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(54) Title: CYANOINDOLINE DERIVATIVES AS NIK INHIBITORS

(57) Abstract: Fused aromatic bicyclic substituted 5-(2-amino-4-pyrimidinyl)- cyanoindoline derivatives (I) useful for therapy and/or prophylaxis in a mammal, and in particular to inhibitors of NF-KB-inducing kinase (NIK - also known as MAP3K14) useful for treating diseases such as cancer, inflammatory disorders, metabolic disorders and autoimmune disorders. The invention is also directed to pharmaceutical compositions comprising such compounds, and to the use of such compounds or pharmaceutical compositions for the prevention or treatment of diseases such as cancer, inflammatory disorders, metabolic disorders including obesity and diabetes, and autoimmune disorders.



CYANOINDOLINE DERIVATIVES AS NIK INHIBITORS

FIELD OF THE INVENTION

5 Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

10 The present invention relates to pharmaceutical agents useful for therapy and/or prophylaxis in a mammal, and in particular to inhibitors of NF- κ B-inducing kinase (NIK - also known as MAP3K14) useful for treating diseases such as cancer (in particular B-cell malignancies including leukemias, lymphomas and myeloma), inflammatory disorders, metabolic disorders including obesity and diabetes, and autoimmune disorders. The invention is also directed to pharmaceutical compositions comprising such compounds, and to the use of such compounds or pharmaceutical compositions for the prevention or treatment of diseases such as cancer, inflammatory disorders, metabolic disorders including obesity and diabetes, and autoimmune disorders.

BACKGROUND OF THE INVENTION

20 The present invention relates to pharmaceutical agents useful for therapy and/or prophylaxis in a mammal, and in particular to inhibitors of NF- κ B-inducing kinase (NIK - also known as MAP3K14) useful for treating diseases such as cancer and inflammatory disorders. Nuclear factor-kappa B (NF- κ B) is a transcription factor regulating the expression of various genes involved in the immune response, cell proliferation, adhesion, apoptosis, and carcinogenesis. NF- κ B dependent transcriptional activation is a tightly controlled signaling pathway, through sequential events including phosphorylation and protein degradation. NIK is a serine/threonine kinase which regulates NF- κ B pathway activation. There are two NF- κ B signaling pathways, the canonical and the non-canonical. NIK is indispensable for the non-canonical signaling pathway where it phosphorylates IKK α , leading to the partial proteolysis of p100; liberating p52 which then heterodimerizes with RelB, translocates to the nucleus and mediates gene expression. The non-canonical pathway is activated by only a handful of ligands such as CD40 ligands, B-cell activating factor (BAFF), lymphotoxin β receptor ligands and TNF-related weak inducer of apoptosis (TWEAK) and NIK has been shown to be required for activation of the pathway by these ligands.

35 Because of its key role, NIK expression is tightly regulated. Under normal non-stimulated conditions NIK protein levels are very low, this is due to its interaction with a range of TNF receptor associated factors (TRAF2 and TRAF3), which are ubiquitin ligases and result in degradation of NIK. It is believed that when the non-canonical pathway is stimulated by ligands, the activated receptors now compete for TRAFs, dissociating the

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TRAF-NIK complexes and thereby increasing the levels of NIK. (Thu and Richmond, *Cytokine Growth F. R.* **2010**, *21*, 213-226)

Research has shown that blocking the NF- κ B signaling pathway in cancer cells can cause cells to stop proliferating, to die and to become more sensitive to the action of other anti-cancer therapies. A role for NIK has been shown in the pathogenesis of both
5 hematological malignancies and solid tumours.

The NF- κ B pathway is dysregulated in multiple myeloma due to a range of diverse genetic abnormalities that lead to the engagement of the canonical and non-canonical pathways
10 (Annuziata *et al. Cancer Cell* **2007**, *12*, 115-130; Keats *et al. Cancer Cell* **2007**, *12*, 131-144; Demchenko *et al. Blood* **2010**, *115*, 3541-3552). Myeloma patient samples frequently have increased levels of NIK activity. This can be due to chromosomal amplification, translocations (that result in NIK proteins that have lost TRAF binding domains), mutations (in the TRAF binding domain of NIK) or TRAF loss of function mutations.

