. LC (irregular SiOH 15-40µm, 80g GraceResolv™, Mobile phase gradient: from heptane 100% to heptane 50%, EtOAc 50%). The pure fractions were collected and solvent evaporated to give 2.18 g Int. **194** (colorless oil; 73%).



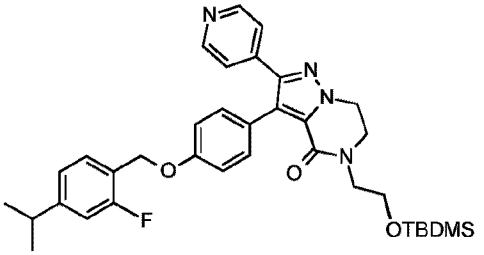
c- Synthesis of Int. 195:

To a sol. of **194** (1.12 g, 6.66 mmol) in dry Et_2O (19 mL) at 0 °C was added dropwise Phosphorus tribromide (0.626 mL, 6.66 mmol). The ice bath was removed and the reaction stirred for 3h. Then, water was carefully added to the mixture, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered off and evaporated *in vacuo* to afford 1.49 g of Int. **195**, colorless liquid (97%).



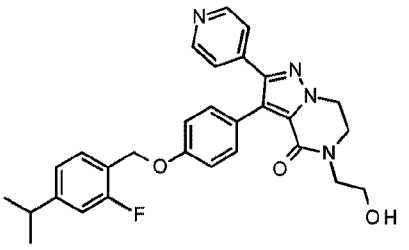
d- Synthesis of Int. 196:

A sol. of **195** (1.49 g, 5.87 mmol) in ACN (15 mL) was treated with K_2CO_3 (1.10 g, 7.98 mmol) and **7** (1.17 g, 5.32 mmol) at r.t. The r.m. was stirred for 20h at r.t. DMF (11mL) was added and the r.m. was stirred at r.t. for 90h. Water and EtOAc were added, and the organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 2.07 g, pale oil. This oil was purified by prep. LC (Irregular SiOH 50 µm, 80 g Grace, mobile phase gradient: from Heptane 100% to EtOAC 10%, Heptane 90%). The fractions were collected and evaporated *in vacuo* to give 360 mg of Int. **196**, colorless oil which crystallized in a solid (68%).



e- Synthesis of Int. 197:

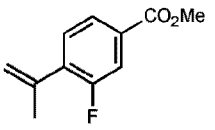
$PdCl_2(dppf)$ (0.141 g, 0.172 mmol) was added to a stirred sol. of **28** (0.778 g, 1.72 mmol), **196** (1.33 g, 3.45 mmol) and K_3PO_4 (1.10 g, 5.17 mmol) in 1,4-dioxane (10.6 mL) and H_2O (5.3 mL) at r.t., under N_2. The resulting mixture was stirred at 120 °C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. [fixed hold time]. The crude material was diluted with DCM and water, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 2.4 g, dark oil. This oil was purified by prep. LC (Irregular SiOH 50 µm, 80 g Grace, mobile phase gradient: from DCM 100% to EtOAc 60%, DCM 40%). The fractions were collected and evaporated *in vacuo* to give 1.03 g of Int. **197**, pale yellow oil (89%).



f- Synthesis of Co. 92:

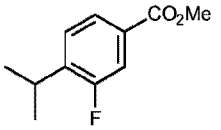
TBAF (1.85 mL, 1.85 mmol) was added to a stirred sol. of **197** (1.03 g, 1.54 mmol) in THF (12 mL) at 0°C, and the r.m. was stirred at 0 °C for 90 min. The crude mixture was diluted with brine and EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford 790 mg of a sticky solid. This solid was purified by prep. LC (Irregular SiOH 50 µm, 80 g Grace, mobile phase gradient: from DCM 100% to DCM 92%, MeOH 8%). The fractions were collected and evaporated *in vacuo* to give 735 mg of colorless sticky oil. This oil was triturated with pentane, and the solvent was removed *in vacuo* to yield 640 mg of white amorphous solid. So it was crystallized from MeOH, and the solvent was evaporated *in vacuo* to yield 560mg of white solid. This solid was purified by prep. LC (Irregular SiOH 50 µm, 80 g Grace, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The fractions were collected and evaporated *in vacuo* to give 555 mg, white solid. The residue was purified by achiral SFC (Stationary phase: Chiralpak AD-H 5µm 250x20mm, mobile phase: 70% CO_2, 30% mixture of MeOH/iPrOH 50/50 v/v). The pure fractions were collected and solvent evaporated until dryness to give a colorless oil which was crystallized from ACN, filtered and dried to give 331 mg of **Co. 92**, white solid (43%). m.p.: 132 °C (dsc).

Example A94: Preparation of Co. 93



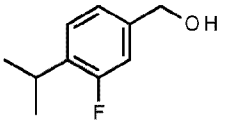
a- Synthesis of Int. 198:

A sol. of methyl 4-bromo-3-fluorobenzoate (= 4-Bromo-3-fluorobenzoic acid methyl ester) (1.22 g, 5.24 mmol) and potassium isopropenyltrifluoroborate (1.60 g, 10.5 mmol) in isopropanol (14 mL) was treated with Et_3N (2.92 mL, 21.0 mmol) and purged with N_2. $PdCl_2(dppf)$ (215 mg, 262 µmol) was then added and the r.m. was carefully purged with N_2. The mixture was heated at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min [fixed hold time]. The crude mixtures were combined and diluted with EtOAc and washed with water and brine. The organic layer was dried over $MgSO_4$ and evaporated to afford 4.53 g of Int. **198**, brown oil (quant. but impurities), used as such for the next step.



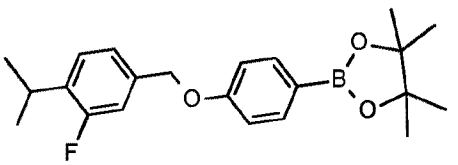
b- Synthesis of Int. 199:

A catalytic amount of Pd/C 10% (600 mg, 564 µmol) was added into a sol. of **198** (4.53 g, 23.3 mmol) in EtOH (50 mL). The r.m. was hydrogenated (7 bars) for 3 h at r.t. The sol. was filtered through a short pad of Celite® and evaporated to afford a red residue. The residue was filtered through a pad of silica gel (mobile phase: Et_2O). The filtrate was evaporated until dryness to afford 2.79 g of Int. **199**, yellow oil (61%).



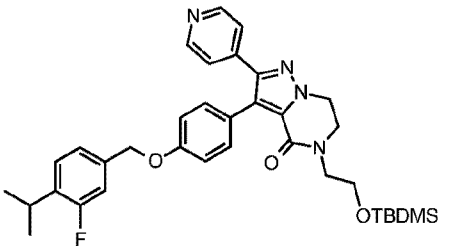
c- Synthesis of Int. 200:

A sol. of **199** (2.69 g, 13.1 mmol) in Et_2O (50 mL) was cooled to 0°C and treated with LAH (1.04g, 27.4 mmol). The r.m. was stirred at 0°C for 90 min. then quenched with water (1.0 mL), a 3N sol. of NaOH (1.0 mL) and water (3 mL). The sol. was filtered on a glass frit and the filtrate was evaporated. The yellow oil was purified by prep. LC (irregular SiOH 15-40 µm, 40 g Merck, Mobile phase gradient: from heptane 80%, EtOAc 20% to heptane 70%, EtOAc 30%). The pure fractions were collected and solvent evaporated to give 1.25 g of Int. **200**, colorless oil (52%).



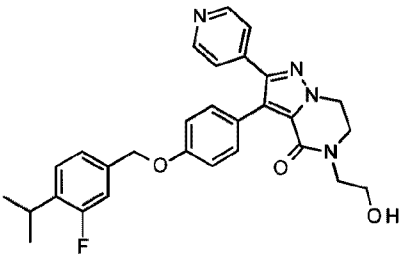
d- Synthesis of Int. 201:

A sol. of 7 (1.36 g, 6.19 mmol) and **200** (1.25 g, 7.43 mmol) in dry THF (20 mL) was treated with PPh_3 (1.95 g, 7.43 mmol) and DBAD (1.71 g, 7.43 mmol). The r.m. was stirred at r.t. for 17 h then concentrated *in vacuo*. The concentrate was poured in EtOAc, washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give an oil. The oil was purified prep. LC (irregular SiOH 15-40 µm, 45 g, Merck, dry loading, mobile phase gradient: from heptane 90%, EtOAc 10% to heptane 70%, EtOAc 30%). The pure fractions were collected and solvent evaporated until dryness to give 2.25g of Int. **201**, white solid (98%).



e- Synthesis of Int. 202:

A sol. of **28** (1.20 g, 2.66 mmol) and **201** (1.97 g, 5.32 mmol) in 1,4-dioxane (12 mL) and H_2O (6 mL) was treated with K_3PO_4 (1.69 g, 7.98 mmol) and purged with N_2. $PdCl_2(dppf)$ (218 mg, 266 µmol) was then added and the r.m. was carefully purged with N_2. The mixture was heated at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min [fixed hold time]. The crude mixture was poured in DCM and water. The organic layer was separated, dried over $MgSO_4$ and evaporated *in vacuo* to give a black residue. The residue was purified by prep. LC (Irregular SiOH 50 µm, 80 g Grace, mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The pure fractions were collected and solvent evaporated until dryness to give 1.53 g of Int. **202**, white solid (94%).

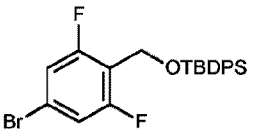


f- Synthesis of Co. 93:

TBAF (2.51 mL, 2.51 mmol) was added to a stirred sol. of **202** (1.53 g, 2.49 mmol) in THF (25 mL) at 0°C, and the r.m. was stirred at 0 °C for 90 min. The crude mixture was diluted with water and a sol. of DCM/MeOH (95:5). The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford 1.52 g. The residue was purified by prep. LC (Irregular SiOH 50 µm, 80 g Grace, mobile phase gradient: from DCM 100% to DCM 92%, MeOH 8%). The desired fractions were

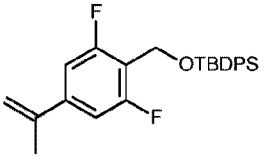
collected and evaporated *in vacuo* to give 572 mg, sticky oil which was crystallized from EtOH, filtered and dried to give 224 mg, white solid. The filtrate and the solid were combined and evaporated *in vacuo* to give 417 mg of a residue. This residue was purified by achiral SFC (Stationary phase: Chiralpak IA 5µm 250*20mm, mobile phase: 70% CO_2, 30% mixture of MeOH/iPrOH 50/50 v/v). The pure fractions were collected and solvent evaporated until dryness to give 267 mg which was crystallized from EtOH, filtered and dried to give 256 mg of **Co. 93**, white solid (45%). m.p.: 183°C (dsc).

Example A95: Preparation of Co. 94



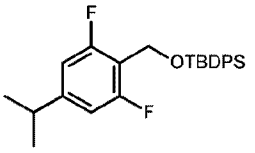
a- Synthesis of Int. 203:

Tert-butyldiphenylchlorosilane (4.3 mL, 17 mmol) was added to a sol. of 4-bromo-2,6-difluorobenzyl alcohol (2.5 g, 11 mmol) and imidazole (2.3 g, 33 mmol) in DCM (106 mL) at r.t. The mixture was stirred at r.t. overnight. The mixture was quenched with water and extracted with DCM. The organic layer was decanted, washed with water then brine, dried over $MgSO_4$, filtered and evaporated to dryness to give 7.5 g, colorless oil. This oil was purified by prep. LC (irregular SiOH 30 µm 120 g GraceResolv™, mobile phase gradient: heptane/EtOAc from 95/15 to 85/15/0.1). The desired fractions were collected and solvent evaporated to give 6.2 g of Int. **203**, colorless oil used as such as for the next step.



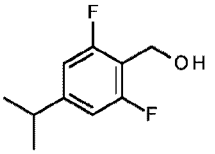
b- Synthesis of Int. 204:

In a microwave vial, a mixture of **203** (2.0 g, 4.3 mmol), CsF (1.5 g, 9.5 mmol) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.9 mL, 4.8 mmol) in dry THF (40 mL) was purged with N_2. $Pd(tBu_3P)_2$ (111 mg, 0.22 mmol) was added and the mixture was purged again with N_2 and heated at 80°C overnight. Water and EtOAc were added, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered on Celite® and evaporated. The residue was purified by prep. LC (Regular SiOH, 30 µm, 80 g GraceResolv™, mobile phase: Heptane/EtOAc 95/5). The pure fractions were collected and solvent evaporated to give 1.8 g of Int. **204**, yellow oil (98%).



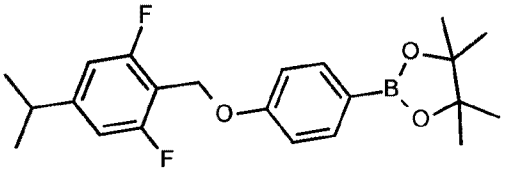
c- **Synthesis of Int. 205:**

A solution of **204** (1.8 g, 4.3 mmol), ammonium formate (1.6 g, 26 mmol), Pd/C 10% (226 mg, 0.21 mmol) in THF (7 mL) and MeOH (22 mL) was refluxed for 30min. The mixture was filtered through Celite®, washed with EtOAc, and the filtrate was concentrated. The residue was partitioned between water and EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated until dryness to give 1.7g of Int. **205**, colorless oil (94%).



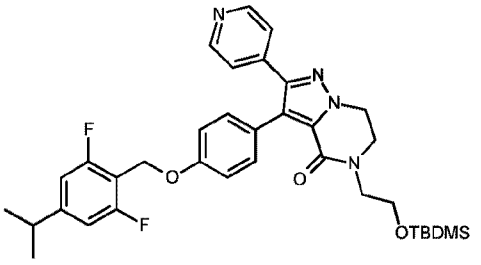
d- **Synthesis of Int. 206:**

TBAF (4.8 mL, 4.8 mmol) was added dropwise to a sol. of **205** (1.7 g, 4.0 mmol) in THF (39 mL) at r.t. The mixture was stirred for 10h at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 µm, 40 g GraceResolv™, mobile phase: Heptane/EtOAc 80/20). The pure fractions were collected and solvent evaporated until dryness to give 1.2g of crude Int. **206**, used like this in the next step.



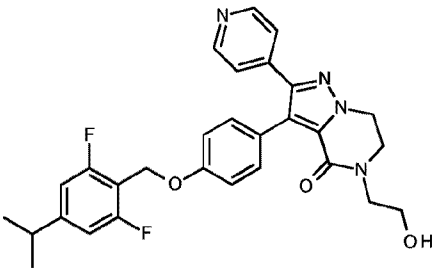
e- **Synthesis of Int. 207:**

Under N_2, DBAD (1.4 g, 6.2 mmol) was added portionwise to a sol. of **206** (1.2 g, 5.1 mmol), **7** (1.4 g, 6.2 mmol), PPh_3 supp. (1.9 g, 6.2 mmol) in dry THF (30 mL). The r.m. was stirred at r.t. for 3 days. PPh_3 supp. was filtered and the filtrate was evaporated to give 5.0 g, yellow oil. The crude residue was purified by prep. LC (irregular SiOH 30 µm 80 g GraceResolv™, mobile phase: heptane/EtOAc 90/10). The pure fractions were collected and the solvent evaporated until dryness to give 1.45 g of Int. **207**, yellow solid (72%).



f- **Synthesis of Int. 208:**

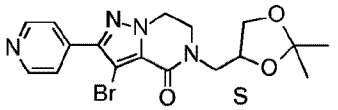
In a microwave vial, a mixture of **28** (0.48 g, 1.1 mmol), **207** (0.5 g, 1.3 mmol), K_3PO_4 (0.91 g, 4.3 mmol) in 1,4-dioxane (4.7 mL) and H_2O (1.7 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (88 mg, 0.11 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3x). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 1g, brown oil. This oil was purified by prep. LC (irregular SiOH 30 µm, 25 g Interchim, mobile phase gradient: DCM/MeOH/NH_4OH from 100/0/0 to 98/2/0.1). The pure fractions were collected and solvent evaporated until dryness to give 0.44 g of Int. **208**, yellow oil used like this in the next step.



g- **Synthesis of Co. 94:**

TBAF (0.84 mL, 0.84 mmol) was added dropwise to a sol. of **208** (0.44 g, 0.69 mmol) in THF (7 mL) at r.t. The mixture was stirred overnight at r.t. The mixture was concentrated. The residue was purified by prep. LC (Regular SiOH, 30 µm, 12 g GraceResolv™, mobile phase: DCM/MeOH/NH_4OH 97/3/0.1). The pure fractions were collected and solvent evaporated until dryness to give 210 mg which was triturated in Et_2O. The white solid was filtrated, washed and dried to give 145 mg of **Co. 94**, white solid (40%). m.p.: 194°C (dsc).

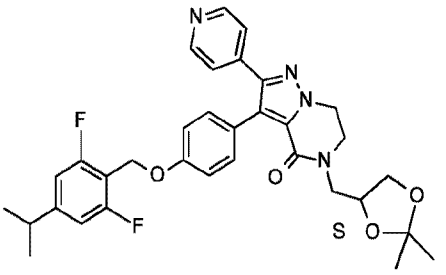
Example A96: Preparation of Co. 95a and Co. 95



a- **Synthesis of Int. 209:**

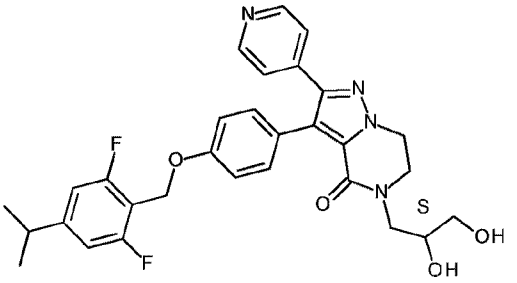
NaH 60% (2.5 g, 61.4 mmol) was added to **4** (12 g, 41 mmol) in DMSO (120 mL) at r.t. under N_2. The mixture stirred for 2h then (R)-(-)-2,2-dimethyl-1,3-dioxolane-4-ylmethyl p-toluenesulfonate (14 g;49.1 mmol) was added portionwise and the r.m. was

stirred for 15h. The mixture was poured into water and K_2CO_3 and extracted with EtOAc. The organic layer was evaporated until dryness. The residue was taken up with DCM and water. The organic layer was extracted, dried over $MgSO_4$, filtered and evaporated to give 15g. The residue was purified by prep. LC (120g of irregular SiOH 35-40µm GraceResolv™, mobile phase gradient: from 100% DCM to 95% DCM 5% CH_3OH 0.1% NH_4OH). The fractions were collected and evaporated to give 8 g of Int. **209** (S) (48%).



b- **Synthesis of Co. 95a:**

In a microwave vial, a mixture of **209** (0.44 g, 1.1 mmol), **207** (0.5 g, 1.3 mmol), K_3PO_4 (0.91 g, 4.3 mmol) in 1,4-dioxane (4.7 mL) and H_2O (1.7 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (88 mg, 0.11 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 0.85 g, brown oil. This oil was purified by prep. LC (irregular SiOH 30 µm, 25 g Interchim, mobile phase gradient: DCM/MeOH/NH_4OH from 100/0/0 to 98/2/0.1). The fractions were collected and evaporated until dryness to give 0.3g of **Co. 95a** (S), yellow oil (47%).

