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(71) Applicant: JANSSEN PHARMACEUTICA NV

[BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors: MEVELLEC, Laurence, Anne; Janssen Research & Development a division of Janssen-Cilag Campus de Maigremont CS10615, F-27106 Val de Reuil Cedex (FR). PASQUIER, Elisabeth, Thérèse, Jeanne; Janssen Research & Development a division of Janssen-Cilag Campus de Maigremont CS10615, F-27106 Val de Reuil Cedex (FR). DESCAMPS, Sophie; Janssen Research & Development a division of Janssen-Cilag Campus de Maigremont CS10615, F-27106 Val de Reuil Cedex (FR). MERCEY, Guillaume, Jean, Maurice; Janssen Research & Development a division of Janssen-Cilag Campus de Maigremont CS10615, F-27106 Val de Reuil Cedex (FR). WROBLOWSKI, Berthold; Janssen Pharmaceutica NV Turnhoutseweg 30, B-2340 Beerse (BE). VIALARD, Jorge, Eduardo; Janssen Pharmaceutica NV Turnhout-

seweg 30, B-2340 Beerse (BE). MEERPOEL, Lieven; Janssen Pharmaceutica NV Turnhoutseweg 30, B-2340 Beerse (BE). JEANTY, Matthieu, Ludovic; NovAliX, BioParc 2, Boulevard Sébastien Brant 850, Illkirch, 67400 (FR). JOUSSEAUME, Thierry, François, Alain, Jean; Cilag AG, Hochstrasse 201, Schaffhausen, 8200 (CH).

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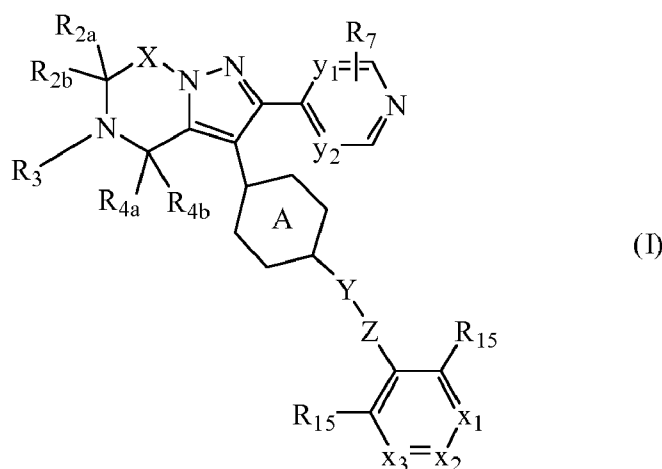
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[Continued on next page]

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



(57) Abstract: The present invention relates to substituted 4,5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyrazine derivatives and 5,6,7,8-tetrahydro-4H-pyrazolo[1,5-*a*][1,4]diazepine derivatives of formula (I) wherein the variables have the meaning defined in the claims. 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*]
a][1,4]DIAZEPINE DERIVATIVES AS ROS1 INHIBITORS

5 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
10 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
15 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.
20 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
25 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
30 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,
35 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
5 (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
10 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,
15 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.
20 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
25 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.

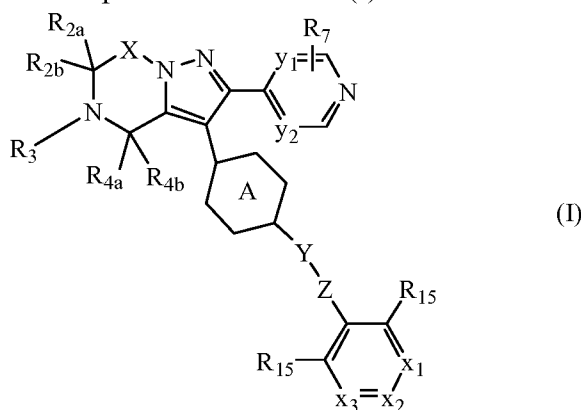
30 It is accordingly an object of the present invention to provide such compounds.

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
35 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)



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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;

- 10 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;

- 15 R_{1a} is hydrogen; C_{1-6} alkyl; mono-or polyhalo C_{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 polyhalo C_{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;

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

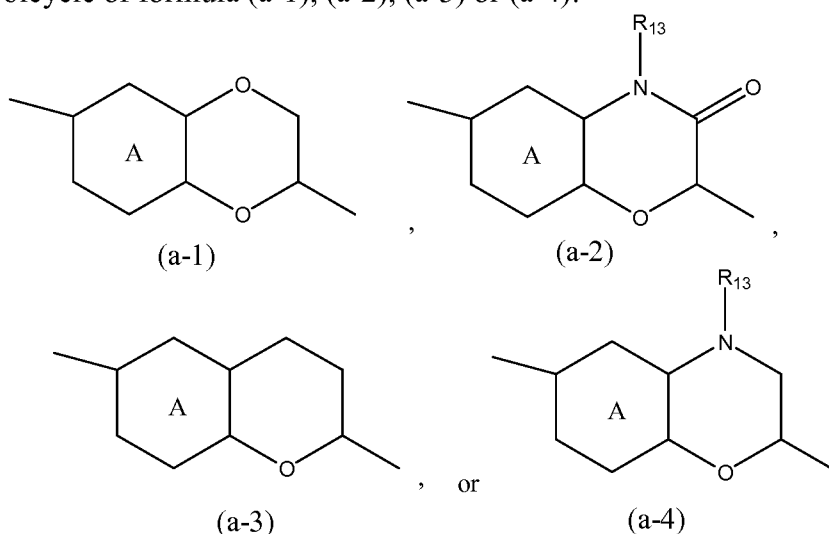
R_{2a} and R_{2b} are taken together to form $-CH_2-CH_2-$, $-CH_2-NR_{2c}-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-NR_{2c}-CH_2-$ or $=O$;

R_{2c} is hydrogen; C_{1-4} alkyl optionally substituted with one or two hydroxyl groups; mono-or polyhalo C_{1-6} alkyl; C_{1-6} alkyloxy; C_{1-6} alkyl substituted with one cyano group;

- 25 or C_{1-6} alkyl substituted with one $-NR_{9a}R_{9b}$;

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

- O-carbonyl-; C₁₋₆alkylcarbonyloxy-; C₁₋₆alkyl substituted with one R₁₁; C₁₋₆alkyloxy optionally substituted with one -NR_{10a}R_{10b}; C₂₋₆alkenyl; C₂₋₆alkynyl; hydroxyC₂₋₆alkenyl; hydroxyC₂₋₆alkynyl; C₁₋₆alkyloxyC₂₋₆alkenyl; C₁₋₆alkyloxyC₂₋₆alkynyl; C₂₋₆alkenyl substituted with one -NR_{10a}R_{10b}; C₂₋₆alkynyl substituted with one -NR_{10a}R_{10b}; C₁₋₆alkyl substituted with one or two hydroxyl groups and one -NR₁₀R_{10b}; -C₁₋₆alkyl-C(R₁₃)=N-O-R₁₃; -S(=O)₂-C₁₋₆alkyl; -S(=O)₂-NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one -(C=O)-R₁₄; C₁₋₆alkyl substituted with one or two hydroxyl groups and one R₁₄; C₁₋₆alkyl substituted with one R₁₄; C₂₋₆alkenyl substituted with one R₁₄; C₂₋₆alkynyl substituted with one R₁₄; or R₁₄;
- 10 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 -CHR₆- or -CH₂-C≡C-;
- 15 R₆ is hydrogen; C₁₋₄alkyl-O-carbonyl-; C₁₋₄alkyl; C₁₋₄alkyl substituted with one or two hydroxyl groups; C₁₋₄alkyl 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 R₈ substituents;
- 20 each R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; C₁₋₄alkyl or halo; or a R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R₆ 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):



- 25 R_{9a} and R_{9b} each independently represent hydrogen; mono-or polyhaloC₁₋₄alkyl; C₁₋₄alkylcarbonyl-; C₁₋₄alkyl-O-carbonyl-; C₁₋₄alkyl substituted with one or two

- hydroxyl groups; or C₁₋₄alkyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyloxy, cyano, amino and mono-or di(C₁₋₄alkyl)amino; R_{10a} and R_{10b} each independently represent hydrogen; C₁₋₄alkyl; cyanoC₁₋₆alkyl; C₁₋₆alkyl substituted with one NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one -C(=O)-
- 5 NR_{9a}R_{9b}; C₁₋₆alkyloxy optionally substituted with one or two hydroxyl groups; C₁₋₆alkyloxyC₁₋₆alkyl wherein each C₁₋₆alkyl is optionally substituted with one or two hydroxyl groups; R₁₄; C₁₋₆alkyl substituted with one R₁₄; -(C=O)-R₁₄; C₁₋₆alkylcarbonyl-; C₁₋₆alkyl-O-carbonyl-; mono-or polyhaloC₁₋₆alkylcarbonyl-substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkyl substituted
- 10 with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkylcarbonyl-; C₁₋₆alkyl substituted with one -Si(CH₃)₃; -S(=O)₂-C₁₋₆alkyl optionally substituted with one or more halo substituents; -S(=O)₂-NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one -S(=O)₂-C₁₋₆alkyl wherein -S(=O)₂-C₁₋₆alkyl is optionally substituted with one or more halo substituents;
- 15 C₁₋₆alkyl substituted with one -S(=O)₂-NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one -NH-S(=O)₂-C₁₋₆alkyl wherein -NH-S(=O)₂-C₁₋₆alkyl is optionally substituted on a carbon atom with one or more halo substituents; C₁₋₆alkyl substituted with one -NH-S(=O)₂-NR_{9a}R_{9b}; mono-or polyhaloC₁₋₄alkyl; or C₁₋₄alkyl substituted with one or two hydroxyl groups;
- 20 R₁₁ is cyano; -NR_{10a}R_{10b}; C₁₋₆alkyloxy optionally substituted with one or two hydroxyl groups; -S(=O)₂-C₁₋₆alkyl; -S(=O)₂-NR_{9a}R_{9b}; -NR₁₃-S(=O)₂-C₁₋₆alkyl; -NR₁₃-S(=O)₂-NR_{9a}R_{9b}; C₁₋₆alkylcarbonyloxy-; -C(=O)-NR_{10a}R_{10b}; -O-C(=O)-NR_{10a}R_{10b}; -COOH; -P(=O)(OH)₂; or -P(=O)(O-C₁₋₄alkyl)₂; R₁₂ is -NR_{9a}R_{9b}, C₁₋₆alkyloxy, or cyano;
- 25 R₁₃ is hydrogen or C₁₋₄alkyl; R₁₄ is a C₃₋₈cycloalkyl; 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, C₁₋₄alkyl, halogen, cyano, hydroxyl, C₁₋₆alkyloxy and NR_{9a}R_{9b}; x₁ is CR_{5a} or N;
- 30 x₂ is CR_{5b} or N; x₃ is CR_{5c} or N; each R₁₅ is independently selected from the group consisting of hydrogen, methyl, halo, C₁₋₄alkyloxy and hydroxyl; R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen;
- 35 hydroxyl; cyano; halo; C₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyloxy; C₁₋₆alkyl substituted with one -NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one cyano; C₁₋₆alkyloxyC₁₋₆alkyl wherein

each of the C₁₋₆alkyl groups are optionally substituted with one or two hydroxyl groups; C₂₋₆alkenyl; C₁₋₆alkyl-O-carbonyl-; C₁₋₆alkyloxy; C₁₋₆alkyloxy substituted with one or two hydroxyl groups; C₁₋₆alkyloxyC₁₋₆alkyloxy wherein each of the C₁₋₆alkyl groups are optionally substituted with one or two hydroxyl groups; C₁₋₆alkyloxy substituted with one cyano; and C₁₋₆alkyloxy substituted with one -NR_{9a}R_{9b}; R_{5b} is hydrogen; C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; hydroxyl; cyano; mono-or polyhaloC₁₋₆alkyloxy; mono-or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one or two hydroxyl groups; C₂₋₆alkenyl; C₁₋₄alkyloxy; -Si(CH₃)₃; C₁₋₆alkyl substituted with one R₁₂; C₁₋₆alkyl-O-carbonyl-; or C₁₋₆alkyloxy substituted with one R₁₂; 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 occurrence is independent of its definition at every other occurrence.

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

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 C₁₋₆alkyl group contains from 1 to 6 carbon atoms, a C₃₋₆cycloalkyl group contains from 3 to 6 carbon atoms, a C₁₋₄alkoxy 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 polyhaloC₁₋₄alkyl’ or ‘mono- or polyhaloC₁₋₆alkyl’ as used herein as a group or part of a group refers to a C₁₋₄alkyl or C₁₋₆alkyl 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 polyhaloC₁₋₄alkyl’ or ‘mono- or polyhaloC₁₋₆alkyl’ may have one, two, three or more halogens. Examples of such groups include fluoroethyl, fluoromethyl, trifluoromethyl or trifluoroethyl and the like.

The term "C₁₋₆alkyl" 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. C₁₋₆alkyl 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, C₁₋₆alkyl 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, *isobutyl* and *tert*-butyl), pentyl and its isomers, hexyl and its isomers, and the like.

The term "C₁₋₄alkyl" 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. C₁₋₄alkyl groups comprise from 1 to 4 carbon atoms, preferably from 1 to 3 carbon atoms, more preferably 1 to 2 carbon atoms. C₁₋₄alkyl 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. C₁₋₄alkyl includes all linear, or branched alkyl groups with between 1 and 4 carbon atoms, and thus includes methyl, ethyl, *n*-propyl, *i*-propyl, 2-methyl-ethyl, butyl and its isomers (e.g. *n*-butyl, *isobutyl* and *tert*-butyl), and the like.

The term "C₁₋₆alkyloxy" as a group or part of a group refers to a radical having the Formula -OR^b wherein R^b is C₁₋₆alkyl. Non-limiting examples of suitable alkyloxy include methyloxy, ethyloxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, *sec*-butyloxy, *tert*-butyloxy, pentyloxy, and hexyloxy.

The term "C₁₋₄alkyloxy" as a group or part of a group refers to a radical having the Formula -OR^c wherein R^c is C₁₋₄alkyl. Non-limiting examples of suitable C₁₋₄alkyloxy include methyloxy (also methoxy), ethyloxy (also ethoxy), propyloxy, isopropyloxy, butyloxy, isobutyloxy, *sec*-butyloxy and *tert*-butyloxy.

The term "C₁₋₆alkylcarbonyl" as a group or part of a group refers to a radical -C(=O)-C₁₋₆alkyl. The term "C₁₋₄alkylcarbonyl" as a group or part of a group refers to a radical -C(=O)-C₁₋₄alkyl.

The term "C₃₋₈cycloalkyl" alone or in combination, refers to a cyclic saturated hydrocarbon radical having from 3 to 8 carbon atoms. Non-limiting examples of suitable C₃₋₈cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term “C₃₋₆cycloalkyl” alone or in combination, refers to a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms. Non-limiting examples of suitable C₃₋₆cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

5 The term “C₂₋₄alkenyl” or “C₂₋₆alkenyl” 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.

10 The term “C₂₋₄alkynyl” or “C₂₋₆alkynyl” 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 “cyanoC₁₋₆alkyl” means C₁₋₆alkyl substituted with one cyano.

The term “hydroxyC₂₋₆alkenyl” means C₂₋₆alkenyl substituted with one hydroxy.

The term “hydroxyC₂₋₆alkynyl” means C₂₋₆alkynyl substituted with one hydroxy.

15 In particular, the 4, 5 or 6 membered saturated heterocyclyls (e.g. in the definition of R₁₄), 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.

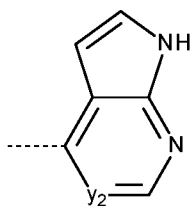
20 Examples of 6-membered aromatic heterocyclyls containing one or two nitrogen atoms (e.g. in the definition of ring A), include, but are not limited to, pyrimidinyl, pyridinyl, pyrazinyl and the like.

25 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.

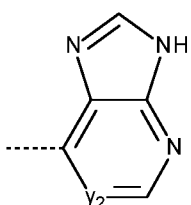
30 In case R_{7a} is taken together with a R₇ on an adjacent carbon atom to form –CH=CH–

NH–, it is intended that the CH in position alpha —CH=CH—NH— is attached to the carbon atom in the position of yl 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 α $\text{—}\overset{\alpha}{N}=\text{CH—NH—}$ is attached to the carbon atom in the position of y_1 as clearly shown below:

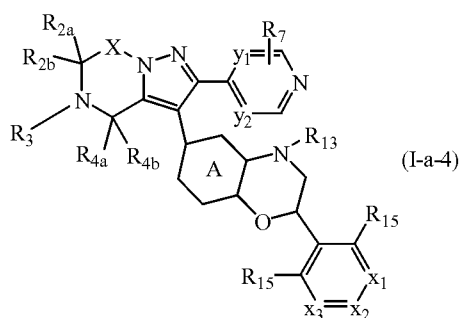
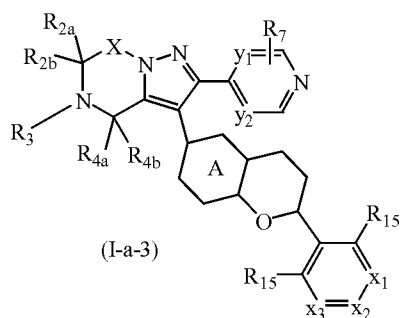
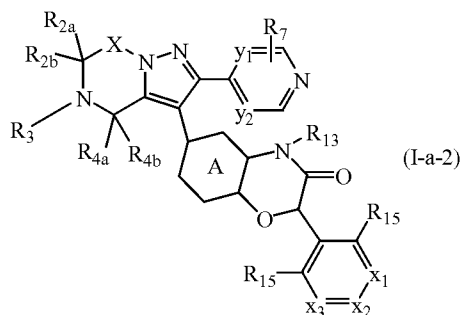
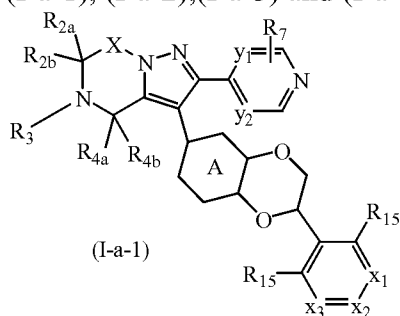


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In case X is $-\text{CH}_2-\text{CHR}_1-$, it is intended that the carbon atom with the R_1 substituent is attached to the nitrogen atom of the pyrazole ring.

In case Z is $-\text{CH}_2-\text{C}\equiv\text{C}-$, it is intended that the CH_2 group is attached to variable Y .

- 10 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:



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.

- 5 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.

- 10 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.

- 15 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.

- 20 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.

- 25 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.

- 30 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
 5 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
 10 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 ^2H , ^3H , ^{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 ^2H , ^3H , ^{11}C and ^{18}F . More preferably, the radioactive isotope is ^2H .
 15 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.

- 20 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;
 - 25 R_7 is hydrogen, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{CH}_2\text{CH}_3)$, methyl, $-\text{CH}_2\text{OH}$, 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 $-\text{CH}=\text{CH}-\text{NH}-$ or $-\text{N}=\text{CH}-\text{NH}-$;
 - X is $-\text{CR}_1\text{R}_{1a}-$, $-\text{CH}_2-\text{CHR}_1-$;
 - R_1 is hydrogen or C_{1-6} alkyl;
 - 30 R_{1a} is hydrogen;
 - R_{2a} is hydrogen; C_{1-6} alkyl; mono-or polyhalo C_{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 $-\text{NR}_{9a}\text{R}_{9b}$, cyano and C_{1-4} alkyloxy;
 - R_{2b} is hydrogen; or
 - 35 R_{2a} and R_{2b} are taken together to form $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{NR}_{2c}-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{O}-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{NR}_{2c}-\text{CH}_2-$ or $=\text{O}$;

- R_{2c} is hydrogen; C₁₋₄alkyl optionally substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkyl substituted with one cyano group; or C₁₋₆alkyl substituted with one -NR_{9a}R_{9b};
- R₃ is hydrogen; C₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; C₁₋₆alkyl substituted with one or two hydroxyl groups and one C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl- optionally substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkylcarbonyl-; R_{10a}R_{10b}N-C₁₋₆alkylcarbonyl-; C₁₋₆alkyl-O-carbonyl-; C₁₋₆alkylcarbonyloxy-; C₁₋₆alkyl substituted with one R₁₁; C₁₋₆alkyloxy optionally substituted with one -NR_{10a}R_{10b}; C₁₋₆alkyl substituted with one or two hydroxyl groups and one -NR₁₀R_{10b}; -S(=O)₂-C₁₋₆alkyl; -S(=O)₂-NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one -(C=O)-R₁₄; C₁₋₆alkyl substituted with one or two hydroxyl groups and one R₁₄; C₁₋₆alkyl substituted with one R₁₄; or R₁₄;
- 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 -CHR₆- or -CH₂-C≡C-;
- R₆ is hydrogen; C₁₋₄alkyl-O-carbonyl-; C₁₋₄alkyl; C₁₋₄alkyl substituted with one or two hydroxyl groups; C₁₋₄alkyl 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 R₈ substituents; each R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; C₁₋₄alkyl or halo; or a R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R₆ 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 polyhaloC₁₋₄alkyl; C₁₋₄alkylcarbonyl-; C₁₋₄alkyl-O-carbonyl-; C₁₋₄alkyl substituted with one or two hydroxyl groups; or C₁₋₄alkyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyloxy, cyano, amino and mono-or di(C₁₋₄alkyl)amino;
- R_{10a} and R_{10b} each independently represent hydrogen; C₁₋₄alkyl; cyanoC₁₋₆alkyl; C₁₋₆alkyl substituted with one NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one -C(=O)-NR_{9a}R_{9b}; C₁₋₆alkyloxy optionally substituted with one or two hydroxyl groups;
- C₁₋₆alkyloxyC₁₋₆alkyl wherein each C₁₋₆alkyl is optionally substituted with one or two hydroxyl groups; C₁₋₆alkylcarbonyl-; C₁₋₆alkyl-O-carbonyl-; mono-or polyhaloC₁₋₆alkylcarbonyl- substituted with one or two hydroxyl groups;

- mono-or polyhaloC₁₋₆alkyl substituted with one or two hydroxyl groups;
 mono-or polyhaloC₁₋₆alkylcarbonyl-; mono-or polyhaloC₁₋₄alkyl; or C₁₋₄alkyl
 substituted with one or two hydroxyl groups;
 R₁₁ is cyano; -NR_{10a}R_{10b}; C₁₋₆alkyloxy optionally substituted with one or two hydroxyl
 5 groups; -S(=O)₂-C₁₋₆alkyl; -S(=O)₂-NR_{9a}R_{9b}; -NR₁₃-S(=O)₂-C₁₋₆alkyl; -NR₁₃-S(=O)₂-
 NR_{9a}R_{9b}; C₁₋₆alkylcarbonyloxy-; -C(=O)-NR_{10a}R_{10b}; -O-C(=O)-NR_{10a}R_{10b}; -COOH;
 -P(=O)(OH)₂; or -P(=O)(O-C₁₋₄alkyl)₂;
 R₁₂ is -NR_{9a}R_{9b}, C₁₋₆alkyloxy, or cyano;
 R₁₃ is hydrogen or C₁₋₄alkyl;
 10 R₁₄ 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, C₁₋₄alkyl,
 halogen, cyano, hydroxyl, C₁₋₆alkyloxy and NR_{9a}R_{9b};
 x₁ is CR_{5a} or N;
 x₂ is CR_{5b};
 15 x₃ is CR_{5c} or N;
 each R₁₅ is independently selected from the group consisting of hydrogen, methyl, halo,
 C₁₋₄alkyloxy and hydroxyl;
 R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen;
 hydroxyl; cyano; halo; C₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups;
 20 mono-or polyhaloC₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyloxy; C₁₋₆alkyl substituted with
 one -NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one cyano; C₁₋₆alkyloxyC₁₋₆alkyl wherein
 each of the C₁₋₆alkyl groups are optionally substituted with one or two hydroxyl groups;
 C₂₋₆alkenyl; C₁₋₆alkyl-O-carbonyl-; C₁₋₆alkyloxy; C₁₋₆alkyloxy substituted with one or
 two hydroxyl groups; C₁₋₆alkyloxyC₁₋₆alkyloxy wherein each of the C₁₋₆alkyl groups
 25 are optionally substituted with one or two hydroxyl groups; C₁₋₆alkyloxy substituted
 with one cyano; and C₁₋₆alkyloxy substituted with one -NR_{9a}R_{9b};
 R_{5b} is hydrogen; C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano;
 hydroxyl; cyano; mono-or polyhaloC₁₋₆alkyloxy; mono-or polyhaloC₁₋₆alkyl; C₁₋₄alkyl
 substituted with one or two hydroxyl groups; C₂₋₆alkenyl; C₁₋₄alkyloxy; -Si(CH₃)₃;
 30 C₁₋₆alkyl substituted with one R₁₂; C₁₋₆alkyl-O-carbonyl-; or C₁₋₆alkyloxy substituted
 with one R₁₂;
 and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates
 thereof.
- 35 In an embodiment, the present invention concerns novel compounds of Formula (I),
 tautomers and stereoisomeric forms thereof, wherein
 y₁ 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
 5 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 polyhalo C_{1-6} alkyl; C_{1-6} alkyl substituted with one or
 10 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 $=O$;
 15 R_{2c} is hydrogen; C_{1-4} alkyl optionally substituted with one or two hydroxyl groups;
 mono-or polyhalo C_{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 polyhalo 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
 20 C_{1-6} alkyloxy; C_{1-6} alkylcarbonyl- optionally substituted with one or two hydroxyl
 groups; mono-or polyhalo C_{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
 25 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 $=O$;
 30 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
 35 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;

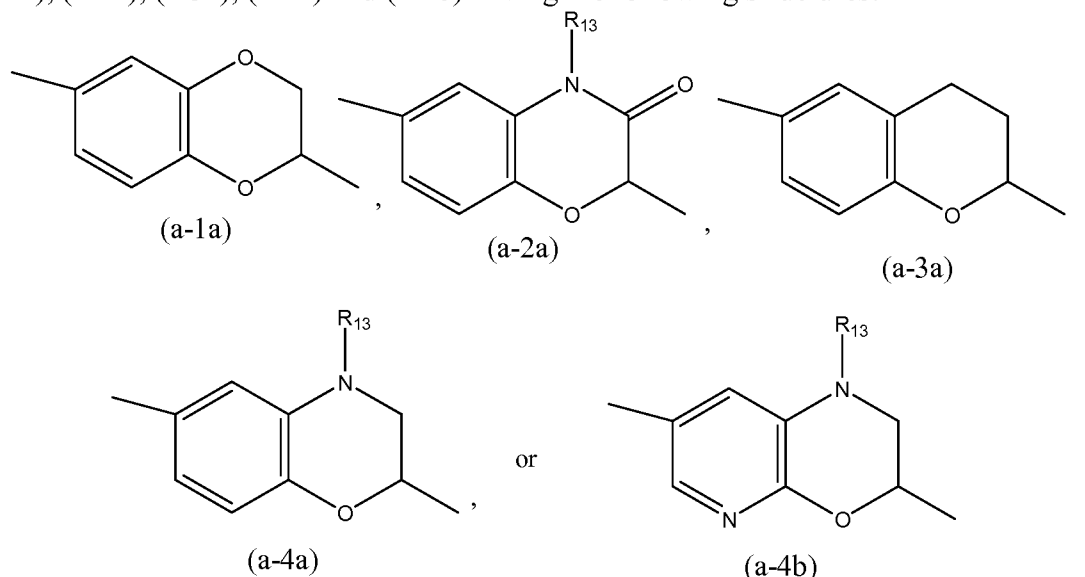
- or a R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R₆ substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-1), (a-2), (a-3) or (a-4);
- R_{9a} and R_{9b} each independently represent hydrogen; mono-or polyhaloC₁₋₄alkyl;
- 5 C₁₋₄alkylcarbonyl-; C₁₋₄alkyl-O-carbonyl-; C₁₋₄alkyl substituted with one or two hydroxyl groups; or C₁₋₄alkyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyloxy, cyano, amino and mono-or di(C₁₋₄alkyl)amino;
- R_{10a} and R_{10b} each independently represent hydrogen; C₁₋₄alkyl; cyanoC₁₋₆alkyl; C₁₋₆alkyl substituted with one NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one -C(=O)-
- 10 NR_{9a}R_{9b}; C₁₋₆alkyloxy optionally substituted with one or two hydroxyl groups; C₁₋₆alkyloxyC₁₋₆alkyl wherein each C₁₋₆alkyl is optionally substituted with one or two hydroxyl groups; C₁₋₆alkylcarbonyl-; C₁₋₆alkyl-O-carbonyl-;
- mono-or polyhaloC₁₋₆alkylcarbonyl- substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkyl substituted with one or two hydroxyl groups;
- 15 mono-or polyhaloC₁₋₆alkylcarbonyl-; mono-or polyhaloC₁₋₄alkyl; or C₁₋₄alkyl substituted with one or two hydroxyl groups;
- R₁₁ is cyano; -NR_{10a}R_{10b}; C₁₋₆alkyloxy optionally substituted with one or two hydroxyl groups; -S(=O)₂-C₁₋₆alkyl; -S(=O)₂-NR_{9a}R_{9b}; -NR₁₃-S(=O)₂-C₁₋₆alkyl; -NR₁₃-S(=O)₂-NR_{9a}R_{9b}; C₁₋₆alkylcarbonyloxy-; -C(=O)-NR_{10a}R_{10b}; -O-C(=O)-NR_{10a}R_{10b}; -COOH;
- 20 -P(=O)(OH)₂; or -P(=O)(O-C₁₋₄alkyl)₂;
- R₁₂ is -NR_{9a}R_{9b}, C₁₋₆alkyloxy, or cyano;
- R₁₃ is hydrogen or C₁₋₄alkyl;
- R₁₄ 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, C₁₋₄alkyl,
- 25 halogen, cyano, hydroxyl, C₁₋₆alkyloxy and NR_{9a}R_{9b};
- x₁ is CR_{5a} or N;
- x₂ is CR_{5b};
- x₃ is CR_{5c} or N;
- each R₁₅ is independently selected from the group consisting of hydrogen, methyl, halo,
- 30 C₁₋₄alkyloxy and hydroxyl;
- R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen; hydroxyl; cyano; halo; C₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyloxy; C₁₋₆alkyl substituted with one -NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one cyano; C₁₋₆alkyloxyC₁₋₆alkyl wherein
- 35 each of the C₁₋₆alkyl groups are optionally substituted with one or two hydroxyl groups; C₂₋₆alkenyl; C₁₋₆alkyl-O-carbonyl-; C₁₋₆alkyloxy; C₁₋₆alkyloxy substituted with one or two hydroxyl groups; C₁₋₆alkyloxyC₁₋₆alkyloxy wherein each of the C₁₋₆alkyl groups

- are optionally substituted with one or two hydroxyl groups; C₁₋₆alkyloxy substituted with one cyano; and C₁₋₆alkyloxy substituted with one -NR_{9a}R_{9b};
- R_{5b} is C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; mono-or polyhaloC₁₋₆alkyloxy; mono-or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one
- 5 hydroxyl group; C₂₋₆alkenyl; -Si(CH₃)₃; C₁₋₆alkyl substituted with one R₁₂; or C₁₋₆alkyl-O-carbonyl-;
- and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.
- 10 In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein
- y₁ is CR_{7a} or N;
- y₂ is CH or N;
- R_{7a} is hydrogen, halo, trifluoromethyl or cyano;
- 15 R₇ is hydrogen, -NH₂, -NHCH₃, -NH(CH₂CH₃), methyl, -CH₂OH, halo or cyano; or when y₁ represents CR_{7a}, this R_{7a} can be taken together with a R₇ on an adjacent carbon atom to form -CH=CH-NH- or -N=CH-NH-;
- X is -CR₁R_{1a}-, -CH₂-CHR₁-;
- R₁ is hydrogen or C₁₋₆alkyl;
- 20 R_{1a} is hydrogen; C₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; C₁₋₆alkyl substituted with one -NR_{9a}R_{9b}; or -C(=O)-NR_{9a}R_{9b};
- R_{2a} is hydrogen; C₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; or C₁₋₆alkyl substituted with one substituent selected from the group consisting of -NR_{9a}R_{9b}, cyano and C₁₋₄alkyloxy;
- 25 R_{2b} is hydrogen or C₁₋₆alkyl; or
- R_{2a} and R_{2b} are taken together to form -CH₂-CH₂-, -CH₂-NR_{2c}-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-O-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-NR_{2c}-CH₂- or =O;
- R_{2c} is hydrogen; C₁₋₄alkyl optionally substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkyl substituted with one cyano group;
- 30 or C₁₋₆alkyl substituted with one -NR_{9a}R_{9b};
- R₃ is hydrogen; C₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; C₁₋₆alkyl substituted with one or two hydroxyl groups and one C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl- optionally substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkylcarbonyl-; R_{10a}R_{10b}N-C₁₋₆alkylcarbonyl-; C₁₋₆alkyl-
- 35 O-carbonyl-; C₁₋₆alkylcarbonyloxy-; C₁₋₆alkyl substituted with one R₁₁; C₁₋₆alkyloxy optionally substituted with one -NR_{10a}R_{10b}; C₂₋₆alkenyl; C₂₋₆alkynyl; hydroxyC₂₋₆alkenyl; hydroxyC₂₋₆alkynyl; C₁₋₆alkyloxyC₂₋₆alkenyl;

- C₁₋₆alkyloxyC₂₋₆alkynyl; C₂₋₆alkenyl substituted with one -NR_{10a}R_{10b}; C₂₋₆alkynyl substituted with one -NR_{10a}R_{10b}; C₁₋₆alkyl substituted with one or two hydroxyl groups and one -NR₁₀R_{10b}; -C₁₋₆alkyl-C(R₁₃)=N-O-R₁₃; -S(=O)₂-C₁₋₆alkyl; -S(=O)₂-NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one -(C=O)-R₁₄; C₁₋₆alkyl substituted with one or two
- 5 hydroxyl groups and one R₁₄; C₁₋₆alkyl substituted with one R₁₄; C₂₋₆alkenyl substituted with one R₁₄; C₂₋₆alkynyl substituted with one R₁₄; or R₁₄;
 R_{4a} is hydrogen;
 R_{4b} is hydrogen; or
 R_{4a} and R_{4b} are taken together to form =O;
- 10 Y is -O- or -C(=O)-; in particular Y is -O-;
 Z is -CHR₆- or -CH₂-C≡C-;
 R₆ is hydrogen; C₁₋₄alkyl-O-carbonyl-; C₁₋₄alkyl; C₁₋₄alkyl substituted with one or two hydroxyl groups; C₁₋₄alkyl 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
- 15 heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R₈ 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 R₈ substituents;
- 20 each R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; or halo;
 R_{9a} and R_{9b} each independently represent hydrogen; mono-or polyhaloC₁₋₄alkyl; C₁₋₄alkylcarbonyl-; C₁₋₄alkyl-O-carbonyl-; C₁₋₄alkyl substituted with one or two hydroxyl groups; or C₁₋₄alkyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyloxy, cyano, amino and mono-or di(C₁₋₄alkyl)amino;
- 25 R_{10a} and R_{10b} each independently represent hydrogen; C₁₋₄alkyl; cyanoC₁₋₆alkyl; C₁₋₆alkyl substituted with one NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one -C(=O)-NR_{9a}R_{9b}; C₁₋₆alkyloxy optionally substituted with one or two hydroxyl groups; C₁₋₆alkyloxyC₁₋₆alkyl wherein each C₁₋₆alkyl is optionally substituted with one or two hydroxyl groups; R₁₄; C₁₋₆alkyl substituted with one R₁₄; -(C=O)-R₁₄;
- 30 C₁₋₆alkylcarbonyl-; C₁₋₆alkyl-O-carbonyl-; mono-or polyhaloC₁₋₆alkylcarbonyl-substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkylcarbonyl-; C₁₋₆alkyl substituted with one -Si(CH₃)₃; -S(=O)₂-C₁₋₆alkyl optionally substituted with one or more halo substituents; -S(=O)₂-NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one
- 35 -S(=O)₂-C₁₋₆alkyl wherein -S(=O)₂-C₁₋₆alkyl is optionally substituted with one or more halo substituents;
 C₁₋₆alkyl substituted with one -S(=O)₂-NR_{9a}R_{9b};

- C₁₋₆alkyl substituted with one -NH-S(=O)₂-C₁₋₆alkyl wherein -NH-S(=O)₂-C₁₋₆alkyl is optionally substituted on a carbon atom with one or more halo substituents;
 C₁₋₆alkyl substituted with one -NH-S(=O)₂-NR_{9a}R_{9b};
 mono-or polyhaloC₁₋₄alkyl; or C₁₋₄alkyl substituted with one or two hydroxyl groups;
- 5 R₁₁ is cyano; -NR_{10a}R_{10b}; C₁₋₆alkyloxy optionally substituted with one or two hydroxyl groups; -S(=O)₂-C₁₋₆alkyl; -S(=O)₂-NR_{9a}R_{9b}; -NR₁₃-S(=O)₂-C₁₋₆alkyl; -NR₁₃-S(=O)₂-NR_{9a}R_{9b}; C₁₋₆alkylcarbonyloxy-; -C(=O)-NR_{10a}R_{10b}; -O-C(=O)-NR_{10a}R_{10b}; -COOH; -P(=O)(OH)₂; or -P(=O)(O-C₁₋₄alkyl)₂;
- R₁₂ is -NR_{9a}R_{9b}, C₁₋₆alkyloxy, or cyano;
- 10 R₁₃ is hydrogen or C₁₋₄alkyl;
 R₁₄ is a C₃₋₈cycloalkyl; or a 4, 5 or 6 membered saturated heterocyclcyl which is optionally substituted with one, two or three substituents selected from the group consisting of oxo, C₁₋₄alkyl, halogen, cyano, hydroxyl, C₁₋₆alkyloxy and NR_{9a}R_{9b};
- x₁ is CR_{5a} or N;
- 15 x₂ is CR_{5b} or N;
 x₃ is CR_{5c} or N;
 each R₁₅ is independently selected from the group consisting of hydrogen, methyl, halo, C₁₋₄alkyloxy and hydroxyl;
- R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen;
- 20 hydroxyl; cyano; halo; C₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyloxy; C₁₋₆alkyl substituted with one -NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one cyano; C₁₋₆alkyloxyC₁₋₆alkyl wherein each of the C₁₋₆alkyl groups are optionally substituted with one or two hydroxyl groups; C₂₋₆alkenyl; C₁₋₆alkyl-O-carbonyl-; C₁₋₆alkyloxy; C₁₋₆alkyloxy substituted with one or
- 25 two hydroxyl groups; C₁₋₆alkyloxyC₁₋₆alkyloxy wherein each of the C₁₋₆alkyl groups are optionally substituted with one or two hydroxyl groups; C₁₋₆alkyloxy substituted with one cyano; and C₁₋₆alkyloxy substituted with one -NR_{9a}R_{9b};
- R_{5b} is hydrogen; C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; hydroxyl; cyano; mono-or polyhaloC₁₋₆alkyloxy; mono-or polyhaloC₁₋₆alkyl; C₁₋₄alkyl
- 30 substituted with one or two hydroxyl groups; C₂₋₆alkenyl; C₁₋₄alkyloxy; -Si(CH₃)₃;
 C₁₋₆alkyl substituted with one R₁₂; C₁₋₆alkyl-O-carbonyl-; or C₁₋₆alkyloxy substituted with one R₁₂;
- and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.
- 35 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:



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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;

10 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 $-CR_1R_{1a}-$, $-CH_2-CHR_1-$;

15 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

20 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

25 substituted with one $-(C=O)-R_{14}$; or C_{1-6} alkyl substituted with one R_{14} ;

R_{4a} is hydrogen;

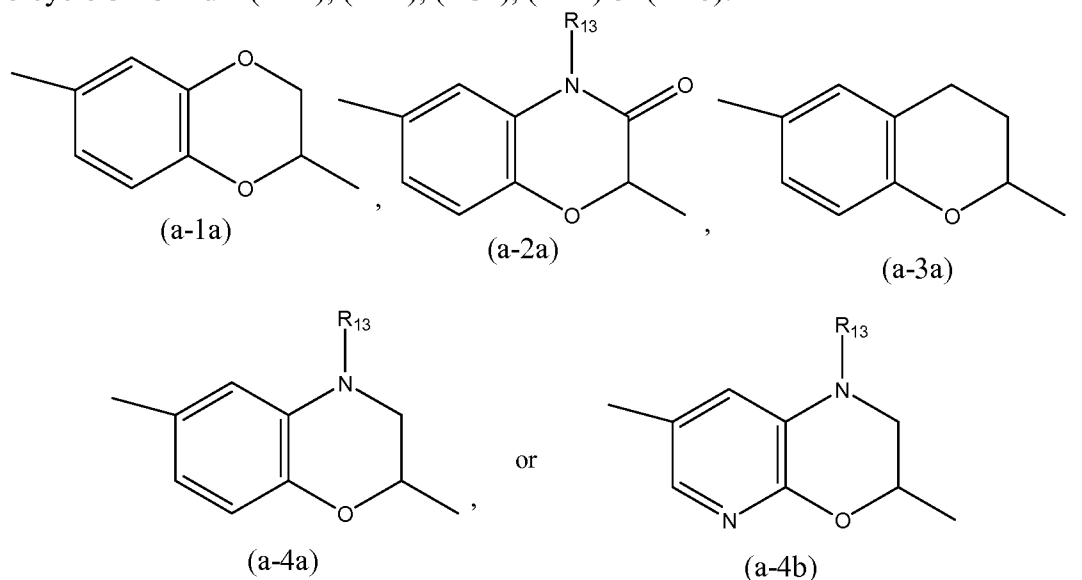
R_{4b} is hydrogen; or

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

Y is $-O-$ or $-C(=O)-$;

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

- 5 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;
 10 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):



- 15 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 polyhalo C_{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;
 20 $-S(=O)_2-C_{1-6}$ 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,
 25 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;
- 5 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} alkyloxy C_{1-6} alkyl; C_{1-6} alkyloxy; C_{1-6} alkyloxy substituted with one hydroxyl group; C_{1-6} alkyloxy C_{1-6} alkyloxy;
 R_{5b} is hydrogen; C_{1-6} alkyl; C_{3-6} cycloalkyl optionally substituted with one cyano; cyano;
- 10 mono-or polyhalo C_{1-6} alkyloxy; mono-or polyhalo C_{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.
- 15 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;
- 20 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 $-CH_2-NH-CH_2-$;
- 25 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 $=O$;
- 30 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;
- 35 each R_8 is independently hydrogen; C_{1-4} alkyloxy; cyano; or halo;

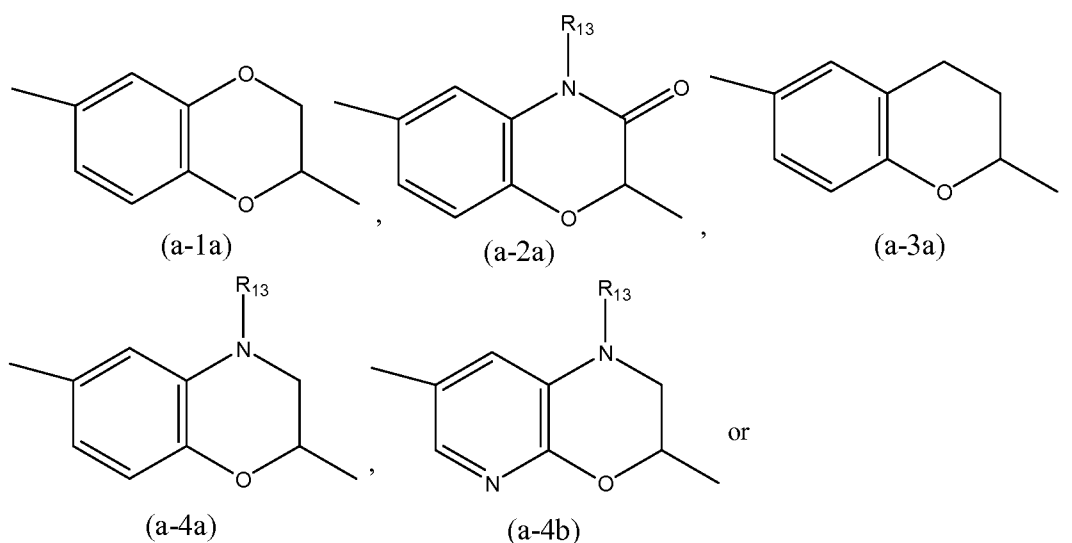
- or a R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R₆ substituent of Z, by which ring A together with Y-Z forms a bicycle of formula (a-3a);
- R₁₁ is C₁₋₆alkyloxy optionally substituted with one hydroxyl group; or -C(=O)-
- 5 NR_{10a}R_{10b};
- R_{10a} and R_{10b} each independently represent hydrogen or C₁₋₄alkyl;
- R₁₄ is a 5 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents selected from the group consisting of C₁₋₄alkyl;
- x₁ is CR_{5a} or N;
- 10 x₂ is CR_{5b};
- x₃ is CR_{5c};
- each R₁₅ is hydrogen;
- R_{5a} is hydrogen or C₁₋₆alkyloxyC₁₋₆alkyl;
- R_{5b} is C₁₋₆alkyl; C₃₋₆cycloalkyl; mono-or polyhaloC₁₋₆alkyloxy; C₂₋₆alkenyl; C₁₋₆alkyl
- 15 substituted with one cyano; C₁₋₄alkyloxy; or C₁₋₆alkyl-O-carbonyl-;
- R_{5c} is hydrogen;
- and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof.
- 20 In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein
- y₁ is CH;
- y₂ is CH;
- R₇ is hydrogen;
- 25 X is CH₂;
- R_{2a} is hydrogen;
- R_{2b} is hydrogen;
- R₃ is hydrogen; or C₁₋₆alkyl substituted with one or two hydroxyl groups;
- R_{4a} and R_{4b} are taken together to form =O;
- 30 Y is -O-;
- Z is -CH₂-;
- Ring A is phenyl optionally substituted with one or two R₈ substituents;
- each R₈ is independently hydrogen; C₁₋₄alkyloxy; cyano; or F;
- x₁ is CH;
- 35 x₂ is CR_{5b};
- x₃ is CH;
- each R₁₅ is hydrogen;

R_{5b} is C₁₋₆alkyl; C₃₋₆cycloalkyl; mono-or polyhaloC₁₋₆alkyloxy; C₂₋₆alkenyl; C₁₋₆alkyl substituted with one cyano; or C₁₋₆alkyl-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) y₂ is CH;
- (ii) R_{7a} is hydrogen;
- (iii) R₇ is hydrogen, -NH₂, -CH₂OH, halo or cyano;
or when y₁ represents CR_{7a}, this R_{7a} can be taken together with a R₇ on an adjacent carbon atom to form -CH=CH-NH-;
- (iv) R_{1a} is hydrogen;
- (v) R_{2a} is hydrogen; C₁₋₆alkyl; C₁₋₆alkyl substituted with one hydroxyl group; or C₁₋₆alkyl substituted with one -NR_{9a}R_{9b} substituent;
R_{2b} is hydrogen; or
- R_{2a} and R_{2b} are taken together to form -CH₂-CH₂-, -CH₂-NR_{2c}-CH₂- or =O;
- (vi) R_{2c} is hydrogen; or C₁₋₆alkyl substituted with one -NR_{9a}R_{9b};
- (vii) R₃ is hydrogen; C₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; C₁₋₆alkyl substituted with one or two hydroxyl groups and one C₁₋₆alkyloxy; R_{10a}R_{10b}N-C₁₋₆alkylcarbonyl-; C₁₋₆alkyl-O-carbonyl-; C₁₋₆alkyl substituted with one R₁₁; C₁₋₆alkyl substituted with one -(C=O)-R₁₄; or C₁₋₆alkyl substituted with one R₁₄;
- (viii) Y is -O- or -C(=O)-;
- Z is -CHR₆- or -CH₂-C≡C-;
- R₆ is hydrogen; C₁₋₄alkyl-O-carbonyl-; C₁₋₄alkyl; C₁₋₄alkyl substituted with one hydroxyl group; C₁₋₄alkyl substituted with one -NR_{9a}R_{9b}; or -C(=O)-NR_{9a}R_{9b};
- each R₈ is independently hydrogen; C₁₋₄alkyloxy; cyano; C₁₋₄alkyl or halo;
or a R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R₆ 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):



- (ix) R_{9a} and R_{9b} each independently represent hydrogen; C₁₋₄alkyl substituted with one hydroxyl group; or C₁₋₄alkyl;
- (x) R_{10a} and R_{10b} each independently represent hydrogen; C₁₋₄alkyl; C₁₋₆alkyl-O-carbonyl-; mono-or polyhaloC₁₋₄alkyl; or C₁₋₄alkyl substituted with one hydroxyl group;
- 5 (xi) R₁₁ is cyano; -NR_{10a}R_{10b}; C₁₋₆alkyloxy optionally substituted with one hydroxyl group; -S(=O)₂-C₁₋₆alkyl; C₁₋₆alkylcarbonyloxy-; -C(=O)-NR_{10a}R_{10b}; -COOH; or -P(=O)(O-C₁₋₄alkyl)₂;
- 10 (xii) R₁₄ is a 5 membered saturated heterocyclcyl which is optionally substituted with one, two or three substituents selected from the group consisting of oxo and C₁₋₄alkyl;
- (xiii) R₆ is hydrogen; C₁₋₄alkyl-O-carbonyl-; C₁₋₄alkyl; C₁₋₄alkyl substituted with one hydroxyl group; C₁₋₄alkyl substituted with one -NR_{9a}R_{9b}; or -C(=O)-NR_{9a}R_{9b};
- (xiv) x₂ is CR_{5b};
- 15 (xv) each R₁₅ is independently selected from the group consisting of hydrogen, methyl, halo, and C₁₋₄alkyloxy;
- (xvi) R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen; hydroxyl; cyano; halo; C₁₋₆alkyl substituted with one or two hydroxyl groups; C₁₋₆alkyl substituted with one -NR_{9a}R_{9b}; C₁₋₆alkyloxyC₁₋₆alkyl; C₁₋₆alkyloxy;
- 20 C₁₋₆alkyloxy substituted with one hydroxyl group; C₁₋₆alkyloxyC₁₋₆alkyloxy;
- (xvii) R_{5b} is hydrogen; C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; cyano; mono-or polyhaloC₁₋₆alkyloxy; mono-or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one hydroxyl group; C₂₋₆alkenyl; C₁₋₄alkyloxy; -Si(CH₃)₃; C₁₋₆alkyl substituted
- 25 with one R₁₂; or C₁₋₆alkyl-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:

- 5 (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;
- 10 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;
- 15 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;
- 20 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
- 25 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 heterocyclcyl which is optionally substituted with one,
- 30 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;
- 35 (xiv) R_{5a} is hydrogen or C_{1-6} alkyloxy C_{1-6} alkyl;
 (xv) R_{5b} is C_{1-6} alkyl; C_{3-6} cycloalkyl; mono-or polyhalo C_{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:

- 5 (i) y₁ is CH;
(ii) y₂ is CH;
(iii) R₇ is hydrogen;
10 (iv) X is CH₂;
(v) R_{2a} is hydrogen;
(vi) R_{2b} is hydrogen;
(vii) R₃ is hydrogen; or C₁₋₆alkyl substituted with one or two hydroxyl groups;
(viii) R_{4a} and R_{4b} are taken together to form =O;
15 (ix) Ring A is phenyl optionally substituted with one or two R₈ substituents;
each R₈ is independently hydrogen; C₁₋₄alkyloxy; cyano; or F;
(x) Y is -O-;
(xi) Z is -CH₂-;
(xii) x₁ is CH;
20 x₂ is CR_{5b};
x₃ is CH;
(xiii) each R₁₅ is hydrogen;
(xiv) R_{5b} is C₁₋₆alkyl; C₃₋₆cycloalkyl; mono-or polyhaloC₁₋₆alkyloxy; C₂₋₆alkenyl;
C₁₋₆alkyl substituted with one cyano; or C₁₋₆alkyl-O-carbonyl-; in particular R_{5b} is
25 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.

- 30 In an embodiment, the present invention relates to those compounds of formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
each R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; or halo; or
a R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent may be
35 taken together with the R₆ 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 R₈ substituents; each R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; C₁₋₄alkyl 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 R₈ substituents; each R₈ is independently hydrogen; C₁₋₄alkyloxy; 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 R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent, and said R₈ substituent is taken together with the R₆ substituent of Z (Z is -CHR₆-), 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 R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent, and said R₈ substituent is taken together with the R₆ substituent of Z (Z is -CHR₆-), 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 R₈ substituents.

- 5 In an embodiment, the present invention relates to those compounds of formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein ring A is phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms.

- 10 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
15 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 R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; or halo.

- In an embodiment, the present invention relates to those compounds of formula (I) and
20 the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein each R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; or halo; or a R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R₆ 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).

- 25 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 -CHR₆- and Y is O.

- In an embodiment, the present invention relates to those compounds of formula (I) and
30 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 R₈ is other than C₁₋₄alkyl.

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 R₈ substituents;

- 5 each R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; or halo; or a R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R₆ 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-.

- 10 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).

- 15 In an embodiment, the present invention relates to those compounds of formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R₁₄ is a 5-membered saturated heterocycle which is optionally substituted with one, two or three substituents selected from the group consisting of oxo, C₁₋₄alkyl, halogen, cyano, hydroxyl, C₁₋₆alkyloxy and NR_{9a}R_{9b}; in particular wherein R₁₄ is a 5-membered saturated heterocycle which is substituted with one or two substituents selected from the group consisting of oxo or C₁₋₄alkyl.

- 25 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 R₁₄ is a 5-membered saturated heterocycle selected from 1-pyrrolidinyl, 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, C₁₋₄alkyl, halogen, cyano, hydroxyl, C₁₋₆alkyloxy and NR_{9a}R_{9b}; in particular wherein R₁₄ is a 5-membered saturated heterocycle selected from 1-pyrrolidinyl, 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 C₁₋₄alkyl.

- 35 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; C₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; or C₁₋₆alkyl 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
- 5 R_{2a} is hydrogen; C₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; or C₁₋₆alkyl substituted with one substituent selected from the group consisting of -NR_{9a}R_{9b}, cyano and C₁₋₄alkyloxy;
- R_{2b} is hydrogen or C₁₋₆alkyl; or
- 10 R_{2a} and R_{2b} are taken together to form -CH₂-CH₂-, -CH₂-NR_{2c}-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-O-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-NR_{2c}-CH₂-.

- 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
- 15 hydrogen; C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; hydroxyl; cyano; mono-or polyhaloC₁₋₆alkyloxy; mono-or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one or two hydroxyl groups; C₂₋₆alkenyl; C₁₋₄alkyloxy; -Si(CH₃)₃; C₁₋₆alkyl substituted with one R₁₂; or C₁₋₆alkyloxy substituted with one R₁₂.

- 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
- 20 C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; mono-or polyhaloC₁₋₆alkyloxy; mono-or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one hydroxyl group; C₂₋₆alkenyl; -Si(CH₃)₃; C₁₋₆alkyl substituted with one R₁₂; or C₁₋₆alkyl-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
- 25 C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; mono-or polyhaloC₁₋₆alkyloxy; mono-or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one hydroxyl group;
- 30 C₂₋₆alkenyl; -Si(CH₃)₃; C₁₋₆alkyl substituted with one R₁₂; or C₁₋₆alkyl-O-carbonyl-; and wherein R₈ is other than C₁₋₄alkyl.

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 R₈ substituents;

each R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; or halo; or

- 5 a R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R₆ 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);

- x₂ is CR_{5b}; R_{5b} is C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; mono- or polyhaloC₁₋₆alkyloxy; mono- or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one
10 hydroxyl group; C₂₋₆alkenyl; -Si(CH₃)₃; C₁₋₆alkyl substituted with one R₁₂; or C₁₋₆alkyl-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

- 15 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 R₈ substituents;

each R₈ is independently hydrogen; C₁₋₄alkyloxy; cyano; or halo; or

- 20 a R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent may be taken together with the R₆ 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);

- x₂ is CR_{5b}; R_{5b} is C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; mono- or polyhaloC₁₋₆alkyloxy; mono- or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one hydroxyl group; C₂₋₆alkenyl; -Si(CH₃)₃; C₁₋₆alkyl substituted with one R₁₂; or C₁₋₆alkyl-
25 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

- 30 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 R₈ substituents;

each R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; or halo; in

particular each R₈ is independently hydrogen; C₁₋₄alkyloxy; cyano; or halo;

- 35 x₂ is CR_{5b}; R_{5b} is C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; mono- or polyhaloC₁₋₆alkyloxy; mono- or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one

hydroxyl group; C₂₋₆alkenyl; -Si(CH₃)₃; C₁₋₆alkyl substituted with one R₁₂; or C₁₋₆alkyl-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,
5 or any subgroup thereof as mentioned in any of the other embodiments, wherein X is -CR₁R_{1a}-; in particular CH₂.

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 R₁ and
10 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-CH₂-.

15 In an embodiment, the present invention relates to those compounds of formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Z is CHR₆, in particular CH₂.

In an embodiment, the present invention relates to those compounds of formula (I) and
20 the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R₆ 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,
25 or any subgroup thereof as mentioned in any of the other embodiments, wherein R₃ is hydrogen or C₁₋₆alkyl 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}
30 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.

- 5 In an embodiment, the present invention relates to those compounds of formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R_{4a} and R_{4b} are taken together to form =O.

- 10 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 x₁ and x₃ are CH₃; and x₂ is CR_{5b}.

- 15 In an embodiment, the present invention relates to those compounds of formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein x₂ is CR_{5b}; R_{5b} is C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; hydroxyl; mono-or polyhaloC₁₋₆alkyloxy; mono-or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one or two hydroxyl groups; C₂₋₆alkenyl; -Si(CH₃)₃; C₁₋₆alkyl substituted with one R₁₂; C₁₋₆alkyl-O-carbonyl-; C₁₋₆alkyloxy substituted with one R₁₂.

- 20 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 C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; hydroxyl; mono-or polyhaloC₁₋₆alkyloxy; mono-or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one or two hydroxyl groups; C₂₋₆alkenyl; -Si(CH₃)₃; C₁₋₆alkyl substituted with one R₁₂; C₁₋₆alkyl-O-carbonyl-; C₁₋₆alkyloxy substituted with one R₁₂.

- 30 In an embodiment, the present invention relates to those compounds of formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen; hydroxyl; cyano; halo; C₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyloxy; C₁₋₆alkyloxyC₁₋₆alkyl wherein each of the C₁₋₆alkyl groups are optionally substituted with one or two hydroxyl groups; C₂₋₆alkenyl; C₁₋₆alkyloxy; C₁₋₆alkyloxy substituted with one or two

hydroxyl groups; C₁₋₆alkyloxyC₁₋₆alkyloxy wherein each of the C₁₋₆alkyl 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 R₃ is
- 5 hydrogen; C₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; C₁₋₆alkyl substituted with one or two hydroxyl groups and one C₁₋₆alkyloxy; C₁₋₆alkylcarbonyloxy-; C₁₋₆alkyl substituted with one R₁₁; C₁₋₆alkyloxy optionally substituted with one -NR_{10a}R_{10b}; C₂₋₆alkenyl; C₂₋₆alkynyl;
- 10 hydroxyC₂₋₆alkenyl; hydroxyC₂₋₆alkynyl; C₁₋₆alkyloxyC₂₋₆alkenyl; C₁₋₆alkyloxyC₂₋₆alkynyl; C₂₋₆alkenyl substituted with one -NR_{10a}R_{10b}; C₂₋₆alkynyl substituted with one -NR_{10a}R_{10b}; C₁₋₆alkyl substituted with one or two hydroxyl groups and one -NR_{10a}R_{10b}; -C₁₋₆alkyl-C(R₁₃)=N-O-R₁₃; -S(=O)₂-C₁₋₆alkyl; -S(=O)₂-NR_{9a}R_{9b}; C₁₋₆alkyl substituted with one -(C=O)-R₁₄; C₁₋₆alkyl substituted with one or two
- 15 hydroxyl groups and one R₁₄; C₁₋₆alkyl substituted with one R₁₄; C₂₋₆alkenyl substituted with one R₁₄; C₂₋₆alkynyl substituted with one R₁₄; or R₁₄.

- 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 R₁₅ is
- 20 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 R₁₅ is hydrogen or F, in particular F.

- 25 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; R₇ is hydrogen, -NH₂, -NHCH₃, -NH(CH₂CH₃), methyl, -CH₂OH, halo or cyano.

- 30 In an embodiment, the present invention relates to those compounds of formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R_{7a} is hydrogen; R₇ is hydrogen, -NH₂, -CH₂OH, halo or cyano.

- In an embodiment, the present invention relates to those compounds of formula (I) and
- 35 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 R₈ substituents;
each R₈ is independently hydrogen; C₁₋₄alkyloxy; cyano; or halo;
Y is -O-; Z is -CH₂-; R₁₅ is H; x₁ and x₃ are CH; x₂ is CR_{5b}; R_{5b} is isopropyl.

- 5 In an embodiment, the present invention relates to those compounds of formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein y₁ and y₂ are CH; R₇ is H; X is CH₂; R_{2a} and R_{2b} are H;
R_{4a} and R_{4b} are taken together to form =O;

- 10 ring A is phenyl optionally substituted with one or two R₈ substituents;
each R₈ is independently hydrogen; C₁₋₄alkyloxy; cyano; or halo;
Y is -O-; Z is -CH₂-; R₁₅ is H; x₁ and x₃ are CH; x₂ 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,

- 15 or any subgroup thereof as mentioned in any of the other embodiments, wherein y₁ and y₂ are CH; R₇ is H; X is CH₂; 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 -CH₂-; R₁₅ is H; x₁ and x₃ are CH; x₂ is CR_{5b}; R_{5b} is isopropyl.

- 20 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 x₁ and x₃ are CH; x₂ 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 y₁ and y₂ 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

- 30 thereof, or any subgroup thereof as mentioned in any of the other embodiments wherein one or more of the following restrictions apply:

(i) y₁ and y₂ are CH;

(ii) R₇ is H;

(iii) X is CH₂;

- 35 (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 $-O-$;
- 5 (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
10 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,
15 or any subgroup thereof as mentioned in any of the other embodiments, wherein C_{1-6} alkyl is limited to C_{1-4} alkyl.

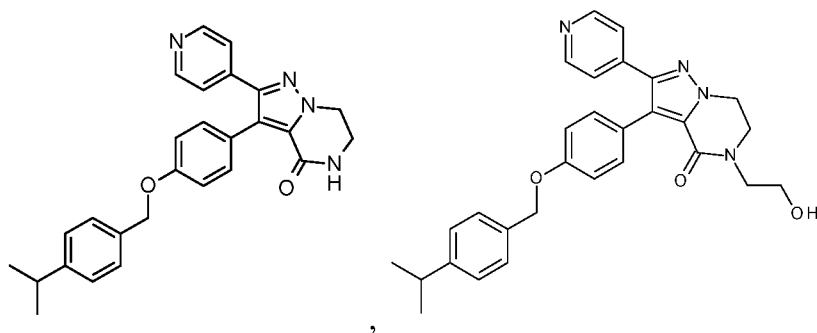
In an embodiment, the present invention relates to those compounds of formula (I) and
the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof,
or any subgroup thereof as mentioned in any of the other embodiments, wherein
20 R_{7a} is hydrogen, halo, trifluoromethyl or cyano;
 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
25 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,
30 two or three substituents selected from the group consisting of oxo, C_{1-4} alkyl, halogen,
cyano, hydroxyl, C_{1-6} alkyloxy and $NR_{9a}R_{9b}$.

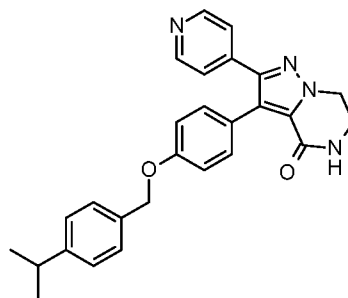
In an embodiment, the present invention relates to a subgroup of formula (I) and the N-oxides, the pharmaceutically acceptable addition salts, and the solvates thereof, as defined in the general reaction schemes.

In an embodiment the compound of Formula (I) is selected from the group consisting of

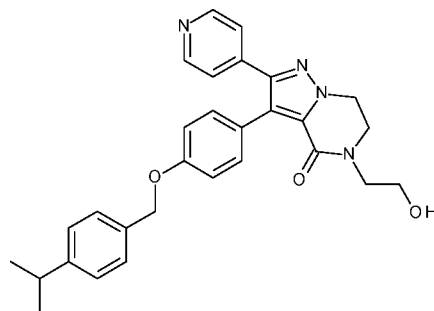


tautomers and stereoisomeric forms thereof,

- 5 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

- 10 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.

- 15 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
5 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
10 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 N₂-gas atmosphere, for example when NaH is used in the reaction.
15 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
20 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.

25 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:

30 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 R₈ substituents;

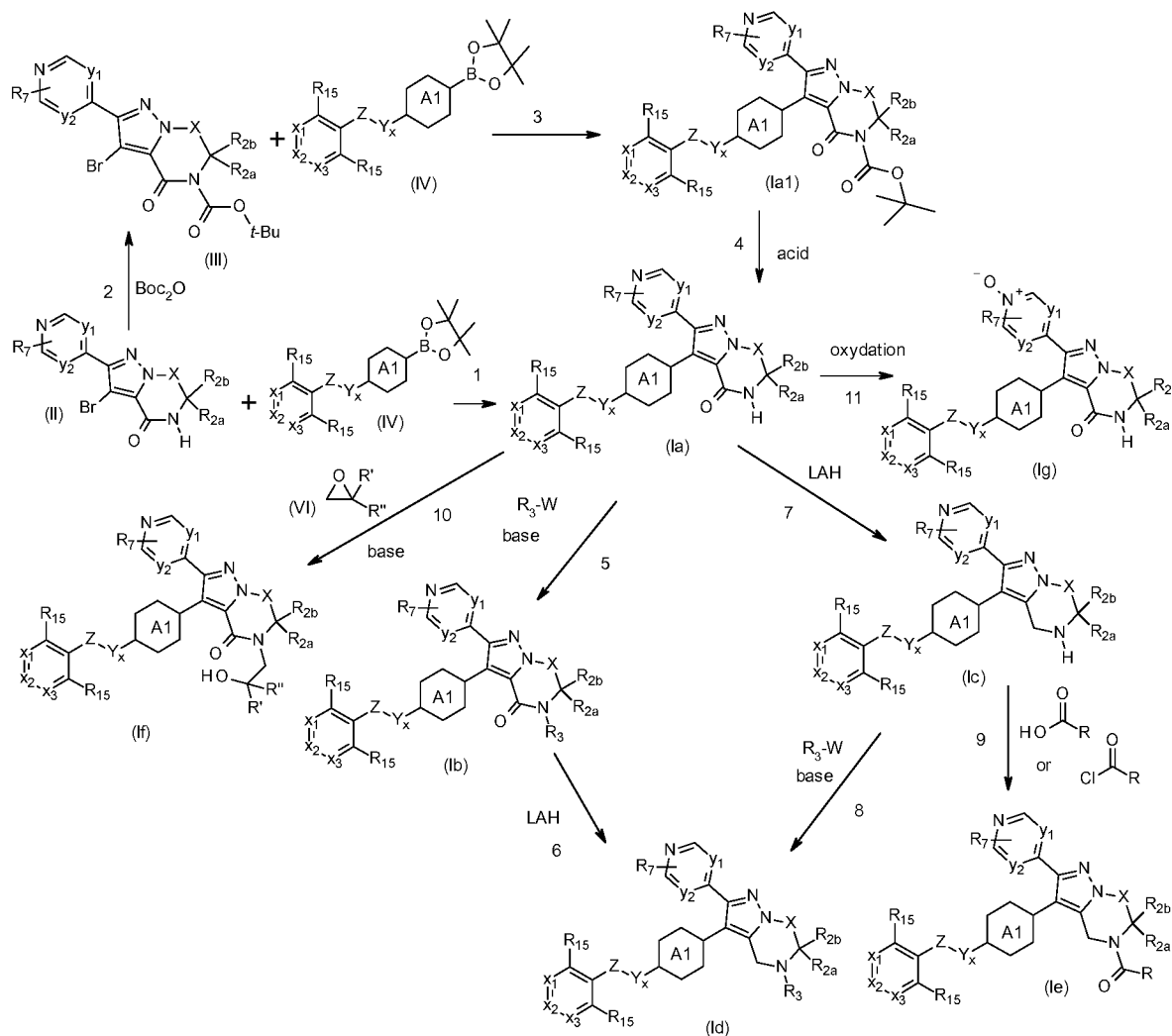
each R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; C₁₋₄alkyl or halo;
35 or a R₈ substituent of ring A1 on an atom adjacent to the atom carrying the Y_x-Z

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

5 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
- 10
- 15 tricyclohexylphosphine.

- 2 : an intermediate of formula (II) can be reacted with *tert*-butoxycarbonyl anhydride (Boc₂O) in the presence of a suitable base, such as for example triethylamine (Et₃N), 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 (PdCl₂dppf), a suitable base, such as potassium phosphate (K₃PO₄), 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 R₃-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 R₃-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, Et₃N or K₂CO₃, 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).

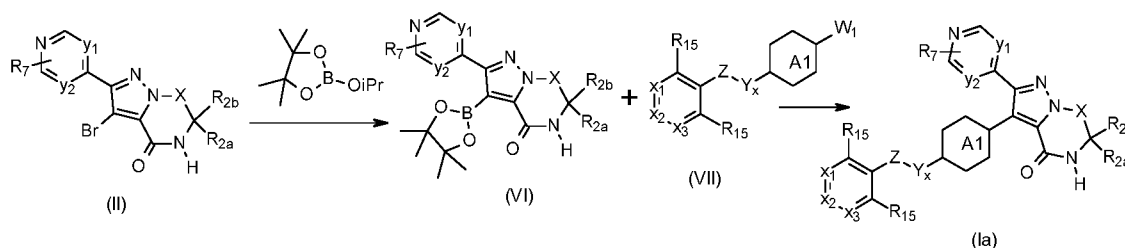
Or alternatively a compound of formula (Ic) can be reacted with an intermediate of formula R-CO-Cl, in the presence of a suitable base, such as for example DIPEA, and a suitable solvent, such as for example dichloromethane.

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.

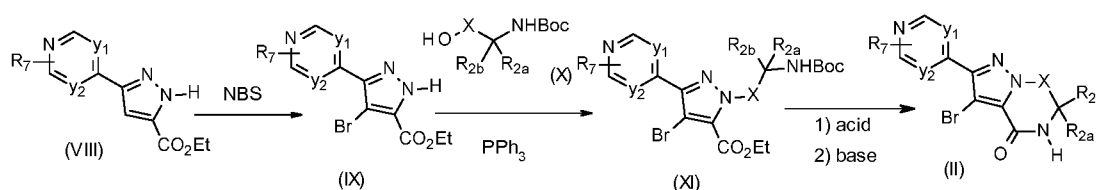


15 In Scheme 1a, an intermediate of formula (II) can be reacted with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in the presence of isopropylmagnesium chloride and a suitable solvent, such as for example tetrahydrofuran (THF), resulting in an intermediate of formula (VI).

20 An intermediate of formula (VI) can be reacted with an intermediate of formula (VII), wherein W1 represents a suitable halogen, such as for example bromide, in the presence of suitable pre-catalyst, such as for example (SP-4-4)-[2'-(amino-κN)[1,1'-biphenyl]-2-yl-κC]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 (K₃PO₄), 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)

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

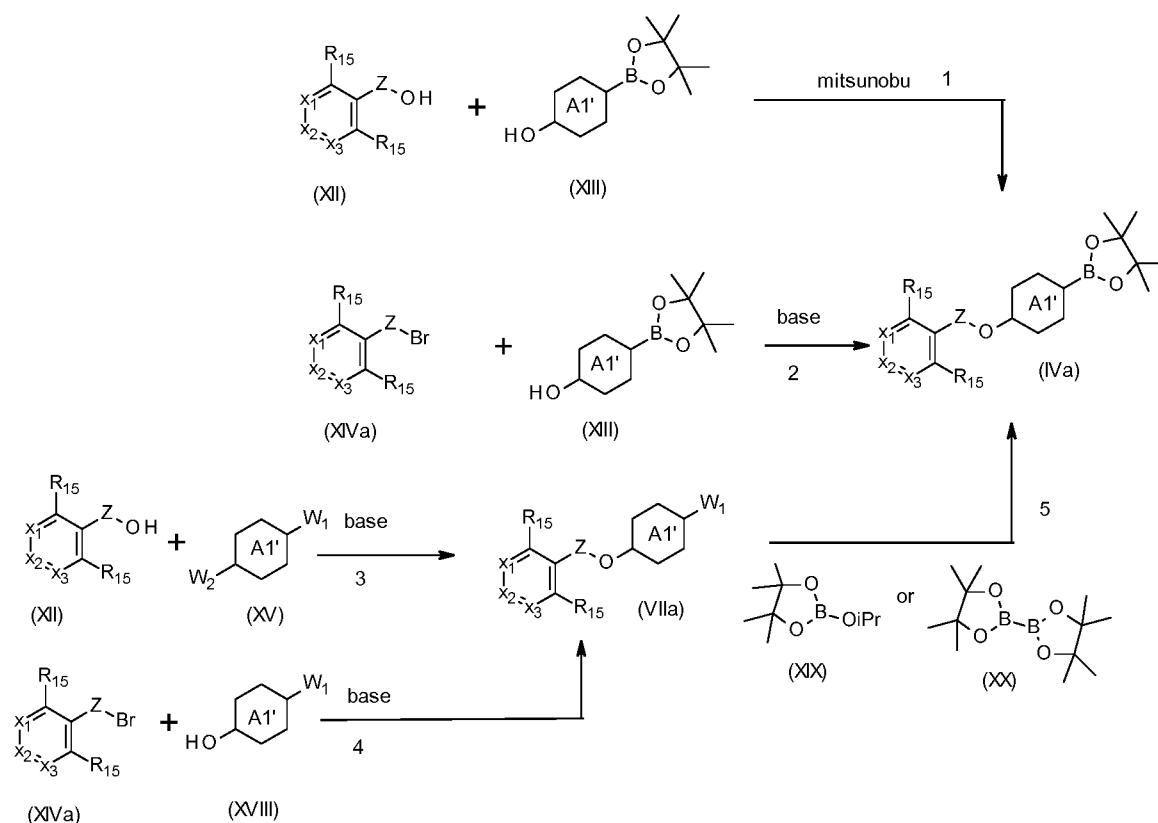


In Scheme 1b, an intermediate of formula (VIII) can be reacted with N-Bromosuccinimide (NBS) in the presence of a suitable solvent, such as for example DCM or DMF, resulting in an intermediate of formula (IX) which can be reacted in a next step with an intermediate of formula (X) in the presence of Triphenylphosphine (PPh₃), 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 example Trifluoroacetic acid (TFA) and a suitable solvent, such as for example DCM. The resulting intermediate can be converted into an intermediate of formula (II) in the presence of a suitable base, such as for example cesium carbonate (Cs₂CO₃) or sodium bicarbonate (NaHCO₃) and a suitable solvent, such as for example 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).
- 5
- 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)
- 10
- 3 : an intermediate of formula (XII) can be reacted with an intermediate of formula (XV), wherein W_1 represents a suitable halogen, such as for example iodide or bromide, and wherein W_2 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).
- 15
- 4 : an intermediate of formula (XIVa) can be reacted with an intermediate of formula (XVIII), wherein W_1 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 CH₃CN or DMF, resulting in an intermediate of formula (VIIa).

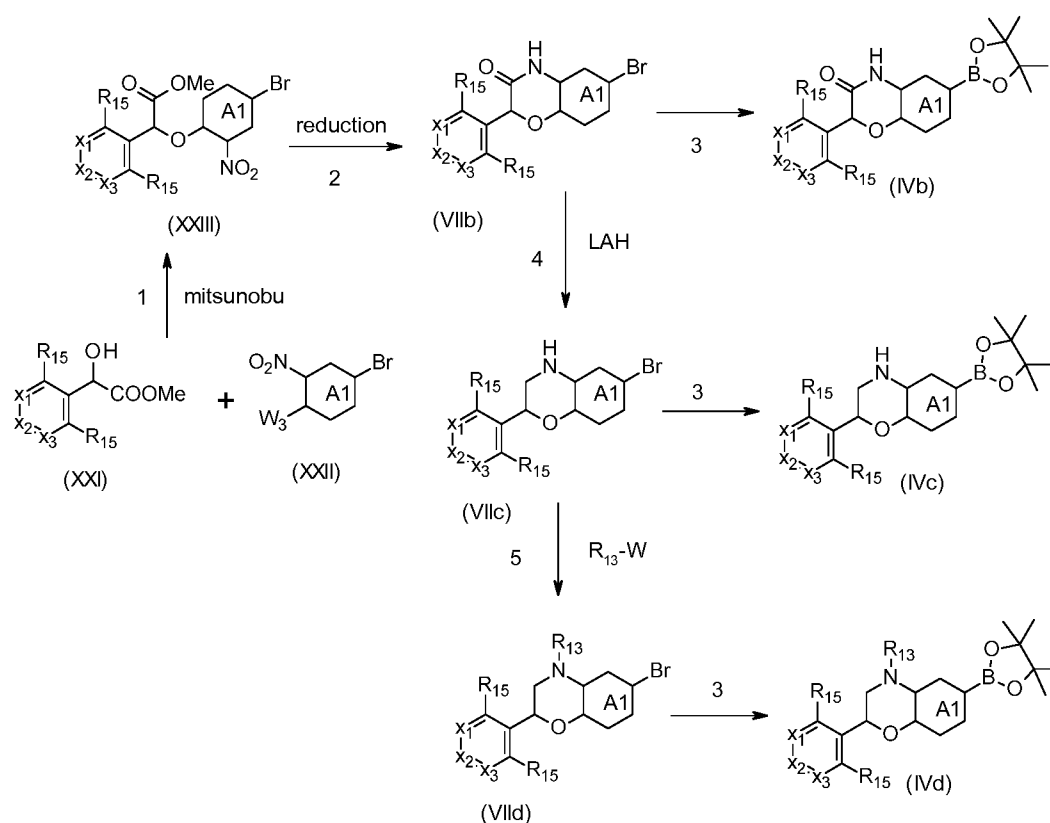
5 : an intermediate of formula (VIIa) can be reacted with intermediates of formula (XIX) or (XX) in the presence of a suitable base, such as for example *n*BuLi or

- 5 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

- 10 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 W₃ represents an hydroxyl, in the presence of PPh₃, 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).

- 15 An intermediate of formula (XXI) can also be reacted with an intermediate of formula (XXII), wherein W₃ 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).

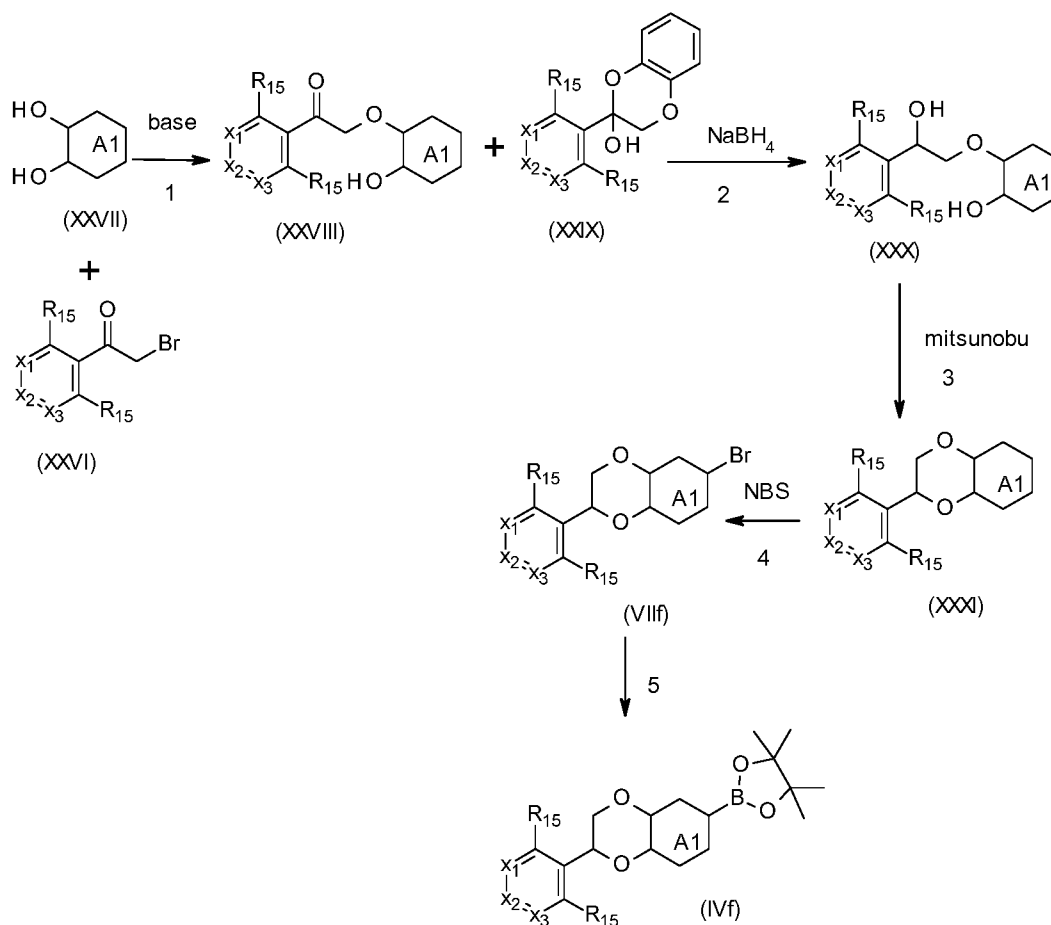
3 : An intermediate of formula (VIIb), (VIIc) or (VIId) can be reacted with

- 5 Bis(pinacolato)diboron in the presence of a suitable base, such as for example potassium acetate (AcOK), a suitable catalyst, such as for example PdCl₂(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
10 (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 R₁₃-W, wherein W represents a suitable leaving group, such as for example iodide, in the presence of a suitable base, such as for example K₂CO₃ and a suitable solvent, such
15 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:

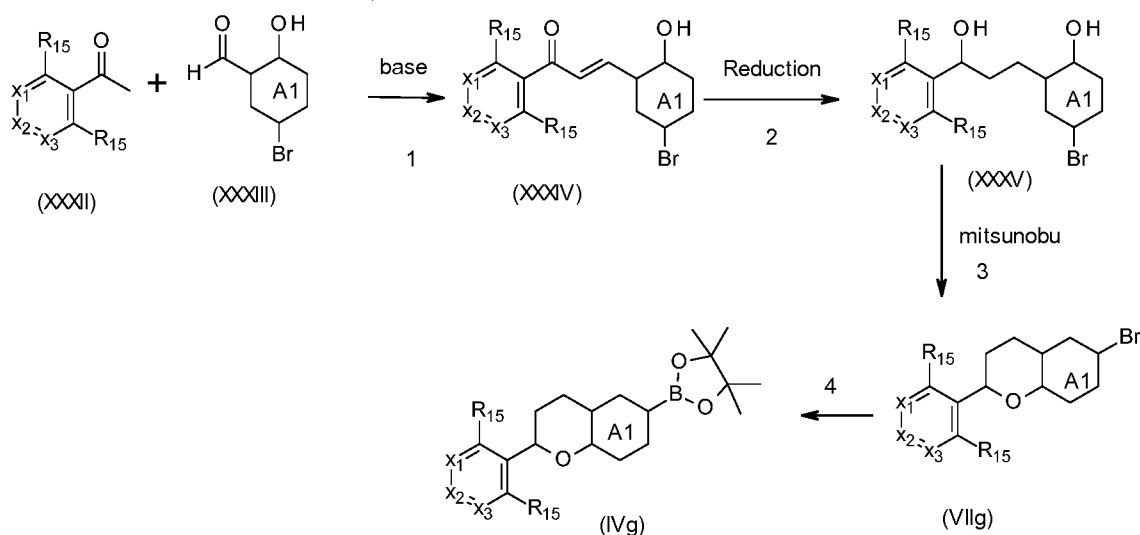


- 1 : an intermediate of formula (XXVI) can be reacted with an intermediate of formula (XXVII) in the presence of a suitable base, such as for example Et₃N, and a suitable solvent, such as for example 2-propanol (iPrOH), resulting in a mixture of intermediate of formula (XXVIII) and intermediate of formula (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 NaBH₄ 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 PPh₃, 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 (VIIIf).
- 5 : An intermediate of formula (VIIIf) 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 $\text{PdCl}_2(\text{dppf})$ and a suitable solvent, such as for example DME resulting in an intermediate of formula (IVf).

Intermediates of formula (IV) wherein $\text{Y}_x\text{-Z}$ 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:

5



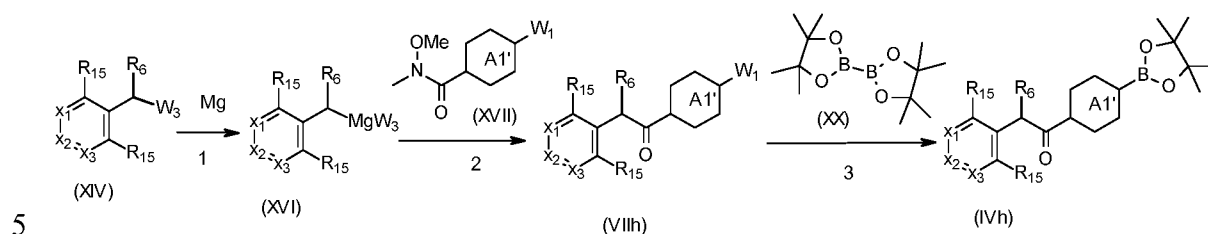
- 1 : an intermediate of formula (XXXII) can be reacted with an intermediate of formula (XXXIII) in the presence of a suitable base, such as for example KOH, and a suitable solvent, such as for example EtOH, resulting in an intermediate of formula (XXXIV).
- 2 : an intermediate of formula (XXXIV) can 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 $\text{PdCl}_2(\text{dppf})$ 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.

25

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:



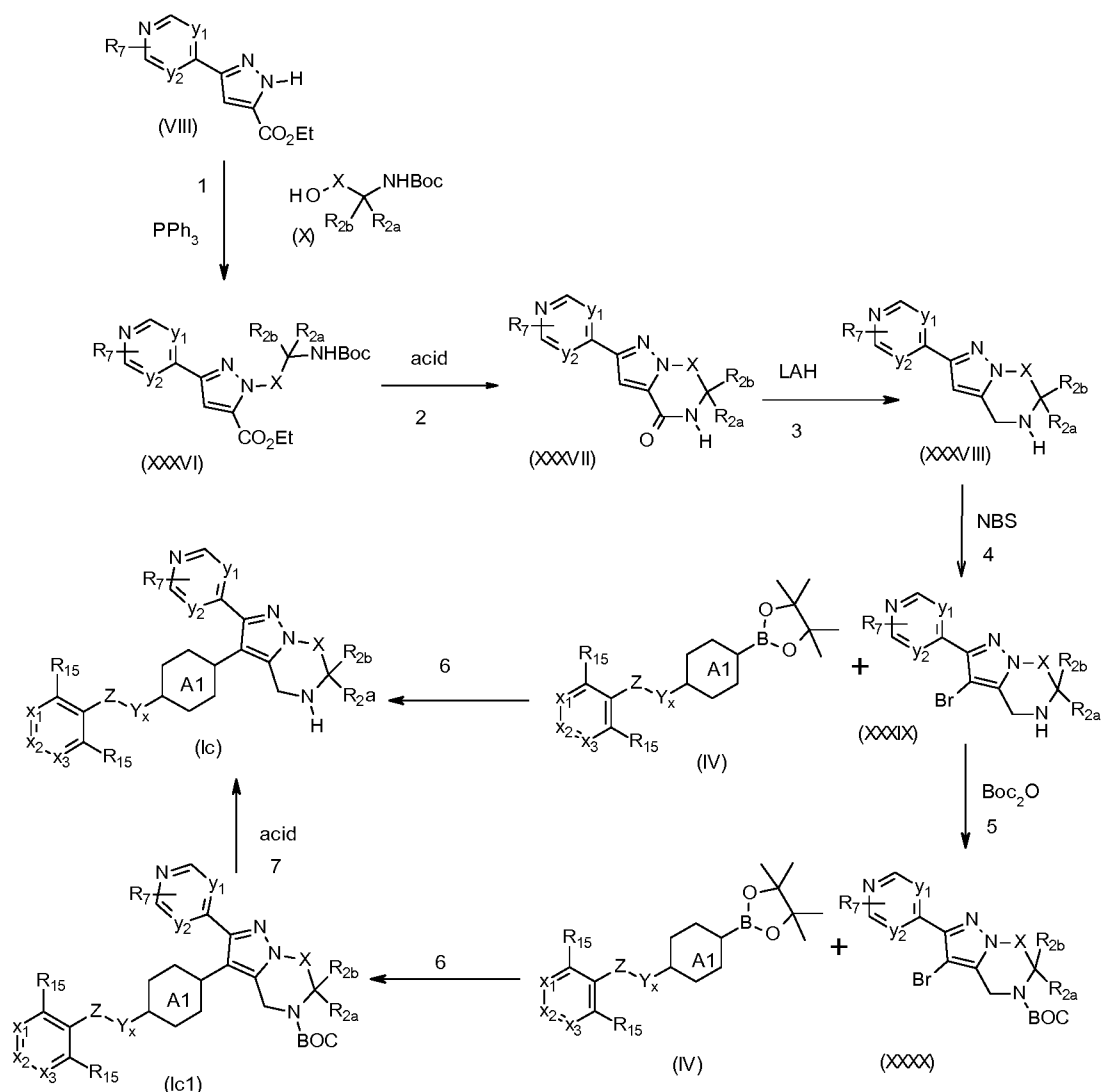
1 : an intermediate of formula (XIV) can be converted into an intermediate of formula (XVI) by reaction with magnesium and a suitable solvent, such as for example THF or diethyl ether (Et_2O). This type of reaction can also be performed in the presence of a suitable reagent, such as for example 1,2-dibromoethane.

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 (VIIIh)

3 : an intermediate of formula (VIIIh) 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).

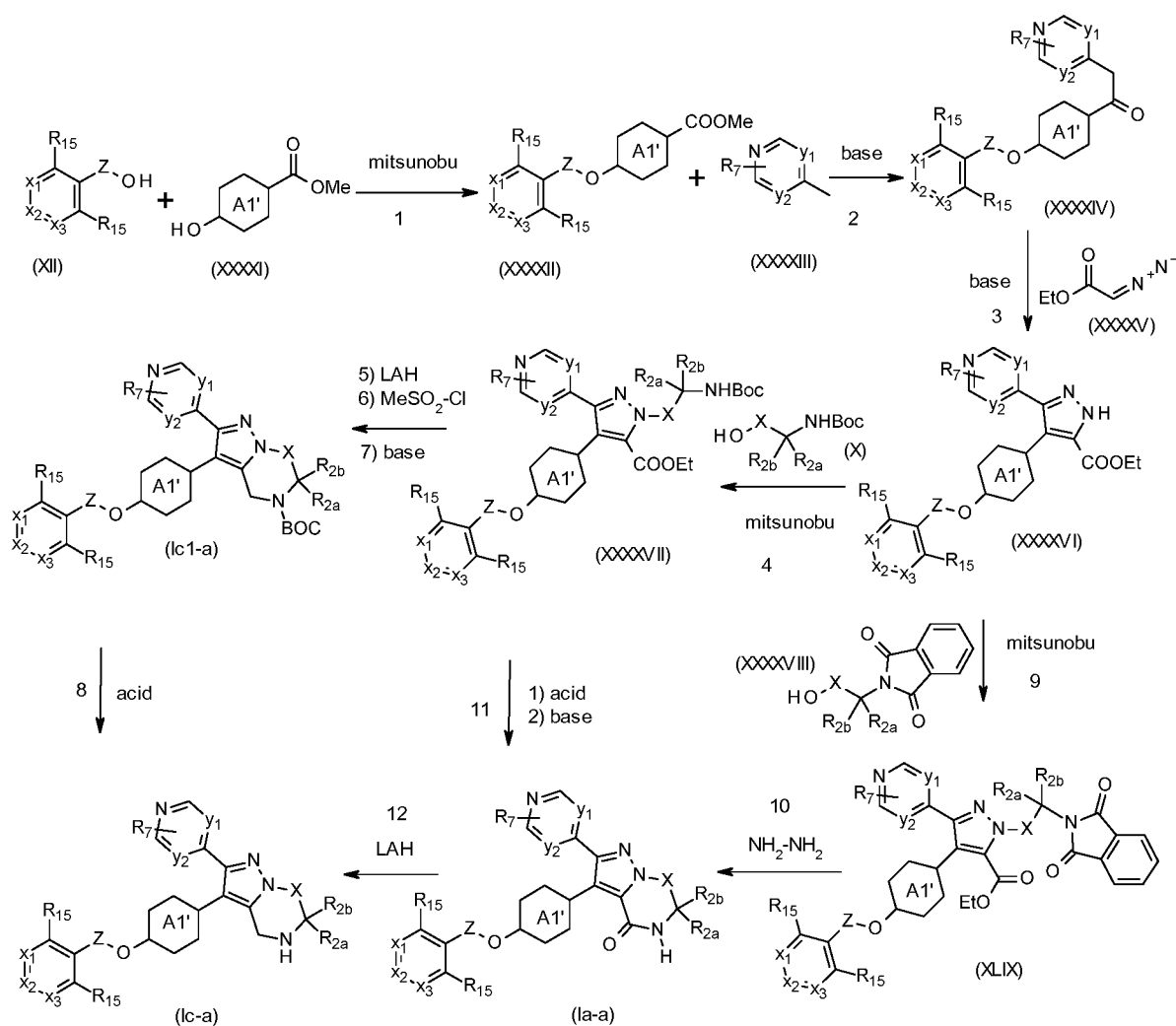
5 : an intermediate of formula (XXXIX) can be reacted with Boc_2O in the presence of a suitable base, such as for example Et_3N , and a suitable solvent, such as for example DCM, resulting in an intermediate of formula (XXXX).

5 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_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 a compound of formula (Ic).

10 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

15 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 Et₃N, 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, and a suitable solvent, such as for example CH₃CN.

9 : an intermediate of formula (XXXXVI) can be reacted with an intermediate of formula (XXXXVIII), in the presence of PPh₃, 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).

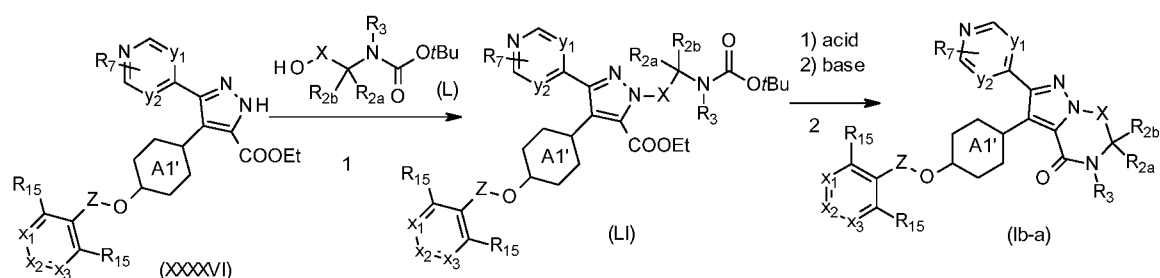
10 : an intermediate of formula (XLIX) can be deprotected to a compound of formula (Ia-a) with hydrazine hydrate and a suitable solvent, such as for example EtOH.

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 Cs₂CO₃ or K₂CO₃, 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:

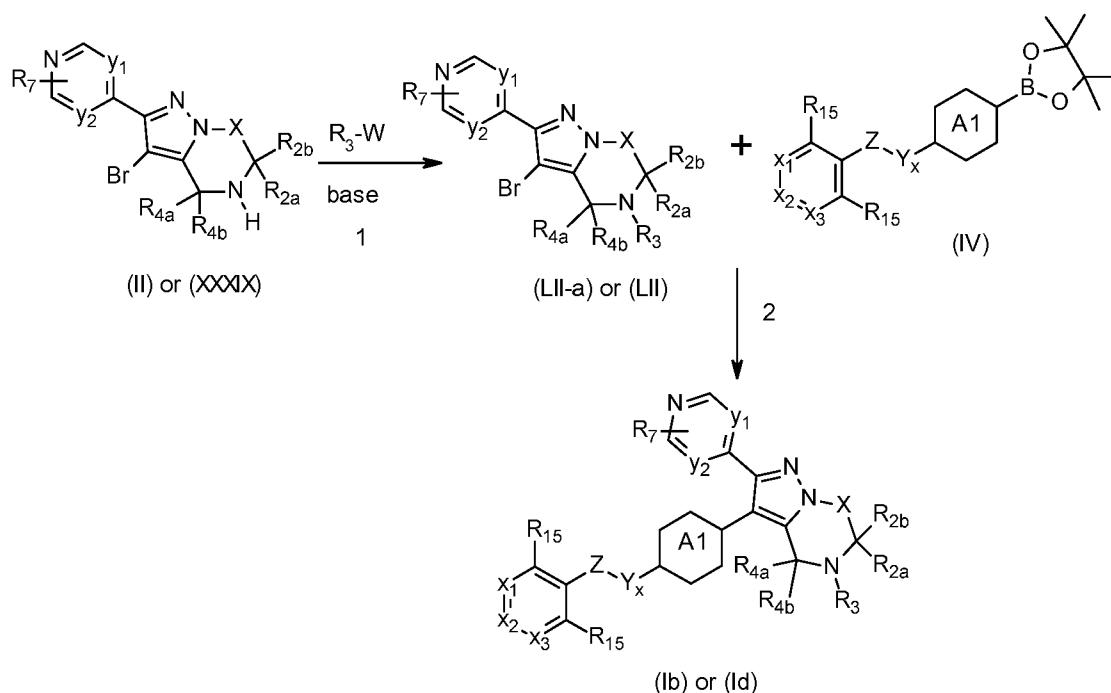


1 : an intermediate of formula (XXXXVI) can be reacted with an intermediate of formula (L) (*t*Bu is *tert*-butyl), in the presence of PPh₃, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example THF resulting in an intermediate of formula (LI).

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 Cs₂CO₃, and a suitable solvent, such as for example DCM or MeOH.

10) Scheme 4 :

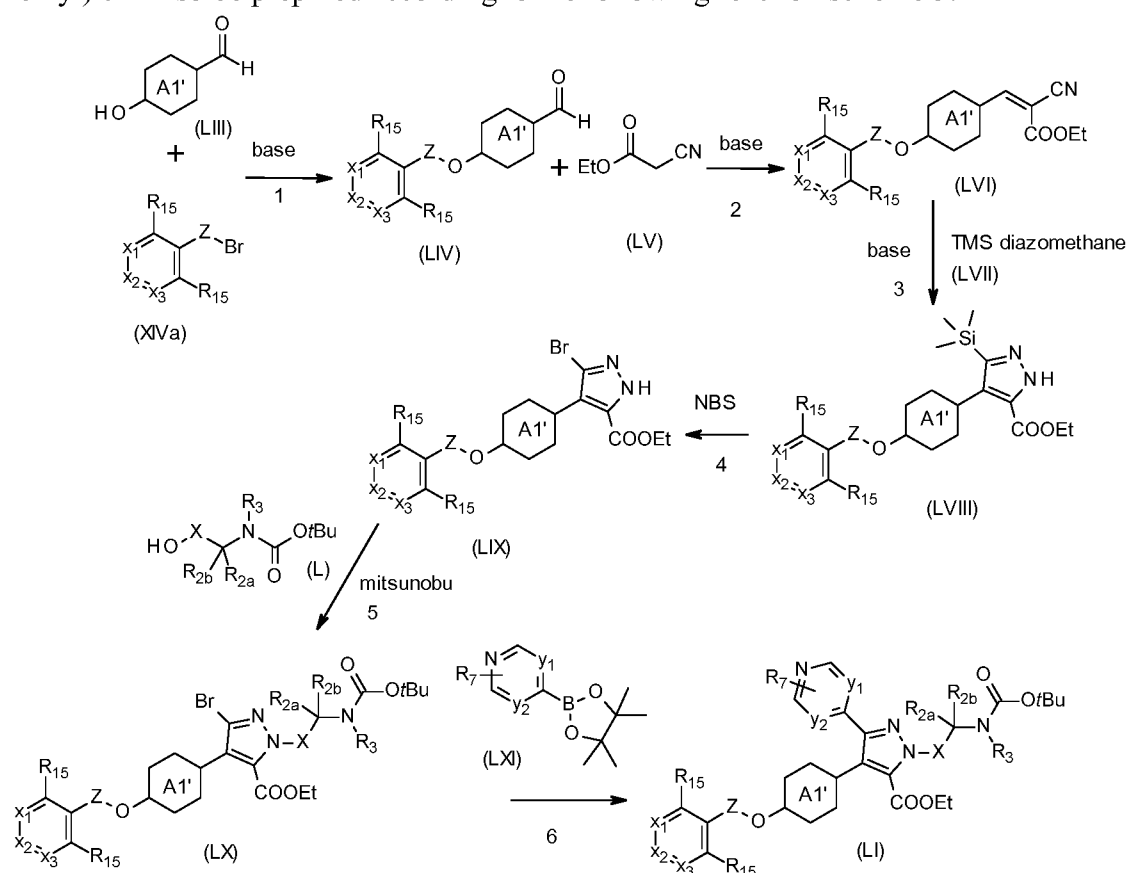
Compounds of formula (Ib), wherein R_{4a} and R_{4b} are taken together to form =O, and (Id), wherein R_{4a} and R_{4b} are hydrogen, can also be prepared according to the following reaction scheme 4.



- 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

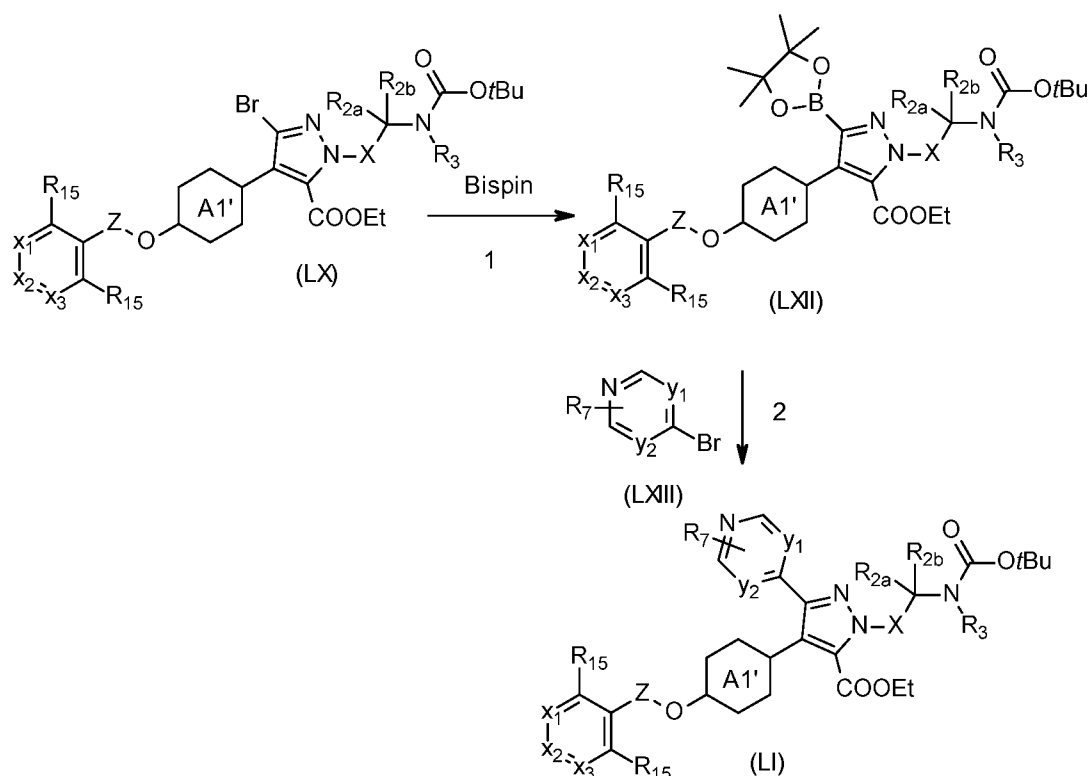
Intermediates of formula (LI) wherein all variables are as defined before (Et means ethyl) can also be prepared according to the following reaction scheme 5:



- 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 $nBuLi$ 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:

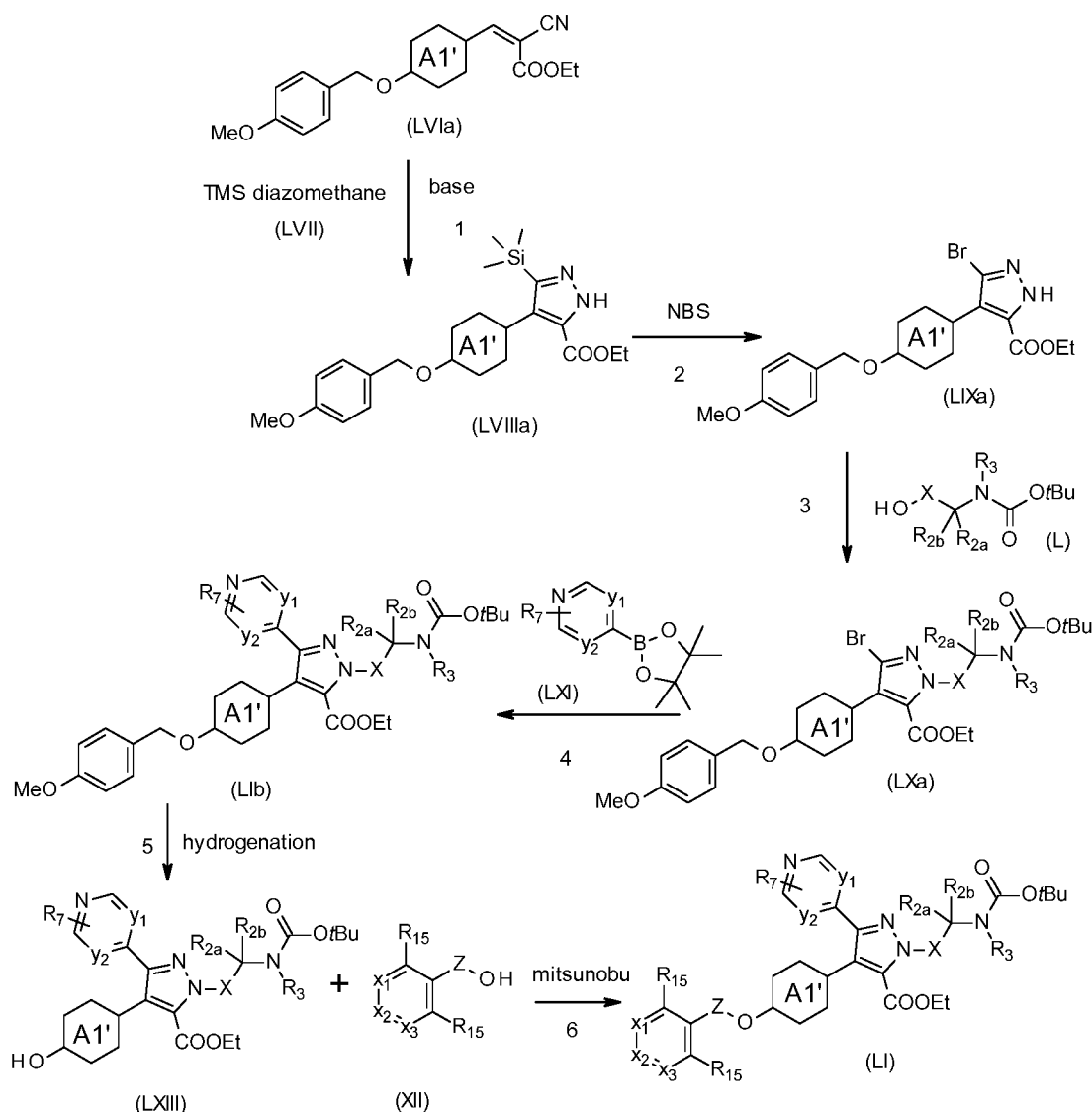


1 : an intermediate of formula (LX) can be reacted with bis(pinacolato)diboron (Bispin) in the presence of a suitable catalyst, such as for example $\text{PdCl}_2(\text{dppf})$, a suitable base, such as for example AcOK and a suitable solvent, such as for example DME, resulting in an intermediate of 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 ($\text{Pd}(\text{OAc})_2$), 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 (LVla) 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

5 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 PPh₃, a suitable Mitsunobu reagent, such as for example DBAD and a suitable solvent, such as for example THF, resulting in an intermediate of formula (LXI).

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

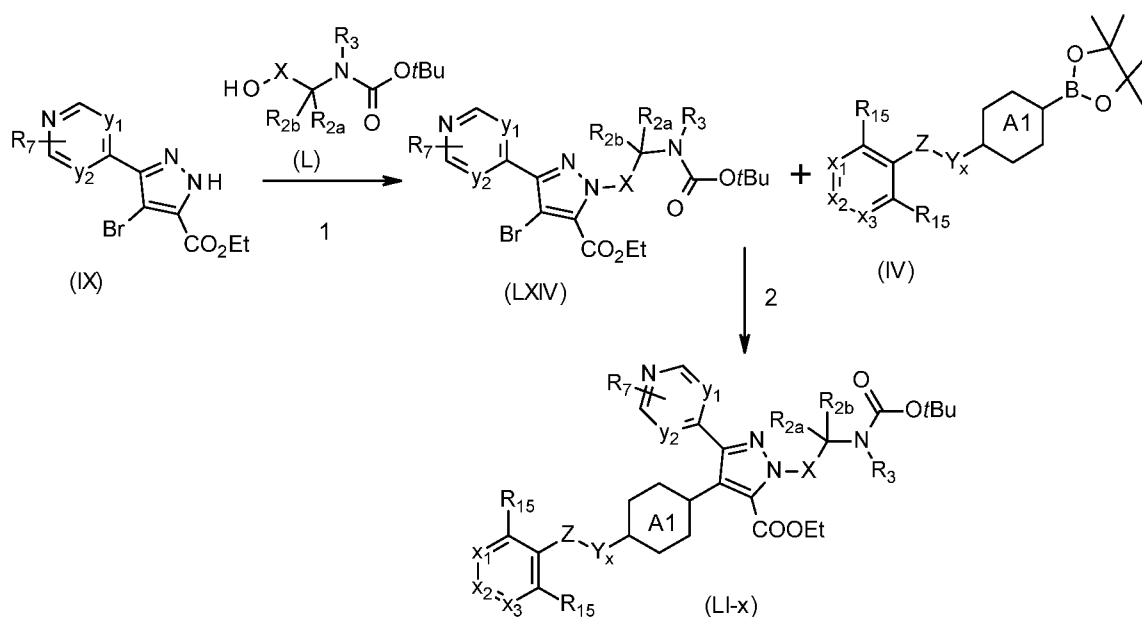
(Pd(OAc)₂), a suitable ligand, such as for example PCy₃, a suitable base, such as potassium phosphate (K₃PO₄), and a suitable solvent or solvent mixture, such as for example dioxane and water, resulting in an intermediate of formula (LIb).

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 PPh₃, 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.



15

1 : an intermediate of formula (IX) can be reacted with an intermediate of formula (L), in the presence of PPh₃, 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).

20

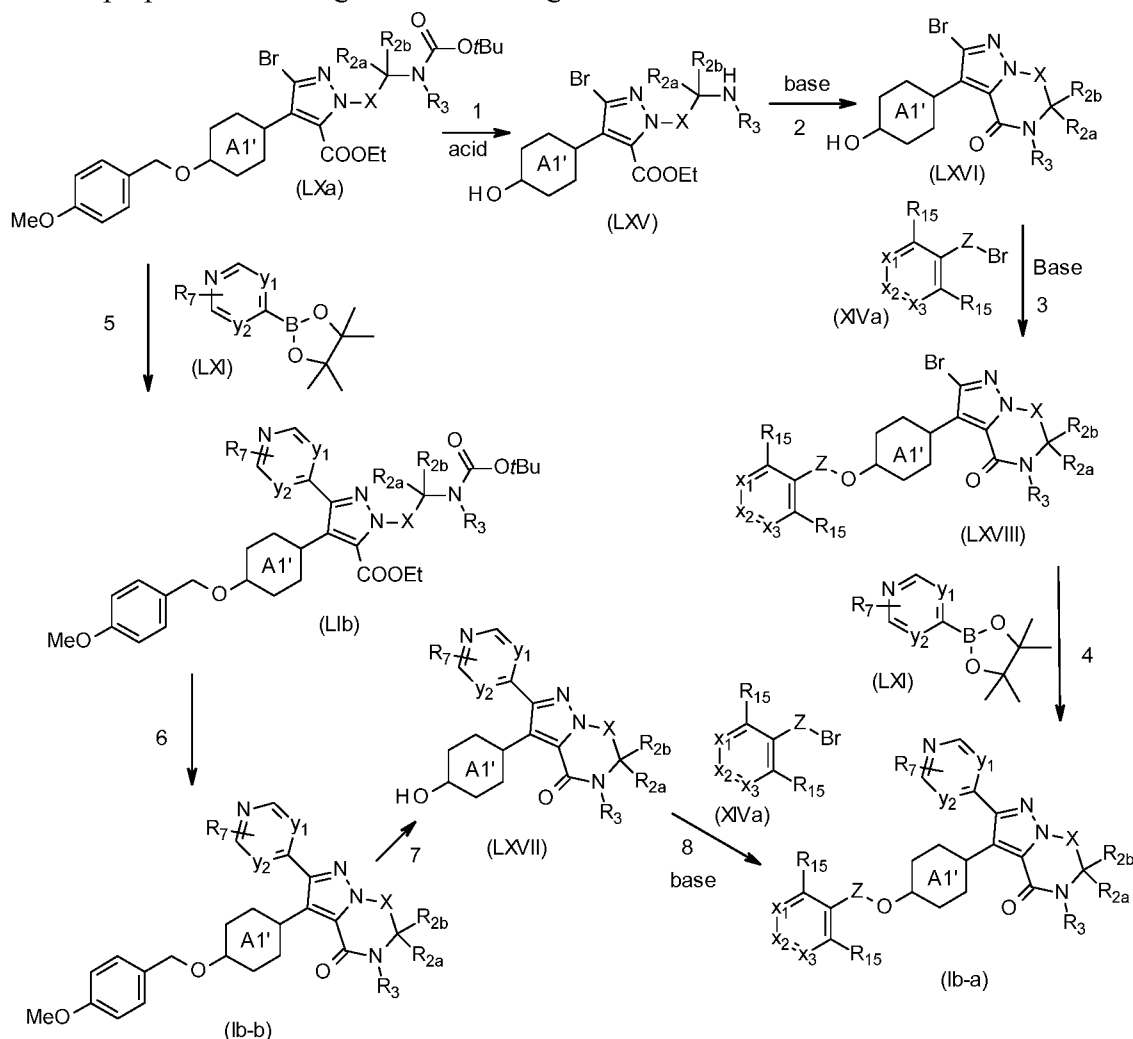
2 : an intermediate of formula (IV) can be reacted with an intermediate of formula (LXIV) in the presence of a suitable catalyst, such as for example PdCl₂dppf, a suitable base, such as for example potassium phosphate (K₃PO₄) and a suitable solvent or

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,

5 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 PCy₃, a suitable base, such as potassium phosphate (K₃PO₄), 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 PCy₃, a suitable base, such as potassium phosphate (K₃PO₄), and a suitable solvent or solvent mixture, such as for example dioxane and water, resulting in an intermediate of formula (LIb).