15 Researchers have shown that myeloma cell lines can be dependent on NIK for proliferation; in these cell lines if NIK activity is reduced by either shRNA or compound inhibition, this leads to a failure in NF- κ B signaling and the induction of cell death (Annuziata 2007).

In a similar manner, mutations in TRAF and increased levels of NIK have also been seen
20 in samples from Hodgkin lymphoma (HL) patients. Once again proliferation of cell lines derived from HL patients is susceptible to inhibition of NIK function by both shRNA and compounds (Ranuncolo *et al. Blood* First Edition Paper, 2012, DOI 10.1182/blood-2012-01-405951).

NIK levels are also enhanced in adult T cell leukemia (ATL) cells and targeting NIK with
25 shRNA reduced ATL growth in vivo (Saitoh *et al. Blood* **2008**, *111*, 5118-5129).

It has been demonstrated that the API2-MALT1 fusion oncoprotein created by the recurrent translocation t(11;18)(q21;q21) in mucosa-associated lymphoid tissue (MALT) lymphoma induces proteolytic cleavage of NF- κ B-inducing kinase (NIK) at arginine 325. NIK cleavage generates a C-terminal NIK fragment that retains kinase activity and is
30 resistant to proteasomal degradation (due to loss of TRAF binding region). The presence of this truncated NIK leads to constitutive non-canonical NF- κ B signaling, enhanced B cell adhesion, and apoptosis resistance. Thus NIK inhibitors could represent a new treatment approach for refractory t(11;18)-positive MALT lymphoma (Rosebeck *et al. Science* **2011**, *331*, 468-472).

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NIK aberrantly accumulates in diffuse large B-cell lymphoma (DLBCL) cells due to constitutive activation of B-cell activation factor (BAFF) through interaction with autochthonous B-lymphocyte stimulator (BLyS) ligand. NIK accumulation in human DLBCL cell lines and patient tumor samples suggested that constitutive NIK kinase
5 activation is likely to be a key signaling mechanism involved in abnormal lymphoma tumor cell proliferation. Growth assays showed that using shRNA to inhibit NIK kinase protein expression in GCB- and ABC-like DLBCL cells decreased lymphoma cell growth *in vitro*, implicating NIK-induced NF- κ B pathway activation as having a significant role in DLBCL proliferation (Pham *et al. Blood* **2011**, *117*, 200-210).

10 More recently, also loss-of-function mutations in TRAF3 have been characterized in human and canine DLBCL (Bushell *et al., Blood* **2015**, *125*, 999-1005).

Recently, similar mutations in the non-canonical NF κ B signaling pathway (TRAF2, TRAF3, NIK, BIRC3) were found in ibrutinib-refractory mantle cell lymphoma cell lines (Rahal *et al., Nat Med* **2014**, *1*, 87-92).

15 As mentioned a role of NIK in tumour cell proliferation is not restricted to hematological cells, there are reports that NIK protein levels are stabilised in some pancreatic cancer cell lines and as seen in blood cells proliferation of these pancreatic cancer lines are susceptible to NIK siRNA treatment (Nishina *et al. Biochem. Bioph. Res. Co.* **2009**, *388*, 96-101).

Constitutive activation of NF- κ B, is preferentially involved in the proliferation of basal-
20 like subtype breast cancer cell lines, including elevated NIK protein levels in specific lines (Yamamoto *et al. Cancer Sci.* **2010**, *101*, 2391-2397). In melanoma tumours, tissue microarray analysis of NIK expression revealed that there was a statistically significant elevation in NIK expression when compared with benign tissue. Moreover, shRNA techniques were used to knock-down NIK, the resultant NIK-depleted melanoma cell lines
25 exhibited decreased proliferation, increased apoptosis, delayed cell cycle progression and reduced tumor growth in a mouse xenograft model (Thu *et al. Oncogene* **2012**, *31*(20), 2580-92). A wealth of evidence showed that NF- κ B is often constitutively activated in non-small cell lung cancer tissue specimens and cell lines. Depletion of NIK by RNAi induced apoptosis and affected efficiency of anchorage-independent NSCLC cell growth.