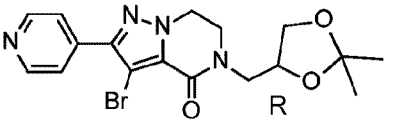


c- **Synthesis of Co. 95:**

A sol. of **Co. 95a** (0.3 g, 0.51 mmol) and HCl 3N (0.85 mL, 2.5 mmol) in 1,4-dioxane (11 mL) were heated to reflux for 1 h. The mixture was cooled to r.t., poured into sat. $NaHCO_3$ and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 4 g, GraceResolv™, Mobile phase gradient: DCM/MeOH/NH_4OH, from 97/3/0.1 to 95/5/0.1). The desired fractions were collected and evaporated until dryness

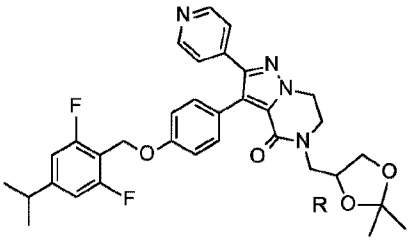
to give 141 mg. The residue was purified again, by prep. LC (Stationary phase: irregular SiOH 15-40µm 300g Merck, Mobile phase: 40% Heptane, 10% MeOH, 50% EtOAc). The pure fractions were collected and the solvent evaporated to give 103 mg of white solid. The solid was triturated in Et_2O, filtrated and dried to give 99 mg of **Co. 95** (S), white powder (35%). m.p.: 227°C (dsc); $[\alpha]_d$: -18.24 ° (589 nm, c 0.34 w/v %, DMF, 20 °C)

Example A97: Preparation of Co. 96a and Co. 96



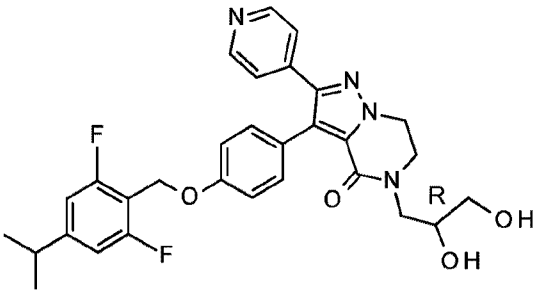
a- Synthesis of Int. 211:

NaH 60% (1.64 g, 41 mmol) was added to **4** (8 g, 27.3 mmol) in DMSO (80 mL) at r.t. under N_2. The mixture was stirred for 2h then (S)-(-)-2,2-dimethyl-1,3-dioxolane-4-ylmethyl P-toluenesulfonate (9.4 g, 32.7 mmol) was added portionwise and the r.m. was stirred for 15h. The mixture was poured into water and K_2CO_3 and extracted with EtOAc. The organic layer was evaporated until dryness. The residue was taken up with DCM and water. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated until dryness to give 10.75 g. The residue was purified by prep. LC (120g of irregular SiOH 35-40µm GraceResolv™, mobile phase gradient: from 100% DCM to 95% DCM 5% CH_3OH 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 5.55 g of Int. **211** (R) (50%).



b- Synthesis of Co. 96a:

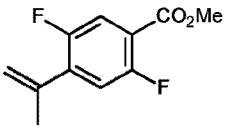
In a microwave vial, a mixture of **211** (0.41 g, 1.0 mmol), **207** (0.47 g, 1.2 mmol), K_3PO_4 (0.86 g, 4.0 mmol) in 1,4-dioxane (4.4 mL) and H_2O (1.6 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (83 mg, 0.10 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic layer was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 1.1g, brown oil. The mixture was purified by prep. LC (irregular SiOH 30 µm, 25 g Interchim, mobile phase: DCM/MeOH/NH_4OH 98/2/0.1). The fractions were collected and evaporated until dryness to give 0.2 g of **Co. 96a** (R), colorless oil.



c- Synthesis of Co. 96:

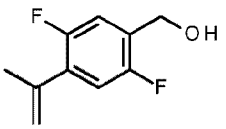
A sol. of **Co. 96a** (0.2 g, 0.34 mmol) and HCl 3N (0.57 mL, 1.7 mmol) in 1,4-dioxane (7.5 mL) were heated to reflux for 1 h. The mixture was cooled to r.t., poured into sat. $NaHCO_3$ and extracted with DCM. The organic layer was dried over $MgSO_4$, filtrated and evaporated until dryness to give 190 mg, colorless oil. This oil was purified by prep. LC (Stationary phase: Sunfire Silica 5µm 150x30.0mm, Mobile phase Gradient: from 0.2% NH_4OH, 98% DCM, 2% MeOH to 1% NH_4OH, 90% DCM, 10% MeOH). The pure fractions were collected and solvent evaporated until dryness to give 63 mg of white solid. This solid was triturated in Et_2O, filtrated and dried to give 50 mg of **Co. 96** (R), white solid (27%). m.p.: 228°C (dsc); $[\alpha]_d$: +17.22 ° (589 nm, c 0.302 w/v %, DMF, 20 °C)

Example A98: Preparation of Co. 97



a- Synthesis of Int. 213:

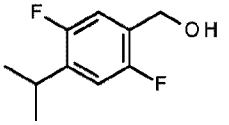
In a microwave vial, a mixture of methyl 4-bromo-2,5-difluorobenzoate (1.5 g, 6.0 mmol), CsF (2.0 g, 13 mmol) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 mL, 6.6mmol) in dry THF (60 mL) was purged with N_2. $Pd(tBu_3P)_2$ (153 mg, 0.30 mmol) was added and the mixture was purged again with N_2 and heated at 80°C overnight. Water and EtOAc were added, the organic layer was separated, washed with brine, dried on $MgSO_4$, filtered over Celite® and evaporated to give 2 g. The residue was purified by prep. LC (Regular SiOH, 30 µm, 40 g Interchim, mobile phase: Heptane/EtOAc 95/5). The pure fractions were collected and solvent evaporated until dryness to give 1g of Int. **213**, yellow oil (79%).



b- Synthesis of Int. 214:

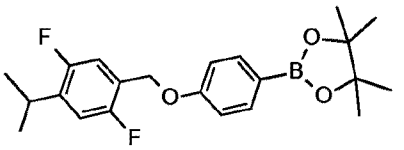
213 (1.0 g, 4.7 mmol) in dry THF (7.5 mL) was added dropwise to a suspension of LAH (0.39 g, 10 mmol) in dry THF (7.5 mL) at 0°C under N_2. The mixture was stirred

overnight at r.t. Water (1.4 mL) then DCM (75 mL) were added very slowly and the mixture was stirred for 20min. $MgSO_4$ was added and the insoluble was filtered on a pad of Celite® and evaporated until dryness to give 0.89 g of Int. **214**, pale brown oil (100%).



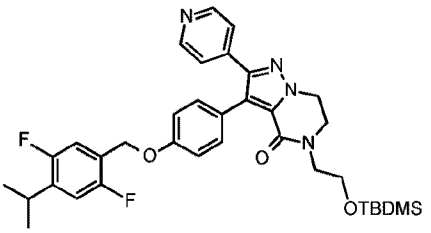
c- Synthesis of Int. 215:

A solution of **214** (0.89 g, 4.8 mmol), ammonium formate (1.8 g, 29 mmol), Pd/C 10% (258 mg, 0.24 mmol) in THF (7mL) and MeOH (22 mL) was refluxed for 30 min. The mixture was filtered through Celite®, washed with EtOAc, and the filtrate was concentrated. The residue was partitioned between water and EtOAc. The organic layer was separated, dried on $MgSO_4$, filtered and evaporated until dryness to give 0.83 g of Int. **215**, colorless oil (92%).



d- Synthesis of Int. 216:

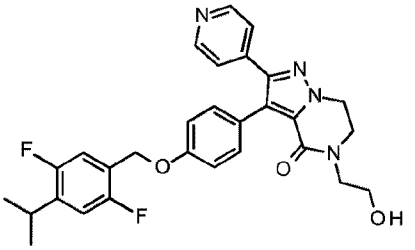
Under N_2, DBAD (1.2 g, 5.3 mmol) was added portionwise to a sol. of **215** (0.83 g, 4.5 mmol), **7** (1.2 g, 5.3 mmol), PPh_3 supp. (1.7 g, 5.3 mmol) in dry THF (30 mL). The mixture was stirred at r.t. overnight. PPh_3 supp. was filtered and the filtrate was evaporated to give 4.0 g, yellow oil. The crude residue was purified by prep. LC (irregular SiOH 30 µm 120 g GraceResolve™, mobile phase: heptane/EtOAc 90/10). The pure fractions were collected and solvent evaporated until dryness to give 1.26 g of Int. **216**, pale yellow oil (73%).



e- Synthesis of Int. 217:

In a microwave vial, a mixture of **28** (0.42 g, 0.94 mmol), **216** (0.4 g, 1.0 mmol), K_3PO_4 (0.80g, 3.7 mmol) in 1,4-dioxane (4.1 mL) and H_2O (1.5 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (77 mg, 0.10 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 0.9 g, brown oil. The crude was purified by prep. LC (irregular SiOH 30 µm, 25 g

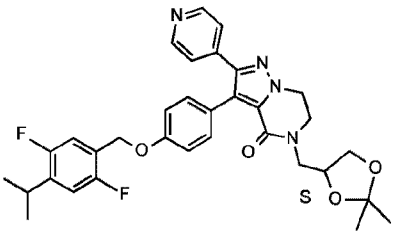
GraceResolve™, mobile phase: DCM/MeOH/NH_4OH 98/2/0.1). The pure fractions were collected and solvent evaporated until dryness to give 0.55 g of Int. **217**, pale yellow oil (93%).



f- Synthesis of Co. 97:

TBAF (1.0 mL, 1.0 mmol) was added dropwise to a sol. of **217** (0.55 g, 0.87 mmol) in THF (8.5 mL) at r.t. The mixture was stirred overnight at r.t.. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 µm, 25 g GraceResolv™, mobile phase gradient: DCM/MeOH/NH_4OH from 97/3/0.1 to 95/5/0.1). The pure fractions were collected and solvent evaporated until dryness to give 370 mg which was triturated in Et_2O. The white solid formed was filtrated, washed and dried to give 0.23 g, white solid. The white solid and filtrate were put together and evaporated to give a residue. The residue was purified by achiral SFC (Stationary phase: Amino 6µm 150x21.2mm, Mobile phase: 85% CO_2, 15% MeOH (0.3% $iPrNH_2$)). The pure fractions were collected and solvent evaporated until dryness to give 287 mg which was triturated in Et_2O. The white solid formed was filtrated and dried to give 199 mg of **Co. 97**, white solid (44%). m.p.: 147°C (dsc).

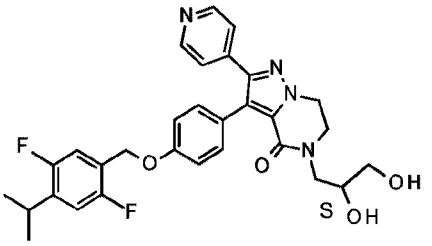
Example A99: Preparation of Co. 98a and Co. 98



a- Synthesis of Co. 98a:

In a microwave vial, a mixture of **209** (0.38 g, 0.94 mmol), **216** (0.4 g, 1.0 mmol), K_3PO_4 (0.80 g, 3.7 mmol) in 1,4-dioxane (4.1 mL) and H_2O (1.5 mL) was carefully purged with N_2. $PdCl_2$(dppf) (77 mg, 0.10 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (1x) and with brine (3x). The organic layer was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give a brown oil (1g). The crude was purified by prep. LC (irregular SiOH 30 µm, 25 g Interchim,

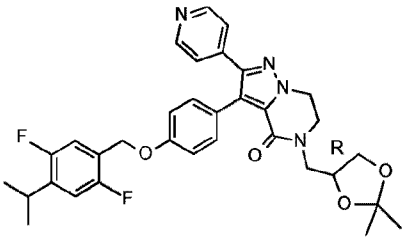
mobile phase: DCM/MeOH/NH_4OH 98/2/0.1). The pure fractions were collected and solvent evaporated until dryness to give 0.43g of **Co. 98a** (S), beige powder (78%).



b- Synthesis of Co. 98:

A sol. of **Co. 98a** (0.43 g, 0.73 mmol) and HCl 3N (1.2 mL, 3.6 mmol) in 1,4-dioxane (16 mL) were heated to reflux for 1 h. The mixture was cooled to r.t., poured into sat. $NaHCO_3$ and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 12g, GraceResolv™, Mobile phase gradient: DCM/MeOH/NH_4OH, from 96/4/0.1 to 95/5/0.1). The pure fractions were collected and solvent evaporated until dryness to give 350 mg, colorless oil. This oil was crystallized from Et_2O and the white solid formed was filtrated and dried to give 318 mg. The solid was purified by achiral SFC (Stationary phase: Amino 6µm 150x21.2mm, Mobile phase: 80% CO_2, 20% MeOH (0.3% $iPrNH_2$)). The pure fractions were collected and solvent evaporated to give 241 mg, white solid, which was triturated in Et_2O, filtrated and dried to give 215 mg of **Co. 98** (S), white solid (54%). m.p.: 184°C (dsc); $[\alpha]_d$: -17.99 ° (589 nm, c 0.339 w/v %, DMF, 20 °C).

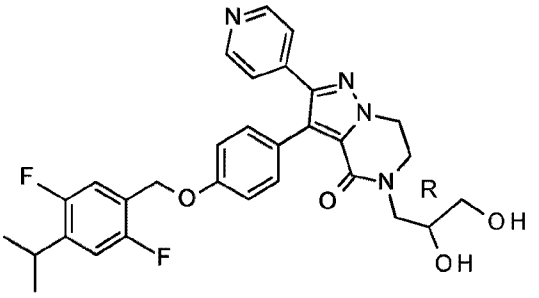
Example A100: Preparation of Co. 99a and Co. 99



a- Synthesis of Co. 99a:

In a microwave vial, a mixture of **211** (0.38 g, 0.94 mmol), **216** (0.4 g, 1.0 mmol), K_3PO_4 (0.80 g, 3.7 mmol) in 1,4-dioxane (4.1 mL) and H_2O (1.5 mL) was carefully purged with N_2. $PdCl_2$(dppf) (77 mg, 0.10 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give a brown oil. This oil was purified by prep. LC (irregular SiOH 30 µm, 25g Interchim,

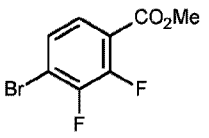
mobile phase: DCM/MeOH/NH_4OH 98/2/0.1). The pure fractions were collected and solvent evaporated until dryness to give 0.32 g of **Co. 99a** (R), colorless oil (58%).



b- Synthesis of Co. 99:

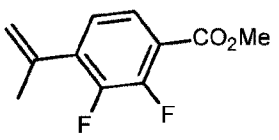
A sol. of **Co. 99a** (0.32 g, 0.54 mmol) and HCl 3N (0.91 mL, 2.7 mmol) in 1,4-dioxane (12 mL) were heated to reflux for 1 h. The mixture was cooled to r.t., poured into sat. $NaHCO_3$ and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness to give 300 mg. The residue was purified by achiral SFC (Stationary phase: Amino 6µm 150x21.2mm, Mobile phase: 80% CO_2, 20% MeOH (0.3% $iPrNH_2$)). The pure fractions were collected and solvent evaporated until dryness to give 191 mg of white solid. This solid was triturated in Et_2O, filtrated and dried to give 160 mg of **Co. 99** (R), white solid (54%). m.p.: 183°C (dsc); $[\alpha]_d$: +17.82 ° (589 nm, c 0.331 w/v %, DMF, 20 °C).

Example A101: Preparation of Co. 100



a- Synthesis of Int. 220:

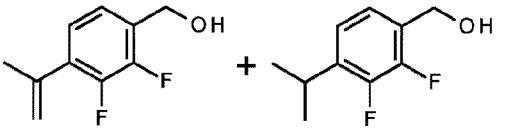
H_2SO_4 (1.1 mL, 21 mmol) was slowly added to a sol. of 4-bromo-2,3-difluorobenzoic acid (2.5 g, 10.5 mmol) in MeOH (40 mL). The mixture was heated at 50°C for 3 days. The mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc and water and basified with K_2CO_3. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 2.6 g of Int. **220**, colorless oil which crystallized in white solid (98%).



b- Synthesis of Int. 221:

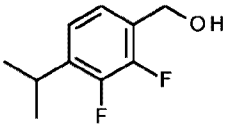
In a schlenk, a mixture of **220** (2. 5g,), CsF (3.3 g, 22 mmol) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.0 mL, 11 mmol) in dry THF (60 mL) was purged with N_2. $Pd(tBu_3P)_2$ (254 mg, 0.50 mmol) was added and the mixture was purged again with N_2 and heated at 80°C overnight. Water and EtOAc were added, the

organic layer was separated, washed with brine, dried on $MgSO_4$, filtered over Celite® and evaporated. The residue was purified by prep. LC (Regular SiOH, 30 µm, 80g GraceResolv™, mobile phase: Heptane/EtOAc 95/5). The pure fractions were collected and solvent evaporated to give 1.8 g of Int. **221**, yellow oil (85%).



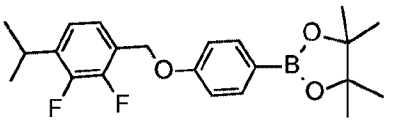
c- **Synthesis of Int. 222:**

221 (1.8 g, 8.5 mmol) in dry THF (14 mL) was added dropwise to a suspension of LAH (0.39 g, 10 mmol) in dry THF (14 mL) at 0°C under N_2. The mixture was stirred for 30 min. Water (1.4 mL) then DCM (75 mL) were added very slowly and stirred overnight. $MgSO_4$ was added and the insoluble was filtered on a pad of Celite® and the filtrate evaporated until dryness to give 1.5g of Int. mixture **222**, brown oil. The mixture was used like this in the next step.



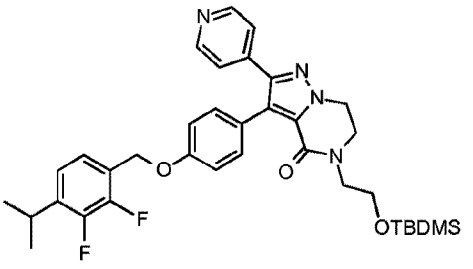
d- **Synthesis of Int. 223:**

222 (1. 5g, 8.1 mmol), ammonium formate (3.0 g, 49 mmol), Pd/C 10% (433 mg, 0.41 mmol), THF (14 mL) and MeOH (44 mL) were refluxed for 30 min. The mixture was filtered through Celite®, washed with EtOAc, and the filtrate was concentrated. The residue was partitioned between brine and EtOAc. The organic layer was separated, dried on $MgSO_4$, filtered and evaporated until dryness to give 1.47 g of Int. **223**, colorless oil (97%).