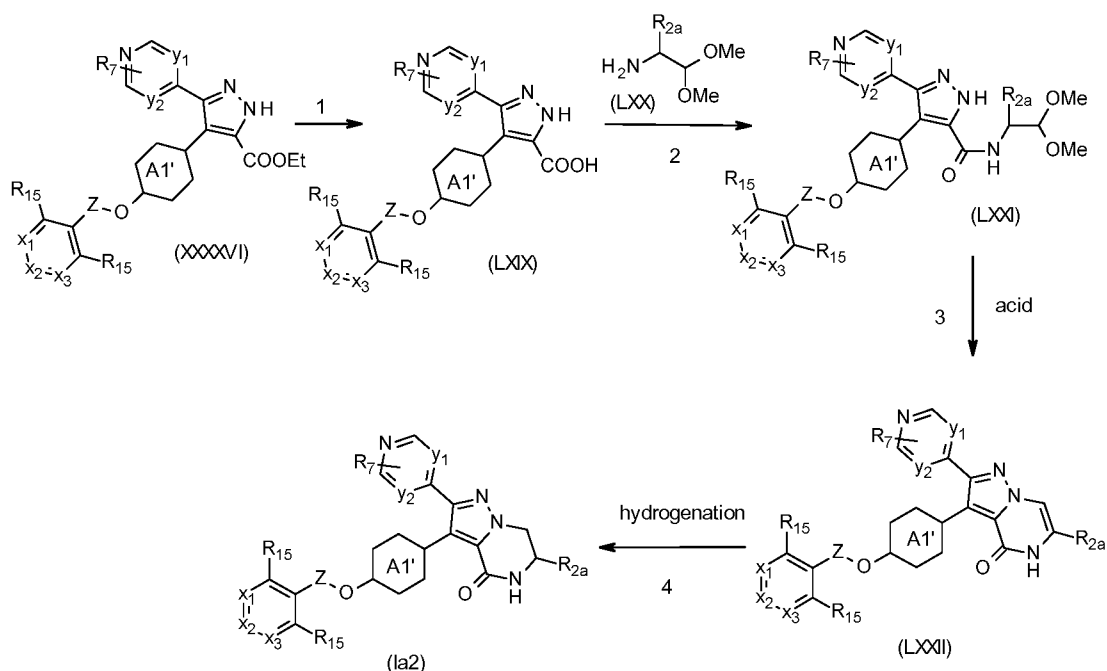
6 : an intermediate of formula (LIb) can be deprotected with a suitable acid, such as for example HCl, and a suitable solvent, such as for example dioxane or ACN. The resulting intermediate can be converted into a compound of formula (Ib-b) in the presence of a suitable base, such as for example Cs₂CO₃ or K₂CO₃, 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 K₂CO₃, 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 CH₂, 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.

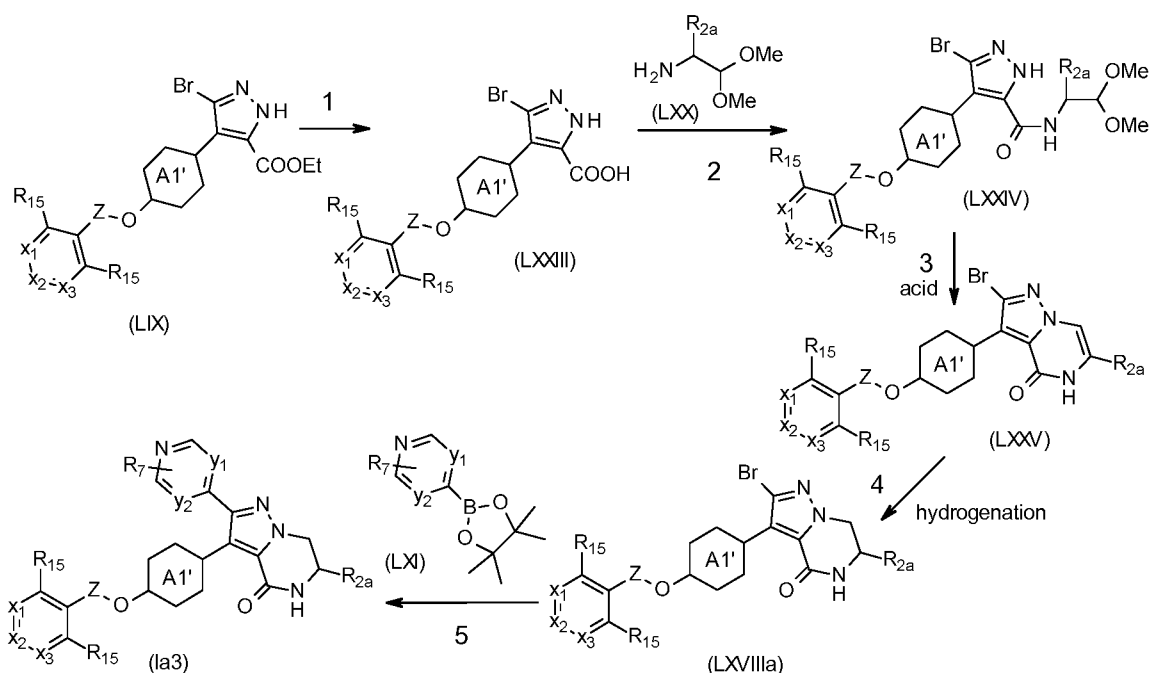
5 2 : an intermediate of formula (LXIX) can be reacted with an intermediate of formula (LXX) in the presence of a suitable peptide coupling agent, such as for example HATU, a suitable base, such as for example, DIPEA, and a suitable solvent, such as for example DMF, resulting in an intermediate of formula (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 PtO₂, and a suitable solvent, such as for example EtOH or MeOH.

15 17) Scheme 8 : Another alternative

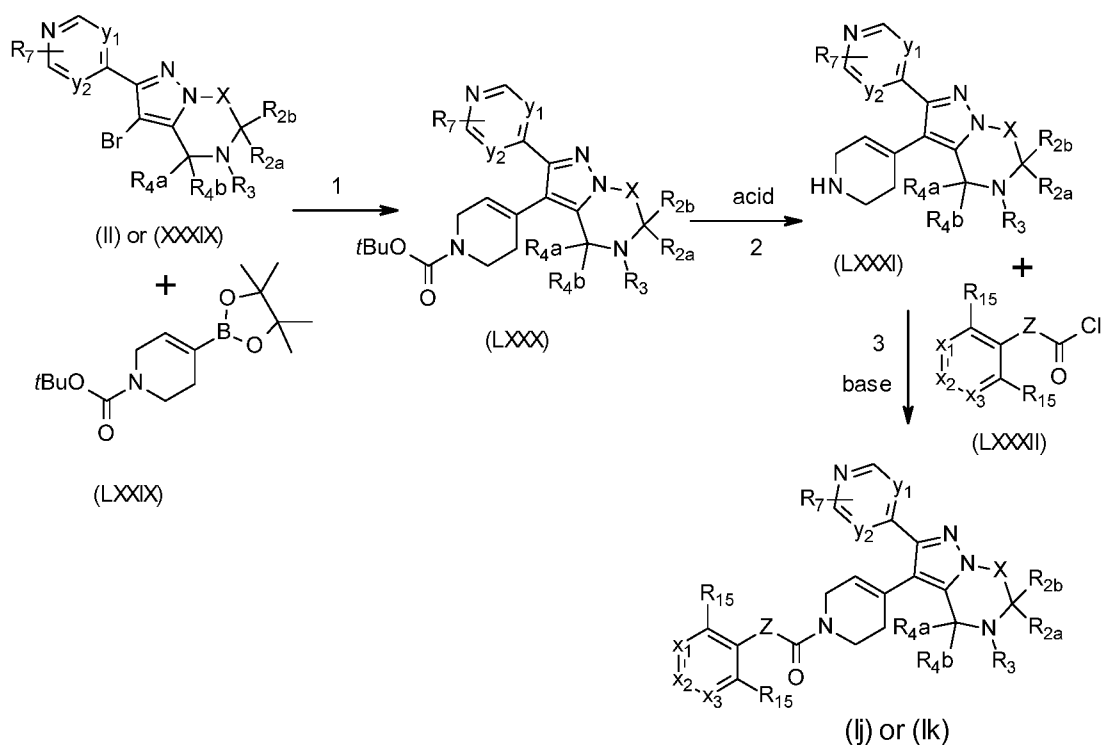
Compounds of formula (Ia3), wherein all variables are defined as described before, can also be prepared according to the following reaction scheme 8.



- 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 PtO₂, and a suitable solvent, such as for example EtOH or MeOH.
- 5 : an intermediate of formula (LXVIIIa) 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 PCy₃ a suitable base, such as potassium phosphate (K₃PO₄), 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:



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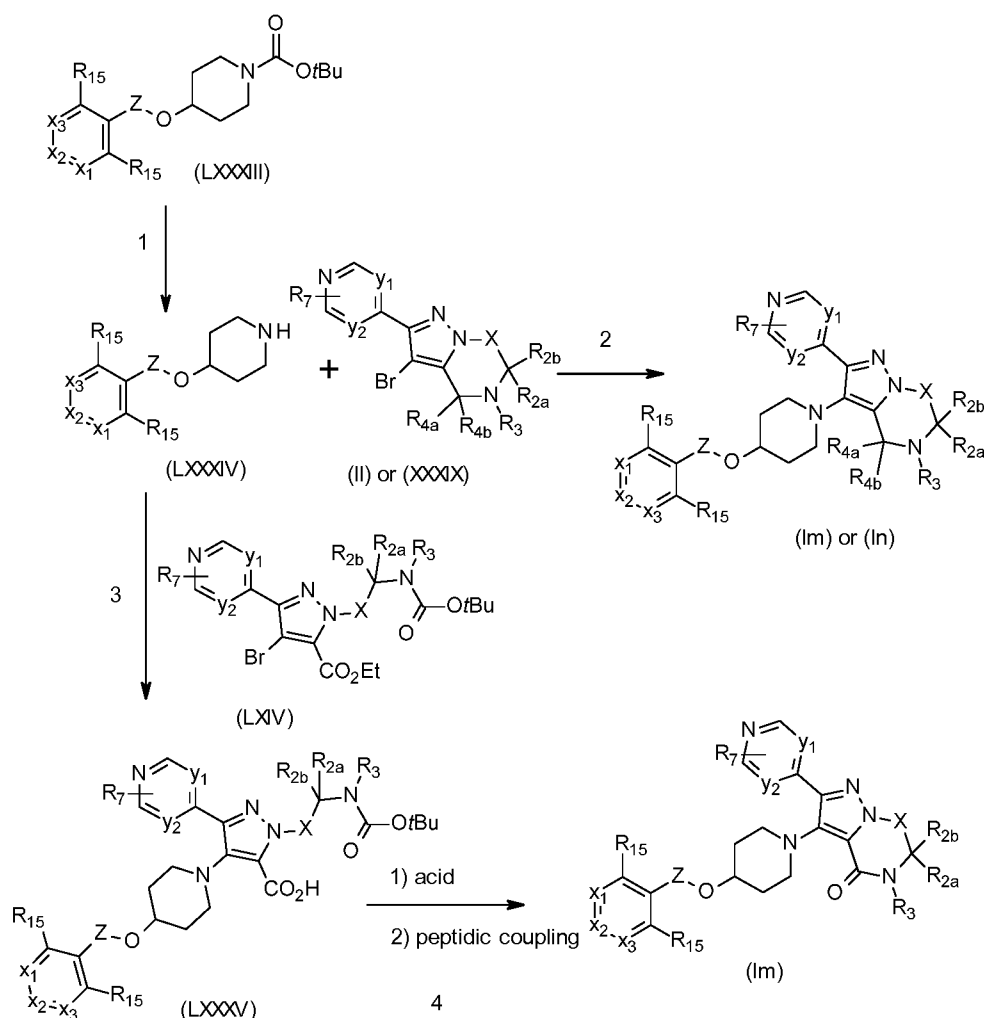
1 : an intermediate of formula (II) or (XXXIX) can be reacted with an intermediate of formula (LXXIX) in the presence of suitable catalyst, such as for example Palladium acetate (PdCl_2dppf), a suitable base, such as Na_2CO_3 , and a suitable solvent, such as for example dioxane, resulting in an intermediate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

10 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 :

20 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:

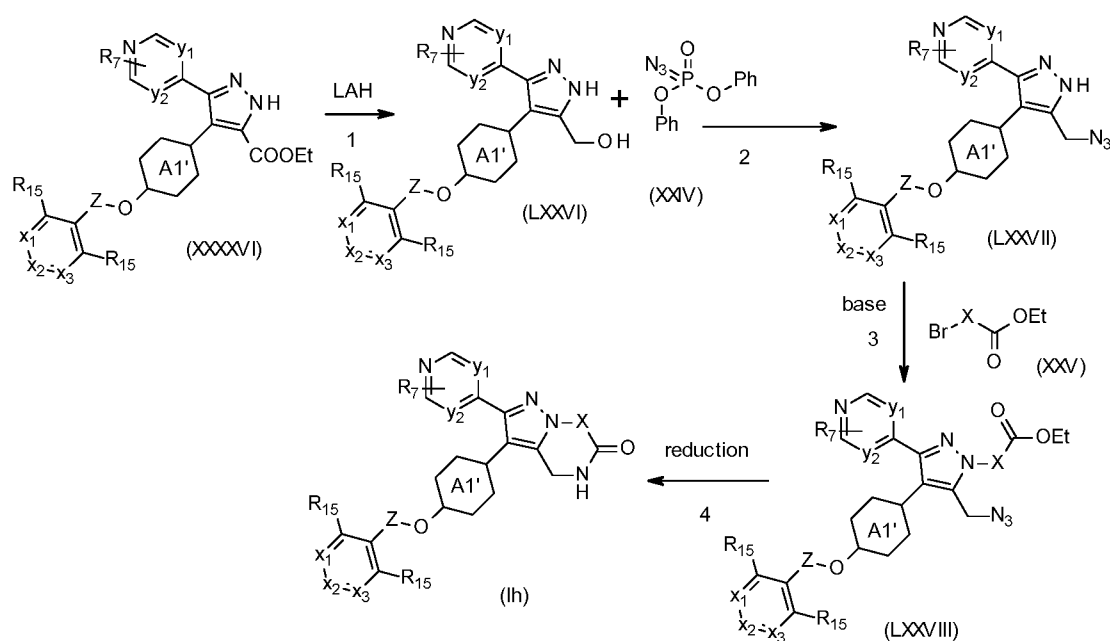


1 : an intermediate of formula (LXXXIII) can be deprotected to an intermediate of formula (LXXXIV) by reaction with a suitable acid, such as for example HCl, in the presence of a suitable solvent, such as for example ACN.

- 5 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,
- 10 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
- 15 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
- 5 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:



10

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).
- 15

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).

20

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
5 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
10 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.

15 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
20 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,
25 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
30 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
35 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; keratocanthoma; 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 hematopoietic 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, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy 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
5 compounds, and benzotriazine dioxide compounds) mimicking oxygen or alternatively behave like bioreductive agents under hypoxia; non-hypoxic cell radiosensitizers (e.g., halogenated pyrimidines) can be analogues of DNA bases and preferentially incorporate into the DNA of cancer cells and thereby promote the radiation-induced breaking of DNA molecules and/or prevent the normal DNA repair mechanisms; and
10 various other potential mechanisms of action have been hypothesized for radiosensitizers in the treatment of disease.

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

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

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

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

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

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

The invention also relates to compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for use in the inhibition of ROS, in particular ROS1, kinase activity.

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

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

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

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

25 The invention also relates to the use of compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament for the inhibition of ROS, in particular ROS1.

30 The invention also relates to the use of compounds of Formula (I) and N-oxides, pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament for the 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
5 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
10 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
15 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
20 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
25 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
30 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
35 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

5 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

10 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,

15 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

20 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

25 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

30 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.

35 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

5 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
10 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,
15 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
20 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 (AbraxaneTM) or docetaxel;
- 25 - 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;
- 30 - 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),
35 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, 5 epirubicin, epirubicin hcl, valrubicin;
 - molecules that target the IGF-1 receptor for example picropodophilin;
 - tetracarcin derivatives for example tetrocarcin A;
 - glucocorticoids for example prednisone;
 - antibodies for example trastuzumab (HER2 antibody), rituximab (CD20 10 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, 15 droloxifene, faslodex, raloxifene or letrozole;
 - aromatase inhibitors such as exemestane, anastrozole, letrozole, testolactone and vorozole;
 - differentiating agents such as retinoids, vitamin D or retinoic acid and retinoic acid metabolism blocking agents (RAMBA) for example accutane;
 - DNA methyl transferase inhibitors for example azacytidine or decitabine; 20
 - antifolates for example pemetrexed disodium;
 - antibiotics for example antinomycin D, bleomycin, mitomycin C, dactinomycin, carminomycin, daunomycin, levamisole, plicamycin, mithramycin;
 - antimetabolites for example clofarabine, aminopterin, cytosine arabinoside or 25 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, 30 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, 35 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;
- 5 - 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;
- 10 - Retinoids for example alitretinoin, bexarotene, tretinoin;
- Arsenic trioxide;
- Asparaginase;
- Steroids for example dromostanolone propionate, megestrol acetate, nandrolone (decanoate, phenpropionate), dexamethasone;
- 15 - 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;
- 20 - 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;
- 25 - a steroidal cytochrome P450 17 α -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;
- 30 - 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), pembrolizumab (anti-PD-1), ipilimumab (anti-CTLA4), and MPDL3280A (anti-PD-L1).

35

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.

5 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
10 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
15 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
20 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
25 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.

30 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 300 mg/m^2 per course of treatment.

35 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/m² and for docetaxel in about 75 to 150 mg/m² per course of treatment.

5 The camptothecin compound is advantageously administered in a dosage of 0.1 to 400 mg per square meter (mg/m²) of body surface area, for example 1 to 300 mg/m², particularly for irinotecan in a dosage of about 100 to 350 mg/m² and for topotecan in about 1 to 2 mg/m² per course of treatment.

10 The anti-tumour podophyllotoxin derivative is advantageously administered in a dosage of 30 to 300 mg per square meter (mg/m²) of body surface area, for example 50 to 250mg/m², particularly for etoposide in a dosage of about 35 to 100 mg/m² and for teniposide in about 50 to 250 mg/m² per course of treatment.

15 The anti-tumour vinca alkaloid is advantageously administered in a dosage of 2 to 30 mg per square meter (mg/m²) of body surface area, particularly for vinblastine in a dosage of about 3 to 12 mg/m², for vincristine in a dosage of about 1 to 2 mg/m², and for vinorelbine in dosage of about 10 to 30 mg/m² per course of treatment.

20 The anti-tumour nucleoside derivative is advantageously administered in a dosage of 200 to 2500 mg per square meter (mg/m²) of body surface area, for example 700 to 1500 mg/m², particularly for 5-FU in a dosage of 200 to 500mg/m², for gemcitabine in a dosage of about 800 to 1200 mg/m² and for capecitabine in about 1000 to 2500 mg/m² per course of treatment.

25 The alkylating agents such as nitrogen mustard or nitrosourea is advantageously administered in a dosage of 100 to 500 mg per square meter (mg/m²) of body surface area, for example 120 to 200 mg/m², particularly for cyclophosphamide in a dosage of about 100 to 500 mg/m², 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/m², and for lomustine in a dosage of
30 about 100 to 150 mg/m² per course of treatment.

The anti-tumour anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter (mg/m²) of body surface area, for example 15 to 60 mg/m², particularly for doxorubicin in a dosage of about 40 to 75 mg/m², for
35 daunorubicin in a dosage of about 25 to 45mg/m², and for idarubicin in a dosage of about 10 to 15 mg/m² 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 $4\text{mg}/\text{m}^2$ 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[®] System from Mettler Toledo. Melting points were measured with a temperature gradient of $10^\circ\text{C}/\text{minute}$ 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(*t*Bu₃P)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; "AcONH₄" means ammonium acetate; "BisPin" means bis(pinacolato)diboron; "DCE"

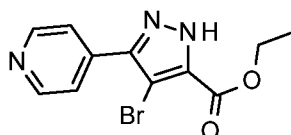
means 1,2-dichloroethane; "DIPE" means diisopropyl ether; "Boc" or "BOC" means *tert*-butoxycarbonyl; "CDI" means 1,1'-carbonyldiimidazole; "N-Boc sarcosine" means *N*-[(1,1-dimethylethoxy)carbonyl]-*N*-methyl-Glycine; "Boc-glycinol" means *N*-(*tert*-Butoxycarbonyl)ethanolamine; "(BOC)₂O" means di-*tert*-butyl dicarbonate; "ACN" means acetonitrile; "EDCI" means *N*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine monohydrochloride; "HOBT" means 1-hydroxy-1*H*-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; "PCy₃" means tricyclohexylphosphine; "LC" means liquid chromatography; "LCMS" means Liquid Chromatography/Mass spectrometry; "HATU" means 1-[bis(dimethylamino)methylene]-1*H*-[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; "N₂" means nitrogen; "DBAD" means di-*tert*-butyl azodicarboxylate; "RP" means reversed phase; "min" means minute(s); "EtOAc" means ethyl acetate; "Et₃N" 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; "iPrNH₂" means isopropylamine; "SFC" means Supercritical Fluid Chromatography; "DIPEA" means *N,N*-diisopropylethylamine; "Pd(PPh₃)₄" means tetrakis(triphenylphosphine)palladium; "w/v" means weight/volume; "PPh₃" means triphenylphosphine; "PPh₃ supp." means triphenylphosphine supported (polymer bound); "Et₂O" 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 "PdCl₂(dppf)" means [1,1'-bis(diphenylphosphino-κ*P*)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'.

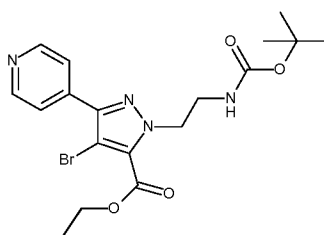
5 Preparation of the Intermediates and the final Compounds

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



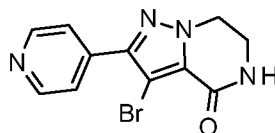
a- Synthesis of Int. 2 :

- A sol. of **1** (3-(4-pyridinyl)-1H-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 Et₂O (200mL) and filtered on a glass frit. The solid was washed with Et₂O (100mL) and twice with MeOH and Et₂O (10mL/40mL). The solid was collected and dried *in vacuo* to give 43.57g of the Int. **2** (92%).



b- Synthesis of Int. 3 :

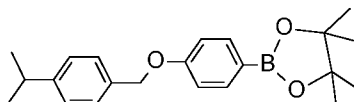
- To a mixture of **2** (Int. 2) (25 g, 84.4 mmol), tert-butyl N-(2-hydroxyethyl)carbamate (20.4 g, 126 mmol) and PPh₃ supp. (39.6 g, 127 mmol) in dry THF (700 mL) was added DBAD (29.2 g, 126.6 mmol). The mixture was stirred for 4 h at r.t. then filtered through a glass frit. The filtrate was evaporated *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% NH₄OH). 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 NaHCO₃ (2000 mL) and stirred for 10 min. The precipitate was filtered on a glass frit and washed with Et₂O 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 Cs₂CO₃ (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 Et₂O (4x 50mL). The white precipitate was collected and dried *in vacuo* to afford 17.8 g of Int. **4** as a white solid (75%).

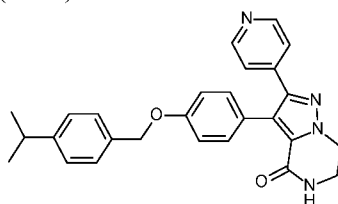


5 **d- Synthesis of Int. 5 :**

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), PPh₃ 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:

15 A sol. of **7** (7.00 g, 31.8 mmol) in ACN (75 mL) was treated with K₂CO₃ (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 Et₂O 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%).

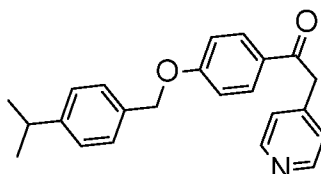


25 **e- Synthesis of Co. 1 :**

A mixture of **4** (9.5 g, 32.4 mmol), **5** (22.8 g, 64.7 mmol), K₃PO₄ (27.5 g, 0.13 mol) in 1,4-dioxane (165 mL) and H₂O (60 mL) was carefully purged with N₂. PCy₃ (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 N₂. 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

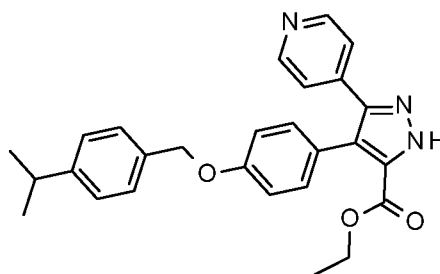
chromatography over silica gel (irregular SiOH 15-40 μ m, 400 g, mobile phase gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH_4OH). The pure fractions were collected and evaporated until dryness to give 6.4 g of a first residue and 2.25 g of a second residue. The first residue was washed with MeOH, 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 :

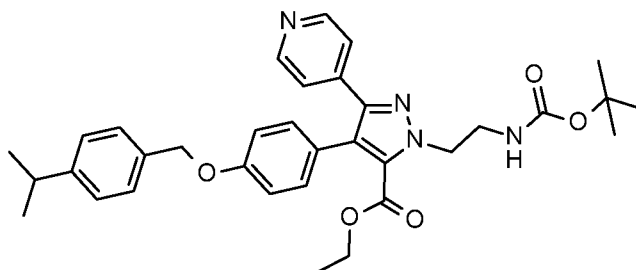
In a dry flask under N_2 , a sol. of **9** (4-[[4-(1-methylethyl)phenyl]methoxy]-benzoic acid, methyl ester) (45 g, 0.158 mol) and 4-picoline (16.9 mL, 0.174 mol) in THF (350 mL) was cooled to 0°C and treated with LiHMDS (316.5 mL, 0.317 mol) (slow addition). The r.m. was stirred at r.t. for 20 h and 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 35-40 μ m, 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, 0.431 mol). 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 35-40 μ m, 2x330g, mobile phase gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH₄OH). The pure fractions were collected and evaporated to give 28.95 g of the second batch of Int. **11** (24%). Global yield: 80%.



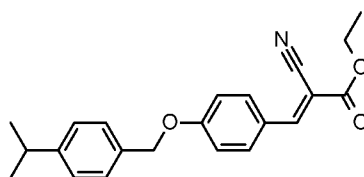
5 **c- Synthesis of Int. 12 :**

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), PPh₃ (36.4 g, 0.139 mol) in THF (960 mL) at r.t. under N₂ flow. The mixture was stirred for 2h at r.t., poured into H₂O and K₂CO₃ and extracted with EtOAc. The organic layer was dried (MgSO₄), filtered and evaporated until dryness to give 154 g of a residue. The residue was purified by chromatography over silica gel (irregular SiOH 35-40 μ m, 330g, mobile phase gradient from 100% DCM to 97% DCM, 3% CH₃OH, 0.1% NH₄OH). 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 6 μ m 150x21.2m, mobile phase 90% CO₂, 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 NaHCO₃ was added and the mixture was stirred at r.t. The organic layer was extracted with DCM, dried (MgSO₄) and concentrated. The residue was stirred for 3 days with Cs₂CO₃ (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%).

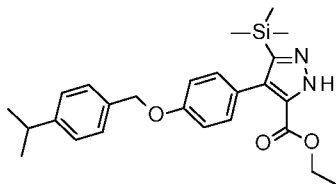
25 **Example A3: Preparation of Co. 1 (3rd approach)**



a- Synthesis of Int. 14 :

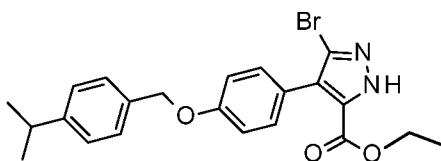
To a sol. of ethylcyanoacetate (2.6 mL, 24 mmol) in EtOH (15 mL) was added **13** (4-[[4-(1-methylethyl)phenyl]methoxy]-benzaldehyde) (5.9 g, 23mmol) and piperidine

(46.0 μ L; 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 :

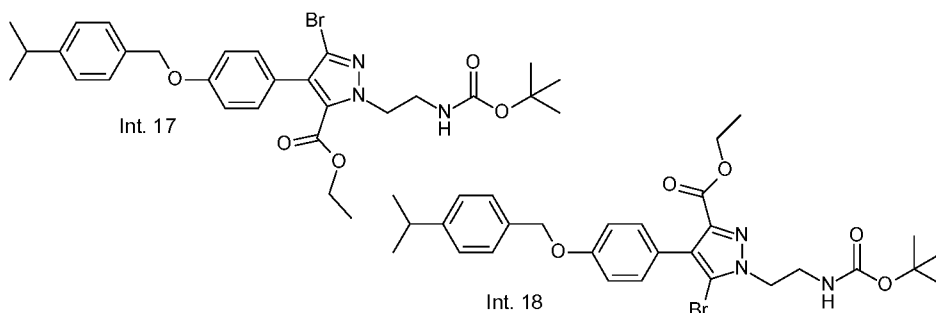
- 5 To a sol. of trimethylsilyldiazomethane (40 mL, 80 mmol) in dry THF (100 mL) at -78°C under N₂ was added *n*BuLi (50 mL, 80mmol) dropwise. The sol. was stirred for 30 min at -78°C and a sol. of **14** (18.6 g, 53.33 mmol) in dry THF (100 mL) was added dropwise at
- 10 -78°C. The sol. was stirred 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 NaHCO₃, dried (MgSO₄), 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%).



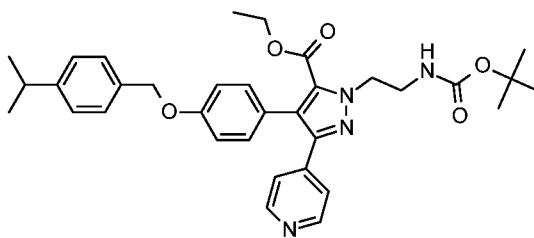
15 **c- Synthesis of Int. 16 :**

- 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 K₂CO₃ were added to the residue. The organic layer was separated, dried over MgSO₄, filtered off and evaporated *in vacuo* to give 4.04 g of a brown oil. The residue was purified by prep. LC (Irregular SiOH 15-40 μ m, 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%).
- 20

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 PPh₃ 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 :

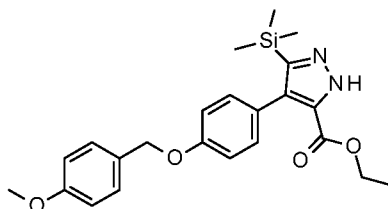
- In a schlenk tube, a mixture of **17** (0.3 g, 0.51 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (314 mg, 1.5 mmol), K₃PO₄ (0.43 g, 2.0 mmol) in 1,4-dioxane (1.4 mL) and H₂O (0.5 mL) was carefully degassed with N₂. PCy₃ (30 mg, 0.11 mmol) and Pd(OAc)₂ (12 mg, 0.054 mmol) were added and the r.m. was purged again with N₂. 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 (MgSO₄), 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% NH₄OH to 96% DCM, 4% MeOH, 0.1% NH₄OH). 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 K₂CO₃ 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

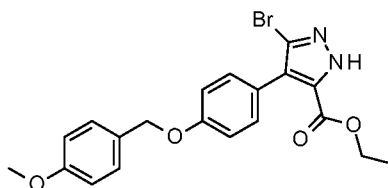
concentrated and the residue was washed with water. The white solid in suspension was filtrated and dried to yield 74 mg of a 2nd batch of Co. 1 as a beige powder (59%).

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



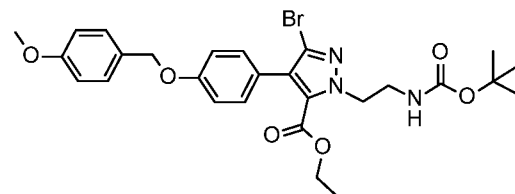
a- Synthesis of Int. 20 :

- 5 To a sol. of Trimethylsilyldiazomethane (17.1 mL, 34.2 mmol) in dry THF (40 mL) at -78°C under N₂ 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) (7.7 g, 22.8 mmol) in dry THF (60 mL) was added dropwise at -78°C. The sol. was stirred for 1 h at -78°C
- 10 then at r.t. for 16 h. EtOAc was added and the organic layer was washed twice with a sat. aq. sol. of NaHCO₃, dried (MgSO₄), filtered off and evaporated *in vacuo* to give a brown solid. The residue was triturated in Et₂O 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 :

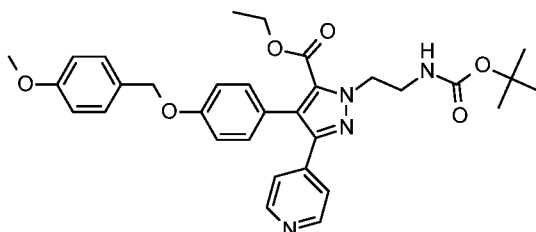
- 15 To a suspension of **20** (9.2 g, 21.67 mmol) in ACN (190 mL) was added NBS (3.86 g, 21.67 mmol) in ACN (95 mL) and the pale brown mixture was stirred at r.t. for 18 h. The solvent was removed *in vacuo*. DCM and a sat. aq. sol. of NaHCO₃ were added to the residue. The organic layer was separated, washed 2x with a aq. sol. of K₂CO₃ 10%, dried (MgSO₄), filtered off and evaporated *in vacuo* to give 9.07 g of Int. **21** as a brown
- 20 solid (97%).



c- Synthesis of Int. 22 :

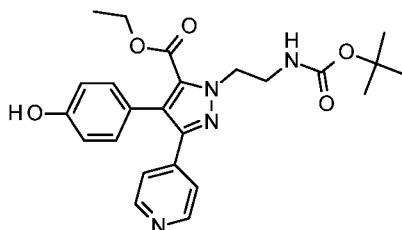
- To a suspension of **21** (2.0 g, 4.6 mmol), Boc-Glycinol (1.1 mL, 7.0 mmol) and diphenylphosphinopolystyrene (2.2 g, 7.0 mmol) in dry THF (60 mL) was added DBAD (1.6 g, 7.0 mmol). The mixture was stirred at r.t. for 4 h. The sol. was filtered
- 25 through a pad of Celite®, the polymer was washed with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

evaporated *in vacuo*. The residue was purified by chromatography over silica gel (Regular SiOH, 30 μ m, 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.



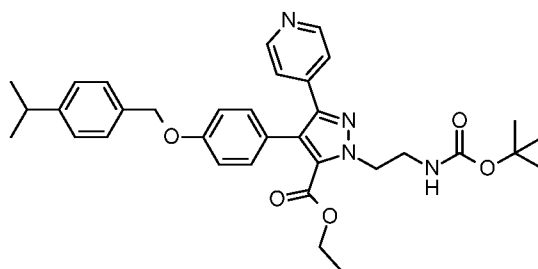
d- Synthesis of Int. 23 :

A mixture of **22** (2.5 g, 4.4 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (2.7 g, 13 mmol), K₃PO₄ (3.7 g, 17 mmol) in 1,4-dioxane (11 mL) and distilled water (4.) was carefully degassed with N₂. PCy₃ (256 mg, 0.91 mmol) and Pd(OAc)₂ (103 mg, 0.46 mmol) were added and the r.m. was purged again with N₂. 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 MgSO₄, filtered through a pad of Celite® and evaporated *in vacuo*. This residue was purified by chromatography over silica gel (irregular SiOH 30 μ m, 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 N₂ degassed sol. of **23** (1.4 g, 2.4 mmol) in EtOH (28 mL). The mixture was hydrogenated under 4 bars of H₂ 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 ; 30 μ m, 40g, mobile phase gradient from 98% DCM, 2% MeOH, 0.1% NH₄OH to 96% DCM, 4% MeOH, 0.1% NH₄OH). The pure fractions were collected and evaporated until dryness to give 160 mg of Int. **24** as a colorless oil (14%).

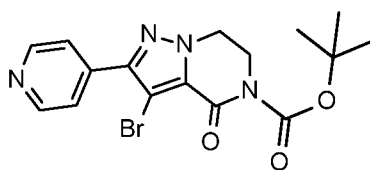


f- Synthesis of Int. 12 :

To a mixture of **24** (158 mg, 0.35 mmol), **6** (79 mg, 0.53 mmol) and PPh₃ (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 concentrated. The residue was purified by chromatography over silica gel (irregular SiOH 15-40µm, 12g, mobile phase gradient from 98% DCM, 2% MeOH, 0.1% NH₄OH to 94% DCM, 6% MeOH, 0.1% NH₄OH) to give 140 mg of the Int. **12** (69%).

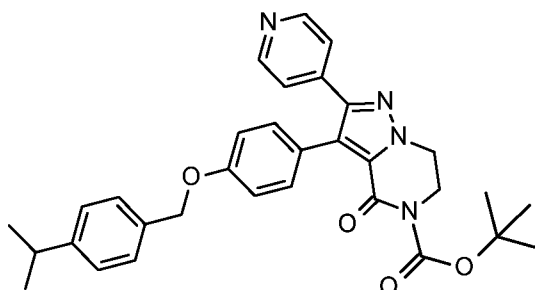
Finally, Int. 12 was reacted to Co. 1 by analogous methods as described in Example A2.d or A3.e.

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), Et₃N (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. H₂O and DCM were added. The organic layer was extracted, dried over MgSO₄, 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% NH₄OH). The fractions were collected and evaporated until dryness to give 12.4 g of Int. **25** (92%).



b- Synthesis of Co. 70 :

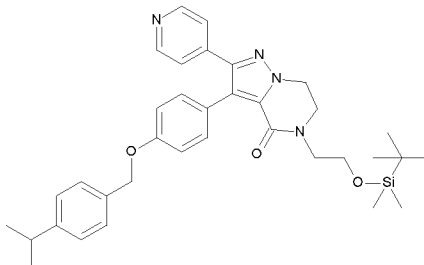
A mixture of **25** (29.4 g, 74.8 mmol), **5** (34.2 g, 97.2 mmol), K₃PO₄ (63.5 g, 300 mmol) in 1,4-dioxane (380 mL) and H₂O (120 mL) was purged with N₂ for 10min. Then

PdCl₂(dppf) (6.1 g, 7.5 mmol) was added and purged with N₂ for 10min. The reaction was heated to 72°C for 3h. The mixture was poured into a aq. sol. of K₂CO₃ and extrated with EtOAc . The organic layer was dried over MgSO₄, filtered and evaporated until dryness. The residue was purified by prep. LC (irregular SiOH 220g 35-40µm
5 GraceResolv™ + 300g 30µm Interchim, mobile phase gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH₄OH). 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,
10 0.1% NH₄OH). 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:

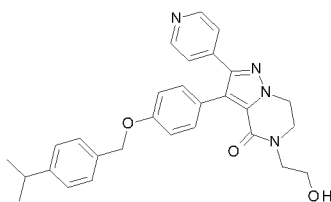
A sol. of **Co. 70** (34.6 g, 64.2 mmol) and HCl 3N (215 mL) in ACN (1700 mL) was heated to 80°C for 1h. Ice was added and the mixture was basified with K₂CO₃ and
15 stirred for 10min. The mixture was filtered off, washed with H₂O then ACN and dried to give 24.55 g of Co. 1 (87%). m.p.: 262°C (DSC).

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



a- Synthesis of Int. 27:

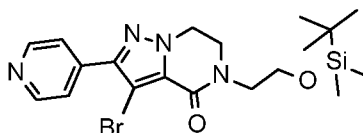
NaH (60%) (1.64 g, 41mmol) was slowly added to a suspension of Co. 1 (12g , 27.4
20 mmol) in DMF (180 mL) at r.t. under N₂. The mixture was stirred for 2h. Then (2-bromomethoxy)-tert-butyldimethylsilane (7mL, 32.8 mmol) was added and the r.m. was stirred for 15h. The reaction was poured into water and K₂CO₃ and extracted with EtOAc. The organic layer was evaporated until dryness. The residue was taken up with DCM, dried over MgSO₄, filtered and evaporated until dryness. The residue was
25 purified by prep. LC (Irregular silica gel 35-40µm, 330g GraceResolv™, mobile phase gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH₄OH). The fractions were collected and evaporated to give 15.52 g of Int. **27** (95%).



b- Synthesis of Co. 2:

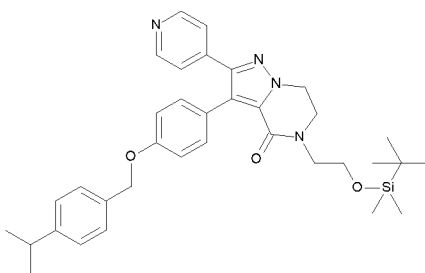
TBAF (1M in THF) (30.6 mL, 30.6 mmol) was added dropwise to a sol. of **27** (15.2 g, 25.5 mmol) in THF (150 mL) at room temperature. The mixture was stirred for 2 days. The mixture was evaporated. The residue was purified by prep. LC (Irregular silica gel SiOH 35-40 μ m, 330g GraceResolvTM, mobile phase gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH₄OH). 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 N₂. 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 K₂CO₃ 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 35-40 μ m, 330g GraceResolvTM, gradient from 100% DCM to 95% DCM, 5% MeOH, 0.1% NH₄OH). The fractions were collected and evaporated until dryness to give 37.3 g of the Int. **28** (81%).



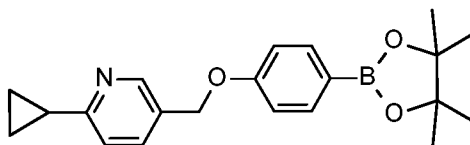
b- Synthesis of Int. 27 :

28 (26 g, 57.6 mmol), **5** (26.4 g, 74.9 mmol) and K₃PO₄ (47 g, 230 mmol) in 1,4-dioxane (270 mL) and H₂O (91 mL) in a sealed reactor were purged with N₂ for 10min. PdCl₂(dppf) (4.7 g, 5.8 mmol) was added and purged with N₂ for 10min. The mixture was heated to 82°C for 20h. The r.m. was poured into a sat. aq. sol. of K₂CO₃ and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and evaporated until dryness. The residue was purified by prep. LC (irregular SiOH 35-

40 μ m, 330g GraceResolv™, gradient from 100% DCM to 97% DCM, 3% MeOH, 0.1% NH₄OH). The fractions were collected and evaporated until dryness to give 32 g of Int. **27** (97%).

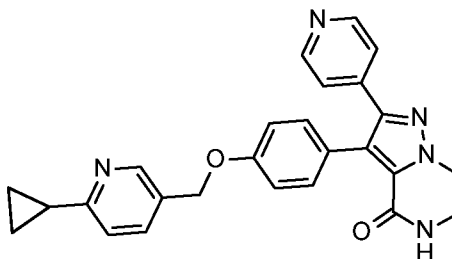
c- **Synthesis of Co. 2:** same procedure as A6b

5 Example A8: Preparation of Co. 3



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

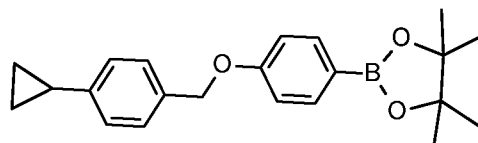
DBAD (2.01 g, 8.71 mmol) was added to a mixture of **7** (1.48 g, 6.70 mmol), **29** (6-cyclopropyl-3-pyridinemethanol) (1.3 g, 8.71 mmol) and PPh₃ supp. (2.91 g, 8.71 mmol) in DCM (30 mL). The r.m. was stirred under N₂ for 17h at r.t. The sol. was filtered and the residual polymer was washed with DCM. 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 μ m, 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%).



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

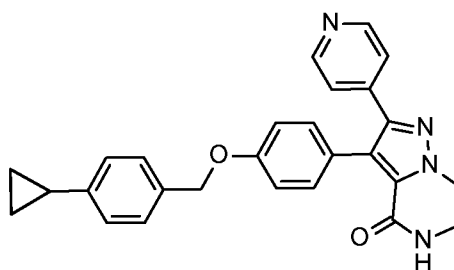
In a Schlenk tube, a mixture of **4** (0.3 g, 1.02 mmol), **30** (1.08 g, 3.07 mmol), K₃PO₄ (0.869 g, 4.09 mmol) in 1,4-dioxane (4.5 mL) and H₂O (1.5 mL) was carefully purged with N₂. PCy₃ (57 mg, 0.205 mmol) and Pd(OAc)₂ (23 mg, 102 μ mol) were added and the r.m. was purged again with N₂. The Schlenk 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 Et₂O (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 μ m, 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).

25 Example A9: Preparation of Co. 4



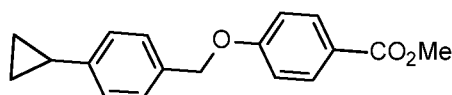
a- Synthesis of Int. 32 :

- Under N₂, 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), PPh₃ (17.7 g, 67 mmol) in dry THF (500 mL). The r.m. was stirred at r.t. overnight. THF was
- 5 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%).



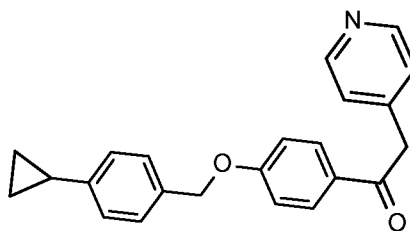
b- Synthesis of Co. 4:

- 10 A mixture of **4** (1 g, 3.4 mmol), **32** (2.39g, 6.8 mmol), K₃PO₄ (2.9 g, 13.6 mmol) in 1,4-dioxane (17 mL) and H₂O (6.2 mL) was carefully purged with N₂. Pd(OAc)₂ (0.077 g, 0.34 mmol) and PCy₃ (0.19 g, 0.68 mmol) were added and the r.m. was purged again with N₂. 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.
- 15 The different organic layers were put together, dried over MgSO₄, 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% NH₄OH). The fractions were collected and evaporated until dryness to give a residue which was crystallized from MeOH, filtered and dried to
- 20 give 0.708 g. The product was purified by prep. LC on (irregular SiOH 15-40μm 30g MERCK, mobile phase 0.1% NH₄OH, 98% DCM, 2% MeOH). The pure fractions were collected and the solvent was evaporated until dryness to give 600 mg which was crystallized from Et₂O, filtered and dried to give 587 mg of **Co. 4** (39%). m.p.: 262°C (dsc).
- 25 Example A10: Preparation of Co. 5



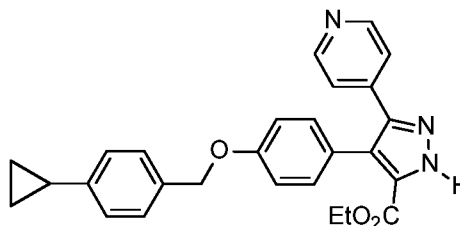
a- Synthesis of Int. 34 :

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 Et₂O to give 4.50 g of Int. **34** as an off-white solid (62%).



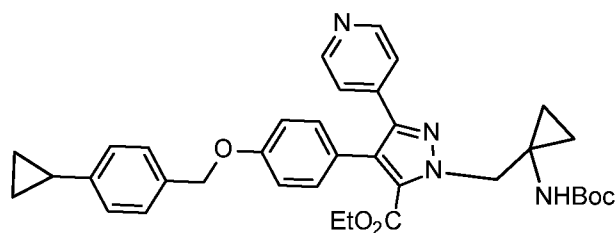
b- Synthesis of Int. 35 :

In a dry flask under N₂, 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 NH₄Cl. The insoluble was filtered off, washed with Et₂O and dried *in vacuo* to give 4.52 g of Int. **35** as a yellow solid (83%).



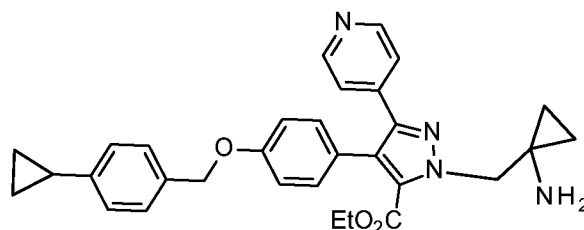
c- Synthesis of Int. 36 :

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 NaHCO₃ and water, dried (MgSO₄), 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%.



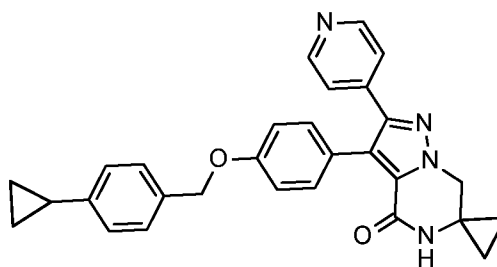
d- Synthesis of Int. 37 :

- 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.
- 5 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 μ m, 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 :

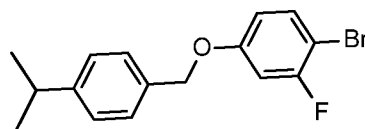
- 10 To a sol. of **37** (0.636 g, 1.05 mmol) in 1,4-dioxane (8 mL) was added HCl 4M in dioxane (2.10 mL, 8.36 mmol). The sol. was stirred at r.t. for 18h and was then poured out into Et₂O. The precipitate was filtered through a glass frit to give 584 mg of Int. **38** as a white solid (100%).



f- Synthesis of Co. 5 :

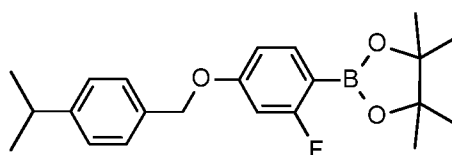
- 15 To a sol. of **38** (0.584 g, 1.07 mmol) in MeOH (10 mL) was added Cs₂CO₃ (1.75 g, 5.36 mmol) and the mixture was stirred at r.t. for 4 h. The solvent was removed *in vacuo* and water (25 mL) and DCM (25 mL) were added to the residue. The layers were separated and the aq. layer was extracted with DCM (25 mL). The organic layers were combined, dried over MgSO₄, filtered off and evaporated *in vacuo* to give 419
- 20 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 :

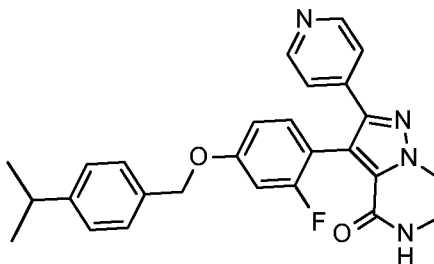
Under N₂, a sol. of **40** (4-bromo-3-fluorophenol) (11g, 58mmol) in ACN (150mL) was treated with K₂CO₃ (16g, 117mmol) and **8** (4-isopropylbenzyl bromide) (9.7mL, 58mmol) and the r.m. was stirred under reflux for 2h. The sol. was filtrated and concentrated to give 18.9 g of Int. **41**, colorless oil (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 N₂. PdCl₂(dppf) (0.253 g, 0.309 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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 K₂CO₃ (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.

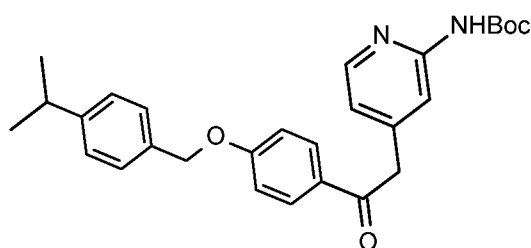


c- Synthesis of Co. 6

In a microwave vial, a mixture of **4** (0.594 g, 2.0 mmol), **42** (1.5 g, 4.0 mmol), K₃PO₄ (1.72 g, 8.1 mmol) in 1,4-dioxane (9.0 mL) and H₂O (3.2 mL) was carefully purged with N₂. PdCl₂(dppf) (0.166 g, 202 μmol) was added and the r.m. was purged again

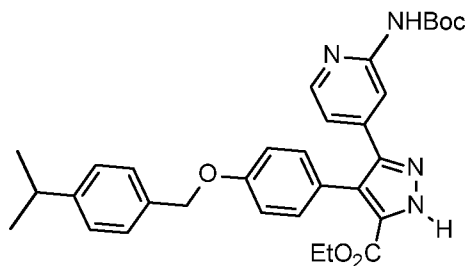
with N₂. The r.m. was heated at 80°C overnight. The crude material was diluted in DCM and washed with a sat. sol. of NaHCO₃. The organic layer was dried over MgSO₄, filtered and evaporated *in vacuo* to afford brown oil. The oil was purified by prep. LC (irregular SiOH 15-40 µm, 40 g GraceResolv™, mobile 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 Et₂O, 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



10 **a- Synthesis of Int. 43 :**

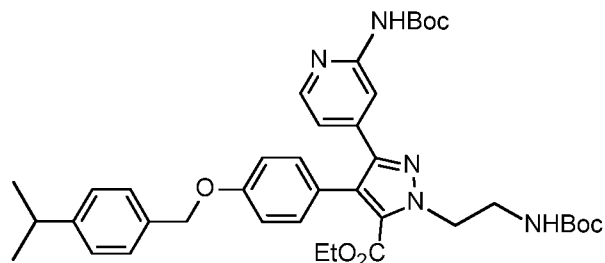
A sol. of **9** (2.0 g, 7.0 mmol) and 2-(4-methyl-2-pyridinyl)-imidodicarbonic acid, 1,3-bis(1,1-dimethylethyl) ester (2.17 g, 7.0 mmol) in dry THF (20 mL) was treated with LiHMDS (14 mL, 14 mmol) at 0°C (addition over 10 min). After stirring for 1h at 0°C, the reaction was allowed to warm to r.t. and was stirred for 17h. The reaction was quenched with a 10% aq. sol. of NH₄Cl (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%).



20 **b- Synthesis of Int. 44 :**

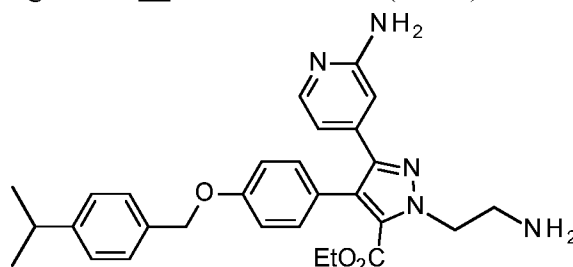
To a suspension of **43** (1.0 g, 2.1 mmol) in ACN (7.7 mL) in a sealed tube was added DBU (0.33 mL, 2.2 mmol) and ethyl diazoacetate (0.39 mL, 3.7 mmol). The mixture was heated at 100°C for 2h then cooled down to r.t. The solvent was removed *in vacuo* and the residue was diluted in EtOAc. The organic layer was washed with a sat. aq. sol. of NaHCO₃, water, dried over MgSO₄, 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%).



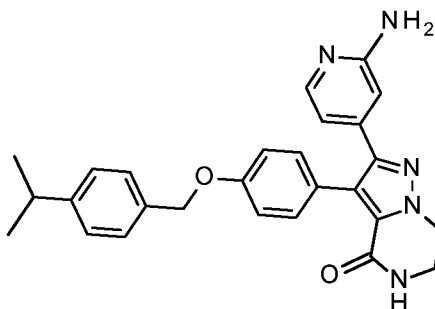
c- Synthesis of Int. 45 :

- 5 To a mixture of **44** (0.428 g, 0.77 mmol), Boc-Glycinol (0.149 g, 0.92 mmol) and PPh₃ (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
- 10 evaporated until dryness to give 0.55g of Int. **45** as a white solid (100%).



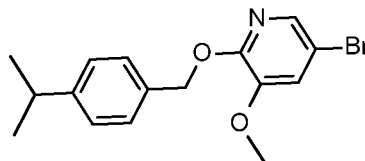
d- Synthesis of Int. 46 :

- 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, K₂CO₃ 10% aq was added and the mixture was extracted with DCM. The organic layer was dried over MgSO₄, filtered
- 15 and evaporated *in vacuo* to give 0.49 g of Int. **46**, white solid (92%).

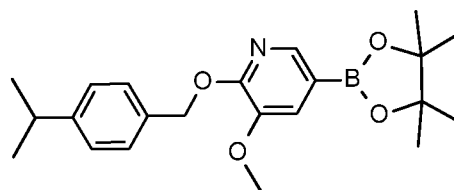


e- Synthesis of Co. 7:

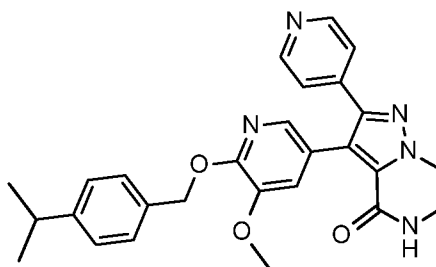
- To a sol. of **46** (0.49 g, 0.98 mol) in MeOH (28 mL) was added Cs₂CO₃ (1.6 g, 4.9 mmol) and the mixture was stirred at r.t. overnight. The mixture was filtered, the white solid was collected and dried to give 0.28 g of **Co. 7**, white solid (63%). m.p.: 267°C
- 20 (dsc).

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 N₂. The mixture was stirred 10 min at 0°C under N₂, 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 MgSO₄, 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 :**

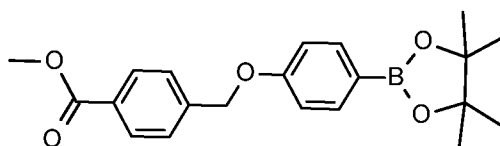
In a sealed tube, a mixture of **47** (751 mg, 2.23 mmol), BisPin (681 mg, 2.68 mmol) and KOAc (658 mg, 6.70 mmol) in DME (12.5 mL) was carefully purged with N₂. PdCl₂(dppf) (183 mg, 0.223 mmol) was added and the r.m. was purged again with N₂. The r.m. was stirred for 17 h at 100°C. The r.m. was diluted with EtOAc and water. The organic layer was washed with brine, dried over MgSO₄, 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), K₃PO₄ (371 mg, 1.75 mmol) in 1,4-dioxane (3 mL) and H₂O (1 mL) was carefully purged with N₂. PCy₃ (25

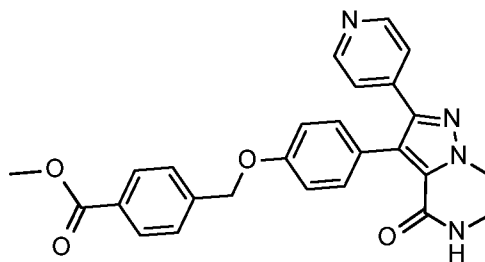
- mg, 87 μ mol) and $\text{Pd}(\text{OAc})_2$ (10 mg, 43.7 μ mol) were added, and the r.m. was purged again with N_2 , and stirred for 15h at 80°C. The crude material was treated with water and extracted with DCM. The organic layer was washed with brine, dried over MgSO_4 , filtered and evaporated *in vacuo* to give a black solid. The solid was purified by prep. LC on (irregular SiOH 15-40 μ m 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 5 μ m 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



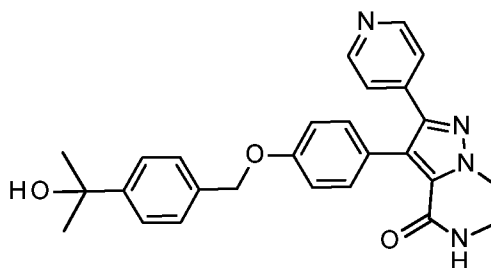
a- Synthesis of Int. 49 :

- 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 MgSO_4 , filtered and evaporated *in vacuo* to give a solid. The solid was purified by prep. LC (irregular SiOH 15-40 μ m, 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:

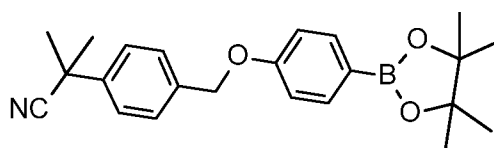
- In a sealed tube, a mixture of **4** (438 mg, 1.5 mmol), **49** (0.5 g, 1.3 mmol), K_3PO_4 (1.1 g, 5.4 mmol) in 1,4-dioxane (8 mL) and H_2O (2mL) was carefully purged with N_2 . PCy_3 (80 mg, 0.28 mmol) and $\text{Pd}(\text{OAc})_2$ (32 mg, 0.1 mmol) were added and the r.m. was purged again with N_2 . 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 15-40 μ m 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 :

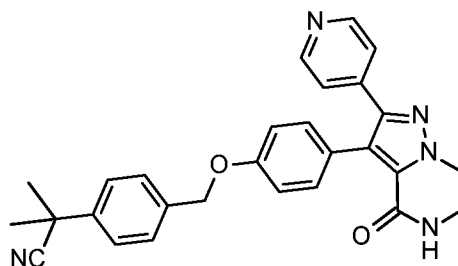
MeMgCl (0.567 mL, 1.68 mmol) was added to a stirred suspension of **Co. 9a** (153 mg, 0.337 mmol) in THF (5mL) under N₂ at 0 °C. The mixture was stirred at 0° C for 5 min, and then it was warmed to r.t. and stirred for 2h. The r.m. was quenched with 10% NH₄Cl sol., and treated with EtOAc and a mixture of MeOH/DCM (90:10). The organic layer was separated, washed with brine, dried over MgSO₄, 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% iPrNH₂, 80% CO₂, 20% MeOH to 0.3% iPrNH₂, 60% CO₂, 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% (NH₄HCO₃ 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), freeze-dried 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 :

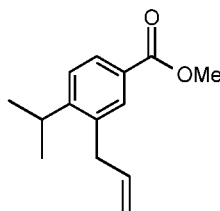
To a suspension of **7** (2.5 g, 11.3 mmol), 2-[4-(hydroxymethyl)phenyl]-2-methylpropanenitrile (1.8 g, 10.3 mmol), PPh₃ supp (3.8 g, 12.3 mmol) in dry DCM (50 mL) was added DBAD (2.8 g, 12.3 mmol) and the r.m. was stirred at r.t. for 18 h. The mixture was filtered through Celite®, washed with DCM and 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 :

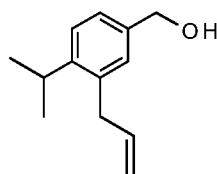
A mixture of **4** (400 mg, 1.36 mmol), **51** (0.77 g, 2 mmol), K₃PO₄ (1.16 g, 5.46 mmol) in 1,4-dioxane (7 mL) and H₂O (3mL) was carefully purged with N₂. PCy₃ (80.4 mg, 0.29 mmol) and Pd(OAc)₂ (32 mg, 0.14 mmol) were added and the r.m. was purged again with N₂. The r.m. was stirred for 8h at 80°C. 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 Et₂O, 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 NH₄OH/DCM/MeOH 0.2/98/2 to NH₄OH/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 Et₂O, filtered and dried to give 210 mg of **Co. 10** (33%). m.p.: 280°C (dsc).

Example A16: Preparation of Co. 11



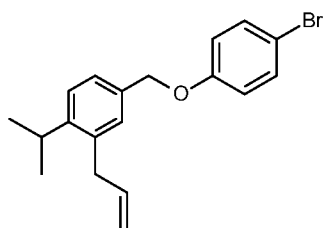
a- Synthesis of Int. 52 :

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 N₂ were added Pd(PPh₃)₄ (270 mg, 0.23 mmol) and allyltri-N-butyltin (1.85 g, 5.6 mmol). The mixture was flushed again with N₂ 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%).



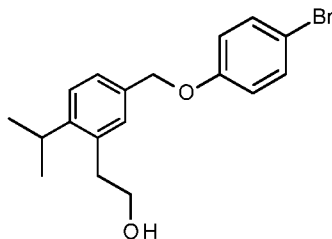
b- Synthesis of Int. 53:

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. H₂O (1 mL) then DCM were added very slowly and stirred for
 5 20min. The mixture was filtered on a pad of Celite® and the filtrate was dried over MgSO₄, filtered and evaporated until dryness to give 845 mg of Int. **53**, colorless oil (100%).



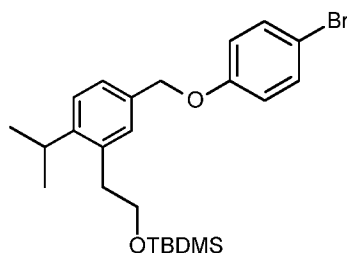
c- Synthesis of Int. 54:

To a suspension of **53** (6.52 g, 34 mmol), 4-bromophenol (5.9 g, 34 mmol) and PPh₃
 10 (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
 15 until dryness to give 9.6 g of Int. **54**, pale yellow oil (81%).



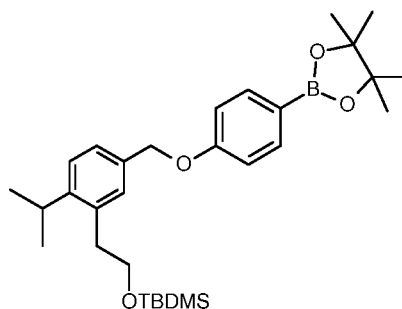
d- Synthesis of Int. 55:

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 N₂ purge and the residue was partitioned between EtOAc and NH₄Cl
 20 10% aq. The organic layer was washed with brine twice, dried over MgSO₄ 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).



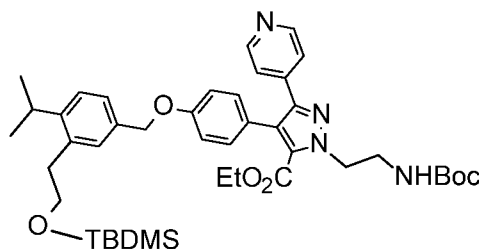
e- Synthesis of Int. 56:

- Under N₂, 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 MgSO₄, 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:

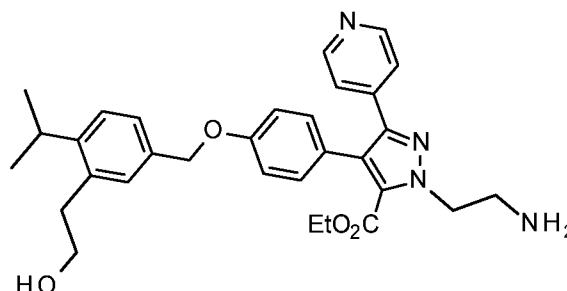
- In a microwave vial, a mixture of **56** (1.69 g, 3.6 mmol), KOAc (1.1 g, 11 mmol), BisPin (1.4 g, 5.5 mmol) in DME (11 mL) was carefully purged with N₂. PdCl₂(dppf) (0.30 g, 0.36 mmol) was added and the r.m. was purged again with N₂. The r.m. was stirred overnight at 100°C. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over MgSO₄, 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:

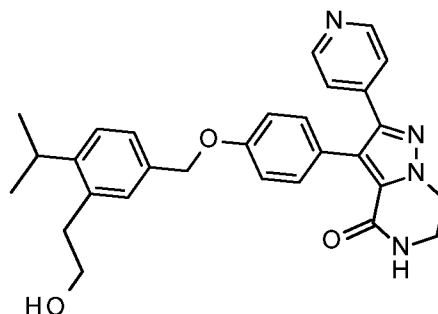
- In a microwave vial, a mixture of **3** (0.86 g, 2.0 mmol), **57** (1.2 g, 2.35 mmol), K₃PO₄ (1.2 g, 5.9 mmol) in 1,4-dioxane (8.6 mL) and H₂O (3.1 mL) was carefully purged with

- N₂. PdCl₂(dppf) (0.16 g, 0.20 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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:

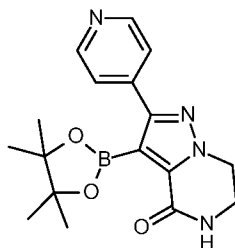
- A solution of **58** (1.1 g, 1.5 mmol), HCl 3N (2.5 mL, 7.4 mmol), in ACN (26 mL) was stirred at 80°C for 2h. The mixture was concentrated, and NaHCO₃ sat aq (25 mL) was added and the mixture was stirred at r.t. 15 min and extracted with DCM. The organic layer was separated, dried and concentrated to give 780 mg of Int. **59** (100%). This residue was used like this for the next step.



i- Synthesis of Co. 11:

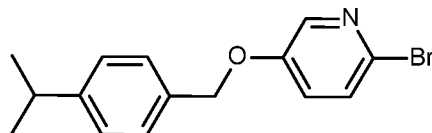
- To a sol. of **59** (780 mg, 1.5 mmol) in MeOH (42 mL) was added Cs₂CO₃ (2.4 g, 7.4 mmol) and the mixture was stirred at r.t. overnight. The mixture was filtered and the white solid was collected and dried to give 180 mg. The filtrate was concentrated and taken in DCM and washed once with brine, dried 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/NH₄OH 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 Et₂O, 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



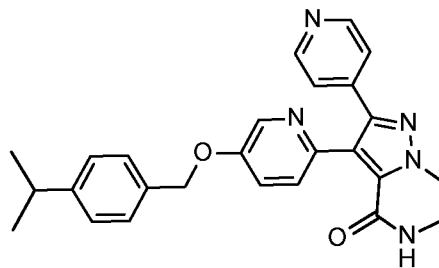
a- Synthesis of Int. 60:

A mixture of **4** (800 mg, 2.73 mmol) in THF (16 mL) was carefully purged with N₂. 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 MgSO₄, 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 K₂CO₃ (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 MgSO₄, 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%).

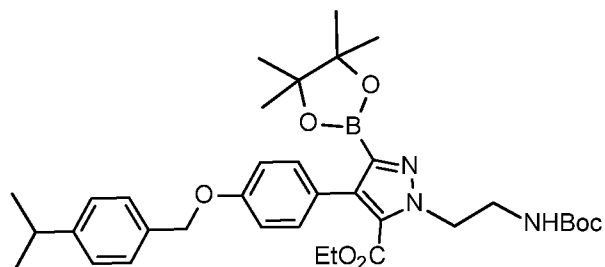


c- Synthesis of Co. 12:

A mixture of **60** (417 mg, 1.23 mmol), **61** (751 mg, 2.45 mmol), K₃PO₄ (781 mg, 3.68 mmol) in THF (5 mL) and H₂O (5 mL) was carefully purged with N₂. Precatalyst (96 mg, 123 μmol) was added and the r.m. was purged again with N₂. 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

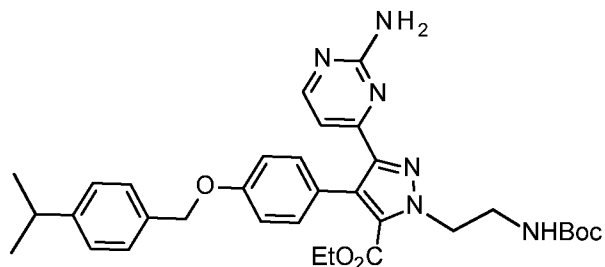
Merck, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%) to give 290 mg of **Co. 12**, white solid (54%). m.p.: 84 °C (DSC).

Example A18: Preparation of Co. 13



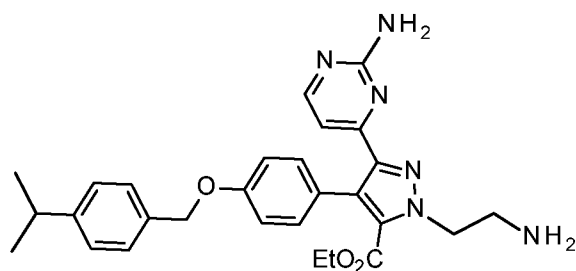
a- Synthesis of Int. 62 :

- 5 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 N₂. PdCl₂(dppf) (233 mg, 0.29 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄,
 10 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.



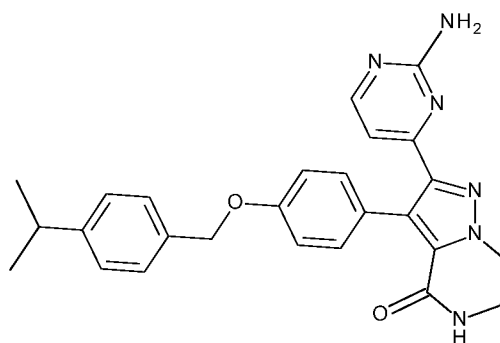
15 **b- Synthesis of Int. 63:**

- A mixture of **62** (impure) (630 mg, 0.99 mmol), 2-amino-4-bromopyrimidine (173 mg, 0.99 mmol), K₃PO₄ (633 mg, 2.98 mmol) in 1,4-dioxane (2.5 mL) and H₂O (1.1 mL) was carefully degassed with N₂. Pd(OAc)₂ (47 mg, 0.21 mmol) and PCy₃ (29 mg, 0.10 mmol) were added and the r.m. was purged again with N₂. The r.m. was stirred
 20 overnight at 80°C. The crude material was dissolved in water (30 mL) and extracted with DCM (2x). The organic layer was dried over MgSO₄, filtered through 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% NH₄OH to 95% DCM, 5% MeOH, 0.1% NH₄OH).
 25 The pure fractions were collected and solvent was evaporated to give 170 mg of Int. **63**, yellow oil (28%).



c- Synthesis of Int. 64:

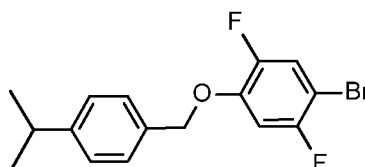
A solution of **63** (0.2 g, 0.33 mmol), HCl 3N (0.55 mL, 1.7 mmol), in ACN (6 mL) was heated at 80°C for 2h. ACN was concentrated, and NaHCO₃ sat aq (50 mL) was slowly added and the mixture was extracted with DCM, dried over MgSO₄ and concentrated until dryness to give 135 mg of Int. **64** (81%). This residue was used like this in the next step.



d- Synthesis of Co 13:

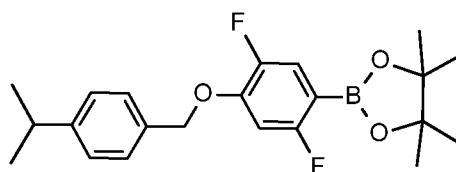
To a sol. of **64** (0.14 g, 0.28 mmol) in MeOH (8 mL) was added Cs₂CO₃ (0.46 g, 1.4 mmol) and the mixture was stirred at r.t. for 3 days. The mixture was concentrated and taken in DCM, the solid was filtered and the filtrate was concentrated to give 162 mg of a residue. The residue was purified by prep. LC on (Stability Silica 5µm 150x30.0mm), mobile phase (Gradient from NH₄OH/DCM/MeOH 0.2/98/2 to NH₄OH/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



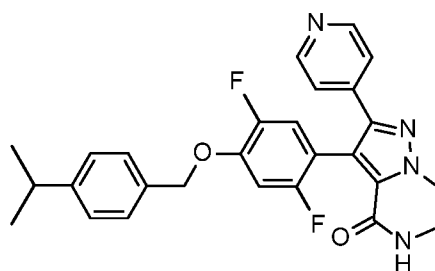
a- Synthesis of Int. 65 :

Under N₂, a sol. of 4-bromo-2,5-difluorophenol (12 g, 58 mmol) in ACN (150 mL) was treated with K₂CO₃ (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:

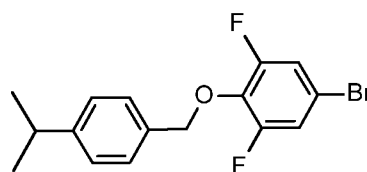
In a Schlenk tube, a mixture of **65** (10.0 g, 29 mmol), KOAc (8.6 g, 88 mmol), BisPin (11 g, 44 mmol) in dry DME (150 mL) was carefully purged with N₂. PdCl₂(dppf) (2.4 g, 2.9 mmol) was added and the r.m. was purged again with N₂. The r.m. was stirred overnight at 100°C. The r.m. was diluted with EtOAc and washed with water (1x) and with brine (2x). The organic layer was dried over MgSO₄ 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:

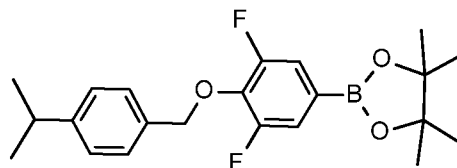
A sol. of **4** (660 mg, 2.25 mmol) and **66** (1.74 g, 4.50 mmol) in 1,4-dioxane (10 mL) and H₂O (8 mL) was treated with K₃PO₄ (1.43 g, 6.76 mmol) and purged with N₂. PdCl₂(dppf) (184 mg, 0.225 mmol) was then added and the r.m. was carefully purged with N₂. The mixture was heated at 120°C using one 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 MgSO₄ 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



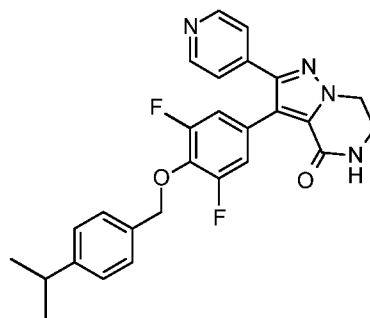
a- Synthesis of Int. 67:

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 K₂CO₃ (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%).



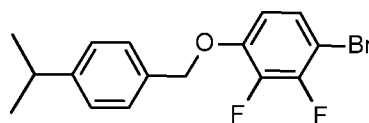
b- Synthesis of Int. 68:

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 N₂. PdCl₂(dppf) (0.117 g, 0.142 mmol) was added and the r.m. was purged again with N₂. 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%).

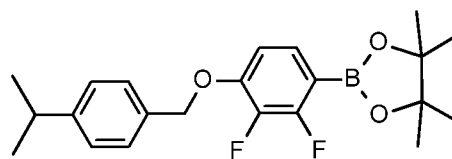


c- Synthesis of Co. 15:

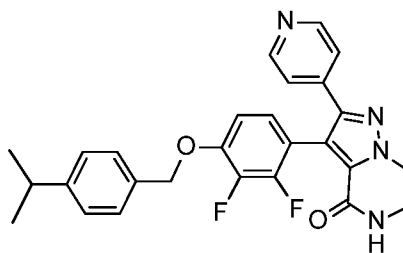
In a microwave vial, a mixture of **4** (0.3 g, 1.02 mmol), **68** (0.516 g, 1.33 mmol), K₃PO₄ (0.911 g, 4.29 mmol) in 1,4-dioxane (4.8 mL) and H₂O (1.6 mL) was carefully purged with N₂. PCy₃ (60 mg, 0.214 mmol) and Pd(OAc)₂ (24 mg, 0.11 mmol) were added and the r.m. was purged again with N₂. The r.m. 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 MgSO₄, 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 NH₄OH/DCM/MeOH 0.2/98/2 to NH₄OH/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 N₂, a sol. of 4-bromo-2,3-difluorophenol (5.00 g, 23.9 mmol) in DMF (25 mL) was treated with K₂CO₃ (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 MgSO₄, filtered off and evaporated *in vacuo* to give 9.49 g of Int. **69**, colorless oil (100%).

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

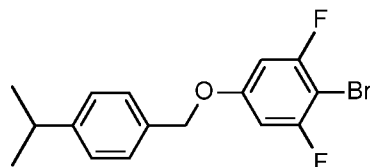
A mixture of **69** (7.30 g, 19.3 mmol), BisPin (7.34g, 28.9 mmol) and KOAc (5.67 g, 57.8 mmol) in DME (90 mL) was carefully purged with N₂. PdCl₂(dppf) (1.58 g, 1.93 mmol) was added and the r.m. was purged again with N₂. The r.m. was stirred at 18h at 100°C. The r.m. was diluted with EtOAc and water. The organic layer was washed with brine, dried over MgSO₄, 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: from 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 K₃PO₄ (1.2 g, 5.64 mmol) in 1,4-dioxane (8 mL) and H₂O (7.5 mL) was purged with N₂, and then PdCl₂(dppf) (84 mg, 0.102 mmol) was added at rt. The resulting mixture was purged again with N₂, 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).

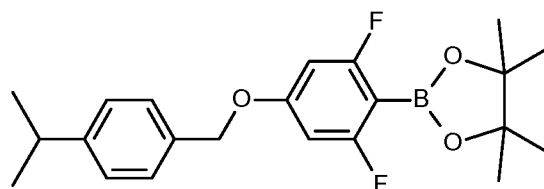
5 Example A22: Preparation of Co. 17



a- Synthesis of Int. 71:

Under N₂, a sol. of 4-bromo-3,5-difluorophenol (3.0 g, 14.4 mmol) in ACN (37 mL) was treated with K₂CO₃ (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.

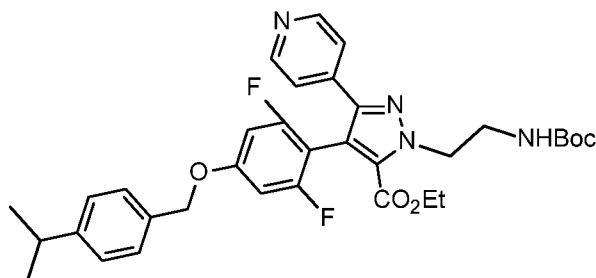
10 **71**, colorless oil (100%). The product was used like this in the next step.



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 N₂. PdCl₂(dppf) (321 mg, 0.392 mmol) was added and the r.m. was purged again with N₂.

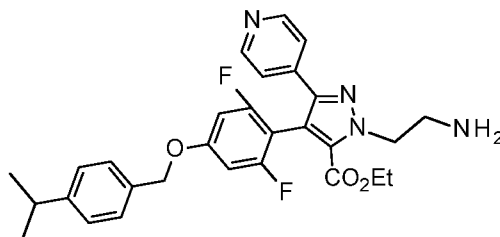
15 The r.m. was stirred for 17 h at 100°C. The r.m. was diluted with EtOAc and washed with water (once) and with brine (thrice). The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give 2.50 g of brown oil. The oil was purified by prep. LC (irregular SiOH 15-40 μm, 50 g, MERCK, Mobile phase gradient: from 100% Heptane to 90% Heptane, 10% EtOAc). The pure fractions were collected and solvent
20 was evaporated until dryness to give 1.10 g of Int. **72**, colorless oil (72%).



c- Synthesis of Int. 73:

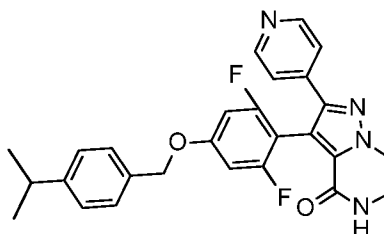
In a microwave vial, a mixture of **3** (570 mg, 1.3 mmol), **72** (1.0 g, 2.6 mmol), K₃PO₄ (1.1 g, 5.2 mmol) in 1,4-dioxane (5.7 mL) and H₂O (2.0 mL) was carefully purged with N₂. Precatalyst (100 mg, 130 μmol) was added and the r.m. was purged again with N₂.

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 MgSO₄, 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/NH₄OH, 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:

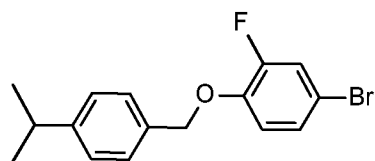
A solution of **73** (65 mg, 0.11 mmol), HCl 3N (0.18 mL, 0.53 mmol), in ACN (2 mL) was stirred at 80°C for 2h. ACN was concentrated, and NaHCO₃ sat aq (25mL) was added and the mixture was stirred at r.t. 15 min, extracted with DCM, dried and concentrated to give 63 mg of Int. **74** (quant.). This residue was used like this in the next step.



e- Synthesis of Co. 17:

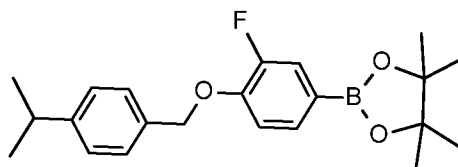
To a sol. of **74** (63 mg, 0.12 mmol) in MeOH (3.5 mL) was added Cs₂CO₃ (0.20 g, 0.61 mmol) and the mixture was stirred at r.t. overnight. The mixture was concentrated and taken in DCM and washed once with water, dried over MgSO₄ and concentrated. The crude product was purified by prep. LC (irregular SiOH 30 μm, 12 g GraceResolv™, mobile phase gradient from DCM/MeOH/NH₄OH 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% NH₄OH, 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:

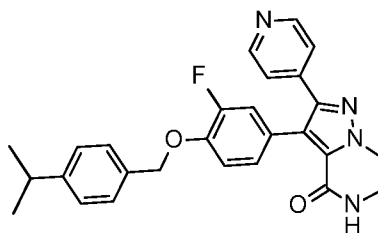
To a sol. of 4-bromo-2-fluorophenol (5 g, 26.1 mmol), **8** (4.6 mL; 27.5 mmol) in ACN (50 mL) was added K₂CO₃ (3.98 g, 28.8 mmol). The mixture was stirred at r.t. overnight. Water and DCM were added and the product was extracted with DCM. The organic layer was separated, dried, filtered and evaporated 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 N₂. PdCl₂(dppf) (0.228 g, 0.278 mmol) was added and the r.m. was purged again with N₂. 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%.

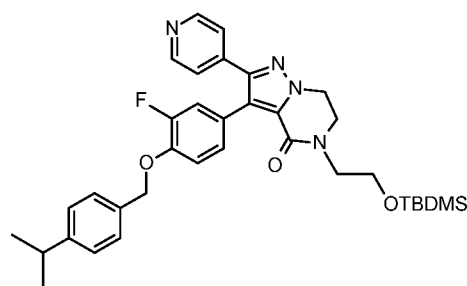
Second method: A sol. of 3-fluoro-4-hydroxyphenylboronic acid pinacol ester (0.91 g, 3.82 mmol) in ACN (10 mL) was treated with K₂CO₃ (0.634 g, 4.56 mmol) and **8** (0.725 mL, 4.2 mmol) at r.t. The r.m. was stirred for 18 h at r.t. Then water and DCM were added, and the organic layer was washed with brine, separated, dried over MgSO₄, 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:

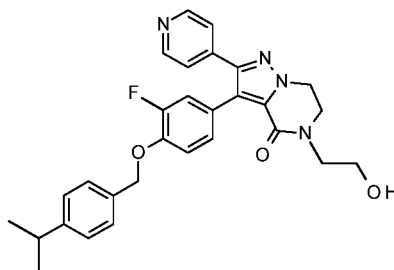
In a microwave vial, a mixture of **4** (0.3 g, 1.02 mmol), **76** (0.53 g, 1.43 mmol), K₃PO₄ (0.91 g, 4.29 mmol) in 1,4-dioxane (4.8 mL) and H₂O (1.6 mL) was carefully purged with N₂. PCy₃ (60 mg, 0.214 mmol) and Pd(OAc)₂ (24 mg, 0.107 mmol) were added and the r.m. was purged again with N₂. The r.m. 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 MgSO₄, 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: NH₄OH/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), K₃PO₄ (0.788 g, 3.7 mmol) in 1,4-dioxane (4.2 mL) and H₂O (1.4 mL) was carefully purged with N₂. PdCl₂(dppf) (73 mg, 0.09 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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%.

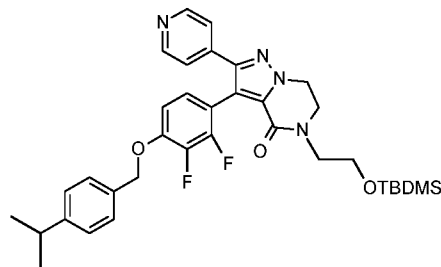


b- Synthesis of Co. 19:

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 K₂CO₃, extrated with EtOAc. The organic layer was dried over MgSO₄, filtered and evaporated until dryness to give 422 mg of a residue. The residue

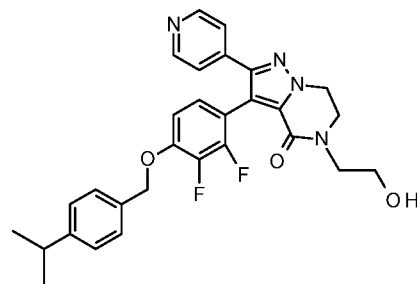
was purified by prep. LC (Stationary phase: Stability Silica 5 μ m 150x30.0mm), Mobile phase: Gradient from NH₄OH/DCM/MeOH 0.2/98/2 to NH₄OH/DCM/MeOH 0.9/90/9). The pure fractions were collected and evaporated until dryness to give 230 mg which was crystallized from Et₂O, filtered and dried to give 196 mg of **Co. 19** (54%) m.p.: 172°C (dsc).

Example A25: Preparation of Co. 20



a- Synthesis of Int. 78:

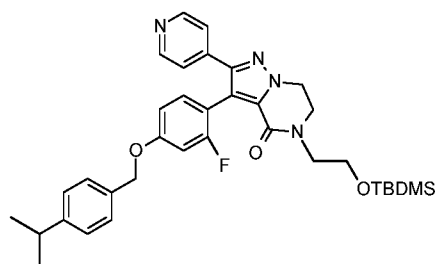
Under N₂, a sol. of **Co. 16** (915 mg, 1.93 mmol) in dry DMSO (17 mL) was treated with NaH (60%) (116 mg, 2.89 mmol). The r.m. was stirred at r.t. for 2h. Then, (2-bromomethoxy)-tert-butyldimethylsilane (496 μ L, 2.31 mmol) was added and the reaction was stirred at r.t. for 17 h. The crude mixture was poured in EtOAc and washed with brine. The organic layer was dried over MgSO₄ 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:

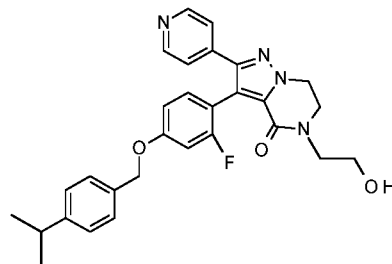
A sol. of mixture with **78** (1.00 g) in THF (35 mL) was treated with TBAF (790 μ L, 790 μ mol) and stirred at r.t. for 4 h. The crude mixture was then diluted in DCM, washed with water and brine. The organic layer was dried over MgSO₄ and evaporated *in vacuo* to afford a brown residue. The residue was purified by prep. LC (irregular SiOH 15-40 μ m, 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 N₂. 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 MgSO₄, 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.

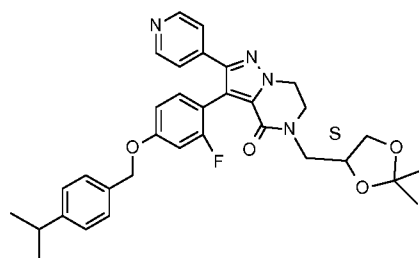


b- Synthesis of Co. 21:

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/NH₄OH 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% CO₂, 10% MeOH). The pure fractions were collected and solvent was evaporated to give 2.1 g which was crystallized from Et₂O, filtrated and dried to give 1.9 g of **Co. 21**, white solid (50%). m.p.: 141°C (dsc).

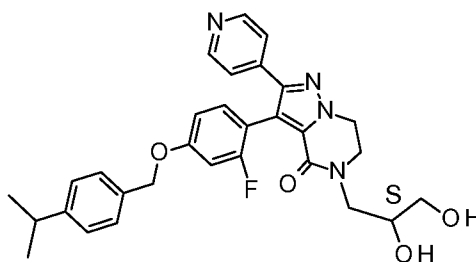
20

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



a- Synthesis of Co. 22a:

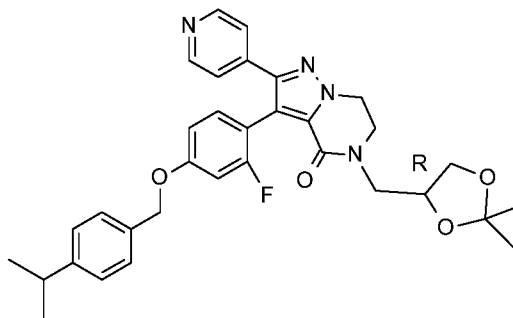
NaH (60%) (79 mg, 2.0 mmol) was added to **Co. 6** (0.60 g, 1.3 mmol) in DMF (8 mL) at r.t. under N₂. The mixture was stirred for 2h then (R)-(-)-2,2-dimethyl-1,3-dioxolane-4-ylmethyl P-toluenesulfonate (0.57 g, 2.0 mmol) was added and the mixture was stirred overnight. Water was added and the mixture was diluted with 150 mL of EtOAc and washed 4x with brine. The organic layer was dried on MgSO₄ and evaporated until dryness to give a white solid. The solid was purified by prep. LC (irregular SiOH 15-40 μ m, 12g, GraceResolv™, Mobile phase: DCM/MeOH/NH₄OH, 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. NaHCO₃ and extracted with DCM. The organic layer was dried over MgSO₄, filtered and evaporated until dryness. The residue was purified by prep. LC (irregular SiOH 15-40 μ m, 4 g, GraceResolv™, Mobile phase: DCM/MeOH/NH₄OH, 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 Et₂O and triturated and the white solid formed was progressively solubilized in Et₂O. 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); [α]_D: -18.42 ° (589 nm, c 0.2715 w/v %, DMF, 20 °C).

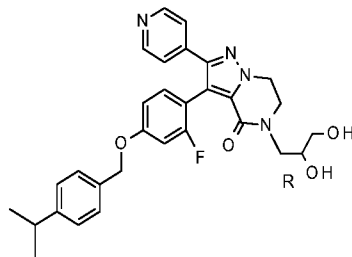
Example A28: Preparation of Co. 23a and Co. 23



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 N₂. The mixture was stirred for 2h then (S)-(-)-2,2-dimethyl-1,3-dioxolane-

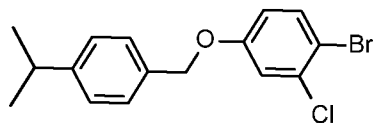
- 4-ylmethyl P-toluenesulfonate (0.57 g, 2.0 mmol) was added and the mixture was stirred overnight. Water was added and the mixture was diluted with 200 mL of EtOAc and washed four times with brine. The organic layer was dried on MgSO₄ and evaporated until dryness to give 0.80 g, white solid. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 12 g, GraceResolv™, Mobile phase: DCM/MeOH/NH₄OH, 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:

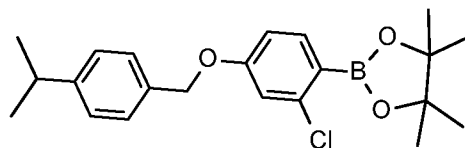
- A sol. of **Co. 23a** (0.165 g, 0.29 mmol) and HCl 3N (0.4 mL, 1.5 mmol) in 1,4-dioxane (6.4 mL) was heated to reflux for 2h. The mixture was cooled to r.t., poured into sat. NaHCO₃ and extracted with DCM. The organic layer was dried (MgSO₄), filtered and evaporated until dryness. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 4 g, GraceResolv™, Mobile phase: DCM/MeOH/NH₄OH 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 Et₂O 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); [α]_D: +18.59 ° (589 nm, c 0.2475 w/v %, DMF, 20 °C).

Example A29: Preparation of Co. 24

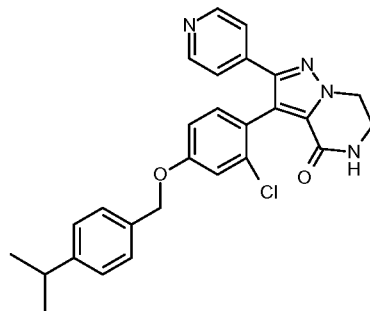


a- Synthesis of Int. 82:

- A sol. of 4-bromo-3-chlorophenol (2.00 g, 9.64 mmol) in ACN (25 mL) was treated with K₂CO₃ (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 MgSO₄, 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%).

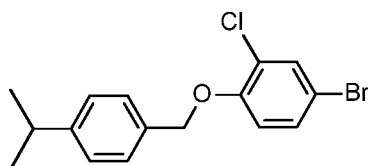
**b- Synthesis of Int. 83:**

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 N₂. 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 N₂. 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 MgSO₄, 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:**

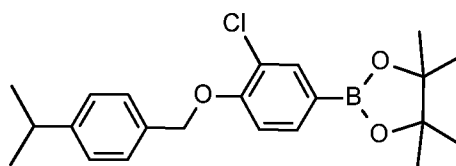
A sol. of **4** (258 mg, 0.882 mmol), **83** (750 mg, 1.94 mmol) and K₃PO₄ (655 mg, 3.09 mmol) in 1,4-dioxane (3.8 mL) and H₂O (1.2 mL) in a sealed tube was purged with N₂. Precatalyst (69 mg, 88.2 μmol) was added, the mixture was purged again with N₂ and stirred at 130°C using one single mode microwave (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% NH₄OH, 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



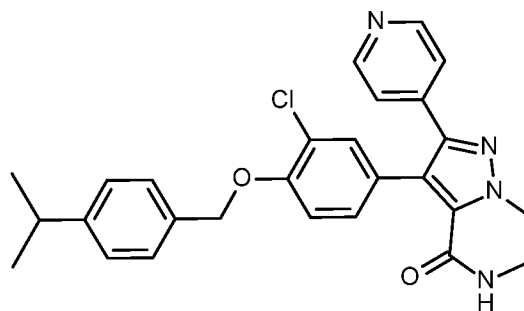
a- Synthesis of Int. 84:

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 K₂CO₃ (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 N₂. PdCl₂(dppf) (36 mg, 0.044 mmol) was added and the r.m. was purged again with N₂. 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%).

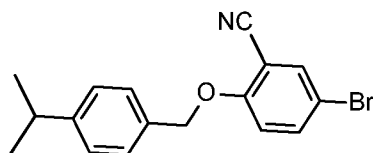


c- Synthesis of Co. 25:

In a microwave vial, a mixture of **4** (251 mg, 0.86 mmol), **85** (430 mg, 1.11 mmol), K₃PO₄ (761 mg, 3.59 mmol) in 1,4-dioxane (1.6 mL) and H₂O (0.53 mL) was carefully purged with N₂. PCy₃ (50 mg, 0.18 mmol) and Pd(OAc)₂ (20 mg ; 0.09 mmol) were added and the r.m. was purged again with N₂. 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 MgSO₄, 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: NH₄OH/DCM/MeOH 0.3/97/3). The pure fractions were collected and

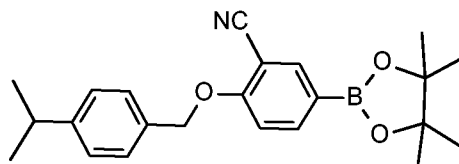
the solvent was evaporated until dryness to give 250 mg which was crystallized from DIPE, filtered and dried to give 188 mg of **Co. 25** (46%). m.p.: 251°C (dsc).

Example A31: Preparation of Co. 26



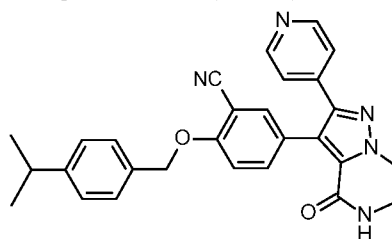
a- Synthesis of Int. 86:

- 5 To a sol. of 5-bromo-2-hydroxybenzonitrile (0.6g, 3.03mmol), **8** (0.532mL, 3.18mmol) in DMF (6mL) was added K₂CO₃ (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%).



10 **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 N₂. PdCl₂(dppf) (22 mg, 0.027mmol) was added and the r.m. was purged again with N₂. 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%).

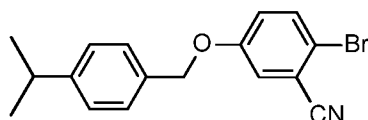


c- Synthesis of Co. 26:

- 20 In a microwave vial, a mixture of **4** (0.17 g, 0.58 mmol), **87** (0.371 g, 0.86 mmol), K₃PO₄ (0.516 g, 2.43 mmol) in 1,4-dioxane (2.72 mL) and H₂O (0.91 mL) was carefully purged with N₂. PCy₃ (34 mg, 0.122 mmol) and Pd(OAc)₂ (14 mg, 0.061 mmol) were added and the r.m. was purged again with N₂. 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 MgSO₄, 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,

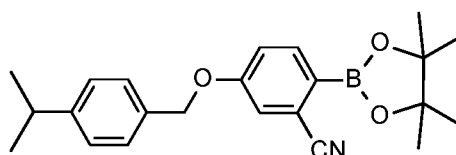
mobile phase: $\text{NH}_4\text{OH}/\text{DCM}/\text{MeOH}$ 0.2/96/4). The pure fractions were collected and the solvent was evaporated until dryness to give 85 mg which was crystallized from DIPE, filtered and dried to give 84 mg of **Co. 26** (31%). m.p.: 235°C (dsc).

Example A32: Preparation of Co. 27



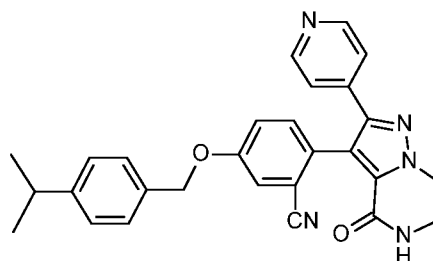
5 **a- Synthesis of Int. 88:**

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.).



10 **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 . $\text{PdCl}_2(\text{dppf})$ (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%).

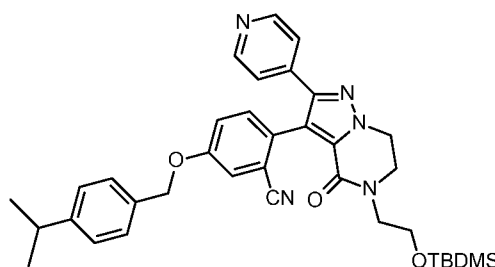


15 **c- Synthesis of Co. 27:**

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 . $\text{Pd}(\text{PPh}_3)_4$ (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

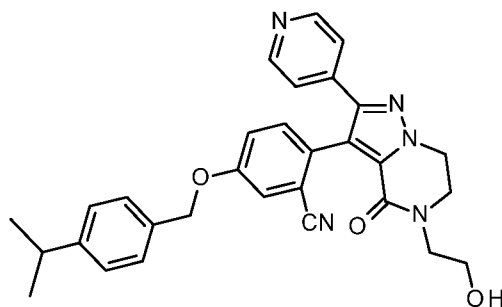
DCM/MeOH sol. (95/5) and brine. The organic layer was separated, dried over MgSO_4 , filtered off and evaporated *in vacuo* to yield 1.85 g of a sticky brown solid. The solid was purified by prep. LC (Irregular SiOH 50 μm , 80 g Grace, mobile phase gradient: from DCM 100% to DCM 85%, MeOH 15%). The fractions 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 $\text{Et}_2\text{O}/\text{EtOH}$ (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:

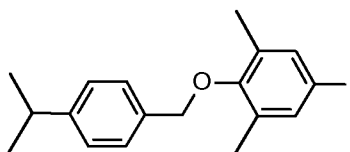
A sol. of **28** (1.20 g, 2.66 mmol), **89** (1.81 g, 4.79 mmol) and Cs_2CO_3 (2.17 g, 6.65 mmol) in DMF (16 mL) in a sealed tube was purged with N_2 . $\text{Pd}(\text{PPh}_3)_4$ (0.307 g, 0.266 mmol) was added, and the mixture was purged again with N_2 and stirred at 150°C using one single mode microwave (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 $\text{Pd}(\text{PPh}_3)_4$ (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 MgSO_4 , 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 purity of 70%. The product was used as such as for the next step.



b- Synthesis of Co. 28:

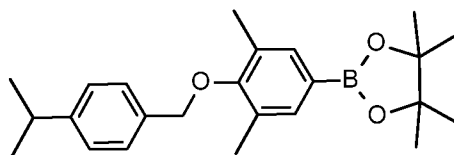
TBAF (0.580 mL, 0.580 mmol) was added to a stirred sol. of **90** (510 mg, 0.574 mmol) in THF (5 mL) at 0°C, and the r.m. was stirred at r.t. for 18 h. The crude mixture was diluted with water and a sol. of DCM/MeOH (96:4). The organic layer was separated,
 5 washed with brine, dried over MgSO₄, filtered 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**,
 10 crystalline white solid (79%). m.p.: 185 °C (DSC).

Example A34: Preparation of Co. 29 :



a- Synthesis of Int. 91:

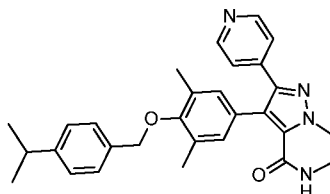
To a sol. of 2,6-dimethyl-4-iodophenol (2.48 g, 10 mmol), **8** (1.76 mL, 10.5 mmol) in ACN (25 mL) was added K₂CO₃ (1.52 g, 11 mmol). The mixture was stirred at r.t.
 15 overnight. Water and DCM were added and the product was extracted with DCM. The organic layer was separated, dried, filtered and evaporated 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 N₂. PdCl₂(dppf) (0.158 g, 0.193 mmol) was added and the r.m. was purged again with N₂. The mixture was heated at 100°C overnight. EtOAc and water were added and the

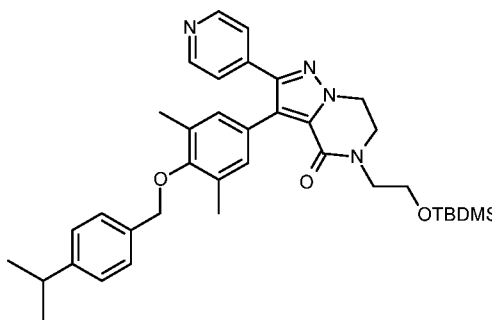
mixture was extracted with EtOAc. The organic layer was separated, dried, filtered and evaporated until dryness to give 4.09 g of a residue. The residue was purified by prep. LC on (Irregular SiOH 15-40 μ m 90g Merck, mobile phase: 90/10 Heptane/EtOAc). The pure fractions were collected and evaporated 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), K₃PO₄ (1.21 g, 5.72 mmol) in 1,4-dioxane (6.4 mL) and H₂O (2.13 mL) was carefully purged with N₂. PdCl₂(dppf) (112 mg, 0.14 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, filtered and evaporated *in vacuo* to give 1.16 g of a residue. The residue was purified by prep. LC (Stationary phase: irregular SiOH 15-40 μ m 300g Merck, Mobile phase: NH₄OH/DCM/MeOH 0.2/97/3). The pure fractions were collected and evaporated until dryness to give 475 mg which was crystallized from Et₂O, filtered and dried to give 443mg of **Co. 29** (70%). m.p.: 260°C (dsc)

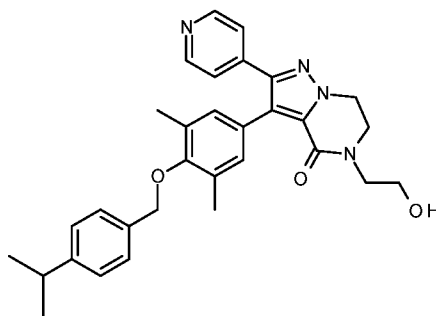
Example A35: Preparation of Co. 30



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), K₃PO₄ (1.13 g, 5.3 mmol) in 1,4-dioxane (5.84 mL) and H₂O (2 mL) was carefully purged with N₂. PdCl₂(dppf) (109 mg, 0.13 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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 μ m, 40 g Interchim, mobile phase: DCM/MeOH/NH₄OH 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

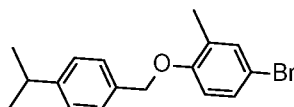
residue was purified by prep. LC (irregular SiOH 30 μ m, 40g Interchim, mobile phase: DCM/MeOH/NH₄OH 98/2/0.1). The pure fractions were collected and evaporated until dryness to give 588 mg of **93**. Both fractions were combined to yield 699mg of Int. **93** (84%).



5 **b- Synthesis of Co. 30:**

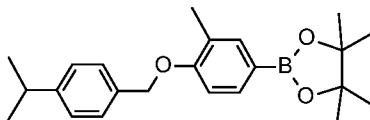
TBAF (1.44 mL, 1.44 mmol) was added dropwise to a sol. of **93** (0.752 g, 1.2 mmol) in THF (12 mL) at r.t. The mixture was stirred for 3h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 626 mg of a residue. The residue was purified by prep. LC (Regular SiOH, 30 μ m, 12g GraceResolvTM, mobile phase gradient: DCM/MeOH/NH₄OH 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 Et₂O, filtered and dried to give 218 mg of **Co. 30** (35%). m.p.: 170°C (dsc).

Example A36: Preparation of Co. 31



15 **a- Synthesis of Int. 94:**

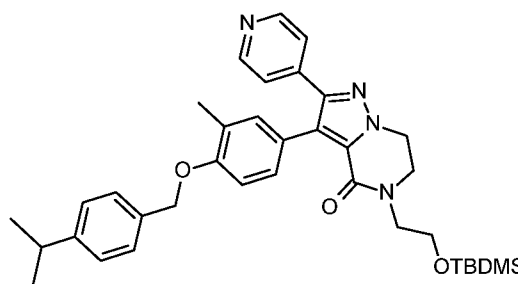
To a sol. of 4-bromo-2-methylphenol (2.5g, 13.4mmol), **8** (2.35mL, 14mmol) in ACN (25mL) was added K₂CO₃ (2.03g, 14.7mmol). The mixture was stirred at r.t. overnight. Water and DCM were added and the product was extracted with DCM. The organic layer was separated, dried, filtered and evaporated until dryness to give 4.33g of Int. **94** (100%).



b- Synthesis of Int. 95:

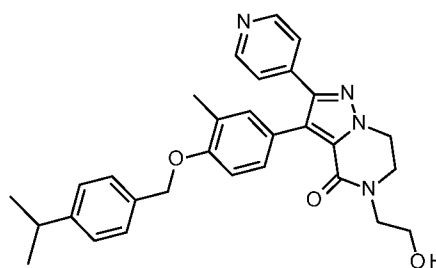
In a sealed tube, a mixture of **94** (3 g, 9.4 mmol), BisPin (3.58 g, 14 mmol), KOAc (2.77 g, 28.2 mmol) in DME (30 mL) was carefully purged with N₂. PdCl₂(dppf) (0.230 g, 0.282 mmol) was added and the r.m. was purged again with N₂. The mixture was

- 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), K₃PO₄ (1.32 g, 6.2 mmol) in 1,4-dioxane (6.8 mL) and H₂O (2.42 mL) was carefully purged with N₂. PdCl₂(dppf) (127 mg, 0.16 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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/NH₄OH 97/3/0.1). The pure fractions were collected and evaporated until dryness to give 1.2 g of Int. **96** (100%).

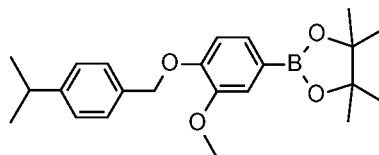


d- Synthesis of Co. 31:

- 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/NH₄OH, 95/5/0.1). The pure fractions were collected and evaporated until dryness to give 780

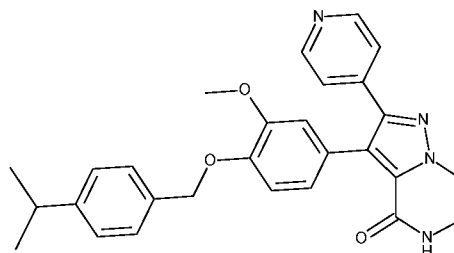
mg which was crystallized from DIPE, filtered and dried to give 491 mg of **Co. 31** (50%).