30 In addition research has shown that NF- κ B controls the expression of many genes involved in inflammation and that NF- κ B signalling is found to be chronically active in many inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, sepsis and others. Thus pharmaceutical agents capable of inhibiting NIK and thereby reducing

NF- κ B signaling pathway can have a therapeutic benefit for the treatment of diseases and disorders for which over-activation of NF- κ B signaling is observed.

5 Dysregulated NF- κ B activity is associated with colonic inflammation and cancer, and it has been shown that Nlrp12 deficient mice were highly susceptible to colitis and colitis-associated colon cancer. In this context work showed that NLRP12 functions as a negative regulator of the NF- κ B pathway through its interaction and regulation of NIK and TRAF3, and as a checkpoint of critical pathways associated with inflammation and inflammation-associated tumorigenesis (Allen *et al. Immunity* **2012**, *36*, 742-754).

10 Tumor necrosis factor (TNF)- α , is secreted in response to inflammatory stimuli in diseases such as rheumatoid arthritis and inflammatory bowel disease. In a series of experiments in colonic epithelial cells and mouse embryonic fibroblasts, TNF- α mediates both apoptosis and inflammation, stimulating an inflammatory cascade through the non-canonical pathway of NF- κ B activation, leading to increased nuclear RelB and p52. TNF- α induced

15 the ubiquitination of TRAFs, which interacts with NIK, leading to increased levels of phospho-NIK (Bhattacharyya *et al. J Biol. Chem.* **2011**, *285*, 39511-39522).

Inflammatory responses are a key component of chronic obstructive pulmonary disease (COPD) as such it has been shown that NIK plays a key role in exacerbating the disease

20 following infection with the Gram-negative bacterium nontypeable *Hemophilus influenza* (Shuto *et al. PNAS* **2001**, *98*, 8774-8779). Likewise cigarette smoke (CS) contains numerous reactive oxygen/nitrogen species, reactive aldehydes, and quinones, which are considered to be some of the most important causes of the pathogenesis of chronic inflammatory lung diseases, such as COPD and lung cancer. Increased levels of NIK and

25 p-IKK α have been observed in peripheral lungs of smokers and patients with COPD. In addition it has been shown that endogenous NIK is recruited to promoter sites of pro-inflammatory genes to induce post-translational modification of histones, thereby modifying gene expression profiles, in response to CS or TNF α (Chung *et al. PLoS ONE* **2011**, *6(8)*: e23488. doi:10.1371/journal.pone.0023488). A shRNA screen was used in an

30 *in vitro* model of oxidative stress induced cell death (as a model of COPD) to interrogate a human drugable genome siRNA library in order to identify genes that modulate the cellular response to stress. NIK was one of the genes identified in this screen as a potential new therapeutic target to modulate epithelial apoptosis in chronic lung diseases (Wixted *et al. Toxicol. In Vitro* **2010**, *24*, 310-318).

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Diabetic individuals can be troubled by a range of additional manifestations associated with inflammation. One such complication is cardiovascular disease and it has been shown that there are elevated levels of p-NIK, p-IKK- α/β and p-I κ B- α in diabetic aortic tissues (Bitar *et al. Life Sci.* **2010**, *86*, 844-853). In a similar manner, NIK has been shown to regulate proinflammatory responses of renal proximal tubular epithelial cells via mechanisms involving TRAF3. This suggests a role for NF- κ B noncanonical pathway activation in modulating diabetes-induced inflammation in renal tubular epithelium (Zhao *et al. Exp. Diabetes Res.* **2011**, 1-9. doi:10.1155/2011/192564). The same group has shown that NIK plays a critical role in noncanonical NF- κ B pathway activation, induced skeletal muscle insulin resistance *in vitro*, suggesting that NIK could be an important therapeutic target for the treatment of insulin resistance associated with inflammation in obesity and type 2 diabetes (Choudhary *et al. Endocrinology* **2011**, *152*, 3622-3627).