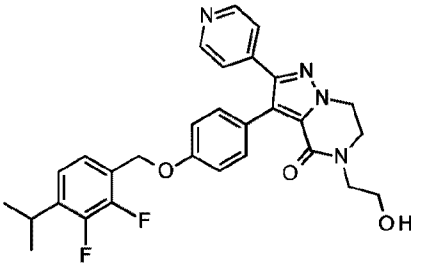
e- **Synthesis of Int. 224:**

Under N_2, DBAD (2.2 g, 9.5 mmol) was added portionwise to a sol. of **223** (1.47 g, 7.9 mmol), **7** (2.1 g, 9.5 mmol), PPh_3 supp. (3.0 g, 9.5 mmol) in dry THF (60 mL). The mixture was stirred at r.t. for 3days. PPh_3 supp. was filtered and the filtrate was evaporated to give 8 g, yellow oil. The crude residue was purified by prep. LC (irregular SiOH 30 µm 120 g GraceResolv™, mobile phase: heptane/EtOAc 90/10). The pure fractions were collected and solvent evaporated until dryness to give 2.36 g of Int. **224**, pale yellow oil which crystallized in beige solid (77%).



f- **Synthesis of Int. 225:**

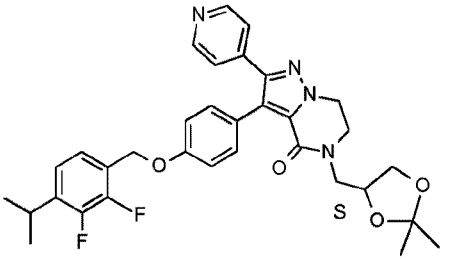
In a microwave vial, a mixture of **28** (0.42 g, 0.94 mmol), **224** (0.4 g, 1.0 mmol), K_3PO_4 (0.80 g, 3.7 mmol) in 1,4-dioxane (4.1mL) and H_2O (1.5mL) was carefully purged with N_2. $PdCl_2$(dppf) (77 mg, 0.10 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 1g of a residue which was purified by prep. LC (irregular SiOH 30 µm, 25g GraceResolv™, mobile phase: DCM/MeOH/NH_4OH 98/2/0.1). The pure fractions were collected and solvent evaporated until dryness to give 0.6 g of Int. **225**, yellow oil (100%).



g- **Synthesis of Co. 100:**

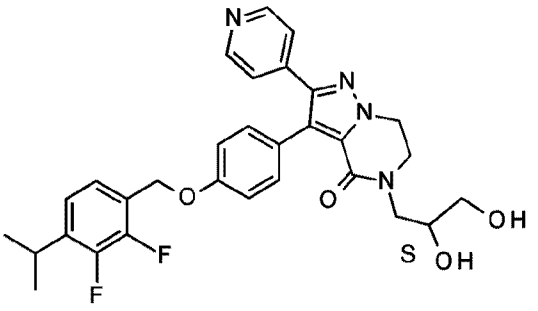
TBAF (1.1 mL, 1.1 mmol) was added dropwise to a sol. of **225** (0.60 g, 0.95 mmol) in THF (9.3 mL) at r.t. The mixture was stirred overnight at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 µm, 25 g GraceResolv™, mobile phase gradient: DCM/MeOH/NH_4OH from 96/4/0.1 to 95/5/0.1).The pure fractions were collected and solvent evaporated until dryness to give 450 mg. This residue was purified by prep. LC (Stationary phase: Sunfire C18 Xbridge 5µm 150x30.0mm, Mobile phase Gradient: from 70% (NH_4HCO_3 0.5% aq. sol.), 30% ACN to 100% ACN). 295 mg was collected and triturated in Et_2O. The white solid formed was filtrated, washed and dried to give 257 mg of **Co. 100**, white solid (52%). m.p.: 172°C (dsc).

Example A102: Preparation of Co. 101a and Co. 101



a- **Synthesis of Co. 101a**

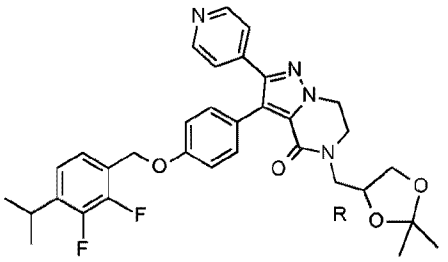
In a microwave vial, a mixture of **209** (0.38 g, 0.94 mmol), **224** (0.4 g, 1.), K_3PO_4 (0.80 g, 3.7 mmol) in 1,4-dioxane (4.1 mL) and H_2O (1.5 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (77 mg, 0.10 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give brown oil. This oil was purified by prep. LC (irregular SiOH 30 µm, 25g Interchim, mobile phase: DCM/MeOH/NH_4OH 98/2/0.1). The desired fractions were collected and solvent evaporated until dryness to give 0.33g of **Co. 101a** (S), beige powder (60%).



b- **Synthesis of Co. 101:**

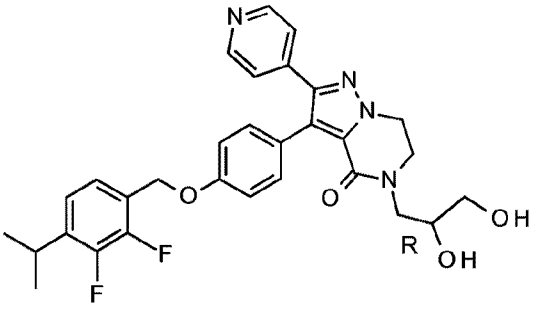
A sol. of **Co. 101a** (0.32 g, 0.54 mmol) and HCl 3N (0.91 mL, 2.7 mmol) in 1,4-dioxane (12 mL) were heated to reflux for 1 h. The mixture was cooled to r.t., poured into sat. $NaHCO_3$ and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness to give 0.4 g, colorless oil. This oil was purified by prep. LC (Stationary phase: Sunfire C18 Xbridge 5µm 150x30.0mm, Mobile phase Gradient: from 70% (NH_4HCO_3 0.5% aq. sol.), 30% ACN to 100% ACN). The pure fractions were collected and solvent evaporated until dryness to give 210 mg which was triturated in Et_2O. The white solid formed was filtrated, washed and dried to give 0.18 g of **Co. 101** (S), white solid (61%). m.p.: 192°C (dsc); $[\alpha]_d$: -19.88 ° (589 nm, c 0.2515 w/v %, DMF, 20 °C)

Example A103: Preparation of Co. 102a and Co. 102



a- **Synthesis of Co. 102a:**

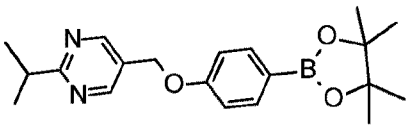
In a microwave vial, a mixture of **211** (0.38 g, 0.), **224** (0.4g , 1.0 mmol), K_3PO_4 (0.80 g, 3.7 mmol) in 1,4-dioxane (4.1 mL) and H_2O (1.5 mL) was carefully purged with N_2. $PdCl_2$(dppf) (77 mg, 0.10 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of celite® and evaporated *in vacuo* to give brown oil. The crude mixture was purified by prep. LC (irregular SiOH 30 µm, 25g Interchim, mobile phase: DCM/MeOH/NH_4OH 98/2/0.1). The pure fractions were collected and solvent evaporated until dryness to give 0.48 g of **Co. 102a** (R), colorless oil (87%).



b- **Synthesis of Co. 102:**

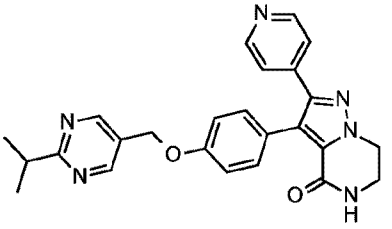
A sol. of **Co. 102a** (0.48 g, 0.82 mmol) and HCl 3N (1.4 mL, 4.1 mmol) in 1,4-dioxane (18 mL) were heated to reflux for 1 h. The mixture was cooled to r.t., poured into sat. $NaHCO_3$ and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness to give 520 mg, colorless oil. The crude was purified by prep. LC (Stationary phase: Sunfire C18 Xbridge 5µm 150x30.0mm, Mobile phase Gradient: from 70% (NH_4HCO_3 0.5% aq. sol.), 30% ACN to 100% ACN). The pure fractions were collected and solvent evaporated until dryness to give 241 mg which was triturated in Et_2O. The white solid formed was filtrated, washed and dried to give 215 mg of **Co. 102** (R), white solid (48%). m.p. = 191°C (dsc); $[\alpha]_d$: +19.28 ° (589 nm, c 0.249 w/v %, DMF, 20 °C).

Example A104: Preparation of Co. 103



a- Synthesis of Int. 228:

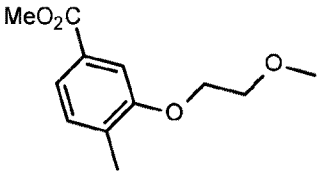
DBAD (446 mg, 1.94 mmol) was added to a stirred sol. of 7 (305 mg, 1.38 mmol), (2-isopropylpyrimidin-5-yl)methanol (295 mg, 1.94 mmol) and PPh_3 supp. (606 mg, 1.94 mmol) in THF (7 mL) under N_2 at r.t. The mixture was stirred at r.t. for 16 h. Then, additional PPh_3 supp. (130 mg; 0.416mmol) and DBAD (96 mg, 0.416 mmol) were added under N_2, and the mixture was stirred at r.t. for 16 h. The crude mixture was filtered off and the filtrate was evaporated *in vacuo* to give an oil. The oil was purified by prep. LC (Irregular SiOH 15-40 µm, 80g Grace, mobile phase gradient: from Heptane 100% to EtOAc 50%, Heptane 50%). The desired fractions were collected and solvent evaporated until dryness to give 800 mg of a solid which was purified by prep. LC (Irregular SiOH 15-40 µm, 30 g Grace, mobile phase gradient: from Heptane 100% to EtOAc 40%, Heptane 60%). The pure fractions were collected and solvent evaporated until dryness to give 590 mg of Int. **228**, solid (90%, purity 75%), used as such as for the next step.



b- Synthesis of Co. 103:

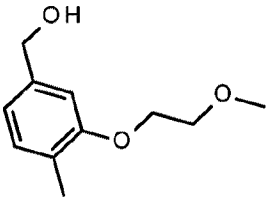
A mixture of 4 (150 mg, 0.512 mmol), 228 (590 mg, 1.25 mmol), K_3PO_4 (434 mg, 2.05 mmol) in 1,4-dioxane (3 mL) and H_2O (1 mL) was carefully purged with N_2. PCy_3 (29 mg, 0.102 mmol) and $Pd(OAc)_2$ (11 mg, 51.2 µmol) were added and the r.m. was purged again with N_2, and stirred for 68 h at 80°C. The crude material was treated with water and extracted with DCM. The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give a black solid. The solid was purified by prep. LC on (irregular SiOH 15-40µm 24g Grace, Mobile phase gradient: from DCM 100% to MeOH 10%, DCM 90%). The desired fractions were combined and the solvent was removed *in vacuo* to give 175 mg, white solid. The solid was purified by achiral SFC on (2-ethylpyridine 6µm 150x21.2mm; Mobile phase: 0.3% $iPrNH_2$, 80% CO_2, 20% MeOH). The pure fractions were collected and concentrated *in vacuo* to yield 161 mg of **Co. 103**, white solid (71%). m.p.: 235 °C (dsc).

Example A105: Preparation of Co. 104



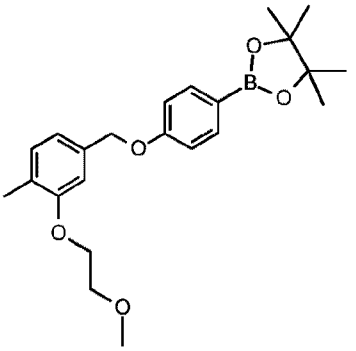
a- **Synthesis of Int. 229:**

Methyl 3-hydroxy-4-methylbenzoate (2.5 g, 15 mmol), 2-bromoethyl methyl ether (1.5 mL, 16.5 mmol), K_2CO_3 (3.1 g, 22.5 mmol) in ACN (40 mL) at 80°C overnight. Water and EtOAc were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The residue was purified by prep. LC on (Irregular SiOH 20-45µm 40g GRACE, Mobile phase gradient: 100% DCM to 99/1 DCM/MeOH). The pure fractions were collected and solvent evaporated until dryness to give 2.8g of Int. **229** (78%).



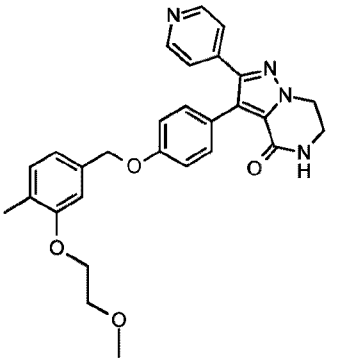
b- **Synthesis of Int. 230:**

LAH (287 mg, 7.5 mmol) was added carefully at 5°C to a sol. of **229** (1.5 g, 6.3 mmol) in THF (20 mL). The mixture was stirred at r.t. for 1h. Water was carefully added at 5°C and EtOAc were added. The mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated to give 1.2 g of Int. **230** (97%).



c- **Synthesis of Int. 231:**

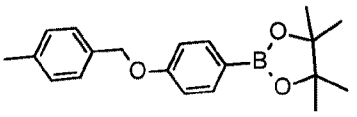
230 (1.2 g, 6.1 mmol), **7** (1.6 g, 7.3 mmol), PPh_3 supp. (2.4 g, 9.2 mmol) in THF (40 mL). DBAD (2.1 g, 9.2 mmol) was added portionwise at r.t. and the mixture was stirred at r.t. overnight. Water and EtOAc were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The residue was purified by prep. LC on (irregular 15-40µm 30g Merck, Mobile phase: 60/40 heptane/EtOAc). The pure fractions were collected and the solvent evaporated until dryness to give 1.2 g of Int. **231** (49%).



d- Synthesis of Co. 104:

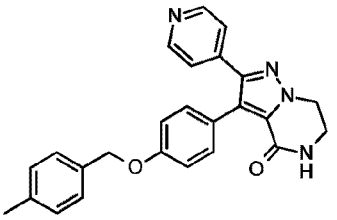
A mixture of **4** (400 mg, 1.36 mmol), **231** (0.71 g, 1.8 mmol), K_3PO_4 (1.16 g, 5.46 mmol) in 1,4-dioxane (7 mL) and H_2O (3 mL) was carefully purged with N_2. PCy_3 (80.4 mg, 0.29 mmol) and $Pd(OAc)_2$ (32 mg, 0.14 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 8h at 80°C. The crude material was poured in water and DCM, the residue was taken up in DCM and the precipitate was filtered off. The mother layer was evaporated and the residue was purified by prep. LC on (Irregular SiOH 20-45µm 40g MATREX, Mobile phase: 97/3 DCM/MeOH). The pure fractions were collected and solvent evaporated until dryness to give 150 mg of a residue which was taken up in Et_2O, the precipitate was filtered off and dried to give 79 mg of **Co. 104** (12%). m.p.: 190°C (dsc).

Example A106: Preparation of Co. 105



a- Synthesis of Int. 232:

A sol. of 4-methybenzylbromide (1.06 g, 4.81 mmol) in ACN (10 mL) was treated with K_2CO_3 (0.798 g, 5.78 mmol) and **7** (0.98 g, 5.3 mmol) at r.t. The r.m. was stirred for 18 h at r.t. Then, water and DCM were added, and the organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 1.6 g of Int. **232** (100%).

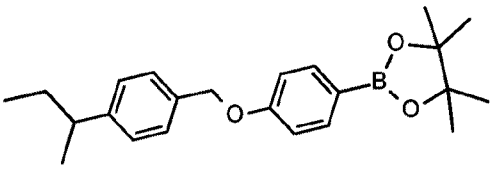


b- Synthesis of Co. 105:

In a microwave vial, a mixture of **4** (300 mg, 1.02 mmol), **232** (431 mg, 1.33 mmol), K_3PO_4 (911 mg, 4.29 mmol) in 1,4-dioxane (4.8 mL) and H_2O (1.6 mL) was carefully purged with N_2. PCy_3 (60 mg, 0.214 mmol) and $Pd(OAc)_2$ (24 mg, 0.107 mmol) were

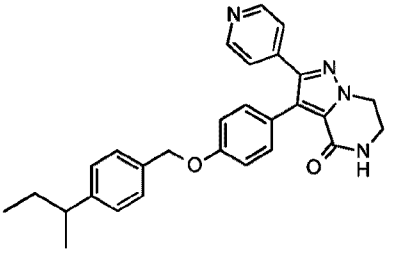
added and the r.m. was purged again with N_2. The r.m. was stirred for 16 h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 530 mg of crude residue. The residue was purified by prep. LC on (Stability Silica 5µm 150x30.0mm, Mobile phase Gradient: from 0.2% NH_4OH, 98% DCM, 2% MeOH to 1% NH_4OH, 89% DCM, 10% MeOH). The pure fractions were collected and the solvent was evaporated. 255 mg was obtained as a white solid. The solid was taken up in Et_2O, filtrated and dried to give 225 mg of **Co. 105**, white powder (54%). m.p.: 259°C (dsc).

Example A107: Preparation of Co. 106



a- Synthesis of Int. 233:

DBAD (3.8 g, 16.4 mmol) was added portionwise to a mixture of 4-(1-methylpropyl)-benzenemethanol (1.8 g, 11 mmol), **7** (2.4 g, 11 mmol), PPh_3 supp. (5.1 g, 16.4 mmol) in THF (30mL) at r.t. The mixture was stirred for 15h, filtered and washed with EtOAc. The filtrate was poured into water and K_2CO_3. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness to give 7 g. The residue was purified by prep. LC (120g of SiOH 35-40µm GraceResolv™, mobile phase gradient: from 95% heptane 5% EtOAc to 80% heptane 20% EtOAc). The fractions were collected and evaporated until dryness to give 3.3 g which was crystallized from heptane, filtered and dried to give 0.726 g of Int. **233** (18%). The filtrate was evaporated until dryness to give 2.6 g. This residue was purified by prep. LC (Stationary phase: irregular SiOH 15-40µm 300g MERCK, Mobile phase: 95% Heptane, 0.3% MeOH, 5% EtOAc). The desired fractions were collected and evaporated until dryness to give 1.75 g of Int. **233**. The both fractions were put together to give 2.47g of Int. **233** (Global yield: 62%).

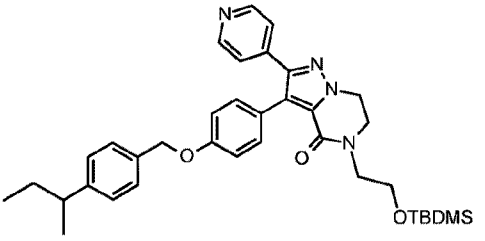


b- Synthesis of Co. 106:

A mixture of **4** (380 mg, 1.3 mmol), **233** (726 mg, 2 mmol), K_3PO_4 (1.1 g, 5.2 mmol) in 1,4-dioxane (7 mL) and H_2O (2.5 mL) was carefully purged with N_2. PCy_3 (72.7 mg, 0.26 mmol) and $Pd(OAc)_2$ (29.1 g, 0.13 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 18h at 80°C. Water and K_2CO_3 were added then

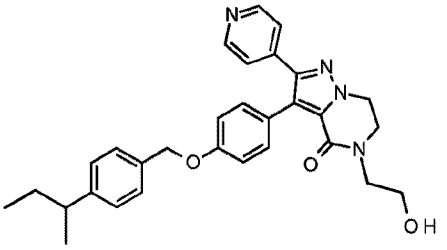
EtOAc. The mixture was filtered and the organic layer was extracted, dried over $MgSO_4$, filtered and evaporated until dryness. The residue was purified by prep. LC (40g of irregular SiOH 35-40µm GraceResolv™, mobile phase gradient: from 100% DCM to 95% DCM 5% CH_3OH 0.1% NH_4OH). The fractions were collected and evaporated until dryness. The product was crystallized from Et_2O, filtered and dried to give 188 mg of **Co. 106** (32%). m.p.: 229 °C (dsc).