Example A37: Preparation of Co. 32



a- Synthesis of Int. 97:

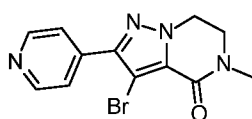
- 5 A flask was charged with 4-hydroxy-3-methoxyphenyl boronic acid pinacol ester (1.50 g, 6.00 mmol), **6** (1.35 g, 9.00 mmol), diphenylphosphinopolystyrene (3.00 g, 9.00 mmol) and DCM (40 mL). DBAD (2.07 g, 9.00 mmol) was then added and the r.m. was stirred at r.t. for 17 h. After filtration on a glass frit, the residual polymer was washed with DCM. The filtrate was evaporated *in vacuo* to afford yellow oil. This oil
- 10 was purified by prep. LC (irregular SiOH 15-40 μ m, 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:

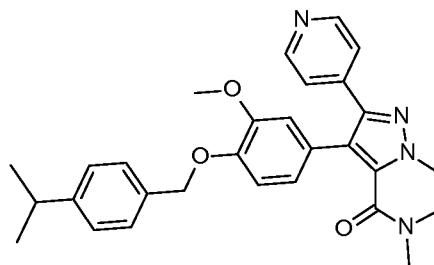
- 15 In a Schlenk tube, a mixture of **4** (250 mg, 0.853 mmol), **97** (815 mg, 2.13 mmol), K_3PO_4 (724 mg, 3.41 mmol) in 1,4-dioxane (6 mL) and H_2O (2 mL) was carefully purged with N_2 . $Pd(OAc)_2$ (19 mg, 85.3 μ mol) and PCy_3 (48 mg, 171 μ mol) were added and the r.m. was purged again with N_2 . 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
- 20 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 μ m, 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



- 25 **a- Synthesis of Int. 98:**

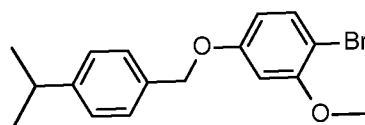
- NaH (60%) (655 mg, 216.4 mmol) was added to a suspension of **4** (4.00 g, 13.6 mmol) in DMSO (50 mL) at r.t. under N₂. The mixture was stirred for 2h. MeI (1020 µL, 16.4 mmol) was added and the mixture was stirred for 2h. The mixture was poured into water and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and evaporated until dryness to give 5.00 g of Int. **98**, yellow solid (quant.).



b- Synthesis of Co. 33:

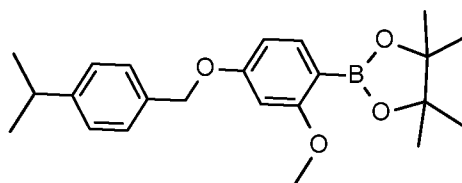
- In a sealed tube, a mixture of **98** (154 mg, 501 µmol), **97** (766 mg, 2.00 mmol), K₃PO₄ (425 mg, 2.00 mmol) in 1,4-dioxane (3 mL) and H₂O (1 mL) was carefully purged with N₂. PCy₃ (28 mg, 100 µmol) and Pd(OAc)₂ (11 mg, 50.1 µmol) were added and the r.m. was purged again with N₂. The r.m. was stirred 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 MgSO₄, 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 triturated with Et₂O, 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



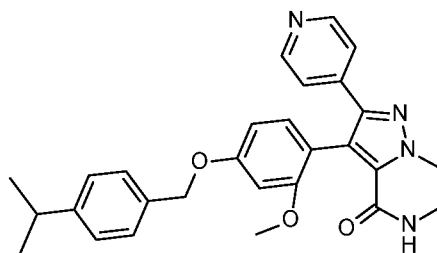
a- Synthesis of Int. 99:

- Under N₂, a sol. of 4-bromo-3-methoxyphenol (4.00 g, 19.7 mmol) in ACN (19 mL) was treated with K₂CO₃ (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 MgSO₄, filtered off and evaporated *in vacuo* to give 7.99 g of yellow oil. This oil was diluted in Et₂O and washed with brine (3x50mL), the organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give 6.8 g of Int. **99**, yellow oil (quant.).



b- Synthesis of Int. 100:

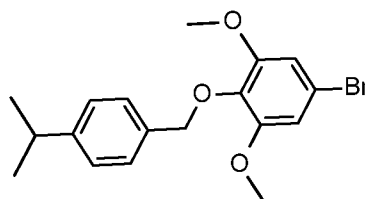
A mixture of **99** (5.57 g, 16.6 mmol) in dry THF (70 mL) was carefully purged with N₂. nBuLi 1.6N in hexane (11.4 mL, 18.3 mmol) was added at -78°C and the r.m. was stirred 2h at -78°C. Isopropoxyboronic acid pinacol ester (3.8 mL, 18.3 mmol) was added at -78°C and the r.m. was stirred for 3h at -78°C. The sol. was diluted in DCM and water. The organic layer was washed with HCl 1N, dried over MgSO₄, 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:

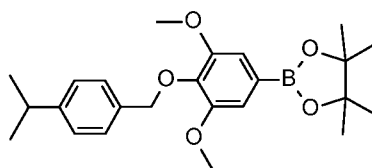
In a sealed tube, a mixture of **4** (500 mg, 1.71 mmol), **100** (1.63 g, 4.26 mmol), K₃PO₄ (1.45 g, 6.82 mmol) in 1,4-dioxane (8 mL) and H₂O (2.6 mL) was carefully purged with N₂. PCy₃ (96 mg, 341 μmol) and Pd(OAc)₂ (38 mg, 171 μmol) were added and the r.m. was purged again with N₂. The r.m. was stirred for 18h at 100°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over MgSO₄, 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



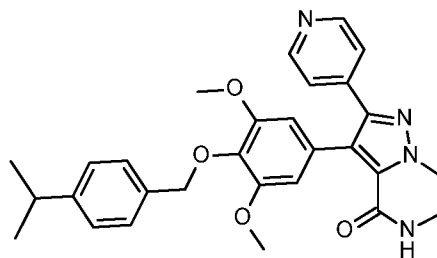
a- Synthesis of Int. 101:

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 K₂CO₃ (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%).



10 **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 N₂. PdCl₂(dppf) (0.122 g, 0.15 mmol) was added and the r.m. was purged again with N₂. 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.

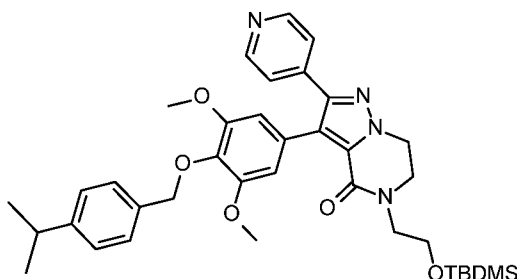


20 **c- Synthesis of Co. 35:**

In a microwave vial, a mixture of **4** (0.3 g, 1.02 mmol), **102** (0.686 g, 1.33 mmol), K₃PO₄ (0.911 g, 4.29 mmol) in 1,4-dioxane (4.8 mL) and H₂O (1.6 mL) was carefully purged with N₂. PdCl₂(dppf) (84 mg, 0.1 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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% NH₄OH, 95% DCM, 5% MeOH). The pure fractions were collected and

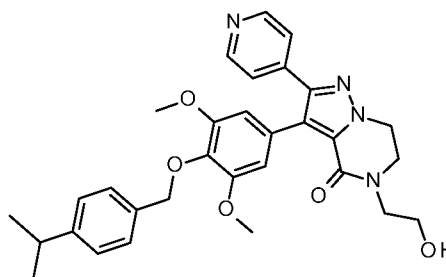
evaporated until dryness to give 290 mg which was crystallized in Et₂O, filtered and dried to give 255 mg of **Co. 35** (50%). m.p.: 192°C (dsc).

Example A41: Preparation of Co. 36



a- Synthesis of Int. 103:

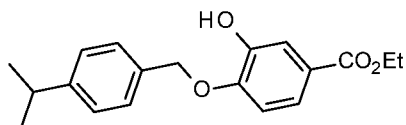
- 5 In a microwave vial, a mixture of **28** (0.7 g, 1.55 mmol), **102** (0.96 g, 1.86 mmol), K₃PO₄ (1.32 g, 6.2 mmol) in 1,4-dioxane (6.8 mL) and H₂O (2.42 mL) was carefully purged with N₂. PdCl₂(dppf) (127 mg, 0.16 mmol) was added and the r.m. was purged again with N₂. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3x). The organic phase was dried
- 10 over MgSO₄, 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/NH₄OH 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:

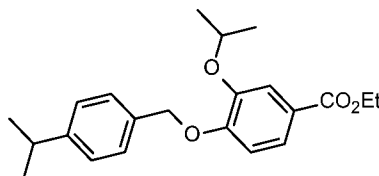
- 15 TBAF (0.93 mL, 0.93 mmol) was added dropwise to a sol. of **103** (509 mg, 0.775 mmol) in THF (8 mL) at r.t. The mixture was stirred for 3h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 463 mg of a residue. The residue was purified by prep. LC (Regular SiOH, 30 µm, 12g GraceResolv™, mobile phase gradient: from DCM 100% to
- 20 DCM/MeOH/NH₄OH 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



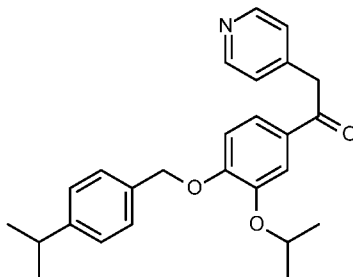
a- Synthesis of Int. 104:

DBAD (7.6 g, 33 mmol) was added to a sol. of ethyl-3,4-dihydroxybenzoate (4 g, 22 mmol), PPh₃ 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
 5 extracted, the organic layer was separated, dried over MgSO₄, 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%).



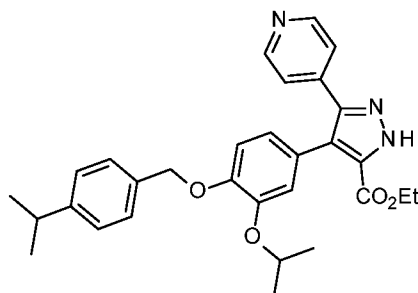
b- Synthesis of Int. 105:

A solution of **104** (1.5 g, 4.8 mmol), 2-bromopropane (0.5 ml, 5.2 mmol), K₂CO₃ (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 MgSO₄, filtered and evaporated. The residue was purified by prep. LC on (Irregular SiOH 20-45μm
 15 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%).



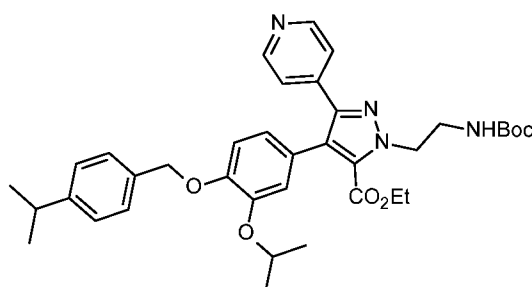
c- Synthesis of Int. 106:

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
 20 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 NH₄Cl (50mL). The mixture was extracted with DCM. The organic layer was separated, dried over MgSO₄, filtered and evaporated. The residue was purified by prep. LC (Irregular SiOH 20-45μm 80g MATREX, mobile phase: 95/5/0.1 DCM/MeOH/NH₄OH). The pure
 25 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.

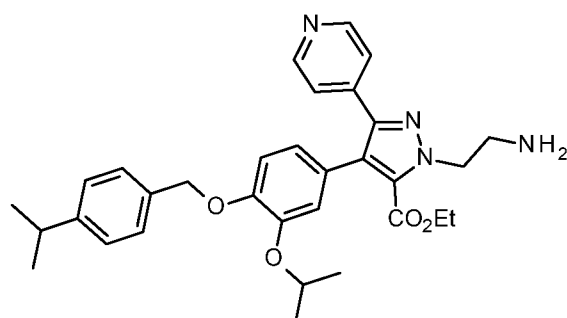
- 5 The organic layer was washed with a sat. aq. sol. of NaHCO₃, dried over MgSO₄, filtered off and evaporated *in vacuo*. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 40 g Grace, mobile phase: 97/3 DCM/MeOH). The pure fractions were collected and the solvent was evaporated until dryness to give 460 mg of Int. **107** (41%, beige powder).



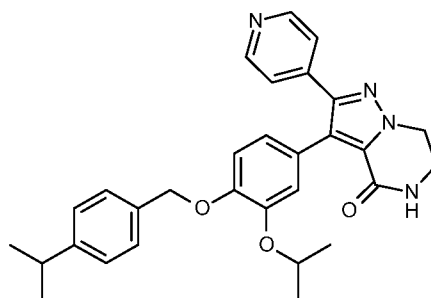
10 **e- Synthesis of Int. 108:**

To a mixture of **107** (460 mg, 0.921 mmol), Boc-Glycinol (222 mg, 1.4 mmol) and PPh₃ 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

- 15 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:**

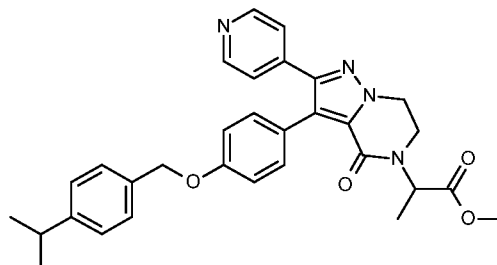
A solution of **108** (250 mg, 0.39 mmol) and HCl 3N (0.65 mL, 1.9 mmol) in ACN (5mL) was stirred at 80°C for 2h. K₂CO₃ 10% and EtOAc were added and the mixture was extracted. The organic layer was separated, dried over MgSO₄, filtered and evaporated to give 250 mg of Int. **109** (100%).



5 **g- Synthesis of Co. 37:**

To a sol. of **109** (250 mg, 0.46 mmol) in MeOH (10 mL) was added Cs₂CO₃ (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 Et₂O and dried to give 138 mg. The solid was taken up in H₂O and DCM and extracted. The organic layer was separated, dried over
10 MgSO₄, filtered and evaporated. The residue was taken up in Et₂O, the precipitate was filtered off and dried to give 97 mg of **Co. 37** (42%). m.p.: 206°C (dsc).

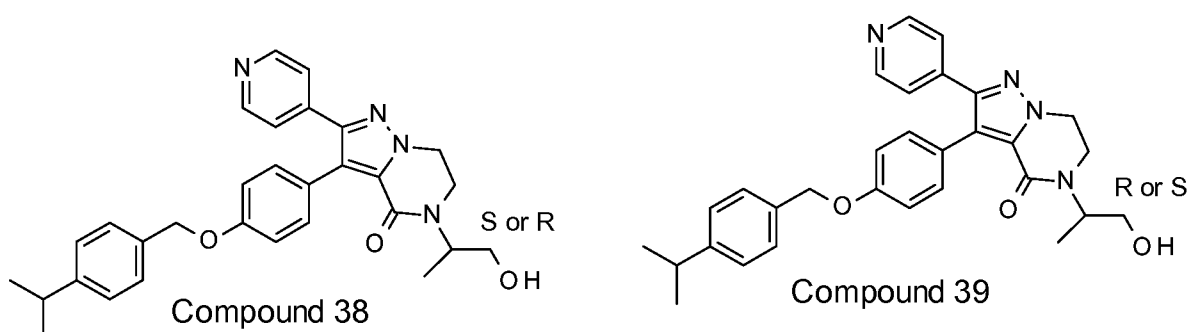
Example A43: Preparation of Co. 38 and Co. 39



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
15 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 K₂CO₃, and extracted with EtOAc. The organic layer was evaporated until dryness. The residue was taken up with DCM, dried over MgSO₄, filtered and evaporated until dryness to give 2.6 g. The
20 residue was purified by prep. LC (80g of SiOH 30µm Interchim, mobile phase gradient: from 100% DCM to 95% DCM 5% MeOH 0.1% NH₄OH). 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:

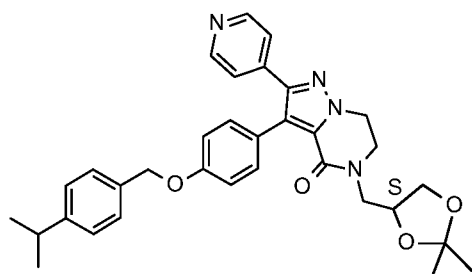


120 (2.47 g, 4.7 mmol) in THF (20 mL) was added dropwise to a suspension of LAH (268 mg, 7.06 mmol) in THF (30 mL) at 0°C under N₂. The mixture was stirred for 1.5h. Ice water was added dropwise then DCM was added. The mixture was filtered and the filtrate was dried over MgSO₄, filtered and evaporated until dryness to give 2.6 g which was purified by prep. LC (80g of irregular SiOH 30µm Interchim, gradient from 100% DCM to 95% DCM 5% CH₃OH 0.1% NH₄OH). 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% CO₂, 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% CO₂, 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 Et₂O, filtered and dried to give 97 mg of **Co. 39** (4%). m.p.: 144°C (dsc). The second residue was crystallized from Et₂O, filtered and dried to give 100 mg of **Co. 38** (4%). m.p.: 144°C (dsc).

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

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

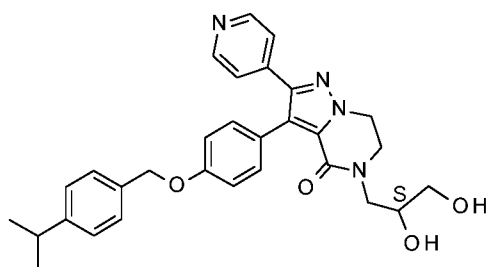
20 Example A44: Preparation of Co. 40



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 N₂. 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 20-45 μ m 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); $[\alpha]_D^{20}$: -16.95 ° (589 nm, c 0.295 w/v %, meOH, 20 °C).

Example A45: Preparation of Co. 41

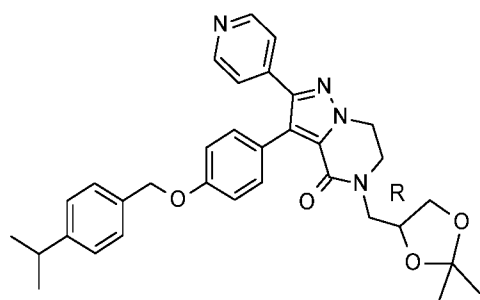


10

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 μ m 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); $[\alpha]_D^{20}$: -18.85 ° (589 nm, c 0.2705 w/v %, DMF, 20 °C)

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Example A46: Preparation of Co. 42



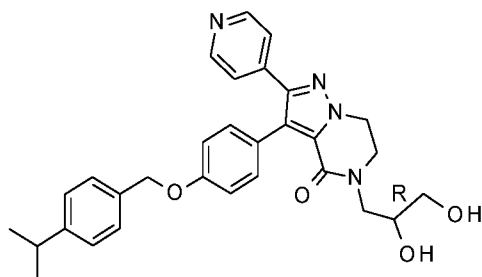
20

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

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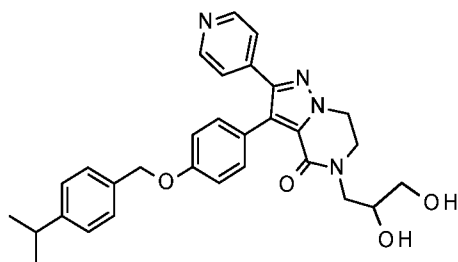
taken up with DCM, dried over MgSO_4 , filtered and evaporated until dryness to give 9.7g which was purified by prep. LC (120 g of silica gel 30 μm Interchim, mobile phase gradient: from 100% DCM to 95% DCM 5% CH_3OH 0.1% NH_4OH). The desired fractions were collected and evaporated until dryness to give 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 30 μm 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).

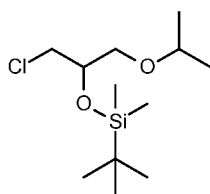
Example A48: Preparation of Co. 44



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-

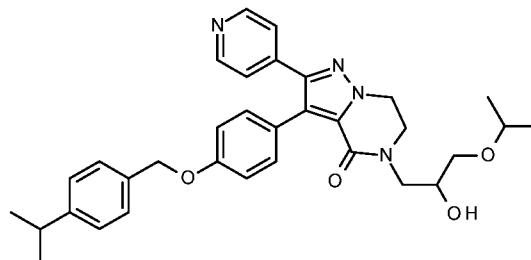
bromo-1,2-propanediol (88 μ L, 1.0 mmol) was added and stirred overnight. Water was added and the mixture was filtered, dissolved in DCM with CH₃OH. The organic layer was separated, dried on MgSO₄ and evaporated until dryness to give 530 mg of a residue. This residue was purified by prep. LC (irregular SiOH 30 μ m, 25g, Interchim, mobile phase gradient: DCM/MeOH/NH₄OH 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 Et₂O 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 H₂O then brine, dried (MgSO₄), filtered and evaporated to dryness to give 0.5 g of Int. **121**, colorless oil (purity 70%), used as such for the next step.

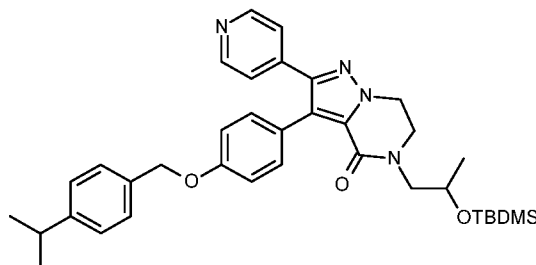


b- Synthesis of Co. 45:

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 N₂. 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 MgSO₄, filtered and concentrated to give 0.4 g of a residue. The residue was purified by prep. LC (Stationary phase: Sunfire Silica 5 μ m 150x30.0mm, mobile phase gradient: from 71% Heptane, 1% MeOH (+10% NH₄OH), 28% EtOAc to 20% MeOH (+10% NH₄OH), 80% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 72 mg which was taken in Et₂O 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).

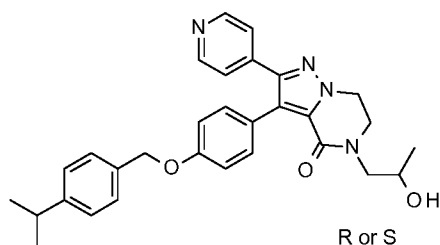
Example A50: Preparation of Co. 46 and Co. 47



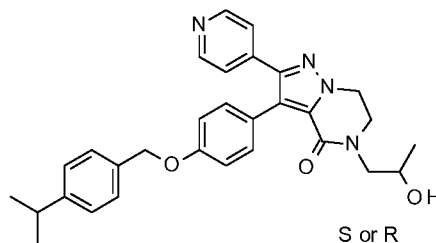
a- Synthesis of Int. 122:

- 5 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 N₂. 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, K₂CO₃ and extracted with EtOAc. The organic layer was evaporated until dryness to give 1.21 g. The residue
- 10 was taken up in DCM, dried over MgSO₄, 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% NH₄OH, 95% DCM, 5% CH₃OH). 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

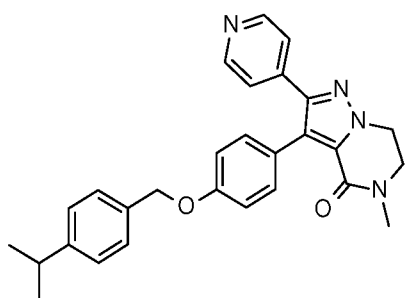
- 15 TBAF (1.49 mL, 1.49 mmol) was added dropwise to a sol. of **122** (0.76 g, 1.24 mmol) in THF (7 mL) at r.t.. The mixture was stirred for 15h. The mixture was evaporated until dryness. The residue was purified by prep. LC (25g of SiOH 30μm Interchim, mobile phase gradient from 100% DCM to 95% DCM 5% MeOH 0.1% NH₄OH). The
- 20 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% CO₂, 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
- 25 enantiomer. The first one was purified again by achiral SFC on (Amino 6μm

150x21.2mm), mobile phase (80% CO₂, 20% MeOH). The fractions were collected and solvent was evaporated until dryness to give 340 mg of the first enantiomer which was crystallized in Et₂O, 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 Et₂O, filtered and dried to give 395 mg of **Co. 47** (global yield: 17%). m.p.: 177°C (dsc).

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

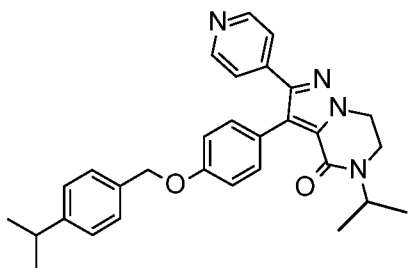
Co. 47: [α]_D: +27.06 ° (589 nm, c 0.3585 w/v %, DMF, 20 °C).

Example A51: Preparation of Co. 48



- 10 In a sealed tube, a mixture of **98** (250 mg, 0.81 mmol), **5** (1.15 g, 3.26 mmol), K₃PO₄ (724 mg, 3.41 mmol) in 1,4-dioxane (3.8 mL) and H₂O (1.3 mL) was carefully purged with N₂. PCy₃ (48 mg, 0.171 mmol) and Pd(OAc)₂ (19 mg, 0.085 mmol) were added and the r.m. was purged again with N₂. The r.m. was stirred for 17h at 100°C. The crude material was dissolved in water (10 mL) and extracted with Et₂O (2x 40mL). The
- 15 organic phase was dried over MgSO₄, 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).

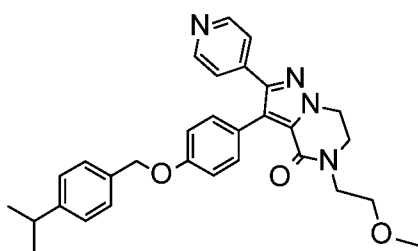
20 Example A52: Preparation of Co. 49



- 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 N₂. 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,
- 25 the mixture was filtered and washed with water. The residue was dissolved in DCM,

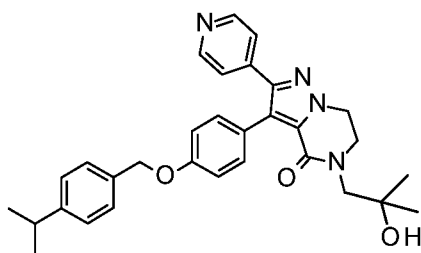
dried over MgSO_4 , filtered and evaporated until dryness to give 0.34 g which was purified by prep. LC (irregular SiOH 12g 35-40 μm GraceResolv™, mobile phase gradient from 100% DCM to 95% DCM 5% MeOH 0.1% NH_4OH). The fractions were collected and evaporated until dryness to give 203 mg of Co. 49 (62%). This batch was
5 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
10 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/
15 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).

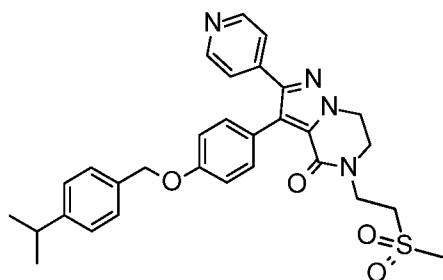
Example A54: Preparation of Co. 51



20 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,
25 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 15-40 μm , 300g MERCK,

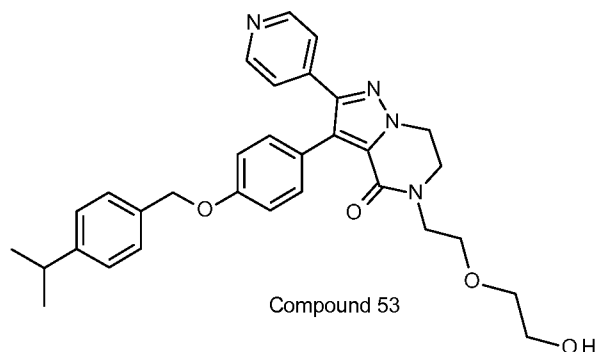
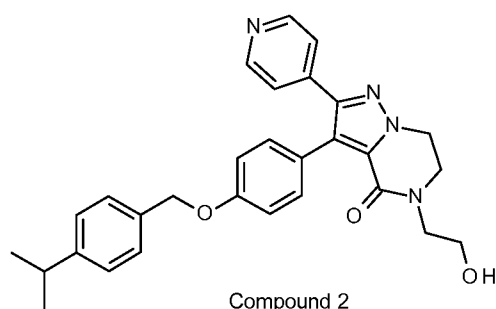
mobile phase): 0.1% NH_4OH , 98% DCM, 2% MeOH). The pure fractions were collected and the solvent was evaporated until dryness to give 290 mg of 2.1g of Co. 1 and **Co. 51**, white solid (10%). m.p. : 211°C (dsc).

Example A55: Preparation of Co. 52



5 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 5 μm 150x30.0mm, mobile phase gradient: from 100% DCM to $\text{NH}_4\text{OH}/\text{DCM}/\text{MeOH}$ 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

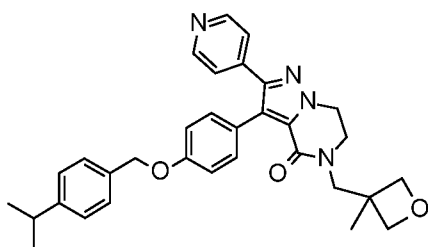


20

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 35-40 μm GraceResolvTM, mobile phase gradient: from 100% DCM to 95% DCM 5%

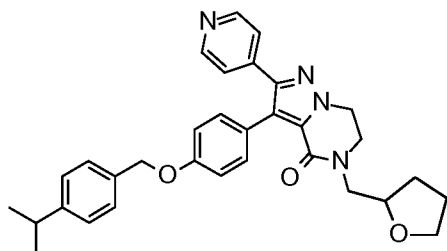
MeOH 0.1% NH₄OH). The fractions were collected and evaporated until dryness to give 8.76 g (94%). Another batch (4 g) was purified by prep. LC (120g of SiOH 35-40µm GraceResolv™, mobile phase gradient: from 100% DCM to 96% DCM 4% MeOH 0.1% NH₄OH). The fractions were collected and evaporated until dryness 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 Et₂O, 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% CO₂, 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% CO₂, 20% MeOH). The pure fractions were collected and solvent was evaporated to give 641 mg which was crystallized from Et₂O, filtered and dried to give 557 mg of **Co. 53**. m.p.: 121°C (dsc).

Example A57: Preparation of Co. 54



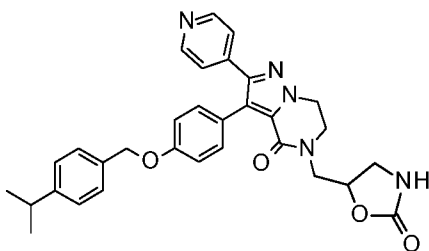
NaH 60% (54.7 mg, 1.4 mmol) was added slowly to a suspension of **Co. 1** (0.4 g, 0.9 mmol) in DMSO (5 mL) at r.t. under N₂. The mixture was stirred for 2h, then 2-(chloromethyl)-2-methyl-1,3-epoxypropane (0.12 mL, 1 mmol) was added and the r.m. was stirred for 24h. Water was added and the insoluble was filtered off. The insoluble was dissolved in DCM and MeOH, dried over MgSO₄ 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: NH₄OH/DCM/MeOH 0.2/98/2 to NH₄OH/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 Et₂O, 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 N₂. 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 MgSO₄ 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/NH₄OH, 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 Et₂O, filtrated and dried to give 90 mg of **Co. 55**, white solid (19%). m.p.: 165°C (dsc).

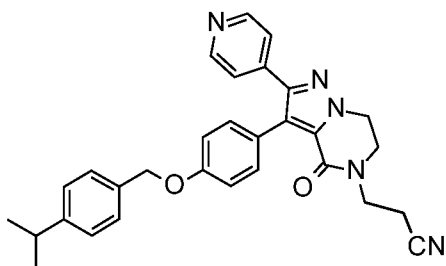
15 Example A59: Preparation of Co. 56



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 N₂. 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 MgSO₄, 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% NH₄OH), 50% EtOAc to 40% Heptane, 10% MeOH (+10% NH₄OH), 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

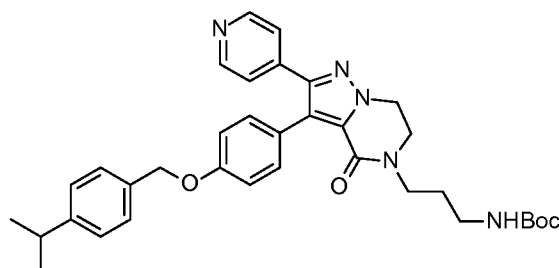
white powder residue. The residue was taken in Et₂O, triturated and the white solid formed was filtrated and dried to give 17 mg of **Co. 56** (2.3%).

Example A60: Preparation of Co. 57



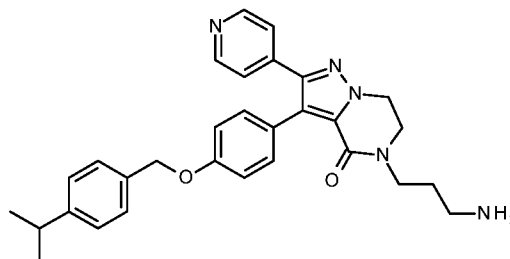
- 5 NaH 60% (55 mg, 1.4 mmol) was added portionwise to a suspension of **Co. 1** (0.40 g, 0.91 mmol) in dry DMF (5.5 mL) at r.t. under N₂. The mixture was stirred for 2h then 3-bromopropionitrile (0.13 g, 1.0 mmol) was added and the r.m. was stirred overnight at r.t. Water was added and the mixture was diluted with 150 mL of EtOAc and washed 4x with brine. The organic layer was dried on MgSO₄ and evaporated until dryness to
- 10 give 0.62 g. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 12g, GraceResolv™, Mobile phase: DCM/MeOH/NH₄OH, 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 Et₂O. The solid formed was filtered and dried to give 132 mg of **Co. 57**, white solid (29%). m.p.: 158°C (dsc).

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



a- Synthesis of Co. 58a

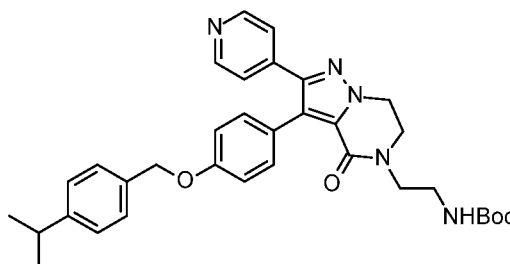
- NaH 60% (68 mg, 1.7 mmol) was added slowly to a suspension of **Co. 1** (0.5 g, 1.1 mmol) in dry DMF (7.0mL) at r.t. under N₂. The mixture was stirred for 2h then tert-butyl N-(3-bromopropyl) carbamate (543 mg, 2.3 mmol) was added and the r.m. was
- 20 stirred overnight. Water was added and the mixture 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:

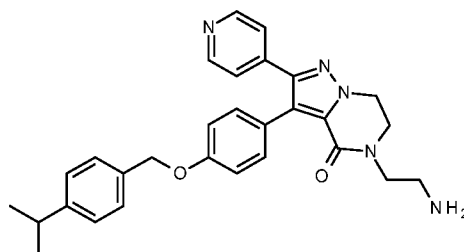
A solution of **Co. 58a** (680 mg, 1.1 mmol), HCl 3N (1.9 mL, 5.7mmol), in ACN (20mL) was stirred at 80°C for 2h. The mixture was concentrated, and NaHCO₃ sat aq (100 mL) was added and the mixture was stirred at r.t. for 15 min, extracted with DCM, dried and concentrated. The residue (550 mg) was purified by prep. LC (Regular SiOH, 30 μm, 12 g Interchim, mobile phase gradient: DCM/MeOH/NH₄OH 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 Et₂O. The solid formed was filtered and dried to give 192 mg of **Co. 58**, white solid (34%).

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



a- Synthesis of Co. 238

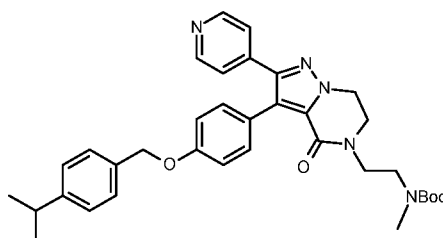
NaH 60% (0.41 g, 10.3 mmol) was added slowly to a suspension of **Co. 1** (3 g, 6.8 mmol) in dry DMSO (45 mL) at r.t. under N₂. The mixture was stirred for 2h then tert-butyl N-(2-bromoethyl) carbamate (2.3 g, 10.26 mmol) was added and the r.m. was stirred for 20h. The mixture was poured into water and EtOAc was added. The insoluble was filtered and washed with EtOAc. K₂CO₃ 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 MgSO₄, 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:

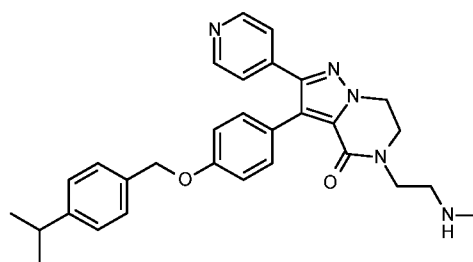
Co. 238 (650 mg, 1.12 mmol), HCl 3N (1.9mL, 5.6mmol) in ACN (20mL) was heated at 70°C for 1.5 h. The mixture was cooled to r.t. and the insoluble was filtered, washed with ACN and Et₂O and dried to give 379 mg of Co. 59a (HCl salt; .2 HCl .1.78 H₂O) (58%). Part of Co. 59a was converted to the free base (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 N₂. 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 K₂CO₃ and extracted with EtOAc. The organic layer was dried over MgSO₄, 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% NH₄OH). The fractions were collected and evaporated until dryness to give 308 mg of **Co. 60a** (62%).

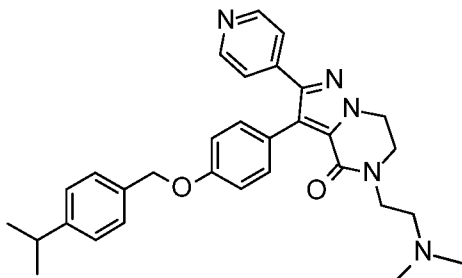


b- Synthesis of Co. 60:

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 K₂CO₃ and extracted with DCM. The organic layer was dried over MgSO₄, filtered and evaporated until dryness. The residue (0.22 g) was purified by achiral SFC (Stationary phase: Amino 6μm 150x21.2mm, mobile phase: 70% CO₂, 30% MeOH (0.3% iPrNH₂)). The pure fractions were collected and the solvent was evaporated until

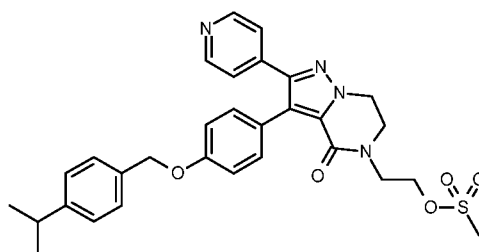
dryness to give 180 mg which was crystallized from Et₂O, filtered and dried to give 131 mg of **Co. 60** (51%).

Example A64: Preparation of Co. 61



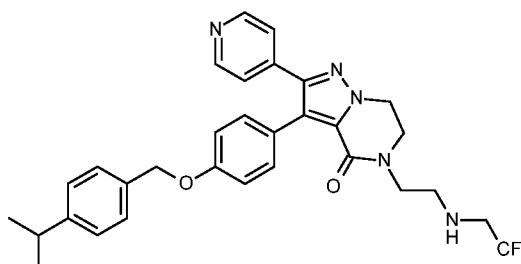
- 5 Formaldehyde (46.7 μ L, 0.623 mmol) was added to a sol. of **Co. 59** (100 mg, 0.21 mmol) in DCM (2 mL) and THF (1 mL) at r.t. The mixture was stirred for 1h then sodium triacetoxyborohydride (88 mg, 0.415 mmol) was added and the r.m. was stirred for 15h. The mixture was poured into water and K₂CO₃ and extracted with DCM. The organic layer was dried over MgSO₄, filtered and evaporated until dryness. The residue
- 10 (103 mg) was purified by prep. LC (Stationary phase: irregular 15-40 μ m 30g Merck, mobile phase: 1% NH₄OH, 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:

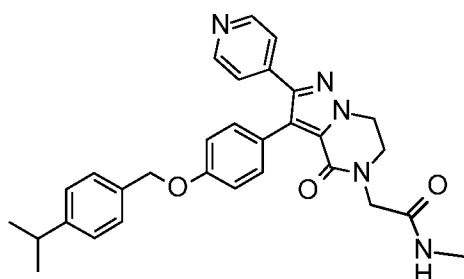
- 15 Methanesulfonyl chloride (49 μ L, 0.64 mmol) was added dropwise to a sol. of **Co. 2** (205 mg, 0.43 mmol) and Et₃N (178 μ L, 1.3 mmol) in dry DCM (5 mL) at 0°C under N₂ atmosphere. The r.m. was stirred at 0°C for 2h. Water was added and the mixture was extracted with DCM. The organic layer was separated, dried over MgSO₄, filtered and the solvent was evaporated until dryness to give 280 mg of Int. mixture **126**, yellow
- 20 solid. The solid was used in the next reaction step without further purification.



b- Synthesis of Co. 62:

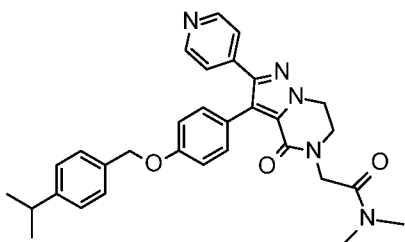
In a microwave vial, a sol. of **126** (225 mg, 0.43 mmol) in 2,2,2-trifluoroethylamine (6.3 mL, 80 mmol) was stirred at 80°C overnight. Water was added and the mixture was extracted with DCM. The organic layer was separated, dried over MgSO₄, filtered and the solvent was concentrated to obtain a residue (120 mg). The aq. layer was
5 basified with NaHCO₃ 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 NH₄OH/DCM/MeOH 0.9/91/9). The pure fractions were collected and evaporated until dryness to give 46 mg of **Co. 62**, beige
10 solid (17%).

Example A66: Preparation of Co. 63



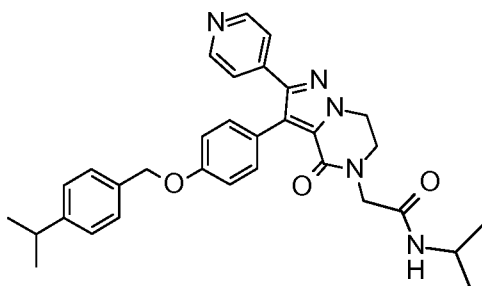
NaH 60% (27.4 mg, 0.68 mmol) was added to a sol. of **Co. 1** (200 mg, 0.46 mmol) in DMSO (4 mL) at r.t. under N₂. The mixture was stirred for 2h. 2-bromo-N-methylacetamide (104 mg, 0.68 mmol) was added and stirred for 15h. The mixture was
15 poured into water and extracted with EtOAc (another batch with 102mg of initial reactant, Co. 1 was put together for work up). The organic layer was dried over MgSO₄, 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
20 NH₄OH/DCM/MeOH 0.2/98/2 to NH₄OH/DCM/MeOH 0.8/92/8). The pure fractions were collected and solvent was evaporated to give 290 mg which was crystallized from Et₂O, filtered and dried to give 233 mg of **Co. 63**, (global yield : 66%). m.p.: 161°C (dsc).

Example A67: Preparation of Co. 64



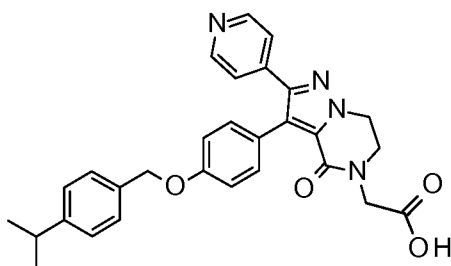
NaH 60% (72 mg, 1.8 mmol) was added portionwise to a suspension of **Co. 1** (0.52 g, 1.2 mmol) in dry DMF (7.1 mL) at r.t. under N₂. The mixture was stirred for 2h then N,N-dimethylchloroacetamide (0.18 mL, 1.8 mmol) was added and the r.m. was stirred overnight at r.t. Water was added and the mixture was concentrated under reduced pressure. The residue was taken in EtOAc and washed 5x with brine. The organic layer was dried over MgSO₄, filtrated and concentrated. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 25 g, Interchim, mobile phase: DCM/MeOH/NH₄OH, 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 Et₂O. The solid formed was filtered and dried to give 390 mg of **Co. 64**, white solid (63%).

Example A68: Preparation of Co. 65



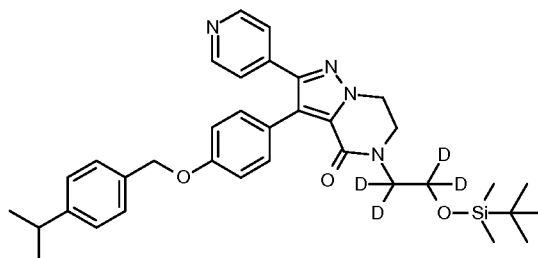
NaH 60% (72 mg, 1.8 mmol) was added portionwise to a suspension of **Co. 1** (0.52 g, 1.2 mmol) in dry DMF (7.1 mL) at r.t. under N₂. The mixture was stirred for 2h then N-isopropyl-2-chloroacetamide (0.24 g, 1.8 mmol) was added and stirred overnight at r.t. Water was added and the mixture was concentrated under reduced pressure. The residue was taken in EtOAc and washed 5x with brine. The organic layer was dried over MgSO₄, 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/NH₄OH, 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 Et₂O. 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



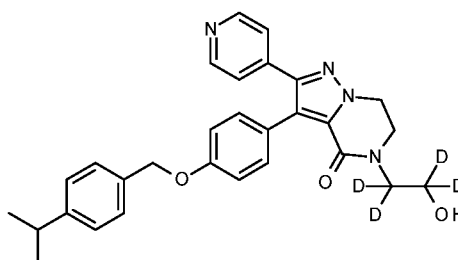
NaH 60% (68 mg, 1.7 mmol) was added slowly to a suspension of **Co. 1** (0.50 g, 1.1 mmol) in dry DMSO (6.3 mL) at r.t. under N₂. The mixture was stirred for 2h and then methylbromoacetate (0.12 mL, 1.25 mmol) was added and stirred overnight. Water was added and the mixture was concentrated under reduced 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 MgSO₄, filtered and evaporated to give 75 mg of **Co. 66**, white solid.

10 Example A70: Preparation of Co. 67



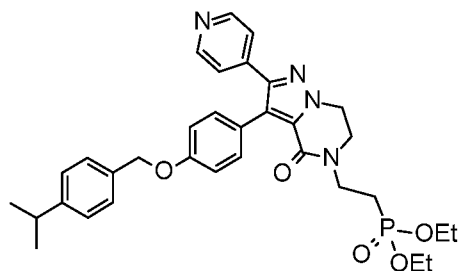
a- Synthesis of Int. 127:

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 N₂. The mixture was stirred for 2h then (2-bromoethoxy-1,1,2,2-d₄)(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 MgSO₄, filtered and concentrated to give 750 mg of Int. **127**, yellow oil as a mixture which was used like this in the next step.

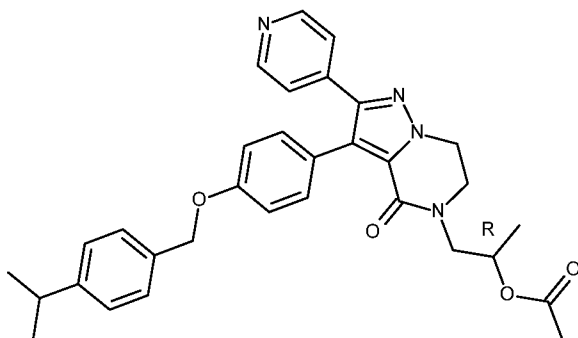


b- Synthesis of Co. 67:

20 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/NH₄OH 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 Et₂O. 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

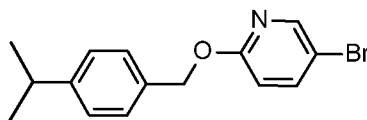
NaH 60% (27.4 mg, 0.68 mmol) was added to **Co. 1** (0.2 g, 0.46 mmol) in DMSO (2.8 mL) at r.t. under N₂. The mixture was stirred for 2h then diethyl-2-bromoethylphosphonate (0.13 mL, 0.68 mmol) was added and the r.m. was stirred for 20h. The mixture was poured into water, K₂CO₃ was added and extracted 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 MgSO₄, 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% NH₄OH). 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 N₂. 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 MgSO₄, 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%

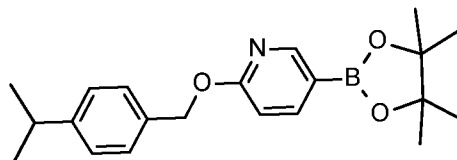
MeOH (+10% NH₄OH), 50% EtOAc). The pure fractions were collected and the solvent was evaporated to give 1.02 g which was triturated in Et₂O and the white solid formed was filtrated and dried to give 450 mg of **Co. 69** (R) (10%).

Example A73: Preparation of Co. 71



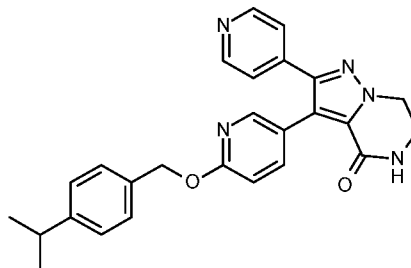
5 **a- Synthesis of Int. 128:**

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
10 EtOAc and dried on MgSO₄, 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 N₂ and charged with
15 PdCl₂(PPh₃)₂ (0.60 g, 0.85 mmol). The resulting sol. was purged again with N₂ 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 MgSO₄ and evaporated to afford 12 g of brown oil. This oil was purified by prep. LC (irregular SiOH 15-40 μm, 120 g GraceResolvTM, mobile phase: heptane/EtOAc 80/20). The pure fractions were
20 collected and solvent was evaporated to give 5.6 g of Int. **129**, brown solid (93%).

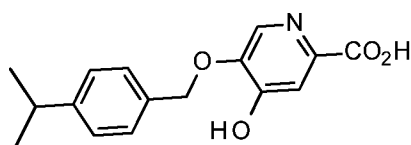


c- Synthesis of Co. 71:

In a Schlenk tube, a mixture of **4** (150 mg, 0.512 mmol), **129** (452 mg, 1.28 mmol), K₃PO₄ (434 mg, 2.05 mmol) in 1,4-dioxane (3.75 mL) and H₂O (1.5 mL) was carefully purged with N₂. Pd(OAc)₂ (11 mg, 51.2 μmol) and PCy₃ (29 mg, 102 μmol) were
25 added and the r.m. was purged again with N₂. The Schlenk tube was then sealed and the

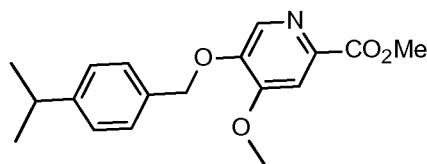
r.m. was stirred for 17 h at 80°C. The crude mixture was then diluted in DCM and washed with water (2 x 10mL). The organic layer was collected, dried over MgSO₄ and evaporated *in vacuo* to afford brown oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 50 g Merck, Mobile phase gradient: 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



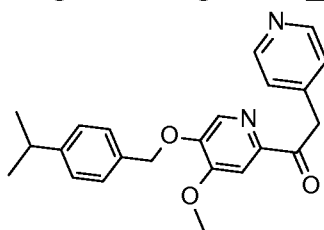
a- Synthesis of Int. 130:

A sol. of 5-[[4-(1-methylethyl)phenyl]methoxy]-4-oxo-4H-pyran-2-carboxylic acid (2.82 g, 9.78 mmol) in NH₃ (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:

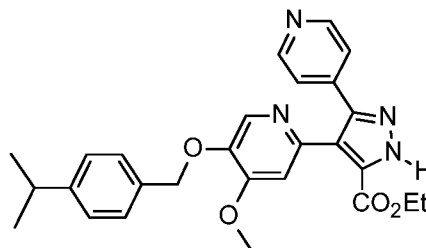
(Trimethylsilyl)diazomethane, 2M in hexane (10.4 mL, 20.8 mmol) was added to a stirred sol. of **130** (1.05 g, 3.66 mmol) in MeOH (5 mL) and toluene (20 mL) at 0°C under N₂. The crude mixture was stirred warming to r.t. for 1 h, and then water and EtOAc were added. The organic layer was washed with brine, separated, dried over MgSO₄, 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:

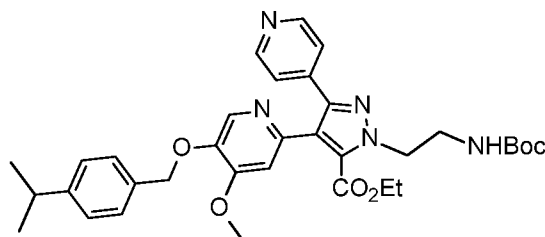
In a dry flask under N₂, a sol. of **131** (283 mg, 0.897 mmol) and 4-picoline (0.140 mL, 1.44 mmol) in THF (7 mL) was cooled to 0°C and treated with LiHMDS (1.80 mL, 1.80 mmol). The r.m. was stirred at r.t. for 20 h. The crude mixture was quenched with an aq. sol. of NH₄Cl, and EtOAc was added. The 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.



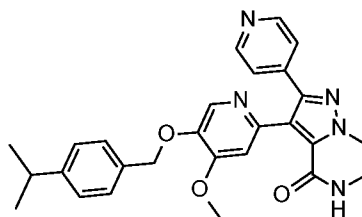
d- Synthesis of Int. 133:

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, GraceResolvTM, 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, GraceResolvTM, 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%).



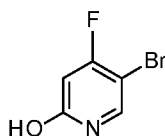
f- Synthesis of Co. 72:

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

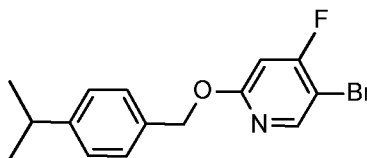
added, and the r.m. was stirred at r.t. for 20h. Water and more EtOAc were added, and the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and evaporated *in vacuo*. The residue (114 mg) was purified by prep. LC (Irregular SiOH 50 μm , 10 g Grace, mobile phase gradient: from 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

10 **a- Synthesis of Int. 135:**

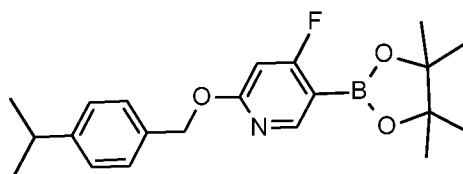


To a sol. of 2-hydroxy-4-fluoropyridine (1.0 g, 8.8 mmol) in ACN (23 mL) was added dropwise N-bromosuccinimide (1.6 g, 8.8 mmol) in ACN (23 mL) at r.t. in darkness. The sol. was stirred at r.t. for 3 days. The solvent was removed *in vacuo*. EtOAc and a sat. aq. sol. of brine were added to the residue, 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%).



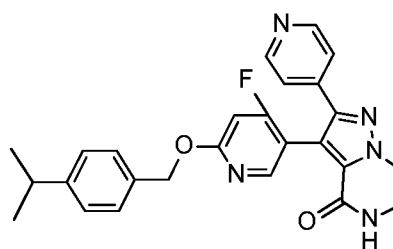
20 **b- Synthesis of Int. 136:**

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:

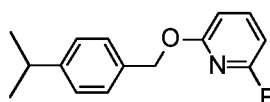
In a microwave vial, BisPin (0.33 g, 1.3 mmol) and KOAc (0.21 g, 2.2 mmol) were added to a sol. of **136** (0.35 g, 1.1 mmol) in 1,4-dioxane (3.6 mL). The sol. was purged with N₂ and charged with PdCl₂(dppf) (38 mg, 54 μmol). The resulting sol. was purged again with N₂ and stirred at 80°C for 17h. After dilution in EtOAc, the crude material was washed with water and brine. The organic layer was dried over MgSO₄ 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), K₃PO₄ (0.74 g, 3.5 mmol) in 1,4-dioxane (3.8 mL) and H₂O (1.4 mL) was carefully purged with N₂. PdCl₂(dppf) (72 mg, 88 μmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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 NH₄OH/DCM/MeOH 0.1/99/1 to NH₄OH/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 Et₂O. The solid was filtrated and dried to give 33 mg of **Co. 73**, white solid (8%). m.p.: 207°C (dsc).

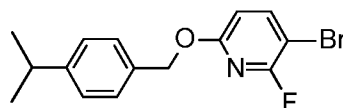
Example A76: Preparation of Co. 74



a- Synthesis of Int. 138:

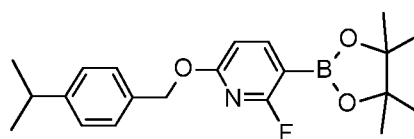
A sol. of **6** (3.1 g, 20 mmol) in dry DMF (60 mL) was treated at 0°C with NaH 60% (0.99 g, 25 mmol). After stirring for 1h at r.t., 2,6-difluoro-pyridine (2.4 g, 21 mmol)

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.



5 **b- Synthesis of Int. 139:**

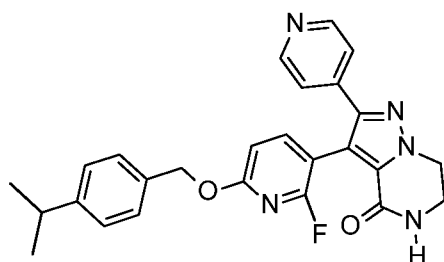
To a sol. of **138** (4.7 g, 17 mmol) in ACN (60 mL) was slowly added N-bromosuccinimide (3.0 g, 17 mmol) in ACN (60 mL) at r.t. The sol. was stirred at 80°C overnight. The solvent was removed *in vacuo* and the residue was taken in EtOAc and washed with NaCl sat, NaHCO₃, filtrated and dried. The residue and the mixture was
10 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:
15 80%) which was used such as for the next step.



c- Synthesis of Int. 140:

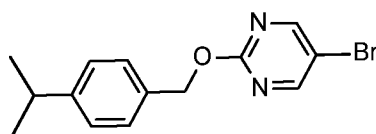
BisPin (0.94 g, 3.7 mmol) and KOAc (0.61 g, 6.2 mmol) were added to a sol. of **139** (1g, 3.1 mmol) in 1,4-dioxane (10 mL). The sol. was purged with N₂ and charged with PdCl₂(dppf) (0.11 g, 0.15 mmol). The resulting sol. was purged again with N₂ and
20 stirred at 80°C for 17h. After dilution in EtOAc, the crude material was washed with water and brine. The organic layer was dried over MgSO₄ 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
25 50%) which was used like this in the next step.

d- Synthesis of Co. 74 :



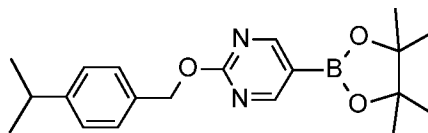
In a microwave vial, a mixture of **4** (0.72 g, 2.5 mmol), **140** (1.1 g, 3.0 mmol), K₃PO₄ (2.1 g, 10 mmol) in 1,4-dioxane (11 mL) and H₂O (4 mL) was carefully purged with N₂. PdCl₂(dppf) (200 mg, 0.25 mmol) was added and the r.m. was purged again with N₂. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over MgSO₄, 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 NH₄OH/DCM/MeOH 0.2/98/2 to NH₄OH/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 Et₂O. 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:

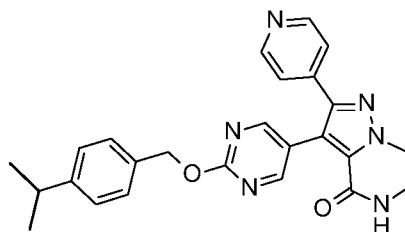
A sol. of **6** (4.66 g, 31.0 mmol) in dry THF (200 mL) was treated with NaH 60% (1.29 g, 32.3 mmol) and stirred at r.t. for 10 min. 5-bromo-2-chloropyrimidine (5.00 g, 25.8 mmol) was then added and the r.m. was stirred at r.t. for 17 h. The r.m. was then heated at 70°C for 5 extra h and concentrated *in vacuo*. The concentrate was taken up with EtOAc, washed with water and brine, dried over MgSO₄ 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 N₂. PdCl₂(dppf) (800 mg, 0.977 mmol) was added to the mixture and the mixture was purged with N₂ 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 MgSO₄ and evaporated *in vacuo* to give a black residue. The residue was filtered through a short pad of silica gel (eluent: EtOAc

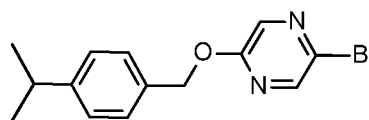
100%) and the filtrate was evaporated *in vacuo* to give a brown solid. This solid was purified by prep. LC (irregular SiOH 15-40 μ m, 80 g, Grace, dry loading, mobile phase: heptane 80% to EtOAc 20%). The pure fractions were collected and solvent was evaporated to give 2.20g of Int. **142**, white solid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



5 **c- Synthesis of Co. 75:**

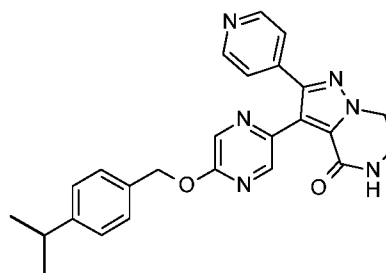
A sol. of **4** (400 mg, 1.37 mmol) and **142** (967 mg, 2.73 mmol) in 1,4-dioxane (8 mL) and H₂O (4 mL) was treated with K₃PO₄ (869 mg, 4.09 mmol) and purged with N₂. PdCl₂(dppf) (112 mg, 137 μ mol) was then added and the r.m. was carefully purged with N₂. The mixture was heated at 120°C using one single 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 MgSO₄ and evaporated *in vacuo* to give a black residue which was purified by prep. LC (irregular SiOH 15-40 μ m, 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 Et₂O. 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 Et₂O, 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:

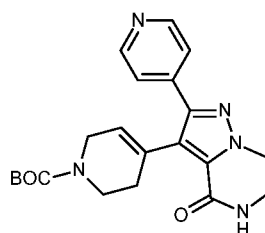
Under N₂, a sol. of 2,5-dibromopyrazine (1.97 g, 8.28 mmol) and **6** (1.57 mL, 9.94 mmol) in dry DMF (45 mL) was treated with NaH 60% (397 mg, 9.94 mmol) and stirred at r.t. for 18 h. The r.m. was poured in EtOAc and water, and the organic layer was washed with brine (twice), dried over MgSO₄, filtered and evaporated *in vacuo* to give 2.83 g, brown oil. This oil was purified by prep. LC (irregular SiOH 15-40 μ m, 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:

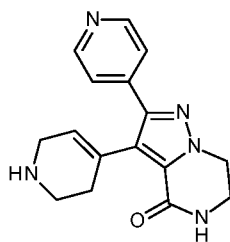
A mixture of **60** (304 mg, 0.894 mmol), **143** (549 mg, 1.79 mmol), K₃PO₄ (569 mg, 2.68 mmol) in THF (6 mL) and H₂O (3 mL) was carefully purged with N₂. Precatalyst (70 mg, 89.4 μmol) was added and the r.m. was purged again with N₂. The r.m. was stirred at r.t. for 66h, and then a sol. of DCM/MeOH 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% CO₂, 15% MeOH (0.3% iPrNH₂)). 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 Et₂O, 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



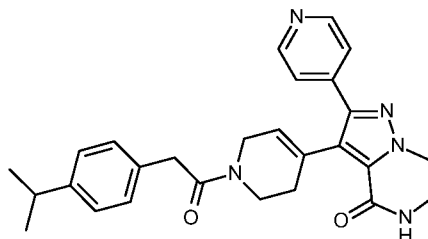
a- Synthesis of Int. 153:

4 (1.9 g, 6.5 mmol), N-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (2 g, 6.5 mmol), Na₂CO₃ (13 mL, 13 mmol) in 1,4-dioxane (21 mL) were degassed with N₂. PdCl₂(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 MgSO₄, 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/CH₃OH/NH₄OH). The pure fractions were collected and evaporated until dryness to give 2.3g of Int. **153** (89%).



b- Synthesis of Int. 154:

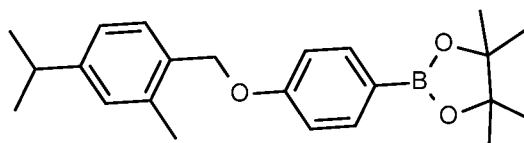
HCl 3N (9.7 mL, 29.08 mmol) was added to **153** (2.3 g, 5.8 mmol) in ACN (100 mL). The mixture was heated for 30min at 80°C and poured into water, basified with K₂CO₃ and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and evaporated until dryness to give 0.62 g of Int. **154** (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), Et₃N (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 MgSO₄, 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%, NH₄OH). The fractions were collected and evaporated until dryness to give 315mg which was crystallized from Et₂O, filtered and dried to give 246 mg of **Co. 77** (41%).

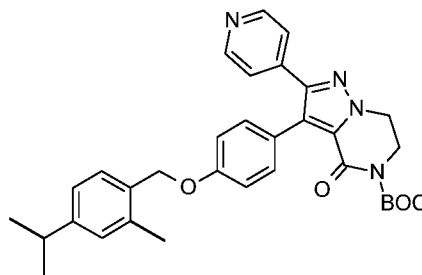
Example A80: Preparation of Co. 78a and Co. 78



a- Synthesis of Int. 155:

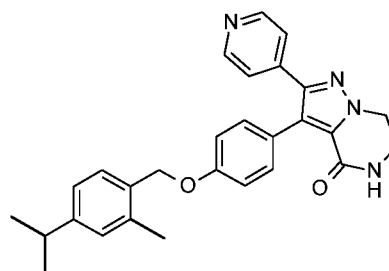
To a sol. of 2-methyl-4-(1-methylethyl)-benzenemethanol (0.97 g, 5.9 mmol), **7** (1.3 g, 5.9 mmol), PPh₃ (1.7 g, 6.5 mmol) in dry DCM (40 mL) was added DBAD (1.5 g, 6.5 mmol) and the r.m. was stirred at r.t. for 2 days. The mixture was poured into water and the organic layer was extracted, dried over MgSO₄, filtered and evaporated until dryness to give 6 g. The residue was triturated 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:

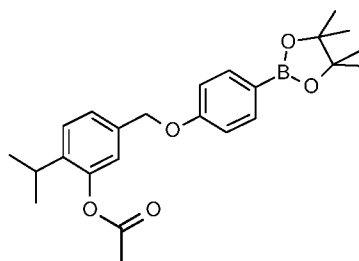
25 (0.97 g, 2.5 mmol), **155** (0.94 g, 2.5mmol), K₃PO₄ (2.1 g, 9.8 mmol) in 1,4-dioxane (13 mL) and H₂O (3.5 mL) were purged with N₂ for 10min. Then, PdCl₂(dppf) (0.2 g, 0.25 mmol) was added and purged with N₂ for 10min. The mixture was heated to 75°C for 15h, cooled to r.t., poured into water and K₂CO₃ and extracted with EtOAc. The organic layer was dried over MgSO₄, 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% NH₄OH). 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 K₂CO₃ and EtOAc was added. The insoluble was filtered and the organic layer was separated, dried over MgSO₄, 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% NH₄OH). The pure fractions were collected and evaporated until dryness to give 153 mg which was crystallized from Et₂O, filtered and dried to give 136 mg of **Co. 78** (33%). m.p.: 247°C (dsc).

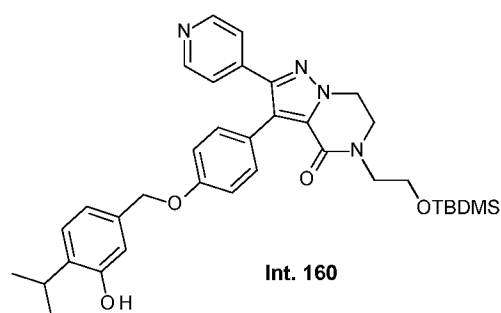
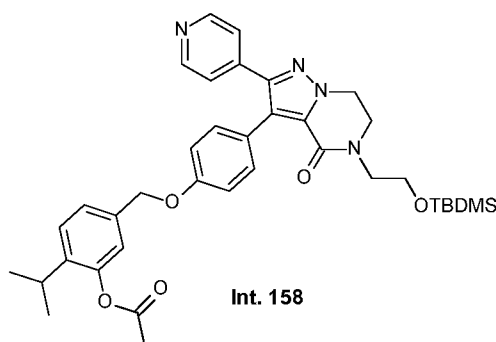
Example A81: Preparation of Co. 79



a- Synthesis of Int. 157:

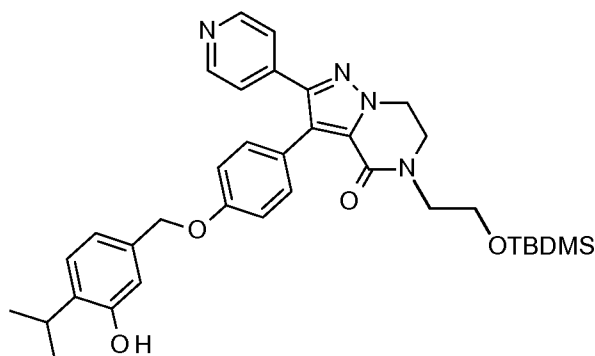
To a suspension of 3-(acetoxymethyl)-4-(1-methylethyl)benzenemethanol (498 mg, 2.39 mmol), **7** (632 mg, 2.87 mmol), PPh₃ supp. (661 mg, 2.87 mmol) in dry DCM (10 mL) was added DBAD (897 mg, 2.87 mmol) and the r.m. was stirred at r.t. for 18 h. The insoluble was filtered through Celite®, washed with 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:

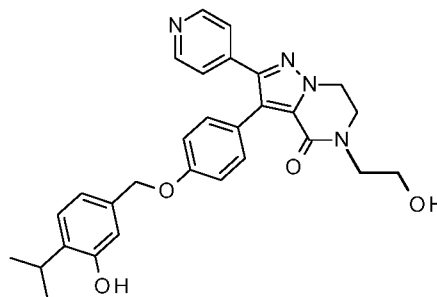


In a microwave vial, a mixture of **28** (0.413 g, 0.92 mmol), **157** (0.413 g, 1 mmol), K₃PO₄ (0.78 g, 3.7 mmol) in 1,4-dioxane (4 mL) and H₂O (1.43 mL) was carefully purged with N₂. PdCl₂(dppf) (75 mg, 0.09 mmol) was added and the r.m. was purged again with N₂. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over MgSO₄, 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/NH₄OH 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:



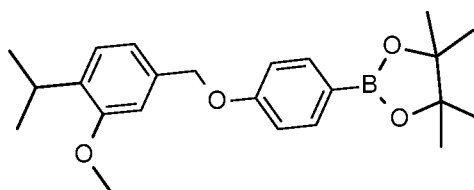
To a sol. of **158** (270 mg, 0.41 mmol) in MeOH (4 mL) was added KOH (69 mg, 1.24 mmol) and the mixture was heated at 50°C for 3h. Water and DCM were added and the organic layer was separated, dried, filtered and concentrated until dryness to give 235 mg of Int. **160** as a (crude) mixture which was 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 μ m, 12g GraceResolv™, mobile phase gradient: from DCM 100% to DCM/MeOH/NH₄OH 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).

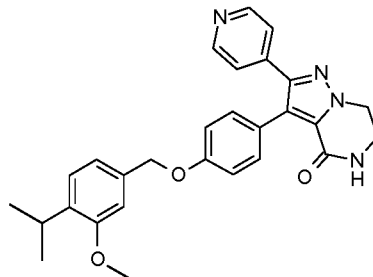
Example A82: Preparation of Co. 80



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 PPh₃ 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

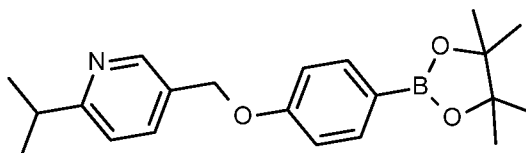
was purified by prep. LC on (Irregular SiOH 15-40µm 30g Merck, mobile phase: 90/10 Heptane/EtOAc). The pure fractions were collected and evaporated until dryness to give 411mg of Int. **161** (67%).



b- Synthesis of Co. 80:

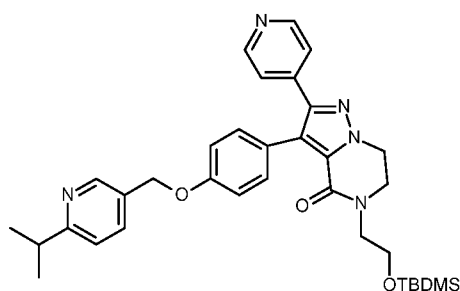
- 5 In a microwave vial, a mixture of **4** (0.25 g, 0.853 mmol), **161** (0.391 g, 1.023 mmol), K₃PO₄ (0.76 g, 3.58 mmol) in 1,4-dioxane (4 mL) and H₂O (1.33 mL) was carefully purged with N₂. PCy₃ (50 mg, 0.179 mmol) and Pd(OAc)₂ (20 mg, 0.089 mmol) were added and the r.m. was purged again with N₂. The r.m. was stirred for 16 h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic
- 10 phase was dried over MgSO₄, 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% NH₄OH), 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
- 15 (dsc).

Example A83: Preparation of Co. 81



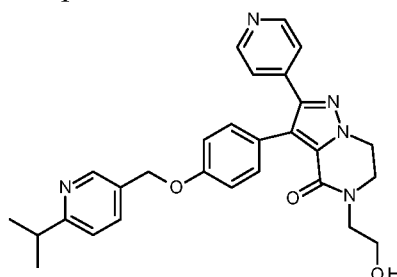
a- Synthesis of Int. 162:

- A mixture of **7** (2.20 g, 10.0 mmol), 6-(1-methylethyl)-3-pyridinemethanol (1.97 g, 13.0 mmol) and PPh₃ (3.41 g, 13.0 mmol) in dry THF (30 mL) was treated with DBAD
- 20 (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 MgSO₄ 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
- 25 solvent evaporated until dryness to give 4.08 g of Int. **162**, colorless oil (Quant.).



b- Synthesis of Int. 163:

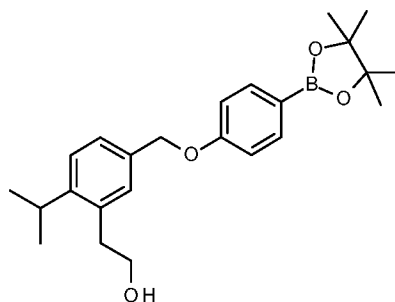
A sol. of **28** (800 mg, 1.77 mmol) and **162** (1.25 g, 3.54 mmol) in 1,4-dioxane (11 mL) and H₂O (5.5 mL) was treated with K₃PO₄ (1.13 g, 5.32 mmol) and purged with N₂. PdCl₂(dppf) (145 mg, 0.177 mmol) was then added and the r.m. was carefully purged with N₂. The mixture was heated at 120°C using 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 MgSO₄ 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:

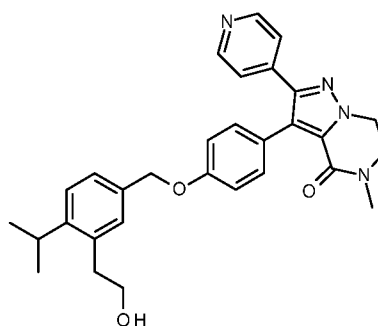
A sol. of **163** (1.30 g, 2.18 mmol) in THF (40 mL) was treated with TBAF (1.74 mL, 1.74 mmol) and stirred for 2h at r.t. The r.m. was poured in H₂O and extracted 2x with DCM. The organic layers were combined, dried over MgSO₄ and evaporated *in vacuo* to afford yellow oil. The oil was purified by prep. 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 N₂, and PdCl₂(dppf) (239 mg, 292 μmol) was added. The r.m. was purged again with N₂, 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 MgSO₄ 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%).

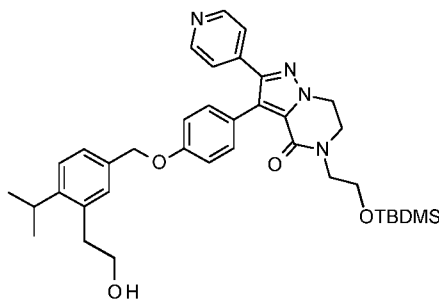


b- Synthesis of Co. 82:

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 H₂O (6 mL) was purged with N₂. PdCl₂(dppf) (160 mg; 195 μmol) was then added. The mixture was purged again with N₂ 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 MgSO₄ 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%

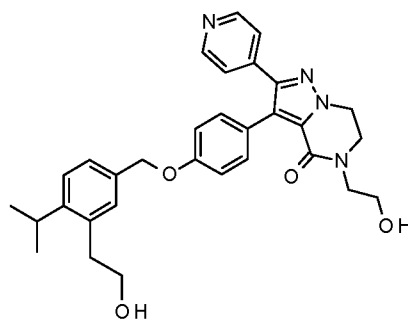
(NH_4HCO_3 0.5% aq. sol.), 20% ACN to 100% ACN). The fractions containing the pure product were combined and evaporated *in vacuo* to give 340 mg, a white foam. The residue was finally dissolved in a small amount of MeOH and triturated while Et_2O was added. The white solid was filtered on a glass frit 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 . $\text{PdCl}_2(\text{dppf})$ (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.

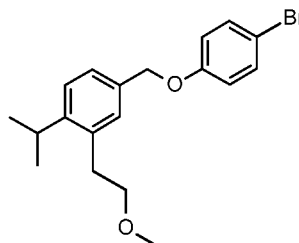


b- Synthesis of Co. 83:

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

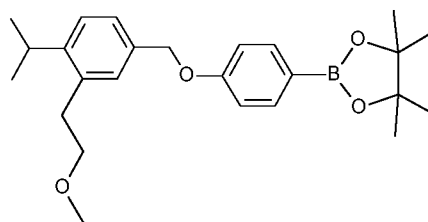
MeOH (1mL). The solvent was allowed to slowly evaporate, yielding 246 mg of **Co. 83**, crystalline white solid (32%). m.p.: 176 °C (DSC).

Example A86: Preparation of Co. 84



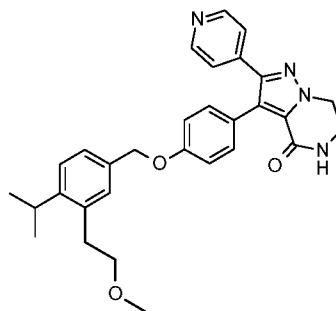
5 **a- Synthesis of Int. 166:**

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 N₂. 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 MgSO₄ 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%).



10 **b- Synthesis of Int. 167:**

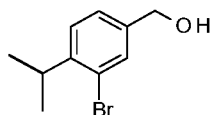
In a microwave vial, a mixture of **166** (0.25 g, 0.69 mmol), KOAc (0.20 g, 2.1 mmol), BisPin (0.26 g, 1.0 mmol) in DME (2 mL) was carefully purged with N₂. PdCl₂(dppf) (56 mg, 69 μmol) was added and the r.m. was purged again with N₂. The r.m. was stirred overnight at 100°C. The r.m. was diluted with EtOAc and washed with water (1x) and with brine (3x). The organic phase was dried over MgSO₄, 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:

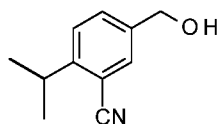
In a microwave vial, a mixture of **4** (167 mg, 0.57 mmol), **167** (0.28 g, 0.68 mmol), K_3PO_4 (0.36 g, 1.7 mmol) in 1,4-dioxane (2.5 mL) and H_2O (0.89 mL) was carefully purged with N_2 . $PdCl_2(dppf)$ (47 mg, 57 μ mol) was added and the r.m. was purged again with N_2 . The r.m. was heated at 80°C 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 μ m, 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:

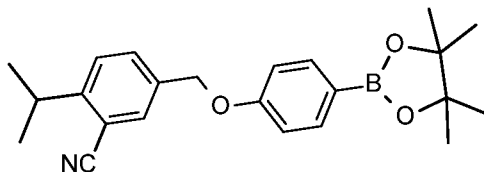
LAH (5.52g, 145mmol) was added to a stirred sol. of methyl-3-bromo-4-isopropylbenzoate (34.0g, 132mmol) in THF (600mL) at -20°C. The r.m. was stirred at -20°C for 2h. The r.m. was quenched with H_2O (5.26mL), NaOH 3N (5.52mL) and H_2O (16mL). The cake was filtered and washed (DCM). The filtrate was evaporated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



b- Synthesis of Int. 169:

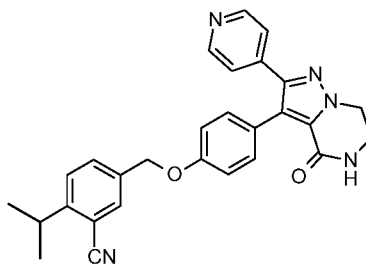
$Pd(PPh_3)_4$ (1.6g, 1.4mmol) was added to a mixture of **168** (3.2g, 14mmol) and $Zn(CN)_2$ (1.7g, 14mmol) in DMF (10mL) in a sealed tube. The mixture was heated at 120°C for 60 min using one single mode microwave (Biotage) with a power output ranging from 0 to 400 W. The r.m. was cooled to r.t., poured 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 15-40 μ m 50g Merck, mobile phase: 70/30 heptane/EtOAc). The pure fraction was collected and evaporated to give 1.4g of Int. **169** (57%).



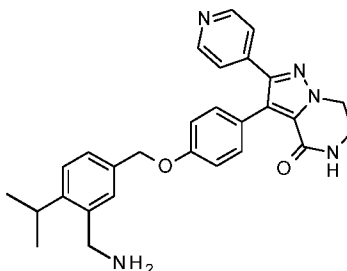
c- Synthesis of Int. 170:

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), PPh₃ 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 30 μ m 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:

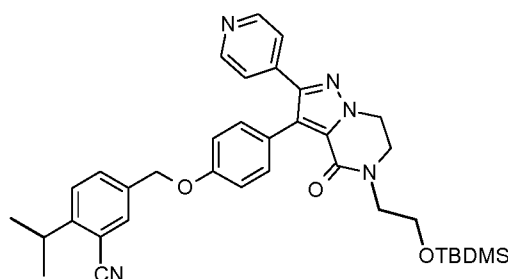
A mixture of **4** (867 mg, 2.96 mmol), **170** (0.93 g, 2.5 mmol), K₃PO₄ (1.57 g, 7.4 mmol) in 1,4-dioxane (11 mL) and H₂O (4 mL) was carefully purged with N₂. PdCl₂(dppf) (201.7 mg, 0.25 mmol) were added and the r.m. was purged again with N₂. The r.m. was stirred for 8h at 80°C in a sealed tube. Water and DCM were added, the mixture was extracted, the organic layer was separated, dried over MgSO₄, filtered and evaporated. The residue was purified by prep. LC on (irregular 15-40 μ m 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 Et₂O, the precipitate was filtered off and dried to give 453mg of Co. **85** (40%). m.p.: 240°C (dsc).



e- Synthesis of Co. 86:

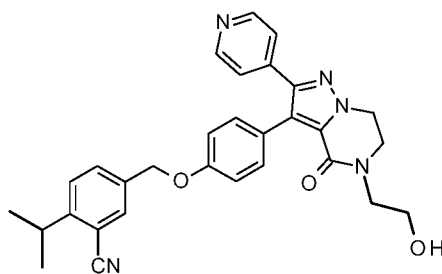
- A solution of **Co. 85** (280 mg, 0.604 mmol), MeOH/NH₃ (10 mL), Ni Raney (300 mg), THF (5 mL), DCM (5 mL) was hydrogenated under a 3 bars pressure at r.t. overnight. The catalyst was filtered over a Celite® pad, the filtrate was evaporated and the residue was purified by prep. LC (irregular SiOH 30 µm, 25 g, Interchim, Mobile phase gradient: DCM/MeOH/NH₄OH from 96/4/0.1 to 92/8/0.1). The pure fractions were put together and evaporated. The residue was taken up in Et₂O, filtrated and dried to give 15 mg of **Co. 86** (5%).

Example A88: Preparation of Co. 87



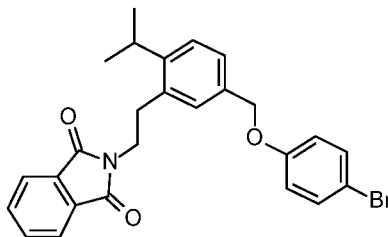
a- Synthesis of Int. 171:

- In a microwave vial, a mixture of **28** (0.5 g, 1.1 mmol), **170** (0.5 g, 1.3 mmol), K₃PO₄ (0.94 g, 4.4 mmol) in 1,4-dioxane (4.9 mL) and H₂O (1.7 mL) was carefully purged with N₂. PdCl₂(dppf) (90 mg, 0.11 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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/NH₄OH 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%).

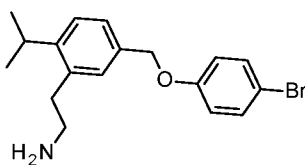


b- Synthesis of Co. 87:

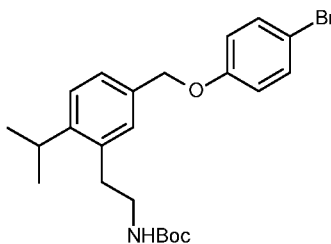
- TBAF (1.4 mL, 1.4 mmol) was added dropwise to a sol. of **171** (0.72 g, 1.2 mmol) in THF (11 mL) at r.t.. The mixture was stirred overnight at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 µm, 25 g GraceResolv™, mobile phase: DCM/MeOH/NH₄OH 98/2/0.1). The pure fractions were collected and the solvent was evaporated until dryness to give 0.38 g which was triturated in Et₂O. 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:**

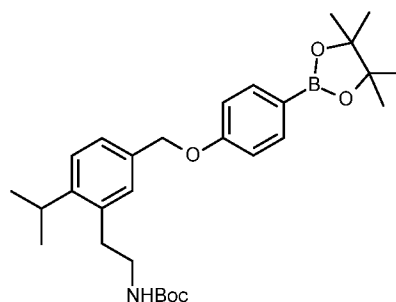
DBAD (99 mg, 0.43 mmol) was added portionwise to a sol. of **55** (100 mg, 0.29 mmol), phthalimide (63 mg, 0.43 mmol), diphenylphosphinopolystyrene (134 mg, 0.43 mmol) in THF (3.3 mL) at r.t. under N₂. The mixture was stirred for 3 days. The mixture was filtrated through a pad of Celite®, washed with 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).

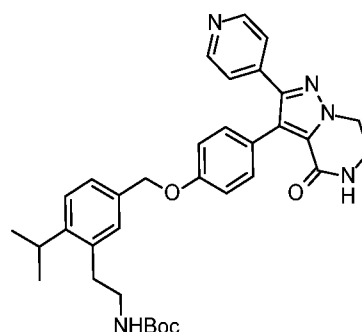
**c- Synthesis of Int. 174:**

Boc₂O (203 mg, 0.93 mmol) and Et₃N (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 NaHCO₃, dried over MgSO₄, filtered and evaporated to give 300 mg of Int. **174**, colorless oil (79%).



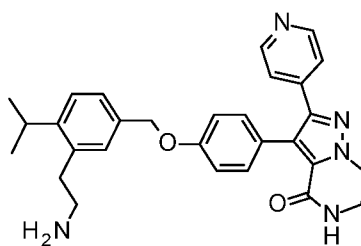
d- Synthesis of Int. 175:

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 N₂. PdCl₂(dppf) (55 mg, 67 μmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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

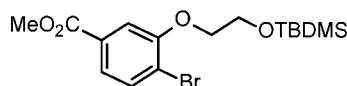
In a microwave vial, a mixture of **4** (164 mg, 0.56 mmol), **175** (333 mg, 0.67 mmol), K₃PO₄ (357 mg, 1.68 mmol) in 1,4-dioxane (2.5 mL) and H₂O (0.8 mL) was carefully purged with N₂. PdCl₂(dppf) (46 mg, 56 μmol) was added and the r.m. was purged again with N₂. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over MgSO₄, 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/NH₄OH 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:

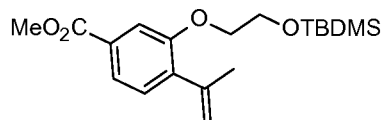
A solution of **Co. 88a** (220 mg, 0.38 mmol), HCl 3N (0.63 mL, 1.9 mmol), in ACN (6.7 mL) was stirred at 80°C for 2h. The mixture was concentrated, and NaHCO₃ sat aq was added and the mixture was stirred at r.t. 15 min. The mixture was extracted with DCM, dried, filtered and concentrated to give 213 mg of a solid. This solid was triturated in Et₂O, filtrated and dried to give 127 mg of **Co. 88**, beige powder (70%). m.p.: 181°C (dsc).

Example A90: Preparation of Co. 89



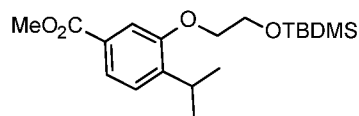
a- Synthesis of Int. 177:

A solution of Methyl 4-bromo-3-hydroxybenzoate (2.5 g, 10.8 mmol), (2-bromoethoxy)-tert-butyldimethylsilane (2.5 mL, 11.9 mmol), K₂CO₃ (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 MgSO₄, 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%).



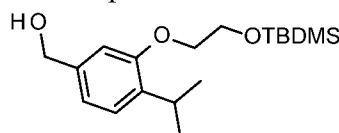
b- Synthesis of Int. 178:

A solution of **177** (3.2 g, 8.2 mmol), Pd(tBu₃P)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 MgSO₄, 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%).



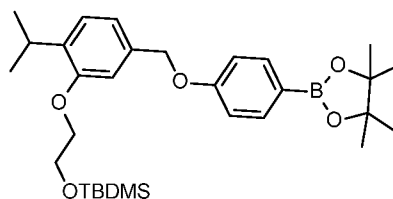
c- Synthesis of Int. 179:

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 MgSO₄, filtered and dried to give 2.2 g of Int. **179** (87%) used as such for the next step.



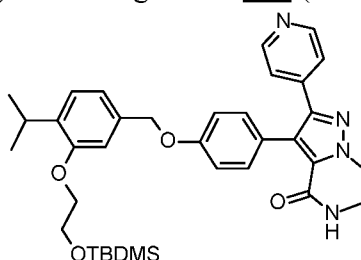
d- Synthesis of Int. 180:

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 MgSO₄, filtered and evaporated until dryness to give 2.4g of Int. **180** (quant.).



e- Synthesis of Int. 181:

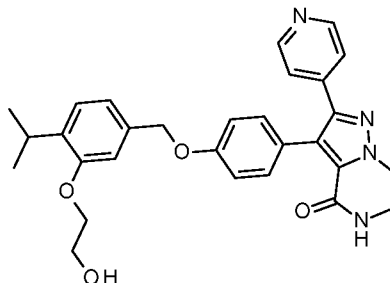
DBAD (0.7 g, 2.9 mmol) was added portionwise to **180** (640 mg, 2 mmol), **7** (520 mg, 2.4 mmol), PPh₃ supp. (0.9 g, 3 mmol) in THF (10 mL). The mixture was stirred at r.t. overnight. PPh₃ supp. was filtered and the filtrate was evaporated. The residue was purified by prep. LC on (Stability Silica 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), K₃PO₄ (1.4 g, 6.5 mmol) in 1,4-dioxane (10 mL) and H₂O (3 mL) was carefully purged with N₂. PdCl₂(dppf) (179 mg, 218 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, filtered on a pad of Celite® and evaporated *in vacuo*. The residue was purified

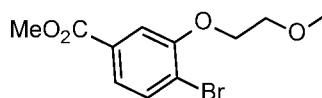
by prep. LC (Stationary phase: irregular SiOH 15-40 μ m 300g Merck, mobile phase: 43% Heptane, 7% MeOH, 50% EtOAc). The pure fractions were collected and evaporated till dryness to give 640 mg of Int. **182** (48%).



g- Synthesis of Co. 89:

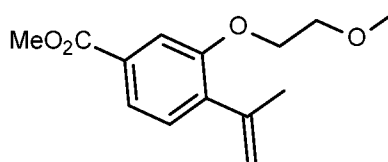
- 5 TBAF (0.45 mL, 0.45 mmol) was added dropwise to a sol. of **182** (230 mg, 0.375 mmol) in THF (5 mL) at r.t.. The mixture was stirred 90 min at r.t. The mixture was poured into water, extracted with DCM. The organic layer was dried over MgSO₄, filtered and evaporated until dryness. The residue was purified by prep. LC (Regular SiOH, 30 μ m, 25 g grace, mobile phase gradient: DCM/MeOH/NH₄OH from 97/3/0.1
- 10 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 5 μ m 250*20mm, mobile phase: 50% CO₂, 50% MeOH). The pure fractions were collected and evaporated till dryness to give 105 mg. The product was crystallized from Et₂O. The solid was filtered off and dried to give 91 mg of **Co. 89** (49%).

15 **Example A91: Preparation of Co. 90**



a- Synthesis of Int. 183:

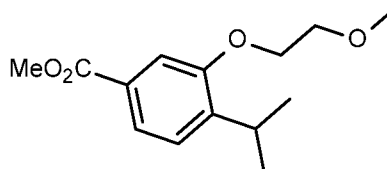
- Methyl 4-bromo-3-hydroxybenzoate (2g, 8.6mmol), 2-bromo ethyl methylether (0.9mL, 9.5mmol), K₂CO₃ (1.8g, 13mmol) in ACN (40ml) at 80°C overnight. Water and EtOAc were added, the mixture was extracted, the organic layer was separated,
- 20 dried over MgSO₄, filtered and evaporated. The residue was purified by prep. LC on (Irregular SiOH 20-45 μ m 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:

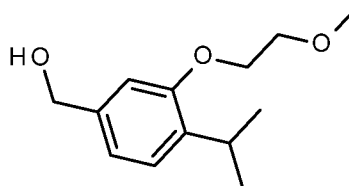
- 25 A solution of **183** (1.9 g, 6.6 mmol), CsF (2.2 g, 14.4 mmol), 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 g, 7.2 mmol), Pd(tBu₃P)₂ (168 mg, 0.3 mmol) in

- 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 MgSO₄, 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
- 5 fractions were collected and the solvent was evaporated until dryness to give 560 mg of Int. **184** (34%).



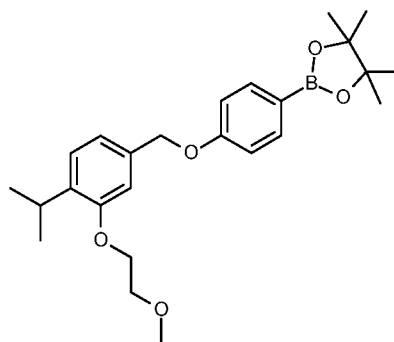
c- Synthesis of Int. 185:

- 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.
- 10 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:

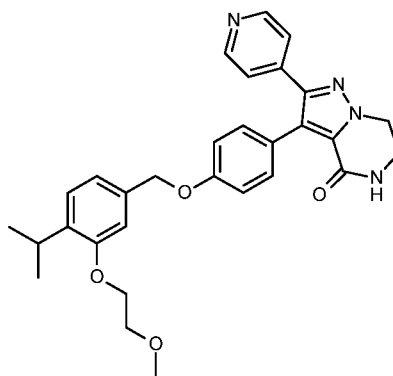
- LAH (106 mg, 2.8 mmol) was added carefully at 5°C to a sol. of **185** (590 mg, 2.3 mmol) in THF (10 mL). The mixture was stirred at r.t. for 1h. Water was carefully added at 5°C and EtOAc was added, the mixture was extracted, the organic layer was separated, dried over MgSO₄, filtered and evaporated until dryness to give 450 mg of Int. **186** (86%).



e- Synthesis of Int. 187:

- 20 DBAD (692 mg, 3 mmol) was added portionwise to **186** (450 mg, 2 mmol), **7** (529 mg, 2.4 mmol), PPh₃ supp. (0.94 g, 3 mmol) in THF (10 mL). The mixture was stirred at r.t. overnight. PPh₃ supp. was filtered and the filtrate was evaporated. The residue was

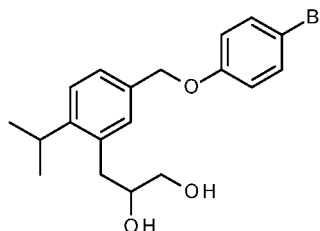
- purified by prep. LC on (Stability Silica 5 μ m 150x30.0mm, mobile phase gradient: from 85% heptane, 15% EtOAc to 100% EtOAc). The pure fractions were collected and solvent was evaporated until dryness to give 350 mg of a first residue and 300 mg of second residue. The last residue was purified by prep. LC on (Stability Silica 5 μ m 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), K₃PO₄ (0.7 g, 3.3 mmol) in 1,4-dioxane (5 mL) and H₂O (1.2 mL) was carefully purged with N₂. PCy₃ (48 mg, 0.17 mmol) and Pd(OAc)₂ (19 mg, 0.09 mmol) were added and the r.m. was purged again with N₂. 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 MgSO₄, filtered and evaporated until dryness to give 530 mg. The residue was purified by prep. LC on (irregular 15-40 μ m 30g Merck, mobile phase: 0.1% NH₄OH, 98% DCM, 2% MeOH). The pure fractions were collected and the solvent evaporated until dryness to give 130 mg which was taken up in Et₂O. The solid was filtered off and dried to give 90 mg of **Co. 90** (21%). m.p.: 209°C (dsc).

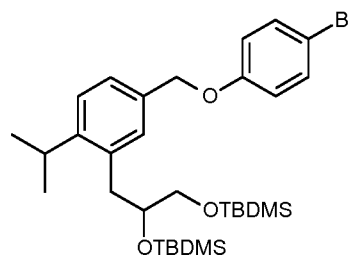
- Example A92: Preparation of Co. 91**



a- Synthesis of Int. 188:

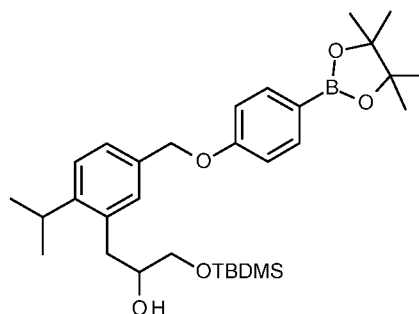
- Under N₂ atmosphere, to a sol. of **54** (0.75 g, 2.2 mmol) in acetone (16 mL) and H₂O (2 mL), was successively added 4-methylmorpholine-4-oxide (305 mg, 2.6 mmol) and OsO₄ 2.5% in butanol (1.5 mL, 0.11 mmol). The mixture was stirred at r.t. overnight.
- An aq. sol. of Na₂SO₃ sol. (7.5 mL, 10%) was 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 MgSO₄ 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%).



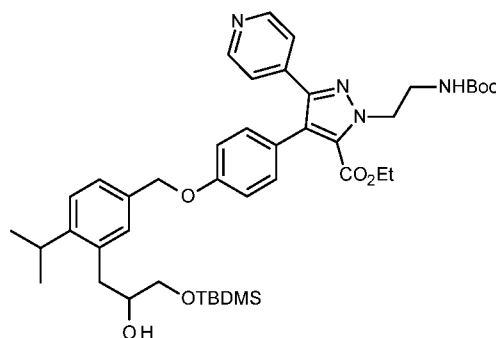
b- Synthesis of Int. 189:

- Under N₂, 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 MgSO₄, filtered and evaporated to dryness to give 1.29 g of Int. **189**, colorless oil (99%).



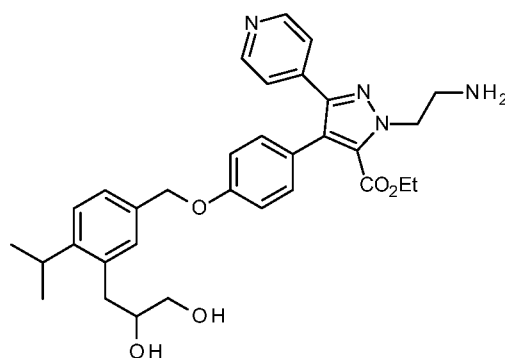
c- Synthesis of Int. 190:

- 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 N₂. PdCl₂(dppf) (0.18 g, 0.21 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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%).



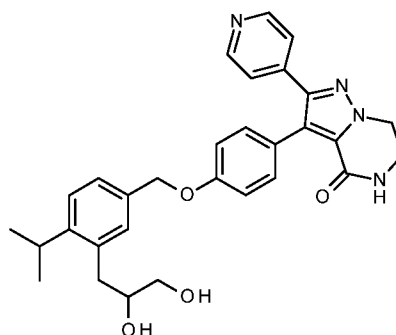
d- Synthesis of Int. 191:

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 μ mol) was added and the r.m. was purged again with N_2 . The r.m. was heated at $80^\circ C$ 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 μ m, 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:

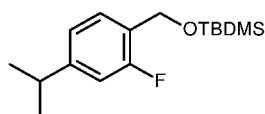
A solution of **191** (0.50 g, 0.65 mmol), HCl 3N (1.1 mL, 3.2 mmol), in ACN (11 mL) was stirred at $80^\circ C$ for 2h. The mixture was concentrated, and $NaHCO_3$ sat. aq. (25mL) was added and the mixture was extracted with DCM, dried and evaporated until dryness to give 0.36 g of Int. **192** (quant.). This residue was used like this in the next step.



f- Synthesis of Co. 91:

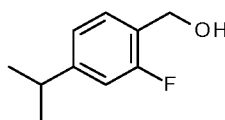
To a sol. of **192** (360 mg, 0.64 mmol) in MeOH (18 mL) was added Cs₂CO₃ (1.1 g, 3.2 mmol) and the mixture was stirred at r.t. overnight. The mixture was concentrated and taken in DCM and washed once with brine, dried of MgSO₄ and concentrated till dryness to give 520 mg, white solid. The crude product was purified by prep. LC (irregular SiOH 30 μm, 12 g graceResolv™, mobile phase gradient from DCM/MeOH/NH₄OH 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%NH₄OH), 50% Heptane to 75% EtOAc, 25% MeOH(+0.2% NH₄OH)). 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: CO₂, MeOH (0.3% iPrNH₂)) followed by prep. LC (Stationary phase: irregular 15-40μm 30g Merck, mobile phase: 0.5% NH₄OH, 95% DCM, 5% MeOH). 108 mg of white solid was collected and it was washed with Et₂O. The white solid was filtered and dried to give 90mg of **Co. 91** (27%).

Example A93: Preparation of Co. 92

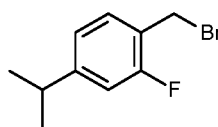


a- Synthesis of Int. 193:

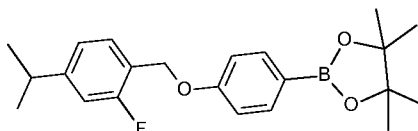
Under N₂, a sol. of [(4-bromo-2-fluorobenzyl)oxy](tert-butyl)dimethylsilane (6.0 g, 18.8 mmol) in dry THF (50 mL) was treated with isopropylmagnesium chloride 2M in THF (47.0 mL, 94.0 mmol) at r.t. The r.m. was then purged with N₂ and PdCl₂(dppf) (1.54 g, 1.88 mmol) was added. The r.m. was purged again with N₂ and stirred at 50°C for 5h. After being quenched with water, the r.m. was diluted with Et₂O, washed with water (1x) and brine (2x). The organic layer was dried over MgSO₄ 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%, Et₂O 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:**

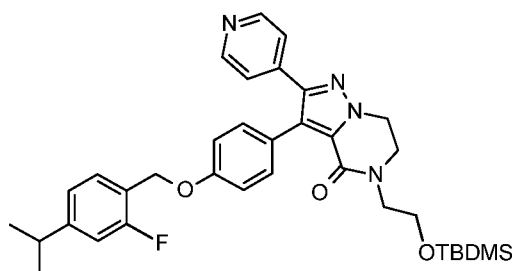
- A sol. of **193** (5.0 g, 17.7 mmol) in THF (150 mL) was cooled to 0°C and treated with TBAF (21.2 mL, 21.2 mmol). The r.m. was stirred for 90 min at 0°C, concentrated and poured in Et₂O. The organic layer was washed with water (3x 50mL), dried over MgSO₄ and evaporated *in vacuo* to afford a yellow 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:**

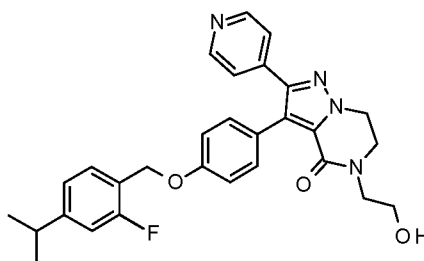
- To a sol. of **194** (1.12 g, 6.66 mmol) in dry Et₂O (19 mL) at 0 °C was added dropwise Phosphorus tribromide (0.626 mL, 6.66 mmol). The ice bath was removed and the reaction stirred for 3h. Then, water was carefully added to the mixture, and the layers were separated. The organic layer was washed with brine, dried over MgSO₄, 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 K₂CO₃ (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 MgSO₄, 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:**

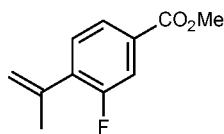
PdCl₂(dppf) (0.141 g, 0.172 mmol) was added to a stirred sol. of **28** (0.778 g, 1.72 mmol), **196** (1.33 g, 3.45 mmol) and K₃PO₄ (1.10 g, 5.17 mmol) in 1,4-dioxane (10.6 mL) and H₂O (5.3 mL) at r.t., under N₂. The resulting mixture was stirred at 120 °C using one single mode microwave (Biotage Initiator 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 MgSO₄, 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%).



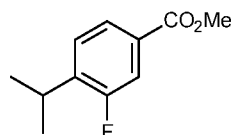
f- Synthesis of Co. 92:

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 MgSO₄, 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% CO₂, 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).

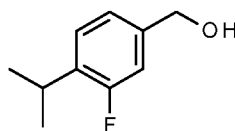
Example A94: Preparation of Co. 93

**a- Synthesis of Int. 198:**

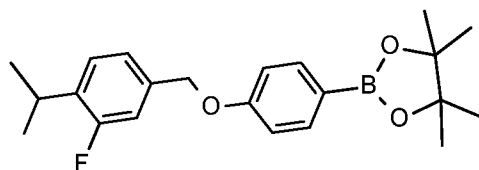
A sol. of methyl 4-bromo-3-fluorobenzoate (= 4-Bromo-3-fluorobenzoic acid methyl ester) (1.22 g, 5.24 mmol) and potassium isopropenyltrifluoroborate (1.60 g, 10.5 mmol) in isopropanol (14 mL) was treated with Et₃N (2.92 mL, 21.0 mmol) and purged with N₂. PdCl₂(dppf) (215 mg, 262 μmol) was then added and the r.m. was carefully purged with N₂. 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 MgSO₄ 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: Et₂O). The filtrate was evaporated until dryness to afford 2.79 g of Int. **199**, yellow oil (61%).

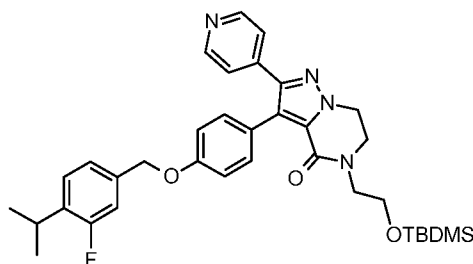
**c- Synthesis of Int. 200:**

A sol. of **199** (2.69 g, 13.1 mmol) in Et₂O (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:**

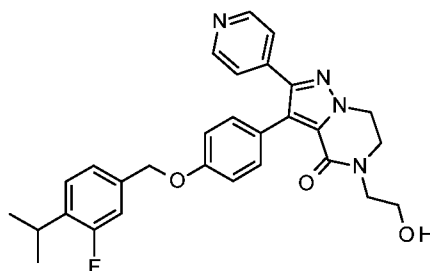
A sol. of **7** (1.36 g, 6.19 mmol) and **200** (1.25 g, 7.43 mmol) in dry THF (20 mL) was treated with PPh₃ (1.95 g, 7.43 mmol) and DBAD (1.71 g, 7.43 mmol). The r.m. was stirred at r.t. for 17 h then concentrated *in vacuo*. The concentrate was poured in EtOAc, washed with water, dried over MgSO₄ and evaporated *in vacuo* to give an oil.

- 5 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:

- 10 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 H₂O (6 mL) was treated with K₃PO₄ (1.69 g, 7.98 mmol) and purged with N₂. PdCl₂(dppf) (218 mg, 266 μmol) was then added and the r.m. was carefully purged with N₂. 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
- 15 time]. The crude mixture was poured in DCM and water. The organic layer was separated, dried over MgSO₄ 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
- 20 (94%).



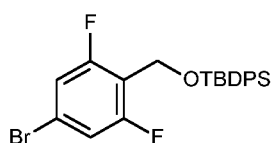
f- Synthesis of Co. 93:

- 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
- 25 with brine, dried over MgSO₄, 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

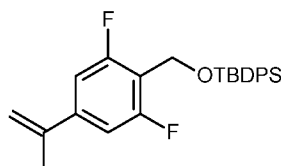
- collected and evaporated *in vacuo* to give 572 mg, sticky oil which was crystallized from EtOH, filtered and dried to give 224 mg, white solid. The filtrate and the solid were combined and evaporated *in vacuo* to give 417 mg of a residue. This residue was purified by achiral SFC (Stationary phase: Chiralpak IA 5 μ m 250*20mm, mobile phase: 70% CO₂, 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

10 **a- Synthesis of Int. 203:**

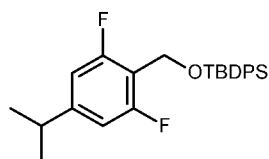


- Tert-butyldiphenylchlorosilane (4.3 mL, 17 mmol) was added to a sol. of 4-bromo-2,6-difluorobenzyl alcohol (2.5 g, 11 mmol) and imidazole (2.3 g, 33 mmol) in DCM (106 mL) at r.t. The mixture was stirred at r.t. overnight. The mixture was quenched with water and extracted with DCM. The organic layer was decanted, washed with water then brine, dried over MgSO₄, filtered and evaporated to dryness to give 7.5 g, colorless oil. This oil was purified by prep. LC (irregular SiOH 30 μ m 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.



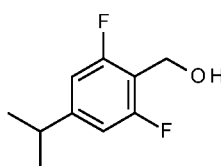
20 **b- Synthesis of Int. 204:**

- 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 N₂. Pd(tBu₃P)₂ (111 mg, 0.22 mmol) was added and the mixture was purged again with N₂ and heated at 80°C overnight. Water and EtOAc were added, the organic layer was separated, washed with brine, dried over MgSO₄, filtered on Celite® and evaporated. The residue was purified by prep. LC (Regular SiOH, 30 μ m, 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%).



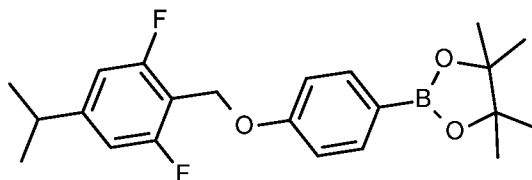
c- Synthesis of Int. 205:

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 MgSO₄, filtered and evaporated until dryness to give 1.7g of Int. **205**, colorless oil (94%).



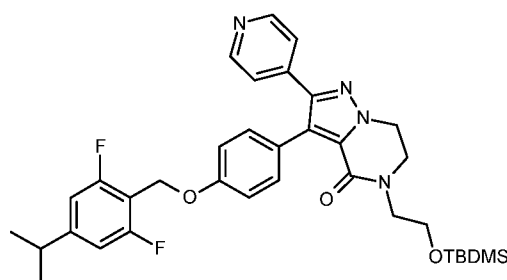
d- Synthesis of Int. 206:

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.



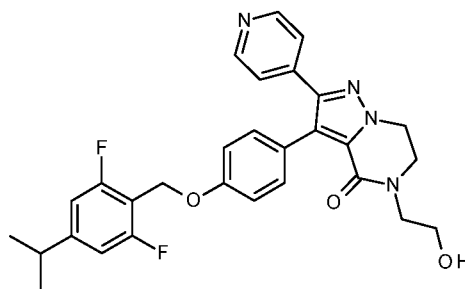
e- Synthesis of Int. 207:

Under N₂, 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), PPh₃ supp. (1.9 g, 6.2 mmol) in dry THF (30 mL). The r.m. was stirred at r.t. for 3 days. PPh₃ 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:

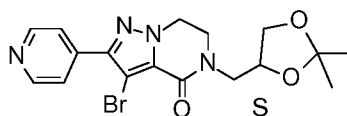
In a microwave vial, a mixture of **28** (0.48 g, 1.1 mmol), **207** (0.5 g, 1.3 mmol), K₃PO₄ (0.91 g, 4.3 mmol) in 1,4-dioxane (4.7 mL) and H₂O (1.7 mL) was carefully purged with N₂. PdCl₂(dppf) (88 mg, 0.11 mmol) was added and the r.m. was purged again with N₂. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3x). The organic phase was dried over MgSO₄, 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/NH₄OH 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/NH₄OH 97/3/0.1). The pure fractions were collected and solvent evaporated until dryness to give 210 mg which was triturated in Et₂O. The white solid was filtrated, washed and dried to give 145 mg of **Co. 94**, white solid (40%). m.p.: 194°C (dsc).

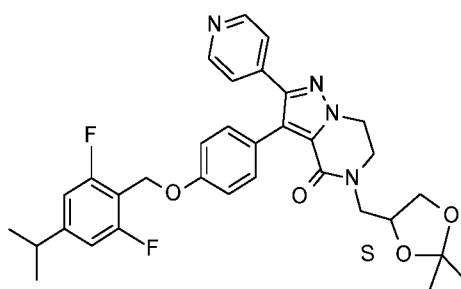
20 Example A96: Preparation of Co. 95a and Co. 95



a- Synthesis of Int. 209:

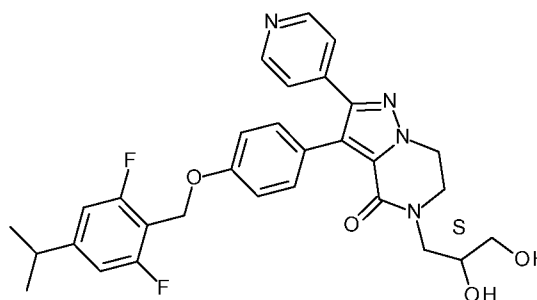
NaH 60% (2.5 g, 61.4 mmol) was added to **4** (12 g, 41 mmol) in DMSO (120 mL) at r.t. under N₂. The mixture stirred for 2h then (R)-(-)-2,2-dimethyl-1,3-dioxolane-4-ylmethyl p-toluenesulfonate (14 g; 49.1 mmol) was added portionwise and the r.m. was

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 35-40 μ m GraceResolvTM, 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 μ m, 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%).