NF- κ B is an important component of both autoimmunity and bone destruction in rheumatoid arthritis (RA). Mice lacking functional NIK have no peripheral lymph nodes, defective B and T cells, and impaired receptor activator of NF- κ B ligand-stimulated osteoclastogenesis. Aya *et al. (J. Clin. Invest.* **2005**, *115*, 1848-1854) investigated the role of NIK in murine models of inflammatory arthritis using *Nik*^{-/-} mice. The serum transfer arthritis model was initiated by preformed antibodies and required only intact neutrophil and complement systems in recipients. While *Nik*^{-/-} mice had inflammation equivalent to that of *Nik*^{+/+} controls, they showed significantly less periarticular osteoclastogenesis and less bone erosion. In contrast, *Nik*^{-/-} mice were completely resistant to antigen-induced arthritis (AIA), which requires intact antigen presentation and lymphocyte function but not lymph nodes. Additionally, transfer of *Nik*^{+/+} splenocytes or T cells to *Rag2*^{-/-} mice conferred susceptibility to AIA, while transfer of *Nik*^{-/-} cells did not. *Nik*^{-/-} mice were also resistant to a genetic, spontaneous form of arthritis, generated in mice expressing both the KRN T cell receptor and H-2g7. The same group used transgenic mice with OC-lineage expression of NIK lacking its TRAF3 binding domain (NT3), to demonstrate that constitutive activation of NIK drives enhanced osteoclastogenesis and bone resorption, both in basal conditions and in response to inflammatory stimuli (Yang *et al. PLoS ONE* **2010**, *5(11)*: e15383. doi:10.1371/journal.pone.0015383). Thus this group concluded that NIK is important in the immune and bone-destructive components of inflammatory arthritis and represents a possible therapeutic target for these diseases.

It has also been hypothesized that manipulating levels of NIK in T cells may have therapeutic value. Decreasing NIK activity in T cells might significantly ameliorate autoimmune responses and alloresponses, like GVHD (Graft Versus Host Disease) and transplant rejection, without crippling the immune system as severely as do inhibitors of canonical NF- κ B activation.

WO2003030909 describes the preparation of 2- and 4-aminopyrimidines N-substituted by a bicyclic ring for use as kinase inhibitors in the treatment of cancer.

WO2002079197 describes 4-aryl-substituted 2-pyrimidinamines and 2-pyridinamines, useful as inhibitors of c-Jun N-terminal kinases (JNK) and other protein kinases.

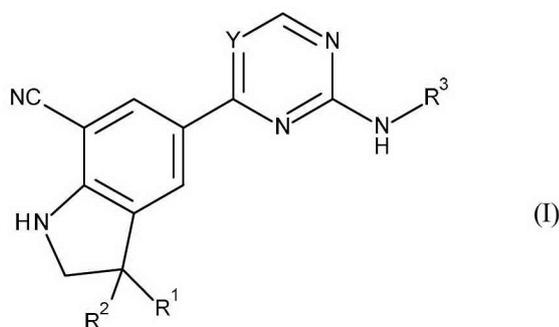
WO2014174021, WO2015044267 and WO2015044269 describe NIK inhibitors for the treatment of cancer.

WO2010042337 describes 6-azaindole aminopyrimidine derivatives having NIK inhibitory activity.

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

DESCRIPTION OF THE INVENTION

In a first aspect, the present invention concerns novel compounds of Formula (I):



tautomers and stereoisomeric forms thereof, wherein

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

R^2 represents C_{1-6} alkyl, C_{1-6} alkyl substituted with one R^5 , or C_{1-6} alkyl substituted with one, two or three fluoro atoms;

Y represents CR^4 or N ;

R^4 represents hydrogen or halo;

R^5 represents Het^{3a} , $-NR^{6a}R^{6b}$, or $-OR^7$;

R^{6a} represents hydrogen or C_{1-4} alkyl;

R^{6b} represents hydrogen; C_{1-4} alkyl; C_{3-6} cycloalkyl; $-C(=O)-C_{1-4}$ alkyl; $-C(=O)-Het^4$;

$-S(=O)_2-C_{1-4}$ alkyl; $-C(=O)-C_{1-4}$ alkyl substituted with one substituent selected from the

group consisting of $-OH$ and $-NR^{16a}R^{16b}$; or C_{1-4} alkyl substituted with one substituent selected from the group consisting of $-OH$ and $-S(=O)_2-C_{1-4}$ alkyl;