Example A108: Preparation of Co. 107



a- Synthesis of Int. 234:

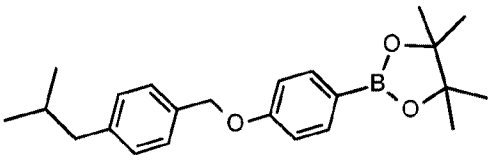
NaH 60% (0.115 g, 2.9 mmol) was added to a suspension of **Co. 106** (1 g, 2.21 mmol) in DMF (15 mL) at r.t. under N_2. The mixture was stirred for 2h. (2-bromoethoxy)-tert-butyldimethylsilane (0.57 mL, 2.65 mmol) was added and stirred for 20h. The mixture was poured into water and K_2CO_3 and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered and evaporated until dryness. The residue was purified by prep. LC (120 g of irregular SiOH 35-40µm GraceResolv™, mobile phase gradient: from 100% DCM to 97% DCM 3% CH_3OH 0.1% NH_4OH). The fractions were collected and evaporated to give 1.07 g of Int. **234** (79%).



b- Synthesis of Co. 107:

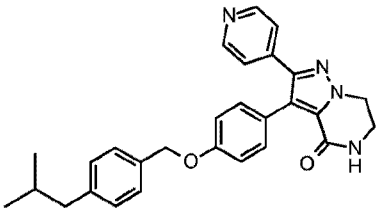
TBAF (2.1 mL, 2.1 mmol) was added dropwise to a sol. of **234** (1.1 g, 1.8 mmol) in THF (17 mL) at r.t. The mixture was stirred overnight at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 µm, 40g Interchim, mobile phase gradient: DCM/MeOH/NH_4OH from 98/2/0.1 to 96/4/0.1). The pure fractions were collected and solvent evaporated until dryness to give colorless oil which was crystallized from Et_2O. The white solid formed was filtrated, washed and dried to give 0.64 g of **Co. 107** (74%). m.p.: 163°C (dsc).

Example A109: Preparation of Co. 108



a- Synthesis of Int. 235:

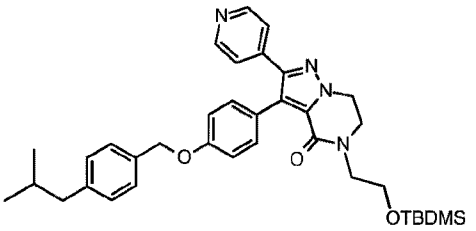
DBAD (3.8 g, 16.4 mmol) was added portionwise to a mixture of 4-iso-butylbenzyl alcohol (1.8 g, 11 mmol), **7** (2.4 g, 11 mmol), PPh_3 supp. (5.1 g, 16.4 mmol) in THF (30 mL) at r.t.. The mixture was stirred for 15h. The insoluble was filtered and washed with EtOAc. The filtrate was poured in water and K_2CO_3. The organic layer was extracted, dried over $MgSO_4$, filtered and evaporated until dryness to give 7.9 g. Heptane was added and the insoluble was filtered. The filtrate was purified by prep. LC (120g of SiOH 35-40µm GraceResolv™, mobile phase gradient: from 100% heptane to 90% heptane 10% EtOAc). The fractions were collected and evaporated until dryness to give 2.8 g. The residue was purified by prep. LC (Stationary phase: irregular SiOH 15-40µm 300g MERCK, Mobile phase: 95% Heptane, 0.3% MeOH, 5% EtOAc). The pure fractions were collected and solvent evaporated until dryness to give 1.8 g of Int. **235** (37%).



b- Synthesis of Co. 108:

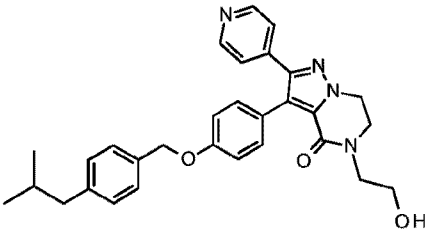
A mixture of **4** (0.96 g, 3.3 mmol), **235** (1.8 g, 4.9 mmol), K_3PO_4 (2.8 g, 13.1 mmol) in 1,4-dioxane (20 mL) and H_2O (2.5 mL) was carefully purged with N_2 in sealed tube. PCy_3 (184 mg, 0.655 mmol) and $Pd(OAc)_2$ (73.6 mg, 0.33 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 18h at 80°C. Water and K_2CO_3 were added then EtOAc. The mixture was filtered and the organic layer was extracted, dried over $MgSO_4$, filtered and evaporated until dryness to give 2 g. The residue was crystallized from MeOH, filtered and dried to give 1.33 g which was purified by prep. LC (40g of SiOH 30µm Interchim, mobile phase gradient: from 100% DCM to 95% DCM, 5% CH_3OH, 0.1% NH_4OH). The pure fractions were collected and evaporated until dryness to give 0.88 g which was crystallized from MeOH, filtered and dried to give 249 mg of **Co. 108** (17%). m.p.: 233°C (dsc).

Example A110: Preparation of Co. 109



a- Synthesis of Int. 236:

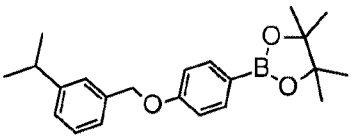
NaH 60% (78.1 mg, 1.9 mmol) was added to a suspension of **Co. 108** (0.68 g, 1.5 mmol) in DMF (10 mL) at r.t. under N_2. The mixture was stirred for 2h. (2-bromoethoxy)-tert-butyldimethylsilane (0.39 mL, 1.8 mmol) was added and stirred for 20h. The mixture was poured into water and K_2CO_3, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness. The residue was purified by prep. LC (120g of irregular SiOH 35-40µm GraceResolv™, mobile phase gradient: from 100% DCM to 97% DCM, 3% CH_3OH, 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 0.75 g of Int. **236** (86 %).



b- Synthesis of Co. 109:

TBAF (1.5 mL, 1.5 mmol) was added dropwise to a sol. of **236** (0.75 g, 1.3 mmol) in THF (12 mL) at r.t. The mixture was stirred overnight at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 µm, 25g Interchim, mobile phase: DCM/MeOH/NH_4OH, 98/2/0.1). The pure fractions were collected and solvent evaporated until dryness to give 0.60 g, colorless oil which was crystallized from Et_2O. The white solid formed was filtrated, washed and dried to give 0.38 g of **Co. 109** (62%).

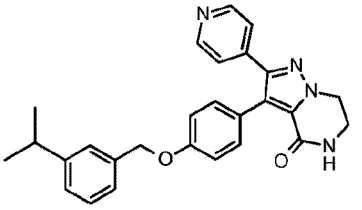
Example A111: Preparation of Co. 110



a- Synthesis of Int. 237:

To a suspension of (3-isopropylphenyl)methanol (586 mg, 2.66 mmol), 7 (520 mg, 2.77 mmol), PPh_3 supp. (2.86 g, 3.46 mmol) in dry THF (30 mL) was added DBAD (797 mg, 3.46 mmol) and the r.m. was stirred at r.t. for 18h. The r.m. was then filtered through a glass frit and washed with EtOAc. The filtrate was evaporated *in vacuo* to give 1.88 g. The residue was purified by prep. LC (irregular SiOH 15-40 µm, solid

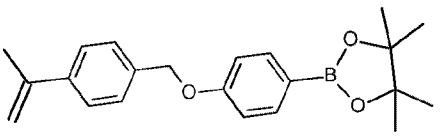
loading, 30 g Merck, mobile phase: heptane 90%, EtOAc 10%). The pure fractions were collected and solvent evaporated until dryness to give 710 mg of Int. **237**, colorless oil (76%).



b- Synthesis of Co. 110:

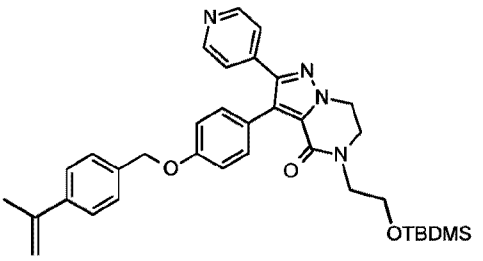
In a sealed tube, a mixture of **4** (197 mg, 0.672 mmol), **237** (710 mg, 2.015 mmol), K_3PO_4 (570 mg, 2.69 mmol) in 1,4-dioxane (3 mL) and H_2O (1 mL) was purged with N_2. PCy_3 (38 mg, 0.134 mmol) and $Pd(OAc)_2$ (15 mg, 67.2 µmol) were added and the r.m. was purged again with N_2. The tube was then sealed and the r.m. was stirred for 18h at 80°C. The crude material was dissolved in water (30 mL) and extracted with EtOAc (2x 40mL). The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 600 mg, brown oil. This oil was purified by prep. LC (irregular SiOH 15-40µm, 30g Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 269 mg, white solid. The solid was washed by Et_2O, filtered and dried to give 202 mg of **Co. 110**, white solid (69%). m.p.: 268°C (dsc).

Example A112: Preparation of Co. 111



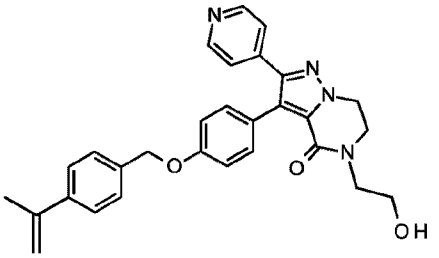
a- Synthesis of Int. 238:

To a suspension of 4-(1-methylethenyl)-benzenemethanol (0.675 g, 4.56 mmol), **7** (1.2 g, 5.47 mmol), DBAD (1.26 g, 5.47 mmol) in dry DCM (10 mL) was added PPh_3 supp. (1.7 g, 5.47 mmol) and the r.m. was stirred at r.t. for 18 h. The insoluble was filtered through Celite®, washed with DCM. Water was added and the organic layer was separated, dried, filtered and concentrated until dryness to give 2.76 g. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, Mobile phase: Heptane 90/EtOAc 10). The fractions were collected and evaporated until dryness to give 648 mg of Int. **238** (40%, purity 70%). The Co. was used as such for the next step.



b- Synthesis of Int. 239:

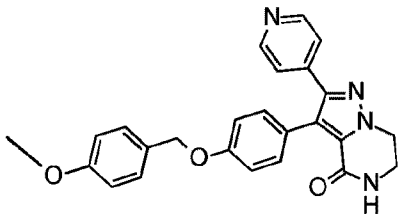
In a microwave vial, a mixture of **28** (0.663 g, 1.47 mmol), **238** (0.617 g, 1.76 mmol), K_3PO_4 (1.25 g, 5.87 mmol) in 1,4-dioxane (6.5 mL) and H_2O (2.3 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (120 mg, 0.15 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (1x) and with brine (3x). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 1.39 g. The residue was purified by prep. LC (Stationary phase: irregular SiOH 15-40µm 300g Merck, Mobile phase: 0.1% NH_4OH, 99% DCM, 1% MeOH). The desired fractions were collected and solvent evaporated until dryness to give 736 mg. This residue was purified again by achiral SFC (Stationary phase: Amino 6µm 150x21.2mm, Mobile phase: 90% CO_2, 10% MeOH). The pure fractions were collected and the solvent evaporated until dryness to give 385 mg of Int. **239** (44%).



c- Synthesis of Co. 111:

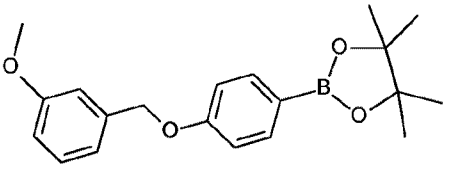
TBAF (0.78 mL, 0.78 mmol) was added dropwise to a sol. of **239** (0.385 g, 0.65 mmol) in THF (6 mL) at r.t. The mixture was stirred for 3h at r.t.. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 356 mg. The residue was purified by prep. LC (Regular SiOH, 30 µm, 12g GraceResolv™, mobile phase gradient: from DCM 100% to DCM/MeOH/NH_4OH 95/5/0.1). The pure fractions were collected and evaporated until dryness to give 282 mg which was crystallized from DIPE, filtered and dried to give 235 mg of **Co. 111** (76%). m.p.: 165°C (dsc).

Example A113: Preparation of Co. 112



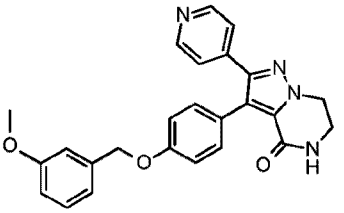
In a Schlenk tube, a mixture of **4** (700 mg, 2.39 mmol), 4-(4'-methoxybenzyloxy)phenylboronic acid (1.85 g, 7.16 mmol), K_3PO_4 (2.03 g, 9.55 mmol) in 1,4-dioxane (10.5 mL) and H_2O (3.5 mL) was carefully purged with N_2. PCy_3 (134 mg, 0.478 mmol) and $Pd(OAc)_2$ (54 mg, 239 µmol) were added and the r.m. was purged again with N_2. The Schlenk tube was then sealed and the r.m. was stirred for 17 h at 80°C. The crude material was dissolved in water (17mL) and filtered on glass frit. The grey precipitate was washed with water (2x 20mL) and with Et_2O (2x 40mL). The solid was collected to afford 1.40 g which was purified by prep. LC (irregular SiOH 15-40 µm, 50g Merck, mobile phase gradient: from DCM 100% to DCM 85%, MeOH 15%). The pure fractions were collected and solvent evaporated to give 700 mg of **Co. 112**, white solid (69%).

Example A114: Preparation of Co. 113



a- Synthesis of Int. 240:

A sol. of **7** (500 mg, 2.27 mmol) in ACN (5 mL) and DMF (1 mL) was treated with K_2CO_3 (377 mg, 2.73 mmol) and 3-methoxybenzyl bromide (360 µL, 2.50 mmol) at r.t. The r.m. was stirred for 54h at rt. Then water and EtOAc were added, and the organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 800 mg of Int. **240**, colorless oil (quant. yield).

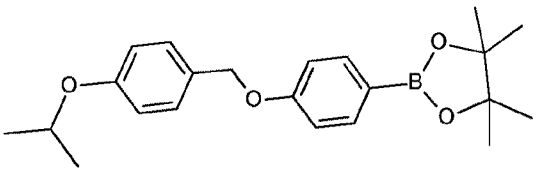


b- Synthesis of Co. 113:

In a sealed tube, a mixture of **4** (230 mg, 0.784 mmol), **240** (800 mg, 2.35 mmol), K_3PO_4 (665 mg, 3.14 mmol) in 1,4-dioxane (3.5 mL) and H_2O (1.2 mL) was carefully purged with N_2. PCy_3 (44 mg, 0.157 mmol) and $Pd(OAc)_2$ (18 mg, 78.4 µmol) were added and the r.m. was purged again with N_2. The sealed tube was then sealed and the

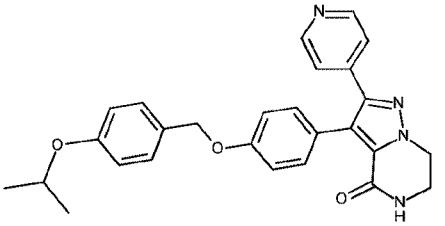
r.m. was stirred for 17 h at 80°C. The crude material was dissolved in water (10 mL) and extracted with EtOAc (2 x 40mL). The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 640 mg. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 30g Merck, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%). The pure fractions were collected and solvent evaporated until dryness to give 50 mg, white solid, which was washed by Et_2O, filtered and dired to give 36 mg of **Co. 113**, a white solid (11%). m.p.: 242°C (dsc).

Example A115: Preparation of Co. 114



a- Synthesis of Int. 241:

A sol. of 7 (700 mg, 3.18 mmol), 4-isopropoxybenzylalcohol (793 mg, 4.77 mmol) and PPh_3 (1.25 g, 4.77 mmol) in dry DCM (20 mL) was treated with DBAD (1.10 g; 4.77 mmol) and stirred at r.t. for 18h. The crude mixture was diluted with water and EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 590 mg of residue was purified by prep. LC (Irregular SiOH 15-40µm, 30g Merck, mobile phase gradient: from DCM 100% to MeOH 3%, DCM 97%). The desired fractions were collected and solvent evaporated until dryness to give 590 mg of a solid wich was purified by prep. LC (Irregular SiOH 15-40µm, 24g Grace, mobile phase gradient from Heptane 100% to EtOAc 40%, Heptane 60%). The pure fractions were collected and solvent evaporated to give 472 mg of Int. **241** (solid; 40%).

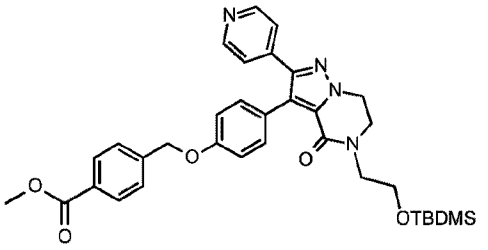


b- Synthesis of Co. 114:

A mixture of 4 (120 mg, 0.409 mmol), **241** (471 mg, 1.02 mmol), K_3PO_4 (348 mg, 1.64 mmol) in 1,4-dioxane (2.1 mL) and H_2O (0.7 mL) was carefully purged with N_2. PCy_3 (23 mg, 81.9 µmol) and $Pd(OAc)_2$ (9 mg, 40.9 µmol) were added and the r.m. was purged again with N_2, and stirred for 17h at 80°C. The crude material was dissolved in water and extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 447 mg, brown solid. The crude residue was purified by prep. LC on (irregular SiOH 15-40µm 300g MERCK, Mobile phase: 95% DCM, 5%

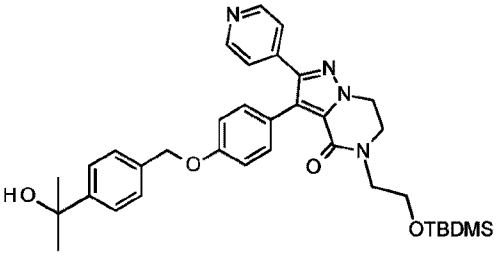
MeOH). The desired fractions were combined and the solvent was removed *in vacuo* to give 100 mg of **Co. 114**, white solid (54%). m.p.: 252 °C (dsc).