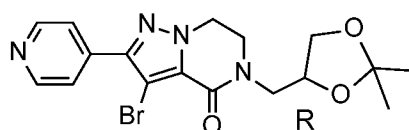


c- Synthesis of Co. 95:

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 μ m, 4 g, GraceResolvTM, 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

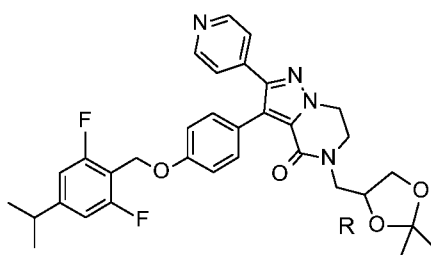
- to give 141 mg. The residue was purified again, by prep. LC (Stationary phase: irregular SiOH 15-40µm 300g Merck, Mobile phase: 40% Heptane, 10% MeOH, 50% EtOAc). The pure fractions were collected and the solvent evaporated to give 103 mg of white solid. The solid was triturated in Et₂O, filtrated and dried to give 99 mg of **Co. 95** (S), white powder (35%). m.p.: 227°C (dsc); [α]_D: -18.24 ° (589 nm, c 0.34 w/v %, DMF, 20 °C)

Example A97: Preparation of Co. 96a and Co. 96



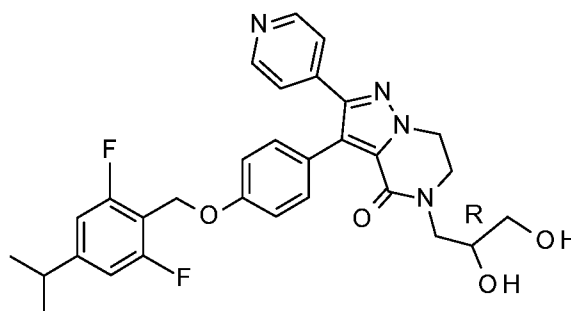
a- Synthesis of Int. 211:

- NaH 60% (1.64 g, 41 mmol) was added to **4** (8 g, 27.3 mmol) in DMSO (80 mL) at r.t. under N₂. 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 K₂CO₃ 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 MgSO₄, 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% CH₃OH 0.1% NH₄OH). The fractions were collected and evaporated until dryness to give 5.55 g of Int. **211** (R) (50%).



b- Synthesis of Co. 96a:

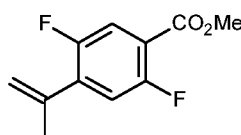
- In a microwave vial, a mixture of **211** (0.41 g, 1.0 mmol), **207** (0.47 g, 1.2 mmol), K₃PO₄ (0.86 g, 4.0 mmol) in 1,4-dioxane (4.4 mL) and H₂O (1.6 mL) was carefully purged with N₂. PdCl₂(dppf) (83 mg, 0.10 mmol) was added and the r.m. was purged again with N₂. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic layer was dried over MgSO₄, 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/NH₄OH 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:

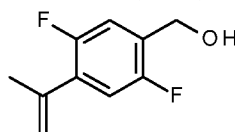
A sol. of **Co. 96a** (0.2 g, 0.34 mmol) and HCl 3N (0.57 mL, 1.7 mmol) in 1,4-dioxane (7.5 mL) were heated to reflux for 1 h. The mixture was cooled to r.t., poured into sat. NaHCO₃ and extracted with DCM. The organic layer was dried over MgSO₄, filtrated and evaporated until dryness to give 190 mg, colorless oil. This oil was purified by prep. LC (Stationary phase: Sunfire Silica 5μm 150x30.0mm, Mobile phase Gradient: from 0.2% NH₄OH, 98% DCM, 2% MeOH to 1% NH₄OH, 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 Et₂O, filtrated and dried to give 50 mg of **Co. 96** (R), white solid (27%). m.p.: 228°C (dsc); [α]_D: +17.22 ° (589 nm, c 0.302 w/v %, DMF, 20 °C)

Example A98: Preparation of Co. 97



a- Synthesis of Int. 213:

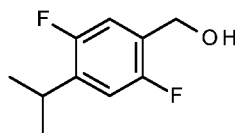
In a microwave vial, a mixture of methyl 4-bromo-2,5-difluorobenzoate (1.5 g, 6.0 mmol), CsF (2.0 g, 13 mmol) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 mL, 6.6mmol) in dry THF (60 mL) was purged with N₂. Pd(tBu₃P)₂ (153 mg, 0.30 mmol) was added and the mixture was purged again with N₂ and heated at 80°C overnight. Water and EtOAc were added, the organic layer was separated, washed with brine, dried on MgSO₄, 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:

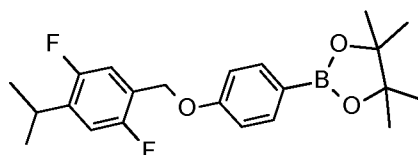
213 (1.0 g, 4.7 mmol) in dry THF (7.5 mL) was added dropwise to a suspension of LAH (0.39 g, 10 mmol) in dry THF (7.5 mL) at 0°C under N₂. The mixture was stirred

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%).



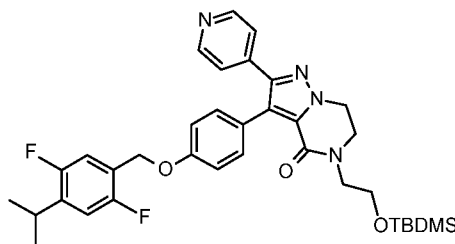
5 **c- Synthesis of Int. 215:**

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
10 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:

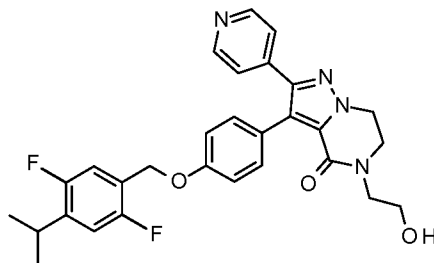
Under N_2 , DBAD (1.2 g, 5.3 mmol) was added portionwise to a sol. of **215** (0.83 g, 4.5 mmol), **7** (1.2 g, 5.3 mmol), PPh_3 supp. (1.7 g, 5.3 mmol) in dry THF (30 mL). The
15 mixture was stirred at r.t. overnight. PPh_3 supp. was filtered and the filtrate was evaporated to give 4.0 g, yellow oil. 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%).



20 **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
25 purged with N_2 . $\text{PdCl}_2(\text{dppf})$ (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

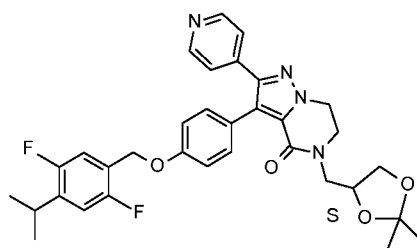
GraceResolve™, mobile phase: DCM/MeOH/NH₄OH 98/2/0.1). The pure fractions were collected and solvent evaporated until dryness to give 0.55 g of Int. **217**, pale yellow oil (93%).



f- Synthesis of Co. 97:

- 5 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 GraceResolve™, mobile phase gradient: DCM/MeOH/NH₄OH from 97/3/0.1 to 95/5/0.1). The pure fractions were collected and solvent evaporated until dryness to
- 10 give 370 mg which was triturated in Et₂O. 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% CO₂, 15% MeOH (0.3% iPrNH₂)). The pure fractions were collected and solvent evaporated until dryness
- 15 to give 287 mg which was triturated in Et₂O. The white solid formed was filtrated and dried to give 199 mg of **Co. 97**, white solid (44%). m.p.: 147°C (dsc).

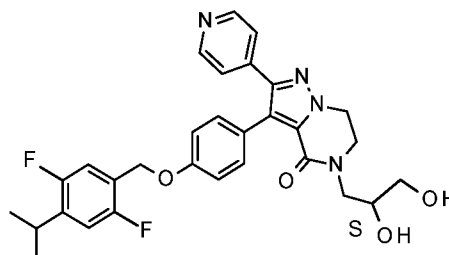
Example A99: Preparation of Co. 98a and Co. 98



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),
- 20 K₃PO₄ (0.80 g, 3.7 mmol) in 1,4-dioxane (4.1 mL) and H₂O (1.5 mL) was carefully purged with N₂. PdCl₂(dppf) (77 mg, 0.10 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, filtered on a pad of Celite® and evaporated *in vacuo* to give a brown oil
- 25 (1g). The crude was purified by prep. LC (irregular SiOH 30 μm, 25 g Interchim,

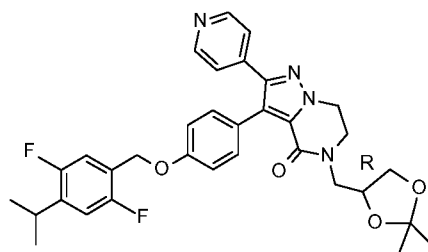
mobile phase: DCM/MeOH/NH₄OH 98/2/0.1). The pure fractions were collected and solvent evaporated until dryness to give 0.43 g of **Co. 98a** (S), beige powder (78%).



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. NaHCO₃ and extracted with DCM. The organic layer was dried over MgSO₄, filtered and evaporated until dryness. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 12g, GraceResolv™, Mobile phase gradient: DCM/MeOH/NH₄OH, 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 Et₂O 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% CO₂, 20% MeOH (0.3% iPrNH₂)). The pure fractions were collected and solvent evaporated to give 241 mg, white solid, which was triturated in Et₂O, filtrated and dried to give 215 mg of **Co. 98** (S), white solid (54%). m.p.: 184°C (dsc); [α]_D: -17.99° (589 nm, c 0.339 w/v %, DMF, 20 °C).

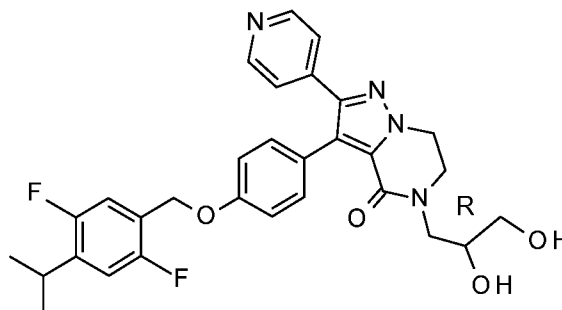
Example A100: Preparation of Co. 99a and Co. 99



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), K₃PO₄ (0.80 g, 3.7 mmol) in 1,4-dioxane (4.1 mL) and H₂O (1.5 mL) was carefully purged with N₂. PdCl₂(dppf) (77 mg, 0.10 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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,

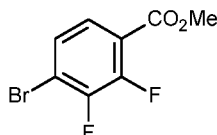
mobile phase: DCM/MeOH/NH₄OH 98/2/0.1). The pure fractions were collected and solvent evaporated until dryness to give 0.32 g of **Co. 99a** (R), colorless oil (58%).



b- Synthesis of Co. 99:

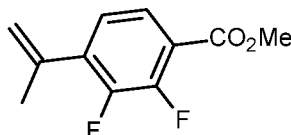
A sol. of **Co. 99a** (0.32 g, 0.54 mmol) and HCl 3N (0.91 mL, 2.7 mmol) in 1,4-dioxane (12 mL) were heated to reflux for 1 h. The mixture was cooled to r.t., poured into sat. NaHCO₃ and extracted with DCM. The organic layer was dried over MgSO₄, filtered and evaporated until dryness to give 300 mg. The residue was purified by achiral SFC (Stationary phase: Amino 6μm 150x21.2mm, Mobile phase: 80% CO₂, 20% MeOH (0.3% iPrNH₂)). The pure fractions were collected and solvent evaporated until dryness to give 191 mg of white solid. This solid was triturated in Et₂O, filtrated and dried to give 160 mg of **Co. 99** (R), white solid (54%). m.p.: 183°C (dsc); [α]_d: +17.82 ° (589 nm, c 0.331 w/v %, DMF, 20 °C).

Example A101: Preparation of Co. 100



a- Synthesis of Int. 220:

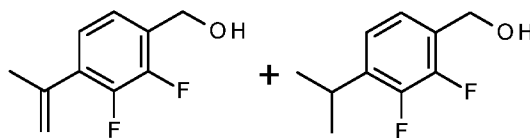
H₂SO₄ (1.1 mL, 21 mmol) was slowly added to a sol. of 4-bromo-2,3-difluorobenzoic acid (2.5 g, 10.5 mmol) in MeOH (40 mL). The mixture was heated at 50°C for 3 days. The mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc and water and basified with K₂CO₃. The combined organic layers were washed with brine, dried (MgSO₄), 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:

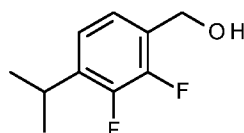
In a schlenk, a mixture of **220** (2.5 g, 10.5 mmol), CsF (3.3 g, 22 mmol) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.0 mL, 11 mmol) in dry THF (60 mL) was purged with N₂. Pd(tBu₃P)₂ (254 mg, 0.50 mmol) was added and the mixture was purged again with N₂ and heated at 80°C overnight. 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%).



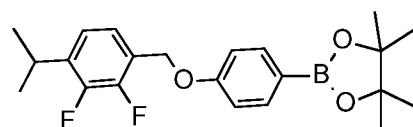
5 **c- Synthesis of Int. 222:**

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
10 evaporated until dryness to give 1.5g of Int. mixture **222**, brown oil. The mixture was used like this in the next step.



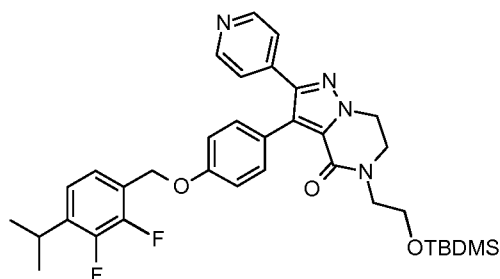
d- Synthesis of Int. 223:

222 (1.5 g, 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
15 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%).



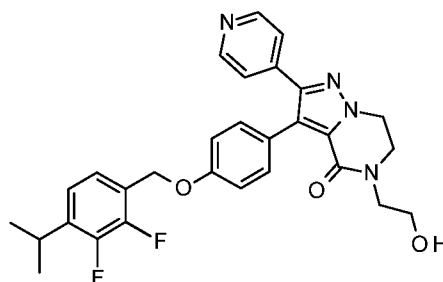
e- Synthesis of Int. 224:

20 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).
25 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:

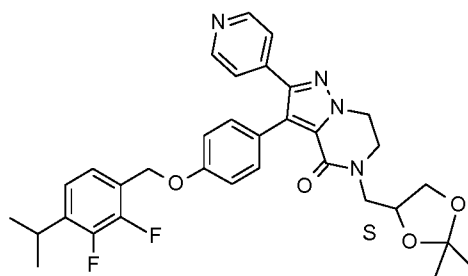
In a microwave vial, a mixture of **28** (0.42 g, 0.94 mmol), **224** (0.4 g, 1.0 mmol), K_3PO_4 (0.80 g, 3.7 mmol) in 1,4-dioxane (4.1mL) and H_2O (1.5mL) was carefully purged with N_2 . $PdCl_2(dppf)$ (77 mg, 0.10 mmol) was added and the r.m. was purged again with N_2 . The r.m. was heated at $80^\circ C$ 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:

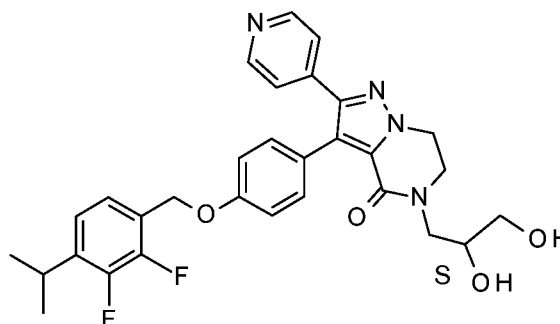
TBAF (1.1 mL, 1.1 mmol) was added dropwise to a sol. of **225** (0.60 g, 0.95 mmol) in THF (9.3 mL) at r.t. The mixture was stirred overnight at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 μm , 25 g GraceResolv™, mobile phase gradient: DCM/MeOH/ NH_4OH 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 5 μm 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.: $172^\circ C$ (dsc).

Example A102: Preparation of Co. 101a and Co. 101



a- Synthesis of Co. 101a

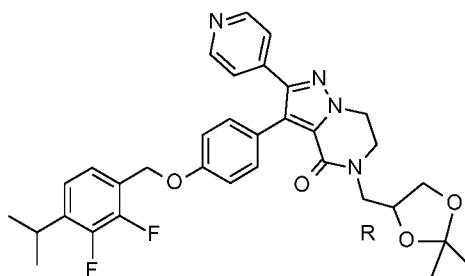
In a microwave vial, a mixture of **209** (0.38 g, 0.94 mmol), **224** (0.4 g, 1.), K₃PO₄ (0.80 g, 3.7 mmol) in 1,4-dioxane (4.1 mL) and H₂O (1.5 mL) was carefully purged with N₂. PdCl₂(dppf) (77 mg, 0.10 mmol) was added and the r.m. was purged again
 5 with N₂. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over MgSO₄, 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/NH₄OH 98/2/0.1). The desired fractions were collected and solvent
 10 evaporated until dryness to give 0.33g of **Co. 101a** (S), beige powder (60%).



b- Synthesis of Co. 101:

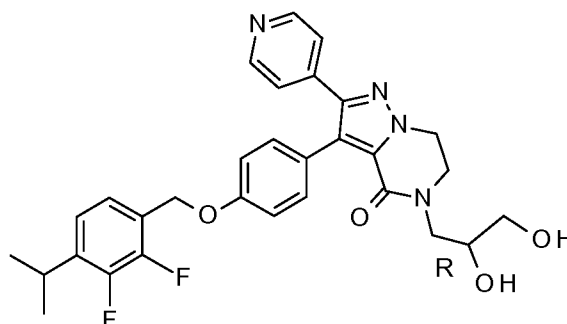
A sol. of **Co. 101a** (0.32 g, 0.54 mmol) and HCl 3N (0.91 mL, 2.7 mmol) in 1,4-dioxane (12 mL) were heated to reflux for 1 h. The mixture was cooled to r.t., poured into sat. NaHCO₃ and extracted with DCM. The organic layer was dried over MgSO₄,
 15 filtered and evaporated until dryness to give 0.4 g, colorless oil. This oil was purified by prep. LC (Stationary phase: Sunfire C18 Xbridge 5µm 150x30.0mm, Mobile phase Gradient: from 70% (NH₄HCO₃ 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 Et₂O. The white solid formed was filtrated, washed and dried to give 0.18
 20 g of **Co. 101** (S), white solid (61%). m.p.: 192°C (dsc); [α]_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:

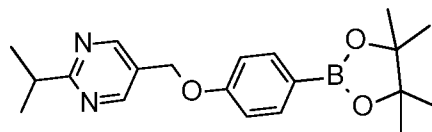
- In a microwave vial, a mixture of **211** (0.38 g, 0.), **224** (0.4g , 1.0 mmol), K₃PO₄ (0.80 g, 3.7 mmol) in 1,4-dioxane (4.1 mL) and H₂O (1.5 mL) was carefully purged with N₂. PdCl₂(dppf) (77 mg, 0.10 mmol) was added and the r.m. was purged again with N₂.
- 5 The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (once) and with brine (3 times). The organic phase was dried over MgSO₄, 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/NH₄OH 98/2/0.1). The pure fractions were collected and solvent
- 10 evaporated until dryness to give 0.48 g of **Co. 102a** (R), colorless oil (87%).



b- Synthesis of Co. 102:

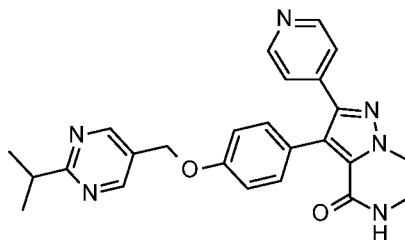
- A sol. of **Co. 102a** (0.48 g, 0.82 mmol) and HCl 3N (1.4 mL, 4.1 mmol) in 1,4-dioxane (18 mL) were heated to reflux for 1 h. The mixture was cooled to r.t., poured into sat. NaHCO₃ and extracted with DCM. The organic layer was dried over MgSO₄, filtered
- 15 and evaporated until dryness to give 520 mg, colorless oil. The crude was purified by prep. LC (Stationary phase: Sunfire C18 Xbridge 5µm 150x30.0mm, Mobile phase Gradient: from 70% (NH₄HCO₃ 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 Et₂O. The white solid formed was filtrated, washed and dried to give 215
- 20 mg of **Co. 102** (R), white solid (48%). m.p. = 191°C (dsc); [α]_d: +19.28 ° (589 nm, c 0.249 w/v %, DMF, 20 °C).

Example A104: Preparation of Co. 103



a- Synthesis of Int. 228:

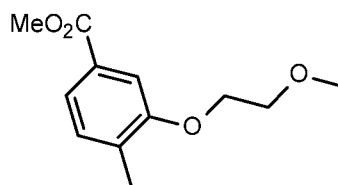
DBAD (446 mg, 1.94 mmol) was added to a stirred sol. of **7** (305 mg, 1.38 mmol), (2-isopropylpyrimidin-5-yl)methanol (295 mg, 1.94 mmol) and PPh₃ supp. (606 mg, 1.94 mmol) in THF (7 mL) under N₂ at r.t. The mixture was stirred at r.t. for 16 h. Then, additional PPh₃ supp. (130 mg; 0.416 mmol) and DBAD (96 mg, 0.416 mmol) were added under N₂, 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:

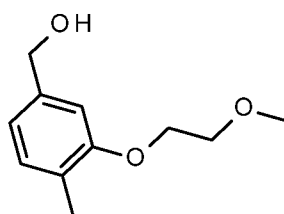
A mixture of **4** (150 mg, 0.512 mmol), **228** (590 mg, 1.25 mmol), K₃PO₄ (434 mg, 2.05 mmol) in 1,4-dioxane (3 mL) and H₂O (1 mL) was carefully purged with N₂. PCy₃ (29 mg, 0.102 mmol) and Pd(OAc)₂ (11 mg, 51.2 μmol) were added and the r.m. was purged again with N₂, and stirred for 68 h at 80°C. The crude material was treated with water and extracted with DCM. The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give a black solid. The solid was purified by prep. LC on (irregular SiOH 15-40 μm 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 6 μm 150x21.2mm; Mobile phase: 0.3% iPrNH₂, 80% CO₂, 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



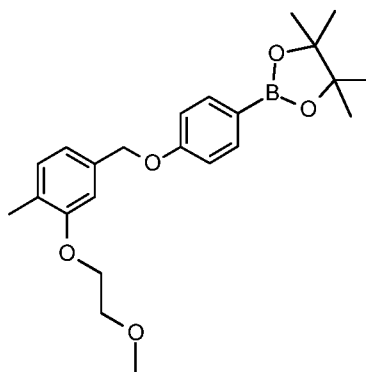
a- Synthesis of Int. 229:

- 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 20-45 μ m 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%).



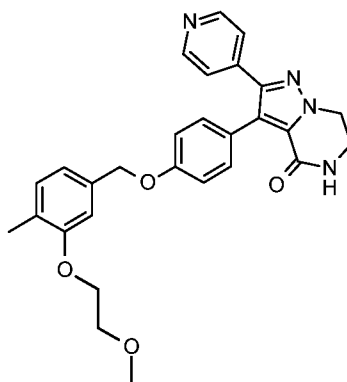
b- Synthesis of Int. 230:

- 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:

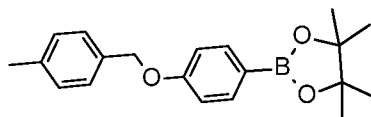
- 230** (1.2 g, 6.1 mmol), **7** (1.6 g, 7.3 mmol), PPh_3 supp. (2.4 g, 9.2 mmol) in THF (40 mL). DBAD (2.1 g, 9.2 mmol) was added portionwise at r.t. and the mixture was stirred at r.t. overnight. Water and EtOAc were added, the mixture was extracted, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The residue was purified by prep. LC on (irregular 15-40 μ m 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:

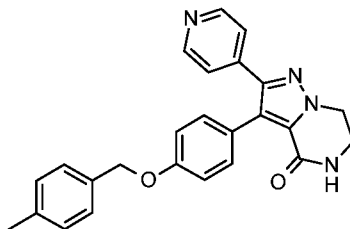
A mixture of **4** (400 mg, 1.36 mmol), **231** (0.71 g, 1.8 mmol), K_3PO_4 (1.16 g, 5.46 mmol) in 1,4-dioxane (7 mL) and H_2O (3 mL) was carefully purged with N_2 . PCy_3 (80.4 mg, 0.29 mmol) and $Pd(OAc)_2$ (32 mg, 0.14 mmol) were added and the r.m. was
 5 purged again with N_2 . The r.m. was stirred for 8 h at $80^\circ C$. 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 20-45 μm 40g MATREX, Mobile phase: 97/3 DCM/MeOH). The pure fractions were collected and solvent evaporated until dryness to give 150 mg of a
 10 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.: $190^\circ C$ (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
 15 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%).

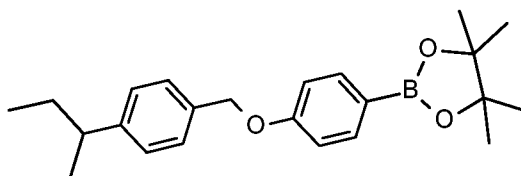


b- Synthesis of Co. 105:

20 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

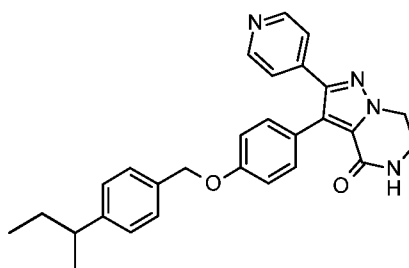
- added and the r.m. was purged again with N₂. The r.m. was stirred for 16 h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give 530 mg of crude residue. The residue was purified by prep. LC on (Stability Silica 5µm 150x30.0mm, Mobile phase Gradient: from 0.2% NH₄OH, 98% DCM, 2% MeOH to 1% NH₄OH, 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 Et₂O, filtrated and dried to give 225 mg of **Co. 105**, white powder (54%). m.p.: 259°C (dsc).

Example A107: Preparation of Co. 106



10 **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), PPh₃ 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 K₂CO₃. The organic layer was dried over MgSO₄, 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%).

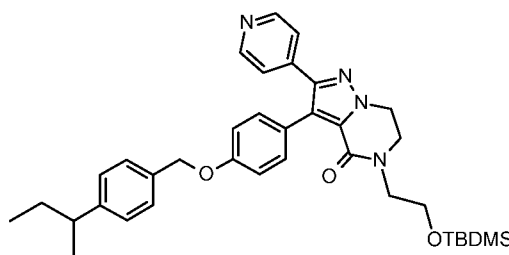


25 **b- Synthesis of Co. 106:**

- A mixture of **4** (380 mg, 1.3 mmol), **233** (726 mg, 2 mmol), K₃PO₄ (1.1 g, 5.2 mmol) in 1,4-dioxane (7 mL) and H₂O (2.5 mL) was carefully purged with N₂. PCy₃ (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 N₂. The r.m. was stirred for 18h at 80°C. Water and K₂CO₃ were added then

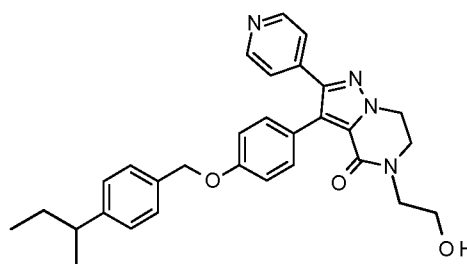
EtOAc. The mixture was filtered and the organic layer was extracted, dried over MgSO₄, filtered and evaporated until dryness. The residue was purified by prep. LC (40g of irregular SiOH 35-40µm GraceResolv™, mobile phase gradient: from 100% DCM to 95% DCM 5% CH₃OH 0.1% NH₄OH). The fractions were collected and
 5 evaporated until dryness. The product was crystallized from Et₂O, 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:

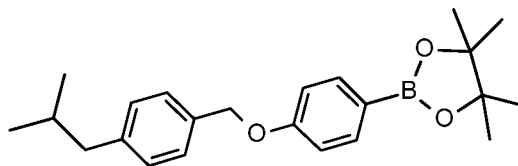
NaH 60% (0.115 g, 2.9 mmol) was added to a suspension of **Co. 106** (1 g, 2.21 mmol) in DMF (15 mL) at r.t. under N₂. The mixture was stirred for 2h. (2-bromoethoxy)-tert-butyltrimethylsilane (0.57 mL, 2.65 mmol) was added and stirred for 20h. The mixture was poured into water and K₂CO₃ and extracted with EtOAc. The organic layer was dried (MgSO₄), filtered and evaporated until dryness. The residue was purified by prep. LC (120 g of irregular SiOH 35-40µm GraceResolv™, mobile phase gradient: from
 10 100% DCM to 97% DCM 3% CH₃OH 0.1% NH₄OH). The fractions were collected and evaporated to give 1.07 g of Int. **234** (79%).



b- Synthesis of Co. 107:

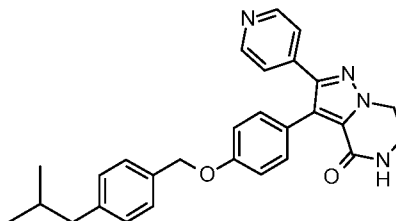
TBAF (2.1 mL, 2.1 mmol) was added dropwise to a sol. of **234** (1.1 g, 1.8 mmol) in THF (17 mL) at r.t. The mixture was stirred overnight at r.t. The mixture was
 20 concentrated and the residue was purified by prep. LC (Regular SiOH, 30 µm, 40g Interchim, mobile phase gradient: DCM/MeOH/NH₄OH from 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 Et₂O. 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:

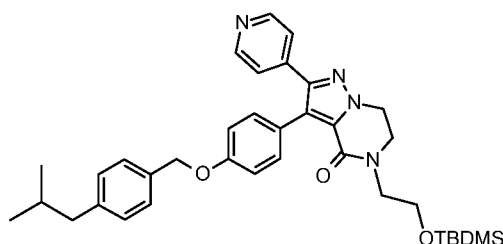
DBAD (3.8 g, 16.4 mmol) was added portionwise to a mixture of 4-iso-butylbenzyl alcohol (1.8 g, 11 mmol), **7** (2.4 g, 11 mmol), PPh₃ supp. (5.1 g, 16.4 mmol) in THF (30 mL) at r.t.. The mixture was stirred for 15h. The insoluble was filtered and washed with EtOAc. The filtrate was poured in water and K₂CO₃. The organic layer was extracted, dried over MgSO₄, 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:

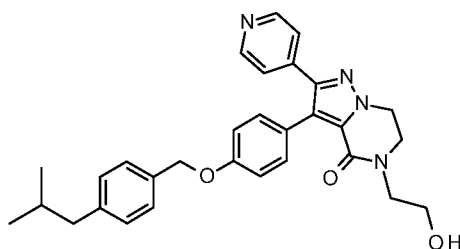
A mixture of **4** (0.96 g, 3.3 mmol), **235** (1.8 g, 4.9 mmol), K₃PO₄ (2.8 g, 13.1 mmol) in 1,4-dioxane (20 mL) and H₂O (2.5 mL) was carefully purged with N₂ in sealed tube. PCy₃ (184 mg, 0.655 mmol) and Pd(OAc)₂ (73.6 mg, 0.33 mmol) were added and the r.m. was purged again with N₂. The r.m. was stirred for 18h at 80°C. Water and K₂CO₃ were added then EtOAc. The mixture was filtered and the organic layer was extracted, dried over MgSO₄, 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% CH₃OH, 0.1% NH₄OH). 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:

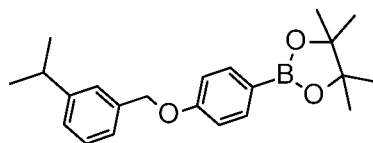
NaH 60% (78.1 mg, 1.9 mmol) was added to a suspension of **Co. 108** (0.68 g, 1.5 mmol) in DMF (10 mL) at r.t. under N₂. The mixture was stirred for 2h. (2-bromoethoxy)-tert-butyldimethylsilane (0.39 mL, 1.8 mmol) was added and stirred for 20h. The mixture was poured into water and K₂CO₃, and extracted with EtOAc. The organic layer was dried over MgSO₄, 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% CH₃OH, 0.1% NH₄OH). 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/NH₄OH, 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 Et₂O. The white solid formed was filtrated, washed and dried to give 0.38 g of **Co. 109** (62%).

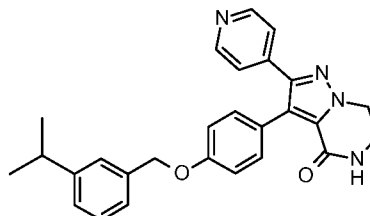
Example A111: Preparation of Co. 110



a- Synthesis of Int. 237:

To a suspension of (3-isopropylphenyl)methanol (586 mg, 2.66 mmol), **7** (520 mg, 2.77 mmol), PPh₃ 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

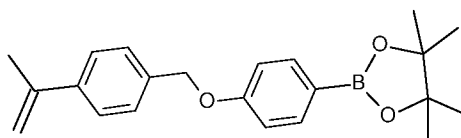
loading, 30 g Merck, mobile phase: heptane 90%, EtOAc 10%). The pure fractions were collected and solvent evaporated until dryness to give 710 mg of Int. **237**, colorless oil (76%).



b- Synthesis of Co. 110:

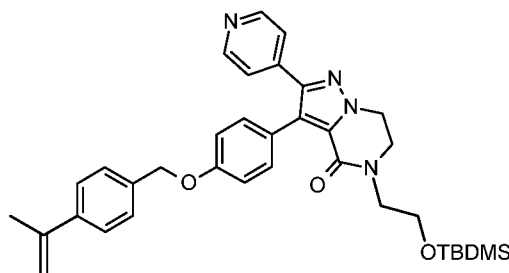
- 5 In a sealed tube, a mixture of **4** (197 mg, 0.672 mmol), **237** (710 mg, 2.015 mmol), K_3PO_4 (570 mg, 2.69 mmol) in 1,4-dioxane (3 mL) and H_2O (1 mL) was purged with N_2 . PCy_3 (38 mg, 0.134 mmol) and $Pd(OAc)_2$ (15 mg, 67.2 μ mol) were added and the r.m. was purged again with N_2 . The tube 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
- 10 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 15-40 μ m, 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
- 15 **Co. 110**, white solid (69%). m.p.: 268°C (dsc).

Example A112: Preparation of Co. 111



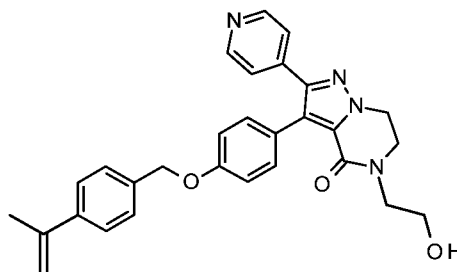
a- Synthesis of Int. 238:

- 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.
- 20 (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 15-40 μ m 50g Merck, Mobile phase: Heptane 90/EtOAc 10). The fractions were collected and evaporated until dryness to give 648
- 25 mg of Int. **238** (40%, purity 70%). The Co. was used as such for the next step.



b- Synthesis of Int. 239:

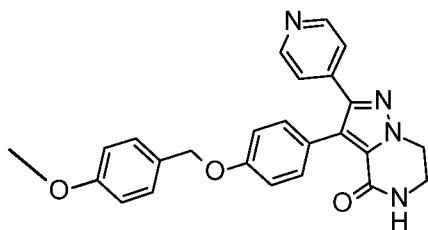
In a microwave vial, a mixture of **28** (0.663 g, 1.47 mmol), **238** (0.617 g, 1.76 mmol), K_3PO_4 (1.25 g, 5.87 mmol) in 1,4-dioxane (6.5 mL) and H_2O (2.3 mL) was carefully purged with N_2 . $PdCl_2(dppf)$ (120 mg, 0.15 mmol) was added and the r.m. was purged again with N_2 . The r.m. was heated at $80^\circ C$ 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 15-40 μm 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 6 μm 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:

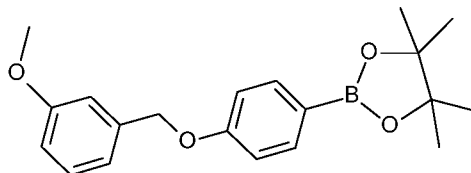
TBAF (0.78 mL, 0.78 mmol) was added dropwise to a sol. of **239** (0.385 g, 0.65 mmol) in THF (6 mL) at r.t. The mixture was stirred for 3h at r.t.. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 356 mg. The residue was purified by prep. 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.: $165^\circ C$ (dsc).

Example A113: Preparation of Co. 112



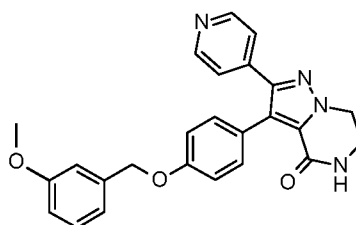
In a Schlenk tube, a mixture of **4** (700 mg, 2.39 mmol), 4-(4'-methoxybenzyloxy)phenylboronic acid (1.85 g, 7.16 mmol), K₃PO₄ (2.03 g, 9.55 mmol) in 1,4-dioxane (10.5 mL) and H₂O (3.5 mL) was carefully purged with N₂. PCy₃ (134 mg, 0.478 mmol) and Pd(OAc)₂ (54 mg, 239 μmol) were added and the r.m. was purged again with N₂. 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 Et₂O (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 K₂CO₃ (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 MgSO₄, filtered and concentrated *in vacuo* to afford 800 mg of Int. **240**, colorless oil (quant. yield).

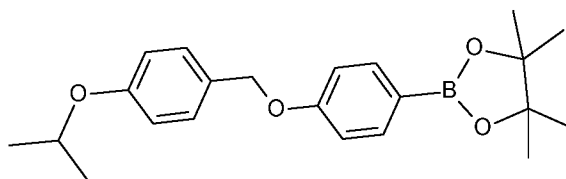


b- Synthesis of Co. 113:

In a sealed tube, a mixture of **4** (230 mg, 0.784 mmol), **240** (800 mg, 2.35 mmol), K₃PO₄ (665 mg, 3.14 mmol) in 1,4-dioxane (3.5 mL) and H₂O (1.2 mL) was carefully purged with N₂. PCy₃ (44 mg, 0.157 mmol) and Pd(OAc)₂ (18 mg, 78.4 μmol) were added and the r.m. was purged again with N₂. The sealed tube was then sealed and the

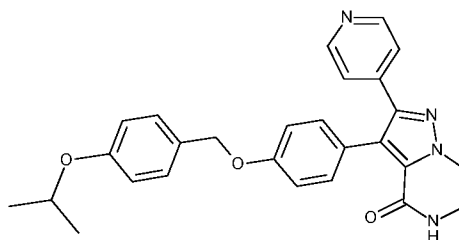
r.m. was stirred for 17 h at 80°C. The crude material was dissolved in water (10 mL) and extracted with EtOAc (2 x 40mL). The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give 640 mg. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 30g Merck, mobile phase gradient: 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 Et₂O, filtered and dried to give 36 mg of **Co. 113**, a white solid (11%). m.p.: 242°C (dsc).

Example A115: Preparation of Co. 114



10 **a- Synthesis of Int. 241:**

A sol. of **7** (700 mg, 3.18 mmol), 4-isopropoxybenzylalcohol (793 mg, 4.77 mmol) and PPh₃ (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 MgSO₄, 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 which 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%).

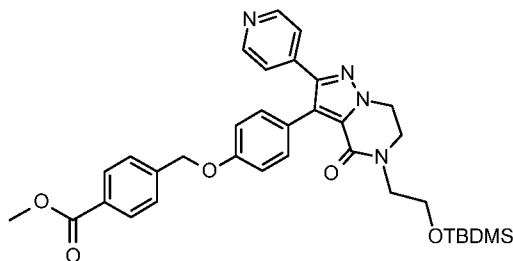


b- Synthesis of Co. 114:

A mixture of **4** (120 mg, 0.409 mmol), **241** (471 mg, 1.02 mmol), K₃PO₄ (348 mg, 1.64 mmol) in 1,4-dioxane (2.1 mL) and H₂O (0.7 mL) was carefully purged with N₂. PCy₃ (23 mg, 81.9 µmol) and Pd(OAc)₂ (9 mg, 40.9 µmol) were added and the r.m. was purged again with N₂, and stirred for 17h at 80°C. The crude material was dissolved in water and extracted with DCM. The organic phase was dried over MgSO₄, 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%

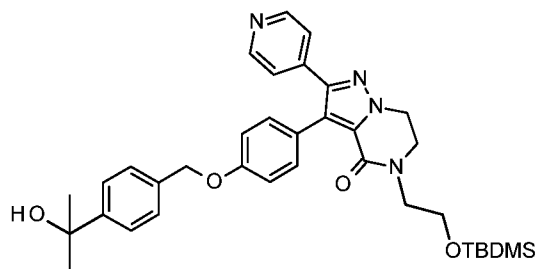
MeOH). The desired fractions were combined and the solvent was removed *in vacuo* to give 100 mg of **Co. 114**, white solid (54%). m.p.: 252 °C (dsc).

Example A116: Preparation of Co. 115



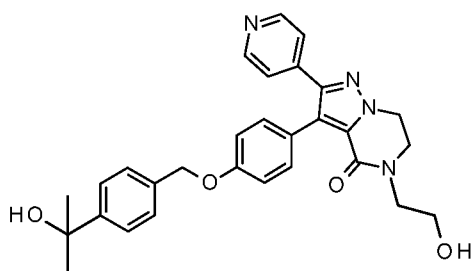
a- Synthesis of Int. 242:

- 5 In a microwave vial, a mixture of **28** (0.8 g, 1.77 mmol), **49** (0.848 g, 2.3 mmol), K₃PO₄ (1.51 g, 7.1 mmol) in 1,4-dioxane (7.8 mL) and H₂O (2.8 mL) was carefully purged with N₂. PdCl₂(dppf) (0.145 g, 0.18 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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/NH₄OH 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:

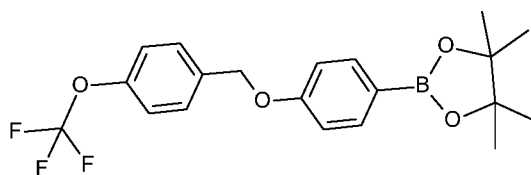
- 15 MeMgCl (3.05 mL, 9.06 mmol) was added to a stirred suspension of **242** (1.11 g, 1.81 mmol) in THF (17 mL) under N₂ at 0 °C. The mixture was stirred at 0 °C for 5 min, and then it was warmed to r.t. and stirred for 2h. The r.m. was quenched with 10% NH₄Cl sol., and treated with EtOAc. The organic layer was separated, washed with brine, dried over MgSO₄, 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:

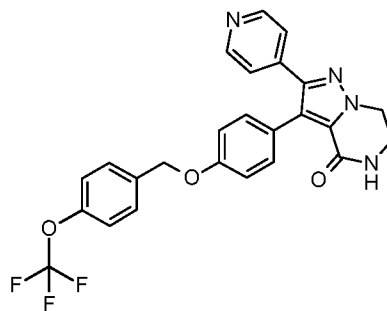
- TBAF (2.02 mL, 2.02 mmol) was added dropwise to a sol. of **243** (1.03 g, 1.68 mmol) in THF (17 mL) at r.t.. The mixture was stirred for 3h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 712 mg. The residue was purified by prep. LC (Regular SiOH, 30 μ m, 24g GraceResolvTM, mobile phase gradient: from DCM 100% to DCM/MeOH/NH₄OH 95/5/0.1). The pure fractions were collected and evaporated until dryness to give 490 mg which was crystallized from Et₂O, 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 alcohol (1.28 mL; 8.86 mmol) and PPh₃ supp. (2.95 g; 8.86 mmol) in DCM (30mL) and the r.m. was stirred under N₂ 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 μ m, 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%).

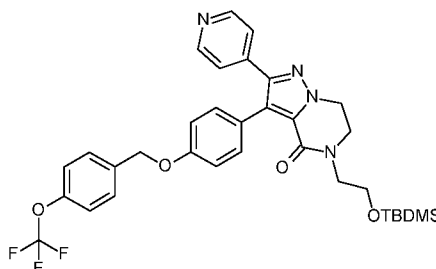


b- Synthesis of Co. 116:

- In a microwave vial, a mixture of **4** (150 mg, 512 μ mol), **244** (504 mg, 1.28 mmol), K₃PO₄ (455 mg, 2.15 mmol) in 1,4-dioxane (2.4 mL) and H₂O (0.8 mL) was carefully purged with N₂. PCy₃ (30 mg, 107 μ mol) and Pd(OAc)₂ (12 mg, 53.6 μ mol) were added and the r.m. was purged again with N₂. 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 MgSO₄, filtered and evaporated *in vacuo* to give 400 mg, brown solid. The solid was purified by prep. LC (irregular SiOH 15-40 μ m, 30g Merck, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%).

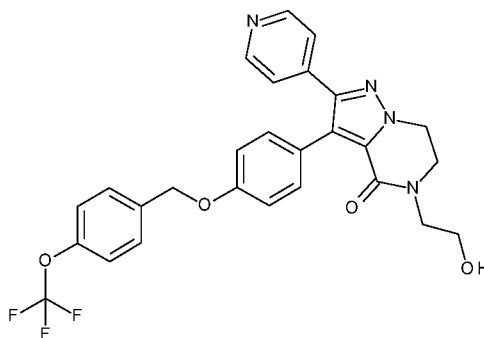
The pure fractions were collected and solvent evaporated until dryness to give 180 mg of **Co. 116**, white solid (73%). m.p.: 260 °C (dsc).

Example A118: Preparation of Co. 117



a- Synthesis of Int. 245:

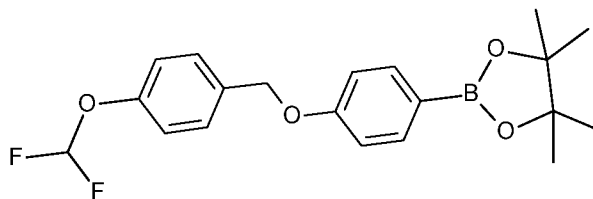
- 5 In a microwave vial, a mixture of **28** (0.7 g, 1.55 mmol), **244** (0.935 g, 2 mmol), K₃PO₄ (1.32 g, 6.2 mmol) in 1,4-dioxane (6.8 mL) and H₂O (2.42 mL) was carefully purged with N₂. PdCl₂(dppf) (127 mg, 0.155 mmol) was added and the r.m. was purged again with N₂. The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc and washed with water (1x) and with brine (3x). The organic phase was dried over MgSO₄,
10 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/NH₄OH 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:

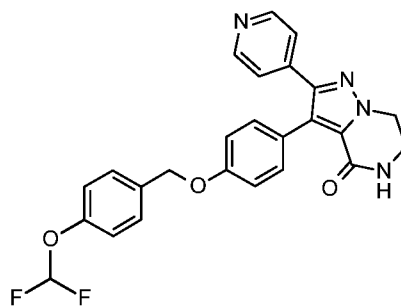
- 15 TBAF (1.73 mL, 1.73 mmol) was added dropwise to a sol. of **245** (920 mg, 1.44 mmol) in THF (14 mL) at r.t. The mixture was stirred for 3h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 865 mg. The residue was purified by prep. LC (Regular SiOH, 30 μm, 12g GraceResolv™, mobile phase gradient: from DCM 100% to DCM/MeOH/NH₄OH
20 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:

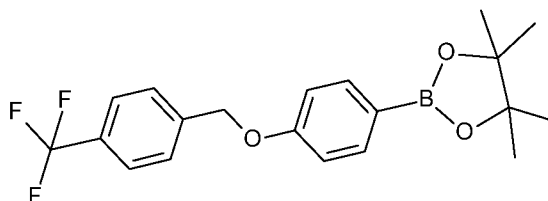
A sol. of **7** (0.76 g, 3.45 mmol) in ACN (10 mL) was treated with K_2CO_3 (0.572 g, 4.14 mmol) and 4-(difluoromethoxy)benzyl bromide (0.9 g, 3.8 mmol) at r.t. The r.m. was stirred for 18 h at r.t. Then, water and DCM were added, and the organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 1.29 g. The residue was purified by prep. LC on (Irregular SiOH 15-40 μ m 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 15-40 μ m 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).

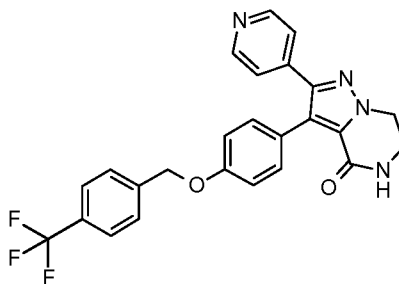
20 Example A120: Preparation of Co. 119



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

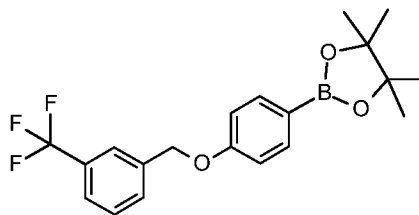
- mmol) in DCM (30 mL) and the r.m. was stirred under N₂ for 17 h at rt. The r.m. was then filtered through a glass frit and washed with EtOAc. The sol. was concentrated to give 5.50 g, yellow oil. The residue was purified by prep. LC (irregular SiOH 15-40 μm, solid loading, 50g Merck, mobile phase: 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), K₃PO₄ (455 mg, 2.15 mmol) in 1,4-dioxane (2.4 mL) and H₂O (0.8 mL) was carefully purged with N₂. PCy₃ (30 mg, 107 μmol) and Pd(OAc)₂ (12 mg, 53.6 μmol) were added and the r.m. was purged again with N₂. 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 MgSO₄, 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).

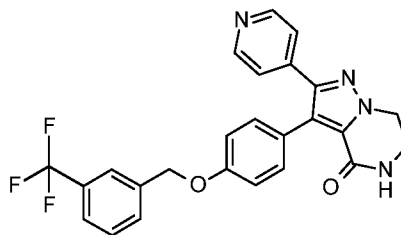
Example A121: Preparation of Co. 120



a- Synthesis of Int. 248:

- K₂CO₃ (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. K₂CO₃ (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

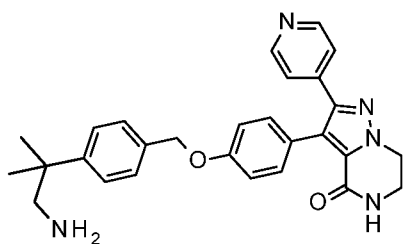
fractions were collected and the solvent was evaporated until dryness to give 0.560 g of Int. **248**, white solid (94%).



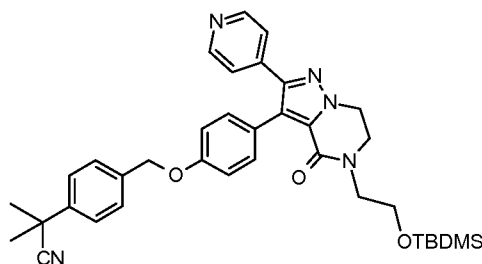
b- Synthesis of Co. 120:

A sol. of **4** (0.143 g, 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).

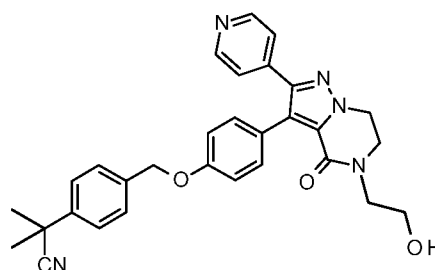
Example A122: Preparation of Co. 121



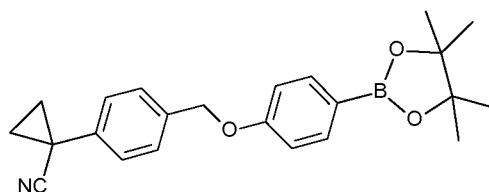
Co. 10 (210 mg, 0.45 mmol), Ni (210 mg) in MeOH (5 mL) was hydrogenated under 3 bars at r.t. for 4 h. The catalyst was filtered over a Celite® pad, the filtrate was evaporated. The residue was purified by prep. LC (Irregular SiOH 35-40 μm 40g GraceResolv™, mobile phase: 90/10/0.1 DCM/MeOH/ NH_4OH). The fractions were collected and evaporated to give 106 mg of initial 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 35-40 μm 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 N₂. The mixture was stirred for 2h, then (2-bromoethoxy)-tert-butyldimethylsilane (128 μ l, 0.62 mmol) was added and stirred overnight. Water and DCM were added, the mixture was extracted, the organic layer was separated, dried over MgSO₄, 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.

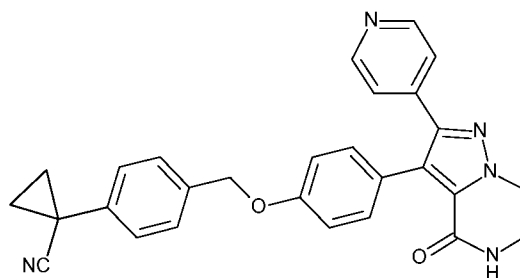
**b- Synthesis of Co. 122:**

- 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 MgSO₄, filtered and evaporated until dryness. The residue was purified by prep. LC (Regular SiOH, 30 μ m, 25g grace, mobile phase gradient: DCM/MeOH/NH₄OH 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 Et₂O, 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:**

- PPh₃ 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 N₂ at r.t. The r.m.

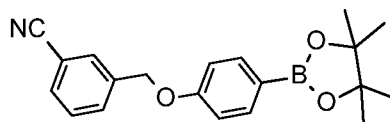
was stirred at r.t. for 2h, and then the crude mixture was filtered off and the filtrate was diluted with DCM and sat NaHCO₃. The organic layer was separated, dried over MgSO₄, filtered and evaporated *in vacuo* to give 2.81 g, brown solid. The solid was purified by prep. LC (Irregular SiOH 50 µm, 120g 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:

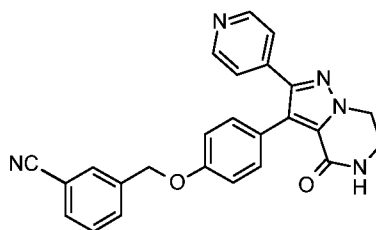
A mixture of **4** (0.464 g, 1.58 mmol), **250** (0.900 g, 2.40 mmol) and K₃PO₄ (1.01 g, 4.75 mmol) in 1,4-dioxane (9 mL) and H₂O (3 mL) was carefully purged with N₂. PCy₃ (89 mg, 0.317 mmol) and Pd(OAc)₂ (36 mg, 0.158 mmol) were added and the r.m. was purged again with N₂. The r.m. was stirred for 18 h at 80°C. The crude material was dissolved in water and extracted with DCM. The organic phase was washed with brine, dried over MgSO₄, 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% (NH₄HCO₃ 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:

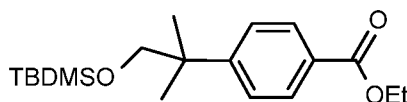
A sol. of **7** (1.5 g, 6.82 mmol) in ACN (15 mL) and DMF (3 mL) was treated with **C** (1.13 g; 8.18 mmol) and 3-(bromomethyl)benzonitrile (1.55 g, 7.50 mmol) at rt. The r.m. was stirred for 36h at r.t. Water and EtOAc were added, and the organic layer was washed with brine, separated, dried over MgSO₄, filtered and evaporated *in vacuo* to afford 2.63 g of Int. **251**, (quant. yield).



b- Synthesis of Co. 124:

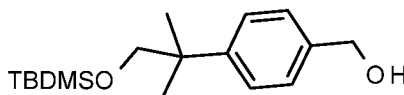
A mixture of **4** (0.87 g, 2.98 mmol), **251** (2.63 g, 7.45 mmol), K₃PO₄ (2.53 g, 11.9 mmol) in 1,4-dioxane (12 mL) and H₂O (4 mL) was carefully purged with N₂. PCy₃ (167 mg, 0.596 mmol) and Pd(OAc)₂ (67 mg, 0.298 mmol) were added, and the r.m. was purged again with N₂. The r.m. was stirred for 17h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried over MgSO₄, 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



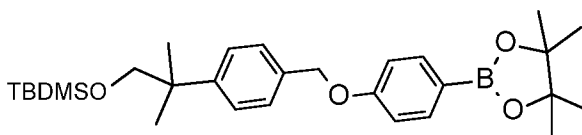
a- Synthesis of Int. 252:

4-(2-hydroxy-1,1-dimethylethyl)-benzoic acid, ethyl ester (0.513g, 2.3mmol), tert-butyl dimethylsilyl 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%).



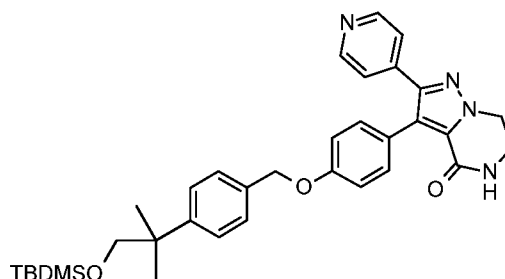
b- Synthesis of Int. 253:

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 MgSO₄, filtered and evaporated to give 180 mg of Int. **253** (98%).



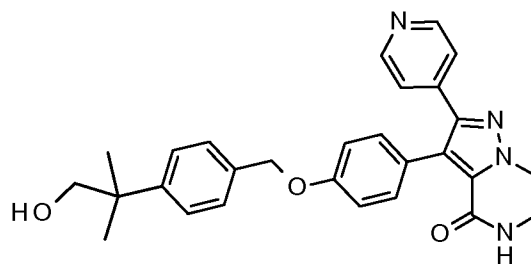
c- Synthesis of Int. 254:

- 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 PPh₃ 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%).



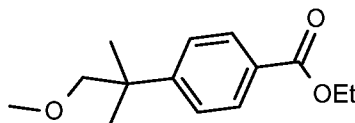
d- Synthesis of Int. 255:

- In a microwave vial, a mixture of **4** (0.218 g, 0.744 mmol), **254** (0.6 g, 0.967 mmol), K₃PO₄ (0.662 g, 3.12 mmol) in 1,4-dioxane (3.5 mL) and H₂O (1.2 mL) was carefully purged with N₂. PdCl₂(dppf) (61mg, 0.074 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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: NH₄OH/DCM/MeOH 0.4/96/4) to give 180 mg of Int. **255** (42%).

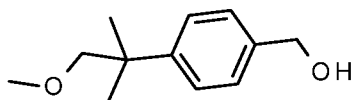


e- Synthesis of Co. 125:

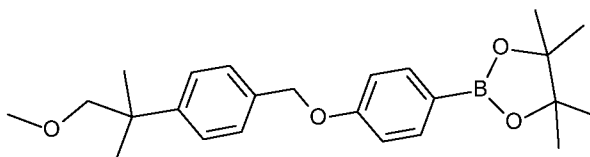
- TBAF (0.37 mL, 0.37 mmol) was added dropwise to a sol. of **255** (0.18 g, 0.31 mmol) in THF (3.0 mL) at r.t. The mixture was stirred 2h at r.t. 1 equivalent of TBAF was added and the reaction was let at r.t. overnight to complete the reaction. The mixture was evaporated to dryness and purified by prep. LC (irregular SiOH 15-40 µm, 12g, GraceResolv™, Mobile phase: DCM/MeOH/NH₄OH, 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 Et₂O, 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:**

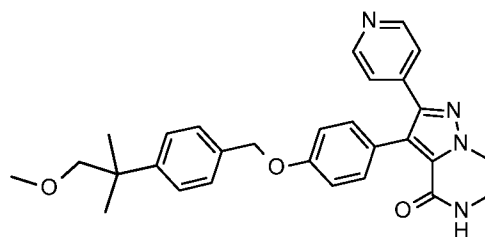
- To a sol. of 4-(2-hydroxy-1,1-dimethylethyl)-benzoic acid, ethyl ester (0.54 g, 2.43 mmol) in DMF (8 mL) was added MeI (0.76 mL, 12.1 mmol) and NaH 60% (0.146 g, 3.65 mmol). The mixture was stirred at r.t. for 3h. The reaction was quenched with water, and extracted with EtOAc. The organic layer was separated, washed with K₂CO₃ 10%, dried over MgSO₄, 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 MgSO₄, filtered and evaporated to give 370 mg of Int. **257** (98%).

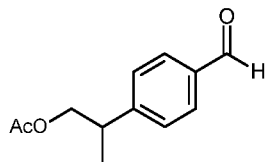
**c- Synthesis of Int. 258:**

- To a suspension of **257** (0.37 g, 1.91 mmol), **7** (0.504 g, 2.29 mmol), PPh₃ 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:**

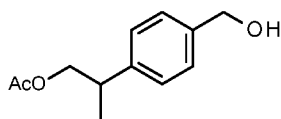
In a microwave vial, a mixture of **4** (0.2 g, 0.682 mmol), **258** (0.439 g, 0.887 mmol), K_3PO_4 (0.607 g, 2.86 mmol) in 1,4-dioxane (3.2 mL) and H_2O (1 mL) was carefully purged with N_2 . $PdCl_2(dppf)$ (56 mg, 0.068 mmol) was added and the r.m. was purged again with N_2 . The r.m. was stirred for 16 h at $80^\circ C$. 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 $5\mu m$ 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.: $212^\circ C$ (dsc).

Example A128: Preparation of Co. 127



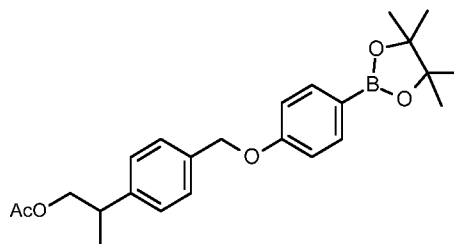
a- Synthesis of Int. 259:

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 $0^\circ C$ 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.



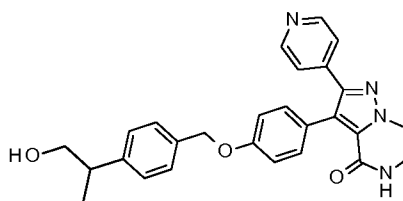
b- Synthesis of Int. 260:

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, GraceResolvTM, 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:

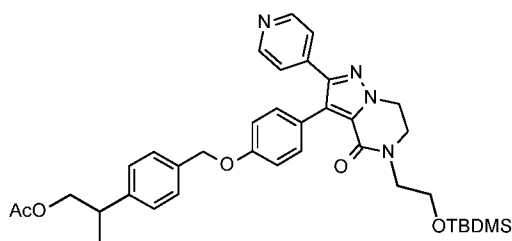
A mixture of **260** (2.19 g, 10.5 mmol), **7** (1.78 g; 8.09 mmol), PPh₃ (2.76 g, 10.5 mmol) in dry THF (50 mL) was treated with DBAD (2.42 g, 10.5 mmol) and stirred at r.t. for 2h30. The r.m. was then poured in DCM, washed with water, dried over MgSO₄ and evaporated *in vacuo* to afford a residue. 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:

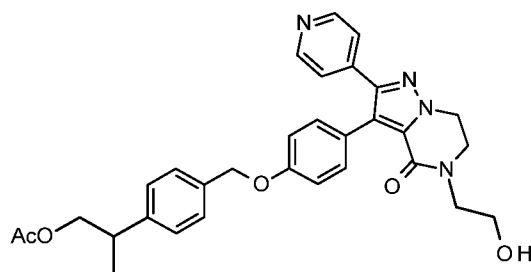
A mixture of **4** (500 mg, 1.71 mmol), **261** (1.40 g, 3.41 mmol) and K₃PO₄ (1.27 g, 5.97 mmol) in 1,4-dioxane (5 mL) and H₂O (10 mL) was purged with N₂. Then, PdCl₂(dppf) (140 mg, 171 μmol) was added. The mixture was purged again with N₂ and heated at 120°C using one single mode microwave (Biotage 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 MgSO₄ 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 Et₂O, 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



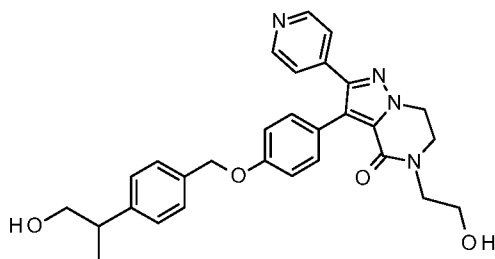
a- Synthesis of Int. 262:

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 $80^\circ C$ 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 15-40 μm , 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:

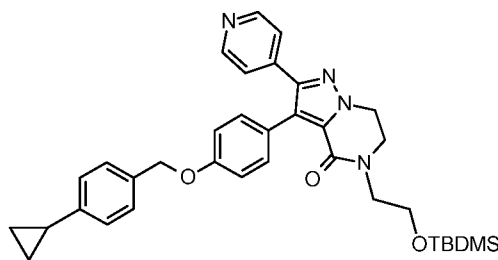
TBAF (2.25 mL, 2.25 mmol) was added dropwise to a sol. of **262** (1.23 g, 1.89 mmol) in THF (18 mL) at r.t. The mixture was stirred for 2h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 1.04 g of Int. **263** (100%).



c- Synthesis of Co. 128:

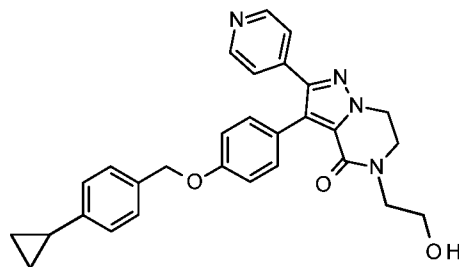
To a sol. of **263** (1g, 1.85 mmol) in MeOH (12 mL) was added Potassium hydroxide (399 mg, 5.55 mmol) and the mixture was heated at 50°C for 3h. The solid formed was filtered and washed from Et₂O then poured into water and extracted with DCM and few MeOH several times. The organic layer was separated, 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/NH₄OH 94/6/0.1). The pure fractions were collected and evaporated until dryness to give 648 mg which was crystallized from Et₂O, filtered and dried to give 538 mg. This residue was purified by achiral SFC (Stationary phase: Chiralpak IA 5μm 250*20mm, Mobile phase: 55% CO₂, 45% MeOH (0.3% iPrNH₂)). The pure fractions were collected and evaporated until dryness to give 400 mg which was crystallized from Et₂O, 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), K₃PO₄ (7.5 g, 35 mmol) in 1,4-dioxane (39 mL) and H₂O (14 mL) was carefully purged with N₂. PdCl₂(dppf) (726 mg, 0.89 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, 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.



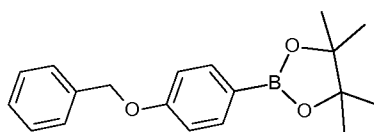
b- Synthesis of Co. 129:

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/NH₄OH 96/4/0.1). The desired fractions

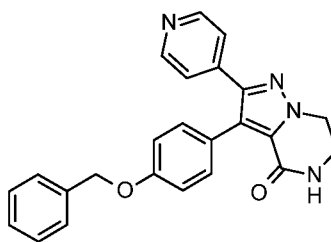
- were collected and solvent evaporated until dryness to give 4.0 g of colorless oil which was triturated in Et₂O. The white solide formed was filtrated, washed and dried to give 3.22g, white solide (3% of TBAF). The residue was added to the previous filtrate and evaporated to give 4.0 g, grey solid and it was purified by achiral SFC (Stationary phase: 2-ethylpyridine 6µm 150x21.2mm, Mobile phase: 80% CO₂, 20% MeOH (0.3% iPrNH₂)). The pure fractions were collected and solvent evaporated until dryness to give 2.96 g which was triturated in Et₂O. 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

10 **a- Synthesis of Int. 265:**



- To a suspension of **7** (0.3g, 1.36mmol), benzyl alcohol (0.169mL, 1.63mmol), PPh₃ 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%).

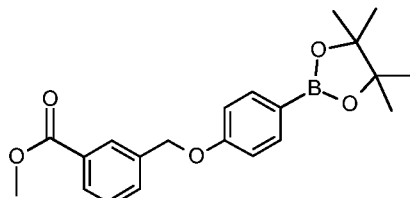


b- Synthesis of Co. 130:

- 20 In a microwave vial, a mixture of **4** (0.137 g, 0.466 mmol), **265** (0.217 g, 0.7 mmol), K₃PO₄ (0.415 g, 1.96 mmol) in 1,4-dioxane (2.19 mL) and H₂O (0.73 mL) was carefully purged with N₂. PCy₃ (27 mg, 0.098 mmol) and Pd(OAc)₂ (11 mg, 0.049 mmol) were added and the r.m. was purged again with N₂. 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 MgSO₄, filtered and evaporated *in vacuo* to give 272 mg.
- 25 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

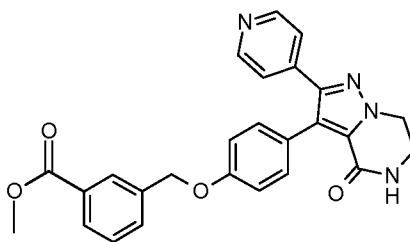
which was crystallized from DIPE, filtered and dried to give 40 mg of **Co. 130** (22%). m.p.: 260°C (dsc).

Example A132: Preparation of Co. 131



a- Synthesis of Int. 266:

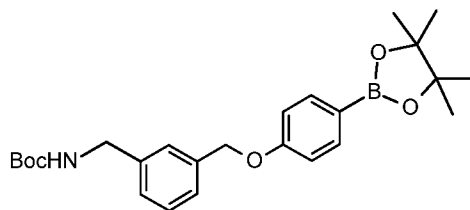
- 5 **7** (2.00g, 9.09mmol) was dissolved in ACN (20mL). K₂CO₃ (1.51g, 10.9mmol) and methyl 3-(bromomethyl)benzoate (2.19g, 9.54mmol) were added. The r.m. was stirred for 2h at r.t. An extra amount of methyl 3-(bromomethyl)benzoate (0.208g, 0.909mmol) was then added, as well as DMF (1mL). The r.m. was stirred at r.t. for 17 h. The crude mixture was diluted in EtOAc, washed with water and brine (3 times). The
10 organic layer was separated, dried over MgSO₄ and evaporated *in vacuo* to afford 3.82g of Int. **266**, pale pink oil (Quant.).



b- Synthesis of Co. 131:

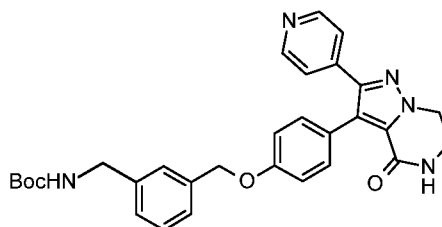
- A mixture of **4** (800 mg, 2.73 mmol), **266** (2.01 g, 5.46 mmol), K₃PO₄ (1.74 g, 8.19 mmol) in 1,4-dioxane (45 mL) and H₂O (15 mL) was carefully purged with N₂. PCy₃
15 (153 mg, 0.546 mmol) and Pd(OAc)₂ (61 mg, 273 μmol) were added, and the r.m. was purged again with N₂. The r.m. was stirred for 17 h at 80°C. The crude material was dissolved in water and extracted 2x with DCM. The organic phase was separated, dried over MgSO₄, filtered and evaporated *in vacuo* to give a solid. The solid was purified by
20 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).

- 25 Example A133: Preparation of Co. 132 and Co. 133



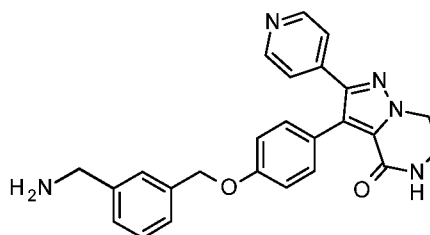
a- Synthesis of Int. 267:

- 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 15-40 μm , 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 $\text{Pd}(\text{OAc})_2$ (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).

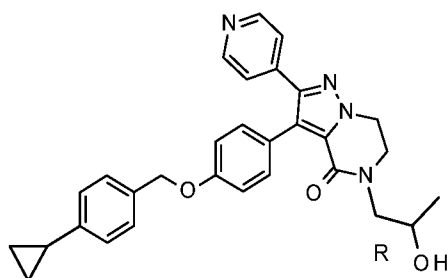


c- Synthesis of Co. 133:

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

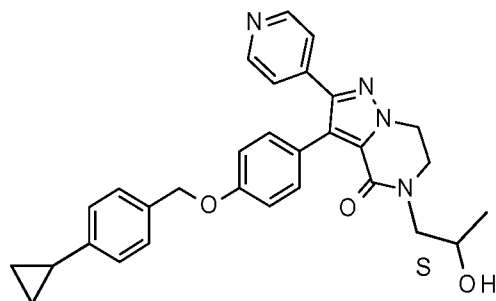
- NaHCO₃. The organic layer was separated, dried over MgSO₄ and evaporated *in vacuo* to afford 180mg. The solid was triturated in Et₂O and the supernatant was removed. This operation was repeated twice and the white powder was dried *in vacuo* to afford 150mg. This solid was purified by prep. LC (irregular SiOH 15-40 μm, 12g Merck, mobile phase gradient: from DCM 98%, MeOH 2% to DCM 95%, MeOH 4.8%, NH₄OH 0.2%). The pure fractions were collected and solvent evaporated until dryness to give 132 mg of **Co. 133**, white solid (71%). m.p.: 154 °C and 238 °C (dsc).

Example A134: Preparation of Co. 134



- NaH (825 mg, 20.6 mmol) was added slowly to a suspension of **Co. 4** (6 g, 13.75 mmol) in dry DMF (80 mL) at r.t. under N₂. The mixture was stirred for 2h then (R)-(+)-propylene oxide (1.92 mL, 27.5 mmol) was added and stirred overnight. The mixture was poured into water and K₂CO₃ and extracted with EtOAc. The organic layer was evaporated until dryness to give 6.7 g. The residue was purified by prep. LC (120g of SiOH 35-40μm GraceResolv™, mobile phase gradient: from 100% DCM to 90% DCM, 10% CH₃OH, 0.1% NH₄OH). The desired fractions were collected and the solvent was evaporated to give a residue (2.96 g) which was crystallized from Et₂O, filtered and dried to give 2.71 g of **Co. 134** (R) (40%). m.p.: 196°C (dsc); [α]_D: -25.87 ° (589 nm, c 0.2435 w/v %, DMF, 20 °C)

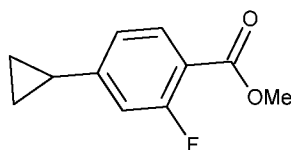
- Example A135: Preparation of Co. 135



- NaH (0.825 g, 20.6 mmol) was added portionwise to a suspension of **Co. 4** (6 g, 13.75 mmol) in DMF (80 mL) at r.t. under N₂. The mixture was stirred for 2h. (S)-(-)-propylene oxide (1.92 mL, 27.5 mmol) was added dropwise and stirred for 20h. The mixture was poured into water and K₂CO₃ and extracted with EtOAc. The organic layer

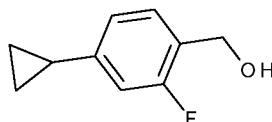
was evaporated until dryness to give 6.6 g. The residue was purified by prep. LC (120g of SiOH 35-40 μ m GraceResolv™, mobile phase gradient: from 100% DCM to 90% DCM, 10% MeOH, 0.1% NH₄OH). The desired fractions were collected and evaporated to give a residue (2.96 g) which was crystallized from Et₂O, filtered and dried to give 2.74 g of **Co. 135** (S) (40%). m.p.: 197°C; (dsc); [α]_d: +23.76 ° (589 nm, c 0.2525 w/v %, DMF, 20 °C)

Example A136: Preparation of Co. 136



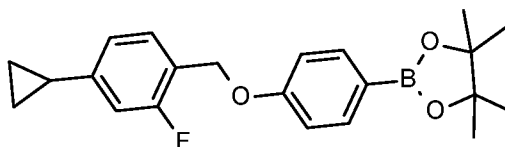
a- Synthesis of Int. 268:

in a microwave vial, a mixture of methyl 4-bromo-2-fluorobenzoate (1.00 g, 4.3 mmol), cyclopropylboronic acid (1.1 g, 13 mmol) and KF (0.75 g, 13 mmol) in dry Toluene (10 mL) was purged with N₂. Pd(PPh₃)₄ (0.25 g, 0.22 mmol) was added and the mixture was purged again with N₂ and heated at 150°C for 2h. The crude mixture was partitioned between DCM and water. The organic layer was separated, dried over MgSO₄, filtered through a pad of silica gel and evaporated *in vacuo* to give 1.0 g of Int. **268** (quant.) used like this in the next step.



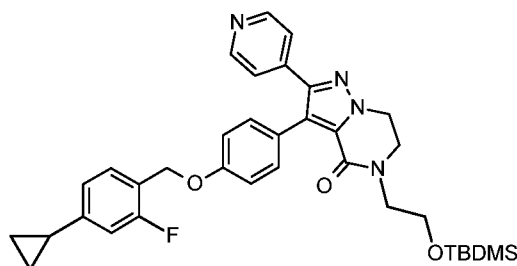
b- Synthesis of Int. 269:

268 (1.0 g, 5.1 mmol) in dry THF (9 mL) was added dropwise to a suspension of LAH (0.24 g, 6.2 mmol) in dry THF (9 mL) at 0°C under N₂. The mixture was stirred for 30min. Water (0.9 mL) then DCM (75 mL) were added very slowly and stirred for 20min. MgSO₄ was added and the insoluble was filtered on a pad of Celite® and evaporated until dryness to give 0.82 g of Int. **269**, colorless oil used like this in the next step.



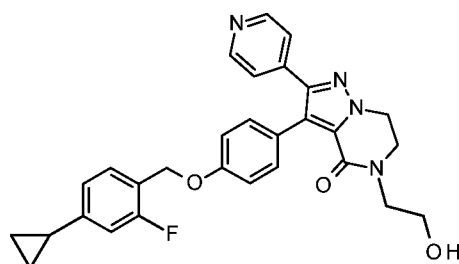
c- Synthesis of Int. 270:

DBAD (1.4 g, 5.9 mmol) was added portionwise to a sol. of **269** (0.82 g, 4.9mmol), **7** (1.3 g, 5.9 mmol), PPh₃ supp. (1.9 g, 5.9 mmol) in dry THF (30 mL). The mixture was stirred at r.t. overnight. PPh₃ supp. was filtered and the filtrate was evaporated to give a yellow oil. The crude residue was purified by prep. LC (irregular SiOH 30 μ m 80g Interchim, mobile phase: heptane/EtOAc 90/10). The desired fractions were collected and solvent evaporated until dryness to give 0.75 g of Int. **270**, pale yellow solid (41%).



d- Synthesis of Int. 271:

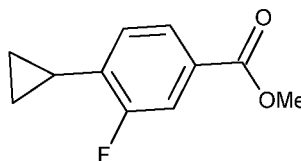
In a microwave vial, a mixture of **28** (0.77 g, 1.7 mmol), **270** (0.75 g, 2.0 mmol), K_3PO_4 (1.4 g, 6.8 mmol) in 1,4-dioxane (7.5 mL) and H_2O (2.7 mL) was carefully purged with N_2 . $PdCl_2(dppf)$ (140 mg, 0.17 mmol) was added and the r.m. was purged again with N_2 . The r.m. was heated at $80^\circ C$ 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 solid. The solid was purified by prep. LC (irregular SiOH 30 μm , 40 g Interchim, mobile phase: DCM/MeOH/ NH_4OH 98/2/0.1). The desired fractions were collected and solvent evaporated until dryness to give 0.8 g of Int. **271**, colorless oil (77%).



e- Synthesis of Co. 136:

TBAF (1.6 mL, 1.6 mmol) was added dropwise to a sol. of **271** (0.8 g, 1.3 mmol) in THF (13 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 to give 0.29g of a colorless oil which was crystallized from Et_2O . The white solid formed was filtrated, washed and dried to give 276mg of **Co. 136**, white solid (42%). m.p.: $183^\circ C$ (dsc).

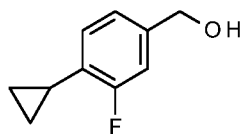
20 Example A137: Preparation of Co. 137



a- Synthesis of Int. 272:

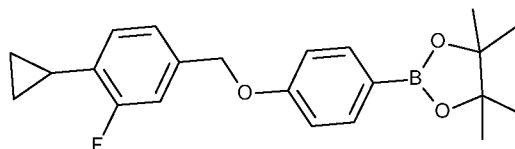
In a microwave vial, a mixture of methyl 4-bromo-3-fluorobenzoate (1.00 g 4.3 mmol), cyclopropylboronic acid (1.1 g, 13 mmol) and KF (0.75 g, 13 mmol) in dry toluene (10 mL) was purged with N_2 . $Pd(PPh_3)_4$ (0.25 g, 0.22 mmol) was added and the mixture

was purged again with N₂ and heated at 150°C for 2h. The crude was partitioned between DCM and water. The organic layer was separated, dried over MgSO₄, filtered through a pad of silica gel and evaporated *in vacuo* to give 0.85 g of Int. **272** (quant.) which was used as such in the next reaction step.



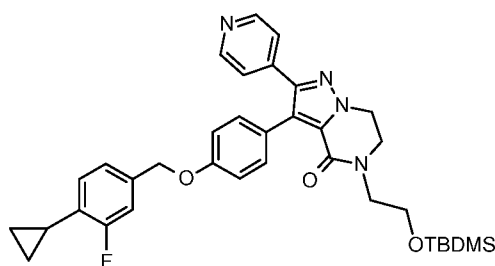
5 **b- Synthesis of Int. 273:**

272 (1.0 g, 5.1 mmol) in dry THF (9 mL) was added dropwise to a suspension of LAH (0. , 6.2 mmol) in dry THF (9 mL) at 0°C under N₂. The mixture was stirred for 30min. Water (0.9 mL) then DCM (75 mL) were added very slowly and stirred for 20min. MgSO₄ was added and the insoluble was filtered on a pad of Celite® and evaporated
10 until dryness to give 0.88g of Int. **273**, brown oil (quant.) used like this in the next step.



c- Synthesis of Int. 274:

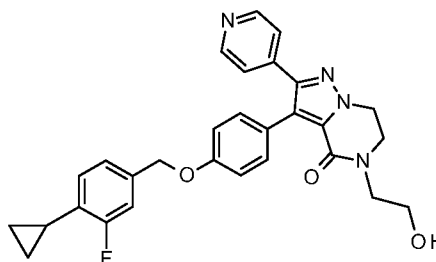
DBAD (1.4 g, 5.9 mmol) was added portionwise to a sol. of **273** (0.82 g, 4.9 mmol), **7** (1.3 g, 5.9 mmol), PPh₃ supp. (1.9 g, 5.9 mmol) in dry THF (30 mL). The mixture was stirred at r.t. overnight. The resin was filtered and the filtrate was evaporated to give
15 4.3g , yellow oil. The crude residue was purified by prep. LC (irregular SiOH 30µm 80g GraceResolv™, mobile phase: heptane/EtOAc 90/10). The desired fractions were collected and solvent evaporated until dryness to give 1.5 g of Int. **274** as a pale yellow oil used as such for the next reaction step.



d- Synthesis of Int. 275:

20 In a microwave vial, a mixture of **28** (1.1 g, 2.4 mmol), **274** (1.5 g, 2.9 mmol), K₃PO₄ (2.0 g, 9.5 mmol) in 1,4-dioxane (10 mL) and H₂O (3.7 mL) was carefully purged with N₂. PdCl₂(dppf) (194 mg, 0.24 mmol) was added and the r.m. was purged again with N₂. 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
25 MgSO₄, filtered on a pad of Celite® and evaporated *in vacuo* to give brown oil. The oil was purified by prep. LC (irregular SiOH 30 µm, 80g Interchim, mobile phase:

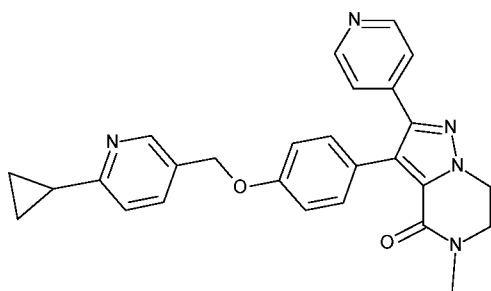
DCM/MeOH/NH₄OH 99/1/0.1). The desired fractions were collected and solvent evaporated until dryness to give 1.52 g of Int. **275**, colorless oil (100%).



e- Synthesis of Co. 137:

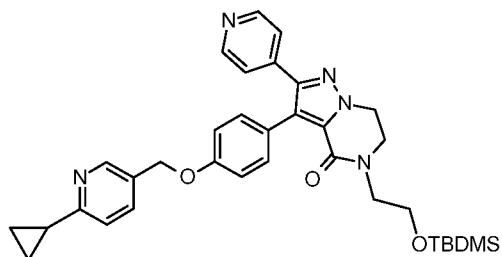
TBAF (2.9 mL, 2.9 mmol) was added dropwise to a sol. of **275** (1.5 g, 2.5 mmol) in THF (24 mL) at r.t. The mixture was stirred overnight at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 μ m, 40 g GraceResolvTM, mobile phase gradient: DCM/MeOH/NH₄OH from 98/2/0.1 to 96/4/0.1). The pure fractions were collected and solvent evaporated to give white foam which was triturated in Et₂O. The white solid formed was filtrated, washed and dried to give 0.84g of **Co. 137**, white solid (69%). m.p.: 185°C (dsc).

Example A138: Preparation of Co. 138



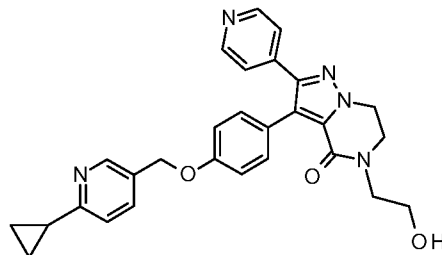
In a sealed tube, a mixture of **30** (200 mg, 651 μ mol), **98** (915 mg, 2.61 mmol), K₃PO₄ (579 mg, 2.73 mmol) in 1,4-dioxane (3 mL) and H₂O (1 mL) was carefully purged with N₂. PCy₃ (38 mg, 136 μ mol) and Pd(OAc)₂ (15 mg, 68.2 μ mol) were added and the r.m. was purged again with N₂. The r.m. was stirred for 17h at 100°C. The crude material was dissolved in water (10mL) and extracted with EtOAc (2 x 40mL). The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give 1.18 g, yellow oil. The crude mixture was purified by prep. LC (irregular SiOH 15-40 μ m, 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 230 mg. The residue was purified by achiral SFC on (2-ethylpyridine 6 μ m 150x21.2mm, mobile phase: 80% CO₂, 20% MeOH). The pure fractions were collected and solvent evaporated until dryness to give 216 mg of **Co. 138**, white solid (73%). m.p.: 175 °C (dsc).

Example A139: Preparation of Co. 139



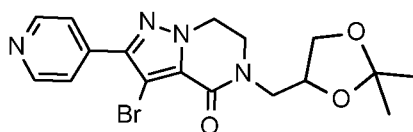
a- Synthesis of Int. 276:

PdCl₂(dppf) (0.109 g, 0.133 mmol) was added to a stirred sol. purged with N₂ of **28** (0.600 g, 1.33 mmol), **30** (0.983 g, 2.66 mmol) and K₃PO₄ (0.846 g, 3.99 mmol) in 1,4-dioxane (7.5 mL) and H₂O (2.5 mL) at r.t. The resulting mixture was purged again with N₂, 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 30 min. [fixed hold time]. The crude material was diluted with a sol. of DCM/MeOH (95:5) and water, and the organic layer was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give brown oil. This oil was purified by prep. LC (Irregular SiOH 50 μm, 80g Grace, mobile phase gradient: from DCM 100% to MeOH 6%, DCM 94%). The desired fractions were collected and evaporated *in vacuo* to give 667 mg of Int. **276** (76%).

**b- Synthesis of Co. 139:**

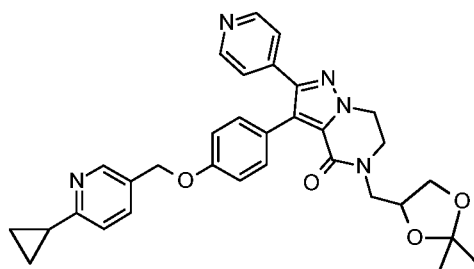
To a stirred sol. of **276** (667 mg, 1.01 mmol) in THF (10 mL) at 0°C was added TBAF (1.02 mL, 1.02 mmol), and the r.m. was stirred warming to r.t. for 17 h. The mixture was diluted with water and a sol. of DCM/MeOH (95:5). The organic layer was washed (brine), dried (MgSO₄), filtered and evaporated *in vacuo* to afford an oil (590 mg) which was purified by prep. LC (Irregular SiOH 50µm, 80g Grace, mobile phase gradient: from DCM 100% to DCM 93%, MeOH 7%). The desired fractions were collected and evaporated *in vacuo* to give a sticky oil. The oil was triturated with a mixture of Et₂O/EtOH (3/1) and a solid was formed. The solvents were removed *in vacuo* to yield 266 mg of **Co. 139**, white solid (55%). m.p.: 97 °C (dsc).

Example A140: Preparation of Co. 140a and Co. 140



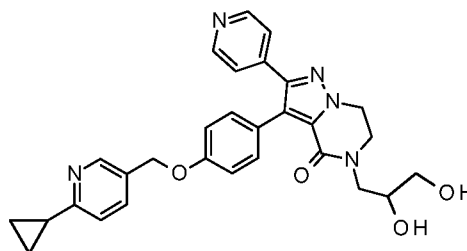
a- Synthesis of Int. 277:

NaH 60% (41 mg, 1 mmol) was added to **4** (0.2 g, 0.68 mmol) in DMSO (2 mL) at r.t. under N₂. The mixture was stirred for 2h then 2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate (0.29 g, 1 mmol) was added portionwise and the r.m. stirred for 2days. The mixture was poured into water and K₂CO₃ and extracted with EtOAc. The organic layer was evaporated until dryness. The residue was taken up with DCM, stirred for 20min then filtered. The filtrate was dried (MgSO₄), filtered and evaporated until dryness to give 0.26 g. The residue was purified by prep. LC (24g of SiOH 35-40µm GraceResolv™, mobil phase gradient: from 100% DCM to 95% DCM, 5% CH₃OH, 0.1% NH₄OH). The fractions were collected and evaporated to give 194 mg of Int. **277** (70%).



b- Synthesis of Co. 140a

277 (800 mg, 1.96 mmol), **30** (1.04 g, 2.95mmol), K₃PO₄ (1.25 g, 5.89 mmol) in 1,4-dioxane (8 mL) and H₂O (4 mL), in a sealed tube, were purged with N₂ for 10 min. Then, PdCl₂(dppf) (161 mg, 0.196 mmol) was added. The resulting mixture was purged again with N₂, 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 30 min. [fixed hold time]. The mixture was diluted in water and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and evaporated to give 1.08 g of **Co. 140a**, brown oil (quant.). The crude **Co. 140a** was used as such as for the next step.

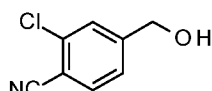


c- Synthesis of Co. 140:

A sol. of **Co. 140a** (1.08 g, 1.95 mmol), HCl 3N (3.3 mL, 9.77 mmol) in 1,4-dioxane (40 mL) were heated to 80°C for 30 min. The mixture was quenched with a 10% sol. of K₂CO₃ and extracted with EtOAc. The organic layer was separated, dried over MgSO₄, filtered and evaporated *in vacuo* to give 800 mg, brown oil. This oil was purified by prep. LC (irregular SiOH 15-40 µm, 80g, Interchim, mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The desired fractions were collected and solvent evaporated until dryness to give 350 mg, grey solid. The solid was purified by prep. LC

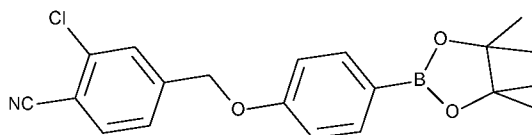
(irregular SiOH 15-40 μ m, 45g, Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The desired fractions were collected and solvent evaporated until dryness to give 310 mg, white solid (31%). The white solid was dissolved in MeOH and concentrated *in vacuo* to afford a thick oil. The oil was triturated with gradual addition of Et₂O to give a white precipitate. The precipitate was filtered off and washed with Et₂O. The solid was collected and dried *in vacuo* to give 292 mg. This 292mg was recrystallized in EtOH (two times) overnight to give 158mg of **Co. 140**, white solid (15%).

Example A141: Preparation of Co. 141



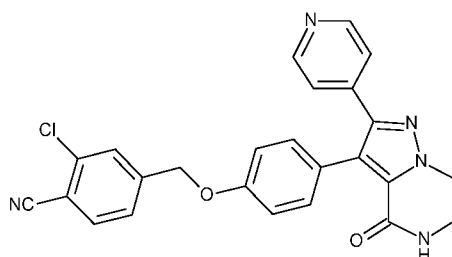
10 **a- Synthesis of Int. 279:**

Pd(PPh₃)₄ (0.78g, 0.68mmol) was added to a mixture of 4-bromo-3-chlorobenzyl alcohol (1.5g, 6.78mmol) and Zn(CN)₂ (0.404g, 3.39mmol) in DMF (15mL) in a sealed tube. The mixture was heated at 120°C for 30 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 with DCM. The organic layer was separated, dried over MgSO₄, filtered and the solvent was evaporated until dryness. The residue was purified (with another batch, initial reactant 0.2g) by prep. LC on (Irregular SiOH 15-40 μ m 50g Merck, Mobile phase gradient: from DCM 100% to DCM 97%, MeOH 3%). The pure fractions were collected and solvent evaporated until dryness to give 1.15g of Int. **279** (89%).



b- Synthesis of Int. 280:

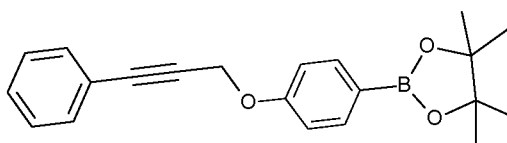
To a suspension of **279** (0.6 g, 3.58 mmol), **7** (0.945 g, 4.3 mmol), DBAD (0.989 g, 4.3mmol) in dry DCM (8 mL) was added PPh₃ supp. (1.34 g, 4.3 mmol) and the r.m. was stirred at r.t. for 18 h. The insoluble was filtered through Celite®, washed with DCM. Water was added and the organic layer was separated, dried, filtered and concentrated until dryness to give 2.4g. The residue was purified by prep. LC on (Irregular SiOH 15-40 μ m 50g Merck, Mobile phase: DCM 100%). The pure fractions were collected and evaporated until dryness to give 679 mg of Int. **280** (51%).



c- Synthesis of Co. 141:

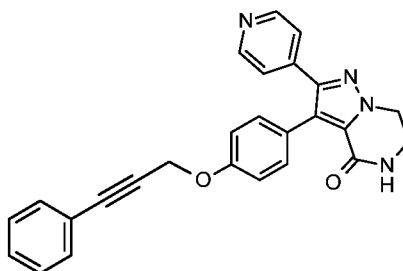
In a microwave vial, a mixture of **4** (0.3 g, 1.02 mmol), **280** (0.492 g, 1.33 mmol), K_3PO_4 (0.911g, 4.29mmol) in 1,4-dioxane (4.8 mL) and H_2O (1.6 mL) was carefully purged with N_2 . $PdCl_2(dppf)$ (84 mg, 0.1mmol) was added and the r.m. was purged with N_2 . The r.m. was stirred for 16 h at $80^\circ C$. 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: irregular 15-40 μm 30g Merck, Mobile phase: 0.5% NH_4OH , 94.5% DCM, 5% MeOH). The pure fractions were collected and evaporated to give 330 mg which was crystallized in Et_2O , filtered and dried to give 275 mg of **Co. 141** (59%). m.p.: $257^\circ C$ (dsc).

Example A142: Preparation of Co. 142



a- Synthesis of Int. 281:

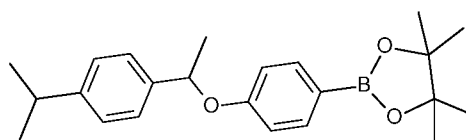
The reaction was performed in anhydrous conditions under Ar-atmosphere. K_2CO_3 (0.240 g, 1.73 mmol) and (3-bromo-1-propynyl)benzene (75 % in toluene) (0.293 mL, 1.59 mmol) were successively added to a sol. of **7** (0.345 g, 1.57 mmol) in ACN (7.22 mL). The r.m. was stirred at r.t. for 18h. K_2CO_3 (0.372 g, 2.69 mmol) and (3-bromo-1-propynyl)benzene (0.300 mL, 2.17mmol) were then successively added again. After 22h at r.t., the r.m. was filtrated, washed with EtOAc and concentrated to dryness. The residue was purified by prep. LC (15-40 μm , 50g, mobile phase gradient: cyclohexane/DCM: 80/20 to 0/100). The pure fractions were collected and the solvent was evaporated to give 0.435g of Int. **281**, yellow solid (90%).



b- Synthesis of Co. 142:

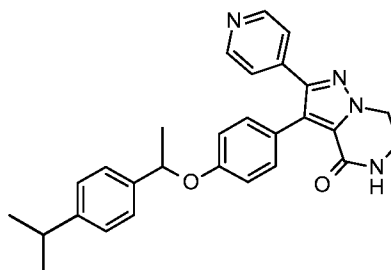
In a Schlenk tube, a mixture of **4** (125 mg, 0.426 mmol), **281** (427 mg, 1.), K₃PO₄ (362mg, 1.) in 1,4-dioxane (1.8 mL) and H₂O (0.6 mL) was carefully purged with N₂. PCy₃ (24 mg, 85.2 μmol) and Pd(OAc)₂ (10mg, 42.6μmol) were added and the r.m. was purged again with N₂. The Schlenk tube was then sealed and the r.m. was stirred for 17h at 80°C. The crude material was dissolved in water (20 mL) and extracted with EtOAc (2x 40mL). The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give 300 mg, yellow oil. The crude mixture was purified by prep. LC (irregular SiOH 15-40 μm, 30g Merck, mobile phase gradient: from DCM 100% to DCM 60%, Acetone 40%). The pure fractions were collected and solvent evaporated to give 90 mg of Co. **142**, white solid (50%). m.p.: 245°C (DSC).

Example A143: Preparation of Co. 143



a- Synthesis of Int. 282:

DBAD (1.05 g, 4.57 mmol) was added to a stirred sol. of 1-(4-iso-propylphenyl)ethanol (500 mg, 3.04 mmol), **7** (1.01 g, 4.57 mmol) and PPh₃ supp. (1.52 g, 4.57 mmol) in THF (18 mL) under N₂ at r.t., and the mixture was stirred at r.t. for 16h. The crude mixture was filtered off and the filtrate was evaporated *in vacuo* to give an oil which was purified by prep. LC (Irregular SiOH 15-40μm, 120g Grace, mobile phase gradient: from Heptane 100% to EtOAc 30%, Heptane 70%). The pure fractions were collected and solvent evaporated to give 554 mg of Int. **282**, solid (50%).

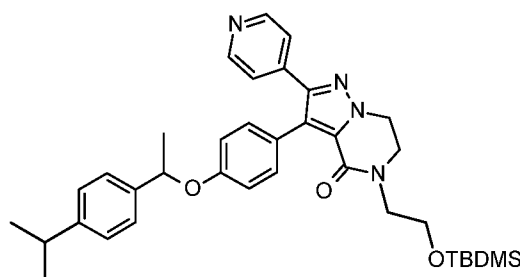


b- Synthesis of Co. 143:

A mixture of **4** (150 mg, 0.512 mmol), **282** (469 mg, 1.28 mmol), K₃PO₄ (434 mg, 2.05 mmol) in 1,4-dioxane (2.4 mL) and H₂O (0.8 mL) was carefully purged with N₂. PCy₃ (29 mg, 0.102 mmol) and Pd(OAc)₂ (11 mg, 51.2 μmol) were added and the r.m. was purged with N₂. The r.m. was stirred at 80°C for 17h. Then, additional **282** (100 mg, 0.273 mmol), PCy₃ (14 mg, 49.8 μmol) and Pd(OAc)₂ (6 mg, 25.6 μmol) were added under N₂ at r.t. The mixture was stirred at 80°C for 16h. The crude material was dissolved in water and extracted with DCM. The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give a solid which was purified by prep. LC (irregular SiOH 15-40μm, 30g Merck, mobile phase gradient: from DCM/MeOH 100/0

to 95/5). The pure fractions were collected and solvent evaporated to give 153 mg, white solid. The solid was triturated with Et₂O, and the solvent was separated. The solid was washed 2x with Et₂O and dried *in vacuo* to yield 105 mg of **Co. 143**, white solid (45%) m.p.: 217 °C (dsc).

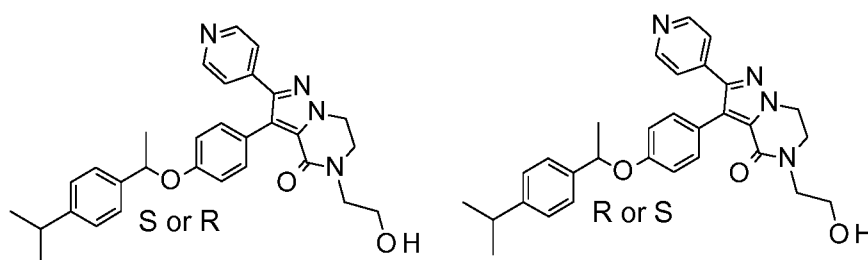
5 Example A144: Preparation of Co. 144 and Co. 145



a- Synthesis of Int. 283:

In a microwave vial, a mixture of **28** (1.078 g, 2.39 mmol), **282** (2.1 g, 2.87 mmol), K₃PO₄ (2.03 g, 9.56 mmol) in 1,4-dioxane (10.5 mL) and H₂O (3.7 mL) was carefully purged with N₂. PdCl₂(dppf) (196 mg, 0.24 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, filtered on a pad of Celite® and evaporated *in vacuo* to give 3.41 g. The residue was purified by prep. LC (Stationary phase: irregular SiOH 15-40µm 300g MERCK, Mobile phase: 0.1% NH₄OH, 99% DCM, 1% MeOH). The pure fractions were collected and evaporated until dryness to give 850 mg of Int. **283** (58%).

b- Synthesis of Co. 144 & Co. 145:



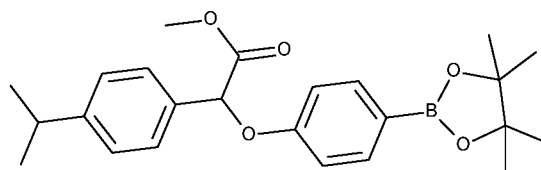
Compound 144

Compound 145

TBAF (1.67 mL, 1.67 mmol) was added dropwise to a sol. of **283** (0.85 g, 1.39 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 845 mg. The crude mixture was purified by prep. LC (Stationary phase: Sunfire Silica 5µm 150x30.0mm, Mobile phase Gradient: from 0.2% NH₄OH, 98% DCM, 2% MeOH to 1.1% NH₄OH, 89% DCM, 10% MeOH). The pure fractions were collected and evaporated until dryness to give 512 mg. The residue was purified by chiral SFC

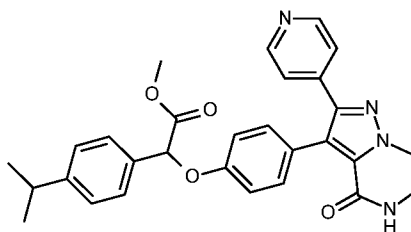
(Stationary phase: Chiralcel OD-H 5 μ m 250x20mm, Mobile phase: 75% CO₂, 25% MeOH(0.3% iPrNH₂)). The pure fractions were collected and evaporated until dryness to give 238 mg of a first compound and 247mg of a second compound. The first compound was crystallized from DIPE, filtered and dried to give 182 mg of **Co. 144** (26%) m.p.: 148°C (dsc). The second compound was crystallized from DIPE, filtered and dried to give 188 mg of **Co. 145** (27%). m.p.: polymorph: 148°C and 162°C (dsc); Co. 144: [α]_d: -48.19 ° (589 nm, c 0.249 w/v %, DMF, 20 °C); Co. 145 : [α]_d: +47.79 ° (589 nm, c 0.249 w/v %, DMF, 20 °C)

Example A145: Preparation of Co. 146a and Co. 146

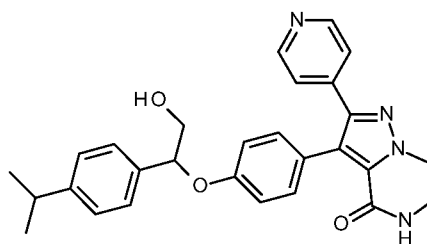


a- Synthesis of Int. 284:

A sol. of methyl 2-hydroxy-2-[(4-(propan-2-yl)]acetate (500 mg, 2.40 mmol), **7** (687 mg, 3.12 mmol) and PPh₃ (756 mg, 2.88 mmol) in dry DCM (12 mL) was treated with DBAD (663 mg, 2.88 mmol) and stirred at r.t. for 19h. Then, EtOAc and brine were added, and the organic layer was separated, dried over MgSO₄, filtered and evaporated *in vacuo* to afford 3.03 g, pale yellow oil. This oil was purified by prep. LC (irregular SiOH 15-40 μm, 120g, GraceResolv™, mobile phase gradient: from heptane 100% to heptane/EtOAc 70/30). The pure fractions were collected and solvent evaporated until dryness to give 760 mg of Int. **284**, sticky colorless solid (77%).

**b- Synthesis of Co. 146a**

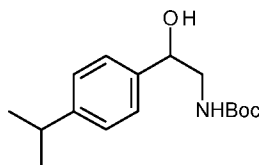
A mixture of **4** (0.298 g, 1.02 mmol), **284** (0.750 g, 1.83 mmol) and K₃PO₄ (0.539 g, 2.54 mmol) in 1,4-dioxane (3mL) and H₂O (1.5 mL) was purged with N₂. PdCl₂(dppf) (71 mg, 86.3 μmol) was then added. The mixture was purged again with N₂ and stirred at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 20 min [fixed hold time]. Then a sol. of DCM/MeOH (95:5) and water were added. The organic layer was separated, washed with brine, separated, dried over MgSO₄, filtered and evaporated *in vacuo* to yield 570 mg, solid. The residue was purified by prep. LC (Irregular SiOH 50 μm, 40g Grace, mobile phase gradient: from DCM 100% to DCM 93%, MeOH 7%). The desired fractions were evaporated *in vacuo* to give 226 mg of **Co. 146a**, white solid (45%).



c- Synthesis of Co. 146:

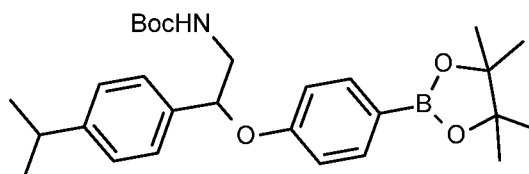
NaBH₄ (76 mg, 2.01 mmol) was added to a stirred suspension of **Co. 146a** (166 mg, 0.334 mmol) in dry THF (4 mL) and MeOH (0.75 mL) at r.t. under N₂. The r.m. was stirred at 50 °C for 3h, and then a sat. sol. of NaHCO₃ and EtOAc were added. The organic layer was washed with brine, separated, dried over MgSO₄, filtered and evaporated *in vacuo* to yield 198 mg, white solid. The residue was purified by prep. LC (Irregular SiOH 50 μm, 40g Grace, mobile phase gradient: from DCM 100% to DCM 91%, MeOH 9%). The desired fractions were evaporated *in vacuo* to give 66 mg, white solid. The solid was triturated in MeOH, and the solvent was allowed to evaporate slowly. The afforded solid was collected and dried *in vacuo* at 50°C for 1h to yield 65 mg of **Co. 146**, white solid (41%). m.p.: 228 °C and 238 °C (dsc- polymorphous compound).

Example A146: Preparation of Co. 147



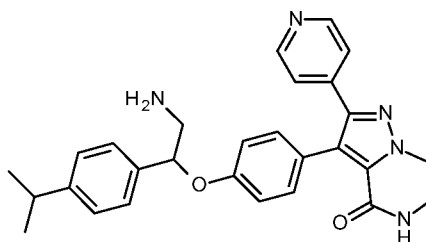
a- Synthesis of Int. 286:

BOC-anhydride (122 mg, 0.558 mmol) and DMAP (68 mg, 0.558 mmol) were added to a stirred sol. of 2-amino-1-(4-isopropylphenyl)ethanol (100 mg, 0.558 mmol) in ACN (3mL) at rt. The r.m. was stirred at r.t. for 2h. Another batch (717mg of initial reactant) was combined with this reaction and the sol. was diluted in DCM and washed successively with HCl 1N and sat. NaHCO₃. The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo*. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 50g, Merck, Mobile phase gradient: DCM/MeOH, from 100/0 to 80/20 The pure fractions were collected and solvent evaporated until dryness to give 500mg of Int. **286**, white solid (global yield: 39%).



b- Synthesis of Int. 287:

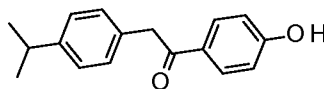
DBAD (495 mg, 2.15 mmol) was added to a mixture of **7** (473 mg, 2.15 mmol), **286** (400 mg, 1.43 mmol) and PPh₃ supp. (563 mg, 2.15 mmol) in DCM (4 mL) and the r.m. was stirred under N₂ for 17h at r.t. The sol. was filtered and the residual polymer was washed with DCM. The filtrate was evaporated *in vacuo*. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 50g Merck, mobile phase gradient: from Heptane 100% to EtOAc 10%, Heptane 90%). The pure fractions were collected and solvent evaporated to give 200 mg of Int. **287**, white gum (29%).



c- Synthesis of Co. 147:

A sol. of **4** (82 mg, 0.277 mmol) and **287** (200 mg, 0.415 mmol) in 1,4-dioxane (2 mL) and H₂O (1 mL) was treated with K₃PO₄ (176 mg, 0.831 mmol) and purged with N₂. PdCl₂(dppf) (23 mg, 27.7 μmol) was then added and the r.m. was carefully purged with N₂. 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]. HCl 3N (2.5mL) was then slowly added and the sol. was stirred at r.t. for 18h. The r.m. was diluted with EtOAc and washed with aq. NaHCO₃ (twice). The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give 260mg, brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 50g, MERCK, Mobile phase gradient: from DCM 100 % to DCM 95%, MeOH 95%). The pure fractions were collected and solvent evaporated until dryness to give 75mg of **Co. 147**, white solid. m.p.: 178°C (dsc).

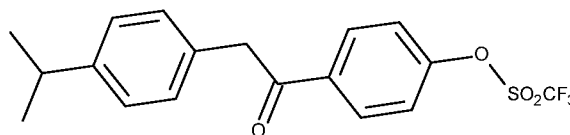
Example A147: Preparation of Co. 148



a- Synthesis of Int. 288:

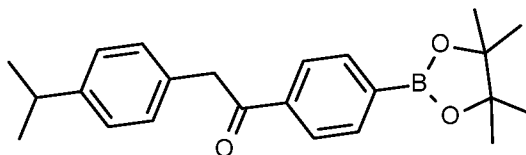
To a sol. of 1-(4-methoxyphenyl)-2-[4-(propan-2-yl)phenyl]ethan-1-one (6.26 g, 23.3 mmol) in acetic acid (43 mL) was added hydriodic acid 57% in water (14 mL, 167 mmol). The sol. was refluxed for 72h and cooled down to 0°C. Water was carefully added and the precipitate was filtered on a glass frit. The brown solid obtained was washed with Et₂O and dried *in vacuo* to give 798 mg, beige solid (13%). The Et₂O filtrate was evaporated *in vacuo* and coevaporated with toluene (3 times). The residue was taken up in DCM and the precipitate was filtered on a glass frit, washed with DCM and dried *in vacuo* to give 2.07 g of pale brown solid (35%). The DCM filtrate was

evaporated again, the residue was taken up in a minimum of DCM, the precipitate was filtered on a glass frit and dried *in vacuo* to give 687 mg of pale brown solid (12%). The three solids were put together to give 3.55g of Int. **288** (60%).



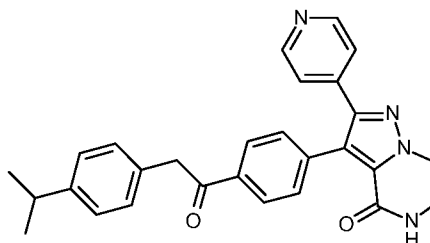
b- Synthesis of Int. 289:

- 5 To a sol. of **288** (798 mg, 3.14 mmol) in DCM (7 mL) were added DMAP (38.3 mg, 0.314 mmol), Et₃N (1.31 mL, 9.41 mmol) and N-phenyltrifluoromethanesulfonimide (1.68 g, 4.71 mmol). The sol. was stirred at r.t. for 90 min then concentrated *in vacuo*. The residue was purified by prep. LC (Irregular SiOH 15-40 μm, 50g Merck, solid deposit, mobile phase gradient: from heptane 100% to heptane 80, EtOAc 20%). The
- 10 pure fractions were collected and solvent evaporated until dryness to give 1.17 g of Int. **289**, yellow oil which crystallized (97%).



c- Synthesis of Int. 290:

- To a sol. of **289** (1.10 g, 2.85 mmol) in DME (12 mL) in a schlenk tube were added BisPin (1.08 g, 4.27 mmol) and KOAc (838 mg, 8.54 mmol). The mixture was
- 15 carefully purged with N₂ and PdCl₂(dppf) (233 mg, 0.285 mmol) was added. The mixture was purged again with N₂ and heated at 80°C for 18h. EtOAc and water were added, the organic layer was separated, dried over MgSO₄, filtered off and evaporated *in vacuo* to give a brown oil. This oil was triturated in Et₂O and the precipitate was filtered off on a glass frit. The filtrate was evaporated *in vacuo* to give a black residue.
- 20 This residue was dissolved in MeOH, water was added and the mixture was evaporated *in vacuo* (process repeated 3x). The residue was diluted in DCM, dried over MgSO₄, filtered off and evaporated *in vacuo* to give 942 mg of Int. **290**, black solid (91%).

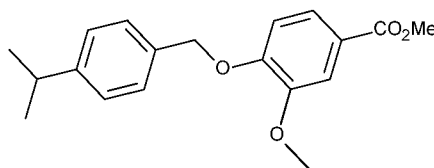


d- Synthesis of Co. 148:

- A mixture of **4** (2.94 g, 10.0 mmol), **290** (3.65 g, 10.0 mmol) and K₃PO₄ (8.51 g, 40.1 mmol) in 1,4-dioxane (50 mL) and H₂O (10 mL) in a Schlenk tube was purged with N₂. PdCl₂(dppf) (820 mg, 1.00 mmol) was added, the mixture was purged again with N₂
- 25

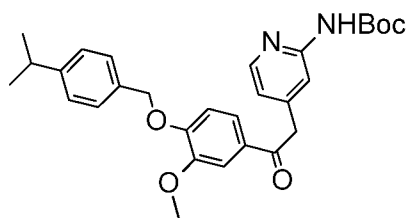
and heated at 80°C for 18h. Another batch (reactant 0.3g of **4**, in the same conditions) was combined with this reaction. The mixture was diluted with DCM and water and the organic layer was separated, dried over MgSO₄, filtered off and evaporated *in vacuo* to give 15 g of brown oil. This oil was purified by prep. LC (Irregular SiOH 15-40 µm, 330g Grace, solid deposit, mobile phase gradient: from DCM 100% to DCM 95%, iPrOH 5%). The pure fractions were collected and solvent evaporated until dryness to give a beige solid which was triturated in Et₂O. The precipitate was filtered on a glass frit to give 3.20 g of Co. 148, off-white solid (global yield 64%, purity 97%). 405 mg of 3.2 g was purified by achiral SFC (Stationary phase: diethylaminopropyl 5µm 150x21.2mm, Mobile phase: 85% CO₂, 15% MeOH (0.3% iPrNH₂)). The pure fractions were collected and solvent evaporated until dryness to give 289 mg which was crystallized from iPrOH. The precipitate was filtered on a glass frit and the solid was washed with Et₂O twice then dried under high vacuum at 50°C for 18h to give 178 mg of Co. **148**, white solid. m.p.: 259°C (dsc).