R^7 represents hydrogen, C_{1-4} alkyl, $-C_{1-4}$ alkyl- $NR^{8a}R^{8b}$, $-C(=O)-R^9$, $-S(=O)_2-OH$, $-P(=O)_2-OH$, $-(C=O)-CH(NH_2)-C_{1-4}$ alkyl- Ar^1 , or $-C_{1-4}$ alkyl- Het^{3b} ;

5 R^{8a} represents hydrogen or C_{1-4} alkyl;

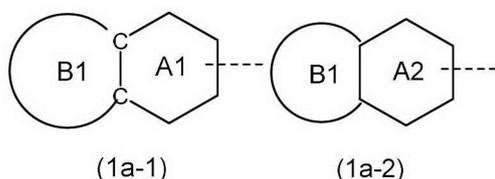
R^{8b} represents hydrogen, C_{1-4} alkyl, or C_{3-6} cycloalkyl;

R^9 represents C_{1-6} alkyl, or C_{1-6} alkyl substituted with one substituent selected from the group consisting of $-NH_2$, $-COOH$, and Het^6 ;

R^{16a} and R^{16b} each independently represents hydrogen, C_{1-4} alkyl or C_{3-6} cycloalkyl;

10 R^3 represents

a) a fused bicyclic ring system of formula (1a-1) or (1a-2):



ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms;

15 ring A2 represents 2-oxo-1,2-dihydropyridin-3-yl;

ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, $S(=O)_p$ and N;

wherein (1a-1) and (1a-2) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group

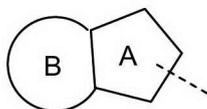
20 consisting of halo; cyano; oxo; $-OH$; C_{1-6} alkyl; $-O-C_{1-4}$ alkyl; $-C(=O)-R^{10}$; $-S(=O)_2-C_{1-4}$ alkyl; $-S(=O)(=N-R^{20a})-C_{1-4}$ alkyl; $-O-C_{1-4}$ alkyl substituted with one, two or three halo atoms; $-O-C_{1-4}$ alkyl- R^{12} ; C_{3-6} cycloalkyl; $-O-C_{3-6}$ cycloalkyl; Het^{1a} ; $-O-Het^{1b}$; R^{18} ; $-P(=O)-(C_{1-4}alkyl)_2$; $-NH-C(=O)-C_{1-4}alkyl$; $-NH-C(=O)-Het^{1g}$; $-NR^{17a}R^{17b}$; $C_{1-4}alkyl$ substituted with one, two or three halo atoms; $C_{1-4}alkyl$ substituted with one, two or three $-OH$ substituents; $C_{1-4}alkyl$ substituted with one R^{13} ; $C_{1-4}alkyl$ substituted with one R^{18} ; $C_{2-6}alkenyl$; and $C_{2-6}alkenyl$ substituted with one R^{13} ;

wherein ring A2 may optionally be substituted, where possible, on the N-atom with a substituent selected from the group consisting of C_{1-6} alkyl; C_{3-6} cycloalkyl; Het^{1a} ; R^{18} ;

30 $C_{1-4}alkyl$ substituted with one, two or three halo atoms; $C_{1-4}alkyl$ substituted with one, two or three $-OH$ substituents; $C_{1-4}alkyl$ substituted with one R^{13} ; $C_{1-4}alkyl$ substituted with one R^{18} ; $C_{2-6}alkenyl$; and $C_{2-6}alkenyl$ substituted with one R^{13} ; provided that when Het^{1a} or R^{18} are directly attached to the N-atom of ring A2, said Het^{1a} or R^{18} are attached to the N-atom via a ring carbon atom; and

wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when Het^{1a} or R¹⁸ are directly attached to the N-atom of ring B1, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom; or

10 b) a fused bicyclic ring system of formula (2a-1):



(2a-1)

ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, and C₁₋₄alkyl substituted with one, two or three halo atoms;

15 ring B represents a C₅₋₇cycloalkyl or a 5- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N; wherein said C₅₋₇cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring carbon atoms with one or two substituents each independently selected from the group consisting of C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl and -C₁₋₄alkyl-OH, or one ring carbon atom may optionally be substituted with oxo; and