Example A116: Preparation of Co. 115



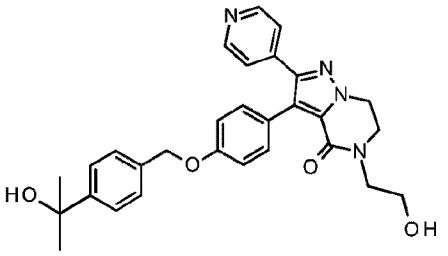
a- Synthesis of Int. 242:

In a microwave vial, a mixture of **28** (0.8 g, 1.77 mmol), **49** (0.848 g, 2.3mmol), K_3PO_4 (1.51 g, 7.1 mmol) in 1,4-dioxane (7.8 mL) and H_2O (2.8 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (0.145 g, 0.18 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water and with brine. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 1.66 g. The residue was purified by prep. LC (irregular SiOH 30 µm, 40g Interchim, mobile phase gradient: from DCM 100% to DCM/MeOH/NH_4OH 97/3/0.1). The pure fractions were collected and evaporated until dryness to give 1.11 g of Int. **242** (100%).



b- Synthesis of Int. 243:

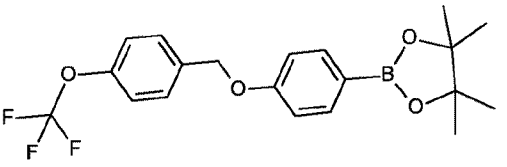
MeMgCl (3.05 mL, 9.06 mmol) was added to a stirred suspension of **242** (1.11 g, 1.81 mmol) in THF (17 mL) under N_2 at 0 °C. The mixture was stirred at 0° C for 5 min, and then it was warmed to r.t. and stirred for 2h. The r.m. was quenched with 10% NH_4Cl sol., and treated with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 1.09 g of Int. **243** (quant.), used as such for next step.



c- Synthesis of Co. 115:

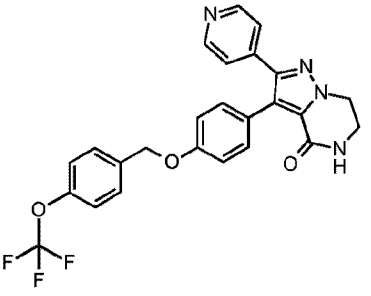
TBAF (2.02 mL, 2.02 mmol) was added dropwise to a sol. of **243** (1.03 g, 1.68 mmol) in THF (17 mL) at r.t.. The mixture was stirred for 3h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 712 mg. The residue was purified by prep. LC (Regular SiOH, 30 µm, 24g GraceResolv™, mobile phase gradient: from DCM 100% to DCM/MeOH/NH_4OH 95/5/0.1). The pure fractions were collected and evaporated until dryness to give 490 mg which was crystallized from Et_2O, filtered and dried to give 413 mg of **Co. 115**, white solid (49%). m.p.: 193°C (dsc).

Example A117: Preparation of Co. 116



a- Synthesis of Int. 244:

DBAD (2.04 g, 8.86 mmol) was added to a mixture of **7** (1.50 g, 6.82 mmol), 4-(trifluoromethoxy)benzyl acohol (1.28 mL; 8.86 mmol) and PPh_3 supp. (2.95 g; 8.86 mmol) in DCM (30mL) and the r.m. was stirred under N_2 for 17 h at rt. The r.m. was then filtered through a glass frit and washed with EtOAc. After concentration of the filtrate, the residue was purified by prep. LC (irregular SiOH 15-40 µm, solid loading, 30g Merck, mobile phase: heptane 80%, EtOAc 20%). The pure fractions were collected and solvent evaporated until dryness to give 2.00g of Int. **244**, yellow oil (74%).

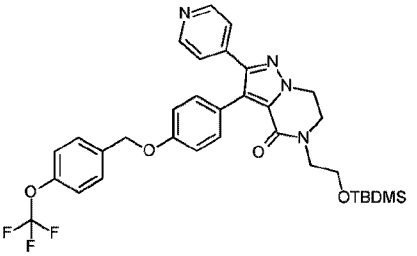


b- Synthesis of Co. 116:

In a microwave vial, a mixture of **4** (150 mg, 512 µmol), **244** (504 mg, 1.28 mmol), K_3PO_4 (455 mg, 2.15 mmol) in 1,4-dioxane (2.4 mL) and H_2O (0.8 mL) was carefully purged with N_2. PCy_3 (30 mg, 107 µmol) and $Pd(OAc)_2$ (12 mg, 53.6 µmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 17 h at 80°C. The crude material was dissolved in water (10 mL) and extracted with EtOAc (2x 40 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 400 mg, brown solid. The solid was purified by prep. LC (irregular SiOH 15-40 µm, 30g Merck, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%).

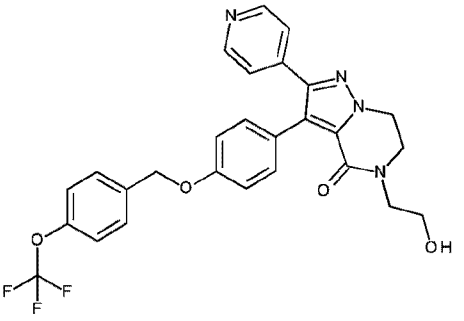
The pure fractions were collected and solvent evaporated until dryness to give 180 mg of **Co. 116**, white solid (73%). m.p.: 260 °C (dsc).

Example A118: Preparation of Co. 117



a- Synthesis of Int. 245:

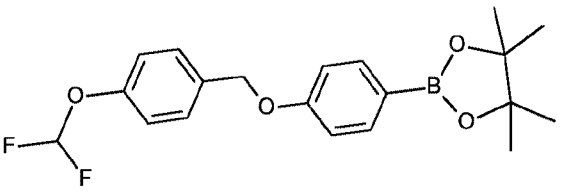
In a microwave vial, a mixture of **28** (0.7 g, 1.55 mmol), **244** (0.935 g, 2 mmol), K_3PO_4 (1.32 g, 6.2 mmol) in 1,4-dioxane (6.8 mL) and H_2O (2.42 mL) was carefully purged with N_2. $PdCl_2$(dppf) (127 mg, 0.155 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (1x) and with brine (3x). The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 2.17 g. The residue was purified by prep. LC (irregular SiOH 30 µm, 40 g Interchim, mobile phase: from DCM 100% to DCM/MeOH/NH_4OH 97/3/0.1). The pure fractions were collected and evaporated until dryness to give 923 mg of Int. **245** (93%, purity 85%), used as such for the next step.



b- Synthesis of Co. 117:

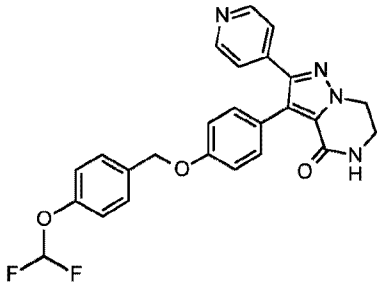
TBAF (1.73 mL, 1.73 mmol) was added dropwise to a sol. of **245** (920 mg, 1.44 mmol) in THF (14 mL) at r.t. The mixture was stirred for 3h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 865 mg. The residue was purified by prep. LC (Regular SiOH, 30 µm, 12g GraceResolv™, mobile phase gradient: from DCM 100% to DCM/MeOH/NH_4OH 95/5/0.1). The pure fractions were collected and evaporated until dryness to give 345 mg which was crystallized from DIPE, filtered and dried to give 319 mg of **Co. 117** (42%). m.p.: 134°C (dsc).

Example A119: Preparation of Co. 118



a- **Synthesis of Int. 246:**

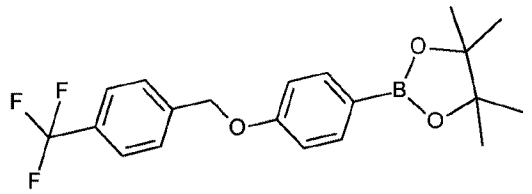
A sol. of 7 (0.76 g, 3.45 mmol) in ACN (10 mL) was treated with K_2CO_3 (0.572 g, 4.14 mmol) and 4-(difluoromethoxy)benzyl bromide (0.9 g, 3.8 mmol) at r.t. The r.m. was stirred for 18 h at r.t. Then, water and DCM were added, and the organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 1.29 g. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 30g Merck, Mobile phase: DCM 100%). The pure fractions were collected and evaporated until dryness to give 0.73 g of Int. **246** (56%).



b- **Synthesis of Co. 118:**

In a microwave vial, a mixture of 4 (0.3 g, 1.023 mmol), **246** (0.5 g, 1.33 mmol), K_3PO_4 (0.91 g, 4.29 mmol) in 1,4-dioxane (4.8 mL) and H_2O (1.6 mL) was carefully purged with N_2. PCy_3 (60 mg, 0.214 mmol) and $Pd(OAc)_2$ (24 mg, 0.11 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 16h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 745 mg. The residue was purified by prep. LC on (irregular SiOH 15-40µm 300g MERCK, Mobile phase: 40% Heptane, 10% MeOH (+10% NH_4OH), 50% EtOAc). The desired fractions were combined and the solvent was removed *in vacuo* to give 295 mg which was crystallized from DIPE, filtered and dried to give 287 mg of **Co. 118** (61%). m.p.: 250°C (dsc).

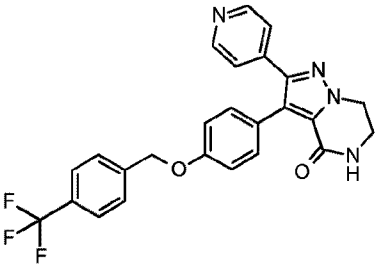
Example A120: Preparation of Co. 119



a- **Synthesis of Int. 247:**

DBAD (2.04 g, 8.86 mmol) was added to a mixture of 7 (1.50 g; 6.82 mmol), 4-(trifluoromethyl)benzyl alcohol (1.21 mL, 8.86 mmol) and PPh_3 supp. (2.95 g, 8.86

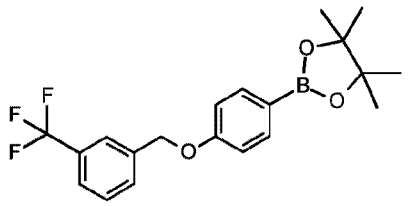
mmol) in DCM (30 mL) and the r.m. was stirred under N_2 for 17 h at rt. The r.m. was then filtered through a glass frit and washed with EtOAc. The sol. was concentrated to give 5.50 g, yellow oil. The residue was purified by prep. LC (irregular SiOH 15-40 µm, solid loading, 50g Merck, mobile phase: heptane 80%, EtOAc 20%). The pure fractions were collected and solvent evaporated until dryness to give 2.23g of Int. **247**, yellow oil (87%).



b- Synthesis of Co. 119:

In a sealed tube, a mixture of **4** (150 mg, 512 µmol), **247** (484 mg, 1.28 mmol), K_3PO_4 (455 mg, 2.15 mmol) in 1,4-dioxane (2.4 mL) and H_2O (0.8 mL) was carefully purged with N_2. PCy_3 (30 mg, 107 µmol) and $Pd(OAc)_2$ (12 mg, 53.6 µmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 17h at 80°C. The crude material was dissolved in water (10mL) and extracted with EtOAc (2 x 40mL). The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 400mg, brown solid. The residue was purified by prep. LC (irregular SiOH 15-40µm, 30 g Merck, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%). The pure fractions were collected and solvent evaporated until dryness to give 109 mg of **Co. 119**, white solid (46 %). m.p.: 280 °C (dsc).

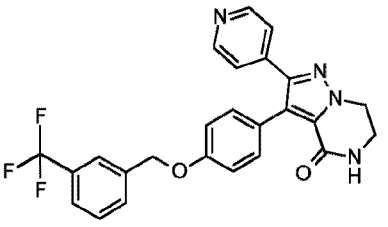
Example A121: Preparation of Co. 120



a- Synthesis of Int. 248:

K_2CO_3 (0.455 g, 3.29 mmol) and 3-(trifluoromethyl)benzyl alcohol (0.479 mL, 3.14 mmol) were successively added to a sol. of **7** (0.345 g, 1.57 mmol) in ACN (7.84 mL). The r.m. was stirred at r.t. for 18h. K_2CO_3 (0.130 g, 0.941 mmol) and 3-(trifluoromethyl)benzyl alcohol (0.120 mL, 0.784 mmol) were then successively added again. After 3h at r.t., the r.m. was filtrated, washed with EtOAc and concentrated to dryness. The residue was purified by column chromatography over silica gel (15-40 µm, 50g, mobile phase gradient: cyclohexane/DCM 50/50 to 0/100). The product

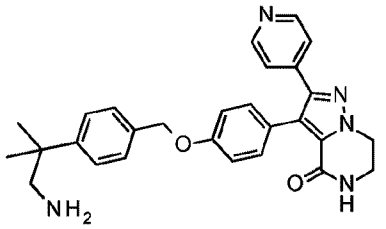
fractions were collected and the solvent was evaporated until dryness to give 0.560 g of Int. **248**, white solid (94%).



b- Synthesis of Co. 120:

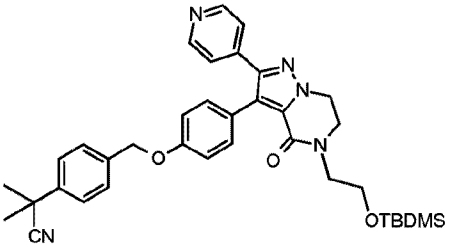
A sol. of **4** (0.14 3g, 0.488 mmol), **248** (0.554 g, 1.46 mmol) and K_3PO_4 (0.414 g, 1.95 mmol) in 1,4-dioxane/H_2O, 3/1 (2.9 mL) was degassed with an Ar-stream for 20 min and $Pd(OAc)_2$ (0.011 g, 0.049 mmol) and PCy_3 (0.027 g, 0.098 mmol) were then successively added. The r.m. was heated at 80 °C for 16h and at 120 °C for 20h. The r.m. was diluted with water (10mL) and extracted with EtOAc (3x 20mL).The combined organic layers were washed with a sat. aq. NaCl sol. (20mL), filtered and concentrated to dryness. The combined aq. layers were extracted with a mixture DCM/MeOH (9/1, 3 x 50mL), dried over sodium sulfate, filtered and concentrated to dryness. The residues were combined to afford 0.517 g, white powder. The powder was purified by column chromatography over silica gel (15-40 µm, 40g, mobile phase gradient: DCM/MeOH 97/3 to 95/5). The pure fractions were collected and the solvent was evaporated to afford 0.115g, white powder which was triturated in pentane (2 mL), filtered, washed with pentane (2 mL) and Et_2O (2 x 1mL) and dried to give 0.104g of **Co. 120**, white solid (46%). m.p.: 293°C (dsc).

Example A122: Preparation of Co. 121



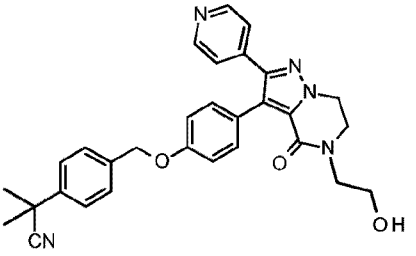
Co. 10 (210 mg, 0.45 mmol), Ni (210 mg) in MeOH (5 mL) was hydrogenated under 3 bars at r.t. for 4 h. The catalyst was filtered over a Celite® pad, the filtrate was evaporated. The residue was purified by prep. LC (Irregular SiOH 35-40 µm 40g GraceResolv™, mobile phase: 90/10/0.1 DCM/MeOH/NH_4OH). The fractions were collected and evaporated to give 106 mg of intial Co., Co. 10 and 49 mg of a residue. This residue was taken up in Et_2O, the precipitate was filtered off and dried to give 39 mg which was purified again by prep. LC (Irregular SiOH 35-40µm 40g GraceResolv™, mobile phase: 95/5/0.1 DCM/MeOH/NH_4OH). The fractions were collected and evaporated to give 15 mg of **Co. 121** (7%). m.p.: 233°C (dsc).

Example A123: Preparation of Co. 122



a- **Synthesis of Int. 249:**

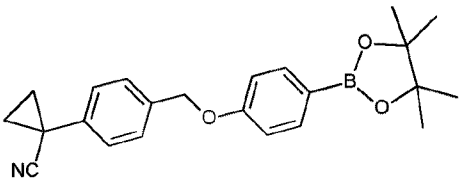
NaH 60% (33.6 mg, 0.8 mmol) was added slowly to a suspension of **Co. 10** (260 mg, 0.56 mmol) in DMSO (5.0 mL) at r.t. under N_2. The mixture was stirred for 2h, then (2-bromoethoxy)-tert-butyldimethylsilane (128 µl, 0.62 mmol) was added and stirred overnight. Water and DCM were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated until dryness to give 440 mg of Int. **249** (mixture with Co. 122). The mixture was used as such for the final step.



b- **Synthesis of Co. 122:**

TBAF (0.90 mL, 0.90 mmol) was added dropwise to a sol. of **249** (440 mg, 0.71 mmol) in THF (10mL) at r.t. The mixture was stirred 90 min at r.t. and poured into water, extrated with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated until dryness. The residue was purified by prep. LC (Regular SiOH, 30 µm, 25g grace, mobile phase gradient: DCM/MeOH/NH_4OH from 97/3/0.1 to 94/6/0.1). The pure fractions were collected and solvent evaporated until dryness to give 150 mg. The residue was crystallized from Et_2O, the solid was filtered off and dried to give 120 mg of **Co. 122** (33%). m.p.: 199°C (dsc).

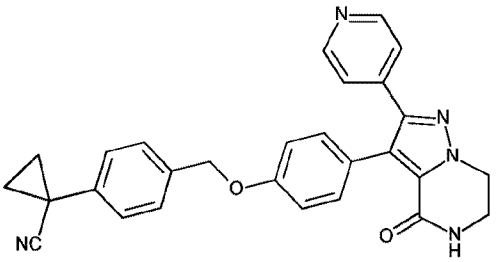
Example A124: Preparation of Co. 123



a- **Synthesis of Int. 250:**

PPh_3 supp. (1.55 g, 4.97 mmol) and DBAD (1.15 g, 4.97 mmol) were added to a stirred sol. of 7 (912 mg, 4.14 mmol) and 1-[4-(hydroxymethyl)phenyl]cyclopropane-1-carbonitrile (970 mg, 4.14 mmol) in anhydrous DCM (20 mL) under N_2 at r.t. The r.m.

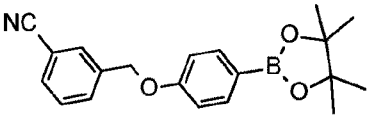
was stirred at r.t. for 2h, and then the crude mixture was filtered off and the filtrate was diluted with DCM and sat $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 2.81 g, brown solid. The solid was purified by prep. LC (Irregular SiOH 50 µm, 120g Grace, mobile phase gradient: from DCM 40%, Heptane 60% to DCM 100%). The desired fractions were collected and evaporated *in vacuo* to give 910 mg of Int. **250** (a solid) which was used as such for the next reaction step.



b- Synthesis of Co. 123:

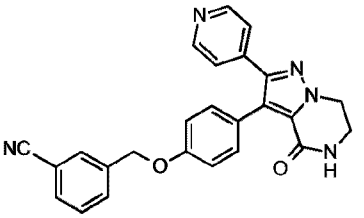
A mixture of **4** (0.464 g, 1.58 mmol), **250** (0.900 g, 2.40 mmol) and K_3PO_4 (1.01 g, 4.75 mmol) in 1,4-dioxane (9 mL) and H_2O (3 mL) was carefully purged with N_2. PCy_3 (89 mg, 0.317 mmol) and $Pd(OAc)_2$ (36 mg, 0.158 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 18 h at 80°C. The crude material was dissolved in water and extracted with DCM. The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 2.29 g, yellow solid. The solid was purified by prep. LC (irregular SiOH 15-40 µm, 80 g Grace, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The desired fractions were collected and solvent evaporated to give 253 mg, white solid. The residue was purified by prep. LC (Stationary phase: X-Bridge-C18 5µm 30*150mm, Mobile phase gradient: from 70% (NH_4HCO_3 0.5% aq. sol.), 30% ACN to 100% ACN). The desired fractions were isolated and evaporated *in vacuo* to yield 70 mg of **Co. 123**, white solid (10%). m.p.: 260 °C (dsc).