Example A148: Preparation of Co. 149



a- Synthesis of Int. 291:

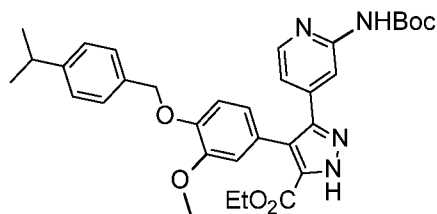
Under N₂, to a suspension of methyl vanillate (2.0 g, 11 mmol), 4-isopropylbenzyl alcohol (1.7 mL, 11 mmol), PPh₃ supp. (3.4 g, 11 mmol) in dry DCM (48 mL) was added DBAD (2.5 g, 11 mmol) and the r.m. was stirred at r.t. for 3 h. The mixture was filtrated through a Celite® pad, evaporated *in vacuo* to give a colorless oil. This oil was purified by prep. LC (irregular SiOH 30 µm, 120g Interchim, mobile phase gradient: heptane/EtOAc, from 90/10 to 80/20). The pure fractions were collected and solvent evaporated to give 2.22 g of Int. **291**, white solid (64%).



b- Synthesis of Int. 292:

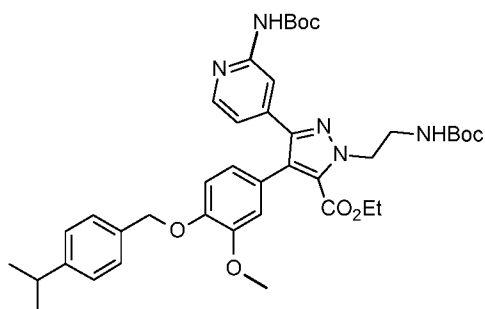
A sol. of **291** (2.2 g, 7.0 mmol) and 2-(4-methyl-2-pyridinyl)-imidodicarbonic acid, 1,3-bis(1,1-dimethylethyl) ester (2.17 g, 7.0 mmol) in dry THF (20 mL) was treated with LiHMDS (14 mL, 14 mmol) at 0°C (addition over 10 min). After stirring for 1h at 0°C, the reaction was allowed to warm to r.t. and was stirred for 17 h. The reaction was quenched with a 10% aq. sol. of NH₄Cl (50mL). The mixture was extracted with DCM.

The organic layer was collected and evaporated *in vacuo* and the residue was taken in Et₂O, the solid formed was filtrated and dried to afford 1.59 g of Int. **292**, beige powder (46%).



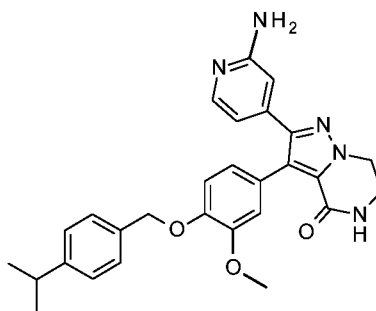
c- Synthesis of Int. 293:

- 5 To a suspension of **292** (1.6 g, 3.2 mmol) in ACN (12 mL) was added 1,8-diazabicyclo(5.4.0)undec-7-ene (0.49 mL, 3.2 mmol) and ethyl diazoacetate (0.58 mL, 5.5 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 NaHCO₃, dried over MgSO₄, filtered off and
- 10 evaporated *in vacuo*. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 80g GraceResolv™, mobile phase gradient: from Heptane/EtOAc 70/30 to 60/40). The pure fractions were collected and solvent evaporated until dryness to give 670 mg of Int. **293**, beige powder (35%).



d- Synthesis of Int. 294:

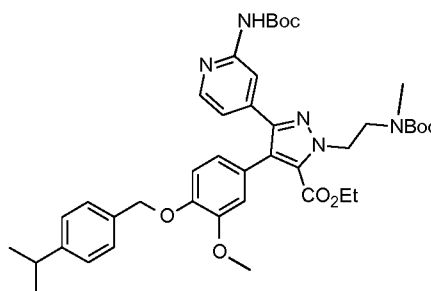
- 15 To a mixture of **293** (330 mg, 0.56 mmol), Boc-glycinol (136 mg, 0.84 mmol) and PPh₃ supp. (703 mg, 0.84 mmol) in dry THF (9 mL) was added DBAD (194 mg, 0.84 mmol). The mixture was stirred at r.t. for 12h. The mixture was filtrated through a Celite® pad, concentrated and purified by prep. LC (irregular SiOH 30 μm, 40g Interchim, Mobile phase gradient: from heptane/EtOAc 75/25 to 70/30). The pure
- 20 fractions were collected and solvent evaporated until dryness to give 251 mg of Int. **294**, white solid (61%).



e- Synthesis of Co. 149:

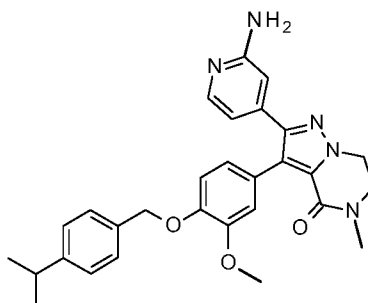
294 (250 mg, 0.34 mmol), HCl 3N (0.57 mL, 1.7 mmol), in ACN (6.1 mL) at 80°C for 3 h. The mixture was concentrated, and K₂CO₃ 10% aq (20 mL) was added and the mixture was extracted with DCM, dried and concentrated. The mixture was put in DCM, filtrated and the filtrate was purified by prep. LC (Irregular SiOH 15-40 µm, 12g GraceResolv™, mobile phase gradient: DCM/MeOH/NH₄OH from 98/2/0.1 to 95/5/0.1) to give 58 mg of **Co. 149**, white solid (35%). m.p.: 179°C (dsc).

Example A149: Preparation of Co. 150



a- Synthesis of Int. 295:

To a mixture of **293** (260 mg, 0.44 mmol), 2-(N-Boc-methylamino)ethanol (116 mg, 0.66 mmol) and PPh₃ supp. (554 mg, 0.66 mmol) in dry THF (7 mL) was added DBAD (153 mg, 0.66 mmol). The mixture was stirred at r.t. for 3 h. The mixture was filtrated throught a celite® pad, concentrated and purified by prep. LC (irregular SiOH 30 µm, 40g Interchim, Mobile phase gradient: from heptane/EtOAc 75/25 to 70/30). The pure fractions were collected and solvent evaporated until dryness to give 270 mg of Int. **295**, white solid (82%).



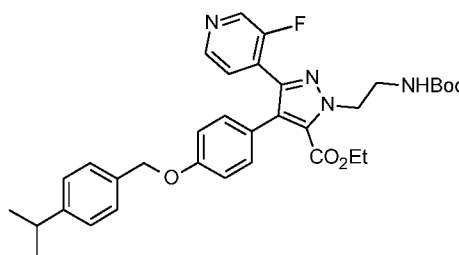
b- Synthesis of Co. 150:

295 (270 mg, 0.36 mmol), HCl 3N (0.61 mL, 1.8 mmol), in ACN (6.4 mL) at 80°C for 2h. The mixture was concentrated, K₂CO₃ 10% aq (20 mL) was added and the mixture

was stirred at r.t. for 30 min. The mixture was extracted with DCM (twice) and the organic layer was dried over MgSO_4 , filtrated and evaporated. The residue was purified by prep. LC (Irregular SiOH 15-40 μm , 12g GraceResolv™, mobile phase gradient: DCM/MeOH/ NH_4OH from 98/2/0.1 to 95/5/0.1). The pure fractions were collected and solvent evaporated until dryness to give 105 mg of **Co. 150**, white powder (58%).

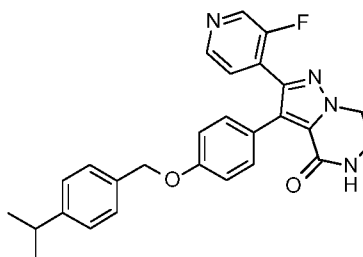
Example A150: Preparation of Co. 151

▪ **First method:**



a- Synthesis of Int. 296:

A sol. of **17** (800 mg, 1.36 mmol), 3-fluoro-4-pyridineboronic acid pinacol ester (608 mg, 2.73 mmol) and Na_2CO_3 (434 mg, 4.09 mmol) in toluene (10 mL), EtOH (5 mL) and H_2O (2 mL) in a sealed tube was purged with N_2 . $\text{PdCl}_2(\text{dppf})$ (112 mg, 0.136 mmol) was added, the mixture was purged again with N_2 and heated at 130°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 5 min [fixed hold time]. The mixture was diluted with DCM and washed with water. The organic layer was separated, dried over MgSO_4 , filtered off and evaporated *in vacuo* to give 1.54 g, brown oil. This oil was purified by prep. LC (Irregular SiOH 15-40 μm , 80g Grace, mobile phase gradient: from DCM 100% to DCM 90%, acetone 10%). The pure fractions were collected and solvent evaporated until dryness to give 720 mg of Int. **296**, yellow oil (78%).



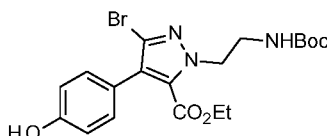
b- Synthesis of Co. 151:

To a sol. of **296** (720 mg, 1.20 mmol) in ACN (15 mL) was added HCl 3N (2.00 mL, 5.97 mmol). The sol. was heated at 80°C for 2h, cooled down to r.t. and the solvent was removed *in vacuo*. DCM and a sat. aq. sol. of NaHCO_3 were added to the residue, the mixture was stirred at r.t. for 10min and the organic layer was separated, dried over MgSO_4 , filtered off and evaporated *in vacuo* to give a brown oil which crystallized. The crude mixture was purified by prep. LC (Irregular SiOH 15-40 μm , 25g Merck, solid deposit, mobile phase gradient: from DCM 100% to DCM 80%, acetone 20%).

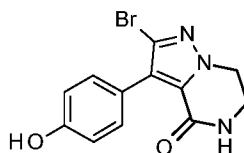
The pure fractions were collected and solvent evaporated until dryness to give 363mg of **Co. 151**, white solid (67%). m.p.: 228°C, 235°C (dsc - polymorphous compound).

▪ **Second Method:**

a- Synthesis of Int. 297:

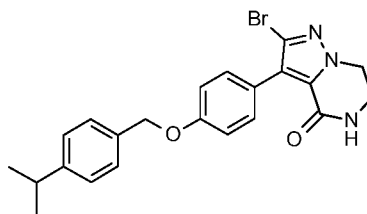


- 5 HCl 3N (8.37 mL, 33.5 mmol) was added to a sol. of **22** (3.91 g, 5.58 mmol) in 1,4-dioxane (30 mL) and the sol. was stirred for 60 h at 50°C. The precipitate formed was filtered on a glass frit and washed with Et₂O to give 2.75 g of Int. **297**, white solid (quant. yield).



b- Synthesis of Int. 298:

- 10 To a sol. of **297** (2.75 g, 5.93 mmol) in MeOH (40 mL) was added Cs₂CO₃ (9.66 g, 29.7 mmol) and the mixture was stirred at r.t. for 1h. The solvent was removed *in vacuo* and the yellow solid obtained was dissolved in a minimum of water and acidified until pH3 with a 1N aq. sol. of HCl. The white precipitate formed was filtered on a glass frit, washed with Et₂O (3 times) and dried to give 1.86g of Int. **298**, white solid
- 15 (quant. yield).

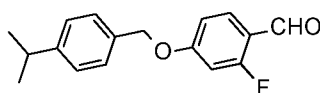


c- Synthesis of Int. 299:

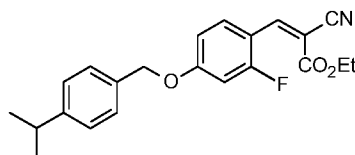
- To a sol. of **298** (1.00 g, 3.25 mmol) in DMF (10 mL) were added K₂CO₃ (673 mg, 4.87 mmol), NaI (24.3 mg, 162 μmol) and 4-isopropylbenzyl bromide (543 μL, 3.25 mmol). The mixture was heated at 150°C for 18h and 4-isopropylbenzyl bromide (543 μL, 3.25 mmol) was added. The mixture was heated at 150°C for 20 h and cooled down to r.t. Water and DCM were added to the crude mixture. The precipitate was filtered off on a glass frit to give a white solid. The organic layer was separated, dried over MgSO₄, filtered off and evaporated *in vacuo* to give a white solid. Both solids were combined, dissolved in a mixture of DCM/MeOH and purified by prep. LC (Irregular
- 20
- 25 SiOH 15-40 μm, 25g Merck, solid deposit, mobile phase gradient: from DCM 100% to DCM 90%, acetone 10%). The pure fractions were collected and solvent evaporated to give 1.00 g of Int. **299**, white solid (70%).

d- Synthesis of Co. 151:

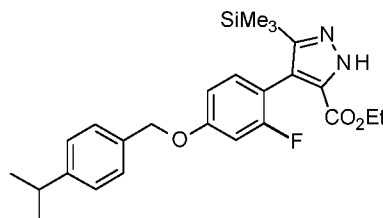
In a sealed tube, a mixture of **299** (130 mg, 295 μ mol), 3-fluoro-4-pyridineboronic acid pinacol ester (132 mg, 590 μ mol), K_3PO_4 (251 mg, 1.18 mmol) in 1,4-dioxane (1.40 mL) and H_2O (0.50 mL) was carefully purged with N_2 . PCy_3 (16.6 mg, 59.1 μ mol) and $Pd(OAc)_2$ (6.63 mg, 29.5 μ mol) were added, the r.m. was purged again with N_2 and heated at 100°C for 18h. After cooling down to rt, EtOAc and water were added to the crude mixture. The organic layer was separated, dried over $MgSO_4$, filtered off and evaporated *in vacuo* to give 137 mg of brown oil. This 137 mg was combined with 103 mg from another batch and purified by prep. LC (Irregular SiOH 15-40 μ m, 10g Merck, mobile phase gradient: from DCM 100% to DCM 80%, acetone 20%). The pure fractions were collected and solvent evaporated until dryness to give 65 mg of **Co. 151**, white solid (27%). m.p.: 222°C (dsc).

Example A151: Preparation of Co. 152**a- Synthesis of Int. 300:**

To a sol. of 2-fluoro-4-hydroxybenzaldehyde (1.3 g, 9.4 mmol) in ACN (34 mL) was added K_2CO_3 (3.2 g, 23 mmol) and **8** (2.1 g, 9.8 mmol), the r.m. was heated at 70 °C for 2h. Then, the mixture was allowed to cool down to rt, filtered and concentrated to give 2.67 g of Int. **300**, colorless oil which quickly crystallized in white solid (100%).

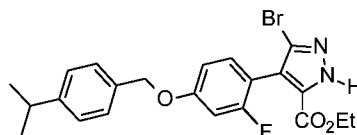
**b- Synthesis of Int. 301:**

To a sol. of ethyl cyanoacetate (1.1 mL, 10.3 mmol) in EtOH (6.5 mL) was added **300** (2.67 g, 9.8 mmol) and piperidine (19 μ L, 0.20 mmol). The mixture was refluxed for 2h and then, allowed to cool down to r.t. overnight. The precipitate formed was filtered on a glass frit to give 2.68 g of Int. **301**, pale yellow powder (74%).

**c- Synthesis of Int. 302:**

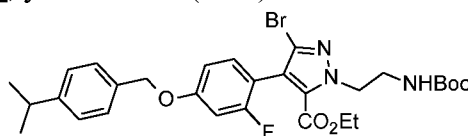
To a sol. of trimethylsilyldiazomethane (5.47 mL, 11 mmol) in dry THF (15 mL) at -78°C under N_2 was added n-BuLi 1.6M in hexane (6.8 mL, 11 mmol) dropwise. The sol. was stirred for 30 min at -78°C and a sol. of **301** (2.68 g, 7.3 mmol) in dry THF (15 mL) was added dropwise at -78°C. The sol. was stirred 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 NaHCO₃, dried over MgSO₄, filtered off and evaporated *in vacuo* to give brown oil. The residue was purified by prep. LC (Irregular SiOH 30 μm, 40g Interchim, mobile phase gradient: from heptane/EtOAc, 75/25 to 65/35). The pure fractions were collected and solvent evaporated until dryness to give 2.0 g of Int. **302**, orange solid (60%).



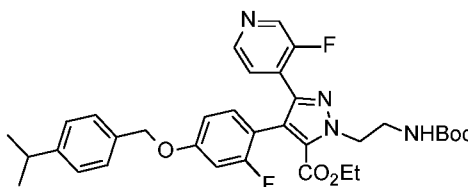
d- Synthesis of Int. 303:

- To a sol. of **302** (2.0 g, 4.4 mmol) in ACN (40 mL) was added dropwise a sol. of N-Bromosuccinimide (0.82 g, 4.6 mmol) in ACN (20 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 K₂CO₃ was added to the residue. The organic layer was separated, dried over MgSO₄, filtered off and evaporated *in vacuo* to give brown oil. The residue was purified by prep. LC (Irregular SiOH 30 μm, 40g Interchim, mobile phase gradient: from heptane/EtOAc, 80/20 to 70/30). The desired fractions were collected and solvent evaporated to give 510 mg of Int. **303**, yellow solid (25%).



e- Synthesis of Int. 304:

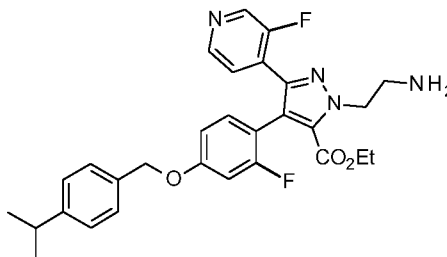
- To a mixture of **303** (0.51 g, 1.1 mmol), Boc-Glycinol (267 mg, 1.7 mmol) and PPh₃ supp. (0.52 g, 1.7 mmol) in dry THF (18 mL) was added DBAD (0.38 g, 1.7 mmol). The mixture was stirred at r.t. for 3 days. The mixture was filtrated throught a Celite® pad, concentrated and purified by prep. LC (irregular SiOH 30 μm, 25g Interchim, Mobile phase gradient: heptane/EtOAc, from 80/20 to 60/40). The desired fractions were collected and solvent evaporated until dryness to give 735 mg of Int. **304**, white solid. This was a mixture 60/40 of 60% Int. 304 and 40% of a dibrominated Co. This mixture was used as such in the next reaction step.



f- Synthesis of Int. 305:

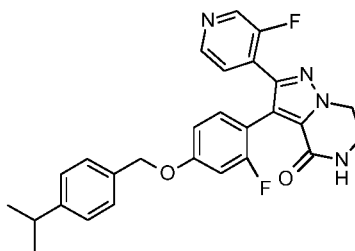
A mixture of **304** (0.35 g, 0.58 mmol), 3-fluoro-4-pyridineboronic acid pinacol ester (0.26 g, 1.2 mmol), K₃PO₄ (0.49 g, 2.3 mmol) in 1,4-dioxane (1.5 mL) and H₂O (0.5 mL) was carefully degazed with N₂. PCy₃ (34 mg, 0.12 mmol) and Pd(OAc)₂ (14 mg, 61 μmol) were added and the r.m. was purged again with N₂. The r.m. was stirred

overnight at 80°C for a day. The crude material was dissolved in water (50 mL) and extracted with DCM. The organic phase was dried over MgSO₄, filtered through a pad of Celite® and evaporated *in vacuo*. This residue was purified by prep. LC (irregular SiOH 30 µm, 25g Interchim, mobile phase gradient: from DCM/MeOH/NH₄OH 98/2/0.1 to 97/3/0.1). The pure fractions were collected and solvent evaporated until dryness to give 100 mg of Int. **305**, pale yellow oil (28%).



g- Synthesis of Int. 306:

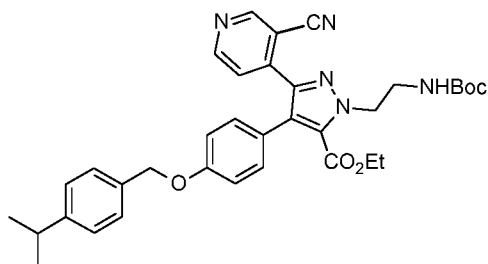
305 (100 mg, 0.16 mmol), HCl 3N (0.27 mL, 0.81 mmol), in ACN (2.9 mL) was stirred at 80°C for 2h. The mixture was concentrated, and NaHCO₃ sat aq (25 mL) was added and the mixture was stirred at r.t. 15min, extracted with DCM, dried, filtered and concentrated to give 33 mg of Int. **306**. This residue was used as such without further purification in the cyclisation step.



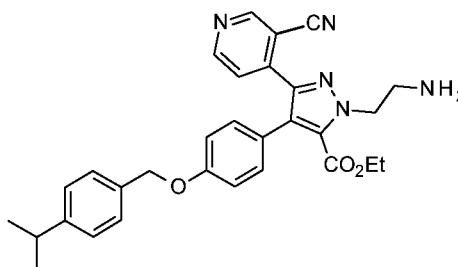
h- Synthesis of Co. 152:

To a sol. of **306** (33 mg, 0.064 mmol) in MeOH (1.8 mL) was added Cs₂SO₄ (0.10 g, 0.32 mmol) and the mixture was stirred at r.t. overnight. The mixture was concentrated and taken in water and extracted with DCM. The organic layer was dried on MgSO₄ and concentrated to give 17 mg. The residue was purified by prep. LC on (Stability Silica 5µm 150x30.0mm, Mobile phase Gradient: from NH₄OH/DCM/MeOH 0.2/98/2 to NH₄OH/DCM/MeOH 0.8/92/8). The pure fractions were collected and solvent evaporated until dryness to give 12 mg of **Co. 152**, white solid (40%). m.p.: 262°C (dsc).

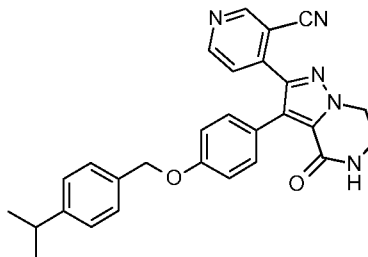
Example A152: Preparation of Co. 153

**a- Synthesis of Int. 307:**

A sol. of **17** (553 mg, 0.943 mmol), 3-cyanopyridine-4-boronic acid pinacol ester (434 mg, 1.89 mmol) and Na_2CO_3 (300 mg, 2.83 mmol) in toluene (6.3 mL), EtOH (3.2 mL) and H_2O (1.3 mL) in a sealed tube was purged with N_2 . $\text{PdCl}_2(\text{dppf})$ (77.2 mg, 94.3 μmol) was added, the mixture was purged again with N_2 and heated at 130°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 5 min [fixed hold time]. The crude was diluted with DCM and washed with water. The organic layer was separated, dried over MgSO_4 , filtered off and evaporated *in vacuo* to give 1.16 g. The crude was purified by prep. LC (Irregular SiOH 15-40 μm , 80g Grace, mobile phase gradient: from DCM 100% to DCM 80%, EtOAc 20%). The pure fractions were collected and solvent evaporated until dryness to give 84 mg of Int. **307**, colorless oil (18%).

**b- Synthesis of Int. 308:**

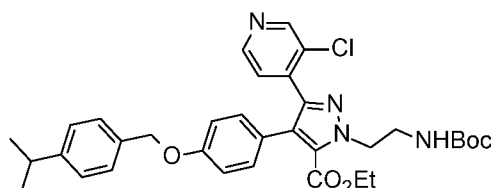
To a sol. of **307** (108 mg, 0.177 mmol) in ACN (2 mL) was added HCl 3N (295 μL , 0.177 mmol). The sol. was heated at 80°C for 10 min then stirred at r.t. for 10 min. DCM and a sat. aq. sol. of NaHCO_3 were added to the residue, the mixture was stirred at r.t. for 10 min and the organic layer was separated, dried over MgSO_4 , filtered off and evaporated *in vacuo* to give 95 mg of Int. **308**, pale yellow oil (quant. yield).

**c- Synthesis of Co. 153:**

To a sol. of **308** (120 mg, 0.235 mmol) in MeOH (2.5 mL) was added Cs_2CO_3 (384 mg, 1.18 mmol) and the mixture was stirred at r.t. for 15 min. The solvent was removed *in vacuo* and the residue was dissolved in DCM and water. The organic layer was

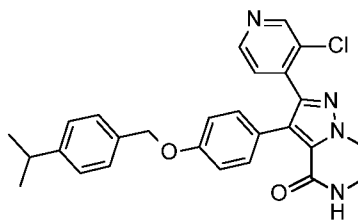
separated, dried over MgSO_4 , filtered off and evaporated *in vacuo* to give 96 mg, pale beige solid. The residue was purified by prep. LC (Irregular SiOH 15-40 μm , 10g Merck, mobile phase gradient: from DCM 100% to DCM 98%, MeOH 2%). The pure fractions were collected and solvent evaporated until dryness to give 79 mg of **Co. 153**,
5 white solid (72%). m.p.: 225°C (dsc).

Example A153: Preparation of Co. 154



a- Synthesis of Int. 309:

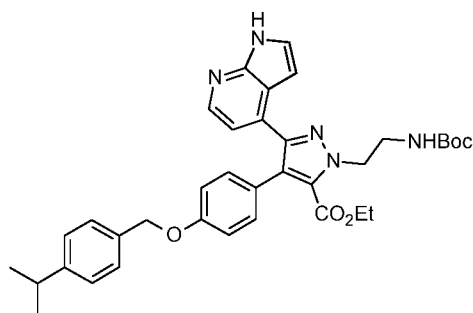
A sol. of **17** (800 mg, 1.36 mmol), 3-chloro-4-pyridineboronic acid pinacol ester (653 mg, 2.73 mmol) and Na_2CO_3 (434 mg, 4.09 mmol) in toluene (10 mL), EtOH (5 mL)
10 and H_2O (2 mL) in a sealed tube was purged with N_2 . $\text{PdCl}_2(\text{dppf})$ (112 mg, 0.136 mmol) was added, the mixture was purged again with N_2 and heated at 130°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 5 min [fixed hold time]. The mixture was diluted with DCM and washed with water. The organic layer was separated, dried over MgSO_4 , filtered off
15 and evaporated *in vacuo* to give 2.07 g, brown oil. The crude was purified by prep. LC (Irregular SiOH 15-40 μm , 80g Grace, mobile phase gradient: from DCM 100% to DCM 90%, acetone 10%). The pure fractions were collected and solvent evaporated until dryness to give 900 mg of Int. **309**, yellow oil (95%).



b- Synthesis of Co. 154:

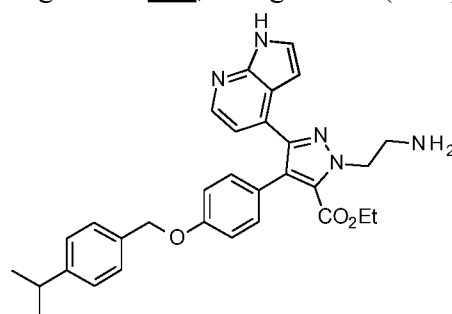
To a sol. of **309** (900 mg, 1.45 mmol) in ACN (20 mL) was added HCl 3N (2.42 mL, 7.27 mmol). The sol. was heated at 80°C for 2h, cooled down to r.t. and the solvent was removed *in vacuo*. DCM and a sat. aq. sol. of NaHCO_3 were added to the residue, the mixture was stirred at r.t. for 10min and the organic layer was separated, dried over MgSO_4 , filtered off and evaporated *in vacuo*. The brown oil was purified by prep. LC
20 (Irregular SiOH 15-40 μm , 30g Merck, mobile phase gradient: from DCM 100% to DCM 80%, acetone 20%). The pure fractions were collected and the solvent evaporated to give 458 mg of **Co. 154**, white solid (67%). m.p.: 207°C (dsc).
25

Example A154: Preparation of Co. 155



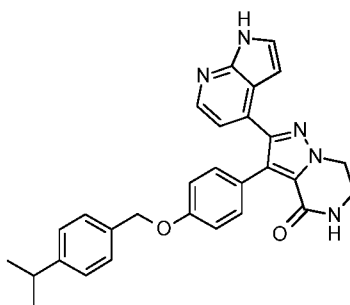
a- Synthesis of Int. 310:

A mixture of **17** (650 mg, 1.11 mmol), 7-azaindole-4-boronic acid pinacol ester (325 mg, 1.33 mmol) and K_3PO_4 (941 mg, 4.43 mmol) in 1,4-dioxane (5 mL) and H_2O (1.2 mL) in a sealed tube was purged with N_2 . $PdCl_2(dppf)$ (91.0 mg, 0.111 mmol) was added, the mixture was purged again with N_2 and heated at $80^\circ C$ for 18 h. This mixture and another batch (with 142mg of **17** in the same conditions) were combined, diluted with DCM and washed with water. The organic layer was separated, dried over $MgSO_4$, filtered off and evaporated *in vacuo* to give brown oil. The crude was purified by prep. LC (Irregular SiOH 15-40 μm , 80g Grace, mobile phase gradient: from DCM 100% to DCM 80%, acetone 20%). The pure fractions were collected and solvent evaporated until dryness to give 478 mg of Int. **310**, orange foam (57%).



b- Synthesis of Int. 311:

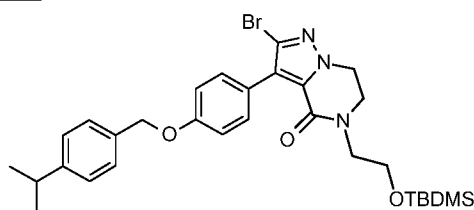
To a sol. of **310** (478 mg, 0.766 mmol) in ACN (6 mL) was added HCl 3N (1.28 mL, 3.83 mmol). The sol. was heated at $50^\circ C$ for 3h then stirred at r.t. for 18h. DCM and a sat. aq. sol. of $NaHCO_3$ were added. The organic layer was separated, dried over $MgSO_4$, filtered off and evaporated *in vacuo* to give 398 mg of Int. **311**, brown oil (99%).



c- Synthesis of Co. 155:

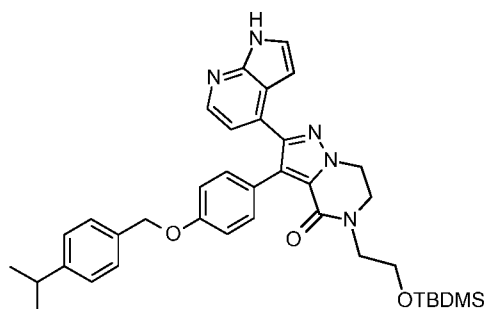
- To a sol. of **311** (398 mg, 0.76 mmol) in MeOH (8 mL) was added Cs₂CO₃ (1.24 g, 3.80 mmol) and the mixture was stirred at r.t. for 15min. The solvent was removed *in vacuo* and the residue was dissolved in DCM and water. The organic layer was separated, dried over MgSO₄, filtered off and evaporated *in vacuo* to give beige solid.
- 5 This solid was purified by prep. LC (Irregular SiOH 15-40 μm, 12g Grace, DCM 100% to DCM 95%, iPrOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 289 mg, white solid (80%). 249 mg of this white solid was crystallized from MeCN. The precipitate was filtered on a glass frit and the filtrate was evaporated *in vacuo*. The residue was recrystallized again from ACN and the
- 10 precipitate was filtered on a glass frit (process repeated 2x). The solids were combined and dried in high vacuum at 55°C for 3h to give 185 mg of **Co. 155**, white solid (51%). m.p.: 266°C (dsc).

Example A155: Preparation of Co. 156



a- Synthesis of Int. 312:

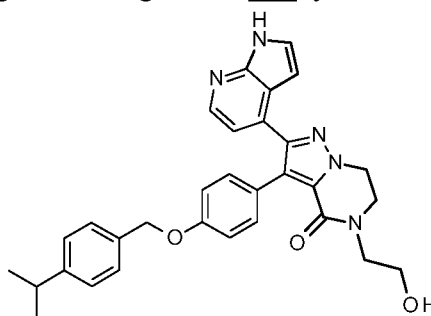
- 15 To a suspension of **299** (264 mg, 600 μmol) in DMSO () at r.t. under N₂ was added NaH 60% (28.8 mg, 719 μmol). The mixture was stirred at r.t. for 2h and (2-bromoethoxy)-tert-butyldimethylsilane (154 μL, 719 μmol) was added. The r.m. was stirred at r.t. for 2h. Water and EtOAc were added. The organic layer was separated, washed with a sat. aq. sol. of NaCl (3 times), dried over MgSO₄, filtered and
- 20 evaporated *in vacuo* to give 368 mg of Int. **312**, yellow oil (quant.). The crude Int. 312 was used as such in the next reaction step without purification.



b- Synthesis of Int. 313:

- A mixture of **312** (150 mg, 251 μmol), 7-azaindole-4-boronic acid pinacol ester (73.4 mg, 301mmol) and K₃PO₄ (213 mg, 1.00 mmol) in 1,4-dioxane (2.25 mL) and H₂O
- 25 (450 μL) in a sealed tube was purged with N₂. PdCl₂(dppf) (20.5 mg, 25.1 μmol) was added, the mixture was purged again with N₂ and heated at 80°C for 18h. DCM and water were added to the crude mixture. The organic layer was separated, dried over

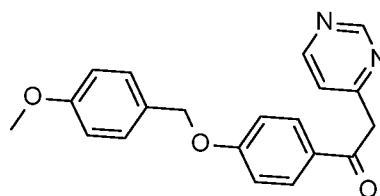
MgSO₄, filtered off and evaporated *in vacuo* to give 300mg, brown oil. The residue was purified by prep. LC (Irregular SiOH 15-40 μm, 12g Grace, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 107 mg of Int. **313**, yellow oil (67%).



5 **c- Synthesis of Co. 156:**

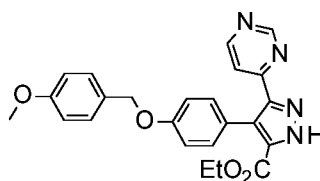
To a sol. of **313** (107 mg, 0.168 mmol) in THF (4 mL) at 0 °C was added TBAF (252 μL, 0.252 mmol). The r.m. was allowed to warm to r.t. and stirred for 1h. The crude mixture was diluted with water and DCM. The organic layer was separated, dried over MgSO₄, filtered off and evaporated *in vacuo* to give 90 mg, pale yellow oil. The residue was purified by prep. LC (Irregular SiOH 15-40 μm, 4g Grace, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 72 mg of colorless oil (82%) which was crystallized from Et₂O and dried *in vacuo* to give 56 mg of **Co. 156**, white solid (64%). m.p.: 219°C (dsc).

15 **Example A156: Preparation of Co. 157**



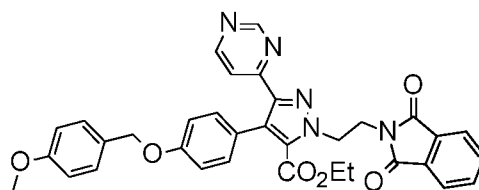
a- Synthesis of Int. 314:

In a dry flask and under N₂ atmosphere, a sol. of Ethyl 4-(4-methoxybenzyloxy)benzoate (2.00 g, 6.99 mmol) and 4-methylpyrimidine (723 mg, 7.68 mmol) in dry THF (10 mL) was cooled to 0°C and treated with LiHMDS (14.0 mL, 14.0 mmol) (slow addition over 10 min). After the end of the addition, the r.m. was allowed to warm to r.t. and stirred for 17 h. The r.m. was then poured in a 10% aq. sol. of NH₄Cl (100 mL). The mixture was filtered on a glass frit. The precipitate was washed with water (2 x 50 mL) and with Et₂O (2x 50 mL). The solid was dissolved in a mixture of DCM and MeOH. The organic sol. was dried over MgSO₄ and evaporated *in vacuo* to give 2.14 g of Int. **314**, white solid (92%).



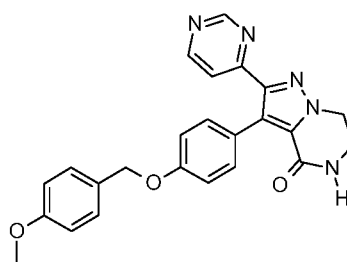
b- Synthesis of Int. 315:

To a suspension of **314** (5.00 g, 15.0 mmol) in ACN (50 mL) in a sealed tube was added DBU (2.24 mL, 15.0 mmol) and ethyldiazoacetate (2.67 mL, 25.4 mmol). The mixture was heated at 60°C for 2h then cooled down to r.t. The solvent was removed *in vacuo* and the residue was diluted in DCM. The organic layer was washed with a sat. aq. sol. of NaHCO₃, water, dried over MgSO₄, filtered off and evaporated *in vacuo* to give 5.32 g, brown oil. This experiment and another batch (with 500mg of **314** in the same conditions) were combined and purified by prep. LC (Irregular SiOH 15-40 μm, 220g Grace, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 3.54 g. The residue was dissolved in DCM and a precipitate was filtered to give 2.30 g of Int. **315**, yellow solid. The filtrate was purified by prep. LC (Irregular SiOH 15-40 μm, 80g Grace, mobile phase gradient: from DCM 100% to DCM 50%, EtOAc 50%). The pure fractions were collected and solvent evaporated to give 784 mg of Int. **315**, yellow solid (global yield: 4.32g, 44%).



c- Synthesis of Int. 316:

To a suspension of **315** (3.00 g, 6.97 mmol), N-(2-hydroxyethyl)phthalimide (1.60 g, 8.36 mmol) and diphenylphosphinopolystyrene (2.79 g, 8.36 mmol) in dry THF (60 mL) was added DBAD (1.93 g, 8.36 mmol). The mixture was stirred for 20h at r.t. then filtered through a glass frit and washed with EtOAc. The filtrate was evaporated *in vacuo* to give 8.20 g, yellow oil. The residue was purified by prep. LC (Irregular SiOH, 15-40 μm, 150g Merck, mobile phase gradient: from DCM 100% to DCM 70%, acetone 30%). The pure fractions were collected and solvent evaporated until dryness to give 2.82 g of Int. **316**, off-white solid (67%).



d- Synthesis of Co. 157:

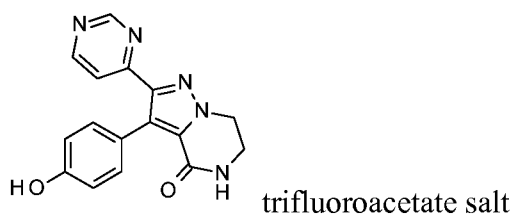
25

- To a mixture of **316** (2.82 g, 4.67 mmol) in EtOH (50 mL) was added hydrazine hydrate (668 μ L, 7.01 mmol) and the mixture was heated at 70°C for 4h. The precipitate formed was filtered on a glass frit to give 1.84 g of a white solid which was dissolved in a mixture of DCM/MeOH/EtOAc and the precipitate filtered on a glass frit. The solid was washed with MeOH and dried to give 986 mg of **Co. 157**, white solid (49%). m.p.: 264°C (DSC).

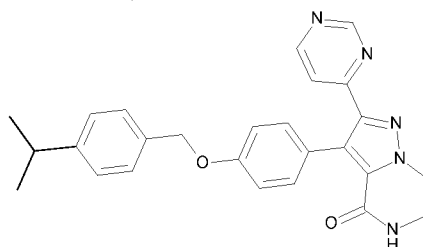
Example A157: Preparation of Co. 158

▪ **First Method:**

a- Synthesis of Int. 317:



- To a sol. of **Co. 157** (200 mg, 0.468 mmol) in toluene (8 mL) in a sealed tube was added TFA (1.00 mL, 13.1 mmol) and the mixture was heated at 75°C for 5h. The yellow sol. was evaporated *in vacuo* and coevaporated 3x with toluene. The yellow residue was triturated in Et₂O and filtered on a glass frit to give 222 mg of **Int. 317**, yellow solid (quant. yield, trifluoroacetate salt).

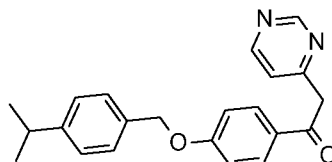


b- Synthesis of Co. 158:

- To a sol. of **317** (100 mg, 0.237 mmol) in DMF (2 mL) was added K₂CO₃ (98.4 mg, 0.712 mmol) and **8** (41.7 μ L, 0.249 mmol). The mixture was heated at 50°C for 18h and refluxed for 18h. **8** (20.0 μ L, 0.119 mmol) and K₂CO₃ (16.4 mg, 0.119 mmol) were added and the mixture was refluxed for 60h. **8** (20.0 μ L, 0.119 mmol) and K₂CO₃ (16.4 mg, 0.119 mmol) were then added and the mixture was refluxed for 18h. DCM was added to the residue and the organic layer was washed with water, dried over MgSO₄, filtered off and evaporated *in vacuo* to give 125 mg, yellow residue. The residue was purified by prep. LC (Irregular SiOH 15-40 μ m, 10g Merck, mobile phase gradient: from DCM 100% to DCM 50%, acetone 50%). The desired fractions were collected and solvent evaporated until dryness to give 46 mg, off-white residue. This residue was purified again by prep. LC on (Irregular SiOH 15-40 μ m, 30g Merck, mobile phase: 96% DCM, 4% MeOH, 0.1% NH₃ aq). The pure fractions were collected

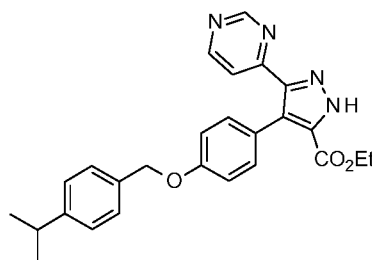
and solvent evaporated until dryness to give 24 mg of **Co. 158**, white solid (23%). m.p.: 252°C (DSC).

▪ **Second Method:**



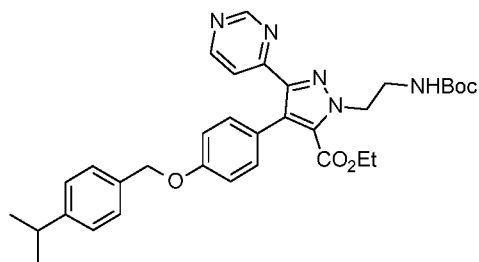
a- Synthesis of Int. 318:

- 5 In a dry flask and under N₂ atmosphere, a sol. of **9** (16.8 g, 59 mmol) and 4-methylpyrimidine (6.1 g, 65 mmol) in dry THF (118 mL) was cooled to 0°C and treated with LiHMDS (118 mL, 118 mmol) dropwise. The r.m. was allowed to warm to r.t. (over 1h) and stirred for 17 h at this temperature. The r.m. was then poured in a 10% aq. sol. of NH₄Cl (300 mL). The mixture was extracted with DCM, dried on MgSO₄
- 10 and concentrated. The residue was taken up in Et₂O and the solid was filtrated, washed with Et₂O and dried to give 19.2 g of Int. **318**, gold solid (94%).



b- Synthesis of Int. 319:

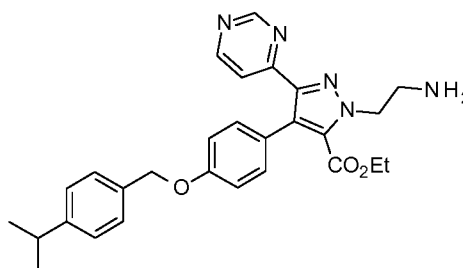
- A suspension of **318** (23.7 g, 68.4 mmol) in ACN (400 mL) was treated with DBU (17.4 mL, 116 mmol) then with ethyl diazoacetate (11.5 mL, 109 mmol). The r.m. was stirred at r.t. for 3 h. The r.m. was poured in a sat. sol. of NaHCO₃ and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄ and evaporated *in vacuo* to give black oil. The oil was purified by prep. LC (irregular SiOH 15-40 μm, 220g, Grace, mobile phase gradient: from DCM 100% to DCM 98%, MeOH 2%). The pure fractions were collected and solvent evaporated until dryness to give 21.1g of Int.
- 15
- 20 **319** (yield: 70%).



c- Synthesis of Int. 320:

A sol. of **319** (13.8 g, 31.2 mmol) and Boc-Glycinol (7.24 mL, 46.8 mmol) in dry THF (250 mL) was treated with diphenylphosphinopolystyrene (14.6 g, 46.8 mmol) then

with DBAD (10.8 g, 46.8 mmol). The r.m. was stirred at r.t. for 17 h, under N₂. The crude mixture was filtered through Celite® and evaporated *in vacuo* to give black oil. The oil was purified by prep. LC (irregular SiOH 15-40 µm, 220g, Grace, dry loading, mobile phase gradient: from DCM 100% to DCM 96%, MeOH 4%). The fractions were collected and solvent evaporated until dryness to give 16.6g of brown oil (which contained 2 isomers). This oil was purified by prep. LC (Stationary phase: Irregular SiOH 20-45µm 450g MATREX, Mobile phase: Gradient from NH₄OH/DCM/iPrOH 0.2/98/2 to NH₄OH/DCM/iPrOH 0.3/97/3). The pure fractions were collected and solvent evaporated until dryness to give 8.40 g of Int. **320**, orange solid (46%).



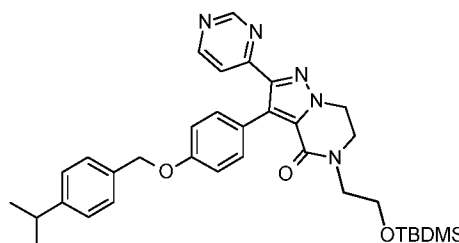
10 d- Synthesis of Int. 321:

A mixture of **320** (3.7 g, 6.3 mmol), HCl 3N (10.5 mL, 32 mmol), in ACN (110 mL) was stirred at 80°C for 2h. The mixture was concentrated, and NaHCO₃ sat aq (200 mL) was added and the mixture was stirred at r.t. 15min, extracted with DCM, dried and evaporated until dryness to give 3.05 g of Int. **321** (99%). The yellow solid obtained was used like in the next step.

15 e- Synthesis of Co. 158:

To a solution of **321** (1.62 g, 3.3 mmol) in MeOH (100 mL) was added Cs₂CO₃ (5.4 g, 17 mmol) and the mixture was stirred at r.t. for 3 days. The mixture was filtrated, the white solid was collected, washed with Et₂O and dried to give 1.07 g of **Co. 158** (73%). m.p.: 259°C (dsc).

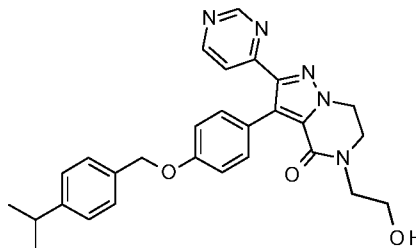
20 Example A158: Preparation of Co. 159



a- Synthesis of Int. 322:

NaH 60% (68 mg, 1.7 mmol) was added slowly to a suspension of Co. 158 (0.50 g, 1.1 mmol) in DMF (6.8 mL) at r.t. under N₂. The mixture was stirred for 2h then (2-bromoethoxy)-tert-butyldimethylsilane (0.28 mL, 1.4 mmol) was added and the r.m. stirred overnight. Water was added and the mixture was concentrated under reduced

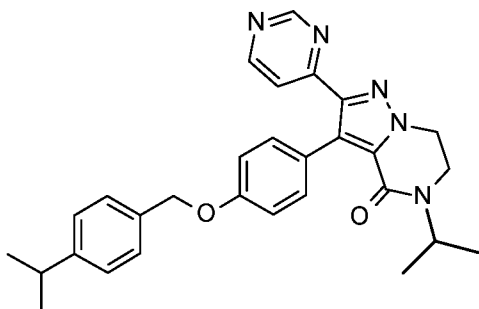
pressure. The residue was taken up in EtOAc and washed 5x with brine. The organic layer was dried, filtered and concentrated to give 0.68 g of Int. **322** (yellow oil; quant.), used as such in the next step.



b- Synthesis of Co. 159:

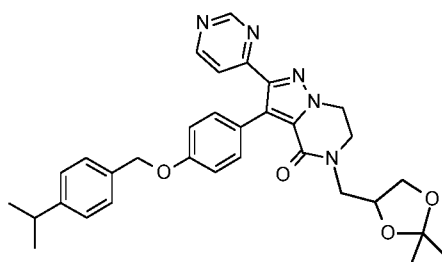
- 5 TBAF (1.4 mL, 1.4 mmol) was added dropwise to a sol. of **322** (0.68 g, 1.1 mmol) in THF (11 mL) at r.t.. The mixture was stirred overnight at r.t.. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 μ m, 25g GraceResolvTM, mobile phase: DCM/MeOH/NH₄OH, 95/5/0.1). The pure fractions were collected and solvent evaporated until dryness to give 450 mg of colorless oil
- 10 which was crystallized from Et₂O. The white solid formed was filtrated, washed and dried to give 0.42 g of **Co. 159**, white solid (77%). m.p.: 160°C (dsc).

Example A159: Preparation of Co. 160



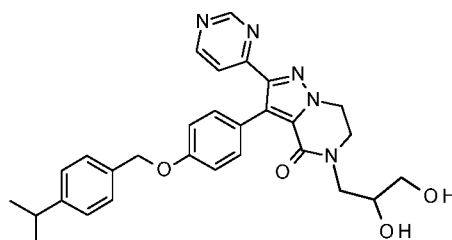
- NaH 60% (41 mg, 1.0 mmol) was added slowly to a suspension of Co. 158 (0.30 g, 0.68 mmol) in DMSO (3.8 mL) at r.t. under N₂. The mixture was stirred for 2h (until a sol. was observed in the flask), then 2-iodopropane (75 μ L; 0.75 mmol) was added and stirred overnight. Water was added and the insoluble was filtered, dissolved in DCM and MeOH, dried on MgSO₄ and evaporated until dryness to give 300 mg of white solid. The residue was purified by prep. LC (Regular SiOH, 30 μ m, 25g Interchim, mobile phase gradient: DCM/MeOH/NH₄OH, from 98/2/0.1 to 96/4/0.1). The pure fractions were collected and solvent evaporated until dryness to give 125 mg, colorless oil. This oil was taken in Et₂O, concentrated and dried to give 121 mg of **Co. 160**, white solid (37%). m.p.: 166°C (dsc).
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Example A160: Preparation of Co. 161a and Co. 161



a- Synthesis of Co. 161a

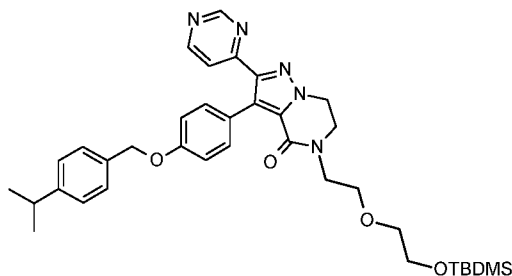
To a suspension of **Co. 158** (300 mg, 0.683 mmol) in DMSO (5.4 mL) was added NaH 60% (41.0 mg, 1.02 mmol). The mixture was stirred at r.t. for 4h to obtain a clear yellow sol. and 2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate (215 mg, 0.751 mmol) was added. The sol. was heated at 50°C for 20h. DCM and water were added, the organic layer was separated, dried, filtered off and evaporated *in vacuo*. The residue (670 mg) 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 to give 260 mg of **Co. 161a** (60%).



b- Synthesis of Co. 161:

A sol. of **Co. 161a** (210 mg, 379 µmol) and HCl 3N (632 µL, 1.90 mmol) in 1,4-dioxane (8 mL) was stirred at r.t. for 1h. The mixture was poured into a sat. aq. sol. of NaHCO₃ and extracted with DCM. The organic layer was separated, dried over MgSO₄, filtered and evaporated *in vacuo* to give 190 mg of **Co. 161**, white solid (98%). m.p.: 209°C (DSC).

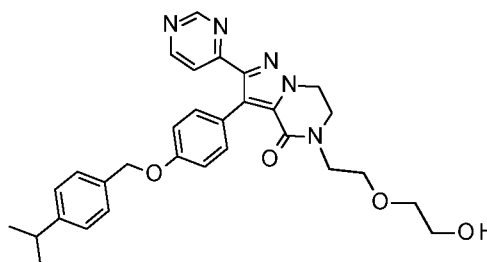
Example A161: Preparation of Co. 162



a- Synthesis of Int. 324:

To a suspension of **Co. 158** (150 mg, 341 µmol) in DMSO (2 mL) at r.t. under N₂ was slowly added NaH 60% (20.5 mg, 512 µmol). The mixture was stirred at r.t. for 2h until complete solubilization then tert-Butyl(2-(2-chloroethoxy)ethoxy)dimethylsilane (245 mg, 1.02 mmol) in DMSO (500 µL) was added. The sol. was heated at 80°C for 18h then cooled down to r.t. and water and DCM were added. The organic layer was

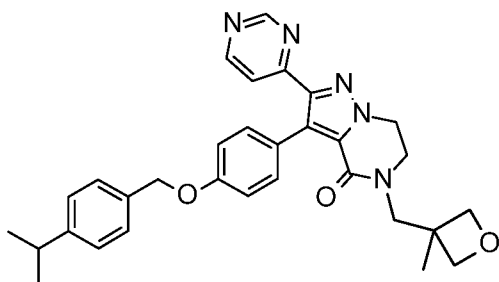
separated, dried over MgSO_4 , filtered off and evaporated *in vacuo* to give 640 mg of Int. **324**, used as such in the next step without purification.



b- Synthesis of Co. 162:

To a sol. of **324** (220 mg, 0.343 mmol) in THF (10 mL) at 0°C was added TBAF (514 μL , 0.514 mmol), and the sol. was stirred at 0 °C for 2h then at r.t. for 18h. The sol. was diluted with water and DCM, the organic layer was separated, washed with a sat. aq. sol. of NaCl, dried over MgSO_4 , filtered off and evaporated *in vacuo* to give 266 mg. The residue was purified by prep. LC (Stationary phase: Stability Silica 5 μm 150x30.0mm, Mobile phase Gradient: from 50% Heptane, 3% MeOH (+10% NH_4OH), 47% EtOAc to 25% MeOH (+10% NH_4OH), 75% EtOAc). The pure fractions were collected and solvent evaporated to give 119 mg, colorless oil (66%). The Co. was diluted in a minimum of DCM and pentane was added until precipitation. The mixture was evaporated *in vacuo* to give 114 mg of **Co. 162**, off-white solid (63%).

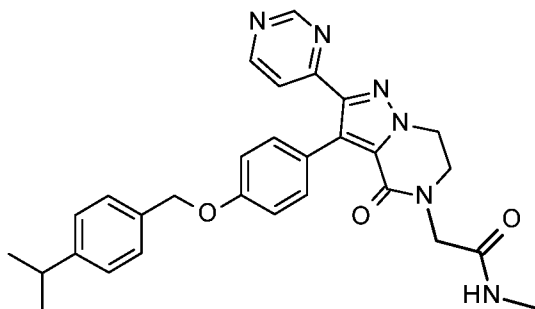
Example A162: Preparation of Co. 163



NaH 60% (55 mg, 1.4 mmol) was added slowly to a suspension of **Co. 158** (0.40 g, 0.91 mmol) in DMSO (5.0 mL) at r.t. under N_2 . The mixture was stirred for 2h (until complete solubilization), then 2-(chloromethyl)-2-methyl-1,3-epoxypropane (110 μL , 1.0 mmol) was added and the r.m. stirred overnight. Water was added and the insoluble was filtrated, dissolved in DCM, dried on MgSO_4 and evaporated until dryness to give 620 mg, white solid. The residue was purified by prep. LC (Regular SiOH, 30 μm , 25g Interchim, mobile phase gradient: DCM/MeOH/ NH_4OH , from 98/2/0.1 to 96/4/0.1). The desired fractions were collected and solvent evaporated until dryness to give 450 mg, colorless oil. This residue was purified by prep. LC on (irregular 15-40 μm 50g Merck, Mobile phase: 0.1% NH_4OH , 97% DCM, 3% MeOH). The desired fractions were collected and solvent evaporated until dryness 300 mg which was purified by

achiral SFC on (2-ethylpyridine 6 μ m 150x21.2mm, Mobile phase: 85% CO₂, 15% MeOH). The pure fractions were collected and solvent evaporated until dryness to give 260 mg of **Co. 163**, white solid (55%).

Example A163: Preparation of Co. 164

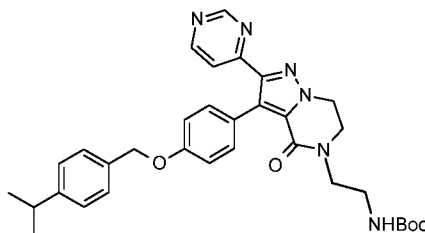


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To a suspension of **Co. 158** (300 mg, 0.683 mmol) in DMF (6 mL) at r.t. under N₂ atmosphere was added NaH 60% (41.0 mg, 1.02 mmol). The mixture was stirred at r.t. until complete solubilization of the mixture (2h). Then 2-bromo-N-methylacetamide (124 mg, 0.819 mmol) was added and the sol. was stirred at r.t. for 3h. EtOAc and water were added and the organic layer was separated, washed with a sat. aq. sol. of NaCl (twice), dried over MgSO₄, filtered off and evaporated *in vacuo*. The residue (382 mg) was purified by prep. LC (Irregular SiOH 15-40 μ m, 12g Grace, mobile phase gradient: from DCM 100% to DCM 80%, iPrOH 20%). The pure fractions were collected and solvent evaporated until dryness to give 222 mg of colorless film which crystallized on standing. The precipitate was filtered on a glass frit to give a white solid (159 mg) of **Co. 164** (46%). m.p.: 97 °C and 157 °C (DSC).

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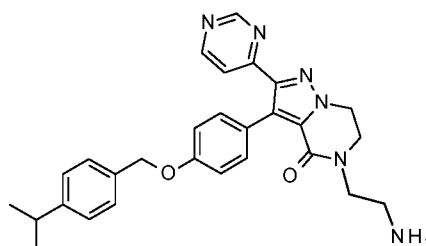
Example A164: Preparation of Co. 165a and Co. 165



a- Synthesis of Co. 165a

NaH 60% (55 mg, 1.4 mmol) was added slowly to a suspension of **Co. 158** (0.4 g, 0.91 mmol) in dry DMSO (5 mL) at r.t. under N₂. The mixture was stirred for 2h then Boc-1-amino-2-bromoethane (224 mg, 1.0 mmol) was added and the r.m. stirred for 3 days. Water was added and the insoluble was filtered, dissolved in DCM and MeOH, dried over MgSO₄ and evaporated until dryness to give 550 mg of **Co. 165a** as a crude (mixture with starting material) which was used as such in the next reaction step.

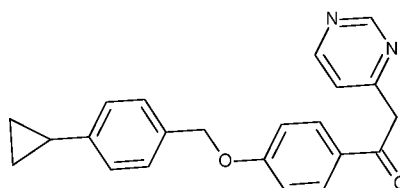
20



b- Synthesis of Co. 165:

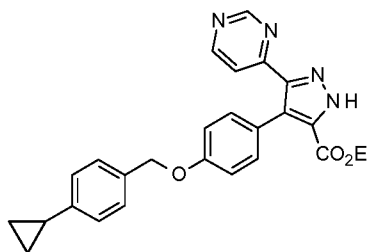
A mixture of **Co. 165a** (550 mg, 0.94 mmol), HCl 3N (1.6 mL, 4.7 mmol), in ACN (17 mL) was stirred at 80°C for 2h. The mixture was concentrated, and NaHCO₃ sat aq (200 mL) was added and the mixture was stirred at r.t. 15 min, extracted with DCM, dried, filtered and concentrated. The residue was purified by prep. LC (Regular SiOH, 30 µm, 25g Interchim, mobile phase gradient: DCM/MeOH/NH₄OH, from 95/5/0.1 to 80/20/0.1). The pure fractions were collected and solvent evaporated until dryness to give 258 mg, colorless oil. This oil was taken in Et₂O, concentrated and dried to give 210 mg of **Co. 165**, white solid (46%).

Example A165: Preparation of Co. 166



a- Synthesis of Int. 326:

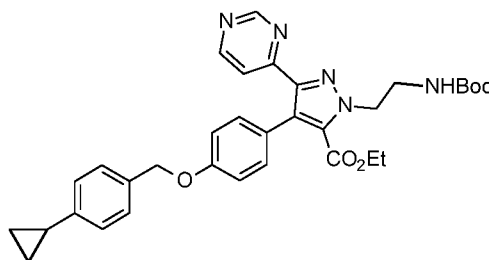
In a dry flask and under N₂ atmosphere, a sol. of **34** (12.6 g, 45 mmol) and 4-methylpyrimidine (4.6 g, 49 mmol) in dry THF (90 mL) was cooled to 0°C and treated with LiHMDS (90 mL, 90 mmol) dropwise. The r.m. was allowed to warm to r.t. (over 1h) and stirred for 17h at this temperature. The r.m. was then poured in a 10% aq. sol. of NH₄Cl (400 mL). The mixture was extracted with DCM, dried on MgSO₄ and concentrated. The residue was taken up in Et₂O and the solid was filtrated, washed with Et₂O and dried to give 13 g of Int. **326**, yellow solid (85%).



b- Synthesis of Int. 327:

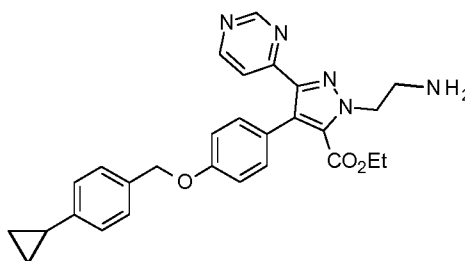
To a suspension of **326** (13 g, 38 mmol) in ACN (135 mL) was added DBU (5.6 mL, 38 mmol) and Ethyl diazoacetate (6.7 mL, 64 mmol). The mixture was heated for 3h at 60°C then cooled down to r.t. The solvent was removed *in vacuo* and the residue was diluted in EtOAc. The organic layer was washed with a sat. aq. sol. of NaHCO₃ (2*500

- mL), dried over MgSO_4 , filtered off and evaporated *in vacuo* to give 19 g of brown residue. The residue was purified by prep. LC (irregular SiOH 15-40 μm , 330g GraceResolvTM, mobile phase gradient, from DCM/MeOH/ NH_4OH , 100/0/0 to 97/3/0.1). The desired fractions were collected and solvent evaporated to give 7.16 g of
- 5 Int. 327, brown solid (43%) used as such for the next step.



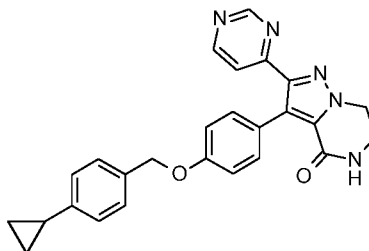
c- **Synthesis of Int. 328:**

- To a suspension of 327 (7.16 g, 16 mmol), Boc-Glycinol (3.9 g, 24 mmol) and Diphenylphosphinopolystyrene (7.6 g, 24 mmol) in dry THF (210 mL) was added DBAD (5.6g, 24mmol). The mixture was stirred at r.t. overnight. The sol. was filtrated
- 10 through a pad of Celite®, and the polymer was washed with EtOAc and the filtrate was evaporated *in vacuo*. The residue was purified by prep. LC (Regular SiOH , 30 μm , 330g GraceResolvTM, mobile phase gradient: DCM/MeOH/ NH_4OH , from 100/0/0 to 97/3/0.1). The desired fractions were collected and solvent evaporated until dryness to give 4.13 g of Int. 328, brown solid (crude).



- 15 d- **Synthesis of Int. 329:**

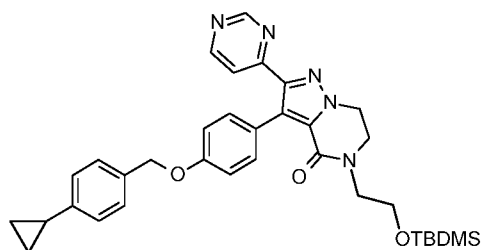
- A solution of 328 (4.13 g, 7.1 mmol), HCl 3N (11.8 mL, 35mmol), in ACN (125 mL) was stirred at 80°C for 2h. The mixture was concentrated, and NaHCO_3 sat aq (200 mL) was added and the mixture was stirred at r.t. 15min, extracted with DCM, dried, filtered and concentrated to give 3.44 g of Int. 329, orange oil (quant.). This residue
- 20 was used like this in the next step.



e- **Synthesis of Co. 166:**

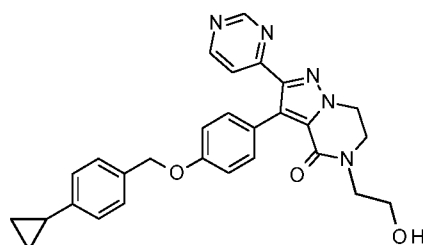
To a sol. of **329** (3.44 g, 7.1 mmol) in MeOH (203 mL) was added Cs_2CO_3 (4.6 g, 14 mmol) and the mixture was stirred at r.t. for overnight. The mixture was filtered. The white solid was collected, washed with Et_2O and dried to give 1.66 g of **Co. 166**, white solid (53%). M.p.: 268°C (dsc).

5 Example A166: Preparation of Co. 167



a- Synthesis of Int. 330:

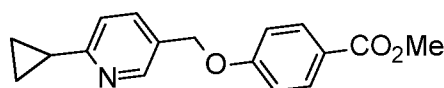
NaH 60% (77 mg, 1.9 mmol) was added slowly to a suspension of Co. 166 (0.56 g, 1.3 mmol) in DMF (7.6 mL) at r.t. under N_2 . The mixture was stirred for 2h then (2-bromoethoxy)-tert-butyldimethylsilane (0.32 mL, 1.5 mmol) was added and stirred overnight. Water was added and the mixture was concentrated under reduced pressure. The residue was taken in EtOAc and washed 5x with brine. The organic layer was dried on MgSO_4 , filtered and concentrated to give 0.76 g of Int. **330**, yellow oil (quant : 80% of Int. 330 and 20% of Co. 167). This mixture was used like this in the deprotection step.



15 b- Synthesis of Co. 167:

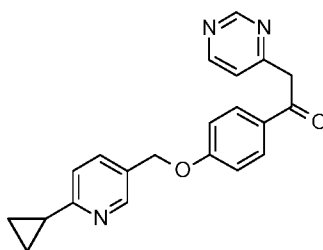
TBAF (1.5 mL, 1.5 mmol) was added dropwise to a sol. of **330** (0.76 g, 1.3 mmol) in THF (12.5 mL) at r.t. The mixture was stirred overnight at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 μm , 25 g GraceResolv™, mobile phase: DCM/MeOH/ NH_4OH 95/5/0.1). 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 0.49 g of **Co. 167** (80%).

Example A167: Preparation of Co. 168



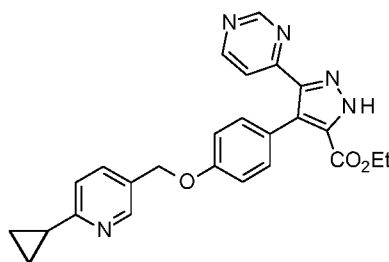
a- Synthesis of Int. 331:

Under N₂ atmosphere, to a sol. of 4-hydroxybenzoic acid methyl ester (6.9 g, 45 mmol), **29** (6.7 g, 45 mmol), PPh₃ (11.8 g, 45 mmol) in THF (275 mL) was added DBAD (10.3 g, 45 mmol) and the r.m. was stirred at r.t. overnight. The mixture was evaporated *in vacuo* to give colorless oil (40g) which was purified by prep. LC (irregular SiOH 15-40 μm, 330g GraceResolv™, mobile phase: heptane/EtOAc 85/15). The desired fractions were collected and solvent evaporated to give 20.2 g, white solid. This solid was purified by prep. LC (Stationary phase: Irregular SiOH 20-45μm 450g MATREX, Mobile phase: 65% Heptane, 2% MeOH, 33% EtOAc). The pure fractions were collected and solvent evaporated to give 7.5 g of Int. **331** white solid (59%).



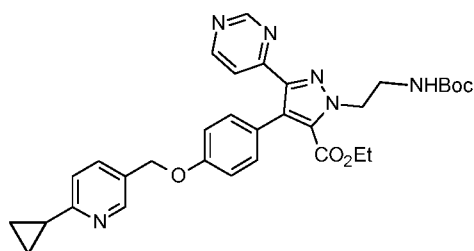
10 **b- Synthesis of Int. 332:**

In a dry flask and under N₂ atmosphere, a sol. of **331** (7.5 g, 26 mmol) and 4-methylpyrimidine (2.7 g, 29 mmol) in dry THF (53 mL) was cooled to 0°C and treated with LiHMDS (53 mL, 53 mmol) dropwise. The r.m. was allowed to warm to r.t. (over 1 h) and stirred for 17 h at this temperature. The r.m. was then poured in a 10% aq. sol. of NH₄Cl (300 mL). The mixture was extracted with DCM, dried over MgSO₄ and concentrated. The residue was taken up in Et₂O and the solid was filtrated, washed with Et₂O and dried to give 8.0 g of Int. **332**, gold solid (87%).



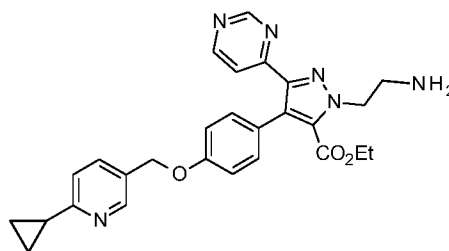
15 **c- Synthesis of Int. 333:**

To a suspension of **332** (8.0 g, 23 mmol) in ACN (73 mL) was added DBU (5.9 mL, 39 mmol) and Ethyl diazoacetate (3.9 mL, 37 mmol). The mixture was stirred at r.t. for 1h then cooled down to rt. The solvent was removed *in vacuo* and the residue was diluted in DCM. The organic layer was washed with a sat. aq. sol. of NaHCO₃, dried over MgSO₄, filtered off and evaporated *in vacuo*. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 220g GraceResolv™, mobile phase gradient, from DCM/MeOH/NH₄OH, 100/0/0 to 95/5/0.1). The desired fractions were collected and solvent evaporated to give 7.7 g of Int. **333**, brown oil (with impurities).



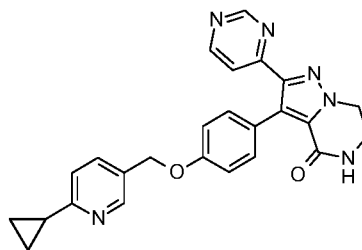
d- Synthesis of Int. 334:

To a suspension of **333** (7.7 g, 17 mmol), Boc-Glycinol (3.1 g, 19 mmol) and Diphenylphosphinostyrene (6.0 g, 19 mmol) in THF (226 mL) was added DBAD (4.4 g, 19 mmol). The mixture was stirred at r.t. overnight. The sol. was filtered through a pad of Celite®, and the polymer was washed with EtOAc and the filtrate was evaporated *in vacuo*. The residue was purified by prep. LC (Regular SiOH, 30 µm, 220g GraceResolv™, mobile phase gradient: DCM/MeOH/NH₄OH, from 100/0/0 to 97/3/0.1). The desired fractions were collected and solvent evaporated until dryness to give 6.0 g of Int. **334**, yellow oil (59%).



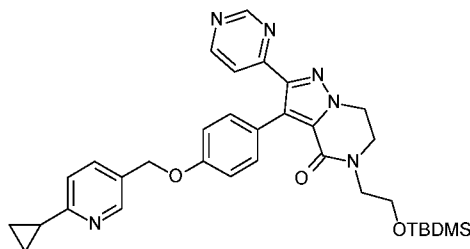
e- Synthesis of Int. 335:

A solution of **334** (6.0 g, 10 mmol), HCl 3N (17 mL, 51 mmol), in ACN (182 mL) was stirred at 80°C for 2h. The mixture was concentrated, and NaHCO₃ sat aq (200 mL) was added and the mixture was stirred at r.t. 15min, extracted with DCM, dried, filtered and concentrated to give 4.2g of Int. **335** (mixture Int. 335 and Co. 168). The red solid obtained was used like this in the next step.

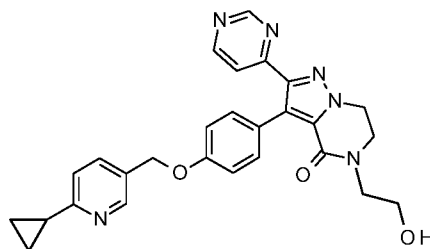


f- Synthesis of Co. 168:

To a sol. of **335** (4.2 g, 8.7 mmol) in MeOH (250 mL) was added Cs₂CO₃ (14 g, 43 mmol) and the mixture was stirred at r.t. for overnight. The mixture was filtered. The white solid was collected, washed with Et₂O and dried to give 2.6 g of white solid (68%). 300 mg of 2.6 g was taken in DCM and washed with brine twice. The organic layer was then dried over MgSO₄, filtrated and concentrated to give a white solid which was triturated in Et₂O. The white solid was filtrated and dried to give 250 mg of **Co. 168**, white solid. m.p.: 254°C (dsc).

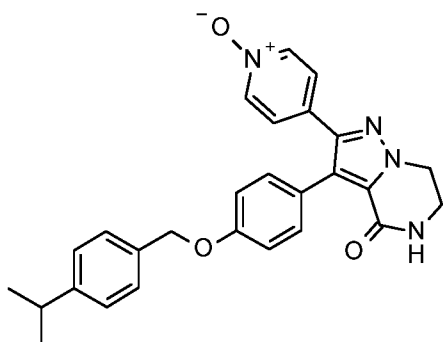
Example A168: Preparation of Co. 169**a- Synthesis of Int. 336:**

NaH 60% (55 mg, 1.4 mmol) was added slowly to a suspension of Co. 168 (0.40 g, 0.91 mmol) in dry DMF (5.4 mL) at r.t. under N₂. The mixture was stirred for 2h then (2-bromoethoxy)-tert-butyldimethylsilane (0.23 mL, 0.1 mmol) was added and the r.m. 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 MgSO₄, filtered and concentrated to give 0.47 g of Int. **336** (mixture of Int. 336 (30%) and Co. 169 (70%)). This crude mixture was used like this in the deprotection step.

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

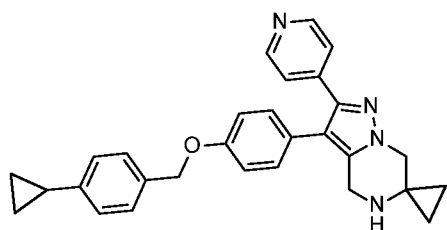
TBAF (0.95 mL, 0.95 mmol) was added dropwise to a sol. of mixture **336** (0.47 g) in THF (7.7 mL) at r.t. The mixture was stirred overnight at r.t. The mixture was concentrated and the residue was purified by prep. LC (Regular SiOH, 30 μm, 25g GraceResolv™, mobile phase: DCM/MeOH/NH₄OH 96/4/0.1). The desired fractions were collected and solvent evaporated to give 340 mg of colorless oil. This oil was purified by achiral SFC (Stationary phase: Amino 6μm 150x21.2mm, Mobile phase: 80% CO₂, 20% MeOH). The pure fractions were collected and the solvent evaporated to give 206 mg of white solid. The solid was triturated in Et₂O, filtered, washed and dried to give 0.19 g of **Co. 169**, white solid (50%). m.p.: 143°C (dsc).

Example A169: Preparation of Co. 170



To a sol. of **Co. 1** (133 mg, 0.303 mmol) in DCM (10 mL) at 0 °C was added portionwise 3-chloroperoxybenzoic acid (157 mg, 0.91 mmol). The r.m. was allowed to warm to r.t. and stirred overnight. The mixture was diluted with DCM and washed with
 5 a 10% sol. of Na₂CO₃. The organic layer was dried over MgSO₄, filtered and evaporated *in vacuo*. The residue (225 mg) was purified by prep. LC (Regular SiOH 50 μm, 24g Grace, dry loading, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%). The pure fractions were collected and solvent evaporated until dryness to give 88 mg of **Co. 170**, white solid (64%).

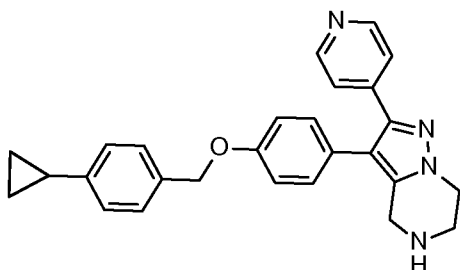
10 Example A170: Preparation of Co. 171



LAH (98.5 mg, 2.59 mmol) was added to a sol. of **Co. 5** (200 mg, 0.432 mmol) in dry ethylene glycol dimethyl ether (8 mL). The r.m. was heated at 60°C for 8h and quenched with water (100 μL, very slow addition) and a 3N sol. of NaOH (100 μL).
 15 Et₂O was added and the crude mixture was filtered on a glass frit. The precipitate was washed with Et₂O and the filtrate was evaporated *in vacuo* to give 330 mg, yellow residue. The residue was purified by prep. LC (Irregular SiOH, 15-40 μm, 24g Grace, mobile phase gradient: from DCM 100% to DCM 50%, acetone 50%). The pure fractions were collected and solvent evaporated until dryness to give 118 mg of **Co.**
 20 **171**, white solid (49%). m.p. : 152°C (DSC).

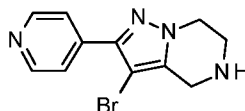
Example A171: Preparation of Co. 172

▪ **First Method**



A sol. of **Co. 4** (150 mg, 0.344 mmol) in dry THF (15 mL) was treated with LAH (52 mg, 1.37 mmol). The r.m. was stirred at room temperature for 18h, then quenched with addition of water (75 μ L, very slow addition), a 3N sol. of NaOH (75 μ L) and water (250 μ L). The crude mixture was filtered on glass frit and the filtrate was taken up in EtOAc, dried, filtered and evaporated *in vacuo* to afford 130mg, white solid. The residue was purified by prep. LC (irregular SiOH 15-40 μ m, 50g Merck, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%). The pure fractions were collected and solvent evaporated until dryness to give 82 mg of **Co. 172**, white solid (56%). m.p.: 215°C (DSC).

■ Second Method



a- Synthesis of Int. 337:

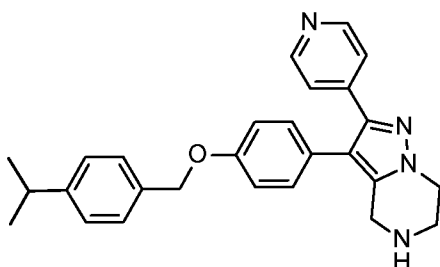
A sol. of 2-pyridin-4-yl-4,5,6,7-tetrahydropyrazolo[1,5- α]pyrazine (3.98 g, 19.9mmol) in HOAc (80 mL) was treated with N-bromosuccinimide (3.89 g, 21.9 mmol) and stirred at r.t. for 2h. The crude mixture was taken up in a sol. of K₂CO₃ 10% and diluted in DCM. The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo*. The crude mixture was coevaporated with toluene (2 times) to give 8.11g, yellow oil. This oil was dissolved in DCM and the precipitate which formed was filtered to give 760 mg of Int. **337**, yellow solid (14%). The filtrate was concentrated *in vacuo* and purified by prep. LC (irregular SiOH 15-40 μ m, 30g Merck, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%). The pure fractions were collected and solvent evaporated to give 3.30 g of Int. **337**, yellow solid (59%). (Global yield: 73%).

b- Synthesis of Co. 172:

In a sealed tube, a mixture of **337** (379 mg, 1.36 mmol), **32** (951 mg, 2.72 mmol), K₃PO₄ (1.15 g, 5.43 mmol) in 1,4-dioxane (7 mL) and H₂O (2.4mL) was carefully purged with N₂. PdCl₂(dppf) (111 mg, 0.136 mmol) was added and the r.m. was purged again with N₂. The sealed tube was then sealed and the r.m. was stirred for 17 h at 80°C. The r.m. was diluted with EtOAc and washed with water (once) and with brine

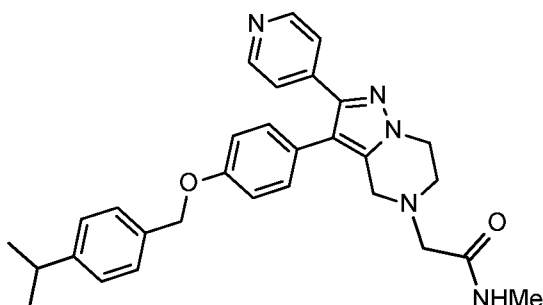
(twice). The organic phase was dried over MgSO_4 , filtered and evaporated *in vacuo* to give 1.30 g, brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 μm , 50g Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The desired fractions were collected and solvent evaporated until dryness to give 350 mg, white solid which was triturated in Et_2O . The supernatant was removed and the solid was dried *in vacuo* to give 320 mg. The product was purified by prep. LC (on Spherical SiOH 10 μm 60g PharmPrep Merck, mobile phase gradient: from DCM 98%, MeOH 2% to DCM 95 %, MeOH 5 %). The pure fractions were collected and solvent evaporated until dryness to give 210 mg of **Co. 172**, white solid (37 %). m.p.: 209°C (DSC).

Example A172: Preparation of Co. 173



To a sol. of **Co. 1** (330 mg, 0.753 mmol) in dry THF (17 mL) was added LAH (114 mg, 3.01 mmol) and the r.m. was stirred for 20h at r.t., then quenched with addition of water (214 μL , very slow addition), a 3N sol. of NaOH (214 μL) and water (642 μL). The crude mixture was filtered on glass frit, the cake was washed with EtOAc and the filtrate was evaporated *in vacuo* to afford 300 mg of a white solid which was purified by prep. LC (irregular SiOH 15-40 μm , 30g Merck, mobile phase gradient: DCM/MeOH from 100/0 to 90/10). The pure fractions were collected and solvent evaporated to give 185 mg of **Co. 173**, white solid (58%). m.p.: 194°C (DSC).

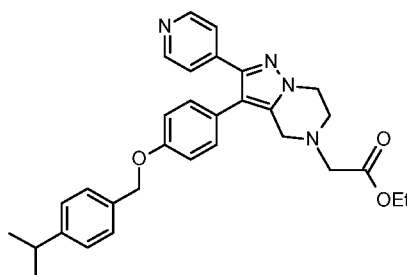
Example A173: Preparation of Co. 174



2-Bromo-N-methylacetamide (0.252 g, 1.66 mmol) was added to a sol. of **Co. 173** (0.4 g, 0.923 mmol) and K_2CO_3 (0.255 g, 1.85 mmol) in DMF (6 mL) at rt. The r.m. was stirred at r.t. for 16h, and then water and EtOAc were added. The organic layer was

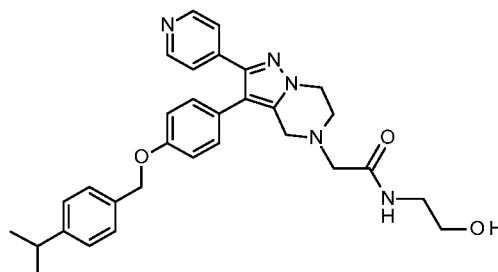
- washed with brine, separated, dried over MgSO_4 , filtered and concentrated *in vacuo* to give 574 mg. The residue was combined with another batch (0.2g of Co. 173 in the same conditions) and purified by prep. LC on (irregular 15-40 μm 30g Merck, Mobile phase: 0.5% NH_4OH , 96% DCM, 4% MeOH). The pure fractions were collected and solvent was removed *in vacuo* to give 340 mg which was crystallized from DIPE, filtered and dried to give 279 mg of **Co. 174** (40%). m.p.: 185°C (dsc).

Example A174: Preparation of Co. 175



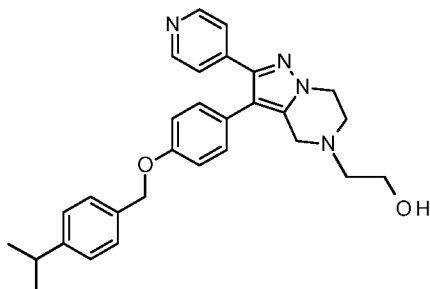
a- Synthesis of Int. 338:

- Ethylbromoacetate (276 μL , 2.49 mmol) was added to a sol. of **Co. 173** (600 mg, 1.39 mmol) and K_2CO_3 (383 mg, 2.77 mmol) in DMF (9 mL) at r.t. The r.m. was then stirred at 55°C for 2h, then water and EtOAc were added. The organic layer was washed with brine, separated, dried over MgSO_4 , filtered and concentrated *in vacuo* to afford 850 mg of Int. **338**, red oil (crude), which was used as such in the next reaction step.

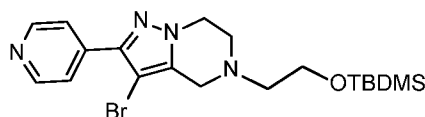


b- Synthesis of Co. 175:

- In a sealed tube, a mixture of **338** (850 mg, 1.67 mmol), ethanolamine (5.0 mL, 83.2 mmol), Magnesium chloride hydrate (475 mg, 4.99 mmol) in 1,4-dioxane (10 mL) was heated at 180°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]. Water and EtOAc were added to the mixture. The organic layer was washed with brine, separated, dried over MgSO_4 , filtered and evaporated *in vacuo*. The residue (500 mg, brown oil) was purified by prep. LC (irregular SiOH 15-40 μm , 80g Grace, mobile phase gradient: from DCM 100% to DCM 92%, MeOH 8%). The pure fractions were collected and solvent evaporated to give 280 mg, yellow oil, which was diluted in a minimum amount of MeOH and triturated in Et_2O . The supernatant was removed and the solid formed was dried *in vacuo* to give 250 mg of **Co. 175**, white solid. m.p.: 189 °C (DSC).

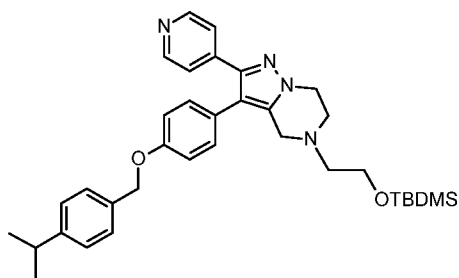
Example A175: Preparation of Co. 176■ **First Method**

- (2-Bromoethoxy)-tert-butyldimethylsilane (0.133 mL, 0.612 mmol) was added to a stirred sol. of **Co. 173** (200 mg, 0.471 mmol) and Et₃N (0.131 mL, 0.942 mmol) in DMF (2.5 mL) at r.t. The r.m. was stirred at 60 °C for 43h. Then, further (2-bromoethoxy)-tert-butyldimethylsilane (31 µL, 0.141 mmol) was added at r.t., and the r.m. was stirred at 60 °C for 16h. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give 250 mg, oil. Then, the oil was dissolved in THF (3mL), and TBAF (0.942 mL, 0.942 mmol) was added at r.t. The r.m. was stirred at r.t. for 4h. The crude material was diluted in a mixture of MeOH/DCM 8/92, and water was added. The organic phase was separated, washed with brine (twice), dried over MgSO₄, filtered and evaporated *in vacuo*. The residue (348 mg) was purified by prep. LC (irregular SiOH 15-40 µm, 12g Grace, Mobile phase gradient: from DCM 100% to DCM 88%, MeOH 12%). The desired fractions were combined and the solvent was removed *in vacuo*. The residue (307 mg) was dissolved in a mixture of MeOH/DCM 2/98, and water was added. The organic phase was separated, washed with brine (twice), dried over MgSO₄, filtered and evaporated *in vacuo* to give 108 mg, pale brown solid. The solid was dissolved in EtOAc, and water was added. The organic phase was separated, washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give oil. The oil was triturated with a sol. of pentane/MeOH 70/30, and the solvents were removed *in vacuo* to afford 105 mg of **Co. 176**, pale brown solid (48%).

■ **Second Method**25 **a- Synthesis of Int. 339:**

(2-Bromoethoxy)-tert-butyldimethylsilane (1.2 mL, 5.73 mmol) was added to a stirred sol. of **337** (1.00 g, 3.58 mmol) and Et₃N (1 mL, 7.17 mmol) in DMF (20 mL) at r.t. The r.m. was stirred at 60°C for 18h. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried over MgSO₄,

- filtered and evaporated *in vacuo* to give 2.00 g, brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 μ m, 50g Grace, Mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 1.00 g, colorless oil. This oil was dissolved in water and extracted with EtOAc. The organic phase was washed with brine (twice), dried over MgSO₄, filtered and evaporated *in vacuo* to give 690 mg of Int. **339**, colorless oil (44%).



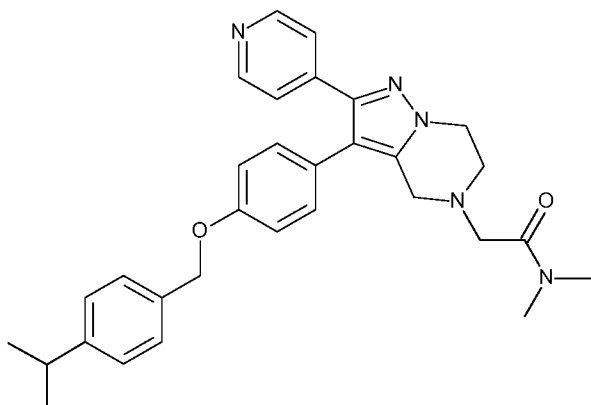
b- Synthesis of Int. 340:

- In a sealed tube, a mixture of **339** (400 mg, 0.914 mmol), **5** (644 mg, 1.83mmol), K₃PO₄ (777 mg, 3.66 mmol) in 1,4-dioxane (4 mL) and H₂O (1.4 mL) was carefully purged with N₂. PdCl₂(dppf) (75 mg, 91.4 μ mol) was added and the r.m. was purged again with N₂. The sealed tube was then sealed and the r.m. was stirred for 17 h at 80°C. The r.m. was diluted with EtOAc and washed with water (once) and with brine (2 times). The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give 1.50 g, brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 μ m, 50g Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The desired fractions were collected and solvent evaporated until dryness to give 570 mg of Int. **340**, orange oil (quant.). The product was used as such for the next step.

c- Synthesis of Co. 176:

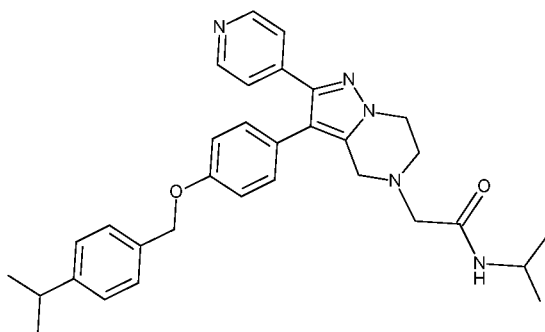
- A sol. of **340** (570 mg, 0.978 mmol) in THF (10 mL) was treated with TBAF (1.20 mL, 1.17 mmol) and stirred at 0°C for 4h. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give 600 mg, brown oil. This oil was purified by prep. LC (irregular SiOH 15-40 μ m, 50g Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 275 mg, yellow oil. This oil was triturated in Et₂O and the precipitate was dried *in vacuo* to give 275 mg, white solid. The white solid was diluted in DCM and Et₂O and the sol. was allowed to evaporate for 4h, the white solid was dried *in vacuo* to give 275 mg of Co. **176**, orange solid. m.p.: 150°C (DSC).

- Example A176: Preparation of Co. 177



2-Bromo-N,N-dimethylacetamide (268 mg, 1.62 mmol) was added to a sol. of **Co. 173** (500 mg, 1.15 mmol) and K_2CO_3 (319 mg, 2.31 mmol) in DMF (7.5 mL) at r.t. The r.m. was stirred at 55°C for 2h. Then, water and EtOAc were added. The organic layer
5 was separated, washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to afford brown oil. The oil was purified by prep. LC (irregular SiOH 15-40 μm , 80g, GraceResolvTM, mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The pure fractions were collected and solvent evaporated until dryness to give 170 mg, yellow solid. This solid was combined with another batch (0.4g of **Co. 173** as initial
10 reactant in the same conditions), dissolved in EtOH and evaporated *in vacuo* to give a yellow foam which was dissolved in iPrOH (200 μL) to get a thick oil. The thick oil was triturated while Et_2O was slowly added. The solid formed was filtered on a glass frit, washed with Et_2O and dried *in vacuo* to give 190 mg of **Co. 177**, pale yellow solid (global yield: 15%). m.p.: 95°C (DSC).

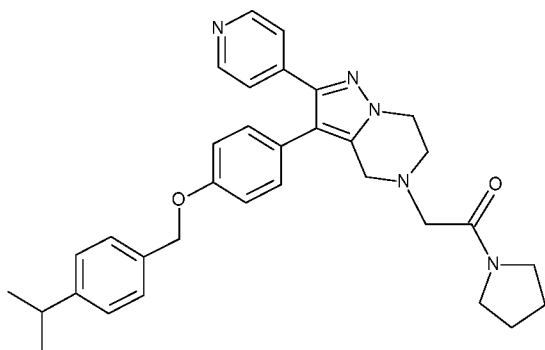
15 Example A177: Preparation of Co. 178



2-Bromo-N-isopropylacetamide (150 mg, 0.831 mmol) was added to a sol. of **Co. 173** (300 mg, 0.693 mmol) and K_2CO_3 (191 mg, 1.39 mmol) in DMF (5 mL) at r.t. The r.m. was stirred at 55°C for 2h and poured in a mixture of water and EtOAc. The organic
20 layer was separated, washed with brine (3x), dried over $MgSO_4$ and evaporated *in vacuo* to give orange oil. The oil was purified by prep. LC (irregular SiOH 15-40 μm , 40g Grace Resolv, mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%).

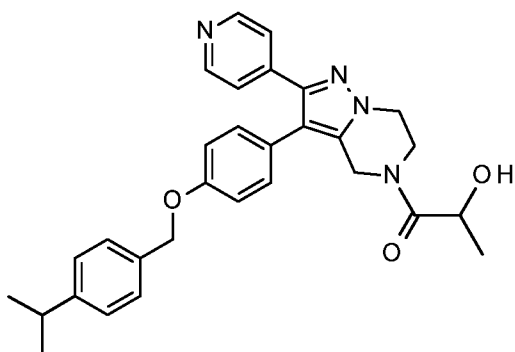
The pure fractions were collected and solvent evaporated until dryness to give 180 mg of white solid. The solid was dissolved in MeOH (1mL) and the MeOH was allowed to slowly evaporate overnight. The solid was crushed and dried *in vacuo* to give 180 mg of **Co. 178**, white solid (50%). m.p.: 188°C (DSC).

5 Example A178: Preparation of Co. 179



A sol. of 2-bromo-1-(1-pyrrolidinyl)-ethanone (137 mg, 0.715 mmol) in DMF (0.5 mL) was added to a sol. of **Co. 173** (172 mg, 0.397 mmol) and K₂CO₃ (110 mg, 0.794 mmol) in DMF (2.5 mL) at r.t. The r.m. was stirred at r.t. for 17h, and water and EtOAc were added. The organic layer was washed with brine, separated, dried (MgSO₄), filtered and evaporated *in vacuo*. The residue (204 mg) was purified by prep. LC (irregular SiOH 15-40μm, 12g Grace, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%). The pure fractions were collected and solvent evaporated to give a sticky solid. The solid was triturated with pentane, filtered off and dried to yield 71 mg of **Co. 179**, pale yellow solid (33%).

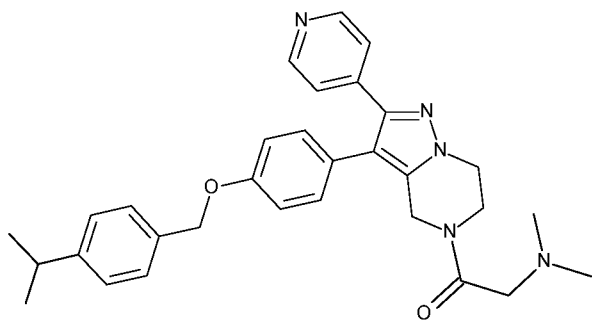
Example A179: Preparation of Co. 180



Lactic Acid 85% (61 μL, 0.693 mmol) was added to a stirred sol. of HATU (298 mg, 0.785 mmol) and DIPEA (143 μL, 0.831 mmol) in DCM (3.5 mL) at r.t. under N₂. The mixture was stirred at r.t. for 65 min. Then, **Co. 173** (200 mg, 0.462 mmol) was added, and the crude mixture was stirred for 17h. Further additions of Lactic Acid 85% (40 μL, 0.462 mmol), HATU (211 mg, 0.555 mmol) and DIPEA (119 μL, 0.693 mmol)

were done at r.t. under N₂, and the mixture was stirred at r.t. for 16h. Then, water and a mixture of MeOH/DCM (4/96) were added. The organic layer was separated, washed with brine, separated, dried over MgSO₄, filtered and evaporated *in vacuo* to afford 256 mg. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 30g Grace, mobile phase gradient: from DCM 100% to DCM 91%, MeOH 9%). The desired fractions were collected and solvent evaporated to give 171 mg, white solid. This white solid was purified by prep. LC (irregular SiOH 15-40μm, 12g Grace, mobile phase gradient: from DCM 100% to DCM 91%, MeOH 9%). The desired fractions were collected and solvent evaporated to give 128 mg, white solid. This residue was purified by achiral SFC (diethylaminopropyl 5μm 150x21.2mm, Mobile phase: 80% CO₂, 20% MeOH). The desired fractions were combined and the solvent was removed *in vacuo* to give colorless oil. The oil was triturated with pentane, and the solvent was evaporated *in vacuo* to yield 90 mg, white solid. The residue was purified by Reverse phase (X-Bridge-C18 5μm 30*150mm, Mobile phase: Gradient from 70% (NH₄HCO₃ 0.5% aq. sol.), 30% ACN to 100% ACN). The pure fractions were collected and the solvent was removed *in vacuo* to give colorless oil. The oil was dissolved in DCM and the solvent was evaporated *in vacuo*. The remaining sticky solid was triturated with pentane, and the solvent was evaporated *in vacuo* to yield 50 mg of **Co. 180**, white solid (22%).

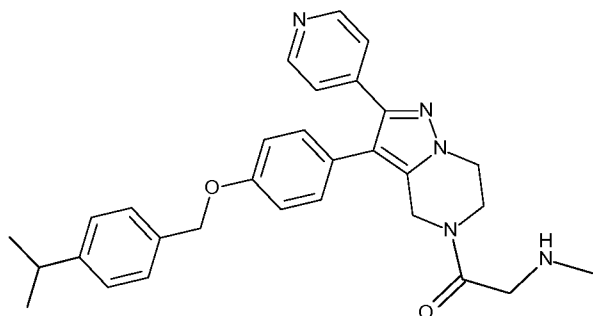
Example A180: Preparation of Co. 181



DIPEA (0.203 mL, 1.18 mmol) was added to a stirred sol. of **Co. 173** (100 mg, 0.236 mmol) in DCM (2 mL) at 0 °C under N₂. Then, 2-(dimethylamino)-acetyl chloride, hydrochloride (88 mg, 0.471 mmol) was added at 0 °C under N₂, and the mixture was stirred at r.t. for 16h. The crude material was quenched with water and extracted with DCM. The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give a solid which was purified by prep. LC (irregular SiOH 15-40μm 12g Grace, Mobile phase gradient: from DCM 100% to DCM 88 %, MeOH 12%). The desired fractions were combined and the solvent was removed *in vacuo* to give 83 mg, white solid. The residue was purified by Reverse phase (X-Bridge-C18 5μm 30*150mm; Mobile phase gradient: from 50% (NH₄HCO₃ 0.5% aq. sol.), 50%

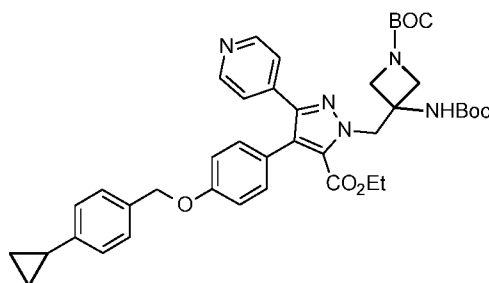
MeOH to 100% MeOH). The pure fractions were collected and solvent evaporated to afford 55 mg, pale oil. The oil was diluted with Et₂O and then concentrated *in vacuo* to give 53 mg of **Co. 181**, waxy solid (44%).

Example A181: Preparation of Co. 182



5 N-Boc-sarcosine (152mg, 0.801 mmol) was added to a sol. of CDI (130 mg, 0.801 mmol) in dry THF (1 mL) at r.t. under N₂. The mixture was stirred for 90min at r.t., and then added over 25min to a sol. of **Co. 173** (200 mg, 0.400 mmol) in THF (1.5 mL) at r.t. under N₂. The r.m. was stirred for 16h at r.t., and then a sol. of additional N-Boc-sarcosine (152 mg, 0.801 mmol) and CDI (130 mg, 0.801 mmol) in dry THF (1 mL) was added slowly at r.t. The r.m. was stirred for 2h at r.t. TFA (1 mL, 26.1 mmol) was added at r.t., and the r.m. was stirred for 22h. Then, additional TFA (1 mL, 26.1 mmol) was added, and the r.m. was stirred for 18h. Then, the r.m. was heated at 80°C, and stirred for 160 min at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give oil. The oil was purified by prep. LC (irregular SiOH 15-40μm, 12g Grace, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 9%, aq. NH₃ 1%). The pure fractions were collected and solvent evaporated to give 158 mg of **Co. 182**, white solid (80%).

20 Example A182: Preparation of Co. 183

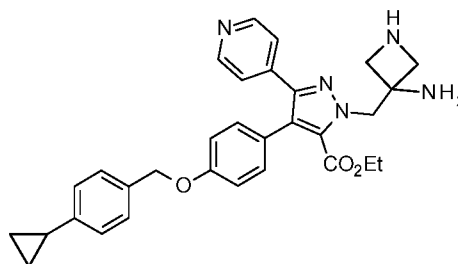


a- Synthesis of Int. 341:

To a suspension of **36** (396 mg, 0.902 mmol), 1-Boc-3-(Boc-amino)azetidine-3-methanol (300 mg, 0.992 mmol) and diphenylphosphinostyrene (601 mg, 1.80 mmol) in dry THF (8 mL) was added DBAD (415 mg, 1.80 mmol). The mixture was stirred at r.t. for 18h. THF (4 mL) was added and the mixture was stirred at r.t. for 18h, then,

heated at 50°C for 20h and refluxed for 68h. The crude mixture was then filtered through a glass frit and washed with EtOAc. The filtrate was evaporated *in vacuo* to give 1.26 g, yellow oil. The residue was purified by prep. LC (Irregular SiOH, 15-40 μ m, 50g Merck, mobile phase gradient: from DCM 100% to DCM 50%, EtOAc 50%).

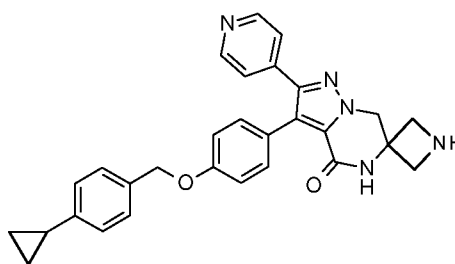
- 5 The pure fractions were collected and solvent evaporated until dryness to give 596 mg of Int. **341**, off-white foam (91%).



b- Synthesis of Int. 342:

HCl salt

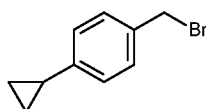
- To a sol. of **341** (596 mg, 0.823 mmol) in 1,4-dioxane (6 mL) was added HCl 4N in dioxane (1.65 mL, 6.59 mmol). The mixture was stirred at r.t. for 18h and HCl 4N in dioxane (0.823 mL, 3.29 mmol) was added. The mixture was stirred for 4h then poured in Et₂O. The precipitate was filtered through a glass frit to give 470 mg of Int. **342**, off-white solid (salt HCl, quant. yield).



c- Synthesis of Co. 183:

- To a sol. of **342** (470 mg, 0.839 mmol) in MeOH (5 mL) was added Cs₂CO₃ (1.37 g, 4.20 mmol) and the mixture was stirred at r.t. for 18h. The solvent was removed *in vacuo* and water and DCM were added. The layers were separated and the aq. layer was extracted with DCM. The organic layers were combined, dried over MgSO₄, filtered off and evaporated *in vacuo* to give 334 mg of white solid. 120 mg of this solid was purified by prep. LC (Irregular SiOH, 15-40 μ m, 24g Grace, mobile phase: DCM/MeOH/NH₃(aq.) 90/10/0.5). The pure fractions were collected and solvent evaporated to give 108 mg of **Co. 183**, white solid. m.p.: 173°C (DSC).

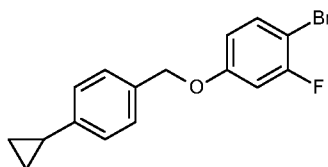
Example A183: Preparation of Co. 184a and Co. 184



a- Synthesis of Int. 343:

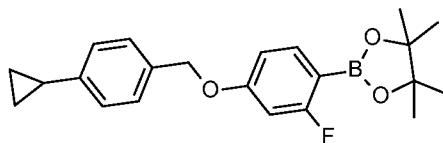
- To a sol. of **31** (1mL, 6.63mmol) in dry Et₂O (20mL) at 0°C was added dropwise PBr₃ (620 μ L, 6.63mmol). The ice bath was removed and the r.m. was stirred for 2h. Then,

water was carefully added to the mixture and the layers separated. The organic one was washed with a sat. sol. of NaCl, dried (MgSO₄) and evaporated *in vacuo* to afford 1.38g of Int. **343**, colorless liquid (99%).



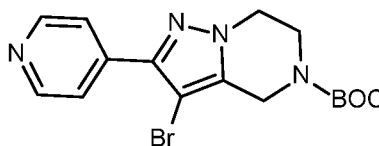
5 **b- Synthesis of Int. 344:**

Under N₂, a sol. of 4-bromo-3-fluorophenol (1.14 g, 5.94 mmol) in DMF (6 mL) was treated with K₂CO₃ (903 mg, 6.54 mmol) and **343** (1.38 g, 6.54 mmol) and the r.m. was stirred for 18h at r.t. An extra amount of 1-(bromomethyl)-4-cyclopropyl-benzene (0.125 g, 0.594 mmol) was added and the r.m. was stirred for 4h, and was then
10 extracted with water and EtOAc. The organic layer was washed with brine (2x), dried (MgSO₄), filtered off and evaporated *in vacuo* to give 2.40 g of a colorless oil. The residue was purified by prep. LC (irregular SiOH 15-40μm, 30g Merck, mobile phase: DCM 100%). The pure fractions were collected and solvent evaporated to give 1.20 g of Int. **344**, white solid (63%, purity 90%).



15 **c- Synthesis of Int. 345:**

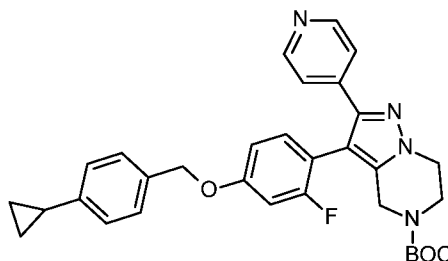
In a sealed tube, a mixture of **344** (1.20 g, 3.74 mmol), BisPin (1.10 g, 11.2 mmol), KOAc (1.14 g, 4.48 mmol) in DME (11 mL) was carefully purged with N₂. PdCl₂(dppf) (306 mg, 0.374 mmol) was added and the r.m. was purged again with N₂. The r.m. was stirred for 17h at 100°C. The r.m. was diluted with EtOAc and washed
20 with water (once) and with brine (3 times). The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give 2.00 g, brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 50g, MERCK, Mobile phase: Heptane/EtOAc, gradient from 100/0 to 90/10). The pure fractions were collected and solvent evaporated until dryness to give 1.03 g of Int. **345**, colorless oil (75%).



25 **d- Synthesis of Int. 346:**

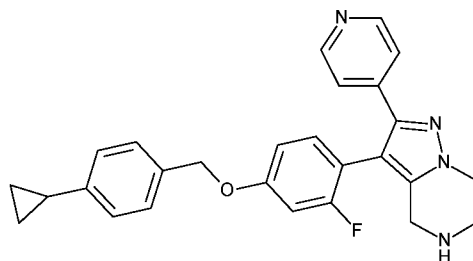
Et₃N (180 μL, 1.29 mmol) was added to a mixture of **337** (300 mg, 1.08 mmol) and Boc₂O (281 mg, 1.29 mmol) in DCM (5 mL). The r.m. was then stirred for 3 h at rt. The sol. was diluted with EtOAc and washed with water (once) and with K₂CO₃ 10% (2

times). The organic phase was dried over MgSO_4 , filtered and evaporated *in vacuo* to give 400 mg of Int. **346**, orange oil (98%).



e- Synthesis of Co. 184a

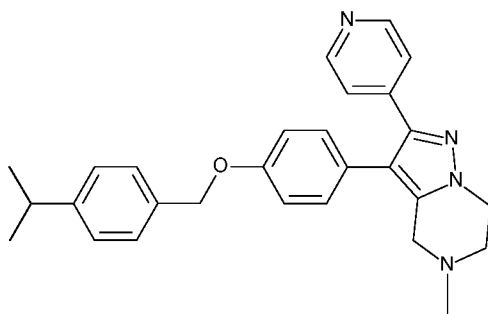
In a sealed tube, a mixture of **346** (330 mg, 870 μmol), **345** (641 mg, 1.74 mmol),
 5 K_3PO_4 (739 mg, 3.48 mmol) in 1,4-dioxane (7 mL) and H_2O (1.7 mL) was carefully
 purged with N_2 . $\text{PdCl}_2(\text{dppf})$ (71 mg, 87.0 μmol) was added and the r.m. was purged
 with N_2 . The sealed tube was then sealed and the r.m. was stirred for 17h at 80°C . The
 r.m. was diluted with EtOAc and washed with water (once) and with brine (2 times).
 The organic phase was dried (MgSO_4), filtered and evaporated *in vacuo* to give 900
 10 mg, brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 μm , 50g
 Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure
 fractions were collected and solvent evaporated to give 370 mg of **Co. 184a**, yellow oil
 (79%).



f- Synthesis of Co. 184:

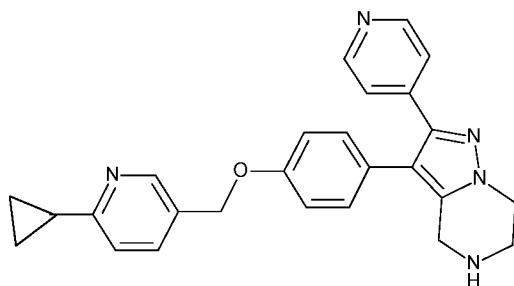
15 A sol. of **Co. 184a** (370 mg, 684 μmol) in MeOH (10 mL) and HCl 3N (5 mL) was
 stirred at 45°C for 1h30. The sol. was then quenched with sat. NaHCO_3 and extracted
 with DCM. The organic phase was dried over MgSO_4 , filtered and evaporated *in vacuo*
 to give 250 mg. The residue was purified by prep. LC (irregular SiOH 15-40 μm , 30g
 Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure
 20 fractions were collected and solvent evaporated to give 127 mg of **Co. 184**, pink solid
 (42%). m.p.: 195°C and 339°C , polymorph (DSC).

Example A184: Preparation of Co. 185



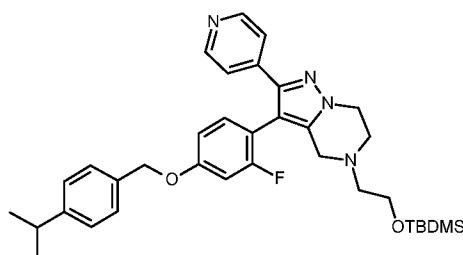
A sol. of **Co. 48** (120 mg, 0.265 mmol) in dry THF (6 mL) was treated with LAH (40 mg, 1.06 mmol). The r.m. was stirred at r.t. for 18h, then, quenched with addition of water (75 μ L, very slow addition), a 3N sol. of NaOH (75 μ L) and water (190 μ L). The crude mixture was filtered on glass frit, the cake was washed with EtOAc and the filtrate was, dried, filtered and evaporated *in vacuo* to afford 160 mg. The residue was purified by prep. LC (irregular SiOH 15-40 μ m, 50g Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 71 mg, colorless oil which was crystallized from Et₂O, filtered and dried to give 71 mg of **Co. 185**, white solid (61%). m.p.: 120 °C (DSC).

Example A185: Preparation of Co. 186

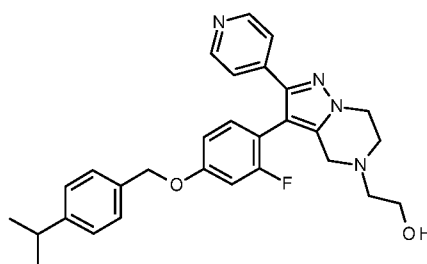


A sol. of **Co. 3** (112 mg, 256 μ mol) in dry THF (2 mL) was treated with LAH (58 mg, 1.54 mmol). The r.m. was stirred at r.t. for 18h, then, quenched successively with addition of water (60 μ L, very slow addition), a 3N sol. of NaOH (60 μ L) and water (180 μ L). The crude mixture was filtered on glass frit. The cake was washed with EtOAc, and the filtrate was evaporated *in vacuo* to afford 80 mg. The residue was purified by prep. LC (irregular SiOH 15-40 μ m, 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 75 mg of **Co. 186**, white solid (69%). m.p.: 195 °C (DSC).

Example A186: Preparation of Co. 187

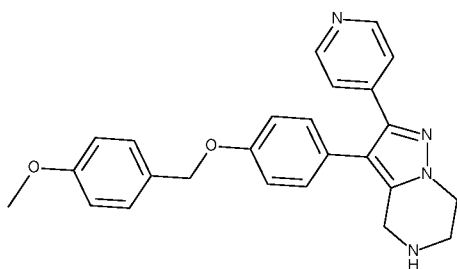
**a- Synthesis of Int. 348:**

In a sealed tube, a mixture of **339** (240 mg, 549 μmol), **42** (406 mg, 1.10 mmol), K_3PO_4 (466 mg, 2.20 mmol) in 1,4-dioxane (5 mL) and H_2O (1.2 mL) was carefully purged with N_2 . $\text{PdCl}_2(\text{dppf})$ (45 mg, 54.9 μmol) was 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 r.m. was diluted with EtOAc and washed with water (once) and with brine (2 times). The organic phase was dried over MgSO_4 , filtered and evaporated *in vacuo* to give 500 mg, brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 μm , 50g Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The desired fractions were collected and solvent evaporated until dryness to give 320 mg of Int. **348**, orange oil. The mixture was used as such for the next step without further purification.