20 wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; or

c) a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N;

30 wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -S(=O)(=N-R^{20a})-C₁₋₄alkyl; -O-C₁₋

4alkyl substituted with one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -
O-C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -
NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three halo atoms;
C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with
5 one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted
with one R¹³; and

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may
optionally be substituted, where possible, on one ring N-atom with a substituent
selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl
10 substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or
three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with
one R¹⁸; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-
C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that
when Het^{1a} or R¹⁸ are directly attached to a N-atom, said Het^{1a} or R¹⁸ are attached to the
15 N-atom via a ring carbon atom;

R¹⁰ represents -OH, -O-C₁₋₄alkyl, -NR^{11a}R^{11b} or Het²;

R¹⁸ represents a 5-membered aromatic ring containing one, two or three N-atoms;
wherein said 5-membered aromatic ring may optionally be substituted with one
substituent selected from the group consisting of C₁₋₄alkyl and C₃₋₆cycloalkyl;

20 Het^{1a}, Het^{1c} and Het^{1d} each independently represents a 4- to 7-membered monocyclic
saturated heterocyclyl containing one or two heteroatoms each independently selected
from O, S, S(=O)_p and N; or a 6- to 11-membered bicyclic saturated heterocyclyl,
including fused, spiro and bridged cycles, containing one, two or three heteroatoms
each independently selected from O, S, S(=O)_p and N;

25 wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-
membered bicyclic saturated heterocyclyl may optionally be substituted, where
possible, on one, two or three ring N-atoms with a substituent each independently
selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl
substituted with one substituent selected from the group consisting of -OH and
30 -O-C₁₋₄alkyl; and

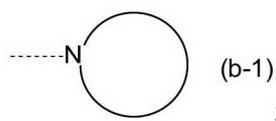
wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-
membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or
three ring C-atoms with one or two substituents each independently selected from the
group consisting of -OH, oxo, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -
35 NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

Het^{1b}, Het^{1c}, Het^{1g} and Het⁴ each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, said Het^{1b}, Het^{1c}, Het^{1g} and Het⁴ containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

Het² represents a heterocyclyl of formula (b-1):



(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N, or a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, optionally containing one or two additional heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein in case (b-1) contains one or two additional N-atoms, said one or two N-atoms may optionally be substituted with C₁₋₄alkyl; and

wherein (b-1) may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of halo, -OH, cyano, C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, and C₁₋₄alkyl-OH;

R^{11b} represents hydrogen; Het^{1c}; C₁₋₄alkyl; C₁₋₄alkyl-Het⁵; C₁₋₄alkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₃₋₆cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

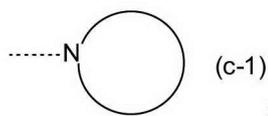
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, -S(=O)₂-C₁₋₄alkyl, -S(=O)(=N-R^{20c})-C₁₋₄alkyl, or -C(=O)-Het^{1f};

R^{12} represents $-\text{OH}$, $-\text{O}-\text{C}_{1-4}\text{alkyl}$, $-\text{NR}^{14a}\text{R}^{14b}$, $-\text{C}(=\text{O})\text{NR}^{14c}\text{R}^{14d}$, $-\text{S}(=\text{O})_2-\text{C}_{1-4}\text{alkyl}$, $-\text{S}(=\text{O})(=\text{N}-\text{R}^{20b})-\text{C}_{1-4}\text{alkyl}$, $\text{C}_{3-6}\text{cycloalkyl}$, Ar^2 , or Het^{1c} ;

Ar^1 represents phenyl optionally substituted with one hydroxy;

Ar^2 represents phenyl optionally substituted with one $\text{C}_{1-4}\text{alkyl}$; or a 5- or 6-membered heteroaromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N;

Het^{3a} , Het^{3b} , Het^5 , Het^6 and Het^{1f} each independently represents a heterocyclyl of formula (c-1):