Example A125: Preparation of Co. 124



a- Synthesis of Int. 251:

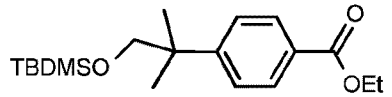
A sol. of **7** (1.5 g, 6.82 mmol) in ACN (15 mL) and DMF (3 mL) was treated with C (1.13 g; 8.18 mmol) and 3-(bromomethyl)benzonitrile (1.55 g, 7.50 mmol) at rt. The r.m. was stirred for 36h at r.t. Water and EtOAc were added, and the organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford 2.63 g of Int. **251**,(quant. yield).



b- Synthesis of Co. 124:

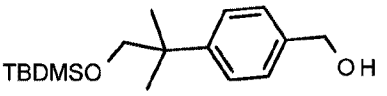
A mixture of 4 (0.87 g, 2.98 mmol), **251** (2.63 g, 7.45 mmol), K_3PO_4 (2.53 g, 11.9 mmol) in 1,4-dioxane (12 mL) and H_2O (4 mL) was carefully purged with N_2. PCy_3 (167 mg, 0.596 mmol) and $Pd(OAc)_2$ (67 mg, 0.298 mmol) were added, and the r.m. was purged again with N_2. The r.m. was stirred for 17h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give a solid. This solid was purified by prep. LC (irregular SiOH 15-40 µm, 120g Grace, mobile phase gradient: from DCM 100% to DCM 89%, MeOH 11%). The pure fractions were collected and solvent evaporated until dryness to give 1.09 g, white solid. The solid was triturated with DCM, filtered and dried to yield 576 mg of **Co. 124**, white solid (46%). m.p.: 238 °C (dsc).

Example A126: Preparation of Co. 125



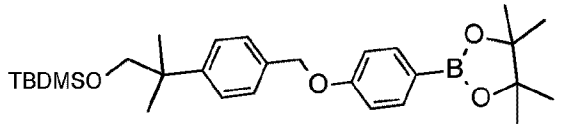
a- Synthesis of Int. 252:

4-(2-hydroxy-1,1-dimethylethyl)-benzoic acid,ethyl ester (0.513g, 2.3mmol), tert-butyldimethylsilyl chloride (0.522g, 3.46mmol), and imidazole (0.47g, 6.92mmol) in DMF (6mL) was stirred at r.t. for 3h. Water and DCM were added and the mixture was extracted with DCM. The organic layer was dried, filtered and evaporated to give 667mg of Int. **252** (86%).



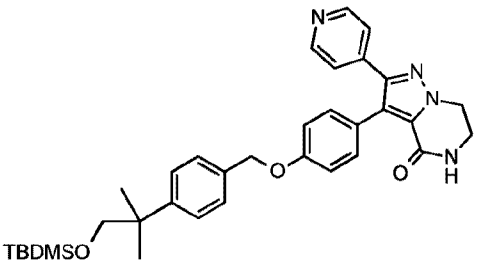
b- Synthesis of Int. 253:

LAH (36 mg, 0.94 mmol) was added carefully at 5°C to a sol. of **252** (210 mg, 0.62 mmol) in THF (3 mL). The mixture was stirred at r.t. for 1h. Water was carefully added at 5°C and EtOAc was added. The mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated to give 180 mg of Int. **253** (98%).



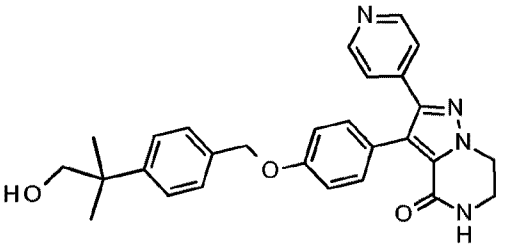
c- Synthesis of Int. 254:

To a suspension of **253** (0.515 g, 1.75 mmol), 7 (0.462 g, 2.1 mmol), DBAD (0.483 g, 2.1 mmol) in dry DCM (6 mL) was added PPh_3 supp. (0.656 g, 2.1 mmol) and the r.m. was stirred at r.t. for 18h. The insoluble was filtered through Celite®, washed with DCM. Water was added and the organic layer was separated, dried, filtered and concentrated until dryness to give 1.29 g. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, Mobile phase gradient: from 100% Heptane to 95/5 Heptane/EtOAc). The pure fractions were collected and evaporated until dryness to give 625 mg of Int. **254** (72%).



d- Synthesis of Int. 255:

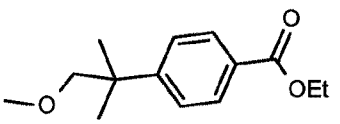
In a microwave vial, a mixture of **4** (0.218 g, 0.744 mmol), **254** (0.6 g, 0.967 mmol), K_3PO_4 (0.662 g, 3.12 mmol) in 1,4-dioxane (3.5 mL) and H_2O (1.2 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (61mg, 0.074 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred for 16 h at 80 °C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 828 mg. The residue was purified by prep. LC (Stationary phase: irregular 15-40µm 30g Merck, Mobile phase: NH_4OH/DCM/MeOH 0.4/96/4) to give 180 mg of Int. **255** (42%).



e- Synthesis of Co. 125:

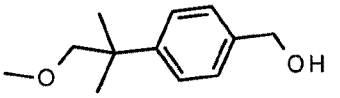
TBAF (0.37 mL, 0.37 mmol) was added dropwise to a sol. of **255** (0.18 g, 0.31 mmol) in THF (3.0 mL) at r.t. The mixture was stirred 2h at r.t. 1 equivalent of TBAF was added and the reaction was let at r.t. overnight to complete the reaction. The mixture was evaporated to dryness and purified by prep. LC (irregular SiOH 15-40 µm, 12g, GraceResolv™, Mobile phase: DCM/MeOH/NH_4OH, 96/4/0.1). The pure fractions were collected and solvent was evaporated until dryness to give 110 mg, white solid. The solid was triturated in Et_2O, filtrated and dried to give 97 mg of **Co. 125**, white solid (67%). m.p.: 280°C (dsc).

Example A127: Preparation of Co. 126



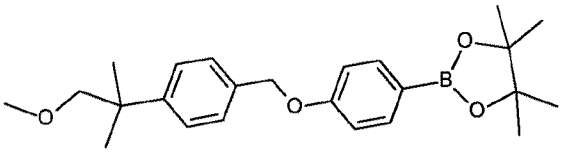
a- Synthesis of Int. 256:

To a sol. of 4-(2-hydroxy-1,1-dimethylethyl)-benzoic acid, ethyl ester (0.54 g, 2.43 mmol) in DMF (8 mL) was added MeI (0.76 mL, 12.1 mmol) and NaH 60% (0.146 g, 3.65 mmol). The mixture was stirred at r.t. for 3h. The reaction was quenched with water, and extracted with EtOAc. The organic layer was separated, whashed with K_2CO_3 10%, dried over $MgSO_4$, filtered and concentrated to give 566 mg of Int. **256** (99%, mixture of ethyl and methyl ester 88/12 was observed).



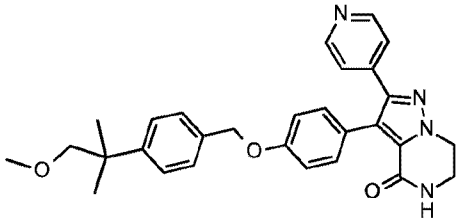
b- Synthesis of Int. 257:

LAH (0.111 g, 2.92 mmol) was added carefully at 10°C to a sol. of **256** (0.46 g, 1.95 mmol) in THF (6 mL). Cooled bath was removed immediately and the mixture was stirred at r.t. for 1h. Water was carefully added at 5°C and EtOAc was added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated to give 370 mg of Int. **257** (98%).



c- Synthesis of Int. 258:

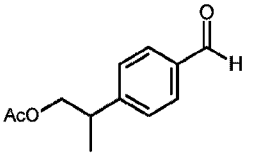
To a suspension of **257** (0.37 g, 1.91 mmol), 7 (0.504 g, 2.2 9mmol), PPh_3 supp. (0.716 g, 2.29 mmol) in dry DCM (6 mL) was added DBAD (0.528 g, 2.29 mmol) and the r.m. was stirred at r.t. for 18 h. The insoluble was filtered through Celite® pad, washed with DCM. Water was added and the organic layer was separated, dried, filtered and concentrated until dryness to give 1.45 g. The residue was purified by prep. LC on (Irregular SiOH 15-40µm 50g Merck, Mobile phase gradient: from 95/5 Heptane/ EtOAc to 90/10 Heptane/EtOAc). The pure fractions were collected and evaporated until dryness to give 421 mg of Int. **258** (56%).



d- Synthesis of Co. 126:

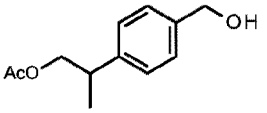
In a microwave vial, a mixture of **4** (0.2 g, 0.682 mmol), **258** (0.439 g, 0.887 mmol), K_3PO_4 (0.607 g, 2.86 mmol) in 1,4-dioxane (3.2 mL) and H_2O (1 mL) was carefully purged with N_2. $PdCl_2$(dppf) (56 mg, 0.068 mmol) was added and the r.m. was purged again with N_2. The r.m. was stirred for 16 h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 680 mg. The residue was purified by prep. LC (Stationary phase: Stability Silica 5µm 150x30.0mm, Mobile phase gradient: from 0.2% NH_4OH, 98% DCM, 2% MeOH to 1% NH_4OH, 89% DCM, 10% MeOH). The pure fractions were collected and solvent was evaporated until dryness to give 85 mg which was crystallized from Et_2O, filtered and dried to give 46 mg of **Co. 126** (14%). m.p.: 212°C (dsc).

Example A128: Preparation of Co. 127



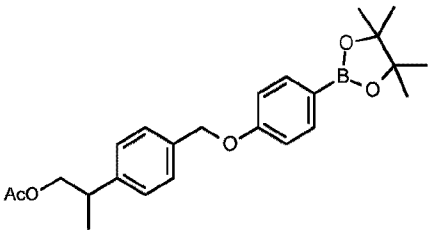
a- Synthesis of Int. 259:

A mixture of 2-phenyl-1-propanol acetate (3.0 g, 16.8 mmol) and Alpha,alpha dichloromethyl methyl ether (3.87 g, 33.7 mmol) in dry DCM (15 mL) was cooled to 0°C and treated with Titanium(IV) chloride 1M in DCM (84 mL, 84.2 mmol) over 15 min. The r.m. was then warmed to r.t. and stirred for 17h at r.t. The crude mixture was poured into ice. DCM was added and the organic layer was separated, washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to afford 3.8g of Int. **259**, black oil (quant.), used as such for the next step.



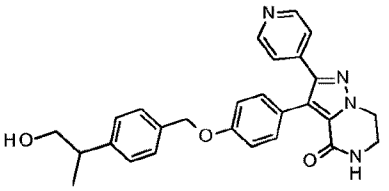
b- Synthesis of Int. 260:

A sol. of **259** (3.70 g, 17.9 mmol) in THF (40 mL) was treated with $NaBH_4$ (1.36 g, 35.9 mmol) and stirred at r.t. for 1h. After addition of water and DCM, the organic layer was separated, washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give 3.6 g. The crude mixture was purified by prep. LC (irregular SiOH 15-40 µm, 120g, GraceResolv™, solid loading, mobile phase gradient: from heptane 60%, EtOAc 40% to heptane 20%, EtOAc 80%). The pure fractions were collected and solvent evaporated until dryness to give 2.19 g of Int. **260**, yellow oil (59%).



c- **Synthesis of Int. 261:**

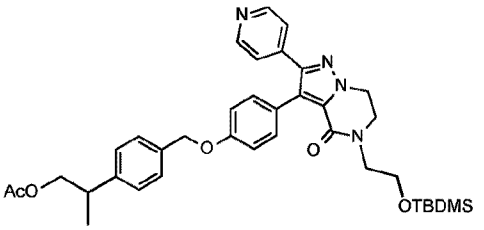
A mixture of **260** (2.19 g, 10.5 mmol), **7** (1.78 g; 8.09 mmol), PPh_3 (2.76 g, 10.5 mmol) in dry THF (50 mL) was treated with DBAD (2.42 g, 10.5 mmol) and stirred at r.t. for 2h30. The r.m. was then poured in DCM, washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to afford a residue. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 120 g, GraceResolv™, solid loading, mobile phase gradient: from heptane 90%, EtOAc 10% to heptane 60%, EtOAc 40%). The pure fractions were collected and solvent evaporated until dryness to give 3.18 g of Int. **261**, colorless oil (96%).



d- **Synthesis of Co. 127:**

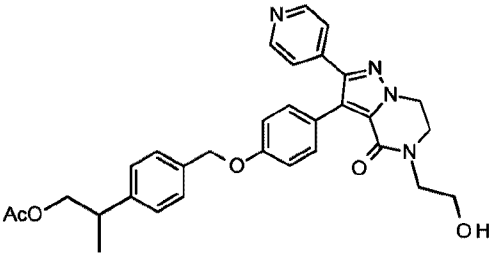
A mixture of **4** (500 mg, 1.71 mmol), **261** (1.40 g, 3.41 mmol) and K_3PO_4 (1.27 g, 5.97 mmol) in 1,4-dioxane (5 mL) and H_2O (10 mL) was purged with N_2. Then, $PdCl_2(dppf)$ (140 mg, 171 µmol) was added. The mixture was purged again with N_2 and heated at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min [fixed hold time]. The r.m. was poured in MeOH (20mL) and stirred at 100°C for 2h and poured in DCM and water. The organic layer was separated, washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The brown residue was purified by prep. LC (irregular SiOH 15-40µm, 80g, GraceResolv™, Mobile phase gradient: from DCM 100% to DCM 92%, MeOH 8%). The pure fractions were collected and solvent evaporated to give 720 mg of off-white solid. The solid was triturated in MeOH. After filtration, the white solid was washed with Et_2O, collected and dried *in vacuo* to afford 558 mg of **Co. 127**, white solid (72%). m.p.: 259°C (dsc).

Example A129: Preparation of Co. 128



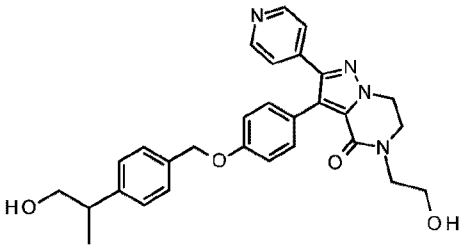
a- Synthesis of Int. 262:

In a microwave vial, a mixture of **28** (0.8 g, 1.77 mmol), **261** (0.945 g, 2.3 mmol), K_3PO_4 (1.51 g, 7.09 mmol) in 1,4-dioxane (7.8 mL) and H_2O (2.8 mL) was carefully purged with N_2. $PdCl_2(dppf)$ (0.145 g, 0.18 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water and with brine. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 2.5 g. The residue was purified by prep. LC (irregular SiOH 15-40µm, 80g grace, mobile phase gradient: from DCM 100% to DCM/MeOH/NH_4OH 97/3/0.1). The desired fractions were collected and evaporated until dryness to give 1.3 g. The residue was purified by prep. LC (Regular SiOH 30 µm, 40g Interchim, liquid loading, mobile phase gradient: DCM 100% to DCM 97%, MeOH 3%). The pure fractions were collected and the solvent was evaporated until dryness to give 996 mg of Int. 262 (yield 86%; purity 100%) and 229 mg of impure Int. 262 (yield 20%; purity 78%). Both fractions were combined and used as such, together, for the next step. Global yield: 1.2g of Int. **262**.



b- Synthesis of Int. 263:

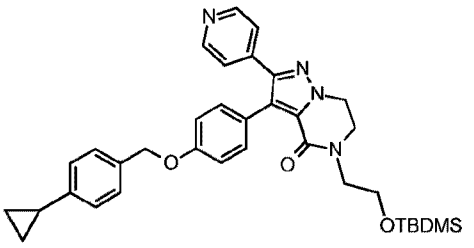
TBAF (2.25 mL, 2.25 mmol) was added dropwise to a sol. of **262** (1.23 g, 1.89 mmol) in THF (18 mL) at r.t. The mixture was stirred for 2h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 1.04 g of Int. **263** (100%).



c- Synthesis of Co. 128:

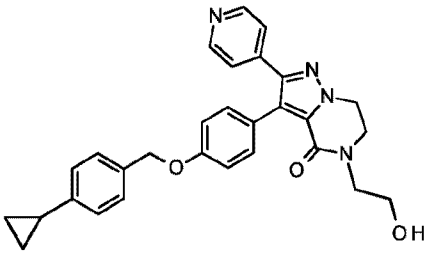
To a sol. of **263** (1g, 1.85 mmol) in MeOH (12 mL) was added Potassium hydroxide (399 mg, 5.55 mmol) and the mixture was heated at 50°C for 3h. The solid formed was filtered and washed from Et_2O then pourred into water and extracted with DCM and few MeOH several times. The organic layer was separated, dried, filtered and evaporated until dryness to give 764 mg. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 24g grace, mobile phase gradient: from DCM 100% to DCM/MeOH/NH_4OH 94/6/0.1). The pure fractions were collected and evaporated until dryness to give 648 mg which was crystallized from Et_2O, filtered and dried to give 538 mg. This residue was purified by achiral SFC (Stationary phase: Chiralpak IA 5µm 250*20mm, Mobile phase: 55% CO_2, 45% MeOH (0.3% $iPrNH_2$)). The pure fractions were collected and evaporated until dryness to give 400 mg which was crystallized from Et_2O, filtered off and dried to give 384 mg of **Co. 128** (42%).

Example A130: Preparation of Co. 129



a- Synthesis of Int. 264:

In a schlenk tube, a mixture of **28** (4.0 g, 8.9 mmol), **32** (3.4 g, 9.8 mmol), K_3PO_4 (7.5 g, 35 mmol) in 1,4-dioxane (39 mL) and H_2O (14 mL) was carefully purged with N_2. $PdCl_2$(dppf) (726 mg, 0.89 mmol) was added and the r.m. was purged again with N_2. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over $MgSO_4$, filtered on a pad of Celite® and evaporated *in vacuo* to give 7.5g of Int. **264**, brown oil (quant. , purity 70%). The Co. was used like this in the next step.