**b- Synthesis of Co. 187:**

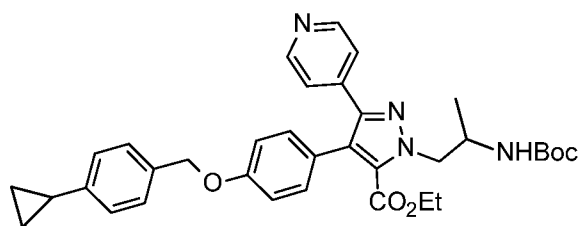
A sol. of **348** (320 mg, 0.533 mmol) in THF (5 mL) was treated with TBAF (640 μL , 0.639 mmol) and stirred at 0°C for 2h. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried over MgSO_4 , filtered and evaporated *in vacuo* to give 350 mg, brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 μm , 30g Merck, mobile phase gradient: from DCM 100% to DCM 98%, MeOH 2%). The pure fractions were collected and solvent evaporated to give 123 mg, yellow oil. This oil was diluted in pentane and evaporated *in vacuo* to give 123 mg of **Co. 187**, white solid (46%).

Example A187: Preparation of Co. 188



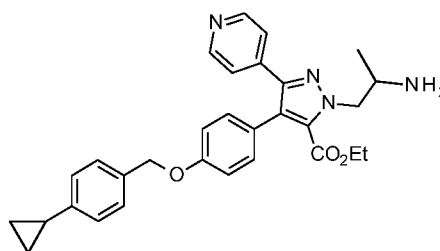
A sol. of **Co. 112** (195 mg, 0.457 mmol) in dry THF (12 mL) was treated with LAH (69 mg, 1.83 mmol). The r.m. was stirred at r.t. for 18h, then, quenched with addition of water (100 μ L, very slow addition), a 3N sol. of NaOH (100 μ L) and water (300 μ L). The crude mixture was filtered on glass frit and the filtrate was taken up in EtOAc and evaporated *in vacuo* to afford 200mg, white solid. The residue was purified by prep. LC (irregular SiOH 15-40 μ m, 50g Merck, mobile phase gradient: from DCM 100% to DCM 90%, MeOH 10%). The pure fractions were collected and solvent evaporated until dryness to give 130 mg, white solid. The solid was triturated in Et₂O and evaporated *in vacuo* to give 115 mg of **Co. 188**, white solid (61%). m.p.: 192°C and 342°C (DSC - polymorphous compound).

Example A188: Preparation of Co. 189



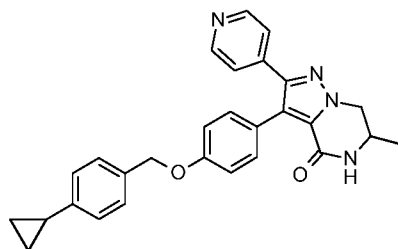
a- Synthesis of Int. 349:

To a mixture of **36** (700 mg, 1.59 mmol), N-Boc-2-amino-1-propanol (558 mg, 3.19 mmol) and diphenylphosphinopolystyrene (1.06 g, 3.19 mmol) in dry THF (13 mL) was added DBAD (734 mg, 3.19 mmol). The mixture was stirred for 2h at r.t. then filtered through a glass frit and washed with EtOAc. The filtrate was evaporated *in vacuo* to give 2.00 g, yellow oil. This oil was purified by prep. LC (Irregular SiOH, 15-40 μ m, 80g Grace, mobile phase gradient: from DCM 100% to DCM 98%, MeOH 2%). The desired fractions were collected and solvent evaporated to give 1.20 g, pale yellow oil. The residue was purified again by prep. LC (Irregular SiOH, 15-40 μ m, 30g Merck, mobile phase gradient: from DCM 100% to DCM 60%, EtOAc 40%). The pure fractions were collected and solvent evaporated to give 753 mg of Int. **349**, white foam (79%).

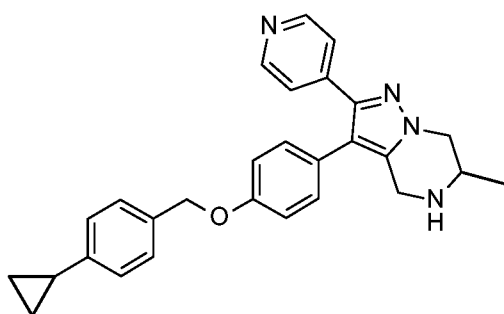
**b- Synthesis of Int. 350:**

HCl salt

To a sol. of **349** (753 mg, 1.26 mmol) in 1,4-dioxane (10 mL) was added HCl 4N in dioxane (2.50 mL, 10.1 mmol). The sol. was stirred at r.t. for 18h, then, poured with Et₂O. The supernatant was removed and the remaining solid was dried *in vacuo*. The residue was triturated 3x in Et₂O to give 686 mg of Int. **350**, pale yellow solid (HCl salt, quant. yield).

**c- Synthesis of Co. 189:**

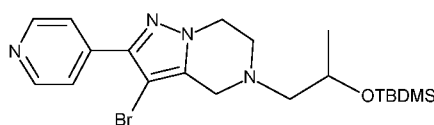
To a sol. of **350** (686 mg, 1.29 mmol) in MeOH (8 mL) was added Cs₂CO₃ (2.10 g, 6.43 mmol) and the mixture was stirred at r.t. for 6h. The solvent was removed *in vacuo* and water (25 mL) and DCM (25 mL) were added to the residue. The layers were separated and the aq. layer was extracted with DCM (25 mL). The organic layers were combined, dried over MgSO₄, filtered off and evaporated *in vacuo* to give 507 mg, white solid. The residue was triturated in Et₂O and the solid was filtered off on a glass frit to give 503 mg, white solid. The solid was triturated in a mixture of DCM/EtOAc 90/10 and was filtered off on a glass frit and dried to give 315 mg of **Co. 189**, white solid (54%). m.p.: 249°C (DSC).

Example A189: Preparation of Co. 190

LAH (88.5 mg, 2.33 mmol) was added to a sol. of **Co. 189** (175 mg, 0.388 mmol) in dry THF (30 mL). The r.m. was stirred at r.t. for 18h and LAH (44.2 mg, 1.17 mmol) was then added. The r.m. was stirred for an additional 18h and quenched with addition

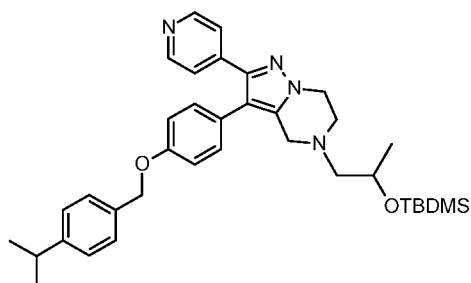
- of water (145 μ L, very slow addition) and a 3N sol. of NaOH (145 μ L). Et₂O was added and the crude mixture was filtered on a glass frit. The precipitate was washed with Et₂O and the filtrate was evaporated *in vacuo* to give 280 mg, yellow residue. The residue purified by prep. LC (Irregular SiOH, 15-40 μ m, 24g Grace, mobile phase gradient: from DCM 100% to DCM 50%, acetone 50%). The pure fractions were collected and solvent evaporated until dryness to give 137 mg of **Co. 190**, white solid (69%). m.p.: 166°C and 177°C (polymorph, DSC).

Example A190: Preparation of Co. 191 and Co. 192



a- Synthesis of Int. 351:

- (2-bromo-1-methylethoxy)(1,1-dimethylethyl)dimethylsilane (2.59 g, 7.17 mmol) was added to a stirred sol. of **337** (1.00 g, 3.58 mmol) and Et₃N (1mL, 7.17 mmol) in DMF (20 mL) at r.t. The r.m. was stirred at 60 °C for 7 days. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give 350 mg of a brown oil. An extra amount of (2-bromo-1-methylethoxy)(1,1-dimethylethyl)dimethylsilane (2.59 g, 7.17 mmol) and Et₃N (1 mL, 7.17 mmol) in DMF (20 ml) was added to the mixture. The r.m. was then stirred at 60 °C for 1 week. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give 4.47 g, brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 μ m, 50g Grace, Mobile phase gradient: from DCM 100%, to DCM 95%, MeOH 5%). The desired fractions were collected and solvent evaporated until dryness to give 640 mg, colorless oil. This oil was dissolved in water and extracted with EtOAc. The organic phase was washed with brine (2x), dried over MgSO₄, filtered and evaporated *in vacuo* to give 530 mg of Int. **351**, colorless oil (33%).

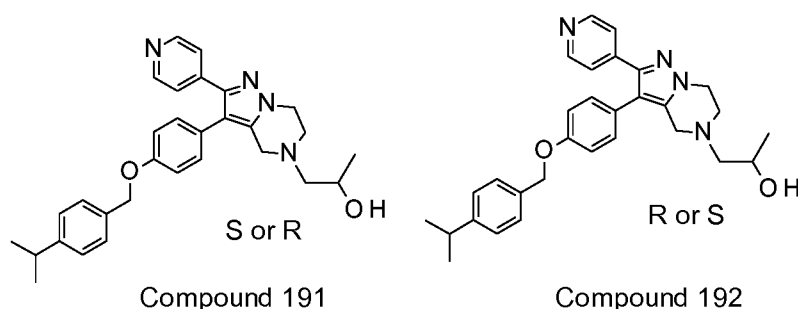


b- Synthesis of Int. 352:

In a sealed tube, a mixture of **351** (530 mg, 1.17mmol), **5** (827 mg, 2.35 mmol), K₃PO₄ (997 mg, 4.70 mmol) in 1,4-dioxane (5 mL) and H₂O (1.8 mL) was carefully purged with N₂. PdCl₂(dppf) (96 mg, 117 μ mol) was added and the r.m. was purged again with

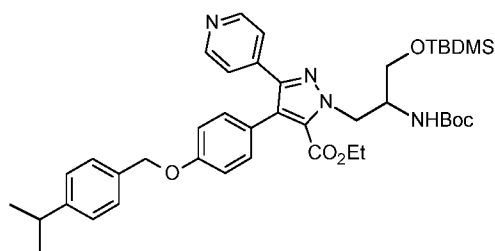
N₂. The sealed tube was then sealed and the r.m. was stirred for 17h at 80°C. The r.m. was diluted with EtOAc and washed with H₂O (1x) and brine (2x). The organic phase was dried (MgSO₄), filtered and evaporated *in vacuo* to give 1.20 g, brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 50g Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated to give 570 mg of Int. **352**, orange oil (82%).

c- Synthesis of Co. 191 & Co. 192



A sol. of **352** (576 mg, 0.965 mmol) in THF (9 mL) was treated with TBAF (1.2 mL, 1.16 mmol) and stirred at 0°C for 1h, then stirred at r.t. for 18h. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give 400 mg. The residue 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 to give 305 mg, white solid. The solid was purified by chiral SFC (Stationary phase: Chiralpak AD-H 5μm 250x20mm, Mobile phase: 70% CO₂, 30% mixture of EtOH/iPrOH 50/50 v/v). The pure fractions were collected and solvent evaporated to give 117 mg of **Co. 191** as a white solid (25%, m.p.: 148°C (DSC)) and 116 mg of **Co. 192** as a white solid (25%, m.p.: 151°C (DSC)). **Co. 191**: [α]_D: -6.44 ° (589 nm, c 0.3105 w/v %, DMF, 20 °C). **Co. 192**: [α]_D: +6.85 ° (589 nm, c 0.292 w/v %, DMF, 20 °C).

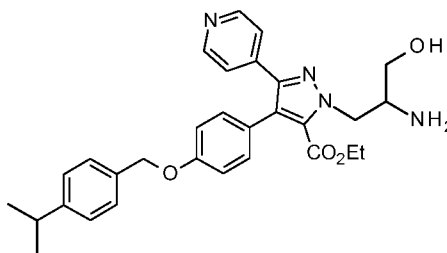
Example A191: Preparation of Co. 193



a- Synthesis of Int. 353:

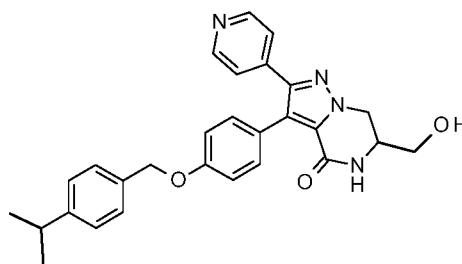
DBAD (1.1 g, 5.0 mmol) was added portionwise to a sol. of **11** (2.0 g, 4.5 mmol), N-(tert-butoxycarbonyl)-O-(tert-butyldimethylsilyl)serinol (1.5 g, 5.0 mmol), diphenylphosphino-polystyrene (1.6 g, 5.0 mmol) in THF (53 mL) at r.t. under N₂. The

mixture was stirred overnight at r.t. The mixture was filtrated throught a pad of Celite®, washed with EtOAc and concentrated to give 4.7 g. The crude residue was purified by prep. LC (irregular SiOH 35-40 µm 120g GraceResolv™, mobile phase: heptane/EtOAc from 80/20 to 70/30). The pure fractions were collected and solvent
5 evaporated until dryness to give 2.41 g of Int. **353** as a colorless oil (73%).



b- Synthesis of Int. 354:

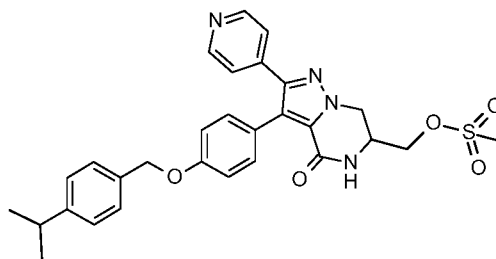
353 (277 mg, 0.38 mmol) and HCl 3N (0.63 mL, 1.9 mmol) in ACN (6.7 mL) was stirred at 80°C for 2h. The mixture was concentrated, NaHCO₃ sat aq (50 mL) was added and the mixture was stirred at r.t. for 15min. Subsequently, the mixture was
10 extracted with DCM, dried, filtered and evaporated to give 197 mg of Int. **354** (100%).



c- Synthesis of Co. 193:

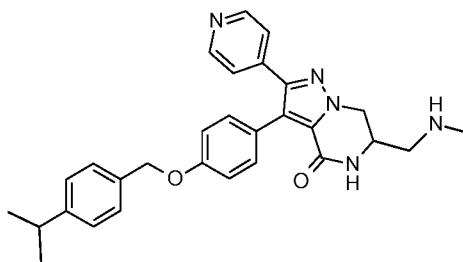
To a sol. of **354** (197 mg, 0.38 mmol) in MeOH (11 mL) was added Cs₂CO₃ (0.62 g, 1.9 mmol) and the mixture was stirred at r.t. overnight. The mixture was concentrated and taken in DCM and washed once with brine, dried over MgSO₄, filtered and
15 concentrated. The crude product was purified by prep. LC (irregular SiOH 30 µm, 12g GraceResolv™, mobile phase gradient: from DCM/MeOH/NH₄OH 97/3/0.1 to 95/5/0.1). The pure fractions were collected and solvent evaporated until dryness to give 146 mg, white solid. The solide was washed in Et₂O, filtrated and dried to give 136 mg of **Co. 193**, white solid (76%). m.p.: 254°C (dsc).

20 Example A192: Preparation of Co. 194



a- Synthesis of Int. 355:

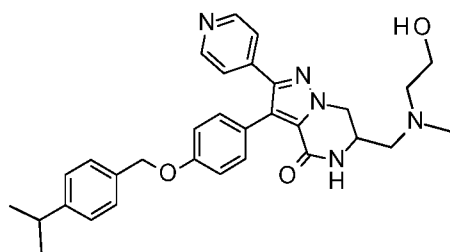
- Methanesulfonyl chloride (64 μ L, 0.83 mmol) was added dropwise to a sol. of Co. 193 (260 mg, 0.56 mmol) and Et₃N (232 μ L, 1.7 mmol) in dry DCM (5 mL) at r.t. under N₂ atmosphere. The r.m. was stirred at r.t. for 1h. Water was added and the mixture was extracted with DCM. The organic layer was separated, dried over MgSO₄, filtered and the solvent was concentrated to give 300mg of Int. **355**, colorless oil (99%).



b- Synthesis of Co. 194:

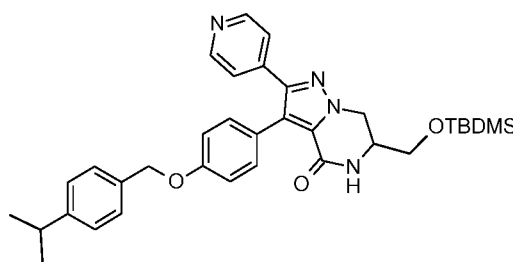
- In a microwave vial, a sol. of **355** (240 mg, 0.44 mmol) in methylamine in 2M THF (4.4 mL, 8.8 mmol) was stirred at 80°C for 3 days. The mixture was concentrated to give 440 mg, yellow oil. The residue was purified by prep. LC (Stationary phase: irregular 15-40 μ m 30g Merck, Mobile phase: 0.5% NH₄OH, 96% DCM, 4% MeOH). The pure fractions were collected and solvent evaporated until dryness to give 46 mg which was triturated in Et₂O and the white solid formed was filtrated and dried to give 23 mg of **Co. 194**, white powder (11%). m.p.: 230°C (dsc).

Example A193: Preparation of Co. 195

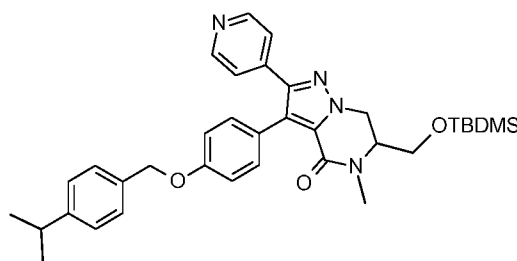


- In a microwave vial, a sol. of **355** (300 mg, 0.55 mmol) and 2-(methylamino)ethanol (0.88 mL, 11 mmol) in THF (4.5 mL) was stirred at 80°C overnight. The mixture was concentrated to give 1.3 g of yellow oil. The residue was purified by prep. LC (Stationary phase: irregular SiOH 15-40 μ m 300g Merck, Mobile phase: 0.5% NH₄OH, 96% DCM, 4% MeOH). The pure fractions were collected and solvent evaporated until dryness to give 105 mg which was crystallized from DIPE, filtered and dried to give 82 mg of **Co. 195** (28%). m.p.: 193°C (dsc).

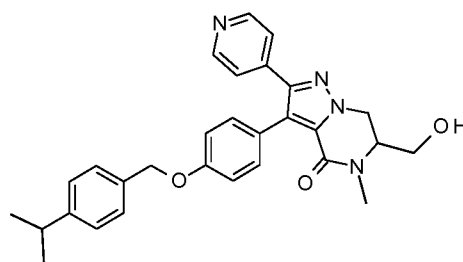
Example A194: Preparation of Co. 196

**a- Synthesis of Int. 356:**

Under N₂, Tert-butyldimethylsilyl chloride (0.12 g, 0.79 mmol) was added to a sol. of Co. 193 (0.25 g, 0.53 mmol) and imidazole (0.11 g, 1.6 mmol) in dry DCM (5.1 mL) at r.t. The mixture was stirred at r.t. for 4h. The mixture was quenched with water and
5 extracted with DCM. The organic layer was decanted, washed with water then brine, dried over MgSO₄, filtered and evaporated to dryness to give 320 mg of crude Int. **356**, white foam (quant.). The crude Int. 356 was used like this in the next step.

**b- Synthesis of Int. 357:**

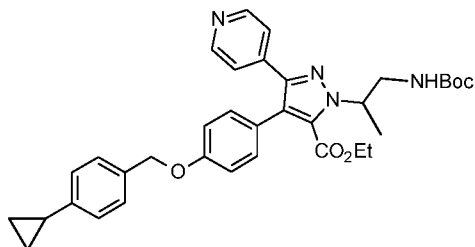
NaH 60% (33 mg, 0.82 mmol) was added slowly to a suspension of **356** (0.32 g, 0.55 mmol, 80%) in dry THF (3.1 mL) at r.t. under N₂. The mixture was stirred for 2h, then, MeI (51 μL, 0.82 mmol) was added and stirred for 3 days at r.t. Water was added and the mixture was extracted with DCM (3x), dried over MgSO₄ and evaporated until dryness and give 0.33 g of Int. **357**, pale yellow oil (quant.). The residue was used like
10 this in the next step.

**c- Synthesis of Co. 196:**

TBAF (2.2 mL, 2.2 mmol) was added dropwise to a sol. of **357** (1.1 g, 1.8 mmol) in THF (18 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/NH₄OH, from 98/2/0.1 to 97/3/0.1).
15
20 The pure fractions were collected and solvent evaporated until dryness to give 380 mg of colorless oil. This oil was purified again by prep. LC (Stationary phase: Sunfire Silica 5μm 150x30.0mm, Mobile phase Gradient: from NH₄OH/DCM/MeOH 0.2/98/2

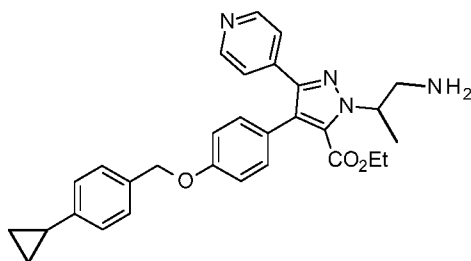
to $\text{NH}_4\text{OH}/\text{DCM}/\text{MeOH}$ 1/90/10). The pure fractions were collected and solvent evaporated until dryness to give 230 mg of white solid which was triturated in DIPE. The white solid was filtrated and dried to give 175 mg of **Co. 196** (20%).

Example A195: Preparation of Co. 197a and Co. 197



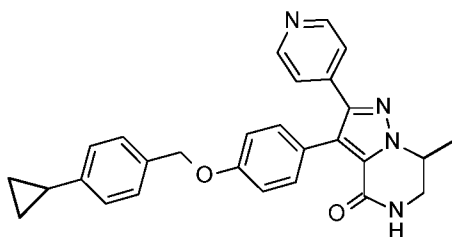
5 **a- Synthesis of Int. 358:**

To a mixture of **36** (350 mg, 0.796 mmol), 1-(Boc-amino)-2-propanol (279 mg, 1.59 mmol) and diphenylphosphinostyrene (531 mg, 1.59 mmol) in dry THF (6.50 mL) was added DBAD (367 mg, 1.59 mmol). The mixture was stirred for 2h at r.t., then, filtered through a glass frit and washed with EtOAc. The filtrate was evaporated *in vacuo* to give 1.00 g, yellow oil. The residue was purified by prep. LC (Irregular SiOH , 15-40 μm , 50g Merck, mobile phase gradient: from DCM 100% to DCM 99%, MeOH 1%).
10 The pure fractions were collected and solvent evaporated until dryness to give 290 mg of Int. **358**, colorless oil (61%).



15 **b- Synthesis of Int. 359:**

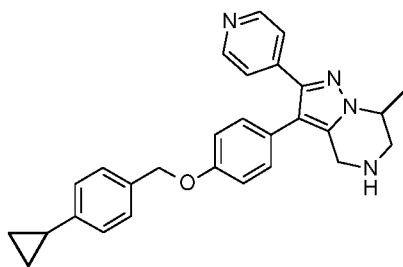
To a sol. of **358** (290 mg, 0.486 mmol) in 1,4-dioxane (4 mL) was added HCl 4N in dioxane (0.970 mL, 3.89 mmol). The sol. was stirred at r.t. for 18h. Then, Et_2O was added. The supernatant was removed and the remaining solid was dried *in vacuo*. The residue was triturated 3x in Et_2O , filtered and dried to give 248 mg of Int. **359**, pale yellow solid (96%).



20 **c- Synthesis of Co. 197a:**

To a sol. of **359** (248 mg, 0.465 mmol) in MeOH (2 mL) was added Cs_2CO_3 (758 mg, 2.33 mmol) and the mixture was stirred at r.t. for 6h. The solvent was removed *in*

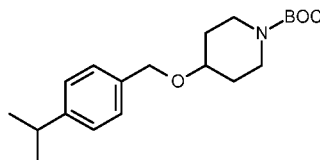
vacuo and water and DCM were added to the residue. The layers were separated and the aq. layer was extracted with DCM. The organic layers were combined, dried over MgSO_4 , filtered off and evaporated *in vacuo* to give 190 mg, white solid. The solid was triturated in Et_2O and the solid was filtered on a glass frit to give 140 mg of **Co. 197a**,
5 white solid (67%).



d- Synthesis of Co. 197:

LAH (55.6 mg, 1.47 mmol) was added to a sol. of **Co. 197a** (110 mg, 0.244 mmol) in dry THF (11 mL). The r.m. was stirred at r.t. for 18h and quenched with water (60 μL , very slow addition) and a 3N sol. of NaOH (60 μL). Et_2O was added and the crude
10 mixture was filtered on a glass frit. The precipitate was washed with Et_2O and the filtrate was evaporated *in vacuo* to give 127 mg, white residue. The residue was purified by prep. LC (Irregular SiOH , 15-40 μm , 10g Merck, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The desired fractions were collected and solvent was evaporated until dryness to give 117 mg. The residue was purified again by
15 prep. LC (Irregular SiOH , 15-40 μm , 10g Merck, mobile phase gradient: from DCM 100% to DCM 50%, acetone 50%). The pure fractions were collected and solvent was evaporated until dryness to give 115 mg, white solid. The white solid was purified by achiral SFC on (diethylaminopropyl 5 μm 150x21.2mm, Mobile phase: $i\text{PrNH}_2/\text{CO}_2/\text{MeOH}$ 0.3/70/30). The pure fractions were collected and solvent was
20 evaporated to give 65 mg, colorless oil, which crystallized to give **Co. 197** as a yellow solid (48%). m.p.: 153°C (DSC).

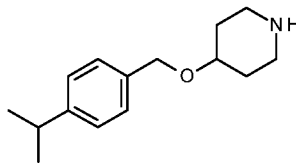
Example A196: Preparation of Co. 198



a- Synthesis of Int. 361:

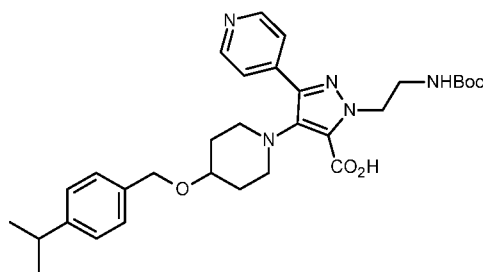
1-Boc-4-hydroxypiperidine (8g, 39.7mmol) was added to a suspension of NaH 60%
25 (2.8g, 119mmol) in THF (100mL). The mixture was stirred at r.t. for 10min, **8** (8.6mL, 51.7mmol) was added. The mixture was stirred at r.t. for 16h. Water and EtOAc were added, the mixture was extracted with EtOAc. The organic layer was separated, dried over MgSO_4 , filtered and evaporated. The residue was purified by prep. LC on

(Irregular SiOH 20-45 μ m 40g MATREX, Mobile phase: 70% Heptane, 30% EtOAc). The pure fractions were collected and solvent evaporated until dryness to give 12.4g of Int. **361** (94%).



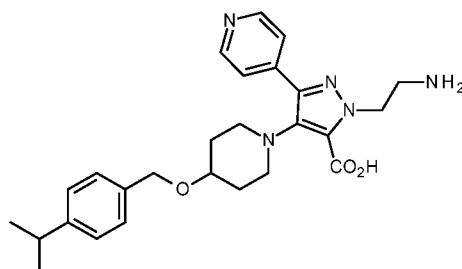
b- Synthesis of Int. 362:

- 5 A mixture of **361** (0.223g, 0.67mmol), HCl 3N (0.89mL, 2.68mmol) in ACN (4mL) was heated at 60°C for 1h. K₂CO₃ 10% and EtOAc were added and the mixture was extracted. The organic layer was separated, dried over MgSO₄, filtered and evaporated to give 150mg of Int. **362** (96%).



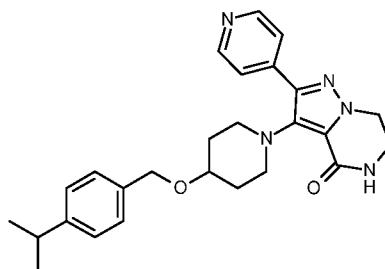
c- Synthesis of Int. 363:

- 10 In a sealed tube, **3** (1 g, 2.3 mmol), CuI (44 mg, 228 μ mol), Cs₂CO₃ (2.2 g, 6.8 mmol), **362** (610 mg, 2.6 mmol) in DMF (20 mL) was purged with N₂ (3x). Then, 2-acetylcyclohexanone (59.2 μ l, 455 μ mol) was added and the r.m. was stirred at 100°C overnight. Water and EtOAc were added and the mixture was extracted. The organic layer was separated, dried over MgSO₄, filtered and evaporated to give 540 mg of a 1st residue. The aqueous layer was acidified by HCl 3N and extracted with EtOAc. The organic layer was separated, dried over MgSO₄, filtered and evaporated to give 220 mg of a 2nd residue. The 1st residue was purified by prep. LC (Irregular SiOH 20-45 μ m 40g MATREX, mobile phase: 85/15/1, DCM/MeOH/NH₄OH). The pure fractions were collected and the solvent evaporated to give 22mg of Int. **363** (1.7%). The 2nd residue was purified by prep. LC (Irregular SiOH 20-45 μ m 40g MATREX, mobile phase: 85/15/1, DCM/MeOH/NH₄OH). The pure fractions were collected and the solvent evaporated until dryness to give 22 mg of Int. **363** (1.7%). The both fractions were put together for the next step (44mg of Int. **363**; 3.4%).



d- Synthesis of Int. 364:

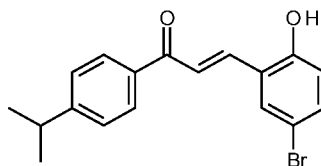
A mixture of **363** (27 mg, 47.9 μ mol), HCl 3N (0.16 mL, 0.48 mmol) in ACN (2 mL) was heated at 80°C for 4 h. K₂CO₃ 10% was added and the mixture was stirred at r.t. for 2h. The mixture was extracted with EtOAc, the organic layer was separated, dried over MgSO₄, filtered and evaporated until dryness to give 16 mg of crude Int. **364** which was used as such for the next step.



e- Synthesis of Co. 198:

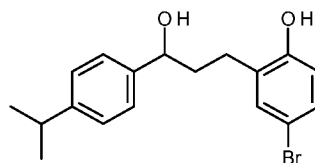
364 (16 mg, 0.03 mmol), EDCI (8 mg, 0.05 mmol), HOBT (7 mg, 0.05 mmol), Et₃N (14 μ l, 0.1mmol) in DCM (3 mL) was stirred at r.t. overnight. Water and DCM were added and the mixture was extracted. The organic layer was separated, dried over MgSO₄, filtered and evaporated. The residue was purified by prep. LC on (Irregular SiOH 20-45 μ m 4g GRACE, Mobile phase: 97/3, DCM/MeOH). The desired fractions were collected and solvent evaporated until dryness to give 8 mg which was purified by prep. LC on (Irregular SiOH 20-45 μ m 4g GRACE, Mobile phase: 97/3, DCM/MeOH). The pure fractions were collected and solvent evaporated until dryness to give 2 mg of **Co. 198** (13%).

Example A197: Preparation of Co. 199



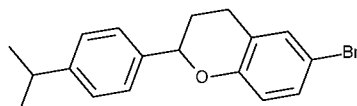
a- Synthesis of Int. 365:

KOH 60% in H₂O (30 mL, 321 mmol) was added to a stirred sol. of 4'-isopropylacetophenone (10.00 g, 61.6 mmol) and 5-bromosalicylaldehyde (13.6 g; 67.8 mmol) in EtOH (30 mL) at 0°C. The r.m. was then stirred at r.t. for 4h. The r.m. was diluted in DCM and quenched with HCl 1N. The precipitate was filtered and washed with water and DCM. The cake was dried *in vacuo* to give 19.8 g of Int. **365**, red solid (93%).



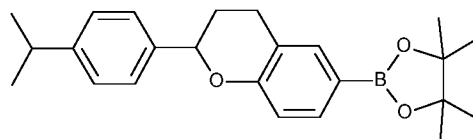
b- Synthesis of Int. 366:

- 365** (10 g, 29.0 mmol) was added to a stirred sol. of NaBH₄ (1.64 g, 43.4 mmol) and indium chloride (3.20 g, 14.5 mmol) in ACN (120 mL) at r.t. The r.m. was then stirred at r.t. for 4h. MeOH (30 mL) and NaBH₄ (2.2 g, 57.9 mmol) were added to the mixture. The sol. was then stirred 1h at r.t. The sol. was then evaporated *in vacuo*. The residue was dissolved in Et₂O and washed with water (2x). The organic phase was dried (MgSO₄), filtered and evaporated *in vacuo* to give 9.00 g of Int. **366** (89%).



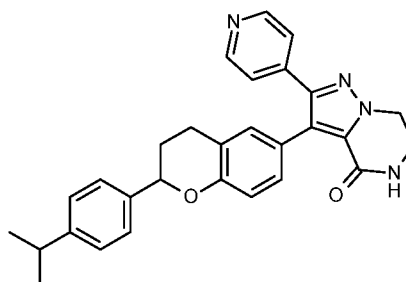
c- Synthesis of Int. 367:

- DBAD (5.93 g, 25.8 mmol) was added to a stirred sol. of **366** (6.00 g, 17.2 mmol) and PPh₃ supp. (8.05 g, 25.8 mmol) in DCM (70 mL) at rt. The r.m. was stirred at r.t. for 18h. Water was added to the mixture and the sol. was extracted with DCM. The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo*. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 80g, Merck, Mobile phase: Heptane/EtOAc, 95/5). The pure fractions were collected and solvent evaporated until dryness to give 3.14g of Int. **367**, white solid (55%).



d- Synthesis of Int. 368:

- A mixture of **367** (3.14 g, 9.48 mmol), BisPin (3.61 g, 14.2 mmol) and KOAc (2.79 g, 28.4 mmol) in DME (45mL) was carefully purged with N₂. PdCl₂(dppf) (776 mg, 0.948 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄, filtered and evaporated *in vacuo* to give brown solid. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 80g, Merck, Mobile phase: DCM 100%). The pure fractions were collected and solvent evaporated until dryness to give 4.15g of Int. **368**, yellow solid (quant.).

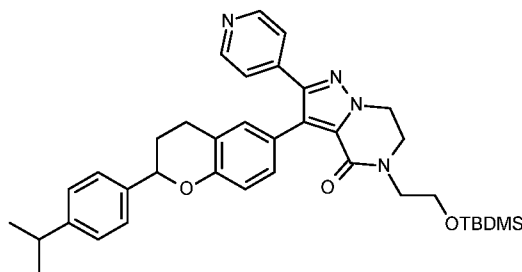


e- Synthesis of Co. 199:

- A sol. of **4** (500 mg, 1.71 mmol) and **368** (1.29 g, 3.41 mmol) in 1,4-dioxane (10 mL) and H₂O (5 mL) was treated with K₃PO₄ (1.09 g, 5.12 mmol) and purged with N₂. PdCl₂(dppf) (140 mg, 171 μmol) was added and the r.m. was carefully purged with N₂.

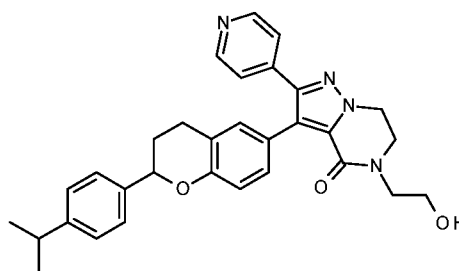
The mixture was heated at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min [fixed hold time]. The r.m. was diluted with EtOAc and washed with water (1x) and with brine (2x). The organic phase was dried (MgSO₄), filtered and evaporated *in vacuo*. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 50g, Merck, Mobile phase gradient: from DCM 100 % to DCM 95%, MeOH 5%. The pure fractions were collected and solvent evaporated until dryness to give 900 mg of a yellow solid which was recrystallized in EtOH. The precipitate which was formed after cooling was filtered, collected and dried *in vacuo* to give 500 mg of **Co. 199** as a white solid (63%).

10 Example A198: Preparation of Co. 200



a- Synthesis of Int. 369:

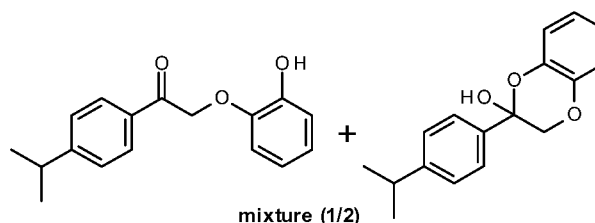
NaH 60% (28 mg, 0.710 mmol) was added slowly to a suspension of **Co. 199** (220 mg, 0.474 mmol) in DMF (3.5 mL) at r.t. under N₂. The mixture was stirred for 2h, then (2-bromoethoxy)-tert-butyldimethylsilane (121 µL, 0.568 mmol) was added and stirred for 18h. Water and K₂CO₃ were added and the mixture was extracted with EtOAc. The organic layer was dried (MgSO₄), filtered and evaporated *in vacuo* to give 300 mg of Int. **369** used as such for the next step.



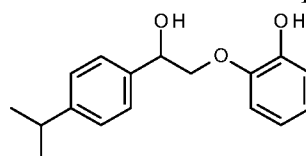
b- Synthesis of Co. 200:

TBAF (722 µL, 722 µmol) was added dropwise to a sol. of **369** (300 mg, 482 µmol, 80%) in THF (3 mL) at r.t. and the sol. was stirred for 18h. The mixture was evaporated *in vacuo* to give 250 mg of a brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 50 g, MERCK, Mobile phase gradient: from DCM 100 % to DCM 95%, MeOH 5%. The pure fractions were collected and solvent evaporated to give 156 mg of **Co. 200** as a white solid (64%).

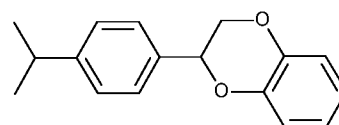
25 Example A199: Preparation of Co. 201

**a- Synthesis of Int. 370:**

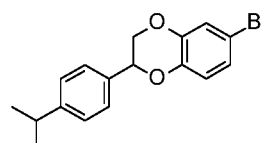
A mixture of 2-bromo-1-(4-isopropylphenyl)ethanone (4.0 g, 16.6 mmol), 1,2-benzenediol (1.83 g, 16.6 mmol) and Et₃N (2.8 mL, 19.9 mmol) in iPrOH (40 mL) was stirred at 70°C for 4h. The crude mixture was diluted in EtOAc washed with 1M HCl and water, dried over MgSO₄ and evaporated *in vacuo* to give brown oil. The residue was purified by prep. LC (irregular SiOH 15-40µm, 80g, GraceResolv™, dry loading, mobile phase: DCM 100%). The desired fractions were collected and solvent evaporated until dryness to give 1.58 g of Int. mixture **370**, yellow oil (35%; mixture 1/2). The mixture was used as such for the next reaction step.

**b- Synthesis of Int. 371:**

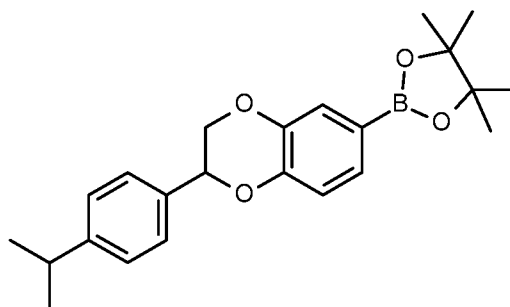
A sol. of **370** (1.58g, 5.85 mmol) in dry THF (10 mL) and MeOH (2 mL) was treated with NaBH₄ (884 mg, 23.4 mmol) and stirred at r.t. for 4 h. The r.m. was diluted in EtOAc and a 1M aq. sol. of HCl. The organic layer was separated, washed with water, dried over MgSO₄ and evaporated *in vacuo* to give 1.66 g of Int. **371**, yellow oil (Quant.).

**c- Synthesis of Int. 372:**

A sol. of **371** (1.66 g, 6.10 mmol) and PPh₃ (2.24 g, 8.53 mmol) in DCM (30 mL) was treated with DBAD (1.97 g, 8.53 mmol) and stirred at r.t. for 17h. The r.m. was poured in a 1M aq. sol. of HCl. The organic layer was separated, dried over MgSO₄ and evaporated *in vacuo* to give 5.2g of a yellow oil. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 120g, Grace, mobile phase: heptane 80%, EtOAc 20%). The pure fractions were collected and solvent evaporated until dryness to give 1.59 g of Int. **372** as a yellow oil (Quant.).

**d- Synthesis of Int. 373:**

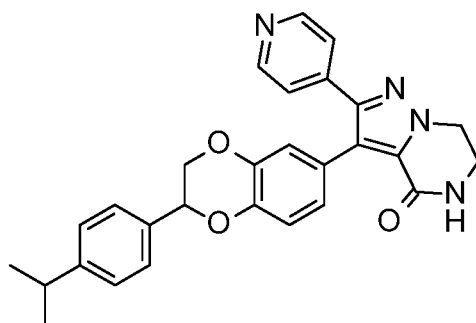
A sol. of **372** (1.42 g, 5.58 mmol) in HOAc (30 mL) was treated with NBS (0.994 g, 5.58 mmol) and stirred at 60°C for 17 h. The r.m. was diluted in DCM, washed with a 10% sol. of K₂CO₃, dried over MgSO₄ and evaporated *in vacuo* to give 1.77 g of Int. **373** (95%; impure), used as such in the next step without any purification.



5 **e- Synthesis of Int. 374:**

A stirred sol. of **373** (1.77 g, 5.31 mmol), BisPin (2.02 g, 7.97 mmol) and KOAc (1.56 g, 15.) in DME (30 mL) was carefully purged with N₂, and PdCl₂(dppf) (348 mg, 425 μmol) was added. The r.m. was purged again with N₂ and stirred for 18h at 105°C. The r.m. was poured in EtOAc and water. The organic layer was separated, washed with
10 brine and evaporated *in vacuo* to give a black residue. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 80g, Grace, dry loading, mobile phase gradient: from heptane 90%, EtOAc 10% to heptane 80%, EtOAc 20%). The pure fractions were collected and solvent evaporated until dryness to give 1.89 g of Int. **374** (94%; impure), used as such in the next step without any purification.

15 **f- Synthesis of Co. 201**

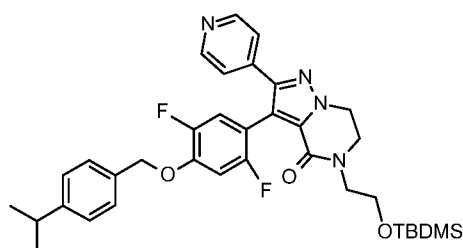


A sol. of **4** (899 mg, 3.07 mmol) and **374** (1.75g, 4.60 mmol) in 1,4-dioxane (12 mL) and H₂O (6 mL) was treated with K₃PO₄ (1.30 g, 6.14 mmol) and purged with N₂. PdCl₂(dppf) (201 mg, 245 μmol) was added and the r.m. was carefully purged with N₂.
20 The mixture was heated at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 25 min [fixed hold time]. The r.m. was poured in water and in DCM/MeOH (98/2). The organic layer was separated, dried over MgSO₄ and evaporated *in vacuo* to give black oil. The oil was

purified by prep. LC (irregular SiOH 15-40 μ m, 220g, Grace, mobile phase gradient: from DCM 100% to DCM 96%, MeOH 4%). The desired fractions were collected and solvent evaporated to give 1.47g of yellow foam (mixture 2 isomers). The residue was purified by achiral SFC (Stationary phase: Chiralpak IA 5 μ m 250*20mm, Mobile phase: 55% CO₂, 45% iPrOH). The pure fractions were combined and evaporated *in vacuo* to give 410 mg of product which was recrystallized from EtOH. The white solid was collected by filtration, washed with Et₂O and dried *in vacuo* to afford 300 mg of **Co. 201**, white solid (21%). m.p.: 290°C (DSC).

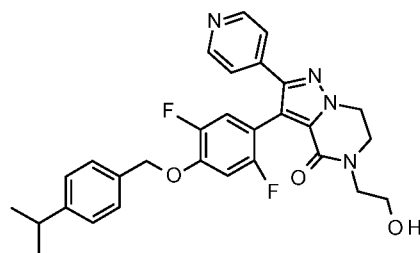
Example A200: Preparation of Co. 203

10 ▪ **First Method:**



a- **Synthesis of Int. 375:**

Under N₂, a sol. of Co. 14 (211 mg, 0.445 mmol) in dry DMSO (4 mL) was treated with NaH 60% (27 mg, 0.667 mmol). The r.m. was stirred at r.t. for 2h. Then, (2-bromoethoxy)-tert-butyldimethylsilane (0.114 mL, 0.534 mmol) was added and the reaction was stirred at r.t. for 17h. TBAF (0.222 mL, 0.222 mmol) was then added and the r.m. was stirred for 2h at r.t. The mixture was poured in EtOAc (150 mL) and washed with brine (5x 40 mL). The organic layer was dried over MgSO₄ and evaporated *in vacuo* to afford 220 mg of Int. **375** as a brown residue which was used as such for the next step.

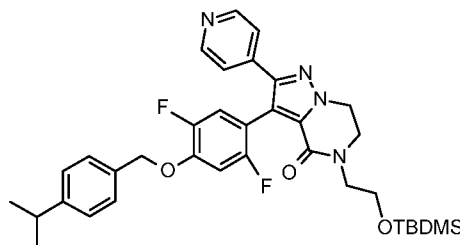


20 b- **Synthesis of Co. 203:**

A sol. of mixture **375** (220 mg, 0.348 mmol) in THF (8 mL) was treated with TBAF (0.174 mL, 0.174 mmol) and stirred at r.t. for 72 h. The crude mixture was then diluted in DCM, washed with water and brine. The organic layer was dried over MgSO₄ and evaporated *in vacuo* to afford a brown residue. The residue was purified by prep. LC (irregular SiOH 15-40 μ m, 30g, GraceResolv™, Mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The pure fractions were collected and solvent

evaporated until dryness to give 115 mg of **Co. 203** as an off-white solid (64%). m.p.: 193°C (DSC).

▪ **Second Method:**



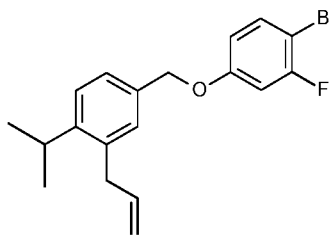
a- Synthesis of Int. 375:

- 5 In a microwave vial, a mixture of **28** (3.4 g, 7.5 mmol), **66** (3.5 g, 9.0 mmol), K₃PO₄ (6.4 g, 30 mmol) in 1,4-dioxane (33 mL) and H₂O (11 mL) was carefully purged with N₂. PdCl₂(dppf) (620 mg, 0.75 mmol) was added and the r.m. was purged again with N₂. 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 MgSO₄,
10 filtered on a pad of Celite® and evaporated *in vacuo* to give brown oil. The oil was purified by prep. LC (irregular SiOH 30 µm, 120g GraceResolv™, mobile phase: DCM/MeOH/NH₄OH 99/1/0.1). The pure fractions were collected and solvent evaporated until dryness to give 3.0 g of Int. **375**, pale yellow oil (63%).

b- Synthesis of Co. 203 :

- 15 TBAF (5.7 mL, 5.7 mmol) was added dropwise to a sol. of **375** (3.0 g, 4.7 mmol) in THF (46mL) at r.t. The mixture was stirred overnight at r.t. The mixture was concentrated (5.1 g) and the residue was purified by prep. LC (Regular SiOH, 30 µm, 80g GraceResolv™, mobile phase: DCM/MeOH/NH₄OH 98/2/0.1). The pure fractions were collected and solvent evaporated to give colorless oil wich was trituated in Et₂O.
20 The white solide formed was filtrated, washed and dried to give 1.26 g of **Co. 203** as a white solid (51% first batch). m.p.: 195°C (dsc). The filtrate was concentrated and the residue was trituated in Et₂O, filtrated and dried to give 0.27g of **Co. 203** as a white solid (11%, second batch). m.p.: 197°C (dsc).

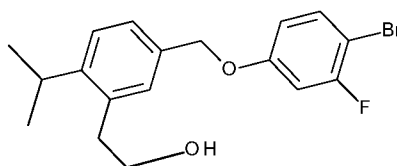
Example A201: Preparation of Co. 204



25 **a- Synthesis of Int. 376:**

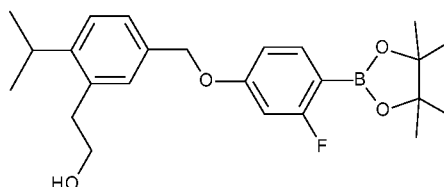
To a sol. of **53** (10.0 g, 52.6 mmol) and 4-bromo-3-fluorophenol (10.0 g, 52.6 mmol) in dry DCM (265 mL) were added PPh₃ (15.2 g, 57.8 mmol) and DBAD (13.3 g, 57.8 g)

at r.t. The r.m. was stirred at r.t. for 17h. Then, EtOAc and brine were added, and the organic layer was dried over MgSO₄, filtered and evaporated *in vacuo* to afford 50.9g of a residue which was filtered over silica washing with a sol. EtOAc/Heptane (30:70) to give 36.9 g, sticky brown solid. This solid was purified by prep. LC (Irregular SiOH 50 μm, 750g Grace, mobile phase gradient: from Heptane 90%, DCM 10% to Heptane 60%, DCM 40%). The desired fractions were collected and solvent evaporated *in vacuo* to give 13.8 g of Int. **376**, pale oil as a mixture which was used as such for the next step.



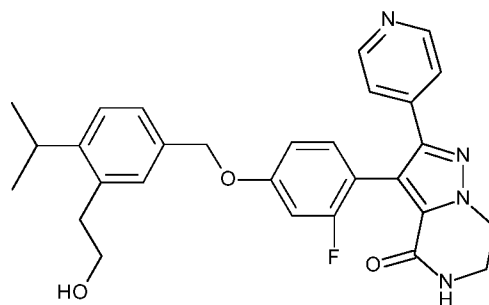
b- Synthesis of Int. 377:

A sol. of mixture **376** (3.00 g, 8.26 mmol) in DCM (60 mL) was cooled to -78 °C. O₃ was bubbled through the sol. (10 min). The excess of O₃ was removed (N₂ purge) and NaBH₄ (1.25 g, 33.0 mmol) and EtOH (20mL) were added. The sol. was warmed to r.t. and stirred for 4h. Then water and DCM were added, and the organic layer was washed (brine), dried (MgSO₄), filtered and evaporated *in vacuo*. The residue (3.2g) was purified by prep. LC (Irregular SiOH 50μm, 120g Grace, mobile phase gradient: from Heptane 100% to Heptane 60%, EtOAc 40%). The desired fractions were collected and evaporated *in vacuo* to give 1.07 g of Int. **377**, colorless oil (35%).



c- Synthesis of Int. 378:

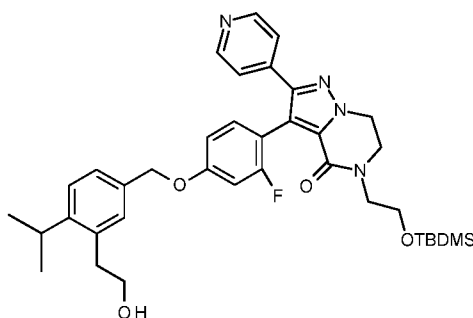
A mixture of **377** (2.85 g, 7.76 mmol), BisPin (3.94 g, 15.5 mmol) and KOAc (2.29 g, 23.3 mmol) in DME (80 mL) was carefully purged with N₂. PdCl₂(dppf) (0.635 g, 0.776 mmol) was added and the r.m. was purged with N₂. The r.m. was stirred at 100°C for 18h. The r.m. was diluted with EtOAc and water. The organic layer was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give 7.2 g of a black solid. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 220g, Grace, Mobile phase gradient: EtOAc 10%, Heptane 90% to EtOAc 40%, Heptane 60%). The pure fractions were collected and solvent evaporated to give 1.93 g of Int. **378** as a sticky oil (60%).



d- Synthesis of Co. 204:

A mixture of **4** (280 mg, 0.955 mmol), **378** (0.652 g, 1.43 mmol) and K₃PO₄ (0.507 g, 2.39 mmol) in 1,4-dioxane (3 mL) and H₂O (1.5 mL) was purged with N₂. PdCl₂(dppf) (78 mg, 95.5 μmol) was then added. The mixture was purged again with N₂ 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 (95/5) and water were added. The organic layer was separated, washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to yield 620 mg of a brown solid. The residue was purified by prep. LC (Irregular SiOH 50 μm, 40g Grace, mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The desired fractions were collected and evaporated *in vacuo* to give 289 mg of a pale beige solid. The residue was purified by achiral SFC (Stationary phase: 2-ethylpyridine 6μm 150x30mm, Mobile phase: 75% CO₂, 25% MeOH). The pure fractions were collected and solvent evaporated until dryness to yield 220 mg of **Co. 204** as a white solid (46%). m.p.: 223 °C (DSC).

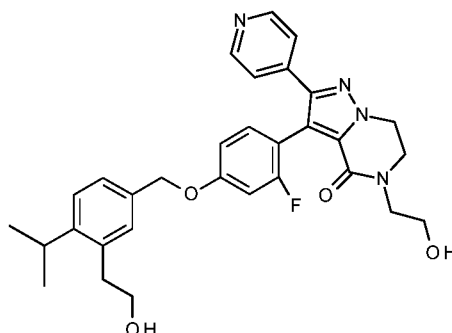
Example A202: Preparation of Co. 205



a- Synthesis of Int. 379:

A mixture of **28** (0.680 g, 1.506 mmol), **378** (1.03 g, 2.26 mmol) and K₃PO₄ (0.959 g, 4.52 mmol) in 1,4-dioxane (9 mL) and H₂O (3.5 mL) was purged with N₂. PdCl₂(dppf) (0.123 g, 0.151 mmol) was then added. The mixture was purged again with N₂ 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 (95/5) and water were added. The organic layer was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to yield 2.20 g, brown solid which was purified by prep. LC (Irregular SiOH50 μm, 80g Grace, mobile phase gradient:

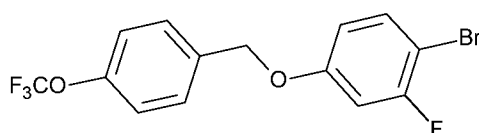
from DCM 100% to DCM 94%, MeOH 6%). The desired fractions were collected and evaporated *in vacuo* to give 800 mg of Int. **379** used as such for the next step.



b- Synthesis of Co. 205:

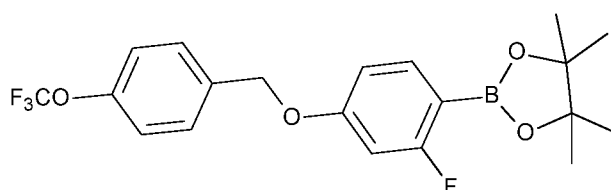
TBAF (0.858 mL, 0.858 mmol) was added to a stirred sol. of **379** (800 mg, 0.850 mmol) in THF (11 mL) at 0°C, and the r.m. was stirred at r.t. for 2h. The crude mixture was diluted with water and a sol. of DCM/MeOH (96/4). The organic layer was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to afford 690 mg, solid. The solid was purified by prep. LC (Irregular SiOH 50 μm, 30g Grace, mobile phase gradient: from DCM 100% to DCM 91%, MeOH 9%). The desired fractions were collected and evaporated *in vacuo* to give 412 mg, white solid. The solid was triturated with DIPE, filtered off, washed with Et₂O and dried *in vacuo* to yield 385mg, white solid which was solubilized in MeOH (1mL). The solvent was allowed to evaporate slowly to give 374mg of **Co. 205**, crystalline white solid (81%). m.p.: 151 °C (DSC).

Example A203: Preparation of Co. 206



a- Synthesis of Int. 380:

To a suspension of 4-(trifluoromethoxy)-benzyl alcohol (1mL, 10.4mmol), 4-bromo-3-fluorophenol (1.58g, 8.28mmol), DBAD (1.9g, 8.28mmol) in dry DCM (20mL) was added PPh₃ supp. (2.59g, 8.28mmol) 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. The residue (4.24g) was purified by prep. LC on (Irregular SiOH 15-40μm 80g Grace, Mobile phase: Heptane/EtOAc 98/2). The pure fractions were collected and evaporated until dryness to give 1.76g of Int. **380** (70%).



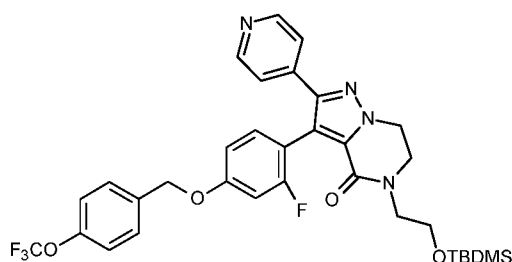
b- Synthesis of Int. 381:

In a sealed tube, a mixture of **380** (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 N₂.

PdCl₂(dppf) (0.122 g, 0.15 mmol) was added and the r.m. was purged again with N₂.

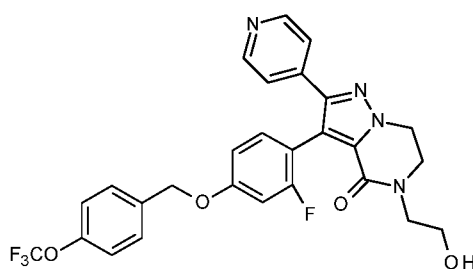
The mixture was heated at 100°C overnight. EtOAc and water were added and the

- 5 mixture was extracted with EtOAc. The organic layer was separated, dried, filtered and evaporated until dryness to give 3.3g. 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 495 mg of Int. **381** (24%).



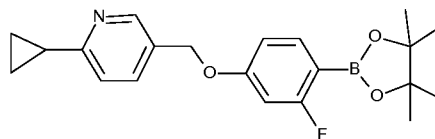
c- Synthesis of Int. 382:

- 10 In a microwave vial, a mixture of **28** (0.7 g, 1.55 mmol), **381** (0.799 g, 1.94 mmol), K₃PO₄ (1.32 g, 6.2 mmol) in 1,4-dioxane (6.8 mL) and H₂O (2.4 mL) was carefully purged with N₂. PdCl₂(dppf) (127 mg, 0.16 mmol) was added and the r.m. was purged again with N₂. 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
- 15 over MgSO₄, filtered and evaporated *in vacuo* to give 1.65g. The residue was purified by prep. LC (irregular SiOH 30 µm, 40g Interchim, mobile phase: from DCM 100% to DCM/MeOH/NH₄OH 97/3/0.1). The pure fractions were collected and evaporated until dryness to give 717 mg of Int. **382** (70%).

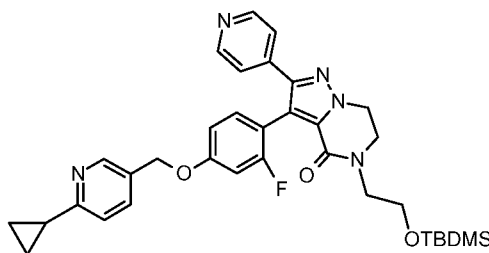


d- Synthesis of Co. 206:

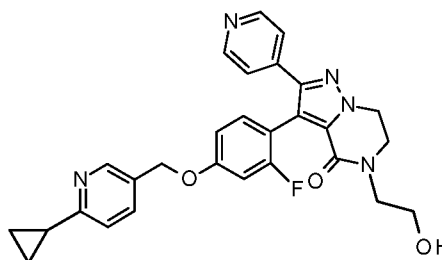
- 20 TABF (1.3 mL, 1.3 mmol) was added dropwise to a sol. of **382** (715 mg, 1.09 mmol) in THF (11 mL) at r.t.. The mixture was stirred for 3h at r.t. EtOAc and water were added. The organic layer was separated, dried, filtered and evaporated until dryness to give 646 mg. The residue was purified by prep. LC (Regular SiOH, 30 µm, 24g GraceResolv™, mobile phase gradient: from DCM 100% to DCM/MeOH/NH₄OH
- 25 95/5/0.1). The pure fractions were collected and evaporated until dryness to give 421 mg which was crystallized from DIPE, filtered and dried to give 390 mg of **Co. 206** (66%). m.p.: 140°C (dsc).

Example A204: Preparation of Co. 207**a- Synthesis of Int. 383:**

DBAD (3.14 g, 13.7 mmol) was added to a mixture of 3-fluoro-4-hydroxybenzeneboronic acid pinacol ester (2.50 g, 10.5 mmol), 6-cyclopropyl-3-pyridinemethanol (2.04 g, 13.6 mmol) and PPh₃ (3.58 g, 13.7 mmol) in dry THF (75 mL) and the r.m. was stirred under N₂ for 20h at r.t. The crude mixture was diluted with EtOAc and water, and the organic layer was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give 12.8 g. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 330g Grace, mobile phase gradient: from Heptane 100% to EtOAc 40%, Heptane 60%). The pure fractions were collected and solvent was evaporated until dryness to give 3.1g of Int. **383**, colorless oil (76%).

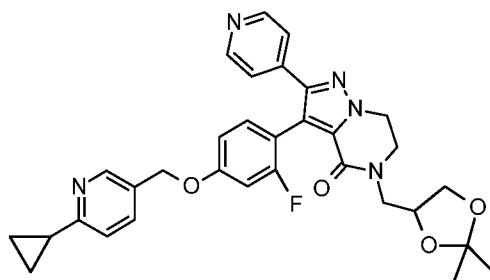
**b- Synthesis of Int. 384:**

PdCl₂(dppf) (0.109 g, 0.133 mmol) was added to a stirred sol. of **28** (0.600 g, 1.33 mmol), **383** (1.03 g, 2.66 mmol) and K₃PO₄ (0.846 g, 3.99 mmol) in 1,4-dioxane (7.5 mL) and H₂O (2.5 mL) at r.t. under N₂. 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 (MgSO₄), filtered and evaporated *in vacuo* to yield 1.9 g of a dark oil. The residue was purified by prep. LC (Irregular SiOH 50 μm, 80g Grace, mobile phase gradient: from DCM 100% to MeOH/DCM 8/92). The desired fractions were collected and evaporated *in vacuo* to give 796 mg of Int. **384**, oil used as such for the next step.

**c- Synthesis of Co. 207:**

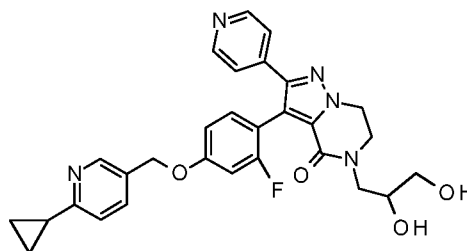
To a stirred sol. of **384** (796 mg, 0.973 mmol) in C (10 mL) at 0°C was added TBAF (0.982 mL, 0.982 mmol), and the r.m. was stirred at 0 °C for 3h. The crude mixture was diluted with water and a sol. of DCM/MeOH (95/5). The organic layer was washed with brine, separated, dried over MgSO₄, filtered and evaporated *in vacuo* to afford 490 mg, oil. This oil was purified by prep. LC (Irregular SiOH 50 µm, 40g Grace, mobile phase gradient: from DCM 100% to DCM 92%, MeOH 8%). The desired fractions were collected and evaporated *in vacuo* to give 410 mg of sticky pale rose solid which was crystallized from MeOH and triturated in a mixture of Et₂O/MeOH (3/1). The solvents were evaporated *in vacuo* and the affording solid was dried under high vacuum at 55°C to yield 360 mg of white solid which was recrystallized in EtOH, filtered on a glass frit and dried *in vacuo* to give 234 mg of white solid which was triturated with Et₂O, and the solvent was evaporated *in vacuo* to yield 156 mg of a white solid which was dried *in vacuo* at 50 °C for 20h to yield 145 mg of **Co. 207** as a white solid (30%).

Example A205: Preparation of Co. 208a and Co. 208



15 **a- Synthesis of Co. 208a**

277 (800 mg, 1.96 mmol), **383** (1.04 g, 2.95 mmol), K₃PO₄ (1.25 g, 5.89 mmol) in 1,4-dioxane (8 mL) and H₂O (4 mL), were purged with N₂ for 10min. Then, PdCl₂(dppf) (161 mg, 0.196 mmol) was added and purged with N₂ for 10min. 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 mixture was diluted in water and extrated with EtOAc. The organic layer was dried over MgSO₄, filtered and evaporated to give 1.20 g of **Co. 208a**, brown oil (quant.). The product was used for the next step without further purification.

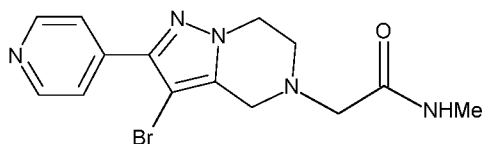


b- Synthesis of Co. 208:

25 **Co. 208a** (1.08 g, 1.90 mmol), HCl 3N (3.16mL, 9.48 mmol) in 1,4-dioxane (40 mL) were heated to 80°C for 30 min. The mixture was quenched with a 10% sol. of K₂CO₃

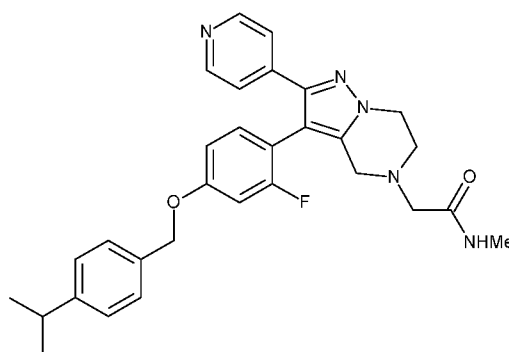
and extracted with EtOAc. The organic layer was separated, dried over MgSO₄, filtered and evaporated *in vacuo* to give 880 mg of brown oil. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 80g, GraceResolv™, dry loading, mobile phase gradient: from DCM 100% to DCM 92%, MeOH 8%). The desired fractions were collected and solvent evaporated to give 570 mg, brown solid (57%). The solid was recrystallized in EtOH to give 450 mg, grey solid which was purified by prep. LC (irregular SiOH 15-40 μm, 80g, GraceResolv™, dry loading, mobile phase gradient: from DCM 100% to DCM 92%, MeOH 8%). The pure fractions were collected and solvent evaporated to give 410mg, white solid. The solid was recrystallized in EtOH three times to give 228 mg of **Co. 208** as a white solid (23%). m.p.: 116°C and 126°C (DSC).

Example A206: Preparation of Co. 209



a- Synthesis of Int. 386:

A mixture of **337** (600 mg, 2.15 mmol), 2-bromo-N-methyl-acetamide (392 mg, 2.58 mmol) and K₂CO₃ (743 mg, 5.37 mmol) in DMF (8 mL) was stirred for 2h at 55°C. The r.m. was then poured in DCM and water. The organic layer was separated, dried over MgSO₄ and evaporated *in vacuo* to afford brown oil. The residue was purified by prep. LC (irregular SiOH 15-40μm, 40g Gotech, mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The pure fractions were collected and solvent evaporated until dryness to give 314 mg of Int. **386**, yellow solid (42%).

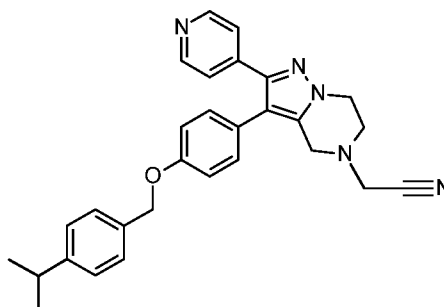


b- Synthesis of Co. 209:

A mixture of **386** (314 mg, 0.897 mmol), **42** (664 mg, 1.79 mmol) and K₃PO₄ (571 mg, 2.69 mmol) in 1,4-dioxane (8 mL) and H₂O (4 mL) was purged with N₂. PdCl₂(dppf) (73 mg, 93.8 μmol) was then added. The mixture was purged again with N₂ 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 35 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

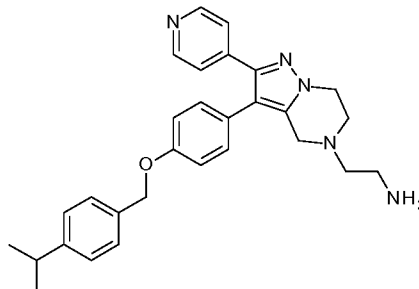
with DCM. The organic layers were combined, dried over MgSO_4 and evaporated *in vacuo* to afford a brown residue. The residue was purified by prep. LC (irregular SiOH 15-40 μm , 80g, GraceResolv™, dry loading, mobile phase gradient: from DCM 100% to DCM 92%, MeOH 8%). The desired fractions were collected and solvent evaporated to give 240 mg of a grey solid. The solid was combined with another batch (initial reactant **386**, 280 mg, in the same conditions of reaction) and purified by prep. LC (irregular SiOH 15-40 μm , 40g, Merck, mobile phase gradient: from DCM 100% to DCM 94%, MeOH 6%). The pure fractions were collected and solvent evaporated to give 280 mg of an off-white solid. The solid was dissolved in a small amount of MeOH and allowed to evaporate slowly overnight. The residue was scratched in Et_2O to obtain a white solid in suspension. The suspension was filtered off and the white precipitate was washed with Et_2O and dried *in vacuo* to give 238 mg of **Co. 209** as a white solid (global yield: 27%). m.p.: 175°C, 159°C (polymorph, DSC).

Example A207: Preparation of Co. 210a and Co. 210



a- Synthesis of Co. 210a:

Bromoacetonitrile (43 μL , 0.601 mmol) was added to a stirred suspension of **Co. 173** (250 mg, 0.501 mmol) and K_2CO_3 (104 mg, 0.751 mmol) in DMF (3 mL) at r.t. The r.m. was stirred at r.t. for 16h, and then it was diluted with EtOAc and water. The organic layer was washed with brine, separated, dried over MgSO_4 , filtered and evaporated *in vacuo* to afford 289mg of **Co. 210a**, pale yellow solid (quant., purity 85%). The product was used as such for the next step.



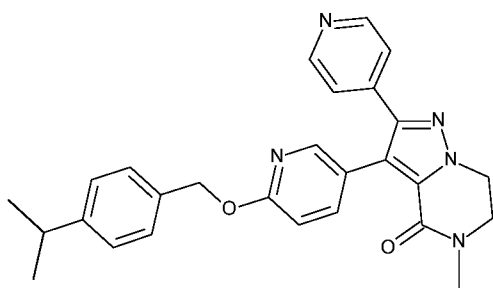
b- Synthesis of Co. 210 :

0.79 eq fumarate

LAH (59 mg, 1.55 mmol) was added to a stirred sol. of **Co. 210a** (240 mg, 0.518 mmol) in THF (4.5 mL) under N_2 at 0 °C. The r.m. was stirred at r.t. for 2h. Then, the crude mixture was quenched with addition of water (60 μL , very slow addition), a 3N

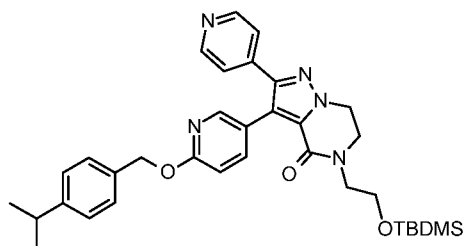
sol. of NaOH (60 μ L) and water (190 μ L). The crude mixture was filtered on a glass frit, the cake was washed with EtOAc and the filtrate was evaporated *in vacuo* to afford 194 mg of oil. The residue was purified by prep. LC (irregular SiOH 15-40 μ m, 12g Grace, Mobile phase gradient: from DCM 100% to DCM 90%, MeOH 9%, NH₄OH 1%). The fractions were combined and the solvent was removed *in vacuo* to give 108 mg, pale yellow oil. Then, MeOH (2mL) and fumaric acid (25 mg, 0.215 mmol) were added, and the solvent was removed *in vacuo* to afford a sticky solid. The solid was triturated with Et₂O, and the solvent removed *in vacuo* to yield 130 mg of **Co. 210**, pale brown solid (45%; fumarate salt (0.79 eq fumarate)). m.p.: 197 °C (DSC).

10 Example A208: Preparation of Co. 211



A mixture of **98** (152 mg, 0.495 mmol), **129** (350 mg, 0.990 mmol) and K₃PO₄ (420 mg, 1.98 mmol) in 1,4-dioxane (3 mL) and H₂O (1 mL) was carefully purged with N₂. PCy₃ (28 mg, 99.0 μ mol) and Pd(OAc)₂ (11 mg, 49.5 μ mol) were added and the r.m. was purged again with N₂. The r.m. was stirred for 67h at 80°C. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried (MgSO₄), filtered and evaporated *in vacuo* to give a solid which was purified by prep. LC (irregular SiOH 15-40 μ m, 24g Grace, mobile phase gradient: from DCM/MeOH from 100/0 to 91/9). The pure fractions were collected and evaporated to give 261 mg of a solid. The solid was purified by trituration with pentane to afford 206 mg of a solid. This solid was purified by achiral SFC (2-ethylpyridine 6 μ m 150x21.2mm. Mobile phase: 80% CO₂, 20% MeOH). The desired fractions were isolated and evaporated *in vacuo* to yield 161 mg of **Co. 211** as a white solid (72%). m.p.: 57 °C (DSC).

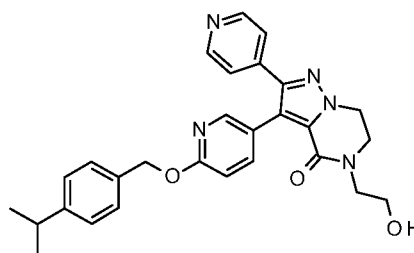
25 Example A209: Preparation of Co. 212



a- Synthesis of Int. 388:

NaH 60% (48 mg, 1.2 mmol) was added slowly to a suspension of **Co. 71** (0.35 g, 0.80 mmol) in dry DMF (4.7 mL) at r.t. under N₂. The mixture was stirred for 2h then (2-bromoethoxy)-tert-butyldimethylsilane (0.20 mL, 0.96 mmol) was added and stirred overnight. Water was added and the mixture was concentrated under reduced pressure.

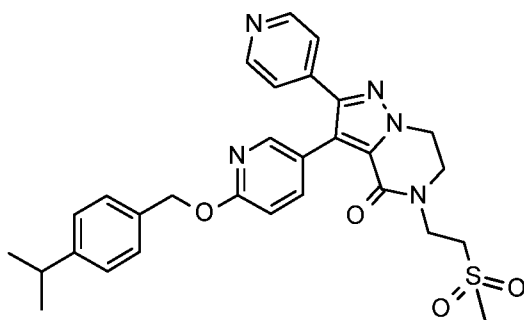
- 5 The residue was taken in EtOAc and washed 5x with brine. The organic layer was dried on MgSO₄, filtrated and concentrated to give 0.45g of Int. **388**, yellow oil. This crude mixture was used like this in the next step.



b- Synthesis of Co. 212:

- TBAF (0.9 mL, 0.9 mmol) was added dropwise to a sol. of **388** (0.45 g, 0.75 mmol) in THF (7.4 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 GraceResolv™, mobile phase: DCM/MeOH/NH₄OH 96/4/0.1). The pure fractions were collected and solvent evaporated until dryness to give 350 mg of colorless oil which was triturated in Et₂O. The white solid formed was filtered, washed and dried to give 175 mg of **Co. 212** as a white solid (48%). m.p.: polymorph 138°C, 161°C (polymorph, dsc).

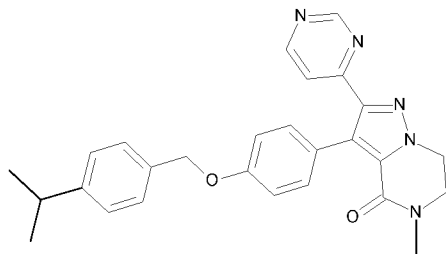
Example A210: Preparation of Co. 213



- NaH 60% (48 mg, 1.2 mmol) was added slowly to a suspension of **Co. 71** (0.35 g, 0.80 mmol) in dry DMF (4.7 mL) at r.t. under N₂. The mixture was stirred for 2h then 2-bromoethyl-methylsulfone (164 mg, 0.88 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 MgSO₄, filtrated and concentrated to give 0.30g. The white solid obtained was

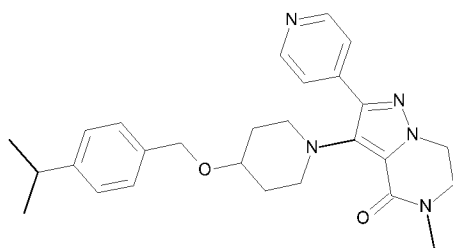
trituated in Et₂O, filtrated and dried to give 296 mg of **Co. 213** as a white powder (68%). m.p.: 200°C (dsc).

Example A211: Preparation of Co. 214



- 5 NaH 60% (57 mg, 1.4 mmol) was added slowly to a suspension of **Co. 158** (0.42 g, 0.96 mmol) in DMSO (5.2 mL) at r.t. under N₂. The mixture was stirred for 2h, then, MeI (65 µL, 1 mmol) was added and stirred overnight. Water was added and the insoluble was filtered, dissolved in DCM and MeOH, dried on MgSO₄ and evaporated until dryness. The residue was purified by prep. LC (Regular SiOH, 30 µm, 25g
- 10 Interchim, mobile phase gradient: DCM/MeOH/NH₄OH from 98/2/0.1 to 96/4/0.1). The pure fractions were collected and solvent evaporated to give 372 mg of colorless oil which was crystallized from Et₂O, filtered and dried to give 283 mg of **Co. 214** as a white solid (65%). m.p.: 160°C (dsc).

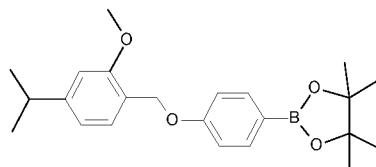
Example A212: Preparation of Co. 215



- 15 (SP-4-4)-[2-[2-(amino-κN)ethyl]phenyl-κC]chloro[dicyclohexyl[3,6-dimethoxy-2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine-κP]-palladium (BrettPhos Palladacycle) (260 mg, 0.33 mmol) was added to a degassed suspension of **98** (500 mg, 1.6 mmol), 4-[(4-isopropylphenyl)methoxy]piperidine (**362**) (417 mg, 1.8 mmol),
- 20 NaOtBu (469 mg, 4.9 mmol) in toluene (10 mL). The r.m. was heated at 90°C for a weekend. Water and EtOAc were added, the mixture was filtered over a Celite® pad. The filtrate was extracted, the organic layer was separated, dried over MgSO₄, filtered and evaporated. The residue was purified by prep. LC (Irregular SiOH 20-45µm 40g MATREX, mobile phase: 70/29/1 toluene/iPrOH/NH₄OH). The fractions were
- 25 collected and the solvent evaporated until dryness. The residue was again purified by prep. LC (irregular 15-40µm 30g Merck, Mobile phase: 99% DCM, 1% MeOH). The

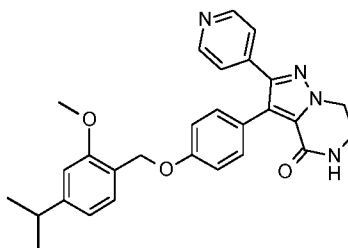
pure fractions were collected and evaporated. The residue was crystallized from Et₂O, the solid was filtered off and dried to give 40 mg of **Co. 215** (5.3%). m.p.: 140°C (dsc).

Example A213: Preparation of Co. 216



a- Synthesis of Int. 391:

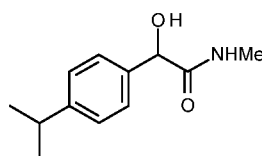
- 5 To a sol. of 2-methoxy-4-isopropyl-benzenemethanol (3.14 g, 17.4 mmol), **7** (3.8 g, 17.4 mmol), PPh₃ (5 g, 19.2 mmol) in dry DCM (120 mL) was added DBAD (4.4 g, 19.2 mmol) and the r.m. was stirred at r.t. for 15h. The mixture was poured into water. The organic layer was extracted, dried over MgSO₄, filtered and evaporated until dryness. The residue was taken up in heptane, stirred for 1.5h and filtered. The filtrate
- 10 was purified by prep. LC (120g of irregular SiOH 35-40μm GraceResolv™, mobile phase gradient: from 100% heptane to 80% heptane 20% EtOAc). The pure fractions were collected and evaporated until dryness to give 2.26g of Int. **391** (34%).



b- Synthesis of Co. 216:

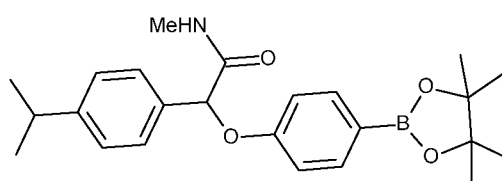
- A mixture of **4** (0.5 g, 1.7 mmol), **391** (0.72 g, 1.9 mmol), K₃PO₄ (1.45 g, 6.8 mmol) in
- 15 1,4-dioxane (10 mL) and H₂O (2.7 mL) was purged with N₂ for 15min. Then, PdCl₂(dppf) (0.14 g, 0.17 mmol) was added and purged again for 10min. The mixture was heated to 80°C for 15h and cooled to r.t. The mixture was poured into water, and K₂CO₃ and EtOAc were added. The insoluble was filtered and the organic layer was
- 20 extrated, dried over MgSO₄, filtered and evaporated to give 1g. The residue was purified by prep. LC (40g of irregular SiOH 35-40μm GraceResolv™, mobile phase gradient from 100% DCM to 95% DCM 5% CH₃OH 0.1% NH₄OH). The pure fractions were collected and evaporated until dryness to give 510 mg which was crystallized from MeOH, filtered and dried to give 439 mg of **Co. 216** (55%). m.p.: 200°C (dsc).

Example A214: Preparation of Co. 217



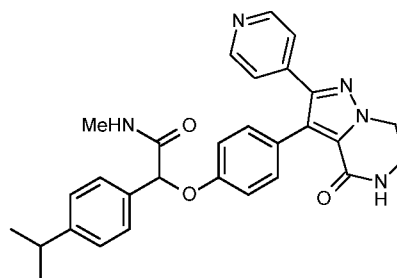
a- Synthesis of Int. 392:

- EDCI (1.2g, 6.2mmol) was added to a sol. of α -hydroxy-4-(1-methylethyl) benzene acetic acid (0.8g, 4.1mmol), HOBt (0.8g, 6.2mmol), DIPEA (1mL, 6.2mmol) methylamine (0.46mL, 5.3mmol) in DCM (25mL). The mixture was stirred at r.t. for 8 h. 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 (irregular SiOH 15-40 μm , 24g, GraceResolvTM, Mobile phase: 98/2 DCM/MeOH). The pure fractions were collected and evaporated until dryness to give yielding 500mg of Int. **392** (59%).



10 **b- Synthesis of Int. 393:**

- A sol. of **392** (500 mg, 2.40 mmol), **7** (690 mg, 3.12 mmol) and PPh_3 (759 mg, 2.89 mmol) in dry DCM (12 mL) was treated with DBAD (666 mg, 2.89 mmol) and stirred at r.t. for 19h. Then, EtOAc and brine were added, and the organic layer was separated, dried over MgSO_4 , filtered and evaporated *in vacuo*. The residue was purified by prep. LC (irregular SiOH 15-40 μm , 120g, GraceResolvTM, mobile phase gradient: from heptane 100% to heptane 70%, EtOAc 30%). The desired fractions were collected and solvent evaporated until dryness to give 320 mg of Int. **393** used as such for the next step.

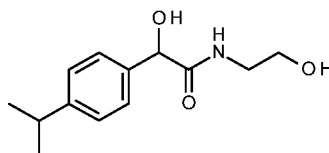


c- Synthesis of Co. 217:

- 20 A mixture of **4** (327 mg, 1.12 mmol), **393** (305 mg, 0.7 mmol) and K_3PO_4 (395 mg, 1.9 mmol) in 1,4-dioxane (3 mL) and H_2O (1.5 mL) was purged with N_2 . $\text{PdCl}_2(\text{dppf})$ (71 mg, 86 μmol) was added. The mixture was purged 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 20 min [fixed hold time]. Then a sol. of DCM/MeOH 95/5 and water were added. The organic layer was separated, washed (brine), separated, dried (MgSO_4), filtered and evaporated *in vacuo*. The residue was purified by prep. LC (Irregular SiOH 50 μm , 24g Grace, mobile phase gradient: from DCM 100% to DCM 93%, MeOH 7%). The desired fractions were evaporated *in vacuo* to give 110 mg. The

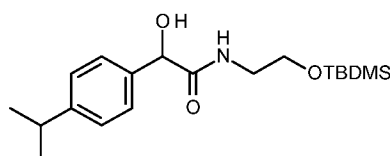
residue was crystallized from Et₂O and the precipitate was filtered off and dried to give 92 mg of **Co. 217** (25%).

Example A215: Preparation of Co. 218



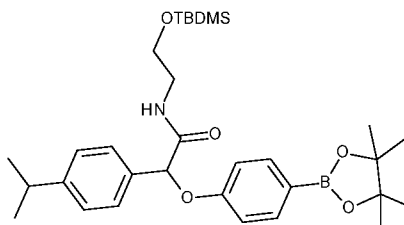
a- Synthesis of Int. 394:

- 5 EDCI (1.2 g, 6.2 mmol) and HOBT (0.8g , 6.2 mmol) were slowly added to a mixture of Hydroxy(4-isopropylphenyl)acetic acid (0.8 g, 4.1 mmol), DIPEA (1 mL, 6.2 mmol), ethanolamine (0.3 mL, 5.3 mmol) in DCM (25 mL). The mixture was stirred at r.t. for 24h. Water and DCM were added. The mixture was extracted, the organic layer was separated, dried over MgSO₄, filtered and evaporated. The residue was purified by
- 10 prep. LC (irregular SiOH 15-40μm, 24g, GraceResolv™, Mobile phase: 98/2 DCM/MeOH). The pure fractions were collected and evaporated until dryness to give 400 mg of Int. **394** (41%).



b- Synthesis of Int. 395:

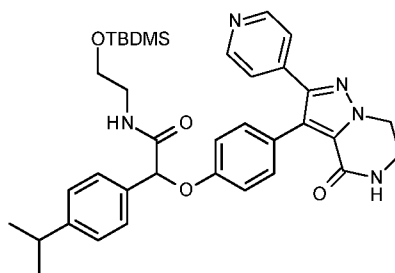
- Tert-butyldimethylsilyl chloride (0.28 g, 1.8 mmol) was added to a sol. **394** (400 mg, 1.7 mmol), imidazole (0.15 g, 2.2 mmol) in DCM (5 mL). The mixture was stirred at r.t. overnight. Water and DCM were added and the mixture was extracted. The organic layer was separated, dried over MgSO₄, filtered and evaporated. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 24g, GraceResolv™, Mobile phase: Heptane 70%, EtOAc 30%). The pure fractions were collected and evaporated until
- 20 dryness to give 220 mg of Int. **395** (37%).



c- Synthesis of Int. 396:

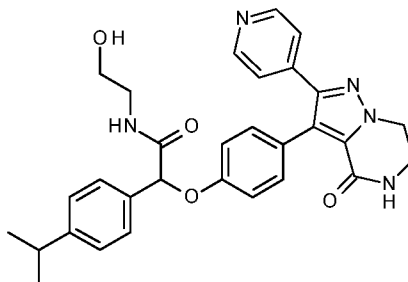
- A sol. of **395** (185 mg, 0.5 mmol), **7** (150 mg, 0.7 mmol) and PPh₃ (207 mg, 0.8 mmol) in dry THF (5 mL) was degassed under N₂ and, then, treated with DBAD (181 mg, 0.8 mmol) and stirred at r.t. for 19h. DCM and brine were added, and the organic layer was
- 25 separated, dried over MgSO₄, filtered and evaporated *in vacuo*. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 12g, GraceResolv™, mobile phase gradient: from heptane 100% to heptane 70%, EtOAc 30%). The desired fractions were

collected and solvent evaporated until dryness to give 130 mg of Int. **396** (45%, purity 80%). The product was used as such for the next step.



d- Synthesis of Int. 397:

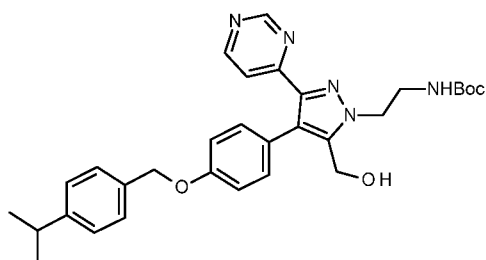
A mixture of **4** (103 mg, 0.3 mmol), **396** (130 mg, 0.23 mmol) and K₃PO₄ (124 mg, 0.6 mmol) in 1,4-dioxane (2 mL) and H₂O (0.6 mL) was purged with N₂. PdCl₂(dppf) (23 mg, 28 mmol) was then added. The mixture was purged again with N₂ and stirred at 110°C overnight. Water and DCM were added and the mixture was extracted. The organic layer was separated, dried over MgSO₄, filtered and evaporated to give 81 mg. The residue was purified by prep. LC (Stationary phase: Spherical bare silica 5µm 150x30.0mm, Mobile phase gradient: from 70% Heptane, 2% MeOH (+10% NH₄OH), 28% EtOAc to 20% MeOH (+10% NH₄OH), 80% EtOAc). The pure fractions were collected and evaporated to give 21 mg of Int. **397** (14%).



e- Synthesis of Co. 218:

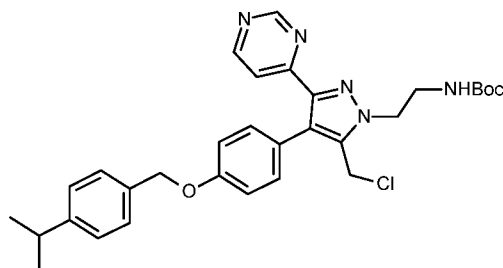
397 (21 mg, 0.033 mmol), TBAF (49 µl, 0.049 mmol) in THF (5 mL) was stirred at r.t. overnight. The mixture was evaporated till dryness and was purified by prep. LC (Stationary phase: Irregular SiOH 20-45µm 24g MATREX, Mobile phase: 95/5/0.1, DCM/MeOH/NH₄OH). The pure fractions were put together and evaporated till dryness to give 15 mg. The residue was purified by Reverse phase (Stationary phase: X-Bridge-C18 5µm 30*150mm, Mobile phase gradient: from 90% (NH₄HCO₃ 0.5% aq. sol.), 10% ACN to 100% ACN). The pure fractions were put together and evaporated till dryness. The residue was taken up in Et₂O and the precipitate was filtered off and dried to give 14 mg of **Co. 218** (81%).

Example A216: Preparation of Co. 219a and Co. 219



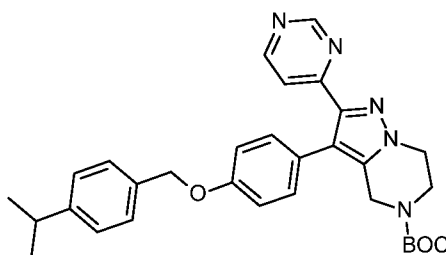
a- Synthesis of Int. 398:

LAH bis(THF) in Toluene (15.9 mL, 15.9 mmol) was added to a stirred suspension of **320** (4.65 g, 7.94 mmol) in dry THF (70 mL) under N₂ at -50°C. The r.m. was stirred at -50 °C for 20 min, and then quenched carefully with water (3 mL), a 3M sol. of NaOH (3 mL) and water (9 mL). EtOAc was added, and the crude mixture was filtered on glass frit, the cake was washed with EtOAc and the filtrate was evaporated *in vacuo* to afford 4.30 g of Int. **398**, pale brown solid (100%).



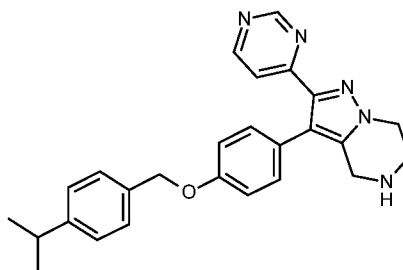
b- Synthesis of Int. 399:

Et₃N (0.679 mL, 4.89 mmol) and methanesulfonyl chloride (0.354 mL, 4.58 mmol) were added to a stirred sol. of **398** (1.66 g, 3.05 mmol) in dry DCM (35 mL) at 0 °C. The r.m. was stirred at r.t. for 18h. Then, sat. sol. of NaHCO₃ and DCM were added, and the organic layer was washed with brine, separated, dried over MgSO₄, filtered and evaporated *in vacuo* to yield 1.76 g of Int. **399**, brown solid (quant.).



c- Synthesis of Co. 219a

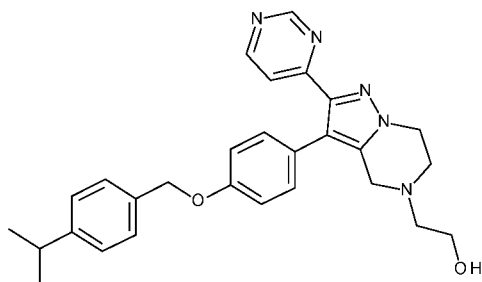
NaH 60% (250 mg, 6.26 mmol) was added to a stirred sol. of **399** (1.76 g, 3.13 mmol) in dry DMF (32 mL) at 0 °C under N₂. The r.m. was stirred at r.t. for 2h. Then, water and EtOAc were added, and the organic layer was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to yield 1.59 g of **Co. 219a**, brown solid. The product was used as such for the next step.



d- Synthesis of Co. 219:

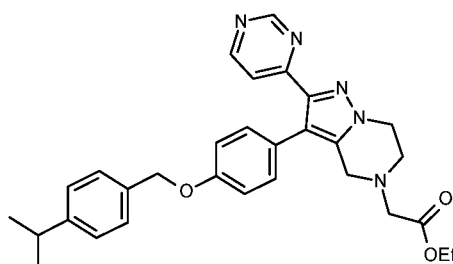
HCl 3N (4 mL) was added to a stirred sol. of **Co. 219a** (1.59 g, 2.57 mmol) in ACN (20 mL) at rt. The r.m. was stirred at 50°C for 3h. EtOAc and water were added, and the organic layer was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to yield 910 mg, brown solid. 310mg of 910mg were purified by prep. LC (Regular SiOH 50 μm, 12g Grace, mobile phase: DCM 100% to DCM 88%, MeOH 12%). The fractions containing the desired Co. were evaporated *in vacuo* to yield 60 mg, sticky pale yellow solid. The solid was triturated in a mixture of pentane/Et₂O (1:1), and the solvents were removed to afford 48 mg of **Co. 219** as a white solid. m.p.: 150 °C (DSC).

Example A217: Preparation of Co. 220



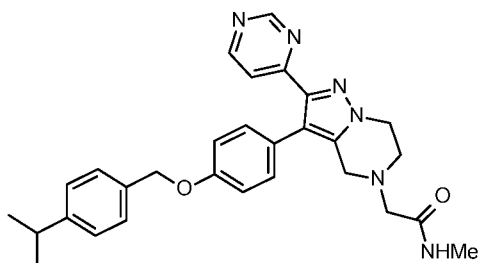
(2-bromoethoxy)-tert-butyldimethylsilane (0.214 mL, 0.987 mmol) was added to a stirred sol. of **Co. 219** (280 mg, 0.658 mmol) and Et₃N (0.183 mL, 1.32 mmol) in DMF (4 mL) at r.t. The r.m. was stirred at 60°C for 22h. The crude material was dissolved in water and extracted with EtOAc. The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to give 386mg of an oil. The oil was dissolved in THF (4.5 mL), and TBAF (1.32 mL, 1.32 mmol) was added at r.t. The r.m. was stirred at r.t. for 16h. The crude material was diluted in a mixture of DCM/MeOH (92/8) and water was added. The organic phase was separated, washed with brine (2x), dried (MgSO₄), filtered and evaporated *in vacuo* to give 260 mg of brown solid. The residue was purified by prep. LC (irregular SiOH 15-40μm, 12g Grace, Mobile phase gradient: from DCM 100% to DCM 92%, MeOH 8%). The desired fractions were combined and the solvent was removed *in vacuo* to give 18mg of **Co. 220** as a sticky solid (6%).

Example A218: Preparation of Co. 221



a- Synthesis of Int. 401:

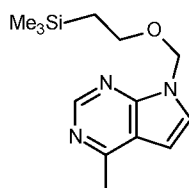
Ethylbromoacetate (0.117 mL, 1.06 mmol) was added to a sol. of **Co. 219** (300 mg, 0.705 mmol) and K_2CO_3 (175 mg, 1.27 mmol) in DMF (4.5 mL) at r.t. The r.m. was then stirred at 55°C for 4h, then water and EtOAc were added. The organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 312 mg of Int. **401**, red oil (74%, purity 85%). The product was used without further purification for the next step.



b- Synthesis of Co. 221:

Triazabicyclo[4.4.0]dec-5-ene (TBD) (51 mg, 0.357 mmol) and methylamine 2M in THF (0.668 mL, 1.34 mmol) were added to a stirred sol. of **401** (228 mg, 0.446 mmol) in dry toluene (8 mL) at r.t. The r.m. was stirred at 50°C for 80 min, and then EtOAc and sat. NH_4Cl sol. were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to yield 198 mg of brown solid. The solid was purified by prep. LC (Regular SiOH 50 μm , 12g Grace, liquid loading, mobile phase: DCM 100% to DCM 80%, MeOH 15%, aqueous NH_3 5%). The desired fractions were evaporated *in vacuo* to yield 40 mg of sticky red solid. This solid was purified by achiral SFC (Stationary phase: Amino 6 μm 150x21.2mm, Mobile phase: 80% CO_2 , 20% MeOH (0.3% $iPrNH_2$)). The desired fractions were collected and evaporated *in vacuo* to yield 17 mg of **Co. 221** as a viscous yellow solid (8%).

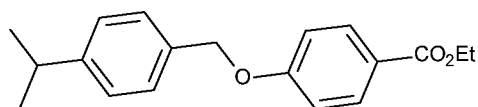
20 Example A219: Preparation of Co. 222



a- Synthesis of Int. 402:

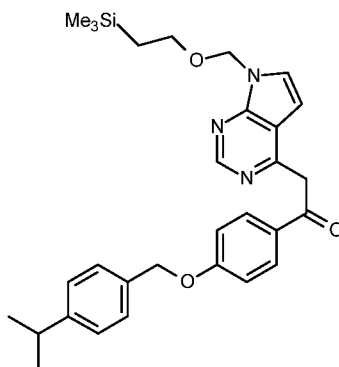
A sol. of 4-methyl-7H-pyrazolo[2,3-d]pyrimidine (3.11 g, 23.4 mmol) in DMF (40 mL) was cooled to 0°C and treated with NaH 60% (1.40 g, 35.0 mmol). The r.m. was

stirred at 0°C for 2h then 2-(trimethylsilyl)ethoxymethyl chloride (4.96 mL, 28.0 mmol) was added. The r.m. was stirred at r.t. for 2h and diluted in EtOAc. The organic layer was washed with water and brine (twice), dried over MgSO₄ and evaporated *in vacuo* to give brown oil. The oil was purified by prep. LC (irregular SiOH 15-40 µm, 80g, Grace, mobile phase gradient: from DCM 100% to DCM 96%, MeOH 4%). The desired fractions were collected and solvent evaporated until dryness to give 3.53 g. The residue was purified by prep. LC (irregular SiOH 15-40 µm, 80g, Grace, mobile phase gradient: from DCM 100% to DCM 96%, MeOH 4%). The pure fractions were collected and solvent evaporated until dryness to give 1.56 g of Int. **402** as a brown oil (25%).



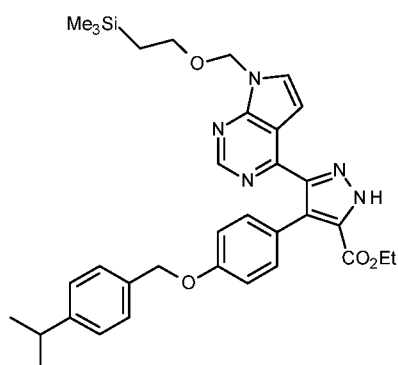
b- Synthesis of Int. 403:

A sol. of ethyl-4-hydroxybenzoate (10 g, 60.2 mmol) in ACN (150 mL) and DMF (10 mL) was treated with K₂CO₃ (10.0 g, 72.2 mmol) and **8** (13.5 g, 63.2mmol). The r.m. was stirred at 50°C for 17h. After concentration, the sol. was poured in EtOAc, washed with water (50mL), brine (4x 50mL) and water (50mL). The organic layer was dried over MgSO₄ and evaporated to give yellow oil. The oil was triturated in cold pentane to obtain a solid. After filtration on a glass frit, the solid was washed with cold pentane, collected and dried *in vacuo* to give 16.2g of Int. **403** as a white solid (90%).



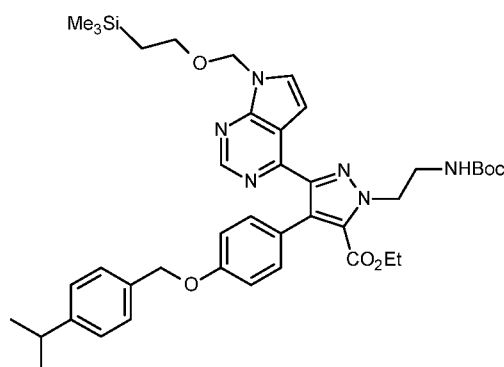
c- Synthesis of Int. 404:

In a dry flask and under N₂ atmosphere, a sol. of **402** (1.56 g, 5.92 mmol) and **403** (1.77 g, 5.92 mmol) in dry THF (15mL) was cooled to 0°C and treated with LiHMDS (11.8 mL, 11.8 mmol) over 10 min. The r.m. was allowed to warm to r.t. and stirred for 17h at this temperature. The r.m. was then poured in a 10% aq. sol. of NH₄Cl. The mixture was extracted with DCM, dried on MgSO₄ and concentrated *in vacuo* to give a beige solid. The solid was triturated in pentane, filtered and dried *in vacuo* to give 1.96 g of Int. **404** as a yellow solid (64%).



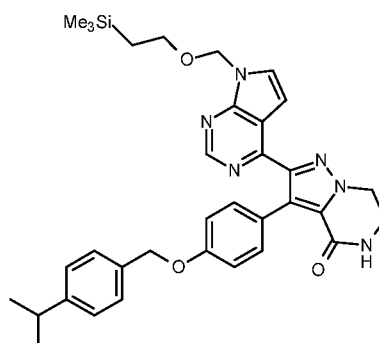
d- Synthesis of Int. 405:

A sol. of **404** (1.55 g, 3.01 mmol) and ethyl diazoacetate (0.506 mL, 4.81 mmol) in ACN (25 mL) was treated with DBU (0.764 mL, 5.11 mmol) and stirred at r.t. for 17 h. The r.m. was diluted in EtOAc and a sat. sol. of NaHCO₃. The organic layer was separated, washed with brine, dried over MgSO₄ and evaporated *in vacuo* to give a brown residue. The residue was purified by prep. LC (irregular SiOH 15 μm, 80g, Interchim, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 1.13 g of Int. **405** as a reddish oil (61%).



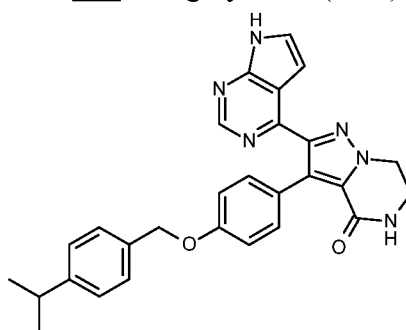
e- Synthesis of Int. 406:

A mixture of **405** (1.13 g, 1.85 mmol), tert-buthyl-N-(2-hydroxyethyl)carbamate (447 mg, 2.77 mmol) and PPh₃ supp. (0.866 mg, 2.77 mmol) in dry THF (40 mL) was treated with DBAD (638 mg, 2.77 mmol) and stirred at r.t. for 24 h. The r.m. was filtered through Celite® and the filtrate was evaporated *in vacuo* to give a red residue. The residue was purified by prep. LC (spheric SiOH 50 μm, 80g, Grace, mobile phase gradient: from DCM 100% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 1.61g of Int. **406** as a reddish oil (Quant.).



f- Synthesis of Int. 407:

A sol. of **406** (1.61 g, 2.13 mmol) in ACN (35 mL) was treated with HCl 3N (3.55 mL, 10.7 mmol) and stirred at 90°C for 4 h. The r.m. was diluted with DCM and washed with a sat. sol. of NaHCO₃. The organic layer was dried over MgSO₄ and evaporated *in vacuo* to give a yellow oil. The oil was dissolved in MeOH (40 mL), treated with Cs₂CO₃ (2.08 g, 6.40 mmol) and stirred at r.t. for 1h. The r.m. was concentrated *in vacuo* and diluted with DCM. The organic layer was washed with water and directly evaporated *in vacuo*. The precipitate was washed with water and with Et₂O, collected and dried *in vacuo* to give 700 mg of Int. **407** as a grey solid (54%).

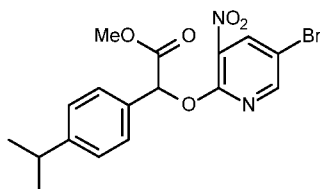


g- Synthesis of Co. 222:

A sol. of **406** (300 mg, 493 μmol) in DCM (7.5 mL) was cooled to 0°C and treated with boron trifluoride diethyl etherate (243 μL, 1.97 mmol). The r.m. was stirred at 0°C for 2h then at r.t. for 2h. An extra amount of boron trifluoride diethyl etherate (122 μL, 0.986 mmol) was added to the mixture which was stirred at r.t. for one extra h. The r.m. was quenched with a sat. sol. of NaHCO₃ and DCM was evaporated *in vacuo*. MeOH was added and the mixture was stirred at r.t. for 24 h. The r.m. was diluted with water and extracted twice with DCM. The organic layers were combined, dried over MgSO₄ and evaporated *in vacuo* to give a white residue. The residue was purified by prep. LC (irregular SiOH 15-40 μm, 40g, Merck, dry loading, mobile phase gradient: from DCM 100%, to DCM 90°C, MeOH 10%). The desired fractions were collected and solvent evaporated until dryness to give 141 mg, white solid. The solid was dissolved in THF (10mL) and NaOH 1N (1mL). The r.m. was stirred at r.t. for 17h and diluted in water. The mixture was extracted twice with DCM/MeOH (95:5). The organic layers were combined, dried over MgSO₄ and evaporated *in vacuo* to give 75 mg of white solid.

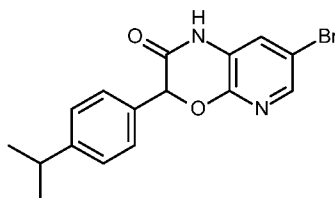
The solid was purified by prep. LC (irregular SiOH 15-40 μ m, 12g, Grace, dry loading, mobile phase gradient: from DCM 100%, to DCM 90°C, MeOH 10%). The pure fractions were collected and solvent evaporated until dryness to give 64 mg of **Co. 222**, white solid (27%). m.p.: 238°C (DSC).

5 Example A220: Preparation of Co. 223



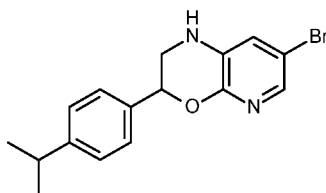
a- Synthesis of Int. 408:

NaH 60% (0.272 g, 7.92 mmol) was added to a stirred sol. of methyl 2-hydroxy-2-[4-(propan-2-yl)phenyl]acetate (1.5 g, 7.2 mmol) in THF (75 mL) at 0°C. The mixture was stirred for 5min and then 5-bromo-2-chloro-3-nitropyridine (1.71 g, 7.2 mmol) was added portionwise. The mixture was stirred at r.t. for 16h. The mixture was treated with water and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvents were evaporated *in vacuo* to give 3g which was crystallized from DIPE. The precipitate was filtered off and dried *in vacuo* to yield 1.29g of Int. **408** (44%).



15 b- Synthesis of Int. 409:

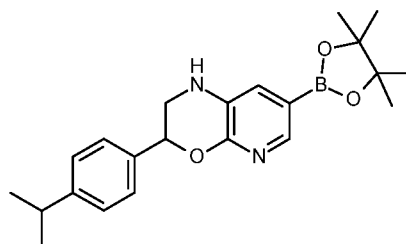
Fe (0.7 g, 12.56 mmol) was added to a stirred sol. of **408** (1.285 g, 3.14 mmol) in Acetic Acid (15 mL) in a sealed tube and under N₂. The mixture was stirred at 60°C for 8h. The mixture was diluted with EtOAc and filtered through a Celite® pad. The filtrate was concentrated, diluted with EtOAc and washed with sat NaHCO₃. The organic layer was separated, dried (MgSO₄), filtered and the solvents evaporated *in vacuo* to yield 0.6g of Int. **409** (55%).



c- Synthesis of Int. 410:

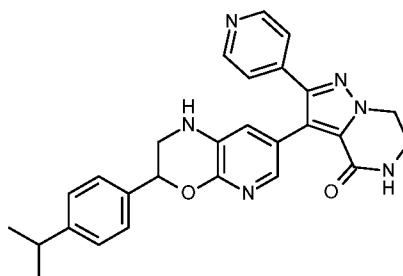
LAH in 1M THF (4.9 mL, 4.896 mmol) was added to a sol. of **409** (0.85 g, 2.45 mmol) in THF (40 mL) at -78°C under N₂. The reaction was stirred at -78°C for 5 min and, then, was allowed to warm to r.t. slowly and stirred at r.t. for 4h. EtOAc followed by Water were added dropwise to the mixture at -5°C. The suspension was filtered through

- a pad of Celite®. The organic layer was separated, dried over MgSO₄, filtered and the solvent was evaporated to give 0.4 g. The residue was purified by prep. LC (Irregular SiOH 15-40µm 25g Merck, mobile phase from: 100% DCM to 98% DCM 2% MeOH). The pure fractions were collected and the solvent was evaporated to give 0.19 g of Int. **410** (23%). The product was used as such for the next step.



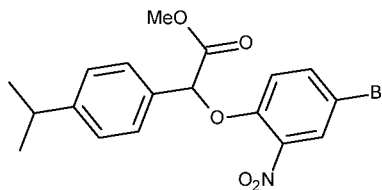
d- Synthesis of Int. 411:

- A mixture of **410** (0.16 g, 0.48 mmol), BisPin (0.183 g, 0.72 mmol) and KOAc (0.141 g, 1.44 mmol) in DME (3.6 mL) was carefully purged with N₂. PdCl₂(dppf) (31 mg, 0.038 mmol) was added and the r.m. was purged again with N₂. The r.m. was stirred at 100°C for 4h. The crude mixture was diluted with EtOAc and filtered over Celite®. The filtrate was washed with water and brine, and the organic layer was separated, dried over MgSO₄, filtered and evaporated *in vacuo* to yield 0.27g of Int. **411** used in the next step without purification.

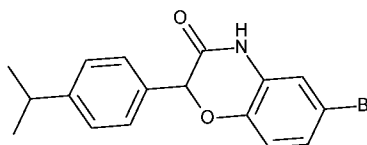


e- Synthesis of Co. 223:

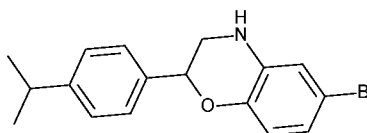
- A mixture of **411** (0.27 g, 0.71 mmol), **4** (0.138 g, 0.473 mmol) and K₃PO₄ (0.251 g, 1.183 mmol) in 1,4-dioxane (2.75 mL) and H₂O (1.375 mL) was purged with N₂. PdCl₂(dppf) (31 mg, 37 µmol) was then added. The mixture was purged again with N₂ and stirred at 120°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 20 min [fixed hold time]. The crude mixture was diluted with a sol. of DCM and water. The organic layer was separated, washed with brine, separated, dried over MgSO₄, filtered and evaporated *in vacuo* to yield 570 mg. The residue was purified by prep. LC (Irregular SiOH 15-40µm 30g Merck, mobile phase gradient: from 100% DCM to 98% DCM, 2% MeOH). The pure fractions were collected and the solvent was evaporated until dryness. The residue was crystallized from DIPE. The precipitate was filtered off and dried to give 15 mg of **Co. 223** (7%).

Example A221: Preparation of Co. 224, Co. 225 and Co. 226**a- Synthesis of Int. 412:**

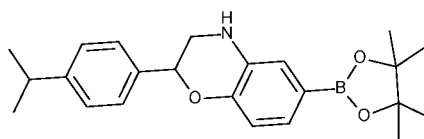
A sol. of methyl 2-hydroxy-2-[4-(propan-2-yl)phenyl]acetate (3.00 g, 14.4 mmol), 4-bromo-2-nitrophenol (4.08 g, 18.7 mmol) and PPh₃ (4.53 g, 17.3 mmol) in dry THF (77 mL) was treated with DBAD (3.98 g, 17.3 mmol) and stirred at r.t. for 18h. Then, EtOAc and water were added. The organic layer was washed with brine, a 10% sol. of K₂CO₃ and brine, and then separated, dried (MgSO₄), filtered and evaporated *in vacuo* to yield 16.3 g of orange oil which was filtered over silica, eluting with a sol. of Heptane/EtOAc (70/30). The filtrate was evaporated *in vacuo* to yield 9.02 g of a yellow solid. The residue was purified by prep. LC (irregular SiOH 15-40µm, 330g, GraceResolvTM, mobile phase gradient: heptane/EtOAc from 100/0 to 50/50). The pure fractions were collected and solvent evaporated to give 5.30 g of Int. **412** as pale yellow oil (85%).

**b- Synthesis of Int. 413:**

Fe (1.91 g, 34.2 mmol) was added to a stirred sol. of **412** (720 mg, 1.71 mmol) in acetic acid (15 mL) at r.t. The r.m. was stirred at 50°C for 20h. The crude mixture was diluted with EtOAc and filtered through Celite®. Water was added to the filtrate, and the organic layer was then treated with sat. NaHCO₃, washed with water, dried over MgSO₄, filtered and evaporated *in vacuo* to yield 520 mg of Int. **413**, white solid (88%).