(c-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, $\text{S}(=\text{O})_p$ and N; wherein in case (c-1) contains one additional N-atom, said additional N-atom may optionally be substituted with $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{3-6}\text{cycloalkyl}$; and wherein (c-1) may optionally be substituted on one or two ring C-atoms atoms with one or two substituents each independently selected from the group consisting of halo, $\text{C}_{1-4}\text{alkyl}$, and $\text{C}_{3-6}\text{cycloalkyl}$;

R^{11a} , R^{14a} , R^{14c} , R^{14g} , R^{14i} , R^{14k} , R^{15a} , R^{17a} and R^{19a} each independently represents hydrogen or $\text{C}_{1-4}\text{alkyl}$;

R^{14b} , R^{14d} , R^{14h} , R^{14j} , R^{14l} , R^{15b} , R^{17b} and R^{19b} each independently represents hydrogen; $\text{C}_{1-4}\text{alkyl}$; $\text{C}_{3-6}\text{cycloalkyl}$; or $\text{C}_{1-4}\text{alkyl}$ substituted with one substituent selected from the group consisting of halo, $-\text{OH}$ and $-\text{O}-\text{C}_{1-4}\text{alkyl}$;

R^{20a} , R^{20b} and R^{20c} each independently represents hydrogen; $\text{C}_{1-4}\text{alkyl}$; $\text{C}_{3-6}\text{cycloalkyl}$; or $\text{C}_{1-4}\text{alkyl}$ substituted with one substituent selected from the group consisting of $-\text{OH}$ and $-\text{O}-\text{C}_{1-4}\text{alkyl}$;

p represents 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

In a second aspect, the present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof, and a pharmaceutically acceptable carrier or excipient.

In a third aspect, the invention relates to a compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof, for use as a medicament.

5 The invention further relates to a compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof, for use in the treatment or in the prevention of cancer, inflammatory disorders, autoimmune disorders, and metabolic disorders such as diabetes and obesity.

10 In a particular embodiment, the invention relates to a compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof, for use in the treatment or in the prevention of a haematological malignancy or solid tumour.

15 In a specific embodiment said haematological malignancy is selected from the group consisting of multiple myeloma, Hodgkin lymphoma, T-cell leukaemia, mucosa-associated lymphoid tissue lymphoma, diffuse large B-cell lymphoma and mantle cell lymphoma. In another specific embodiment of the present invention, the solid tumour is selected from the group consisting of pancreatic cancer, breast cancer, melanoma and non-small cell lung cancer.

20 In a fourth aspect, the present invention provides a method of treating or preventing cancer wherein the cancer is modulated by the NIK pathway and wherein the method comprises administering an effective amount of a compound of the first aspect or a pharmaceutical composition of the second aspect.

25 In a fifth aspect, the present invention provides use of compound of the first aspect, or a pharmaceutical composition of the second aspect, in the manufacture of a medicament for treating or preventing cancer wherein the cancer is modulated by the NIK pathway.

30 In a sixth aspect, the present invention provides a method of treating or preventing a cell proliferative disease modulated by the NIK pathway in a warm-blooded animal which comprises administering to the said animal an effective amount of a compound of the first aspect or a pharmaceutical composition of the second aspect.

35 In a seventh aspect, the present invention provides use of a compound of the first aspect, or a pharmaceutical composition of the second aspect, in the manufacture of a medicament for treating or preventing a cell proliferative disease modulated by the NIK pathway in a warm-blooded animal.

The invention also relates to the use of a compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof, in combination with an additional pharmaceutical agent for use in the treatment or prevention of cancer, inflammatory disorders, autoimmune disorders, and metabolic disorders such as diabetes and obesity.

- 5 Furthermore, the invention relates to a process for preparing a pharmaceutical composition according to the invention, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof.
- 10 The invention also relates to a product comprising a compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof, and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of cancer, inflammatory disorders, autoimmune disorders, and metabolic disorders such as diabetes and obesity.
- 15 Additionally, the invention relates to a method of treating or preventing a cell proliferative disease in a warm-blooded animal which comprises administering to the said animal an effective amount of a compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof, as defined herein, or a pharmaceutical composition or combination as defined herein.
- 20 Some of the compounds of the present invention may undergo metabolism to a more active form in vivo (prodrugs).