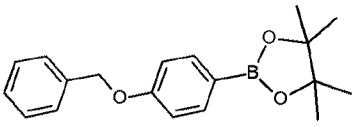


b- Synthesis of Co. 129:

TBAF (10.6 mL, 10.6 mmol) was added dropwise to a sol. of **264** (7.5 g, 8.8 mmol, 70%) in THF (86 mL) at r.t. The mixture was stirred overnight at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 µm, 120g GraceResolv™, mobile phase: DCM/MeOH/NH_4OH 96/4/0.1). The desired fractions

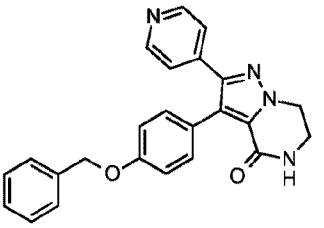
were collected and solvent evaporated until dryness to give 4.0 g of colorless oil which was triturated in Et_2O. The white solide formed was filtrated, washed and dried to give 3.22g, white solide (3% of TBAF). The residue was added to the previous filtrate and evaporated to give 4.0 g, grey solid and it was purified by achiral SFC (Stationary phase: 2-ethylpyridine 6µm 150x21.2mm, Mobile phase: 80% CO_2, 20% MeOH (0.3% $iPrNH_2$)). The pure fractions were collected and solvent evaporated until dryness to give 2.96 g which was triturated in Et_2O. The white solid formed was filtrated and dried to give 2.85 g of **Co. 129**, white solid (67%). m.p.: 194°C (dsc).

Example A131: Preparation of Co. 130



a- **Synthesis of Int. 265:**

To a suspension of 7 (0.3g, 1.36mmol), benzyl alcohol (0.169mL, 1.63mmol), PPh_3 supp. (0.43g, 1.63mmol) in dry DCM (10mL) was added DBAD (0.377g, 1.63mmol) and the r.m. was stirred at r.t. for 18 h. The insoluble was filtered through Celite®, washed with DCM. Water was added and the organic layer was separated, dried, filtered and concentrated until dryness to give 756mg. The residue was purified by prep. LC (irregular SiOH 15-40µm 30g Merck, mobile phase gradient: from DCM 100% to DCM 98%, MeOH 2%). The fractions were collected and evaporated until dryness to give 217mg of Int. **265** (51%).

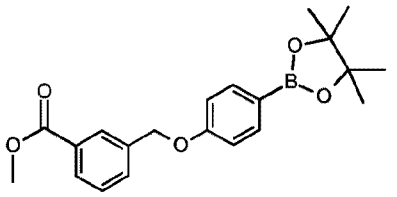


b- **Synthesis of Co. 130:**

In a microwave vial, a mixture of 4 (0.137 g, 0.466 mmol), **265** (0.217 g, 0.7 mmol), K_3PO_4 (0.415 g, 1.96 mmol) in 1,4-dioxane (2.19 mL) and H_2O (0.73 mL) was carefully purged with N_2. PCy_3 (27 mg, 0.098 mmol) and $Pd(OAc)_2$ (11 mg, 0.049 mmol) were added and the r.m. was purged again with N_2. The r.m. was stirred for 16 h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 272 mg. The residue was purified by prep. LC on (Sunfire Silica 5µm 150x30.0mm, Mobile phase Gradient: from 70% Heptane, 2% MeOH, 28% EtOAc to 20% MeOH, 80% EtOAc). The pure fractions were collected and evaporated until dryness to give 42 mg

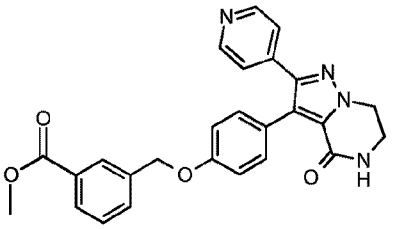
which was crystallized from DIPE, filtered and dried to give 40 mg of **Co. 130** (22%). m.p.: 260°C (dsc).

Example A132: Preparation of Co. 131



a- Synthesis of Int. 266:

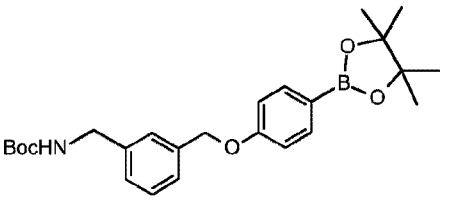
7 (2.00g, 9.09mmol) was dissolved in ACN (20mL). K_2CO_3 (1.51g, 10.9mmol) and methyl 3-(bromomethyl)benzoate (2.19g, 9.54mmol) were added. The r.m. was stirred for 2h at r.t. An extra amount of methyl 3-(bromomethyl)benzoate (0.208g, 0.909mmol) was then added, as well as DMF (1mL). The r.m. was stirred at r.t. for 17 h. The crude mixture was diluted in EtOAc, washed with water and brine (3 times). The organic layer was separated, dried over $MgSO_4$ and evaporated *in vacuo* to afford 3.82g of Int. **266**, pale pink oil (Quant.).



b- Synthesis of Co. 131:

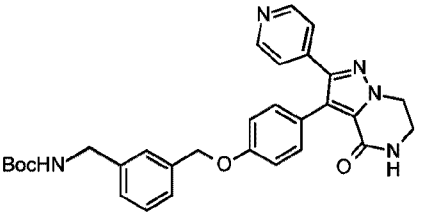
A mixture of **4** (800 mg, 2.73 mmol), **266** (2.01 g, 5.46 mmol), K_3PO_4 (1.74 g, 8.19 mmol) in 1,4-dioxane (45 mL) and H_2O (15 mL) was carefully purged with N_2. PCy_3 (153 mg, 0.546 mmol) and $Pd(OAc)_2$ (61 mg, 273 µmol) were added, and the r.m. was purged again with N_2. The r.m. was stirred for 17 h at 80°C. The crude material was dissolved in water and extracted 2x with DCM. The organic phase was separated, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give a solid. The solid was purified by prep. LC (irregular SiOH 15-40 µm, 30 g Merck, dry loading, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 782 mg, white solid. The solid was triturated in pentane and the supernatant was removed. This operation was repeated twice and the solid was dried *in vacuo* to give 700mg of **Co. 131**, white solid (56%). m.p.: 222 °C (dsc).

Example A133: Preparation of Co. 132 and Co. 133



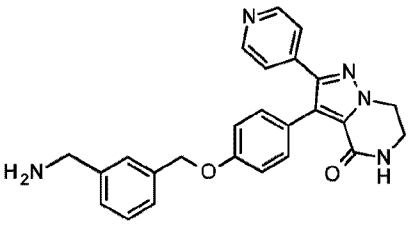
a- Synthesis of Int. 267:

A mixture of 7 (337 mg, 1.53 mmol), (3-hydroxymethyl-benzyl)-carbamic acid tert-butyl ester (450 mg, 1.84 mmol) and PPh_3 supp. (523 mg, 1.99 mmol) in DCM (15 mL) was treated with DBAD (459 mg, 1.99 mmol) and stirred at r.t. for 17 h. Silica gel was added and the crude mixture was directly evaporated *in vacuo* to afford a silica supported material. The material was purified by prep. LC (irregular SiOH 15-40µm, 40g Merck, mobile phase: DCM 100%). The pure fractions were collected and solvent evaporated to give 470mg of Int. **267**, colorless oil (70%).



b- Synthesis of Co. 132:

A mixture of 4 (180 mg, 0.614 mmol), **267** (470 mg, 1.07 mmol), K_3PO_4 (391 mg, 1.84 mmol) in 1,4-dioxane (10 mL) and H_2O (4 mL) was carefully purged with N_2. PCy_3 (34 mg, 0.123 mmol) and $Pd(OAc)_2$ (14 mg, 61.4 µmol) were added, and the r.m. was purged again with N_2. The r.m. was stirred for 17h at 80°C. The crude material was dissolved in water and extracted 2x with DCM. The organic phase was separated, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give a solid. The solid was purified by prep. LC (irregular SiOH 15-40 µm, 30g Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 300 mg, white solid. This solid was triturated in pentane and the supernatant was removed. This operation was repeated 2x and the solid was dried *in vacuo* to afford 280mg of **Co. 132**, white solid (87%). m.p.: 186 °C and 194 °C (dsc).



c- Synthesis of Co. 133:

A sol. of Co. 132 (230 mg, 0.438 mmol) in HCl 3N (5 mL) and EtOH (5 mL) was stirred for 17h at r.t. The r.m. was diluted in DCM and basified with a sat. aq. sol. of

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CONTAINING PAGES 1 TO 235

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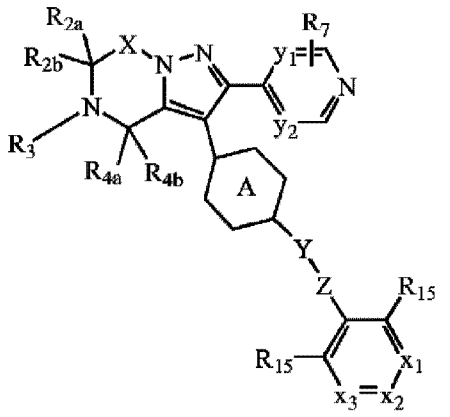
NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

Claims

1. A compound of Formula (I)



(I)

a tautomer or a stereoisomeric form thereof, wherein

y_1 is CR_{7a} or N;

y_2 is CH or N;

R_{7a} is hydrogen, halo, trifluoromethyl or cyano;

R_7 is hydrogen, $-NH_2$, $-NHCH_3$, $-NH(CH_2CH_3)$, methyl, $-CH_2OH$, halo or cyano;

or when y_1 represents CR_{7a}, this R_{7a} can be taken together with a R_7 on an adjacent carbon atom to form -CH=CH-NH- or -N=CH-NH-;

X is $-CR_1R_{1a}$-, or $-CH_2-CHR_1$-;

R_1 is hydrogen or C_{1-6}alkyl;

R_{1a} is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$; or $-C(=O)-NR_{9a}R_{9b}$;

R_{2a} is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; or C_{1-6}alkyl substituted with one substituent of $-NR_{9a}R_{9b}$, cyano or C_{1-4}alkyloxy;

R_{2b} is hydrogen or C_{1-6}alkyl; or

R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2-$, $-CH_2-NR_{2c}-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-NR_{2c}-CH_2-$ or =O;

R_{2c} is hydrogen; C_{1-4}alkyl optionally substituted with one or two hydroxyl groups;

mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyl substituted with one cyano group;

or C_{1-6}alkyl substituted with one -$NR_{9a}R_{9b}$;

R_3 is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one or two hydroxyl groups and one C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl- optionally substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkylcarbonyl-; $R_{10a}R_{10b}$N-C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkylcarbonyloxy-; C_{1-6}alkyl substituted with one R_{11}; C_{1-6}alkyloxy optionally substituted with one –$NR_{10a}R_{10b}$; C_{2-6}alkenyl; C_{2-6}alkynyl; hydroxyC_{2-6}alkenyl; hydroxyC_{2-6}alkynyl; C_{1-6}alkyloxyC_{2-6}alkenyl; C_{1-6}alkyloxyC_{2-6}alkynyl; C_{2-6}alkenyl substituted with one –$NR_{10a}R_{10b}$; C_{2-6}alkynyl substituted with one –$NR_{10a}R_{10b}$; C_{1-6}alkyl substituted with one or two hydroxyl groups and one –$NR_{10}R_{10b}$; -C_{1-6}alkyl-$C(R_{13})$=N-O-R_{13}; -$S(=O)_2$-C_{1-6}alkyl; or -$S(=O)_2$-$NR_{9a}R_{9b}$;
C_{1-6}alkyl substituted with one -(C=O)-R_{14}; C_{1-6}alkyl substituted with one or two hydroxyl groups and one R_{14}; C_{1-6}alkyl substituted with one R_{14}; C_{2-6}alkenyl substituted with one R_{14}; C_{2-6}alkynyl substituted with one R_{14}; or R_{14};

R_{4a} is hydrogen;

R_{4b} is hydrogen; or

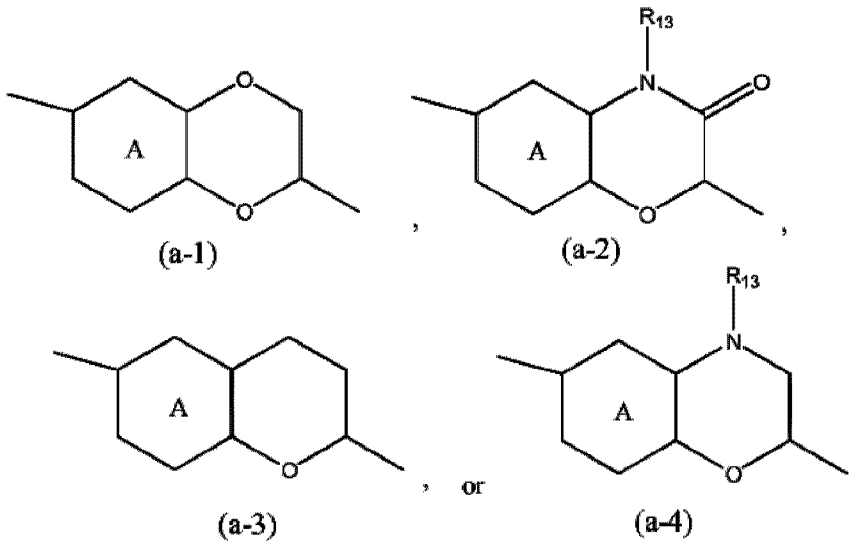
R_{4a} and R_{4b} are taken together to form =O;

Y is -O- or -C(=O)-;

Z is -CHR_6- or -CH_2-C≡C-;

R_6 is hydrogen; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{1-4}alkyl substituted with one -$NR_{9a}R_{9b}$; or -C(=O)-$NR_{9a}R_{9b}$;
Ring A is phenyl or a 6-membered saturated, partially saturated or aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents; each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; C_{1-4}alkyl or halo;

or an R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1), (a-2), (a-3) or (a-4):



R_{9a} and R_{9b} each independently represent hydrogen; mono-or polyhaloC_{1-4}alkyl; C_{1-4}alkylcarbonyl-; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl substituted with one or two hydroxyl groups; or C_{1-4}alkyl optionally substituted with one substituent of C_{1-4}alkyloxy, cyano, amino or mono- or di(C_{1-4}alkyl)amino;

R_{10a} and R_{10b} each independently represent hydrogen; C_{1-4}alkyl; cyanoC_{1-6}alkyl; C_{1-6}alkyl substituted with one $NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one -C(=O)-$NR_{9a}R_{9b}$; C_{1-6}alkyloxy optionally substituted with one or two hydroxyl groups; C_{1-6}alkyloxyC_{1-6}alkyl wherein each C_{1-6}alkyl is optionally substituted with one or two hydroxyl groups; R_{14}; C_{1-6}alkyl substituted with one R_{14}; -(C=O)-R_{14}; C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; mono-or polyhaloC_{1-6}alkylcarbonyl- substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkylcarbonyl-; C_{1-6}alkyl substituted with one -$Si(CH_3)_3$; -S(=O)$_2$-C_{1-6}alkyl optionally substituted with one or more halo substituents; -S(=O)$_2$-$NR_{9a}R_{9b}$;

C_{1-6}alkyl substituted with one -S(=O)$_2$-C_{1-6}alkyl wherein -S(=O)$_2$-C_{1-6}alkyl is optionally substituted with one or more halo substituents;

C_{1-6}alkyl substituted with one -S(=O)$_2$-$NR_{9a}R_{9b}$;

C_{1-6}alkyl substituted with one -NH-S(=O)$_2$-C_{1-6}alkyl wherein -NH-S(=O)$_2$-C_{1-6}alkyl is optionally substituted on a carbon atom with one or more halo substituents;

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C_{1-6}alkyl substituted with one -NH-S(=O)$_2$-$NR_{9a}R_{9b}$;

mono-or polyhaloC_{1-4}alkyl; or C_{1-4}alkyl substituted with one or two hydroxyl groups;

R_{11} is cyano; -$NR_{10a}R_{10b}$; C_{1-6}alkyloxy optionally substituted with one or two hydroxyl groups; -S(=O)$_2$-C_{1-6}alkyl; -S(=O)$_2$-$NR_{9a}R_{9b}$; -NR_{13}-S(=O)$_2$-C_{1-6}alkyl; -NR_{13}-S(=O)$_2$-$NR_{9a}R_{9b}$; C_{1-6}alkylcarbonyloxy-; -C(=O)-$NR_{10a}R_{10b}$; -O-C(=O)-$NR_{10a}R_{10b}$; -COOH; -P(=O)(OH)$_2$; or -P(=O)(O-C_{1-4}alkyl)$_2$;

R_{12} is -$NR_{9a}R_{9b}$, C_{1-6}alkyloxy, or cyano;

R_{13} is hydrogen or C_{1-4}alkyl;

R_{14} is a C_{3-8}cycloalkyl; or a 4, 5 or 6 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents of oxo, C_{1-4}alkyl, halogen, cyano, hydroxyl, C_{1-6}alkyloxy or $NR_{9a}R_{9b}$;

x_1 is CR_{5a} or N;

x_2 is CR_{5b} or N;

x_3 is CR_{5c} or N;

each R_{15} is independently hydrogen, methyl, halo, C_{1-4}alkyloxy or hydroxyl;

R_{5a} and R_{5c} are each independently hydrogen; hydroxyl; cyano; halo; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyloxy; C_{1-6}alkyl substituted with one -$NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one cyano; C_{1-6}alkyloxyC_{1-6}alkyl wherein
each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkyloxy; C_{1-6}alkyloxy substituted with one or two hydroxyl groups; C_{1-6}alkyloxyC_{1-6}alkyloxy wherein each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups; C_{1-6}alkyloxy substituted with one cyano; or C_{1-6}alkyloxy substituted with one -$NR_{9a}R_{9b}$;

R_{5b} is hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; hydroxyl; cyano; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl
substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-4}alkyloxy; -$Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; C_{1-6}alkyl-O-carbonyl-; or C_{1-6}alkyloxy substituted with one R_{12};

or an N-oxide, a pharmaceutically acceptable addition salt or a solvate thereof.