**c- Synthesis of Int. 414:**

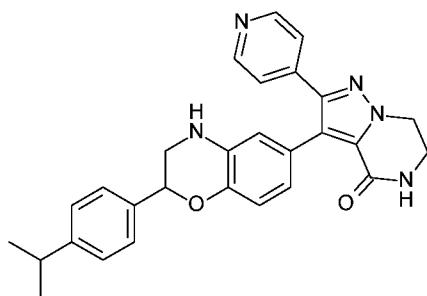
LAH (658 mg, 17.3 mmol) was added to a stirred sol. of **413** (1.50 g, 4.33 mmol) in dry THF (40 mL) at r.t. under N₂. The r.m. was stirred at 50°C for 2h. The sol. was quenched with addition of water (660 µL, very slow addition), a 3N sol. of NaOH (660 µL) and water (1.98 mL). The crude mixture was filtered on glass frit, the cake was washed with EtOAc and the filtrate was evaporated *in vacuo* to afford 1.36g of Int. **414** as pale brown solid (94%).



d- Synthesis of Int. 415:

A mixture of **414** (1.68 g, 5.06 mmol), BisPin (1.93 g, 7.) and KOAc (1.49 g, 15.2 mmol) in DME (38 mL) was carefully purged with N₂. PdCl₂(dppf) (331 mg, 0.405mmol) was added and the r.m. was purged again with N₂. The r.m. was stirred at 100°C for 4h. The crude mixture was diluted with EtOAc and filtered over Celite®. The filtrate was washed with water and brine, and the organic layer was separated, dried over MgSO₄, filtered and evaporated *in vacuo* to yield 3.34 g of black solid. The residue was purified by prep. LC (Irregular SiOH 50 µm, 120g Grace, mobile phase gradient: from Heptane 100% to Heptane 65%, EtOAc 35%). The desired fractions were evaporated *in vacuo* to give 1.52 g of Int. **415**, pale yellow solid (79%).

e- Synthesis of Co. 224 ,Co. 225 and Co. 226



Compound 224 (S or R)

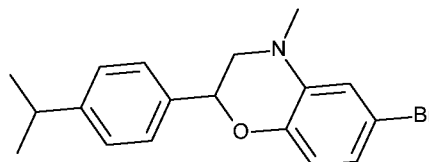
Compound 225 (R or S)

Compound 226 (racemic mixture)

A mixture of **4** (0.2 g, 0.688 mmol), **415** (0.47 g, 1.239 mmol) and K₃PO₄ (0.365 g, 1.721 mmol) in 1,4-dioxane (4 mL) and H₂O (2 L) was purged with N₂. PdCl₂(dppf) (45 mg, 55 µmol) was then added. The mixture was purged again with N₂ 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 20 min [fixed hold time]. The crude mixture was diluted with a sol. of DCM and water. The organic layer was separated, washed with brine, separated, dried over MgSO₄, filtered and evaporated *in vacuo* to yield 0.96 g which was combined with another batch resulting of 50 mg of **4**). The residue was purified by prep. LC (Stationary phase: Spherical bare silica 5µm 150x30.0mm, Mobile phase Gradient: from NH₄OH/DCM/MeOH 0.2/98/2 to 1.3/87/13. The pure fractions were collected and the solvent was evaporated to give 0.088 g of Co. 226 (22%) which was combined with another batch of Co. 226 (0.08 g) for enantiomeric separation. Co. 226 was purified by chiral SFC (Stationary phase: Chiralcel OJ-H 5µm 250x20mm, Mobile phase: 70% CO₂, 30% EtOH). The pure fractions were collected and the solvent was evaporated until dryness. The 1st residue (0.078g) was crystallized from DIPE. The precipitate was filtered off and dried to give 0.068g of **Co. 224** (S or R; 8%). The 2nd

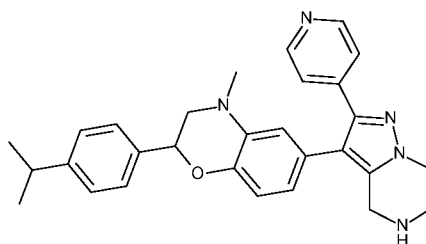
residue (0.085g) was crystallized from DIPE. The precipitate was filtered off and dried to give 0.068 g of **Co. 225** (R or S; 8%). Co. 224: $[\alpha]_d$: -28.35 ° (589 nm, c 0.254 w/v %, DMF, 20 °C); Co. 225: $[\alpha]_d$: +27.23 ° (589 nm, c 0.235 w/v %, DMF, 20 °C).

Example A222: Preparation of Co. 227



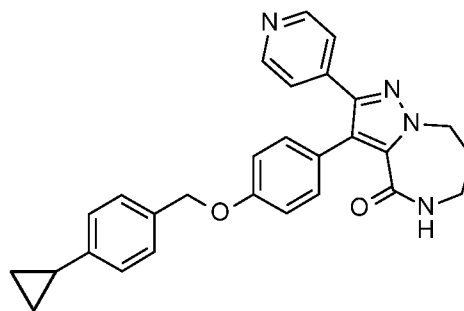
5 **a- Synthesis of Int. 416:**

A mixture of **414** (0.38 g, 1.14 mmol), Iodomethane (0.752 mL, 1.72 mmol) and K_2CO_3 (0.474 g, 3.43 mmol) in DMF (10 mL) was heated at 80°C overnight. The r.m. was cooled to r.t., poured into ice water and extracted with DCM. The organic layer was washed with brine, separated, dried over $MgSO_4$, filtered and the solvent was evaporated until dryness to give 0.45g of Int. **416** which was used in the next step without purification.



10 **b- Synthesis of Co. 227:**

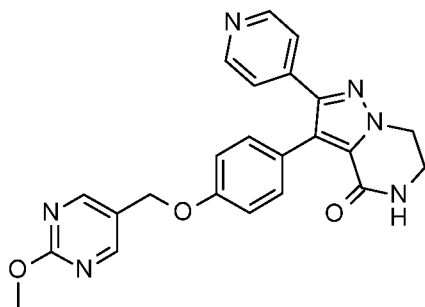
In a microwave vial, a mixture of **60** (0.35 g, 0.514 mmol), **416** (0.148 g, 0.429 mmol), K_3PO_4 (0.364 g, 1.715 mmol) in 1,4-dioxane (3.5 mL) and H_2O (1.05 mL) was carefully purged with N_2 . $PdCl_2(dppf)$ (35 mg, 0.043 mmol) was added and the r.m. was purged again with N_2 . The r.m. was heated at 80°C overnight. The r.m. was diluted with EtOAc, filtered off on a pad of Celite® and washed with EtOAc. The organic layer was washed with water (once) and with brine (3x). The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 0.4g. The residue was put together with another batch (0.1g of reactant **60** in the same conditions) and purified by prep. LC (Irregular SiOH 15-40µm, 40g Merck, mobile phase gradient: from 100% DCM to 98% DCM, 2% MeOH, 0.1% NH_4Cl . The desired fractions were collected and the solvent was evaporated until dryness to give 0.09 g. The residue 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 $NH_4OH/DCM/MeOH$ 0.8/92/8). The pure fractions were collected and the solvent was evaporated. The residue (0.04 g) was crystallized from DIPE. The precipitate was filtered off and dried to give 0.023 g of **Co. 227** (global yield: 9%). m.p.: 291°C (DSC).



Example A223: Preparation of Co. 228

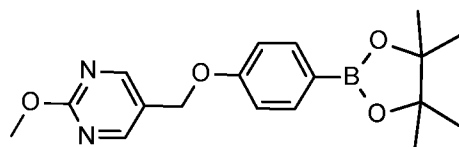
Prepared by using an analogous reaction protocol as described for Co. 197 starting from Int. **36** using 3-(boc-amino)-1-propanol. Yield: 91%; m.p.: 235°C (DSC).

Example A224: Preparation of Co. 229



5

Prepared by using an analogous reaction protocol as described for Co. 3 starting from

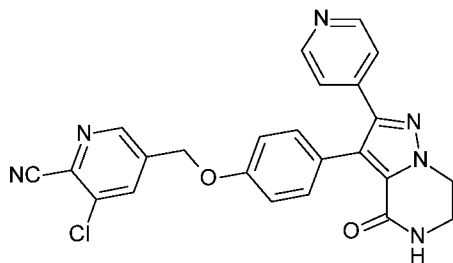


Int. **4** using

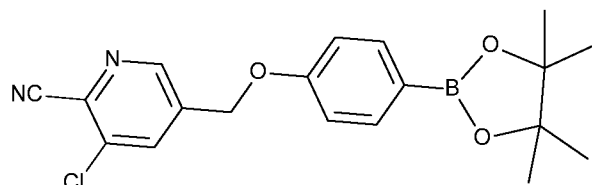
(prepared by using an analogous

reaction protocol as described for Int. **32** starting from Int. **7** using 2-methoxy-5-pyrimidinemethanol). Yield: 53%; m.p.: 248°C (DSC).

10 Example A225: Preparation of Co. 230



Prepared by using an analogous reaction protocol as described for Co. 3 starting from

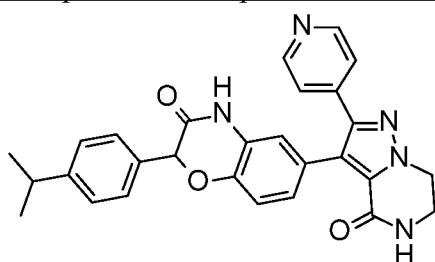


Int. 4 using

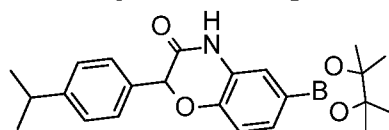
(prepared by using an

analogous reaction protocol as described for Int. 30 starting from Int. 7 using 3-chloro-5-(hydroxymethyl)-2-pyridinecarbonitrile). Yield: 18%; m.p.: 277°C (DSC).

5 Example A226: Preparation of Co. 231



Prepared by using an analogous reaction protocol as described for Co. 226 starting



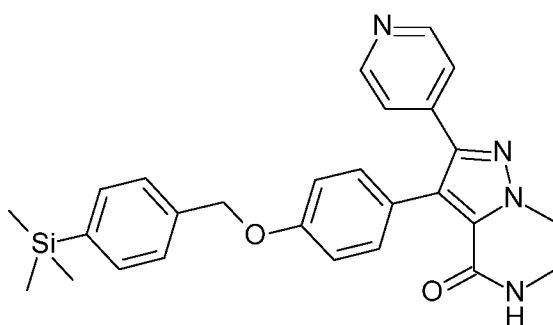
from Int. 4 using

(prepared by using an analogous

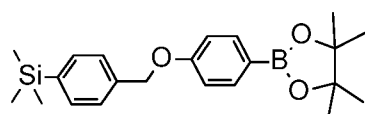
reaction protocol as described for Int. 415 starting from Int. 413). Yield: 53% ; m.p.:

10 291°C (DSC).

Example A227: Preparation of Co. 232



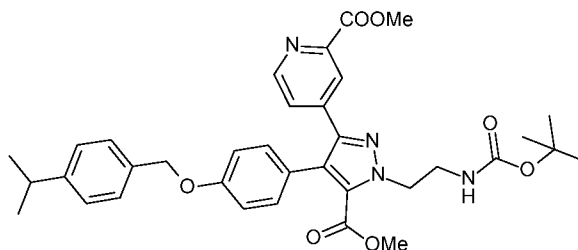
Prepared by using an analogous reaction protocol as described for Co. 6 starting from



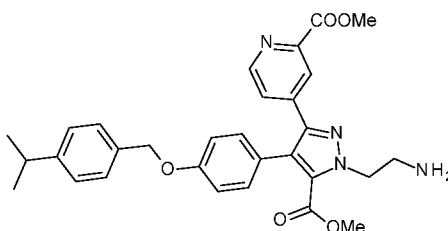
Int. 4 using

(prepared by using an analogous reaction

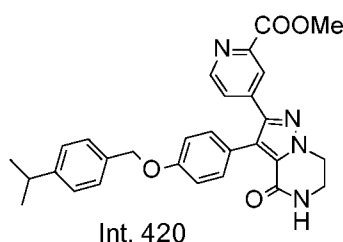
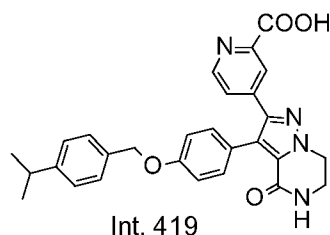
15 protocol as described for Int. 32 starting from Int. 7 using 4-(trimethylsilyl)-benzenemethanol). Yield: 62%.

Example A228: Preparation of Co. 233**a- Synthesis of Int. 417 :**

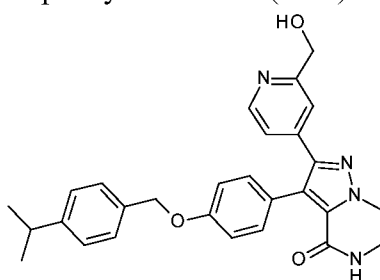
A mixture of **17** (300 mg, 0.511 mmol), methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinate (202 mg, 0.767 mmol) and K_3PO_4 (434 mg, 2.05 mmol) in DME (10 mL) in a sealed tube was purged with N_2 . Pd_2dba_3 (23.4 mg, 25.6 μ mol) and $PtBu_3.BF_4$ (Tri-tert-butylphosphonium tetrafluoroborate) (14.8 mg, 51.2 μ mol) were added, the mixture was purged again with N_2 and heated at $120^\circ C$ using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 45 min [fixed hold time]. The crude mixture was quenched with water and extracted with DCM. The organic layer was separated, dried over $MgSO_4$, filtered off and evaporated *in vacuo* to give a yellow oil. The residue (368 mg) was purified by prep. LC (Irregular SiOH 15-40 μ m, 24 g Grace, DCM deposit, mobile phase: heptane 50%, EtOAc 50%). The pure fractions were collected and solvent evaporated to give 210 mg of Int. **417** as a white residue (60%).

**b- Synthesis of Int. 418 :**

To a sol. of **417** (210 mg, 0.327 mmol) in ACN (2.50 mL) was added an aq. sol. of HCl 3N (545 μ L, 1.63 mmol) and the sol. was heated at $60^\circ C$ for 1 h. After cooling down to r.t., a mixture of DCM and a sat. aq. sol. of $NaHCO_3$ was added. The organic layer was separated, dried over $MgSO_4$, filtered off and evaporated *in vacuo* to give 154 mg of Int. **418** as a white solid (87%).

c- Synthesis of Int. 419 and Int. 420

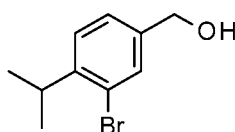
To a sol. of **418** (154 mg, 0.284 mmol) in MeOH (3 mL) was added Cs₂CO₃ (462 mg, 1.42 mmol) and the mixture was stirred at r.t. for 2h. The solvent was removed *in vacuo*. The residue was taken up with water and DCM. The organic layer was separated, dried over MgSO₄, filtered off and evaporated *in vacuo* to give 33 mg of a first batch of Int. **420** as white solid (23%). The aq. layer was extracted again with a mixture of DCM/MeOH 90/10. The organic layer was dried over MgSO₄, filtered off and evaporated *in vacuo* to give 8 mg of a second batch of Int. **420** as white solid (6%). The aq. layer was acidified with a 1N aq. sol. of HCl until pH 6-7 and extracted again with DCM. The organic layer was dried over MgSO₄, filtered off and evaporated *in vacuo* to give 87 mg of Int. **419** as pale yellow solid (64%).



d- Synthesis of Co. 233 :

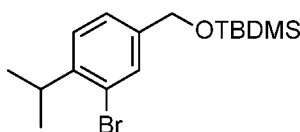
A sol. of Int. **420** (33 mg, 66.5 μmol) in THF (2 mL) and MeOH (0.4 mL) was treated with NaBH₄ (15 mg, 399 μmol) and stirred at 60°C for 17 h. The r.m. was poured in DCM and water. The organic layer was separated. The aq. layer was extracted twice with DCM/MeOH (95/5). The organic layers were combined, dried over MgSO₄ and evaporated *in vacuo* to give 27 mg of Co. **233** as a white solid (87%). M.p.: 232°C (DSC).

Example A229: Preparation of Co. 234



a- Synthesis of Int. 421 :

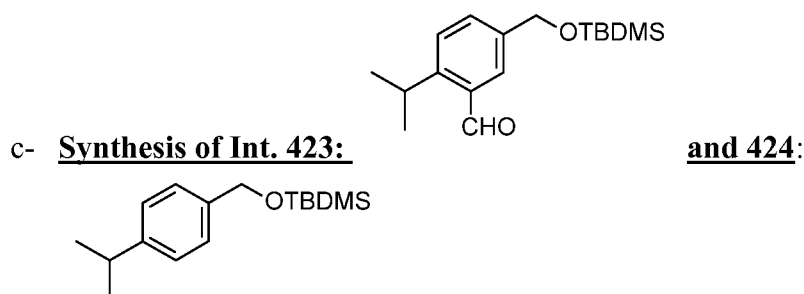
LiAlH₄ (5.52 g, 145 mmol) was added to a stirred sol. of methyl-3-bromo-4-isopropylbenzoate (34.0 g; 132 mmol) in THF (600 mL) at -20°C. The r.m. was stirred at -20°C for 2h. Then, the r.m. was quenched with 5.26 mL of H₂O, 5.52 mL of NaOH 3N and 16 mL of H₂O. The mixture was filtered and washed with DCM. The filtrate was evaporated *in vacuo* to give 20.0 g of Int. **421** as a yellow oil (66%).



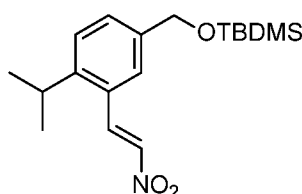
b- Synthesis of Int. 422 :

Tert-butyldimethylsilylchloride (15.8 g, 105 mmol) was added to a sol. of **421** (20.0 g, 87.3 mmol) and imidazole (8.91 g, 131 mmol) in DCM (400 mL) at r.t. The mixture

- was stirred at r.t. for 18h. 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 *in vacuo* to give a yellow oil. This residue (29.85 g) was purified by prep. LC (Stationary phase: Irregular SiOH 20-45 μm 450g MATREX, Mobile phase: 100% Heptane). The pure fractions were collected and solvent evaporated until dryness to give 15.0 g of Int. **422** as a white solid. The product was used without further purification for the next step.

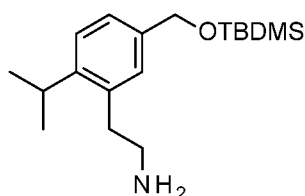


- t -Butyl Lithium 1.6M in pentane (7 mL, 11.2 mmol) was added to a stirred sol. under N_2 of **422** (2.00 g; 3.50 mol) in dry THF (20 mL) at -78°C . The mixture was stirred at -78°C for 30 min, and then DMF (3.8 mL, 51.7 mmol) was added at -78°C . The r.m. was stirred at -78°C to r.t. for 18h, and then quenched with water. DCM was added, and the organic layer was washed with brine, dried over MgSO_4 , filtered and evaporated *in vacuo* to give 2.00 g of a mixture of Int. **423** and Int. **424** ($423/424 = 2/1$) as a yellow oil. This mixture was used without further purification for the next step.



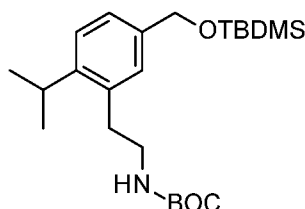
d- Synthesis of Int. 425 :

- AcONH_4 (316 mg, 4.10 mmol) was added to a stirred sol. of a mixture of **423** and **424** (2.00 g, 6.84 mmol) in $\text{CH}_3\text{-NO}_2$ (517 mL). The mixture was stirred at 60°C for 18h. The r.m. was quenched with water and DCM was added. The organic layer was washed with brine, dried over MgSO_4 , filtered and evaporated *in vacuo* to give an orange oil. This residue (1.8 g) was purified by prep. LC (irregular SiOH 15-40 μm , 50 g, MERCK, Mobile phase: from Heptane 100 % to heptane 95%, EtOAc 5%). The pure fractions were collected and solvent evaporated until dryness to give 750 mg of Int. **425** as a yellow oil (33%).



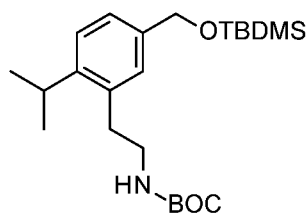
e- **Synthesis of Int. 426 :**

LiAlH₄ (283 mg, 7.45 mmol) was added to a stirred sol. of **425** (1.0 g, 2.98 mmol) in Et₂O (30 mL) at 0°C and the sol. was stirred at 0°C for 1h. To the sol. was added 280 μL of H₂O, 280 μL of an aq. sol. of NaOH 3N and 840 μL of H₂O. The precipitate was
 5 filtered and the filtrate was evaporated *in vacuo* to give a yellow oil. This residue (0.9 g) was purified by prep. LC (irregular SiOH 15-40 μm, 50 g, MERCK, Mobile phase: from DCM 100 % to DCM 80%, MeOH(10%NH₃) 20%). The pure fractions were collected and solvent evaporated until dryness to give 250 mg of Int. **426** as a colorless oil.



10 f- **Synthesis of Int. 427 :**

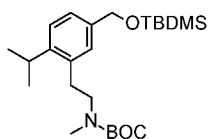
Boc₂O (266 mg, 1.22 mmol), Et₃N (0.169 mL, 1.219 mmol) and DMAP (10 mg, 81.3 μmol) were added to a stirred sol. of **426** (250 mg, 0.813 mmol) in ACN (4 mL) at r.t. The r.m. was stirred at r.t. for 72h and the sol. was diluted in DCM. The organic layer was washed successively with an aq. sol. of HCl 1N and a sat. aq. sol. NaHCO₃. The
 15 organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give 210 mg of Int. **427** (63%).



g- **Synthesis of Int. 427 (alternative) :**

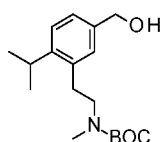
A suspension of Int. **422** (1.0 g, 2.91 mmol), potassium tert-butyl-2-N(2-trifluoroboranuidyl)ethylcarbamate (951 mg, 3.79 mmol), Cs₂CO₃ (2.85 g, 8.74 mmol)
 20 in toluene (15 mL) and H₂O (5 mL) was carefully purged with N₂. Pd(OAc)₂ (33 mg, 146 μmol) and S-Phos (136 mg, 291 μmol) were added to the mixture. The r.m. was purged again with N₂ and stirred at 110°C for 17 h. After dilution in EtOAc, the organic layer was washed with water and brine, dried over MgSO₄ and evaporated *in vacuo*. The residue was purified by prep. LC (spherical SiOH 30 μm, 40 g, Interchim, dry loading, mobile phase gradient: from heptane 100% to heptane 80%, EtOAc 20%).
 25

The pure fractions were collected and solvent evaporated until dryness to give 650 mg of Int. **427** as a colorless oil (55%).



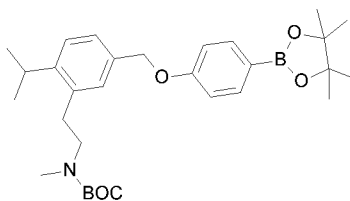
h- **Synthesis of Int. 428 :**

- NaH (60% dispersion in mineral oil) (650 mg, 16.3 mmol) was added to a mixture of **427** (4.44 g, 10.9 mmol) in THF (40 mL) at 0°C. The r.m. was stirred at r.t. for 30 min. MeI (1.4 mL, 21.8 mmol) was then added to the sol. and the mixture was stirred at r.t. for 18h. The sol. was diluted in DCM and washed with water. The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give 4.30 g of Int. **428** as a red oil (94%).



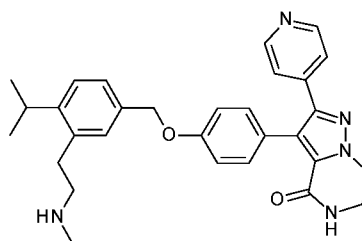
10 i- **Synthesis of Int. 429 :**

- A sol. of TBAF 1M in THF (20.4 mL, 20.4 mmol) was added to a mixture of **428** (4.30 g, 10.2 mmol) in THF (50 mL) and the r.m. was stirred for 17h at r.t. The sol. was diluted in DCM and washed with water. The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo* to give a red oil. This oil (4.71 g) was purified by prep. LC (irregular SiOH 15-40 μm, 50 g Merck, mobile phase gradient: from EtOAc 20%, Heptane 80% to EtOAc 50%, Heptane 50%). The pure fractions were collected and solvent evaporated to give 2.50 g of Int. **429** as a white gum.



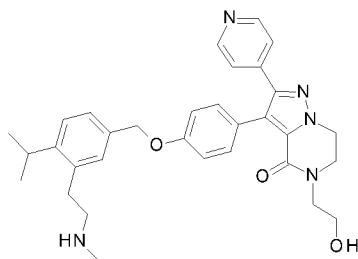
j- **Synthesis of Int. 430 :**

- Prepared by using an analogous reaction protocol as described for Int. **30** starting from Int. **7** using Int. **429** (60%).

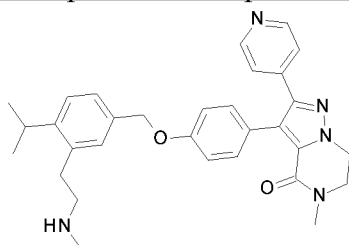


k- **Synthesis of Co. 234:**

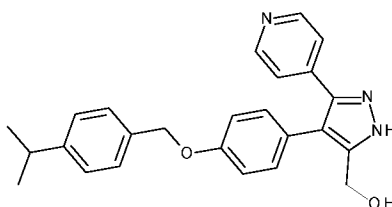
Prepared by using an analogous reaction protocol as described for **Co. 31** starting from Int. **4** using Int. **430**. Yield: 57%; m.p.: 166°C and 200°C (polymorph, DSC).

Example A230: Preparation of Co. 235

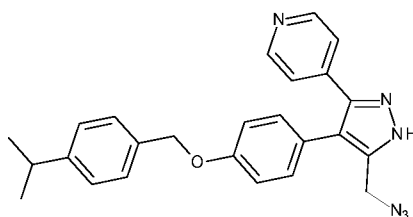
Prepared by using an analogous reaction protocol as described for **Co. 31** starting from Int. **28** using Int. **430**. Yield: 56%.

5 Example A231: Preparation of Co. 236

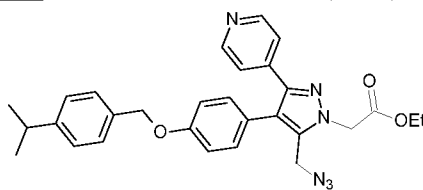
Prepared by using an analogous reaction protocol as described for **Co. 31**, starting from Int. **98** using Int. **430**. Yield: 62%.

Example A232: Preparation of Co. 23710 a- Synthesis of Int. 431 :

LiAlH₄ (0.172 g, 1.36 mmol) was added portionwise to a sol. of **11** (1.00 g, 2.26 mmol) in THF (23 mL) at 0°C under Ar. The resulting sol. was stirred at r.t. for 3 days. The r.m. was quenched by adding EtOAc followed by H₂O. The organic layer was washed with "rochelle salts" and brine, dried over Na₂SO₄, filtered off and concentrated to afford a yellow solid. This residue (0.803 g) was triturated in MeOH and filtered to give 0.755 g of a yellow solid. This second residue was co-evaporated with DCM and dried *in vacuo* to give 0.665 g of Int. **431** as an off-white solid (73%).

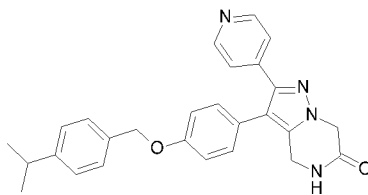
15 b- Synthesis of Int. 432 :

To a suspension of **431** (0.665 g, 1.66 mmol) in THF (10 mL) at r.t. under Ar was added diphenylphosphorylazide (0.400 mL, 1.83 mmol) and DBU (0.297 mL, 1.99 mmol). The resulting mixture was stirred at r.t. for 18h. An additional amount of diphenylphosphorylazide (0.200 mL, 0.916 mmol) and DBU (0.150 mL, 1.00 mmol) were added and the mixture was stirred at r.t. for 3h. The r.m. was quenched by adding an aq. sat. sol. of NaHCO₃ (30 mL). The aq. layer was extracted twice with EtOAc (2x 30 mL) and the combined organic layers were dried over Na₂SO₄, filtered off and concentrated to dryness to a yellow gum. This residue (1.26 g) was purified by prep. LC (irregular SiOH 15-40 µm, mobile phase gradient: from DCM 98%, MeOH 2% to DCM 95%, MeOH 5%). The pure fractions were collected and solvent evaporated until dryness to give 0.370 g of Int. **432** as an off-white solid (52%).



c- Synthesis of Int. 433 :

To a sol. of **432** (347 mg, 0.817 mmol) and K₂CO₃ (249 mg, 1.80 mmol) in DMF (6 mL) was added ethylbromoacetate (0.108 mL, 0.981 mmol) at r.t. The r.m. was stirred at r.t. for 18h. Then, the crude mixture was diluted with EtOAc and water, and the organic layer was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to a viscous orange solid. This residue (0.43g) was purified by prep. LC (Regular SiOH 50µm, liquid loading, 24g Grace, DCM 100 % to DCM 30% EtOAc 70%) to give 247 mg of Int. **433** as a cream solid (66%).



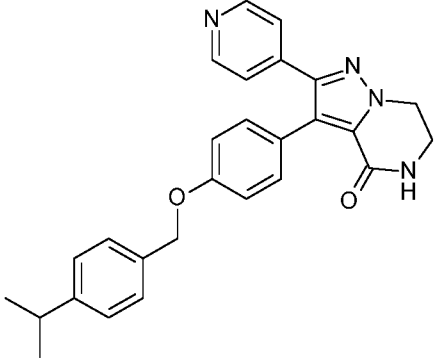
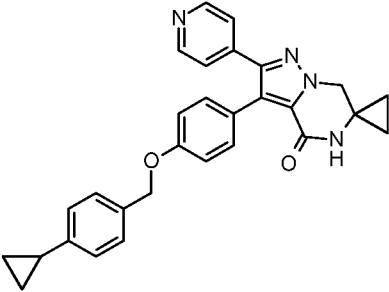
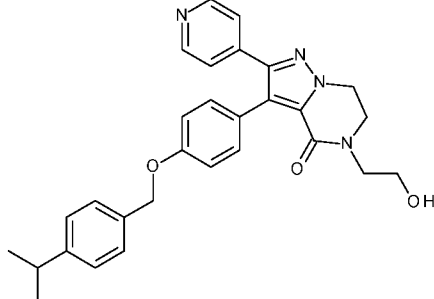
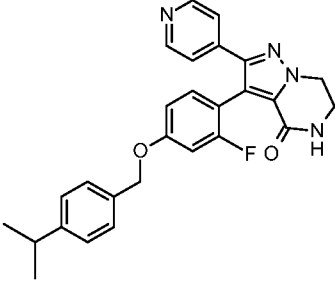
d- Synthesis of Co. 237:

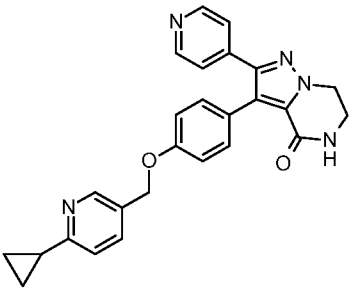
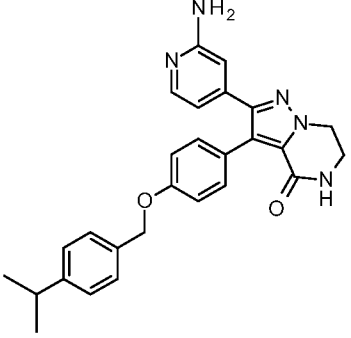
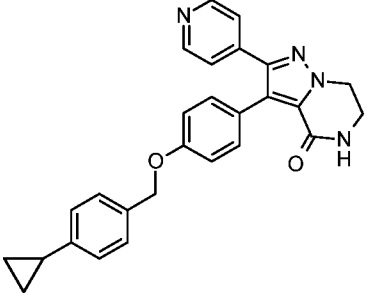
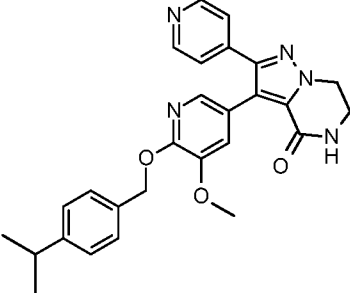
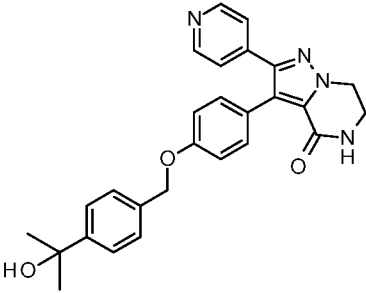
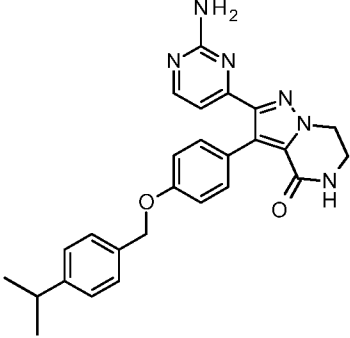
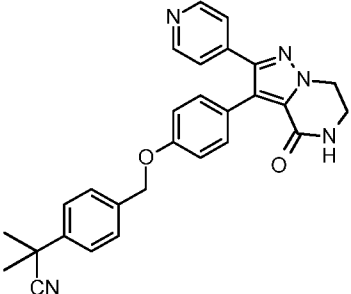
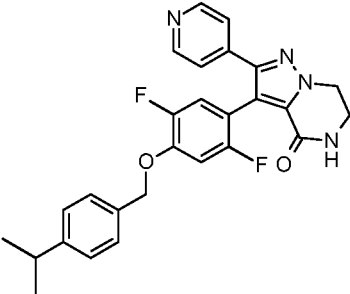
To a stirred sol. of **433** (254 mg, 0.497 mmol) in EtOH (8 mL) was added Raney Nickel (29 mg, 0.497 mmol) at r.t. The r.m. was hydrogenated at r.t. under atmospheric pressure for 1h. The crude mixture was filtered off through a pad of Celite® which was washed with EtOH. The filtrate was evaporated *in vacuo*. The residue (0.185 g) was diluted in EtOH (3 mL) and EtOAc (3 mL), and an extra amount of Raney Nickel (555 mg, 9.45 mmol) was added. The r.m. was hydrogenated at r.t. under atmospheric pressure for 2h. The crude mixture was filtered off through a pad of Celite® which was washed with DCM and EtOAc. The filtrate was evaporated *in vacuo*. The residue (0.130 g) was triturated in Et₂O, and the solvent was removed. The solid was dried *in vacuo* to yield 105 mg of Co. **237** as a white solid (48%). m.p.: 281 °C (DSC).

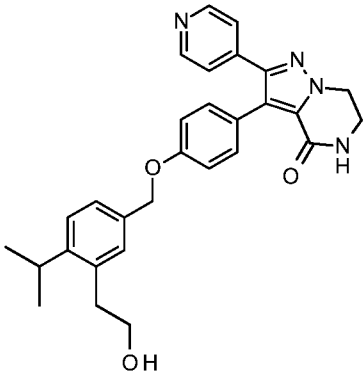
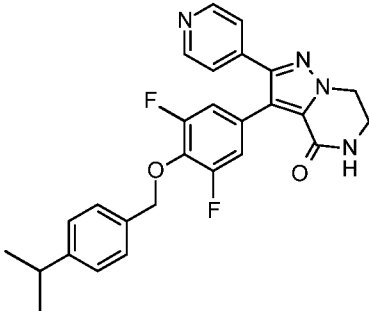
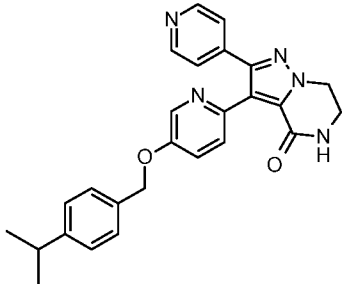
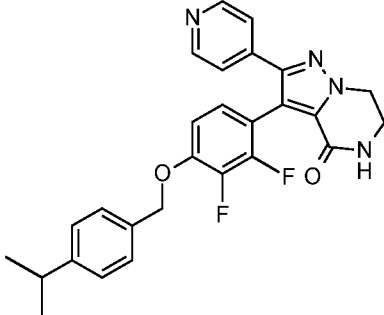
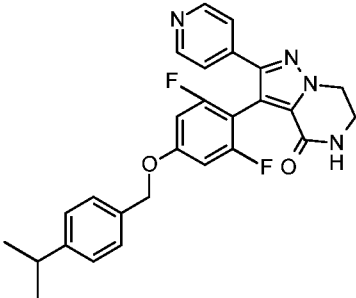
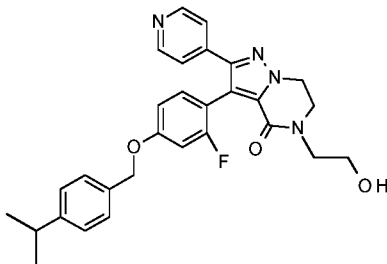
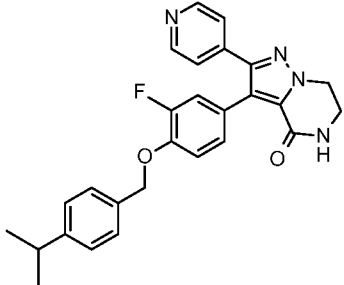
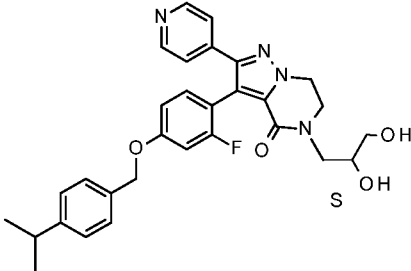
The compounds listed in Table 1 below have been prepared. The values of salt stoichiometry or acid content in the compounds as provided herein, are those obtained experimentally and may vary dependent on the analytical method used (for compound 210, ^1H NMR was used; and for compound 59a, ^1H NMR and elemental analysis was used).

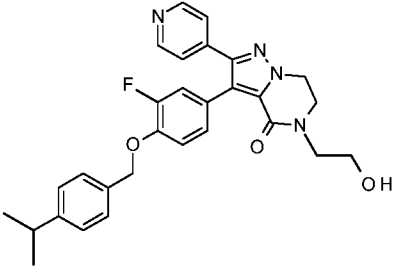
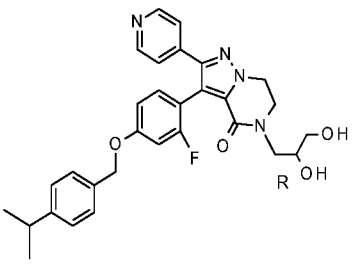
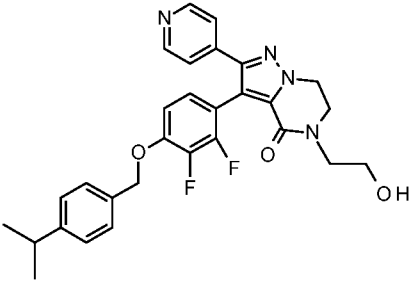
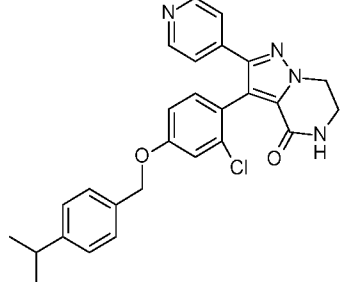
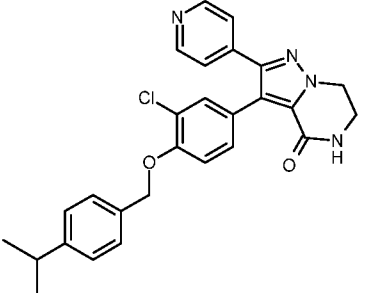
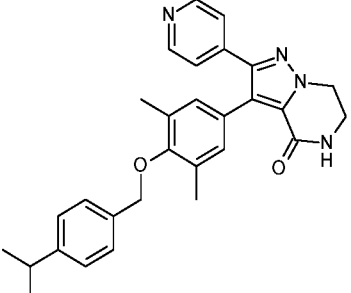
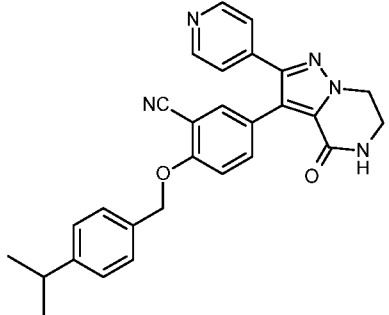
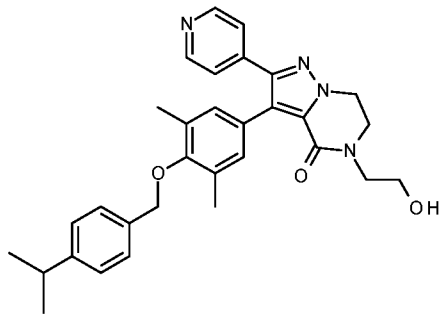
In case no salt form is indicated, the compound was obtained as a free base. Salt forms of the free bases can easily be obtained by using typical procedures known to those skilled in the art. For example Compound 1 (free base) was converted into a HCl salt, a methanesulfonate salt and a sulfate salt.

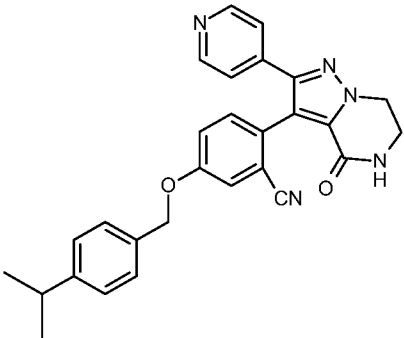
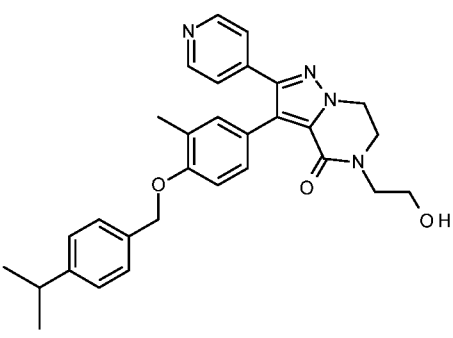
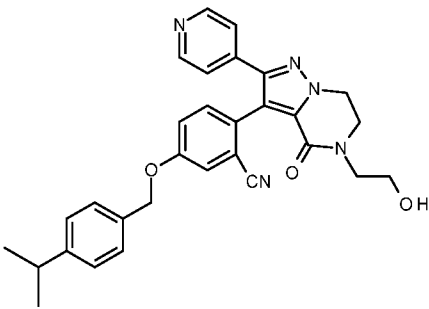
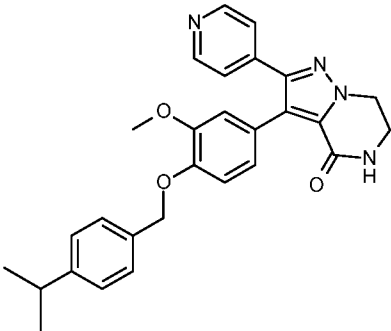
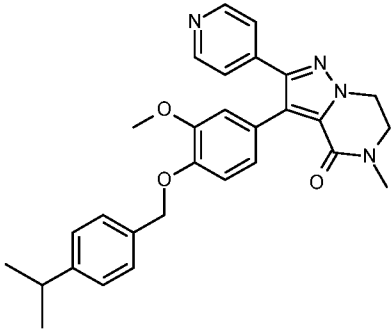
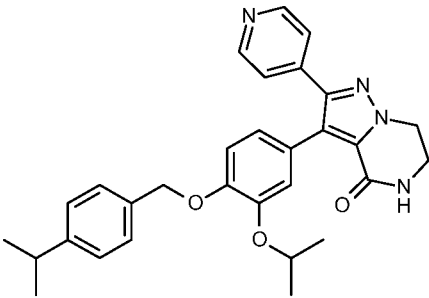
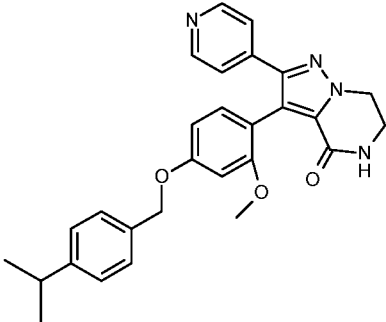
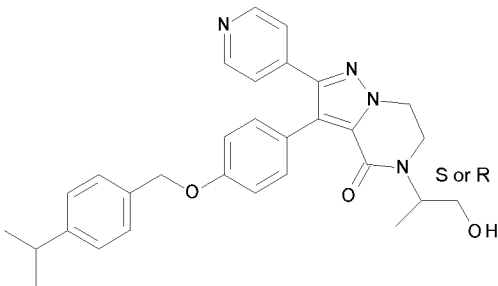
Table 1: Compounds

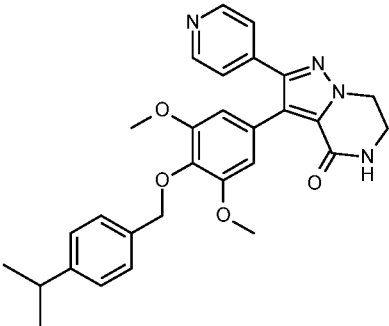
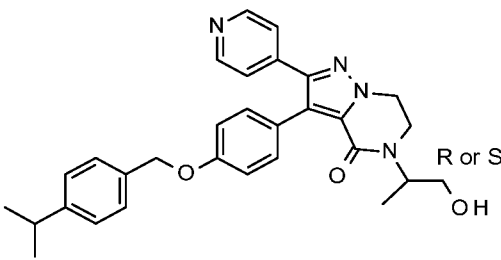
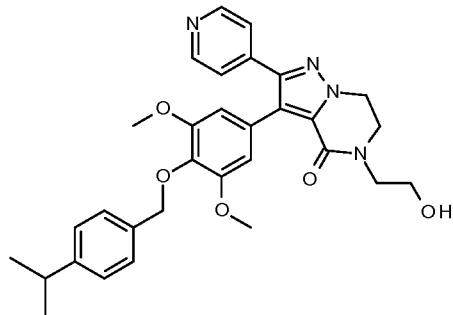
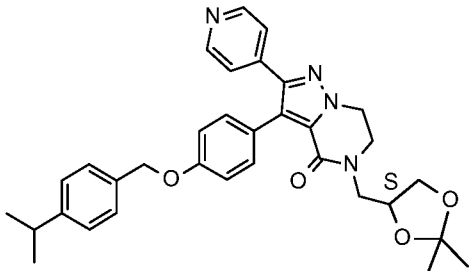
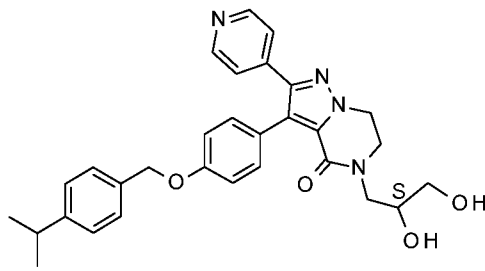
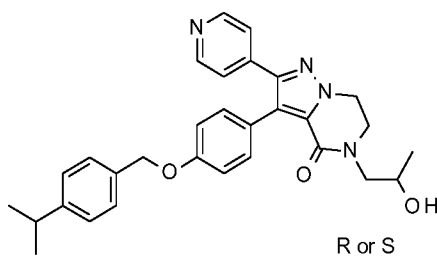
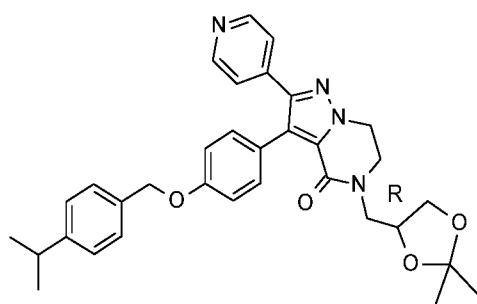
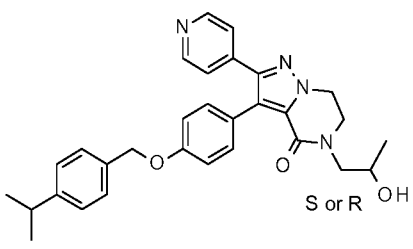
	
Compound 1; Method A1/A2/A3/A4/A5	Compound 5; Method A10
	
Compound 2; Method A6/A7/A56	Compound 6; Method A11

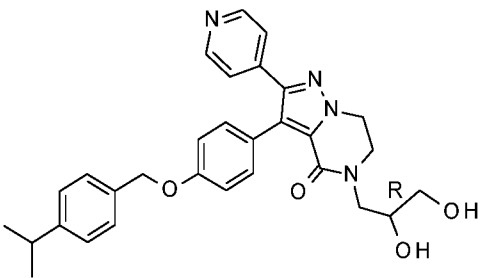
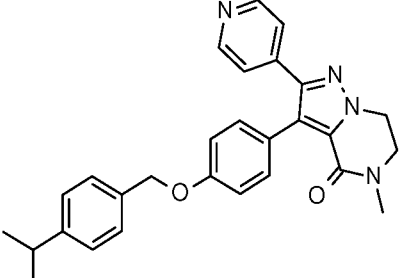
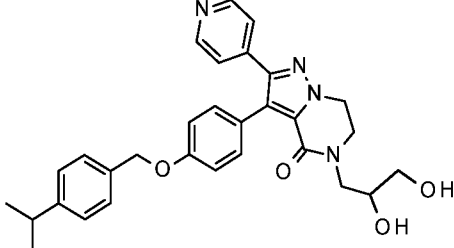
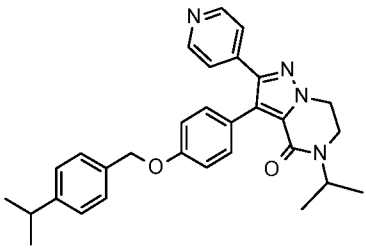
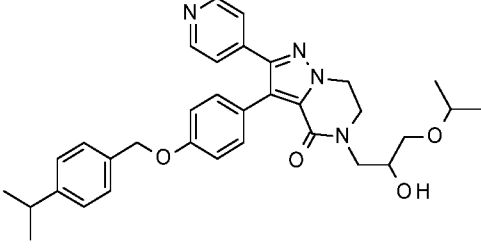
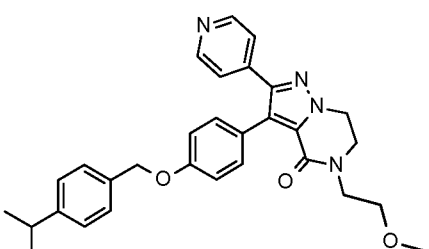
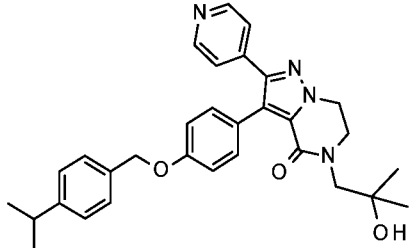
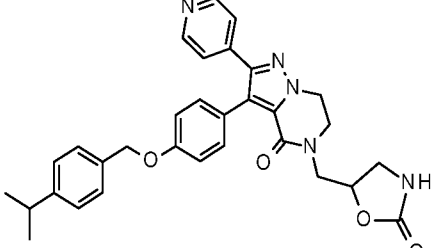
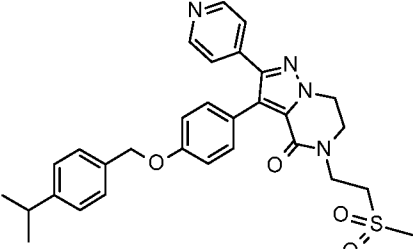
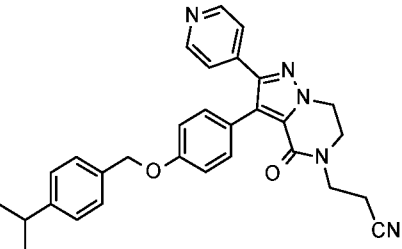
	
Compound 3; Method A8	Compound 7; Method A12
	
Compound 4; Method A9	Compound 8; Method A13
	
Compound 9; Method A14	Compound 13; Method A18
	
Compound 10; Method A15	Compound 14; Method A19

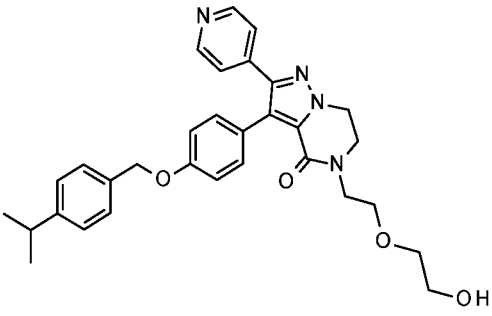
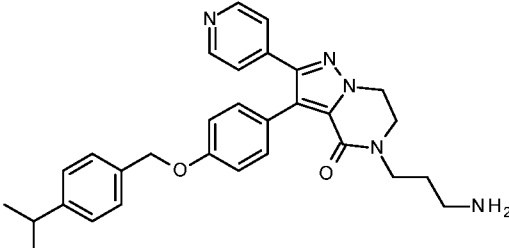
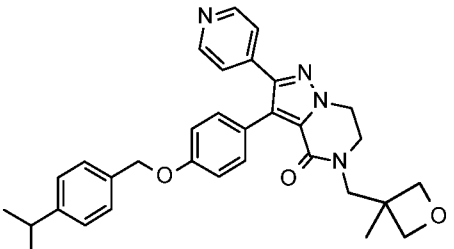
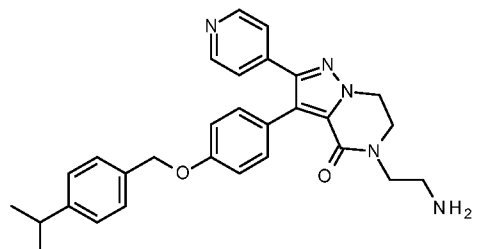
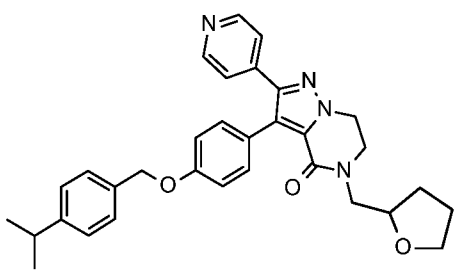
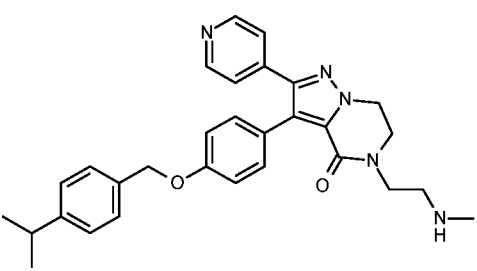
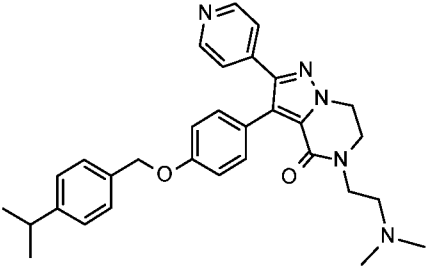
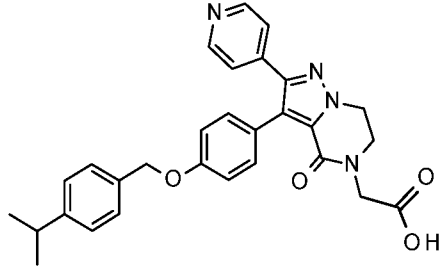
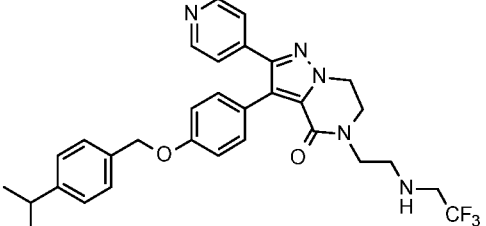
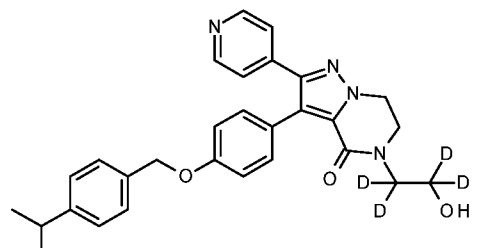
	
Compound 11; Method A16	Compound 15; Method A20
	
Compound 12; Method A17	Compound 16; Method 21
	
Compound 17; Method A22	Compound 21; Method A26
	
Compound 18; Method A23	Compound 22; Method A27

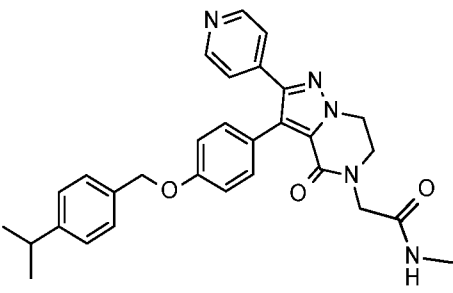
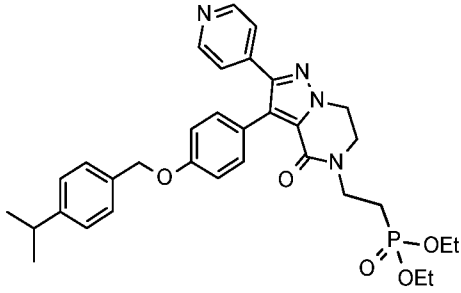
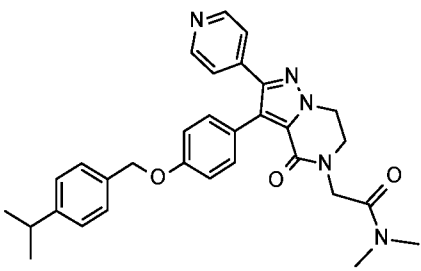
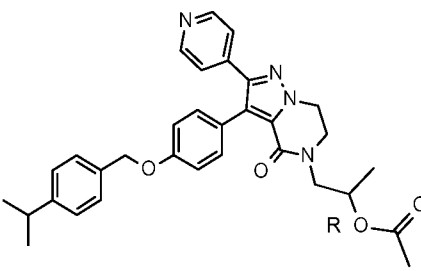
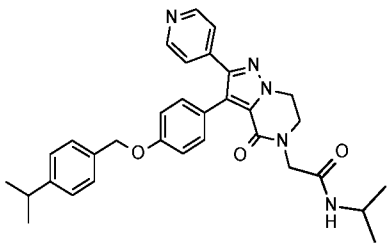
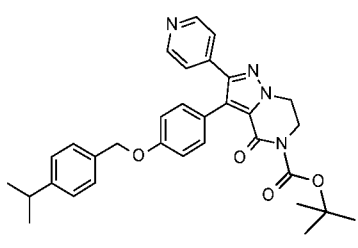
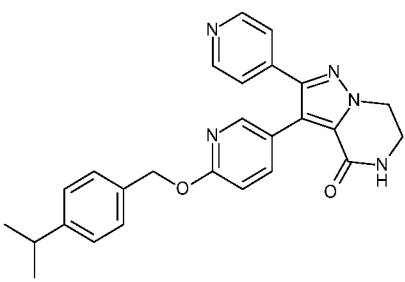
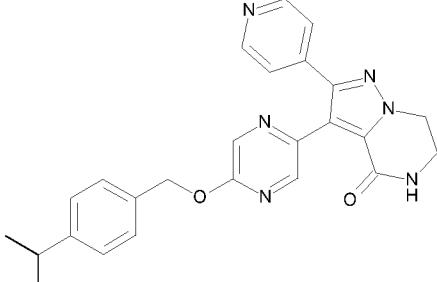
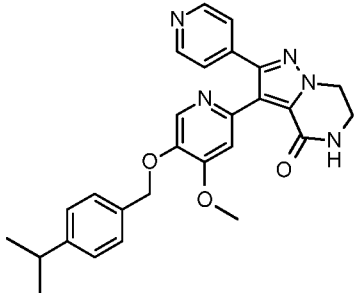
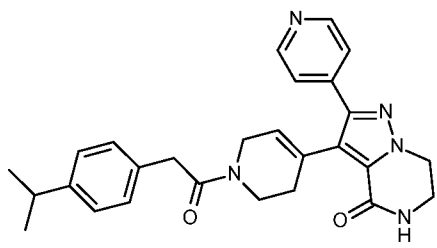
	
Compound 19; Method A24	Compound 23; Method A28
	
Compound 20; Method A25	Compound 24; Method A29
	
Compound 25; Method A30	Compound 29; Method A34
	
Compound 26; Method A31	Compound 30; Method A35

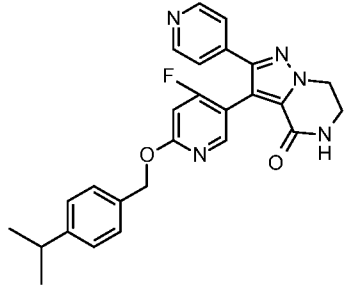
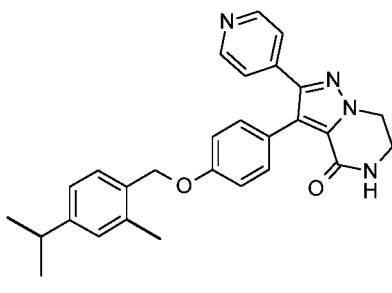
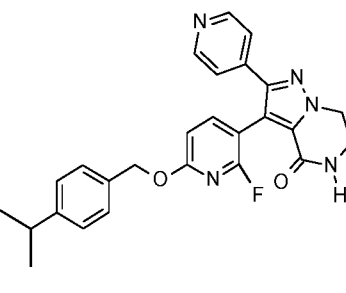
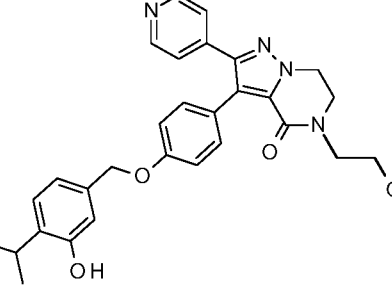
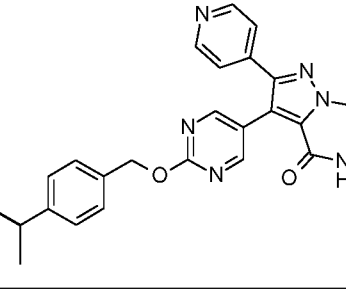
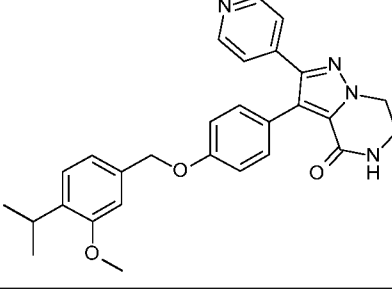
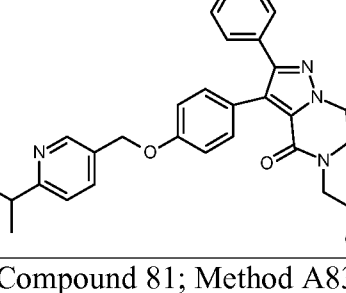
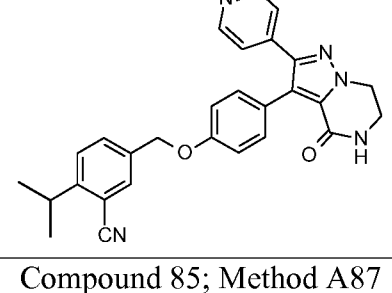
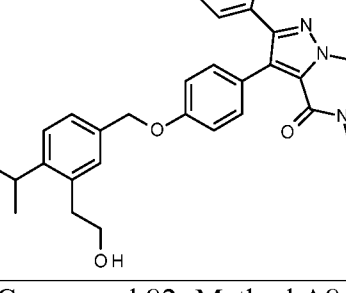
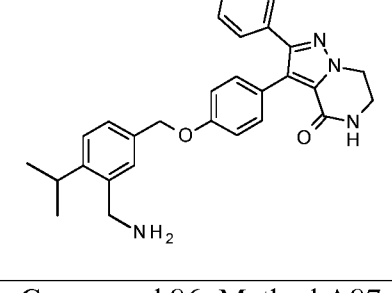
	
Compound 27; Method A32	Compound 31; Method A36
	
Compound 28; Method A33	Compound 32; Method A37
	
Compound 33; Method A38	Compound 37; Method A42
	
Compound 34; Method A39	Compound 38; Method A43

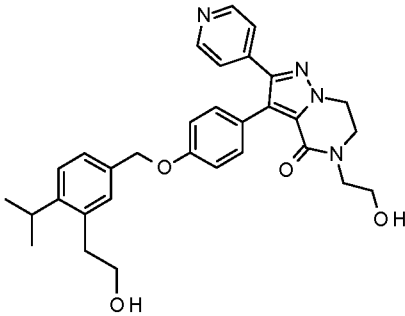
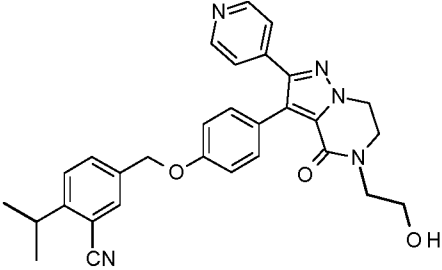
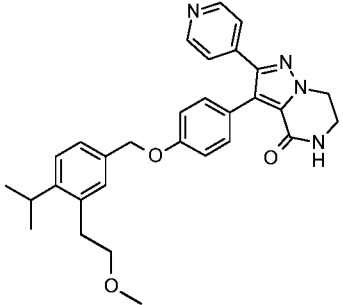
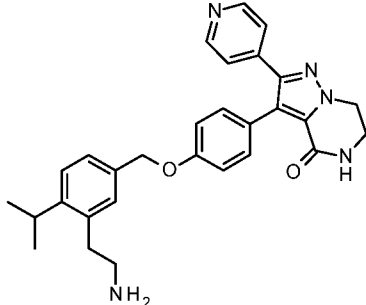
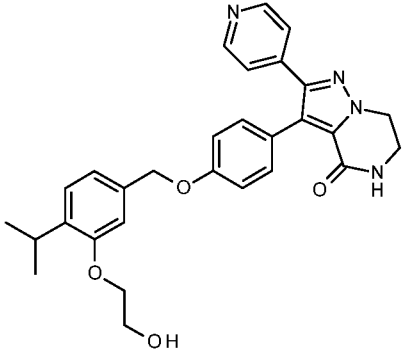
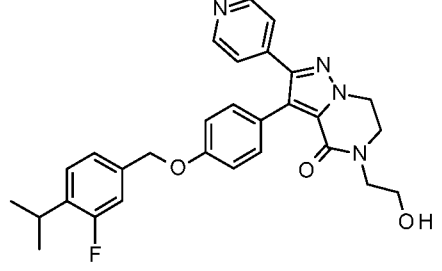
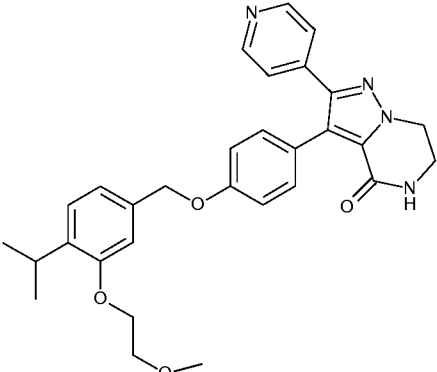
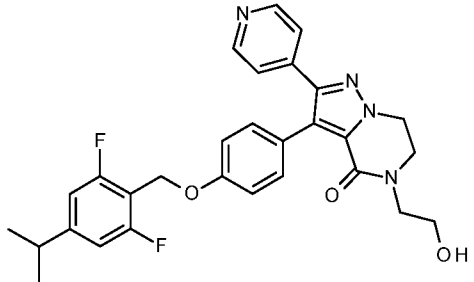
	
Compound 35; Method A40	Compound 39; Method A43
	
Compound 36; Method 41	Compound 40; Method A44
	
Compound 41; Method A45	Compound 46; Method A50
	
Compound 42; Method A46	Compound 47; Method A50

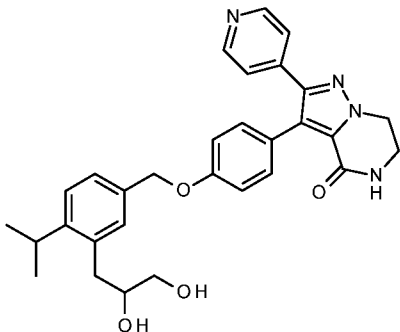
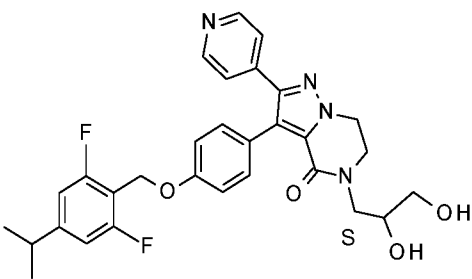
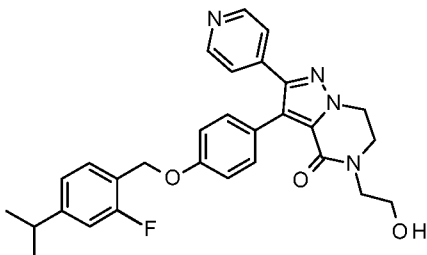
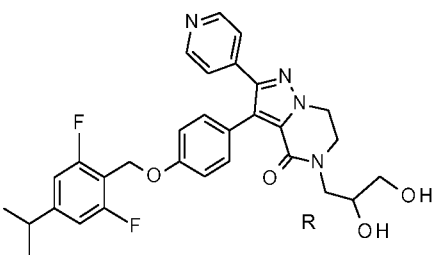
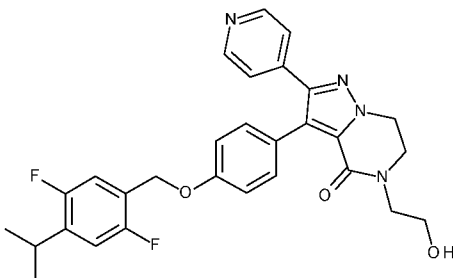
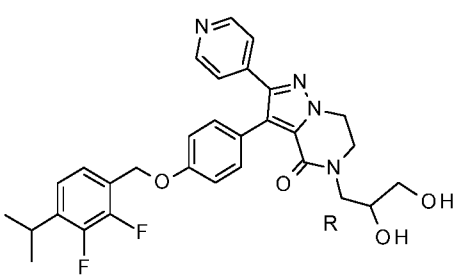
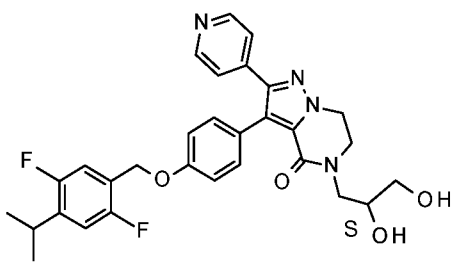
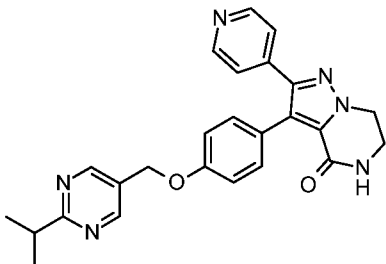
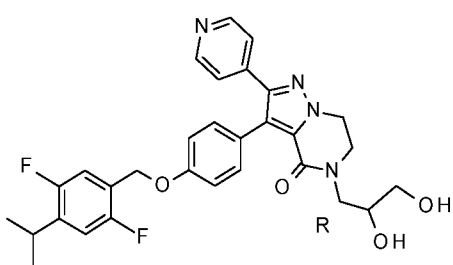
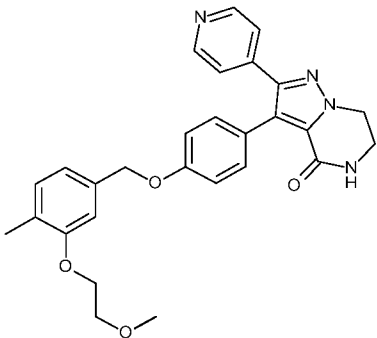
	
Compound 43; Method A47	Compound 48; Method A51
	
Compound 44; Method A48	Compound 49; Method A52
	
Compound 45; Method A49	Compound 50; Method A53
	
Compound 51; Method A54	Compound 56; Method A59
	
Compound 52; Method A55	Compound 57; Method A60

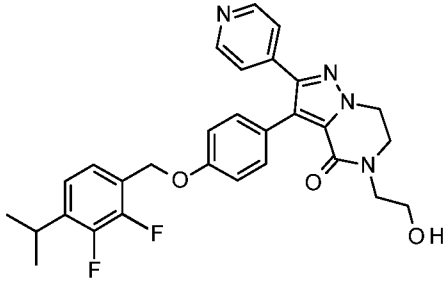
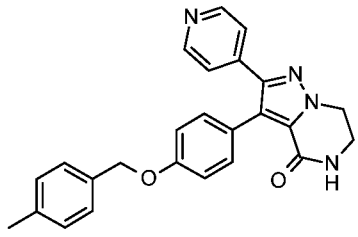
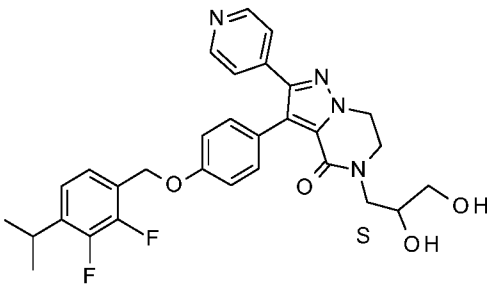
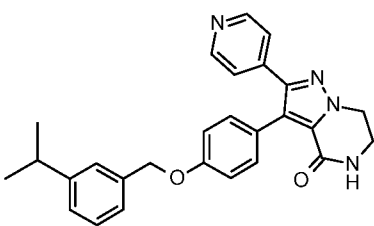
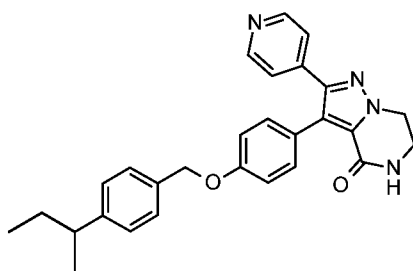
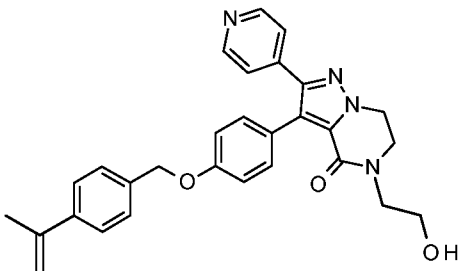
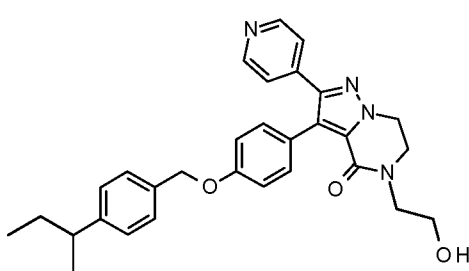
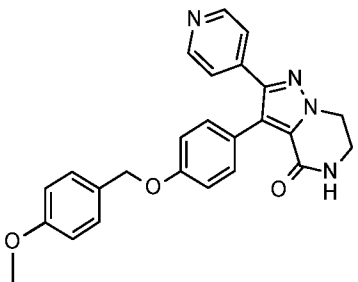
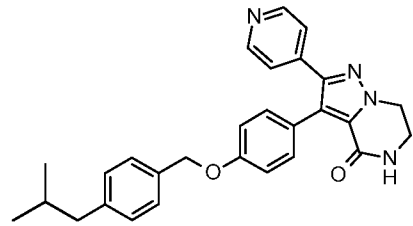
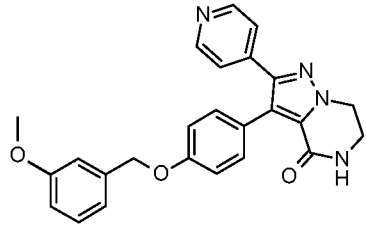
	
Compound 53; Method A56	Compound 58; Method A61
	
Compound 54; Method A57	Compound 59; Method A62
	
Compound 55; Method A58	Compound 60; Method A63
	
Compound 61; Method A64	Compound 66; Method A69
	
Compound 62; Method A65	Compound 67; Method A70

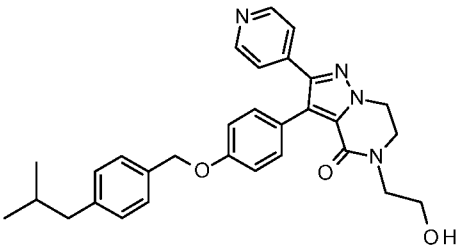
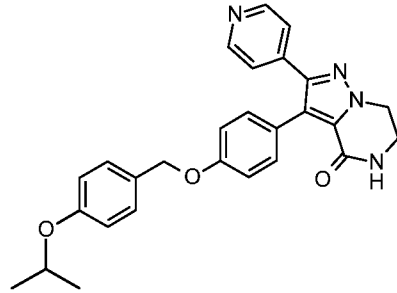
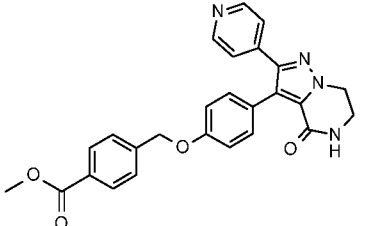
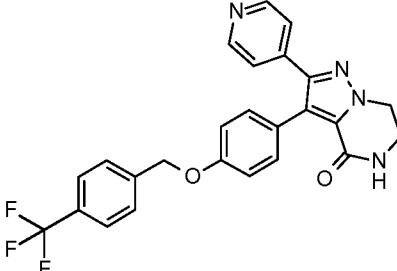
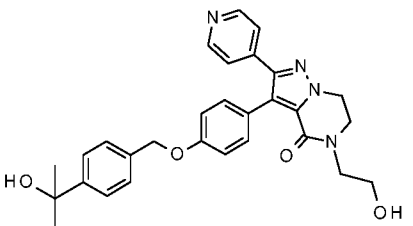
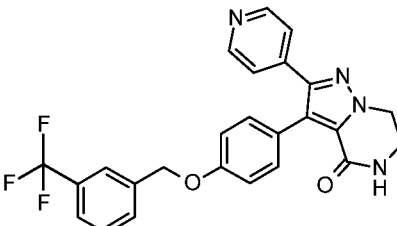
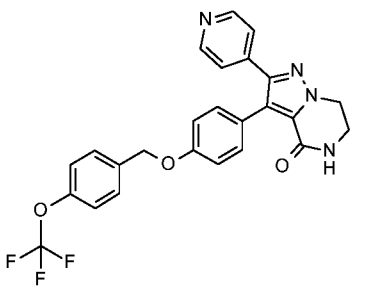
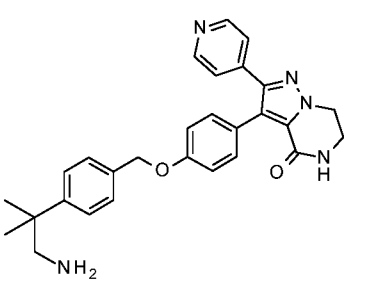
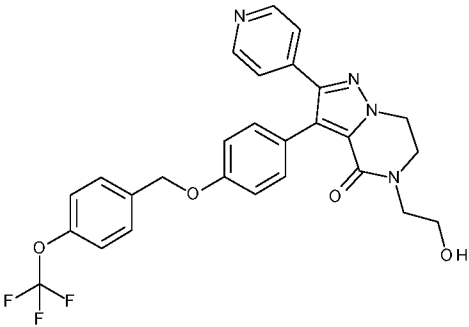
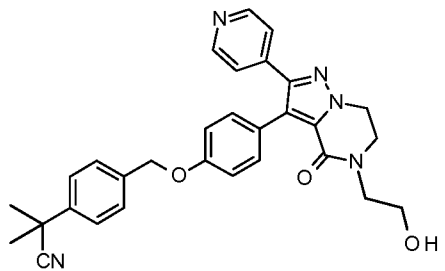
	
Compound 63; Method A66	Compound 68; Method A71
	
Compound 64; Method A67	Compound 69; Method A72
	
Compound 65; Method A68	Compound 70; Method A5.b
	
Compound 71; Method A73	Compound 76; Method A78
	
Compound 72; Method A74	Compound 77; Method A79

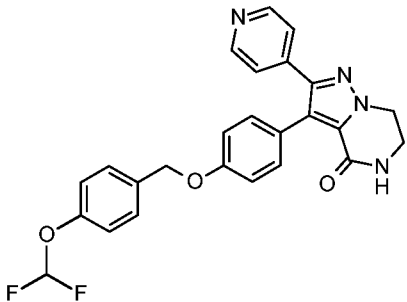
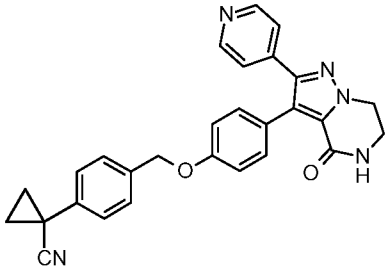
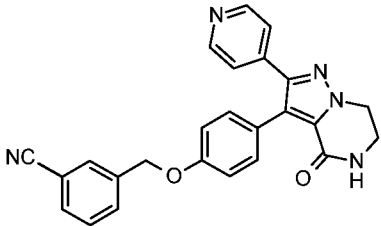
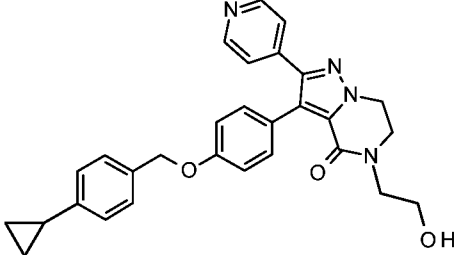
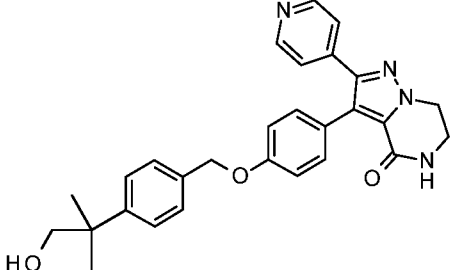
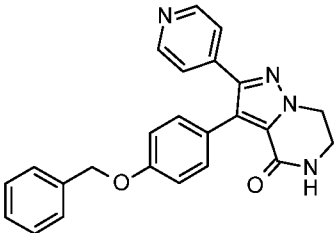
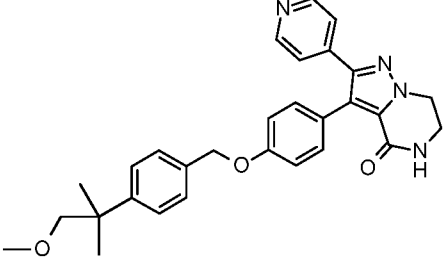
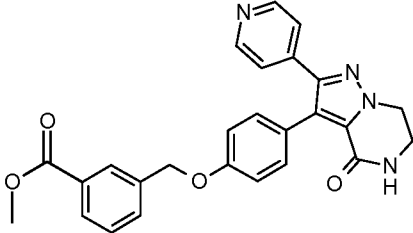
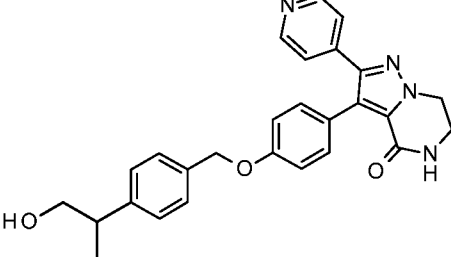
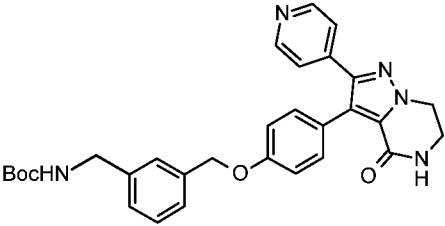
	
Compound 73; Method A75	Compound 78; Method A80
	
Compound 74; Method A76	Compound 79; Method A81
	
Compound 75; Method A77	Compound 80; Method A82
	
Compound 81; Method A83	Compound 85; Method A87
	
Compound 82; Method A84	Compound 86; Method A87

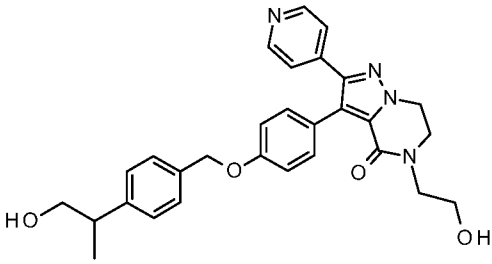
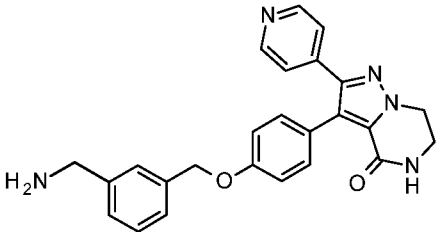
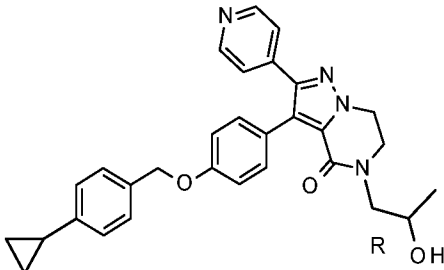
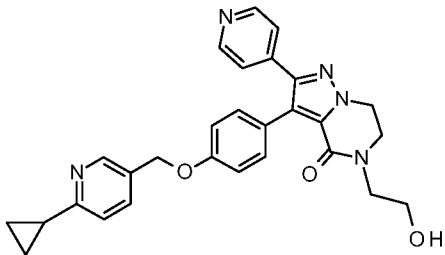
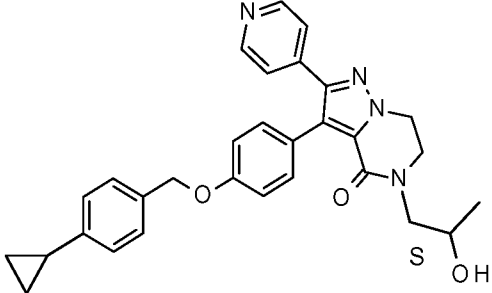
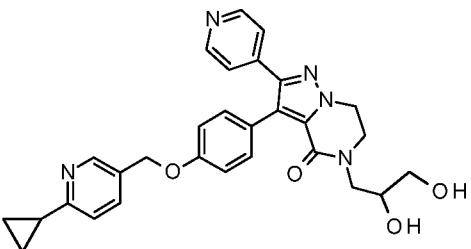
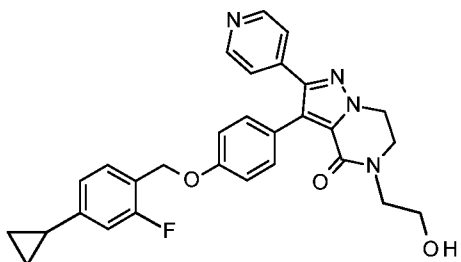
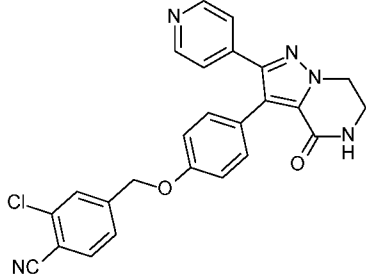
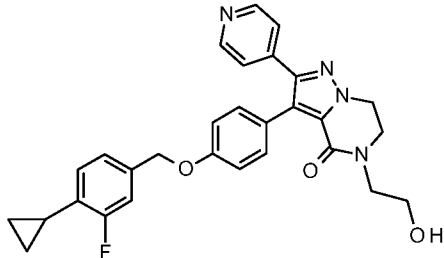
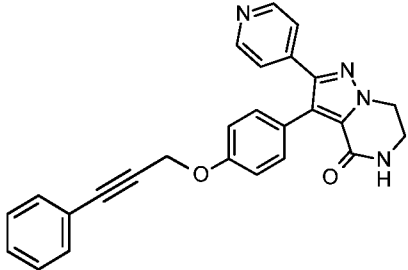
	
Compound 83; Method A85	Compound 87; Method A88
	
Compound 84; Method A86	Compound 88; Method A89
	
Compound 89; Method A90	Compound 93; Method A94
	
Compound 90; Method A91	Compound 94; Method A95

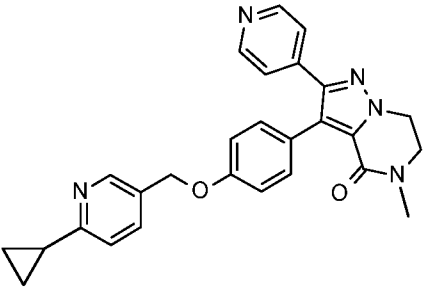
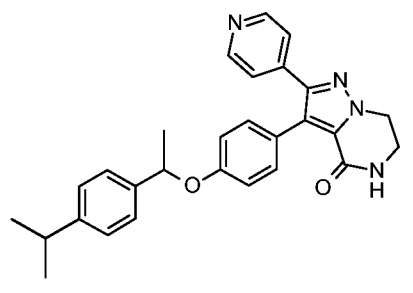
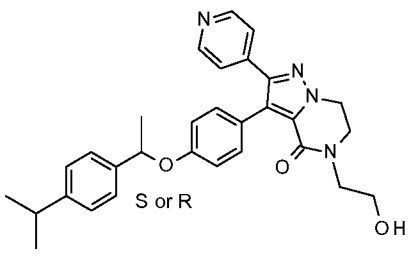
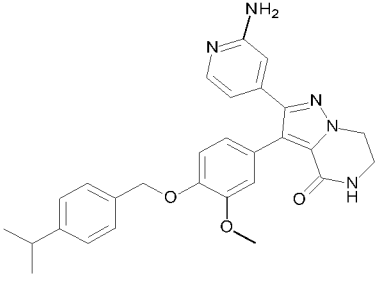
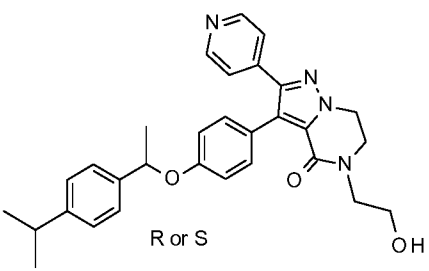
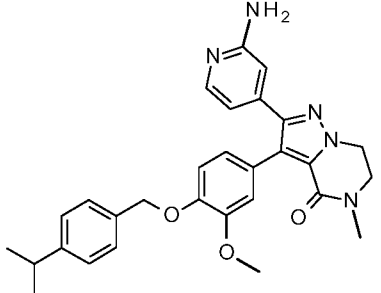
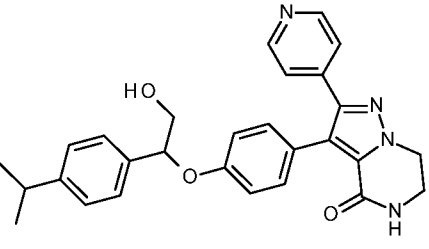
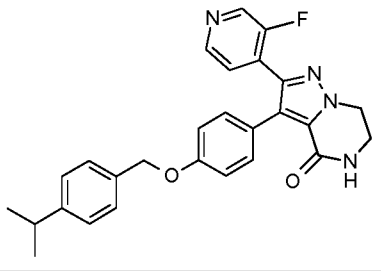
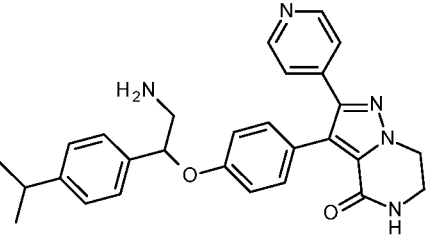
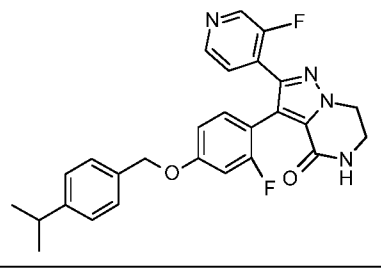
	
Compound 91; Method A92	Compound 95; Method A96
	
Compound 92; Method A93	Compound 96; Method A97
	
Compound 97; Method A98	Compound 102; Method A103
	
Compound 98; Method A99	Compound 103; Method A104
	
Compound 99; Method A100	Compound 104; Method A105

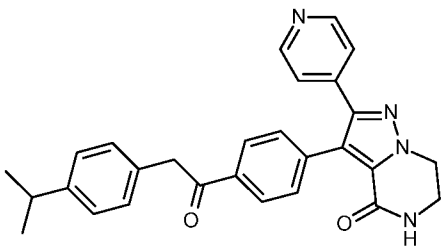
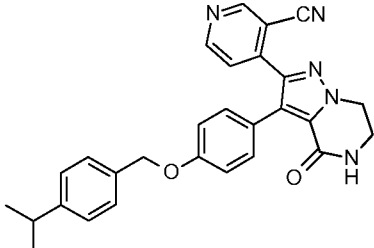
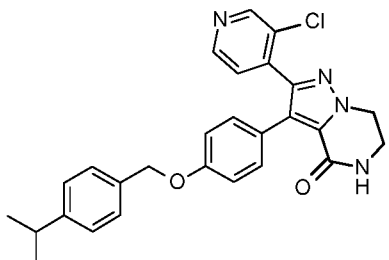
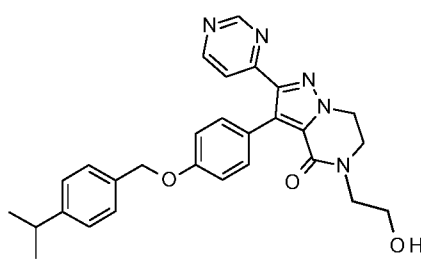
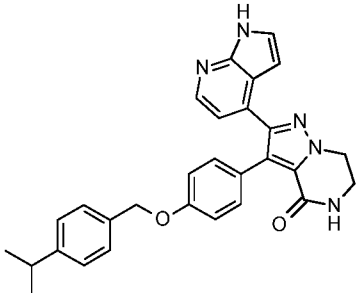
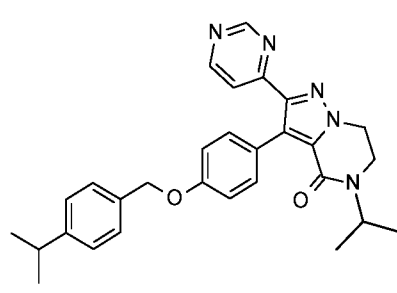
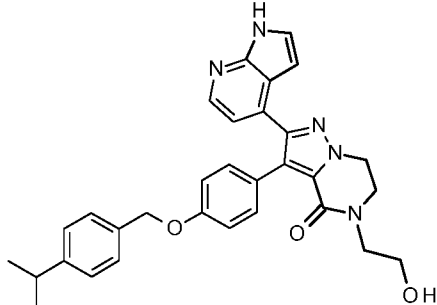
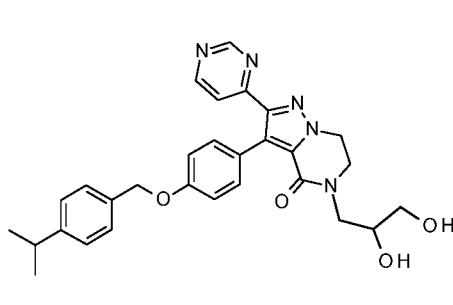
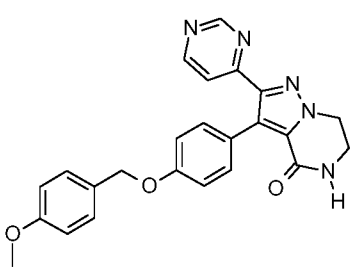
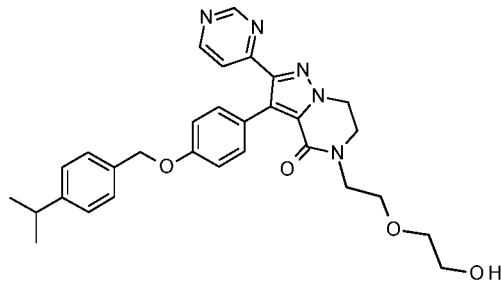
	
Compound 100; Method A101	Compound 105; Method A106
	
Compound 101; Method A102	Compound 110; Method A111
	
Compound 106; Method A107	Compound 111; Method A112
	
Compound 107; Method A108	Compound 112; Method A113
	
Compound 108; Method A109	Compound 113; Method A114

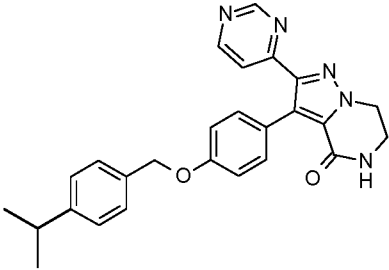
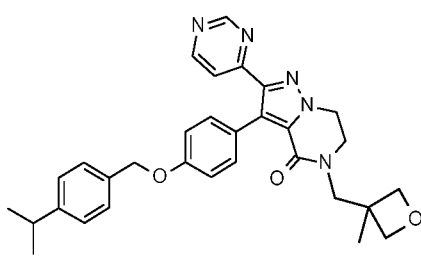
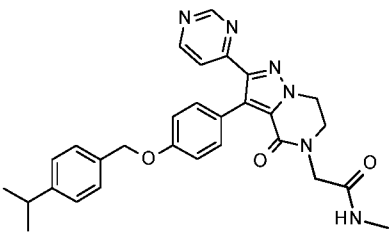
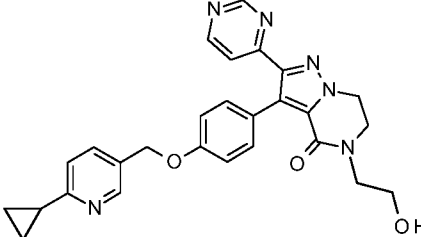
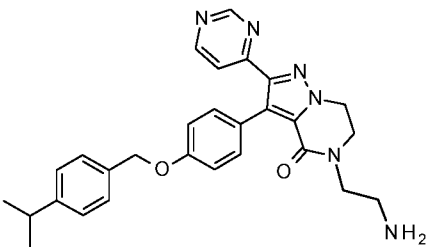
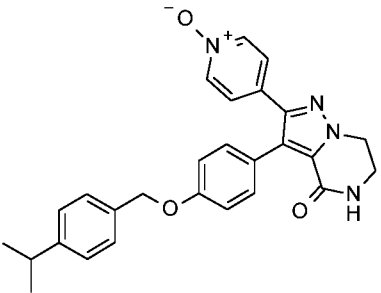
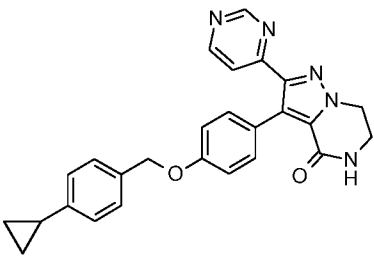
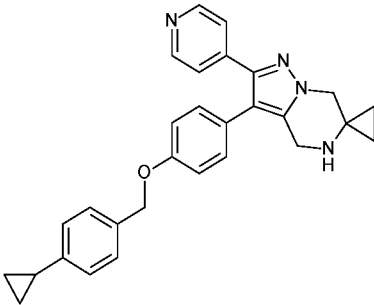
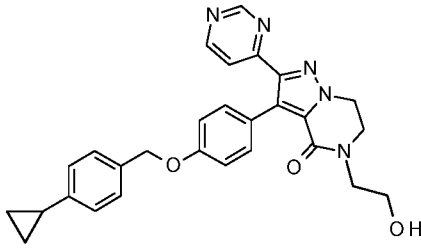
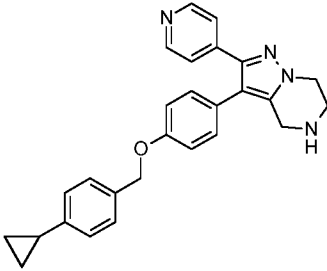
	
Compound 109; Method A110	Compound 114; Method A115
	
Compound 9a; Method A14	Compound 119; Method A120
	
Compound 115; Method A116	Compound 120; Method A121
	
Compound 116; Method A117	Compound 121; Method A122
	
Compound 117; Method A118	Compound 122; Method A123

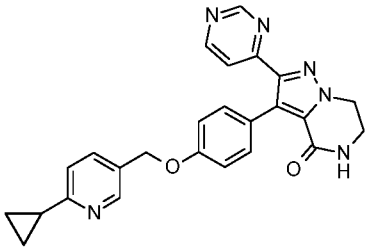
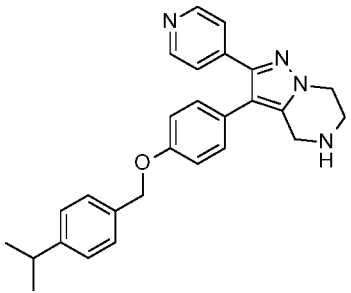
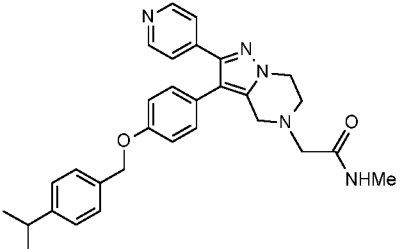
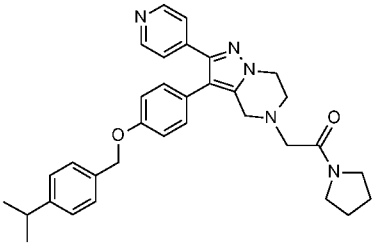
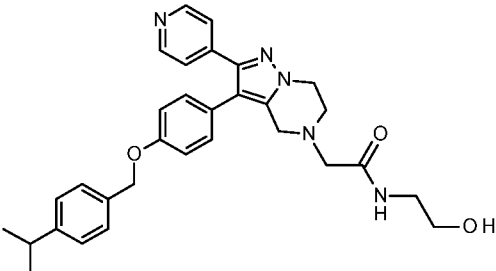
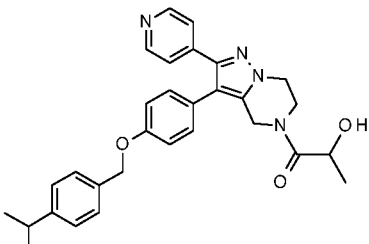
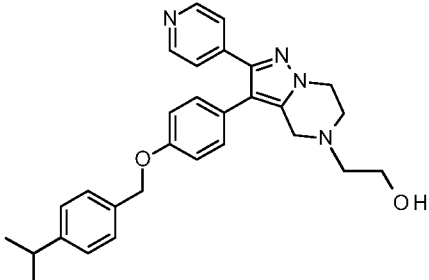
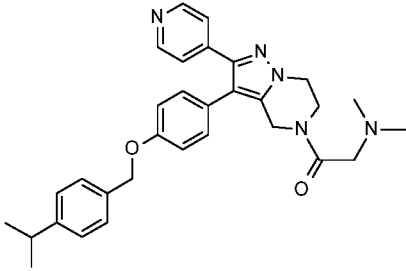
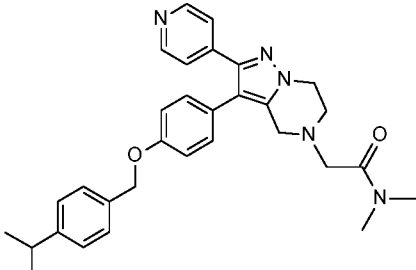
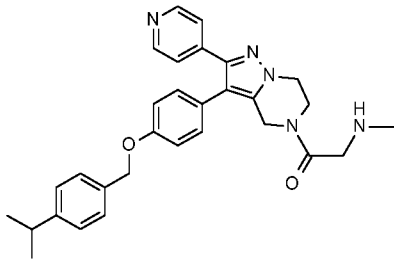
	
Compound 118; Method A119	Compound 123; Method A124
	
Compound 124; Method A125	Compound 129 ; Method A130
	
Compound 125; Method A126	Compound 130; Method A131
	
Compound 126; Method A127	Compound 131; Method A132
	
Compound 127; Method A128	Compound 132; Method A133

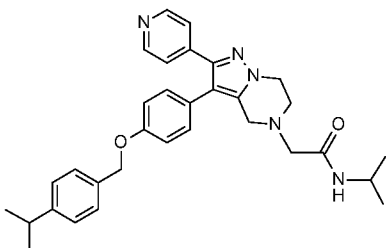
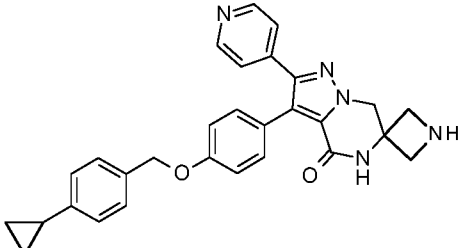
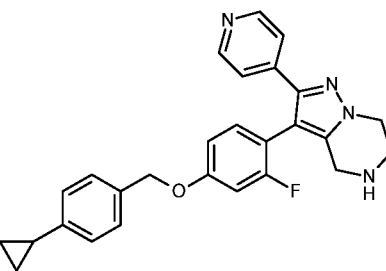
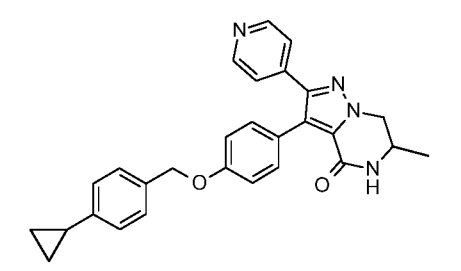
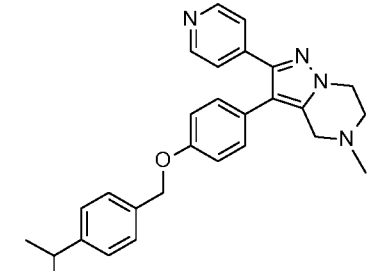
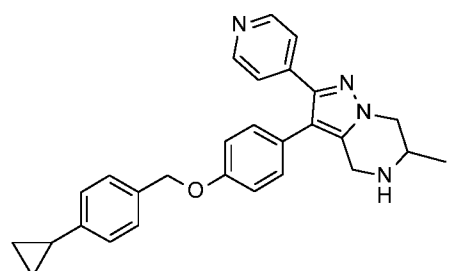
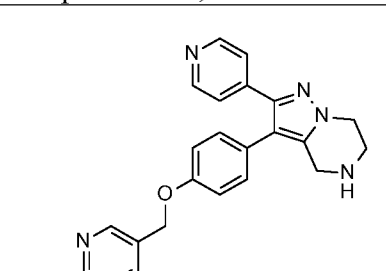
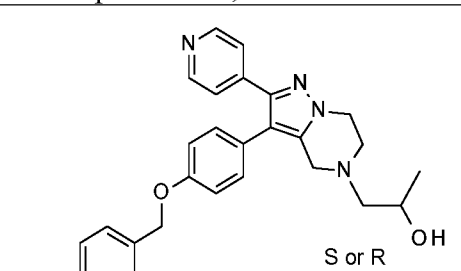
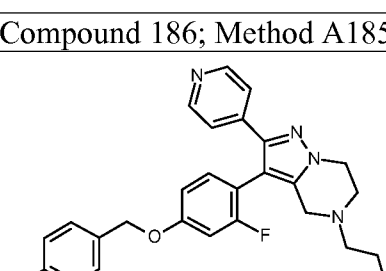
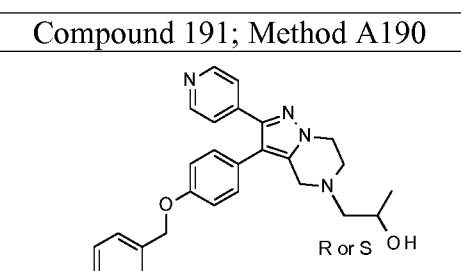
	
Compound 128; Method A129	Compound 133; Method A133
	
Compound 134; Method A134	Compound 139; Method A139
	
Compound 135; Method A135	Compound 140; Method A140
	
Compound 136; Method A136	Compound 141; Method A141
	
Compound 137; Method A137	Compound 142; Method A142

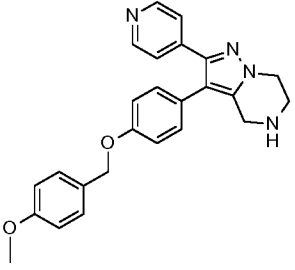
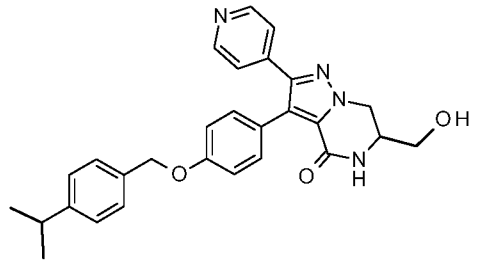
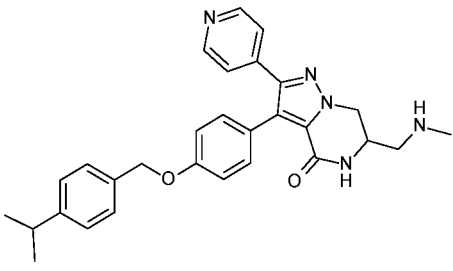
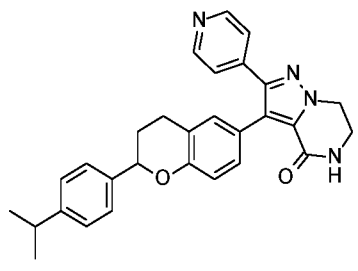
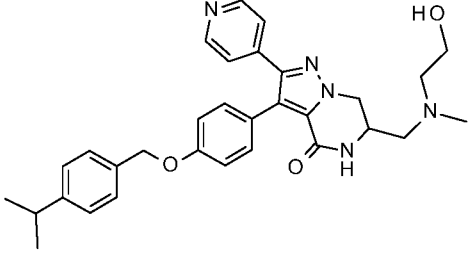
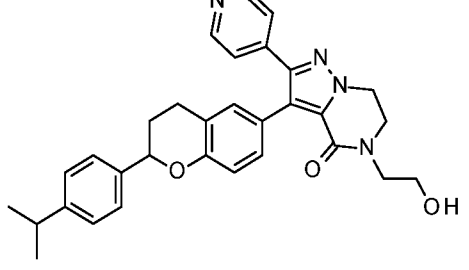
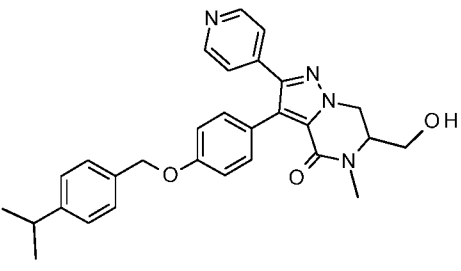
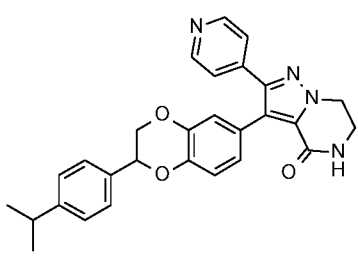
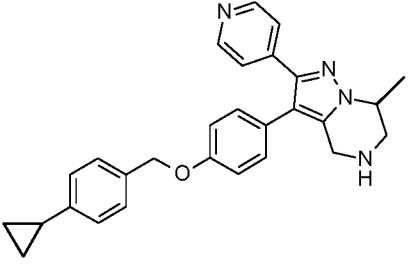
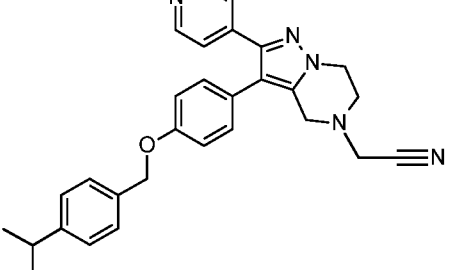
	
Compound 138; Method A138	Compound 143; Method A143
	
Compound 144; Method A144	Compound 149; Method A148
	
Compound 145; Method A144	Compound 150; Method A149
	
Compound 146; Method A145	Compound 151; Method A150
	
Compound 147; Method A146	Compound 152; Method A151

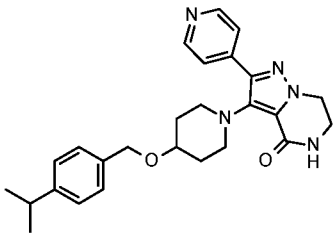
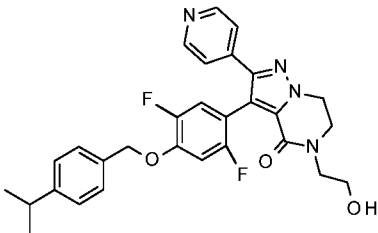
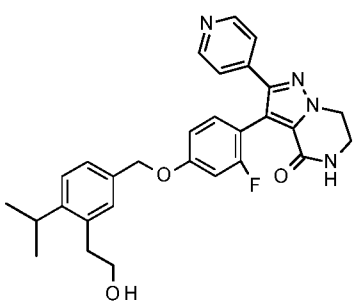
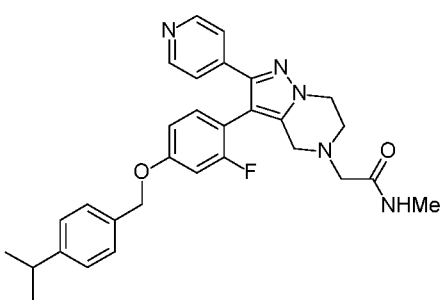
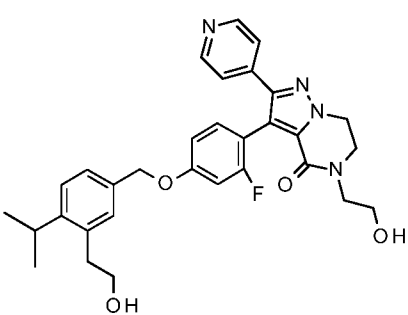
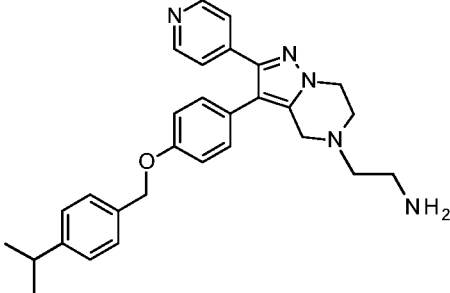
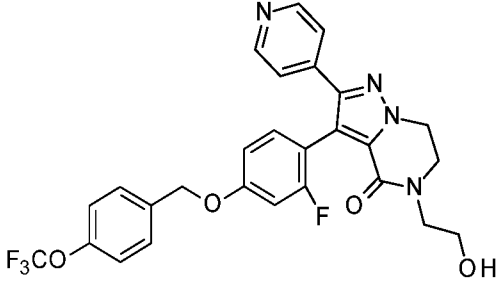
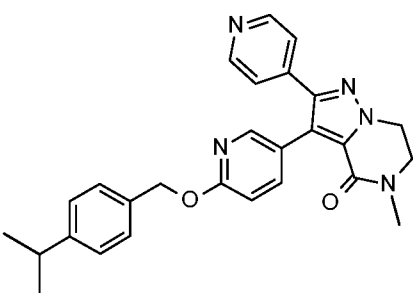
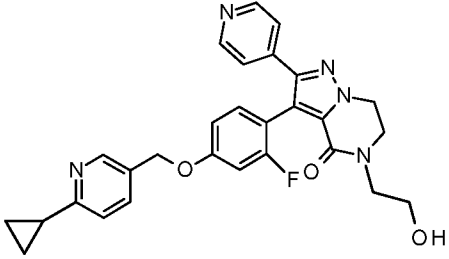
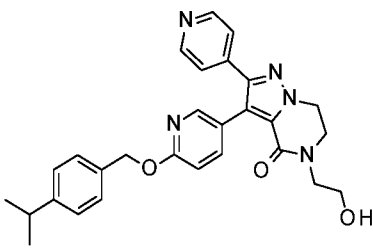
	
Compound 148; Method A147	Compound 153; Method A152
	
Compound 154; Method A153	Compound 159; Method A158
	
Compound 155; Method A154	Compound 160; Method A159
	
Compound 156; Method A155	Compound 161; Method A160
	
Compound 157; Method A156	Compound 162; Method A161

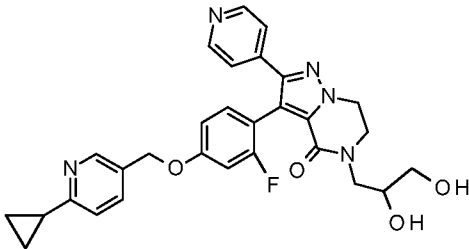
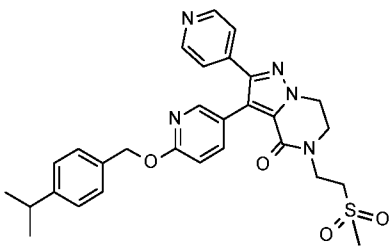
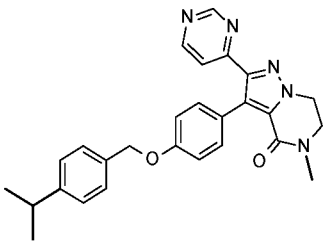
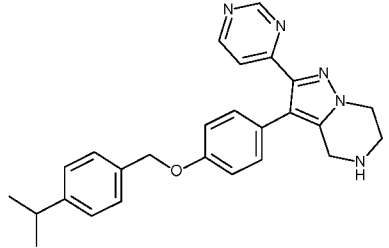
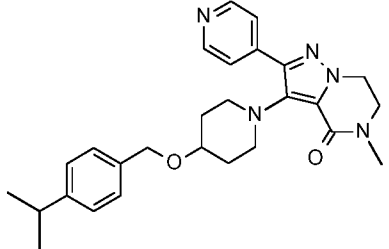
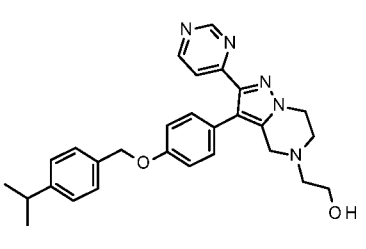
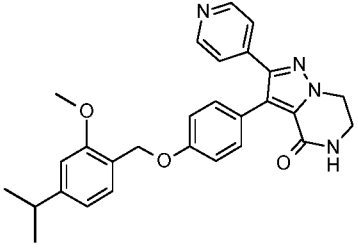
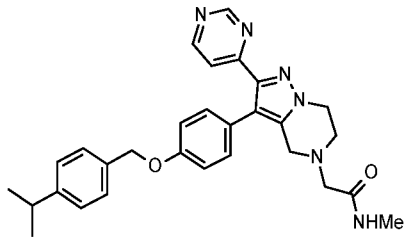
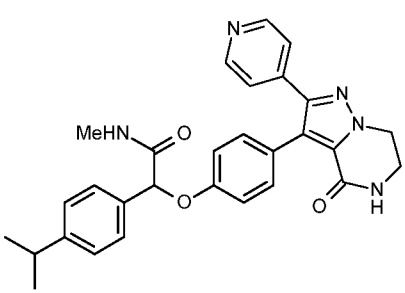
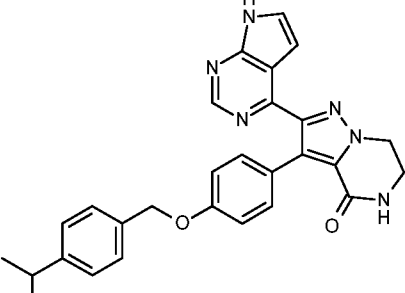
	
Compound 158; Method A157	Compound 163; Method A162
	
Compound 164; Method A163	Compound 169; Method A168
	
Compound 165; Method A164	Compound 170; Method A169
	
Compound 166; Method A165	Compound 171; Method A170
	
Compound 167; Method A166	Compound 172; Method A171

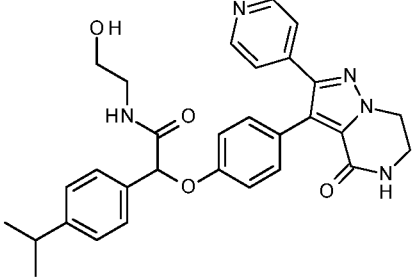
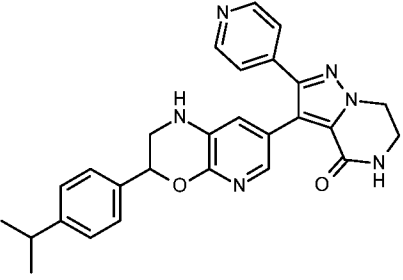
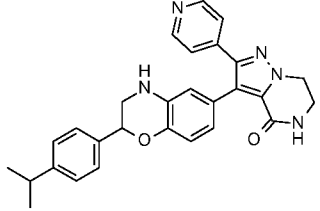
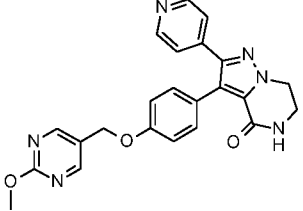
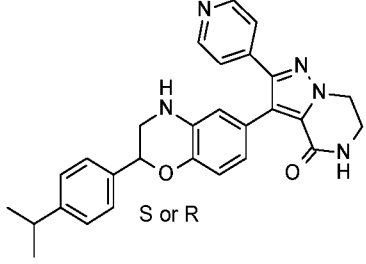
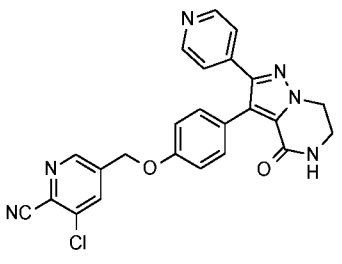
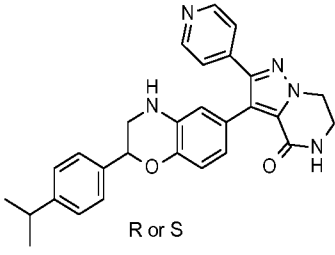
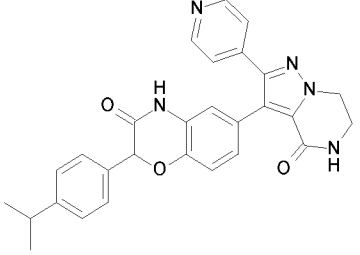
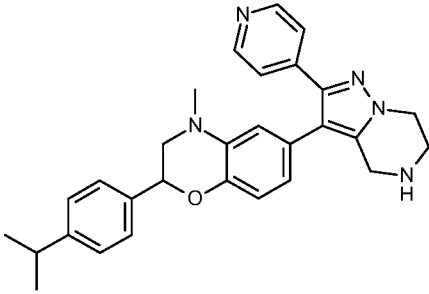
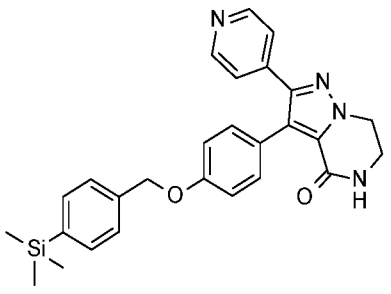
	
Compound 168; Method A167	Compound 173; Method A172
	
Compound 174; Method A173	Compound 179; Method A178
	
Compound 175; Method A174	Compound 180; Method A179
	
Compound 176; Method A175	Compound 181; Method A180
	
Compound 177; Method A176	Compound 182; Method A181

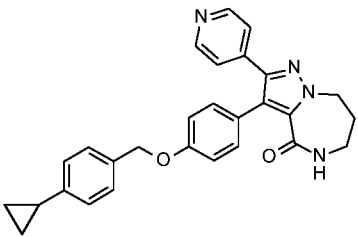
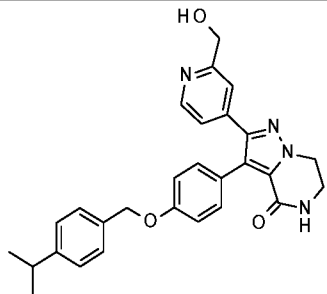
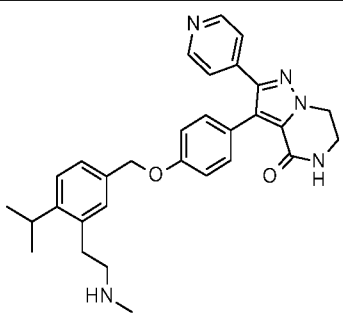
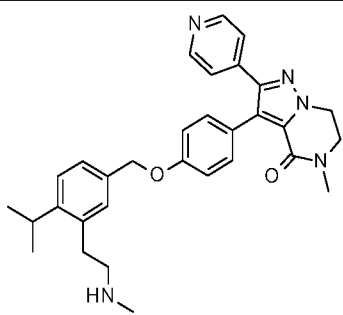
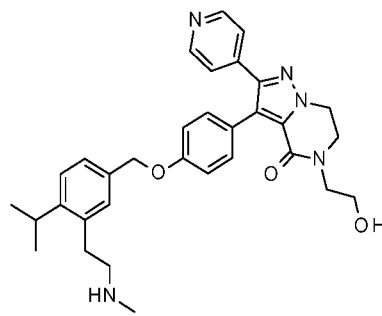
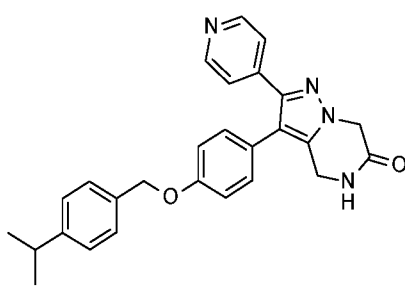
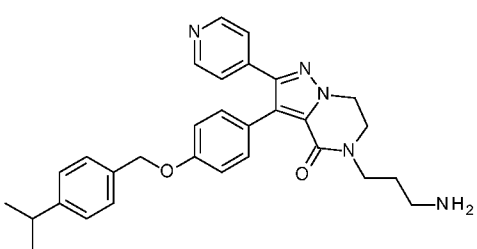
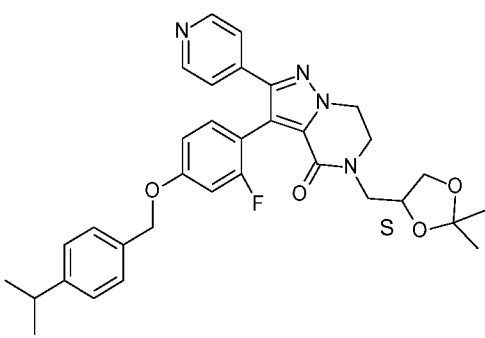
	
Compound 178; Method A177	Compound 183; Method A182
	
Compound 184; Method A183	Compound 189; Method A188
	
Compound 185; Method A184	Compound 190; Method A189
	
Compound 186; Method A185	Compound 191; Method A190
	
Compound 187; Method A186	Compound 192; Method A190

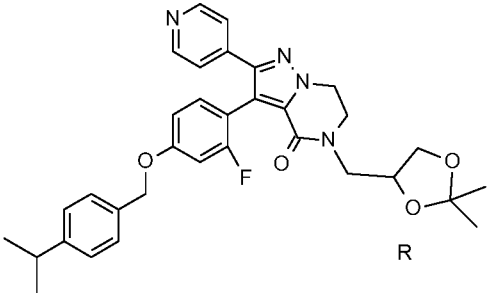
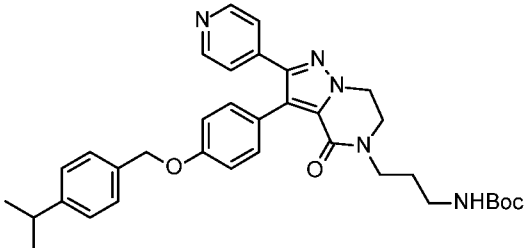
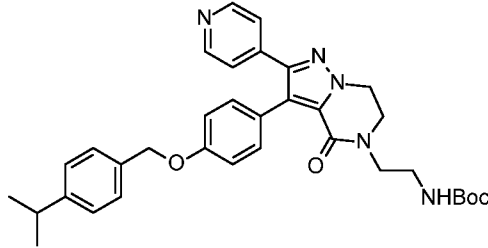
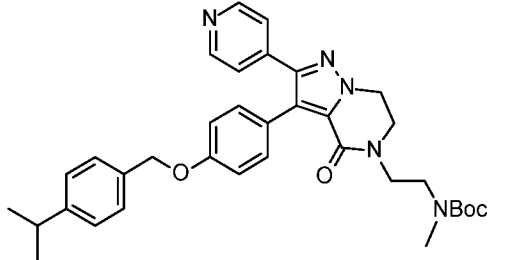
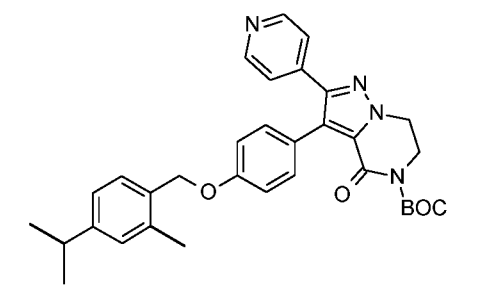
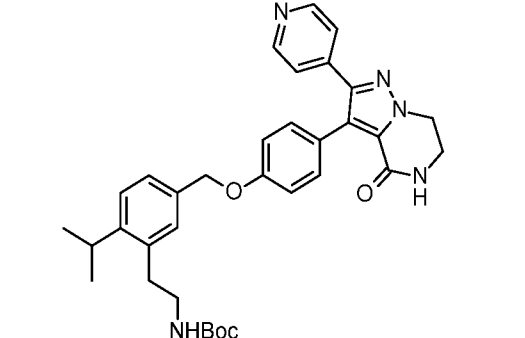
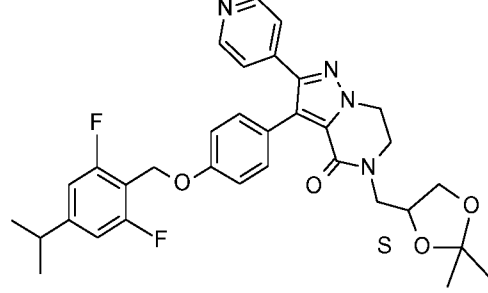
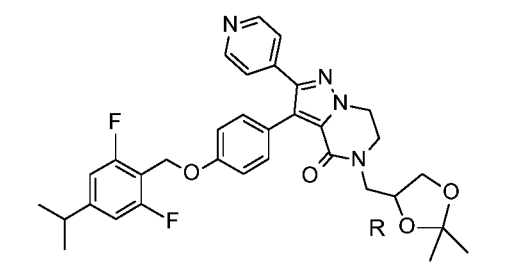
	
Compound 188; Method A187	Compound 193; Method A191
	
Compound 194; Method A192	Compound 199; Method A197
	
Compound 195; Method A193	Compound 200; Method A198
	
Compound 196; Method A194	Compound 201; Method A199
	
Compound 197; Method A195	Compound 210a; Method A207

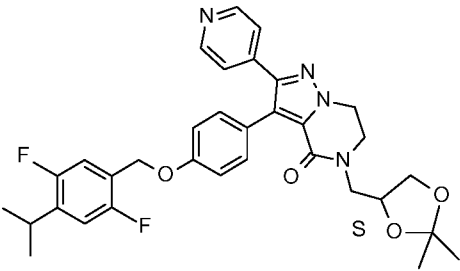
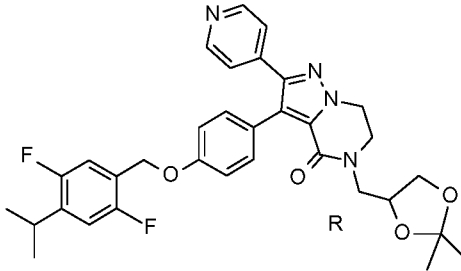
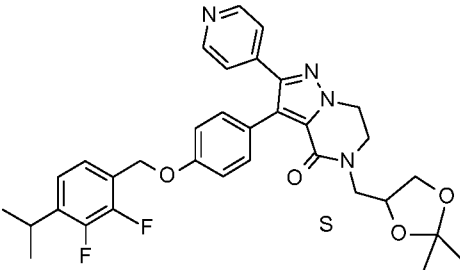
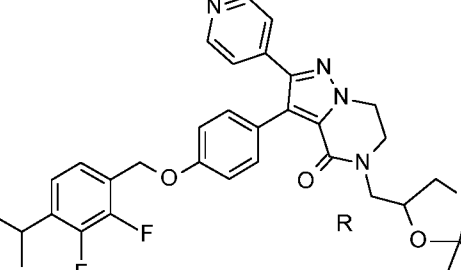
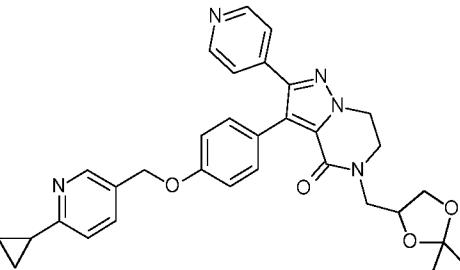
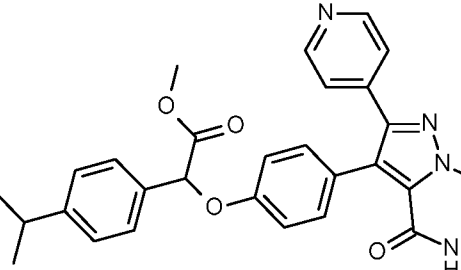
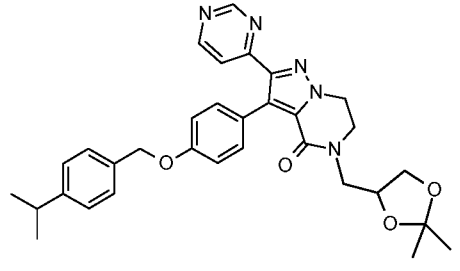
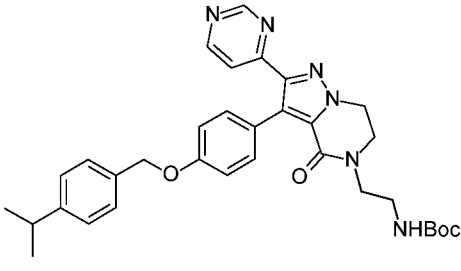
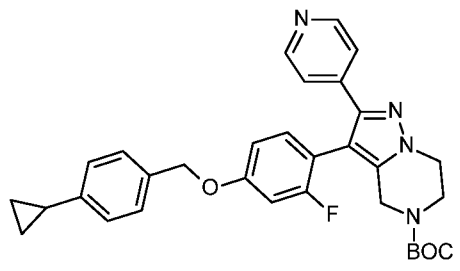
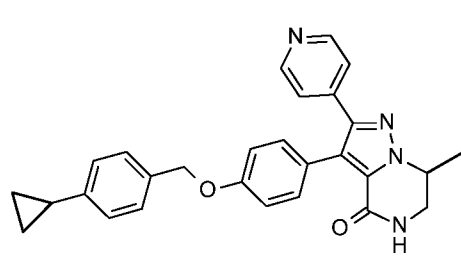
	
Compound 198; Method A196	Compound 203; Method A200
	
Compound 204; Method A201	Compound 209; Method A206
	 fumarate salt (0.79 eq. fumarate)
Compound 205; Method A202	Compound 210; Method A207
	
Compound 206; Method A203	Compound 211; Method A208
	
Compound 207; Method A204	Compound 212; Method A209

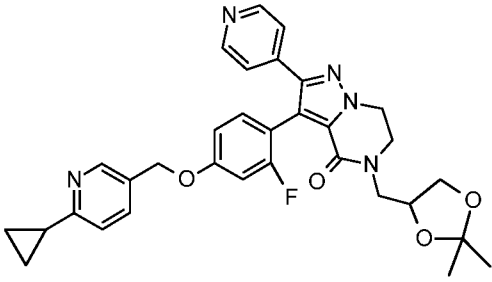
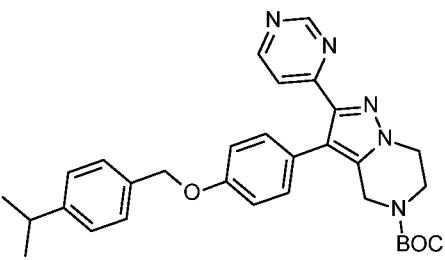
	
Compound 208; Method A205	Compound 213; Method A210
	
Compound 214; Method A211	Compound 219; Method A216
	
Compound 215; Method A212	Compound 220; Method A217
	
Compound 216; Method A213	Compound 221; Method A218
	
Compound 217; Method A214	Compound 222; Method A219

	
Compound 218; Method A215	Compound 223; Method A220
	
Compound 226; Method A221	Compound 229; Method A224
	
Compound 224; Method A221	Compound 230; Method A225
	
Compound 225; Method A221	Compound 231; Method A226
	
Compound 227; Method A222	Compound 232; Method A227

	
Compound 228; Method A223	Compound 233; Method A228
	
Compound 234; Method A229	Compound 236; Method A231
	
Compound 235; Method A230	Compound 237; Method A232
 HCl salt (.2 HCl .1.78 H ₂ O)	
Compound 59a; Method A61	Compound 22a; Method A27

	
Compound 23a; Method A28	Compound 58a; Method A61
	
Compound 238; Method A62	Compound 60a; Method A63
	
Compound 78a; Method A80	Compound 88a; Method A89
	
Compound 95a; Method A96	Compound 96a; Method A97

	
Compound 98a; Method A99	Compound 99a; Method A100
	
Compound 101a; Method A102	Compound 102a; Method A103
	
Compound 140a; Method A140	Compound 146a; Method A145
	
Compound 161a; Method A160	Compound 165a; Method A164
	
Compound 184a; Method A183	Compound 197a; Method A195

	
Compound 208a; Method A205	Compound 219a; Method A216

Analytical Part

LCMS (Liquid Chromatography/Mass spectrometry)

LCMS General procedure

- 5 The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

- Flow from the column was brought to the Mass Spectrometer (MS) which was
 10 configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.
- Compounds are described by their experimental retention times (R_t) and ions. If not
 15 specified differently in the table of data, the reported molecular ion corresponds to the $[M+H]^+$ (protonated molecule) and/or $[M-H]^-$ (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. $[M+NH_4]^+$, $[M+HCOO]^-$, etc...). For molecules with multiple isotopic patterns (Br, Cl...), the reported value is the one obtained for the lowest isotope mass. All results were obtained
 20 with experimental uncertainties that are commonly associated with the method used.

Hereinafter, "SQD" means Single Quadrupole Detector, "RT" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, "HSS" High Strength Silica, "DAD" Diode Array Detector.

25

Table 2: LCMS Method codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes).

LCMS Method	Instrument	Column	Mobile phase	gradient	Flow Column T	Run time
(1)	Waters: Acquity UPLC [®] - DAD and Quattro Micro [™]	Waters: BEH C18 (1.7μm, 2.1x100mm)	A: 95% CH ₃ COONH ₄ 7mM / 5% CH ₃ CN, B: CH ₃ CN	84.2% A for 0.49min, to 10.5% A in 2.18min, held for 1.94min, back to 84.2% A in 0.73min, held for 0.73min.	0.343 ----- 40	6.2
(2)	Waters: Acquity UPLC [®] H-Class – DAD and SQD 2	Waters: BEH C18 (1.7μm, 2.1x100mm)	A: 95% CH ₃ COONH ₄ 7mM / 5% CH ₃ CN, B: CH ₃ CN	84.2% A for 0.49min, to 10.5% A in 1.81min, held for 2.31min, back to 84.2% A in 0.73min, held for 0.73min.	0.343 ----- 40	6.1
(3)	Agilent: 1100/1200 - DAD and MSD	Agilent: Eclipse [®] C18 (5μm, 4.6x150mm)	A: CF ₃ COOH 0.1% in water, B: CH ₃ CN	98% A for 3min, to 100% B in 12min, held for 5min, back to 98% A in 2min, held for 6min.	1 ----- RT	28
(4)	Waters: Acquity UPLC [®] H-Class - DAD and SQD 2	Macherey Nagel: Nucleoshell [®] RP18 (2.7μm, 3x50mm)	A: 95% CH ₃ COONH ₄ 7mM / 5% CH ₃ CN, B: CH ₃ CN	95% A for 0.25min, to 5% A in 0.75min, held for 1.9min, back to 95% A in 0.3min, held for 0.3min.	0.6 ----- 40	3.5
(5)	Waters: Alliance [®] - DAD and ZQ [™]	Waters: XBridge [™] C18 (3.5μm, 4.6x100mm)	A: CH ₃ COONH ₄ 7mM, B: CH ₃ CN	80% A for 0.5min, to 10% A in 4.5min, held for 4min, back to 80% A in 1.5min, held for 1.5min.	0.8 ----- 30	12
(6)	Waters: Acquity UPLC [®] H-Class - DAD and SQD 2	Thermo Scientific [™] : Accucore [®] RP MSC18 (2.6μm, 3x50mm)	A: 95% CH ₃ COONH ₄ 7mM / 5% CH ₃ CN, B: CH ₃ CN	95% A for 0.25min, to 5% A in 0.75min, held for 1.9min, back to 95% A in 0.3min, held for 0.3min.	0.6 ----- 40	3.5

Melting Points

For a number of compounds, melting points (m.p.) were determined with a DSC 1 STAR[®] 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.

- 5 The melting points for compounds 1, 151, 158, 172, 203 and 204 are reported in the experimental part ('exp').

The results of the analytical measurements are shown in table 3.

Table 3: Retention time (R_t) in min., $[M+H]^+$ peak (protonated molecule), LCMS method and m.p. (melting point in °C) (n.d. means not determined).

5

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
1	3.01	439	1	exp
2	2.96	483	1	181
3	2.43	438	1	276
4	2.87	437	1	262
5	3.04	463	1	239
6	3.04	457	1	271
7	2.83	454	1	267
8	2.89	470	1	135
9	2.34	455	1	290
10	2.63	464	1	280
11	2.56	483	1	195
12	2.73	440	1	84
13	2.8	455	1	n.d.
14	3.03	475	1	226/ 231
15	3.11	475	1	n.d.
16	3.04	475	1	214
17	3.1	475	1	235
18	3.02	457	1	241
19	2.96	501	1	172
20	2.98	519	1	138
21	2.97	501	1	141
22	2.84	531	1	188
23	2.84	531	1	192
24	3.13	473	1	267
25	3.13	473	1	251
26	2.91	464	1	235
27	2.94	464	1	268
28	2.89	508	1	185
29	3.21	467	1	260
30	3.14	511	1	170
31	3.1	497	1	n.d.
32	2.93	469	1	187
33	3.1	483	1	151

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
34	3	469	1	276
35	2.91	499	1	192
36	2.85	543	1	176
37	3.18	497	1	206
38	3.05	497	1	144
39	3.05	497	1	144
40	3.44	553	1	113
41	2.82	513	1	191
42	3.44	553	1	114
43	2.82	513	1	190
44	2.85	513	1	192
45	3.29	555	1	148
46	3.59	497	2	177
47	3.09	497	1	177
48	3.22	453	1	155
49	3.47	481	1	168
50	3.32	497	1	167
51	3.18	511	1	211
52	3.08	545	1	219
53	2.98	527	1	121
54	3.23	523	1	204
55	3.4	523	1	165
56	2.93	538	1	n.d.
57	3.18	492	1	158
58	2.69	496	1	n.d.
59	3.28	482	2	n.d.
60	2.78	496	1	n.d.
61	3	510	1	n.d.
62	3.36	564	1	n.d.
63	2.95	510	1	161
64	3.06	524	1	199
65	3.12	538	1	159
66	2.97	497	2	n.d.
67	2.94	487	1	179

Co. No.	R _t	[M+H] ⁺	LCMS Method	m.p. (°C)
68	3.18	603	1	90
69	3.34	539	1	n.d.
70	3.64	539	1	147
71	2.95	440	1	199
72	2.62	470	1	231
73	2.97	458	1	207
74	2.98	458	1	275
75	2.7	441	1	126
76	2.81	441	1	225
77	3.08	456	1	n.d.
78	3.13	453	1	247
79	2.62	499	1	236
80	3.1	469	1	232
81	2.4	484	1	93
82	2.72	497	1	n.d.
83	2.51	527	1	176
84	3.02	497	1	208
85	2.81	464	1	240
86	2.15	468	1	n.d.
87	2.75	508	1	160
88	2.83	482	2	181
89	2.65	499	1	n.d.
90	3.03	513	1	209
91	2.37	513	1	199/ 220
92	2.96	501	1	132
93	2.99	501	1	183
94	2.95	519	1	194
95	2.81	549	1	227
96	2.82	549	1	228
97	3.02	519	1	147
98	2.88	549	1	184
99	2.88	549	1	183
100	3.01	519	1	172
101	2.87	549	1	192
102	2.88	549	1	191
103	2.32	441	1	235
104	2.7	485	1	190
105	2.74	411	1	259

Co. No.	R _t	[M+H] ⁺	LCMS Method	m.p. (°C)
106	3.18	453	1	229
107	3.12	497	1	163
108	3.21	453	1	233
109	3.15	497	1	155
110	3.01	439	1	268
111	2.85	465	1	165
112	2.55	427	1	260
113	2.56	427	1	242
114	2.84	455	1	252
115	2.25	499	1	193
116	2.91	481	1	260
117	2.81	525	1	134
118	2.67	463	1	250
119	2.85	465	1	280
120	9.52	465	3	293
121	2.04	468	1	233
122	2.59	508	1	199
123	2.53	462	1	260
124	2.43	422	1	238
125	2.43	469	1	280
126	2.91	483	1	212
127	2.19	455	1	259
128	2.24	499	1	n.d.
129	2.78	481	1	194
130	2.57	397	1	260
131	2.54	455	1	222
132	2.71	526	1	186/ 194
133	1.83	426	1	154/ 238
134	2.89	495	1	196
135	2.89	495	1	197
136	2.81	499	1	183
137	2.84	499	1	185
138	2.59	452	1	175
139	2.34	482	1	97
140	2.24	512	1	n.d.
141	2.57	456	1	257
142	2.69	421	1	245

Co. No.	R _t	[M+H] ⁺	LCMS Method	m.p. (°C)
143	3.11	453	1	217
144	3.03	497	1	148
145	3.03	497	1	148/ 162
146	2.54	469	1	228/ 238
147	2.23	468	1	178
148	2.86	451	1	259
149	2.74	484	1	179
150	2.91	498	1	n.d.
151	3.09	457	1	exp
152	3.14	475	1	262
153	3.09	464	1	225
154	3.2	473	1	207
155	2.89	478	1	266
156	2.84	522	1	219
157	2.46	428	1	264
158	2.95	440	1	exp
159	2.87	484	1	160
160	3.35	482	1	166
161	2.74	514	1	209
162	2.84	528	1	n.d.
163	3.14	524	1	164/ 180
164	2.84	511	1	97/157
165	2.63	483	1	154
166	2.79	438	1	268
167	2.71	482	1	170
168	2.28	439	1	254
169	2.24	483	1	143
170	2.61	455	1	227
171	3.19	449	1	152
172	2.93	423	1	exp
173	3.1	425	1	194
174	3.05	496	1	185
175	2.85	526	1	189
176	3.6	469	2	150
177	3.14	510	1	95
178	3.26	524	1	188

Co. No.	R _t	[M+H] ⁺	LCMS Method	m.p. (°C)
179	3.29	536	1	n.d.
180	3.09	497	1	n.d.
181	3.14	510	1	n.d.
182	2.8	496	1	n.d.
183	2.66	478	1	173
184	2.92	441	1	195/ 339
185	3.47	439	1	120
186	2.43	424	1	195
187	3.61	487	2	n.d.
188	2.58	413	1	192/ 342
189	2.98	451	1	249
190	3.06	437	1	166/ 177
191	3.28	483	1	148
192	3.28	483	1	151
193	2.91	469	1	254
194	2.86	482	1	230
195	2.99	526	1	193
196	2.99	483	1	n.d.
197	3.09	437	1	153
198	3.09	446	1	n.d.
199	3.12	465	1	262
200	3.06	509	1	118/ 203
201	3	467	1	290
203	2.97	519	1	exp
204	2.59	501	1	exp
205	2.54	545	1	151
206	2.83	543	1	140
207	2.37	500	1	n.d.
208	2.27	530	1	116/ 126
209	3.03	514	1	175/ 159
210	2.76	468	1	197
210a	8.30	464	5	n.d.
211	3.12	454	1	57
212	2.85	484	1	138/

Co. No.	R _t	[M+H] ⁺	LCMS Method	m.p. (°C)
				161
213	2.95	546	1	200
214	3.11	454	1	160
215	3.38	460	1	140
216	3.01	469	1	200
217	2.47	496	1	n.d.
218	2.36	526	1	n.d.
219	3.02	426	1	150
220	3.01	470	1	n.d.
221	2.98	497	1	n.d.
222	2.78	479	1	238
223	2.55	467	1	n.d.
224	2.91	466	1	n.d.
225	2.91	466	1	n.d.
226	2.87	466	1	252
227	3.1	480	1	291
228	2.91	451	1	235
229	2.07	429	1	248
230	2.48	457	1	277
231	2.58	480	1	291
232	3.25	469	1	n.d.
233	2.77	469	1	232
234	2.23	496	1	166/ 200
235	2.21	540	1	n.d.

Co. No.	R _t	[M+H] ⁺	LCMS Method	m.p. (°C)
236	2.36	510	1	n.d.
237	3.01	439	1	281
238	n.d.	n.d.	n.d.	n.d.
9a	2.54	455	1	254
22a	n.d.	n.d.	n.d.	n.d.
23a	n.d.	n.d.	n.d.	n.d.
58a	1.91	596	4	n.d.
59a	3.28	482	2	n.d.
60a	n.d.	n.d.	n.d.	n.d.
78a	1.95	553	6	n.d.
88a	1.74	582	4	n.d.
95a	n.d.	n.d.	n.d.	n.d.
96a	n.d.	n.d.	n.d.	n.d.
98a	1.92	589	4	n.d.
99a	1.92	589	4	n.d.
101a	1.92	589	4	n.d.
102a	1.91	589	4	n.d.
140a	n.d.	n.d.	n.d.	n.d.
146a	2.86	497	1	n.d.
161a	n.d.	n.d.	n.d.	n.d.
165a	1.8	583	4	n.d.
184a	n.d.	n.d.	n.d.	n.d.
197a	6.38	451	5	n.d.
208a	n.d.	n.d.	n.d.	n.d.
219a	1.93	526	6	n.d.

NMR

NMR experiment was carried out using a Bruker Avance 500 spectrometer equipped with a reverse triple-resonance (¹H, ¹³C, ¹⁵N TXI) probe head with z gradients and operating at 500 MHz for the proton and 125 MHz for carbon, or using using a Bruker 500 spectrometer equipped with a reverse resonance (¹H, ¹³C, SEI) probe head with z gradients and operating at 400 MHz for the proton.

Table 4: ¹H NMR results

Co. No.	¹ H NMR result
1	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.0 Hz, 2H), 8.22 (br. s., 1H), 7.39 (d, <i>J</i> = 8.5 Hz, 2H), 7.23 - 7.31 (m, 4H), 7.19 (d, <i>J</i> = 8.5 Hz, 2H), 6.99 (d, <i>J</i> = 8.5 Hz, 2H), 5.07 (s, 2H), 4.43 (t, <i>J</i> = 6.0 Hz, 2H), 3.61 - 3.70 (m, 2H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
2	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 5.7 Hz, 2H), 7.39 (d, <i>J</i> = 8.5 Hz, 2H), 7.22 - 7.31 (m, 4H), 7.18 (d, <i>J</i> = 8.5 Hz, 2H), 6.99 (d, <i>J</i> = 8.5 Hz, 2H), 5.07 (s, 2H), 4.80 (br. s., 1H), 4.48 (t, <i>J</i> = 5.8 Hz, 2H), 3.90 (t, <i>J</i> = 5.8 Hz, 2H), 3.51 - 3.59 (m, 2H), 3.44 - 3.52 (m, 2H), 2.90 (spt, <i>J</i> = 6.6 Hz, 1H), 1.21 (d, <i>J</i> = 6.6 Hz, 6H)
3	(400 MHz, DMSO-d ₆) δ ppm 8.50 (d, <i>J</i> = 2.0 Hz, 1H), 8.46 (d, <i>J</i> = 6.1 Hz, 2H), 8.22 (br. s., 1H), 7.74 (dd, <i>J</i> = 2.0, 7.8 Hz, 1H), 7.33 (d, <i>J</i> = 7.8 Hz, 1H), 7.25 (d, <i>J</i> = 6.1 Hz, 2H), 7.20 (d, <i>J</i> = 8.6 Hz, 2H), 7.00 (d, <i>J</i> = 8.6 Hz, 2H), 5.09 (s, 2H), 4.43 (t, <i>J</i> = 6.1 Hz, 2H), 3.61 - 3.69 (m, 2H), 2.07 - 2.17 (m, 1H), 0.89 - 1.00 (m, 4H)
4	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.0 Hz, 2H), 8.23 (br. s., 1H), 7.34 (d, <i>J</i> = 7.9 Hz, 2H), 7.25 (d, <i>J</i> = 6.0 Hz, 2H), 7.18 (d, <i>J</i> = 8.5 Hz, 2H), 7.10 (d, <i>J</i> = 8.5 Hz, 2H), 6.98 (d, <i>J</i> = 7.9 Hz, 2H), 5.05 (s, 2H), 4.43 (t, <i>J</i> = 6.0 Hz, 2H), 3.62 - 3.68 (m, 2H), 1.89 - 1.97 (m, 1H), 0.92 - 0.98 (m, 2H), 0.65 - 0.70 (m, 2H)
5	(400 MHz, DMSO-d ₆) δ ppm 8.37 - 8.55 (m, 3H), 7.35 (d, <i>J</i> = 8.1 Hz, 2H), 7.26 (d, <i>J</i> = 5.6 Hz, 2H), 7.21 (d, <i>J</i> = 8.6 Hz, 2H), 7.10 (d, <i>J</i> = 8.1 Hz, 2H), 6.98 (d, <i>J</i> = 8.6 Hz, 2H), 5.06 (s, 2H), 4.41 (s, 2H), 1.87 - 1.99 (m, 1H), 0.87 - 1.03 (m, 6H), 0.63 - 0.72 (m, 2H)
6	(500 MHz, DMSO-d ₆) δ ppm 8.49 (d, <i>J</i> = 6.0 Hz, 2H), 8.28 (br. s., 1H), 7.40 (d, <i>J</i> = 7.9 Hz, 2H), 7.26 - 7.32 (m, 4H), 7.23 (t, <i>J</i> = 8.6 Hz, 1H), 6.95 (dd, <i>J</i> = 2.2, 11.7 Hz, 1H), 6.88 (dd, <i>J</i> = 2.2, 8.6 Hz, 1H), 5.10 (s, 2H), 4.45 (t, <i>J</i> = 6.0 Hz, 2H), 3.62 - 3.70 (m, 2H), 2.91 (spt, <i>J</i> = 6.8 Hz, 1H), 1.21 (d, <i>J</i> = 6.8 Hz, 6H)
7	(500 MHz, DMSO-d ₆) δ ppm 8.18 (br. s., 1H), 7.73 (d, <i>J</i> = 5.4 Hz, 1H), 7.39 (d, <i>J</i> = 7.9 Hz, 2H), 7.27 (d, <i>J</i> = 7.9 Hz, 2H), 7.17 (d, <i>J</i> = 8.5 Hz, 2H), 6.96 (d, <i>J</i> = 8.5 Hz, 2H), 6.57 (d, <i>J</i> = 1.4 Hz, 1H), 6.20 (dd, <i>J</i> = 1.4, 5.4 Hz, 1H), 5.87 (s, 2H), 5.06 (s, 2H), 4.38 (t, <i>J</i> = 6.2 Hz, 2H), 3.60 - 3.66 (m, 2H), 2.90 (spt, <i>J</i> = 6.8 Hz, 1H), 1.21 (d, <i>J</i> = 6.8 Hz, 6H)
10	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.3 Hz, 2H), 8.24 (br. s., 1H), 7.51 - 7.59 (m, 4H), 7.25 (d, <i>J</i> = 6.3 Hz, 2H), 7.20 (d, <i>J</i> = 8.5 Hz, 2H), 7.00 (d, <i>J</i> = 8.5 Hz, 2H), 5.14 (s, 2H), 4.43 (t, <i>J</i> = 6.0 Hz, 2H), 3.62 - 3.68 (m, 2H), 1.70 (s, 6H)
18	(500 MHz, DMSO-d ₆) δ ppm 8.48 (d, <i>J</i> = 6.0 Hz, 2H), 8.28 (br. s., 1H), 7.40 (d, <i>J</i> = 8.2 Hz, 2H), 7.29 (d, <i>J</i> = 8.2 Hz, 2H), 7.26 (d, <i>J</i> = 6.0 Hz, 2H), 7.22 (t, <i>J</i> = 8.8 Hz, 1H), 7.19 (dd, <i>J</i> = 1.7, 12.4 Hz, 1H), 6.96 (d, <i>J</i> = 8.8 Hz, 1H), 5.15 (s, 2H), 4.43 (t, <i>J</i> = 5.8 Hz, 2H), 3.63 - 3.68 (m, 2H), 2.91 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
19	(500 MHz, DMSO-d ₆) δ ppm 8.48 (d, <i>J</i> = 5.7 Hz, 2H), 7.40 (d, <i>J</i> = 7.9 Hz, 2H), 7.29 (d, <i>J</i> = 7.9 Hz, 2H), 7.26 (d, <i>J</i> = 5.7 Hz, 2H), 7.15 - 7.25 (m, 2H), 6.95 (d, <i>J</i> = 8.2 Hz, 1H), 5.15 (s, 2H), 4.80 (t, <i>J</i> = 5.2 Hz, 1H), 4.49 (t, <i>J</i> = 5.8 Hz, 2H), 3.90 (t, <i>J</i> = 5.8 Hz, 2H), 3.52 - 3.58 (m, 2H), 3.46 - 3.51 (m, 2H), 2.91 (spt, <i>J</i> = 6.8 Hz, 1H), 1.21 (d, <i>J</i> = 6.8 Hz, 6H)

Co. No.	¹ H NMR result
20	(500 MHz, DMSO-d ₆) δ ppm 8.49 (d, <i>J</i> = 6.0 Hz, 2H), 7.40 (d, <i>J</i> = 7.9 Hz, 2H), 7.27 - 7.32 (m, 4H), 7.23 (t, <i>J</i> = 8.6 Hz, 1H), 6.94 (dd, <i>J</i> = 2.2, 11.7 Hz, 1H), 6.88 (dd, <i>J</i> = 2.2, 8.6 Hz, 1H), 5.10 (s, 2H), 4.81 (t, <i>J</i> = 4.7 Hz, 1H), 4.51 (t, <i>J</i> = 5.9 Hz, 2H), 3.91 (t, <i>J</i> = 5.9 Hz, 2H), 3.52 - 3.58 (m, 2H), 3.45 - 3.50 (m, 2H), 2.91 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
21	(500 MHz, DMSO-d ₆) δ ppm 8.24-8.61 (m, 2H), 7.40 (d, <i>J</i> = 8.2 Hz, 2H), 7.26-7.32 (m, 4H), 7.23 (t, <i>J</i> = 8.6 Hz, 1H), 6.94 (dd, <i>J</i> = 2.2, 11.7 Hz, 1H), 6.88 (dd, <i>J</i> = 2.2, 8.6 Hz, 1H), 5.10 (s, 2H), 4.80 (t, <i>J</i> = 5.5 Hz, 1H), 4.51 (t, <i>J</i> = 6.0 Hz, 2H), 3.92 (t, <i>J</i> = 6.0 Hz, 2H), 3.55 (q, <i>J</i> = 5.5 Hz, 2H), 3.45-3.50 (m, 2H), 2.91 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
28	(500 MHz, DMSO-d ₆) δ ppm 8.49 (d, <i>J</i> = 6.3 Hz, 2H), 7.57 (d, <i>J</i> = 2.5 Hz, 1H), 7.41 (d, <i>J</i> = 8.2 Hz, 2H), 7.34 - 7.39 (m, 2H), 7.30 (d, <i>J</i> = 8.2 Hz, 2H), 7.22 (d, <i>J</i> = 6.3 Hz, 2H), 5.16 (s, 2H), 4.82 (t, <i>J</i> = 5.2 Hz, 1H), 4.49 - 4.61 (m, 2H), 3.91 - 3.96 (m, 2H), 3.55 (q, <i>J</i> = 5.2 Hz, 2H), 3.46 - 3.51 (m, 2H), 2.91 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
32	(500 MHz, DMSO-d ₆) δ ppm 8.47 (d, <i>J</i> = 6.0 Hz, 2H), 8.23 (t, <i>J</i> = 2.7 Hz, 1H), 7.39 (d, <i>J</i> = 8.2 Hz, 2H), 7.24 - 7.32 (m, 4H), 7.02 (d, <i>J</i> = 8.2 Hz, 1H), 6.91 (d, <i>J</i> = 1.9 Hz, 1H), 6.75 (dd, <i>J</i> = 1.9, 8.2 Hz, 1H), 5.04 (s, 2H), 4.39 - 4.47 (m, 2H), 3.61 - 3.69 (m, 5H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
44	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.0 Hz, 2H), 7.39 (d, <i>J</i> = 8.2 Hz, 2H), 7.23 - 7.31 (m, 4H), 7.18 (d, <i>J</i> = 8.8 Hz, 2H), 6.99 (d, <i>J</i> = 8.8 Hz, 2H), 5.07 (s, 2H), 4.89 (d, <i>J</i> = 5.0 Hz, 1H), 4.58 (t, <i>J</i> = 5.7 Hz, 1H), 4.49 (t, <i>J</i> = 6.0 Hz, 2H), 3.84 - 4.01 (m, 2H), 3.66 - 3.75 (m, 1H), 3.61 (dd, <i>J</i> = 4.0, 13.7 Hz, 1H), 3.21 - 3.40 (m, 3H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
46	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.0 Hz, 2H), 7.39 (d, <i>J</i> = 8.2 Hz, 2H), 7.23 - 7.31 (m, 4H), 7.18 (d, <i>J</i> = 8.8 Hz, 2H), 6.99 (d, <i>J</i> = 8.8 Hz, 2H), 5.07 (s, 2H), 4.82 (d, <i>J</i> = 4.7 Hz, 1H), 4.49 (t, <i>J</i> = 6.0 Hz, 2H), 3.82 - 3.98 (m, 3H), 3.45 (dd, <i>J</i> = 4.3, 13.5 Hz, 1H), 3.22 (dd, <i>J</i> = 7.6, 13.5 Hz, 1H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H), 1.04 (d, <i>J</i> = 6.0 Hz, 3H)
47	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.0 Hz, 2H), 7.39 (d, <i>J</i> = 8.2 Hz, 2H), 7.23 - 7.32 (m, 4H), 7.18 (d, <i>J</i> = 8.8 Hz, 2H), 6.99 (d, <i>J</i> = 8.8 Hz, 2H), 5.07 (s, 2H), 4.82 (d, <i>J</i> = 5.0 Hz, 1H), 4.49 (t, <i>J</i> = 6.0 Hz, 2H), 3.80 - 3.98 (m, 3H), 3.45 (dd, <i>J</i> = 4.1, 13.6 Hz, 1H), 3.22 (dd, <i>J</i> = 7.6, 13.6 Hz, 1H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H), 1.04 (d, <i>J</i> = 6.0 Hz, 3H)
49	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.3 Hz, 2H), 7.39 (d, <i>J</i> = 8.2 Hz, 2H), 7.22 - 7.31 (m, 4H), 7.18 (d, <i>J</i> = 8.8 Hz, 2H), 6.99 (d, <i>J</i> = 8.8 Hz, 2H), 5.08 (s, 2H), 4.68 (spt, <i>J</i> = 6.7 Hz, 1H), 4.42 - 4.51 (m, 2H), 3.68 - 3.79 (m, 2H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H), 1.13 (d, <i>J</i> = 6.7 Hz, 6H)
51	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.0 Hz, 2H), 7.39 (d, <i>J</i> = 8.2 Hz, 2H), 7.23 - 7.31 (m, 4H), 7.17 (d, <i>J</i> = 8.5 Hz, 2H), 6.98 (d, <i>J</i> = 8.5 Hz, 2H), 5.07 (s, 2H), 4.61 (s, 1H), 4.46 - 4.54 (m, 2H), 3.94 - 4.03 (m, 2H), 3.37 (s, 2H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H), 1.09 (s, 6H)

Co. No.	¹ H NMR result
53	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.0 Hz, 2H), 7.39 (d, <i>J</i> = 8.2 Hz, 2H), 7.28 (d, <i>J</i> = 8.2 Hz, 2H), 7.26 (d, <i>J</i> = 6.0 Hz, 2H), 7.18 (d, <i>J</i> = 8.5 Hz, 2H), 6.99 (d, <i>J</i> = 8.5 Hz, 2H), 5.07 (s, 2H), 4.59 (t, <i>J</i> = 5.5 Hz, 1H), 4.48 (t, <i>J</i> = 6.0 Hz, 2H), 3.91 (t, <i>J</i> = 6.0 Hz, 2H), 3.54 - 3.62 (m, 4H), 3.46 - 3.51 (m, 2H), 3.41 - 3.45 (m, 2H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
54	(500 MHz, DMSO-d ₆) δ ppm 8.47 (d, <i>J</i> = 5.7 Hz, 2H), 7.39 (d, <i>J</i> = 8.2 Hz, 2H), 7.28 (d, <i>J</i> = 8.2 Hz, 2H), 7.25 (d, <i>J</i> = 5.7 Hz, 2H), 7.17 (d, <i>J</i> = 8.5 Hz, 2H), 6.99 (d, <i>J</i> = 8.5 Hz, 2H), 5.07 (s, 2H), 4.47- 4.55 (m, 4H), 4.17 (d, <i>J</i> = 5.7 Hz, 2H), 3.86 (t, <i>J</i> = 5.8 Hz, 2H), 3.63 (s, 2H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 1.29 (s, 3H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
63	(500 MHz, DMSO-d ₆) δ ppm 8.47 (d, <i>J</i> = 4.7 Hz, 2H), 7.87 - 7.99 (m, 1H), 7.39 (d, <i>J</i> = 7.6 Hz, 2H), 7.23 - 7.32 (m, 4H), 7.18 (d, <i>J</i> = 8.2 Hz, 2H), 6.99 (d, <i>J</i> = 8.2 Hz, 2H), 5.07 (s, 2H), 4.47 - 4.59 (m, 2H), 4.04 (s, 2H), 3.83 - 3.93 (m, 2H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 2.59 (d, <i>J</i> = 4.1 Hz, 3H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
70	(500 MHz, DMSO-d ₆) δ ppm 8.47 (d, <i>J</i> = 6 Hz, 2H), 7.40 (d, <i>J</i> = 7.9 Hz, 2H), 7.28 (d, <i>J</i> = 7.9 Hz, 2H), 7.25 (d, <i>J</i> = 6 Hz, 2H), 7.20 (d, <i>J</i> = 8.5 Hz, 2H), 7.03 (d, <i>J</i> = 8.5 Hz, 2H), 5.08 (s, 2H), 4.51 - 4.58 (m, 2H), 4.20 - 4.25 (m, 2H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 1.46 (s, 9H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
71	(500 MHz, DMSO-d ₆) δ ppm 8.51 (d, <i>J</i> = 6.0 Hz, 2H), 8.32 (br. s., 1H), 8.06 (d, <i>J</i> = 2.5 Hz, 1H), 7.62 (dd, <i>J</i> = 2.5, 8.5 Hz, 1H), 7.39 (d, <i>J</i> = 8.2 Hz, 2H), 7.29 (d, <i>J</i> = 6.0 Hz, 2H), 7.26 (d, <i>J</i> = 8.2 Hz, 2H), 6.87 (d, <i>J</i> = 8.5 Hz, 1H), 5.31 (s, 2H), 4.45 (t, <i>J</i> = 6.0 Hz, 2H), 3.63 - 3.70 (m, 2H), 2.89 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
84	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.3 Hz, 2H), 8.24 (br. s., 1H), 7.24 - 7.32 (m, 5H), 7.19 (d, <i>J</i> = 8.8 Hz, 2H), 6.99 (d, <i>J</i> = 8.8 Hz, 2H), 5.03 (s, 2H), 4.43 (t, <i>J</i> = 6.0 Hz, 2H), 3.62 - 6.68 (m, 2H), 3.49 (t, <i>J</i> = 7.1 Hz, 2H), 3.25 (s, 3H), 3.16 (spt, <i>J</i> = 6.9 Hz, 1H), 2.88 (t, <i>J</i> = 7.1 Hz, 2H), 1.19 (d, <i>J</i> = 6.9 Hz, 6H)
111	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 5.0 Hz, 2H), 7.54 (d, <i>J</i> = 7.9 Hz, 2H), 7.45 (d, <i>J</i> = 7.9 Hz, 2H), 7.25 (d, <i>J</i> = 5.0 Hz, 2H), 7.18 (d, <i>J</i> = 8.2 Hz, 2H), 7.00 (d, <i>J</i> = 8.2 Hz, 2H), 5.45 (s, 1H), 5.09 - 5.17 (m, 3H), 4.79 (t, <i>J</i> = 5.0 Hz, 1H), 4.48 (t, <i>J</i> = 5.4 Hz, 2H), 3.90 (t, <i>J</i> = 5.4 Hz, 2H), 3.45 - 3.59 (m, 4H), 2.12 (s, 3H)
112	(500 MHz, DMSO-d ₆) δ ppm 8.47 (d, <i>J</i> = 4.7 Hz, 2H), 8.23 (br. s., 1H), 7.41 (d, <i>J</i> = 8.2 Hz, 2H), 7.26 (d, <i>J</i> = 4.7 Hz, 2H), 7.18 (d, <i>J</i> = 8.2 Hz, 2H), 6.92 - 7.02 (m, 4H), 5.03 (s, 2H), 4.43 (t, <i>J</i> = 5.2 Hz, 2H), 3.77 (s, 3H), 3.61 - 3.69 (m, 2H)
116	(400 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.1 Hz, 2H), 8.23 (br. s., 1H), 7.62 (d, <i>J</i> = 8.6 Hz, 2H), 7.41 (d, <i>J</i> = 8.6 Hz, 2H), 7.25 (d, <i>J</i> = 6.1 Hz, 2H), 7.20 (d, <i>J</i> = 8.6 Hz, 2H), 7.01 (d, <i>J</i> = 8.6 Hz, 2H), 5.17 (s, 2H), 4.43 (t, <i>J</i> = 6.1 Hz, 2H), 3.61 - 3.69 (m, 2H)
138	(500 MHz, DMSO-d ₆) δ ppm 8.50 (d, <i>J</i> = 2.2 Hz, 1H), 8.46 (d, <i>J</i> = 6.3 Hz, 2H), 7.74 (dd, <i>J</i> = 2.2, 8.2 Hz, 1H), 7.33 (d, <i>J</i> = 8.2 Hz, 1H), 7.25 (d, <i>J</i> = 6.3 Hz, 2H), 7.18 (d, <i>J</i> = 8.8 Hz, 2H), 7.00 (d, <i>J</i> = 8.8 Hz, 2H), 5.09 (s, 2H), 4.50 (t, <i>J</i> = 6.0 Hz, 2H), 3.83 (t, <i>J</i> = 6.0 Hz, 2H), 2.97 (s, 3H), 2.07 - 2.16 (m, 1H), 0.89 - 0.99 (m, 4H)

Co. No.	¹ H NMR result
158	(500 MHz, DMSO-d ₆) δ ppm 9.01 (s, 1H), 8.74 (d, <i>J</i> = 5.4 Hz, 1H), 8.26 (br. s., 1H), 7.58 (d, <i>J</i> = 5.4 Hz, 1H), 7.39 (d, <i>J</i> = 8.2 Hz, 2H), 7.27 (d, <i>J</i> = 8.2 Hz, 2H), 7.22 (d, <i>J</i> = 8.8 Hz, 2H), 6.93 (d, <i>J</i> = 8.8 Hz, 2H), 5.06 (s, 2H), 4.45 (t, <i>J</i> = 5.8 Hz, 2H), 3.62 - 3.69 (m, 2H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
159	(500 MHz, DMSO-d ₆) δ ppm 9.01 (s, 1H), 8.74 (d, <i>J</i> = 5.0 Hz, 1H), 7.58 (d, <i>J</i> = 5.0 Hz, 1H), 7.39 (d, <i>J</i> = 7.9 Hz, 2H), 7.28 (d, <i>J</i> = 7.9 Hz, 2H), 7.22 (d, <i>J</i> = 8.5 Hz, 2H), 6.93 (d, <i>J</i> = 8.5 Hz, 2H), 5.06 (s, 2H), 4.80 (t, <i>J</i> = 5.2 Hz, 1H), 4.51 (t, <i>J</i> = 5.7 Hz, 2H), 3.91 (t, <i>J</i> = 5.7 Hz, 2H), 3.44 - 3.62 (m, 4H), 2.90 (spt, <i>J</i> = 6.7 Hz, 1H), 1.21 (d, <i>J</i> = 6.7 Hz, 6H)
171	(400 MHz, DMSO-d ₆) δ ppm 8.45 (d, <i>J</i> = 6.1 Hz, 2H), 7.30 - 7.38 (m, 4H), 7.07 - 7.16 (m, 4H), 7.02 (d, <i>J</i> = 8.6 Hz, 2H), 5.04 (s, 2H), 4.04 (s, 2H), 3.82 (d, <i>J</i> = 7.2 Hz, 2H), 2.96 (t, <i>J</i> = 7.2 Hz, 1H), 1.87 - 1.99 (m, 1H), 0.91 - 0.99 (m, 2H), 0.63 - 0.76 (m, 6H)
172	(400 MHz, DMSO-d ₆) δ ppm 8.45 (d, <i>J</i> = 6.1 Hz, 2H), 7.28 - 7.37 (m, 4H), 7.07 - 7.16 (m, 4H), 7.02 (d, <i>J</i> = 8.6 Hz, 2H), 5.04 (s, 2H), 4.08 (t, <i>J</i> = 5.3 Hz, 2H), 3.82 (d, <i>J</i> = 4.4 Hz, 2H), 3.12 - 3.19 (m, 2H), 2.59 - 2.67 (m, 1H), 1.86 - 1.99 (m, 1H), 0.91 - 0.99 (m, 2H), 0.63 - 0.71 (m, 2H)
174	(500 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.0 Hz, 2H), 7.86 (q, <i>J</i> = 4.3 Hz, 1H), 7.39 (d, <i>J</i> = 8.2 Hz, 2H), 7.32 (d, <i>J</i> = 6.0 Hz, 2H), 7.28 (d, <i>J</i> = 8.2 Hz, 2H), 7.11 (d, <i>J</i> = 8.8 Hz, 2H), 7.07 (d, <i>J</i> = 8.8 Hz, 2H), 5.06 (s, 2H), 4.26 (t, <i>J</i> = 5.4 Hz, 2H), 3.67 (s, 2H), 3.18 (s, 2H), 3.01 (t, <i>J</i> = 5.4 Hz, 2H), 2.90 (spt, <i>J</i> = 6.9 Hz, 1H), 2.58 (d, <i>J</i> = 4.3 Hz, 3H), 1.21 (d, <i>J</i> = 6.9 Hz, 6H)
183	(400 MHz, DMSO-d ₆) δ ppm 8.92 (s, 1H), 8.47 (d, <i>J</i> = 6.1 Hz, 2H), 7.34 (d, <i>J</i> = 8.1 Hz, 2H), 7.26 (d, <i>J</i> = 6.1 Hz, 2H), 7.18 (d, <i>J</i> = 8.6 Hz, 2H), 7.10 (d, <i>J</i> = 8.1 Hz, 2H), 6.98 (d, <i>J</i> = 8.6 Hz, 2H), 5.06 (s, 2H), 4.68 (s, 2H), 3.63 (d, <i>J</i> = 8.6 Hz, 2H), 3.37 (d, <i>J</i> = 8.6 Hz, 2H), 2.7 (br.s, 1H), 1.86 - 1.99 (m, 1H), 0.91 - 1.00 (m, 2H), 0.63 - 0.72 (m, 2H)
200	(400 MHz, DMSO-d ₆) δ ppm 8.48 (d, <i>J</i> = 5.6 Hz, 2H), 7.38 (d, <i>J</i> = 8.1 Hz, 2H), 7.26 - 7.33 (m, 4H), 7.06 (d, <i>J</i> = 2.0 Hz, 1H), 6.95 (dd, <i>J</i> = 2.0, 8.1 Hz, 1H), 6.78 (d, <i>J</i> = 8.1 Hz, 1H), 5.08 - 5.15 (m, 1H), 4.79 (t, <i>J</i> = 5.3 Hz, 1H), 4.48 (t, <i>J</i> = 6.1 Hz, 2H), 3.90 (t, <i>J</i> = 6.1 Hz, 2H), 3.53 - 3.59 (m, 2H), 3.47 - 3.52 (m, 2H), 2.86 - 3.00 (m, 2H), 2.61 - 2.72 (m, 1H), 2.10 - 2.20 (m, 1H), 1.94 - 2.09 (m, 1H), 1.22 (d, <i>J</i> = 7.1 Hz, 6H)
22a	(400 MHz, DMSO-d ₆) δ ppm 8.49 (d, <i>J</i> = 5.56 Hz, 2H), 7.40 (d, <i>J</i> = 8.08 Hz, 2H), 7.26-7.34 (m, 4H), 7.22 (s, 1H), 6.80-6.98 (m, 2H), 5.10 (s, 2H), 4.52 (br. s., 2H), 4.19-4.32 (m, 1H), 3.90-4.25 (m, 3H), 3.55-3.69 (m, 2H), 3.42-3.55 (m, 1H), 2.87-2.97 (m, 1H), 1.36 (s, 3H), 1.27 (s, 3H), 1.22 (d, <i>J</i> = 7.07 Hz, 6H)
238	(400 MHz, DMSO-d ₆) δ ppm 8.46 (d, <i>J</i> = 6.06 Hz, 2H), 7.39 (d, <i>J</i> = 8.08 Hz, 2H), 7.23-7.32 (m, 4H), 7.18 (d, <i>J</i> = 8.59 Hz, 2H), 6.98 (d, <i>J</i> = 8.59 Hz, 2H), 6.84-6.93 (m, 1H), 5.08 (s, 2H), 4.50 (t, <i>J</i> = 6.06 Hz, 2H), 3.78-3.92 (m, 2H), 3.46 (t, <i>J</i> = 5.81 Hz, 2H), 3.13 (d, <i>J</i> = 6.06 Hz, 2H), 2.90 (td, <i>J</i> = 6.69, 13.89 Hz, 1H), 1.32 (s, 9H), 1.21 (d, <i>J</i> = 6.69 Hz, 6H)

Co. No.	¹ H NMR result
60a	(500 MHz, DMSO-d ₆) δ ppm 8.34-8.52 (m, 2H), 7.39 (d, <i>J</i> =8.20 Hz, 2H), 7.28 (d, <i>J</i> =8.20 Hz, 2H), 7.24 (d, <i>J</i> =5.67 Hz, 2H), 7.17 (d, <i>J</i> =8.83 Hz, 2H), 6.99 (d, <i>J</i> =8.83 Hz, 2H), 5.07 (s, 2H), 4.44-4.54 (m, 2H), 3.83-3.90 (m, 2H), 3.53-3.59 (m, 2H), 3.35-3.42 (m, 2H), 2.84-2.95 (m, 1H), 2.79 (s, 3H), 1.27 (s, 9H), 1.21 (d, <i>J</i> =6.94 Hz, 6H)
95a	(400 MHz, DMSO-d ₆) δ ppm 8.43-8.52 (m, 2H), 7.27 (d, <i>J</i> =6.06 Hz, 2H), 7.21 (d, <i>J</i> =8.59 Hz, 2H), 7.10 (d, <i>J</i> =9.09 Hz, 2H), 7.02 (d, <i>J</i> =8.59 Hz, 2H), 5.09 (s, 2H), 4.44-4.54 (m, 2H), 4.21-4.33 (m, 1H), 3.91-4.04 (m, 3H), 3.42-3.70 (m, 3H), 2.85-3.02 (m, 1H), 1.36 (s, 3H), 1.27 (s, 3H), 1.22 (d, <i>J</i> =7.07 Hz, 6H)
96a	(400 MHz, DMSO-d ₆) δ ppm 8.43-8.51 (m, 2H), 7.25-7.30 (m, 2H), 7.18-7.23 (m, 2H), 7.07-7.12 (m, 2H), 6.95-7.04 (m, 2H), 5.01-5.12 (m, 2H), 4.41-4.54 (m, 2H), 4.20-4.32 (m, 1H), 3.87-4.03 (m, 3H), 3.57-3.69 (m, 2H), 3.43-3.55 (m, 1H), 2.88-3.02 (m, 1H), 1.32-1.38 (m, 3H), 1.24-1.28 (m, 3H), 1.18-1.24 (m, 6H)
161a	(400 MHz, DMSO-d ₆) δ ppm 9.01 (d, <i>J</i> =1.52 Hz, 1H), 8.74 (d, <i>J</i> =5.56 Hz, 1H), 7.58 (dd, <i>J</i> =1.52, 5.56 Hz, 1H), 7.39 (d, <i>J</i> =8.08 Hz, 2H), 7.27 (d, <i>J</i> =8.08 Hz, 2H), 7.22 (d, <i>J</i> =9.09 Hz, 2H), 6.93 (d, <i>J</i> =9.09 Hz, 2H), 5.06 (s, 2H), 4.43-4.55 (m, 2H), 4.20-4.32 (m, 1H), 3.86-4.02 (m, 3H), 3.42-3.70 (m, 3H), 2.85-2.95 (m, 1H), 1.36 (s, 3H), 1.27 (s, 3H), 1.21 (d, <i>J</i> =7.07 Hz, 6H)
184a	(400 MHz, DMSO-d ₆) δ ppm 8.47 (d, <i>J</i> =6.06 Hz, 2H), 7.35 (d, <i>J</i> =8.08 Hz, 2H), 7.31 (d, <i>J</i> =6.06 Hz, 2H), 7.22 (t, <i>J</i> =8.59 Hz, 1H), 7.11 (d, <i>J</i> =8.08 Hz, 2H), 7.03 (dd, <i>J</i> =2.27, 11.87 Hz, 1H), 6.93 (dd, <i>J</i> =2.27, 8.59 Hz, 1H), 5.09 (s, 2H), 4.47 (s, 2H), 4.24 (t, <i>J</i> =5.31 Hz, 2H), 3.84-3.91 (m, 2H), 1.87-1.97 (m, 1H), 1.42 (s, 9H), 0.87-1.00 (m, 2H), 0.61-0.72 (m, 2H)

Pharmacology

A) in vitro tests

Ros1 enzymatic assay

- Compounds were spotted onto white 384-well Proxiplate plus plates (Perkin Elmer) to which 5 µl of enzyme mix (0.5 µg/ml Ros1 enzyme, 50 mM Tris-HCl pH7.5, 1 mM EGTA, 10 mM MgCl₂, 0.01% Tween-20) and 5 µl of substrate mix (6 µg/ml IRS-Tide [American Peptide Company], 20 µM ATP, 13.33 µCi/ml ATP (adenosine 5'-triphosphate) P³³, 50 mM Tris-HCl pH7.5, 1 mM EGTA (ethylene glycol-bis(2-aminoethylether)-*N,N,N',N'*-tetraacetic acid), 10 mM MgCl₂, 0.01% Tween-20) were added. After incubation for 120 minutes at room temperature, 10 µl of stop reaction buffer (5 mM EDTA, 50 µM ATP, 0.1% BSA (bovine serum albumin), 0.1% Triton X-100, 50 mM Tris-HCl pH7.5, 1 mM EGTA, 10 mM MgCl₂, 0.01% Tween-20) containing 2 mg/ml streptavidin coupled polystyrene imaging beads (Amersham Biosciences) was added and incubated for 15 minutes at room temperature. Plates were centrifuged for 3 minutes at 1500 rpm and signals detected in a LEADseeker imaging system (GE).

In this assay, the inhibitory effects of different compound concentrations (ranging from 10 μ M to 0.3 nM) were determined and used to calculate an IC_{50} (M) and pIC_{50} (-log IC_{50}) value.

Ba/F3-Ros1 cell proliferation assay

- 5 This assay was carried out with Ba/F3 cells containing three different versions of Ros1: the wild-type protein, protein with a mutation at the gatekeeper residue (L2026M), and protein with a mutation identified in a tumor from a patient that became resistant to crizotinib (Xalkori®) treatment (G2032R). Compounds were solubilized in 100% DMSO (dimethyl sulfoxide) and sprayed into polystyrene, tissue culture treated 384-
- 10 well plates. A 50 μ l volume of cell culture medium (phenol red free RPMI-1640, 10% FBS (fetal bovine serum), 2 mM L-Glutamine) containing 20000 Ba/F3-Ros1 cells was added to each well and the plates were placed in an incubator at 37°C and 5% CO₂. After 24 hours, 10 μ l of Alamar Blue solution (0.5 mM K₃Fe(CN)₆, 0.5 mM K₄Fe(CN)₆, 0.15 mM Resazurin and 100 mM Phosphate Buffer) was added to the
- 15 wells, incubated for 4 hours at 37°C and 5% CO₂ before RFU's (Relative Fluorescence Units) (ex. 540 nm., em. 590 nm.) were measured in a fluorescence plate reader. In this assay, the inhibitory effects of different compound concentrations (ranging from 10 μ M to 0.3 nM) were determined and used to calculate an IC_{50} (M) and pIC_{50} (-log IC_{50}) value.
- 20 As a counter-screen the same experiment was performed for the wild-type protein in the presence of 10 ng/ml murine IL-3.

HCC78 cell proliferation assay

- Approximately 1000 HCC78 non-small cell lung cancer cells in 180 μ l of cell culture medium (RPMI-1640, 10% FBS, 2 mM L-Glutamine, 10 mM Hepes, 1 mM sodium pyruvate, 4.5 g/L glucose, 1.5 g/L sodium bicarbonate, 25 μ g/ml Gentamycin) were
- 25 seeded in each well of a 96-well polystyrene, tissue-culture treated plate and incubated at 37°C and 5% CO₂. After 24 hours, compounds were diluted in cell culture medium from which 20 μ l was added to the wells containing cells and incubated for 4 days at 37°C and 5% CO₂. A 5 mg/ml solution of the tetrazolium dye MTT was prepared in
- 30 PBS (phosphate-buffered saline) and 25 μ l was added to each well. After 2 hours the medium was removed and replaced by 125 μ L of 4/1 DMSO/glycine buffer (0.1M glycine, 0.1M NaCl, pH 10.5) before absorbance was determined at 538 nm. In this assay, the inhibitory effects of different compound concentrations (ranging from 10 μ M to 30 nM) were determined and used to calculate an EC_{50} (M) and pEC_{50} (-log EC_{50}) value.
- 35

pROS1 immunofluorescence assay in HCC78 cells

- Approximately 20000 HCC78 non-small cell lung cancer cells in 180 μ l of cell culture medium (RPMI-1640, 10% FBS, 2 mM L-Glutamine, 10 mM Hepes, 1 mM sodium pyruvate, 4.5 g/L glucose, 1.5 g/L sodium bicarbonate, 25 μ g/ml Gentamycin) were seeded in each well of a 96-well polystyrene, poly-D-lysine coated plate and incubated at 37°C and 5% CO₂. After 24 hours, compounds were diluted in cell culture medium from which 20 μ l was added to the wells containing cells and incubated for 4 hours at 37°C and 5% CO₂. The medium was removed and the cells were fixed by adding 100 μ l of 5% formaldehyde in TBS (tris-buffered saline) (50 mM Tris.HCl, pH 7.4, 150 mM NaCl) and incubating for 15 minutes at room temperature. The formaldehyde was removed and replaced with methanol for 10 minutes at room temperature, after which the cells were washed 3 times with TBS containing 1% Triton X-100 and incubated in Odyssey (Li-Cor) blocking buffer for 1 hour at room temperature. The cells were then incubated with the primary rabbit antibody directed against Ros pY2274 (cst-3078) diluted 1/200 in blocking buffer for 24 hours at room temperature. The cells were washed three times with TBS containing 0.1% Triton X-100 and incubated with a secondary anti-rabbit antibody conjugated to the fluorescent dye Alexafluor 680 in blocking buffer for 1 hour at room temperature. The cells were washed three times with TBS containing 0.1% Triton X-100 and left to dry before measuring RFUs (Relative Fluorescence Units) at 700 nm using a fluorescence imager.
- The same experiment was performed using total Ros1 antibody (sc-6347) diluted 1/1000 instead of Ros1 pY2274 antibody and an anti-goat antibody conjugated to IRDye800cw as a secondary antibody. RFUs were measured at 800 nm. The signals from total Ros1 detection were used to normalize the Ros1pY2274 values.
- In this assay, the inhibitory effects of different compound concentrations (ranging from 10 μ M to 3 nM) were determined and used to calculate an IC₅₀ (M) and pIC₅₀ (-logIC₅₀) value.

The results of the above in vitro test are shown in table 5:

Co.	ROS1 pIC ₅₀	BaF3- ROS1-IL3 pIC ₅₀	BaF3- ROS1+IL3 pIC ₅₀	Ba/F3 Ros1 L2026M (-IL-3) pIC ₅₀	Ba/3 Ros1 G2032R (-IL-3) pIC ₅₀	HCC-78 PROL pEC ₅₀	HCC78- pRos1 pIC ₅₀
Co. 112	6.8	6.8	<5		5.8	6.0	6.5
Co. 1	7.6	7.6	<5	7.3	7.0	6.9	7.6
Co. 3	7.1	7.3	<5	7.0		6.1	7.1
Co. 4	7.4	7.6	<5	7.4	6.8	6.7	7.1
Co. 172	6.2	6.4	<5	6.3	5.2	5.4	6.5
Co. 188	5.4	5.5	<5				
Co. 228	6.4	6.3	<5			5.7	6.3
Co. 48	7.5	7.1	<5			6.4	7.2

Co.	ROS1 pIC50	BaF3- ROS1-IL3 pIC50	BaF3- ROS1+IL3 pIC50	Ba/F3 Ros1 L2026M (-IL-3) pIC50	Ba/3 Ros1 G2032R (-IL-3) pIC50	HCC-78 PROL pEC50	HCC78- pRos1 pIC50
Co. 32	8.2	8.0	<5	8.0	7.3	7.3	7.8
Co. 189	7.5	7.1	<5			6.7	7.4
Co. 5	7.6	7.6	<5	7.5		6.5	7.3
Co. 138	7.0	6.9	<5	6.8	6.0	6.3	6.5
Co. 185	6.9	6.3	<5			6.1	6.8
Co. 71	7.6	7.7	<5	7.6	7.0	7.0	7.4
Co. 119	6.7	7.2	<5	6.9		6.4	6.5
Co. 197	6.1	5.8	<5				
Co. 190	6.2	6.1	<5				
Co. 171	6.4	6.2	<5		6.0	5.8	6.3
Co. 116	6.9	7.3	<5	7.3	6.6	6.6	6.8
Co. 173	6.4	6.1	<5			5.8	6.5
Co. 157	6.0	6.1	<5				
Co. 143	6.0	6.4	5.3	6.0			
Co. 229	<5	<5	<5				
Co. 114	6.3	6.4	<5				
Co. 6	8.0	7.9	<5	7.7	7.4	7.2	7.8
Co. 183	6.7	6.0	<5		5.6	5.8	6.4
Co. 103	5.9	6.0	<5			5.7	5.4
Co. 7	7.4	7.4	<5	7.4	6.8	6.6	7.0
Co. 8	8.2	7.9	<5	7.8		7.4	7.6
Co. 158	7.3	7.4	<5	7.4	6.5	6.5	6.9
Co. 181	6.1	5.7	5.3			5.7	5.9
Co. 9	6.2	6.4	<5	6.2		5.7	5.6
Co. 120	6.6	6.6	<5				
Co. 124	5.7	5.7	<5				
Co. 33	8.0	7.7	<5	7.4		>7.5	7.9
Co. 142	6.9	6.9	<5	6.4		6.4	6.9
Co. 182	5.9	5.7	5.3				
Co. 149	8.1	7.6	<5	7.4		>7.5	7.9
Co. 150	8.1	7.6	<5	7.4		7.4	8.0
Co. 110	6.9	6.9	<5				
Co. 113	6.1	6.0	<5				
Co. 211	7.5	7.3	<5	7.3			
Co. 49	7.4	7.3	<5	7.2	6.9	7.0	7.5
Co. 10	7.1	7.1	<5	6.9	6.6	6.8	7.6
Co. 2	7.7	7.6	<5	7.4	7.1	6.9	7.6
Co. 12	6.5	6.5	<5	6.7		6.1	6.3
Co. 151	7.5	7.4	<5	7.1		7.2	7.7
Co. 130	5.5	5.8	<5				
Co. 198	6.6	6.6	<5				
Co. 174	6.7	6.8	<5	6.8	6.4	6.1	6.6
Co. 54	7.1	7.3	<5	7.2	6.6	7.1	7.7

Co.	ROS1 pIC50	BaF3- ROS1-IL3 pIC50	BaF3- ROS1+IL3 pIC50	Ba/F3 Ros1 L2026M (-IL-3) pIC50	Ba/3 Ros1 G2032R (-IL-3) pIC50	HCC-78 PROL pEC50	HCC78- pRos1 pIC50
Co. 214	7.5	7.4	<5	7.3		7.0	7.5
Co. 160	7.4	7.3	<5	7.3		7.0	7.5
Co. 165	6.7	6.7	<5	6.5		5.9	6.2
Co. 186	6.0	6.2	<5				
Co. 210	7.2	6.3	5.2				
Co. 26	6.4	6.6	<5	6.5		6.1	6.2
Co. 163	6.9	7.1	<5	7.1		6.9	6.5
Co. 176	6.8	6.9	<5	7.1		7.1	
Co. 18	8.0	7.7	<5	7.7	7.3	7.4	
Co. 25	6.9	6.8	<5	6.5		6.3	
Co. 59	7.2	6.4	5.3	~6.1		6.3	
Co. 59a	7.2	6.6	5.2				
Co. 104	5.9	6.1	<5				
Co. 179	6.3	6.4	<5				
Co. 50	7.3	7.1	<5	7.2		6.8	
Co. 166	7.2	6.9	<5				
Co. 105	6.9	7.0	<5	6.6		6.8	
Co. 37	5.6	5.4	<5				
Co. 121	5.0	6.3	<5	5.9		6.0	
Co. 170	5.2	5.2	<5				
Co. 9a	5.6	<5	<5				
Co. 122	6.9	6.9	<5	7.1		7.2	
Co. 159	7.3	7.3	<5	7.2	6.4	7.2	
Co. 15	7.4	7.5	<5	7.5		7.3	
Co. 132	5.4	5.7	<5				
Co. 154	7.0	6.9	<5	7.1		6.5	
Co. 133	<5	5.6	<5				
Co. 21	8.0	7.8	<5	7.6	7.4	7.4	
Co. 180	6.3	6.5	<5				
Co. 131	6.2	6.2	<5				
Co. 90	7.1	7.2	<5	7.4		6.8	
Co. 13	7.7	7.5	<5				
Co. 17	6.3	6.8	<5				
Co. 34	6.5	6.6	<5				
Co. 153	7.4	7.5	<5	6.8		6.5	
Co. 63	7.0	7.1	<5	7.3	6.7	6.4	
Co. 80	6.9	6.9	<5				
Co. 118	6.8	7.1	<5				
Co. 152	8.0	8.0	<5	8.1		7.2	
Co. 11	8.0	7.7	<5	7.8		7.5	
Co. 24	8.1	7.8	<5	8.2		8.8	
Co. 84	7.6	7.7	<5	7.2	7.0	7.5	
Co. 44	7.3	7.4	<5	6.9	6.8	6.6	

Co.	ROS1 pIC50	BaF3- ROS1-IL3 pIC50	BaF3- ROS1+IL3 pIC50	Ba/F3 Ros1 L2026M (-IL-3) pIC50	Ba/3 Ros1 G2032R (-IL-3) pIC50	HCC-78 PROL pEC50	HCC78- pRos1 pIC50
Co. 230	<5	5.2	<5				
Co. 215	6.9	7.0	<5	7.2		6.6	
Co. 187	7.1	7.2	<5	6.4		7.0	
Co. 89	7.5	7.6	<5	7.1		6.7	
Co. 52	7.3	7.6	<5	6.9		6.6	
Co. 51	7.1	7.2	<5	7.3	6.6	7.0	
Co. 193	7.1	7.3	<5	6.3		6.7	
Co. 77	6.5	6.3	<5	6.3		5.7	
Co. 53	7.4	7.4	<5	6.9	7.0	7.0	
Co. 47	7.3	7.3	<5	7.5	6.9	7.1	
Co. 46	7.3	7.5	<5	7.1	6.9	7.0	
Co. 66	6.6	5.1	<5				
Co. 88	7.9	7.1	<5	6.8		7.1	
Co. 14	8.2	7.8	<5	8.2		>7.5	
Co. 184	7.0	7.3	<5	6.6		6.6	
Co. 19	7.9	8.2	<5	8.0	7.5	>7.5	
Co. 194	7.1	6.6	5.2	6.2		6.3	
Co. 62	6.7	7.0	<5	6.6		6.3	
Co. 123	7.4	7.4	<5	7.1		6.4	
Co. 16	7.0	7.4	<5	7.1		6.4	
Co. 203	8.4	8.2	<5	8.0		8.0	
Co. 85	7.4	7.4	<5	7.1		6.5	
Co. 61		6.3	<5	5.9		6.2	
Co. 195	6.9	6.7	<5	7.0		6.1	
Co. 191	6.8	6.9	<5	7.0		6.3	
Co. 192	6.8	6.9	<5	6.9		6.2	
Co. 60	7.2	6.6	5.4	6.2		6.2	
Co. 86	8.0	7.2	<5	6.9		6.3	
Co. 39	7.1	7.3	<5	7.0		6.8	
Co. 38	7.9	7.9	<5	7.5		7.3	
Co. 106	7.6	7.5	<5				
Co. 20	7.0	6.9	<5	7.0		5.8	
Co. 125	6.5	6.7	<5				
Co. 127	6.4	6.6	<5				
Co. 57	7.6	7.7	<5				
Co. 178	6.7	6.6	<5				
Co. 141	6.2	6.4	<5				
Co. 108	6.9	7.0	<5				
Co. 43	7.3	7.4	<5	7.3		6.9	
Co. 126	6.7	6.9	<5	6.6		5.9	
Co. 55	6.9	7.0	<5	6.8		6.1	
Co. 40	7.0	6.9	<5	6.4		5.4	
Co. 42	6.4	6.7	<5	6.3		5.9	

Co.	ROS1 pIC50	BaF3- ROS1-IL3 pIC50	BaF3- ROS1+IL3 pIC50	Ba/F3 Ros1 L2026M (-IL-3) pIC50	Ba/3 Ros1 G2032R (-IL-3) pIC50	HCC-78 PROL pEC50	HCC78- pRos1 pIC50
Co. 41	7.5	7.4	<5	6.6		7.1	
Co. 23	7.9	7.7	<5	7.2		7.2	
Co. 22	7.9	7.8	<5	7.4		7.7	
Co. 91	7.5	7.3	<5	6.6		7.2	
Co. 129	7.2	7.4	<5	7.0		7.0	
Co. 87	7.4	7.3	<5	7.2		6.7	
Co. 107	7.7	7.7	<5	7.4		7.1	
Co. 109	7.0	7.1	<5	7.2		6.4	
Co. 65	7.0	7.2	<5	6.7		6.5	
Co. 136	7.2	7.1	<5	6.6		6.5	
Co. 64	7.1	7.1	<5	6.6		6.2	
Co. 81	7.2	7.3	<5	6.5		6.8	
Co. 196	6.8	6.9	<5	6.4		6.2	
Co. 175	7.0	6.9	5.3	6.8		6.4	
Co. 27	7.8	7.7	<5	7.1		7.7	
Co. 137	6.9	6.8	<5	6.4		6.4	
Co. 56	7.4	7.5	<5	7.0		6.9	
Co. 139	6.9	6.8	<5	6.0		7.0	
Co. 207	7.7	7.1	<5	6.5		6.3	
Co. 94	7.0	7.0	<5	6.6		6.4	
Co. 29	<5	<5	<5	<5		<5	
Co. 95	6.8	6.8	<5			6.4	
Co. 92	7.3	7.2	<5	6.7		6.7	
Co. 155	7.5	7.8	<5	7.5		7.1	
Co. 209	7.2	7.5	5.3	7.5		6.3	
Co. 30	<5	<5	<5	<5		<5	
Co. 93	7.1	7.2	<5	7.0		6.4	
Co. 161	7.3	7.1	<5	6.7		6.5	
Co. 45	6.8	6.7	<5	6.6		5.9	
Co. 68	6.5	6.7	5.6	6.5		5.6	
Co. 96	6.8	6.9	<5	6.6		5.9	
Co. 177	6.7	6.9	<5	6.6		6.4	
Co. 164	6.8	7.0	<5	6.7		6.1	
Co. 208	7.2	6.8	<5	6.3		6.4	
Co. 167	6.9	7.2	<5	6.2		6.3	
Co. 98	6.6	6.8	<5	6.6		6.5	
Co. 35	5.3	5.7	<5	5.8		<5	
Co. 111	6.9	7.1	<5	6.7	6.6	6.2	
Co. 36	5.3	5.8	<5	5.7		<5	
Co. 97	6.8	6.9	<5	6.3	<5	5.5	
Co. 99	6.3	6.6	<5	6.0		5.7	
Co. 140	6.6	6.4	<5	5.8		5.7	
Co. 148	5.2	5.5	<5	5.9		5.8	

Co.	ROS1 pIC50	BaF3- ROS1-IL3 pIC50	BaF3- ROS1+IL3 pIC50	Ba/F3 Ros1 L2026M (-IL-3) pIC50	Ba/3 Ros1 G2032R (-IL-3) pIC50	HCC-78 PROL pEC50	HCC78- pRos1 pIC50
Co. 144	5.9	6.3	<5	5.7		5.0	
Co. 145	5.5	5.8	<5	5.1		<5.5	
Co. 79	7.6	7.8	<5	7.3		5.6	
Co. 205	8.1	7.8	<5	7.5			
Co. 100	6.7	6.9	<5	6.3			
Co. 101	6.4	6.7	<5	6.4			
Co. 102	6.1	6.7	<5	6.4			
Co. 213	7.0	7.0	<5	6.4			
Co. 212	7.4	7.3	<5	6.8			
Co. 204	8.2	7.9	<5	7.8			
Co. 169	6.0	6.2	<5	5.6			
Co. 168	6.4	6.5	<5	6.2			
Co. 70	5.5	6.4	<5	6.1			
Co. 83	7.7	7.6	<5	7.2			
Co. 82	8.0	7.6	<5	7.3			
Co. 75	7.9	7.9	<5	7.5		7.2	
Co. 117	6.9	7.0	<5	6.9		6.6	
Co. 31	5.8	6.3	<5	5.9		5.2	
Co. 162	7.1	7.2	<5	7.1		6.4	
Co. 28	7.8	7.8	<5	7.7	7.3	7.2	
Co. 206	7.4	7.5	<5	~7.4		7.0	
Co. 199	6.7	7.1	<5	7.5		5.9	
Co. 74	7.8	8.1	<5	7.5		7.9	
Co. 73	7.8	7.9	<5	7.4		6.9	
Co. 146	5.7	6.2	<5	7.6		5.4	
Co. 200	6.9	7.3	<5	6.3	6.6	6.5	
Co. 147	5.4	5.4	5.4	6.7		5.4	
Co. 115	5.9	6.3	<5	<5		5.8	
Co. 69	7.2	7.4	<5	<5		6.7	
Co. 76	6.6	6.8	<5	7.0		6.1	
Co. 72	7.2	7.2	<5	6.0		6.6	
Co. 201	7.6	7.8	<5	7.4		7.4	
Co. 156	7.2	8.0	<5	7.0		7.7	
Co. 58	7.7	7.3	5.2	7.0		6.0	
Co. 134	7.1	7.3	<5	7.0		6.7	
Co. 135	6.8	7.3	<5	7.0		6.5	
Co. 128	5.9	6.6	<5	6.2		6.0	
Co. 226	6.2	7.1	<5	6.8		6.3	
Co. 67	7.6	7.9	<5	7.1			
Co. 231	6.1	6.4	<5	5.7			
Co. 232	5.7	6.7	<5	6.5		5.6	
Co. 233	6.1	6.5	<5	5.9		5.6	
Co. 234	7.7	7.1	<5	6.7		6.9	

Co.	ROS1 pIC50	BaF3- ROS1-IL3 pIC50	BaF3- ROS1+IL3 pIC50	Ba/F3 Ros1 L2026M (-IL-3) pIC50	Ba/3 Ros1 G2032R (-IL-3) pIC50	HCC-78 PROL pEC50	HCC78- pRos1 pIC50
Co. 78	6.6	7.1	<5	6.9		6.1	
Co. 235	7.6	6.7	<5	6.5		6.5	
Co. 236	7.8	7.6	5.4	7.4		6.9	
Co. 216	7.2	7.3	<5	6.9		6.2	
Co. 217	6.4	6.3	<5	6.0		5.5	
Co. 223	6.4	6.5	<5				
Co. 219	5.9	6.0	<5				
Co. 224	6.4	6.7	<5				
Co. 225	6.5	6.7	<5				
Co. 218	6.7	6.3	<5				
Co. 222	6.7	7.0	<5				
Co. 220	6.3	6.5	<5				
Co. 227	6.1	6.3	<5				
Co. 221	6.3	6.5	<5				
Co. 237	6.1	6.8	<5				

B) in vivo test

Efficacy studies in mice bearing Ba/F3-Ros1 tumors

- Approximately 2×10^6 Ba/F3 cells containing either wild-type, L2026M or G2032R mutant Ros1 were inoculated into the inguinal region of NMRI nude mice. When the
- 5 resulting tumors reached a size of 250 to 350 mm³, mice were randomly assigned to the different treatment groups (8 to 12 mice per group). Compounds formulated in 20% cyclodextrin were administered to the mice by oral gavage at various doses for 10-days
- 10 once (QD) or twice (BID) a day. Tumor sizes were determined by caliper measurement on day 1 prior to treatment and then twice weekly for the duration of the study using the commonly following formula: tumor volume (mm³) = (a × b²/2); where 'a' represents the length, and 'b' the width of the tumor. Treatment/control (T/C) ratios were calculated at the end of the study based on the change in final relative tumor volumes.

Tumor model	Co.	Dose (mg/kg)	administration frequency	T/C (%)	number of mice per group
Ba/F3-Ros1 wild-type	Co. 1	1.56	QD	88	12
Ba/F3-Ros1 wild-type	Co. 1	3.125	QD	75	12
Ba/F3-Ros1 wild-type	Co. 1	6.25	QD	35	12
Ba/F3-Ros1 wild-type	Co. 1	12.5	QD	12	12
Ba/F3-Ros1 wild-type	Co. 1	25	QD	-27	12
Ba/F3-Ros1 wild-type	Co. 1	6.25	BID	50	8
Ba/F3-Ros1 wild-type	Co. 1	12.5	BID	20	8
Ba/F3-Ros1 wild-type	Co. 1	25	BID	-13	8

Tumor model	Co.	Dose (mg/kg)	administration frequency	T/C (%)	number of mice per group
Ba/F3-Ros1 wild-type	Co. 2	12.5	QD	61	12
Ba/F3-Ros1 wild-type	Co. 2	25	QD	46	12
Ba/F3-Ros1 wild-type	Co. 2	50	QD	20	12
Ba/F3-Ros1 wild-type	Co. 2	3.125	BID	91	12
Ba/F3-Ros1 wild-type	Co. 2	6.25	BID	67	12
Ba/F3-Ros1 wild-type	Co. 2	12.5	BID	47	12
Ba/F3-Ros1 wild-type	Co. 2	25	BID	5	12
Ba/F3-Ros1 wild-type	Co. 2	50	BID	-15	12
Ba/F3-Ros1 wild-type	Co. 2	12.5	BID	51	8
Ba/F3-Ros1 wild-type	Co. 2	25	BID	41	8
Ba/F3-Ros1 wild-type	Co. 2	50	BID	32	8
Ba/F3-Ros1 wild-type	Co. 2	100	BID	-22	8
Ba/F3-Ros1 L2026M	Co. 1	25	QD	42	8
Ba/F3-Ros1 L2026M	Co. 1	25	BID	-11	8
Ba/F3-Ros1 L2026M	Co. 1	6.25	BID	94	8
Ba/F3-Ros1 L2026M	Co. 1	12.5	BID	23	8
Ba/F3-Ros1 L2026M	Co. 1	25	BID	24	8
Ba/F3-Ros1 L2026M	Co. 2	12.5	BID	82	8
Ba/F3-Ros1 L2026M	Co. 2	25	BID	50	8
Ba/F3-Ros1 L2026M	Co. 2	50	BID	28	8
Ba/F3-Ros1 L2026M	Co. 2	100	BID	-32	8
Ba/F3-Ros1 G2032R	Co. 1	6.25	BID	79	8
Ba/F3-Ros1 G2032R	Co. 1	12.5	BID	43	8
Ba/F3-Ros1 G2032R	Co. 1	25	BID	7	8
Ba/F3-Ros1 G2032R	Co. 2	12.5	BID	89	8
Ba/F3-Ros1 G2032R	Co. 2	25	BID	55	8
Ba/F3-Ros1 G2032R	Co. 2	50	BID	18	8
Ba/F3-Ros1 G2032R	Co. 2	100	BID	-16	8

Composition examples

- “Active ingredient” (a.i.) as used throughout these examples relates to a compound of Formula (I), including any tautomer or stereoisomeric form thereof, or a N-oxide, a pharmaceutically acceptable addition salt or a solvate thereof; in particular to any one of the exemplified compounds.

Typical examples of recipes for the formulation of the invention are as follows:

1. Tablets

Active ingredient	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg
Talcum	10 mg

Magnesium stearate	5 mg
Potato starch	ad 200 mg

2. *Suspension*

- 5 An aqueous suspension is prepared for oral administration so that each milliliter contains 1 to 5 mg of active ingredient, 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

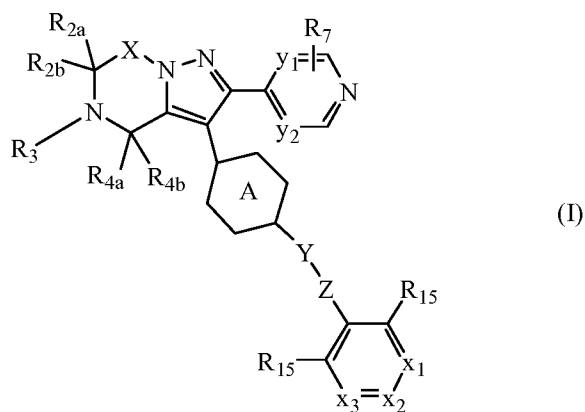
3. *Injectable*

A parenteral composition is prepared by stirring 1.5 % (weight/volume) of active ingredient in 0.9 % NaCl solution or in 10 % by volume propylene glycol in water.

10 4. *Ointment*

- | | |
|-------------------|--------------|
| Active ingredient | 5 to 1000 mg |
| Stearyl alcohol | 3 g |
| Lanoline | 5 g |
| White petroleum | 15 g |
| 15 Water | ad 100 g |

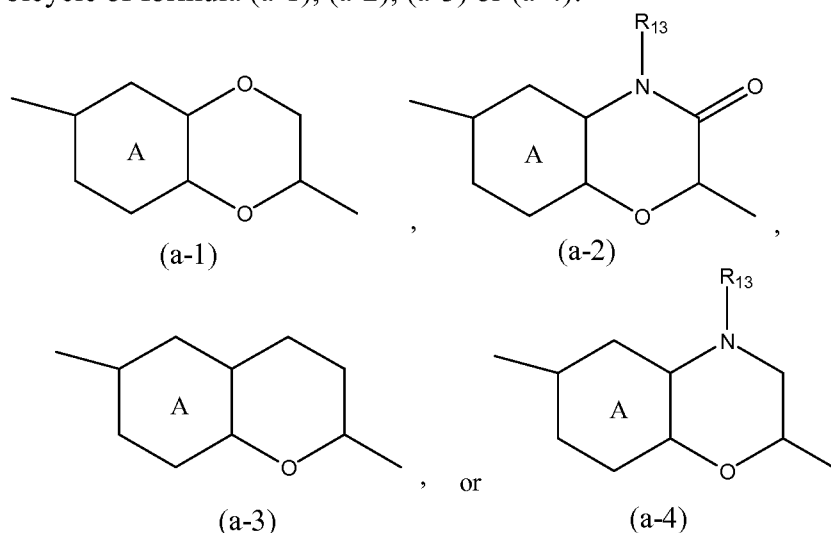
In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

Claims**1.** A compound of Formula (I)

a tautomer or a stereoisomeric form thereof, wherein

- 5 y_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
10 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 polyhalo C_{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 $-C(=O)-NR_{9a}R_{9b}$;
15 R_{2a} is hydrogen; C_{1-6} alkyl; mono-or polyhalo C_{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 $-CH_2-CH_2-$, $-CH_2-NR_{2c}-CH_2-$, $-CH_2-CH_2-CH_2-$,
20 $-CH_2-O-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-NR_{2c}-CH_2-$ or $=O$;
 R_{2c} is hydrogen; C_{1-4} alkyl optionally substituted with one or two hydroxyl groups;
mono-or polyhalo C_{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 polyhalo C_{1-6} alkyl; C_{1-6} alkyl substituted with one or
25 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 polyhalo C_{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;
hydroxy C_{2-6} alkenyl; hydroxy C_{2-6} alkynyl; C_{1-6} alkyloxy C_{2-6} alkenyl;
 C_{1-6} alkyloxy C_{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
5 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;
10 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 or two
15 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;
20 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 polyhalo C_{1-4} alkyl;
25 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; cyano C_{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} alkyloxy C_{1-6} alkyl wherein each C_{1-6} alkyl is optionally substituted with one or two
5 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 polyhalo C_{1-6} alkylcarbonyl-
substituted with one or two hydroxyl groups; mono-or polyhalo C_{1-6} alkyl substituted
with one or two hydroxyl groups; mono-or polyhalo C_{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
10 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
15 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 polyhalo C_{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; $-NR_{13}-S(=O)_2-$
20 $NR_{9a}R_{9b}$; 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
25 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;
30 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 polyhalo C_{1-6} alkyl; mono-or polyhalo C_{1-6} alkyloxy; C_{1-6} alkyl substituted with
35 one $-NR_{9a}R_{9b}$; C_{1-6} alkyl substituted with one cyano; C_{1-6} alkyloxy C_{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; C₁₋₆alkyloxyC₁₋₆alkyloxy wherein each of the C₁₋₆alkyl groups are optionally substituted with one or two hydroxyl groups; C₁₋₆alkyloxy substituted with one cyano; and C₁₋₆alkyloxy substituted with one -NR_{9a}R_{9b};

R_{5b} is hydrogen; C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano;

- 5 hydroxyl; cyano; mono-or polyhaloC₁₋₆alkyloxy; mono-or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one or two hydroxyl groups; C₂₋₆alkenyl; C₁₋₄alkyloxy; -Si(CH₃)₃; C₁₋₆alkyl substituted with one R₁₂; C₁₋₆alkyl-O-carbonyl-; or C₁₋₆alkyloxy substituted with one R₁₂;

or a N-oxide, a pharmaceutically acceptable addition salt or a solvate thereof.

10

2. The compound according to claim 1, wherein

y₁ is CR_{7a} or N;

y₂ is CH;

R_{7a} is hydrogen;

- 15 R₇ is hydrogen, -NH₂, -NHCH₃, -NH(CH₂CH₃), methyl, -CH₂OH, halo or cyano; or when y₁ represents CR_{7a}, this R_{7a} can be taken together with a R₇ on an adjacent carbon atom to form -CH=CH-NH- or -N=CH-NH-;

X is -CR₁R_{1a}-, -CH₂-CHR₁-;

R₁ is hydrogen or C₁₋₆alkyl;

- 20 R_{1a} is hydrogen;

R_{2a} is hydrogen; C₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; or C₁₋₆alkyl substituted with one substituent selected from the group consisting of -NR_{9a}R_{9b}, cyano and C₁₋₄alkyloxy;

R_{2b} is hydrogen; or

- 25 R_{2a} and R_{2b} are taken together to form -CH₂-CH₂-, -CH₂-NR_{2c}-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-O-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-NR_{2c}-CH₂- or =O;

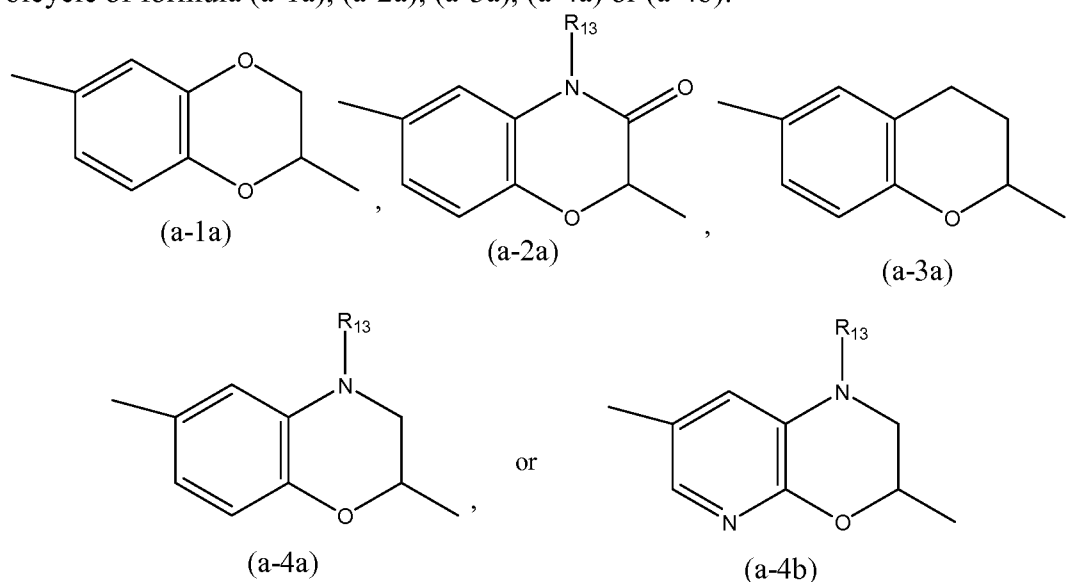
R_{2c} is hydrogen; C₁₋₄alkyl optionally substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkyl substituted with one cyano group; or C₁₋₆alkyl substituted with one -NR_{9a}R_{9b};

- 30 R₃ is hydrogen; C₁₋₆alkyl; mono-or polyhaloC₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; C₁₋₆alkyl substituted with one or two hydroxyl groups and one C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl- optionally substituted with one or two hydroxyl groups; mono-or polyhaloC₁₋₆alkylcarbonyl-; R_{10a}R_{10b}N-C₁₋₆alkylcarbonyl-; C₁₋₆alkyl-O-carbonyl-; C₁₋₆alkylcarbonyloxy-; C₁₋₆alkyl substituted with one R₁₁; C₁₋₆alkyloxy
- 35 optionally substituted with one -NR_{10a}R_{10b}; C₁₋₆alkyl substituted with one or two hydroxyl groups and one -NR₁₀R_{10b}; -S(=O)₂-C₁₋₆alkyl; -S(=O)₂-NR_{9a}R_{9b}; C₁₋₆alkyl

- 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
- 5 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 or two hydroxyl groups; C_{1-4} alkyl substituted with one $-NR_{9a}R_{9b}$; or $-C(=O)-NR_{9a}R_{9b}$;
- 10 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
- 15 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 polyhalo C_{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
- 20 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; cyano C_{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} alkyloxy C_{1-6} alkyl wherein each C_{1-6} alkyl is optionally substituted with one or two
- 25 hydroxyl groups; C_{1-6} alkylcarbonyl-; C_{1-6} alkyl-O-carbonyl-; mono-or polyhalo C_{1-6} alkylcarbonyl- substituted with one or two hydroxyl groups; mono-or polyhalo C_{1-6} alkyl substituted with one or two hydroxyl groups; mono-or polyhalo C_{1-6} alkylcarbonyl-; mono-or polyhalo C_{1-4} alkyl; or C_{1-4} alkyl substituted with one or two hydroxyl groups;
- 30 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;
- 35 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;
- 5 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;
- 10 hydroxyl; cyano; halo; C_{1-6} alkyl; C_{1-6} alkyl substituted with one or two hydroxyl groups; mono-or polyhalo C_{1-6} alkyl; mono-or polyhalo C_{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} alkyloxy C_{1-6} alkyl wherein each of the C_{1-6} alkyl groups are optionally substituted with one or two hydroxyl groups;
- 15 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} alkyloxy C_{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 polyhalo C_{1-6} alkyloxy; mono-or polyhalo C_{1-6} alkyl; C_{1-4} alkyl
- 20 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
- 25 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
- 30 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
- 35 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
 5 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 $-C(=O)-$;
 10 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
 15 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):



20

- 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 polyhalo C_{1-4} alkyl; or C_{1-4} alkyl substituted with one hydroxyl group;

- R₁₁ is cyano; -NR_{10a}R_{10b}; C₁₋₆alkyloxy optionally substituted with one hydroxyl group; -S(=O)₂-C₁₋₆alkyl; C₁₋₆alkylcarbonyloxy; -C(=O)-NR_{10a}R_{10b}; -COOH; or -P(=O)(O-C₁₋₄alkyl)₂;
- R₁₂ is -NR_{9a}R_{9b}, C₁₋₆alkyloxy, or cyano;
- 5 R₁₃ is hydrogen or C₁₋₄alkyl;
- R₁₄ is a 5 membered saturated heterocyclyl which is optionally substituted with one, two or three substituents selected from the group consisting of oxo and C₁₋₄alkyl;
- x₁ is CR_{5a} or N;
- x₂ is CR_{5b};
- 10 x₃ is CR_{5c} or N;
- each R₁₅ is independently selected from the group consisting of hydrogen, methyl, halo, and C₁₋₄alkyloxy;
- R_{5a} and R_{5c} each independently are selected from the group consisting of hydrogen; hydroxyl; cyano; halo; C₁₋₆alkyl substituted with one or two hydroxyl groups; C₁₋₆alkyl
- 15 substituted with one -NR_{9a}R_{9b}; C₁₋₆alkyloxyC₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkyloxy substituted with one hydroxyl group; C₁₋₆alkyloxyC₁₋₆alkyloxy;
- R_{5b} is hydrogen; C₁₋₆alkyl; C₃₋₆cycloalkyl optionally substituted with one cyano; cyano; mono-or polyhaloC₁₋₆alkyloxy; mono-or polyhaloC₁₋₆alkyl; C₁₋₄alkyl substituted with one hydroxyl group; C₂₋₆alkenyl; C₁₋₄alkyloxy; -Si(CH₃)₃; C₁₋₆alkyl substituted with
- 20 one R₁₂; or C₁₋₆alkyl-O-carbonyl-.
4. The compound according to claim 1, wherein
- y₁ is CH or N;
- y₂ is CH;
- 25 R₇ is hydrogen or -NH₂;
- X is CH₂;
- R_{2a} is hydrogen;
- R_{2b} is hydrogen; or
- R_{2a} and R_{2b} are taken together to form -CH₂-CH₂- or -CH₂-NH-CH₂-;
- 30 R₃ is hydrogen; C₁₋₆alkyl; C₁₋₆alkyl substituted with one or two hydroxyl groups; C₁₋₆alkyl substituted with one R₁₁; or C₁₋₆alkyl substituted with one R₁₄;
- R_{4a} is hydrogen;
- R_{4b} is hydrogen; or
- R_{4a} and R_{4b} are taken together to form =O;
- 35 Y is -O-;
- Z is -CHR₆-;
- R₆ is hydrogen;

- Ring A is phenyl or pyridinyl; wherein the phenyl or pyridinyl is optionally substituted with one or two R₈ substituents;
 each R₈ is independently hydrogen; C₁₋₄alkyloxy; cyano; or halo;
 or a R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent may be
 5 taken together with the R₆ substituent of Z, by which ring A together with Y-Z forms a
 bicycle of formula (a-3a);
 R₁₁ is C₁₋₆alkyloxy optionally substituted with one hydroxyl group; or -C(=O)-
 NR_{10a}R_{10b};
 R_{10a} and R_{10b} each independently represent hydrogen or C₁₋₄alkyl;
 10 R₁₄ is a 5 membered saturated heterocyclcyl which is optionally substituted with one,
 two or three substituents selected from the group consisting of C₁₋₄alkyl;
 x₁ is CR_{5a} or N;
 x₂ is CR_{5b};
 x₃ is CR_{5c};
 15 each R₁₅ is hydrogen;
 R_{5a} is hydrogen or C₁₋₆alkyloxyC₁₋₆alkyl;
 R_{5b} is C₁₋₆alkyl; C₃₋₆cycloalkyl; mono-or polyhaloC₁₋₆alkyloxy; C₂₋₆alkenyl; C₁₋₆alkyl
 substituted with one cyano; C₁₋₄alkyloxy; or C₁₋₆alkyl-O-carbonyl-;
 R_{5c} is hydrogen.
 20
- 5.** The compound according to claim 1, wherein
 y₁ is CH;
 y₂ is CH;
 R₇ is hydrogen;
 25 X is CH₂;
 R_{2a} is hydrogen;
 R_{2b} is hydrogen;
 R₃ is hydrogen; C₁₋₆alkyl substituted with one or two hydroxyl groups;
 R_{4a} and R_{4b} are taken together to form =O;
 30 Y is -O-;
 Z is -CH₂-;
 Ring A is phenyl optionally substituted with one or two R₈ substituents;
 each R₈ is independently hydrogen; C₁₋₄alkyloxy; cyano; or F;
 x₁ is CH;
 35 x₂ is CR_{5b};
 x₃ is CH;
 each R₁₅ 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 R₈ substituents;
 5 each R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; or halo.

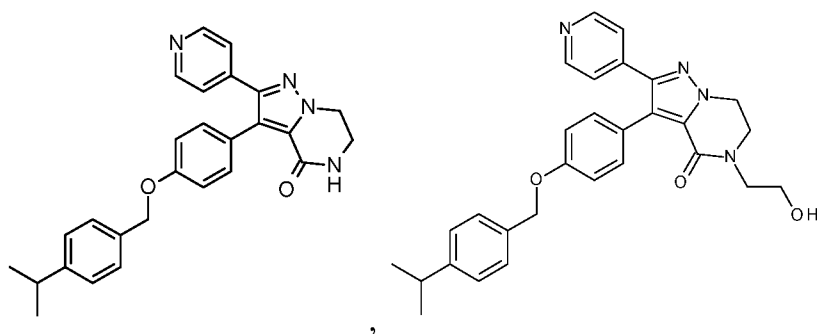
7. The compound according to claim 6, wherein ring A is phenyl or a 6-membered aromatic heterocyclyl, said heterocyclyl containing one or two nitrogen atoms; wherein the phenyl or the heterocyclyl is optionally substituted with one or two R₈ substituents;
 10 each R₈ is independently hydrogen; C₁₋₄alkyloxy; hydroxyl; cyano; or halo.

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 R₈ substituent on an atom adjacent to the atom carrying the Y-Z substituent, and said R₈ substituent is taken together with the R₆ 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).
 15 20

9. The compound according to claim 1, wherein x₁ and x₃ are CH; x₂ is CR_{5b}; R_{5b} is isopropyl.

10. The compound according to claim 1, wherein y₁ and y₂ are CH.

11. The compound according to claim 1 wherein the compound is selected from the group consisting of



tautomers and stereoisomeric forms thereof,

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

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to any one of claims 1 to 11.
- 5
13. A compound as defined in any one of claims 1 to 11 for use as a medicament.
14. A compound as defined in any one of claims 1 to 11 for use in the treatment or prevention of a disease or condition selected from 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.
- 10
15. The compound according to claim 14 wherein the disease or condition is selected from non-small-cell lung cancer, cholangiocarcinoma, and glioblastoma multiforme.
- 15

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2015/056498

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/519 A61K35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/058176 A2 (PHARMACIA CORP [US]; HANAU CATHLEEN E [US]; MERSHON SERENA MARIE [US];) 15 July 2004 (2004-07-15) cited in the application compounds in table 2; page 1, line 11 - page 1, line 16 -----	1-15
A	WO 2009/140128 A2 (IRM LLC [US]; ALBAUGH PAMELA A [US]; CHOI HA-SOON [US]; CHOPIUK GREGOR) 19 November 2009 (2009-11-19) page 1, paragraphs [0003] to [0005]; compounds 1-297 -----	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Schmid, Arnold

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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