2. The compound according to claim 1, wherein

y_1 is CR_{7a} or N;

y_2 is CH;

R_{7a} is hydrogen;

R_7 is hydrogen, $-NH_2$, $-NHCH_3$, $-NH(CH_2CH_3)$, methyl, $-CH_2OH$, halo or cyano;

or when y_1 represents CR_{7a}, this R_{7a} can be taken together with a R_7 on an adjacent carbon atom to form -CH=CH-NH- or -N=CH-NH-;

X is $-CR_1R_{1a}$-, or $-CH_2-CHR_1$-;

R_1 is hydrogen or C_{1-6}alkyl;

R_{1a} is hydrogen;

R_{2a} is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; or C_{1-6}alkyl substituted with one substituent of $-NR_{9a}R_{9b}$, cyano or C_{1-4}alkyloxy;

R_{2b} is hydrogen; or

R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2$-, $-CH_2-NR_{2c}-CH_2$-, $-CH_2-CH_2-CH_2$-, $-CH_2-O-CH_2$-, $-CH_2-CH_2-CH_2-CH_2$-, $-CH_2-CH_2-NR_{2c}-CH_2$- or =O;

R_{2c} is hydrogen; C_{1-4}alkyl optionally substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyl substituted with one cyano group; or C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$;

R_3 is hydrogen; C_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one or two hydroxyl groups and one C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl- optionally substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkylcarbonyl-; $R_{10a}R_{10b}N$-C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkylcarbonyloxy-; C_{1-6}alkyl substituted with one R_{11}; C_{1-6}alkyloxy optionally substituted with one $-NR_{10a}R_{10b}$; C_{1-6}alkyl substituted with one or two hydroxyl groups and one $-NR_{10}R_{10b}$; $-S(=O)_2$-C_{1-6}alkyl; $-S(=O)_2-NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one -(C=O)-R_{14}; C_{1-6}alkyl substituted with one or two hydroxyl groups and one R_{14}; C_{1-6}alkyl substituted with one R_{14}; or R_{14};

R_{4a} is hydrogen;

R_{4b} is hydrogen; or

R_{4a} and R_{4b} are taken together to form =O;

Y is -O- or -C(=O)-;

Z is -CHR_6- or -CH_2-C≡C-;

R_6 is hydrogen; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{1-4}alkyl substituted with one -$NR_{9a}R_{9b}$; or -C(=O)-$NR_{9a}R_{9b}$; Ring A is phenyl or a 6-membered saturated, partially saturated or aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents; each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; C_{1-4}alkyl or halo; or a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1), (a-2), (a-3) or (a-4);

R_{9a} and R_{9b} each independently represent hydrogen; mono-or polyhaloC_{1-4}alkyl; C_{1-4}alkylcarbonyl-; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl substituted with one or two hydroxyl groups; or C_{1-4}alkyl optionally substituted with one substituent of C_{1-4}alkyloxy, cyano, amino or mono-or di(C_{1-4}alkyl)amino;

R_{10a} and R_{10b} each independently represent hydrogen; C_{1-4}alkyl; cyanoC_{1-6}alkyl; C_{1-6}alkyl substituted with one $NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one -C(=O)-$NR_{9a}R_{9b}$; C_{1-6}alkyloxy optionally substituted with one or two hydroxyl groups; C_{1-6}alkyloxyC_{1-6}alkyl wherein each C_{1-6}alkyl is optionally substituted with one or two hydroxyl groups; C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; mono-or polyhaloC_{1-6}alkylcarbonyl- substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkylcarbonyl-; mono-or polyhaloC_{1-4}alkyl; or C_{1-4}alkyl substituted with one or two hydroxyl groups;

R_{11} is cyano; -$NR_{10a}R_{10b}$; C_{1-6}alkyloxy optionally substituted with one or two hydroxyl groups; -S(=O)$_2$-C_{1-6}alkyl; -S(=O)$_2$-$NR_{9a}R_{9b}$; -NR_{13}-S(=O)$_2$-C_{1-6}alkyl; -NR_{13}-S(=O)$_2$-$NR_{9a}R_{9b}$; C_{1-6}alkylcarbonyloxy-; -C(=O)-$NR_{10a}R_{10b}$; -O-C(=O)-$NR_{10a}R_{10b}$; -COOH; -P(=O)(OH)$_2$; or -P(=O)(O-C_{1-4}alkyl)$_2$;

R_{12} is $-NR_{9a}R_{9b}$, C_{1-6}alkyloxy, or cyano;

R_{13} is hydrogen or C_{1-4}alkyl;

R_{14} is a 4, 5 or 6 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents of oxo, C_{1-4}alkyl, halogen, cyano, hydroxyl, C_{1-6}alkyloxy or $NR_{9a}R_{9b}$;

x_1 is CR_{5a} or N;

x_2 is CR_{5b};

x_3 is CR_{5c} or N;

each R_{15} is independently hydrogen, methyl, halo, C_{1-4}alkyloxy or hydroxyl;

R_{5a} and R_{5c} are each independently hydrogen; hydroxyl; cyano; halo; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC_{1-6}alkyl; mono-or polyhaloC_{1-6}alkyloxy; C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$; C_{1-6}alkyl substituted with one cyano; C_{1-6}alkyloxyC_{1-6}alkyl wherein each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkyloxy; C_{1-6}alkyloxy substituted with one or two hydroxyl groups; C_{1-6}alkyloxyC_{1-6}alkyloxy wherein each of the C_{1-6}alkyl groups are optionally substituted with one or two hydroxyl groups; C_{1-6}alkyloxy substituted with one cyano; or C_{1-6}alkyloxy substituted with one $-NR_{9a}R_{9b}$;

R_{5b} is hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; hydroxyl; cyano; mono-or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one or two hydroxyl groups; C_{2-6}alkenyl; C_{1-4}alkyloxy; $-Si(CH_3)_3$;
C_{1-6}alkyl substituted with one R_{12}; C_{1-6}alkyl-O-carbonyl-; or C_{1-6}alkyloxy substituted with one R_{12}.

3. The compound according to claim 1, wherein

y_1 is CR_{7a} or N;

y_2 is CH;

R_{7a} is hydrogen;

R_7 is hydrogen, $-NH_2$, $-CH_2OH$, halo or cyano;

or when y_1 represents CR_{7a}, this R_{7a} can be taken together with a R_7 on an adjacent carbon atom to form -CH=CH-NH-;

X is $-CR_1R_{1a}$-, or $-CH_2-CHR_1$-;

R_1 is hydrogen or C_{1-6}alkyl;

R_{1a} is hydrogen;

R_{2a} is hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one hydroxyl group; or C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$ substituent;

R_{2b} is hydrogen; or

R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2$-, $-CH_2-NR_{2c}-CH_2$- or =O;

R_{2c} is hydrogen; or C_{1-6}alkyl substituted with one $-NR_{9a}R_{9b}$;

R_3 is hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one or two hydroxyl groups and one C_{1-6}alkyloxy; $R_{10a}R_{10b}N$-C_{1-6}alkylcarbonyl-; C_{1-6}alkyl-O-carbonyl-; C_{1-6}alkyl substituted with one R_{11}; C_{1-6}alkyl substituted with one $-(C=O)-R_{14}$; or C_{1-6}alkyl substituted with one R_{14};

R_{4a} is hydrogen;

R_{4b} is hydrogen; or

R_{4a} and R_{4b} are taken together to form =O;

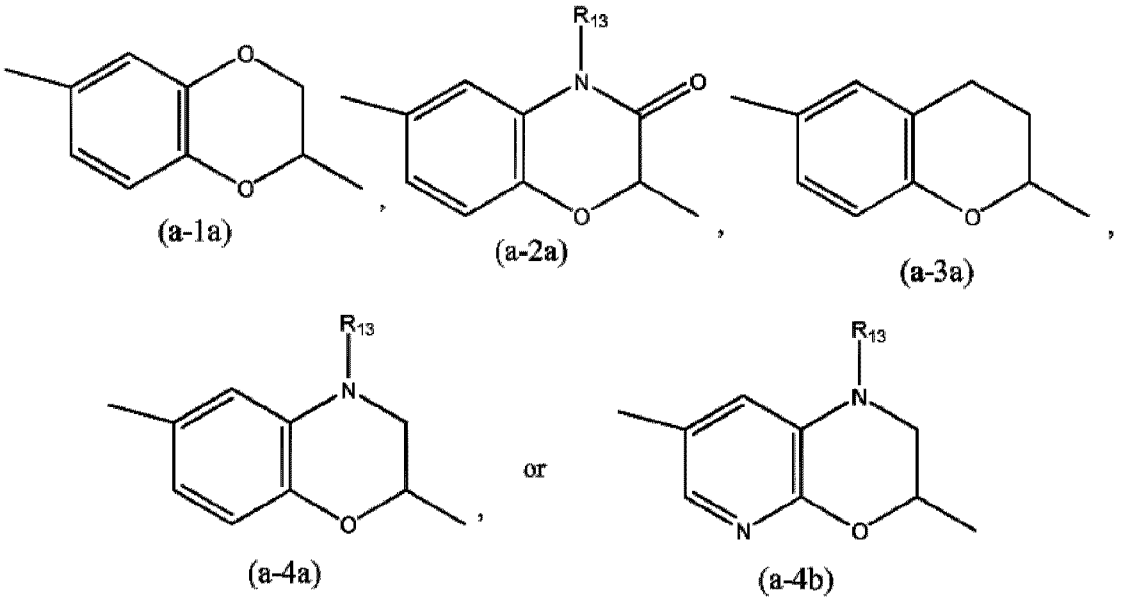
Y is -O- or -C(=O)-;

Z is $-CHR_6$- or $-CH_2-C\equiv C$-;

R_6 is hydrogen; C_{1-4}alkyl-O-carbonyl-; C_{1-4}alkyl; C_{1-4}alkyl substituted with one hydroxyl group; C_{1-4}alkyl substituted with one $-NR_{9a}R_{9b}$; or $-C(=O)-NR_{9a}R_{9b}$; Ring A is phenyl or a 6-membered saturated, partially saturated or aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; C_{1-4}alkyl or halo; or a R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6

substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-la), (a-2a), (a-3a), (a-4a) or (a-4b):



(a-1a), (a-2a), (a-3a), (a-4a) or (a-4b)

R_{9a} and R_{9b} each independently represent hydrogen; C_{1-4}alkyl substituted with one hydroxyl group; or C_{1-4}alkyl;

R_{10a} and R_{10b} each independently represent hydrogen; C_{1-4}alkyl; C_{1-6}alkyl-O-carbonyl-; mono- or polyhaloC_{1-4}alkyl; or C_{1-4}alkyl substituted with one hydroxyl group;

R_{11} is cyano; -$NR_{10a}R_{10b}$; C_{1-6}alkyloxy optionally substituted with one hydroxyl group; -$S(=O)_2$-C_{1-6}alkyl; C_{1-6}alkylcarbonyloxy-; -C(=O)-$NR_{10a}R_{10b}$; -COOH; or -$P(=O)(O\text{-}C_{1-4}alkyl)_2$;

R_{12} is -$NR_{9a}R_{9b}$, C_{1-6}alkyloxy, or cyano;

R_{13} is hydrogen or C_{1-4}alkyl;

R_{14} is a 5 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents of oxo or C_{1-4}alkyl;

x_1 is CR_{5a} or N;

x_2 is CR_{5b};

x_3 is CR_{5c} or N;

each R_{15} is independently hydrogen, methyl, halo, or C_{1-4}alkyloxy;

R_{5a} and R_{5c} are each independently hydrogen; hydroxyl; cyano; halo; C_{1-6}alkyl substituted with one or two hydroxyl groups; C_{1-6}alkyl substituted with one -$NR_{9a}R_{9b}$; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxy substituted with one hydroxyl group; or C_{1-6}alkyloxyC_{1-6}alkyloxy;

R_{5b} is hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with one cyano; cyano; mono- or polyhaloC_{1-6}alkyloxy; mono-or polyhaloC_{1-6}alkyl; C_{1-4}alkyl substituted with one hydroxyl group; C_{2-6}alkenyl; C_{1-4}alkyloxy; -$Si(CH_3)_3$; C_{1-6}alkyl substituted with one R_{12}; or C_{1-6}alkyl-O-carbonyl-.

4. The compound according to claim 1, wherein

y_1 is CH or N;

y_2 is CH;

R_7 is hydrogen or -NH_2;

X is CH_2;

R_{2a} is hydrogen;

R_{2b} is hydrogen; or

R_{2a} and R_{2b} are taken together to form -CH_2-CH_2- or -CH_2-NH-CH_2-;

R_3 is hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or two hydroxyl groups;

C_{1-6}alkyl substituted with one R_{11}; or C_{1-6}alkyl substituted with one R_{14};

R_{4a} is hydrogen;

R_{4b} is hydrogen; or

R_{4a} and R_{4b} are taken together to form =O;

Y is -O-;

Z is -CHR_6-;

R_6 is hydrogen;

Ring A is phenyl or pyridinyl; wherein the phenyl or pyridinyl is optionally substituted with one or two R_8 substituents;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; or halo;

or an R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-3a) defined in claim 3;

R_{11} is C_{1-6}alkyloxy optionally substituted with one hydroxyl group; or -C(=O)-$NR_{10a}R_{10b}$;

R_{10a} and R_{10b} each independently represent hydrogen or C_{1-4}alkyl;

R_{14} is a 5 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents of C_{1-4}alkyl;

x_1 is CR_{5a} or N;

x_2 is CR_{5b};

x_3 is CR_{5c};

each R_{15} is hydrogen;

R_{5a} is hydrogen or C_{1-6}alkyloxyC_{1-6}alkyl;

R_{5b} is C_{1-6}alkyl; C_{3-6}cycloalkyl; mono-or polyhaloC_{1-6}alkyloxy; C_{2-6}alkenyl; C_{1-6}alkyl substituted with one cyano; C_{1-4}alkyloxy; or C_{1-6}alkyl-O-carbonyl-;

R_{5c} is hydrogen.

5. The compound according to claim 1, wherein

y_1 is CH;

y_2 is CH;

R_7 is hydrogen;

X is CH_2;

R_{2a} is hydrogen;

R_{2b} is hydrogen;

R_3 is hydrogen; or C_{1-6}alkyl substituted with one or two hydroxyl groups;

R_{4a} and R_{4b} are taken together to form =O;

Y is -O-;

Z is $-CH_2-$;

Ring A is phenyl optionally substituted with one or two R_8 substituents;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; cyano; or F;

x_1 is CH;

x_2 is CR_{5b};

x_3 is CH;

each R_{15} is hydrogen;

R_{5b} is isopropyl or cyclopropyl.

6. The compound according to claim 1, wherein ring A is phenyl or a 6-membered saturated, partially saturated or aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents;

each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; or halo.

7. The compound according to claim 6, wherein ring A is phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R_8 substituents; each R_8 is independently hydrogen; C_{1-4}alkyloxy; hydroxyl; cyano; or halo.

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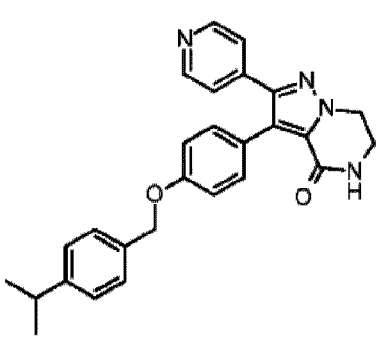
8. The compound according to claim 1, wherein ring A is phenyl or a 6-membered saturated, partially saturated or aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is substituted with one R_8 substituent on an atom adjacent to the atom carrying the Y-Z substituent, and said R_8 substituent is taken together with the R_6 substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1), (a-2), (a-3) or (a-4).

9. The compound according to claim 1, wherein x_1 and x_3 are CH; x_2 is CR_{5b}; and R_{5b} is isopropyl.

10. The compound according to claim 1, wherein y_1 and y_2 are CH.

11. The compound according to claim 1 wherein the compound is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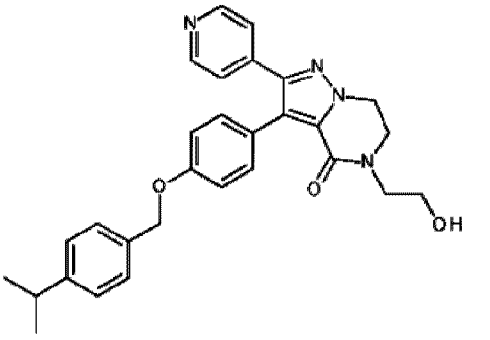
,

a tautomer, stereoisomeric form, N-oxide, pharmaceutically acceptable addition salt, or solvate thereof.

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the compound according to any one of claims 1 to 11.

13. A compound as defined in any one of claims 1 to 11 for use as a medicament.

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14. A compound as defined in any one of claims 1 to 11 for use in the treatment or prevention of non-small cell lung cancer, cholangiocarcinoma, glioblastoma, colorectal cancer, gastric adenocarcinoma, ovarian cancer, angiosarcoma, epithelioid hemangioendothelioma, inflammatory myofibroblastic tumors, breast cancer or chronic myelogenous leukemia.

15. The compound for use according to claim 14 for the treatment or prevention of non-small-cell lung cancer, cholangiocarcinoma, or glioblastoma.

16. The compound for use according to claim 14 for the treatment or prevention of gastric adenocarcinoma.

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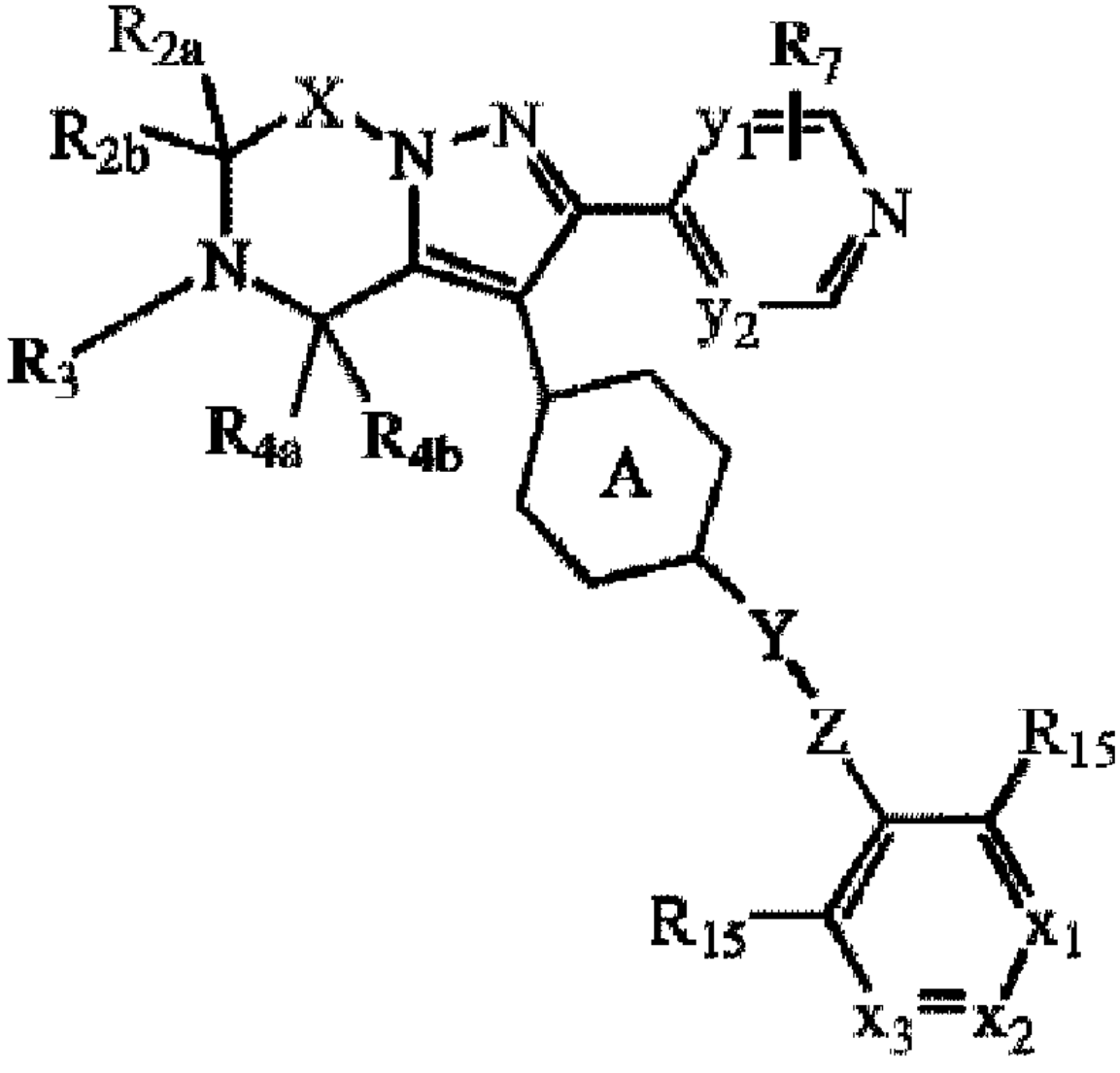

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