DETAILED DESCRIPTION OF THE INVENTION

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

The term ‘halo’ or ‘halogen’ as used herein represents fluoro, chloro, bromo and iodo.

- 30 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, and so on.

The term 'C₁₋₄alkyl' as used herein as a group or part of a group represents a straight or branched chain saturated hydrocarbon radical having from 1 to 4 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, *t*-butyl and the like.

5 The term 'C₁₋₆alkyl' as used herein as a group or part of a group represents a straight or branched chain saturated hydrocarbon radical having from 1 to 6 carbon atoms such as the groups defined for C₁₋₄alkyl and *n*-pentyl, *n*-hexyl, 2-methylbutyl and the like.

10 The term "C₂₋₆alkenyl" as used herein as a group or part of a group represents a straight or branched chain hydrocarbon group containing from 2 to 6 carbon atoms and containing a carbon carbon double bond such as, but not limited to, ethenyl, propenyl, butenyl, pentenyl, 1-propen-2-yl, hexenyl and the like.

The term 'C₃₋₆cycloalkyl' as used herein as a group or part of a group represents cyclic saturated hydrocarbon radicals having from 3 to 6 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

15 In general, 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 4 hydrogens, more 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
20 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.

25 Combinations of substituents and/or variables are permissible only if such combinations result in chemically stable compounds. "Stable compound" is meant to indicate 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.

The skilled person will understand that the term "optionally substituted" means that the atom or radical indicated in the expression using "optionally substituted" may or may not be substituted (this means substituted or unsubstituted respectively).

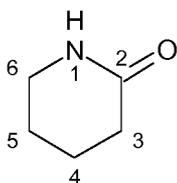
When two or more substituents are present on a moiety they may, where possible and unless otherwise is indicated or is clear from the context, replace hydrogens on the same atom or they may replace hydrogen atoms on different atoms in the moiety.

It will be clear for the skilled person that, unless otherwise is indicated or is clear from the context, a substituent on a heterocyclyl group may replace any hydrogen atom on a ring carbon atom or on a ring heteroatom (e.g. a hydrogen on a nitrogen atom may be replaced by a substituent), for example in saturated heterocyclyl groups or 5-membered aromatic rings as used in the definition of R¹⁸.

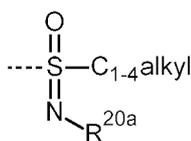
C(O) or C(=O) represents a carbonyl moiety.

S(=O)₂ or SO₂ represents a sulfonyl moiety.

"oxo" means =O; for example piperidine substituted with oxo in position 2 is represented by the following structure:



The skilled person will understand that -S(=O)(=N-R^{20a})-C₁₋₄alkyl corresponds with



Within the context of this invention 'saturated' means 'fully saturated', if not otherwise specified.

Het^{1a}, Het^{1c} and Het^{1d}, may be attached to the remainder of the molecule of Formula (I) through any available ring carbon or nitrogen atom as appropriate, if not otherwise specified.

The 5-membered aromatic ring containing one, two or three N-atoms as referred to in the definition of R¹⁸, may be attached to the remainder of the molecule of Formula (I) through any available ring carbon or nitrogen atom as, if not otherwise specified.

It will be clear that in case a saturated cyclic moiety is substituted on two ring carbon atoms with one substituent, in total two carbon-linked substituents are present on the saturated cyclic moiety (one substituent on each carbon atom).

5 It will be clear that in case a saturated cyclic moiety is substituted on two ring carbon atoms with two substituents, in total four carbon-linked substituents are present on the saturated cyclic moiety (two substituents on each carbon atom).

It will be clear that in case a saturated cyclic moiety is substituted on three ring carbon atoms with two substituents, in total six carbon-linked substituents are present on the saturated cyclic moiety (two substituents on each carbon atom).

10 It will be clear that in case a saturated cyclic moiety is substituted on two ring N-atoms with a substituent, in total two N-linked substituents are present on the saturated cyclic moiety (a substituent on each N-atom).

It will be clear that a saturated cyclic moiety may, where possible, have substituents on both carbon and N-atoms, unless otherwise is indicated or is clear from the context.

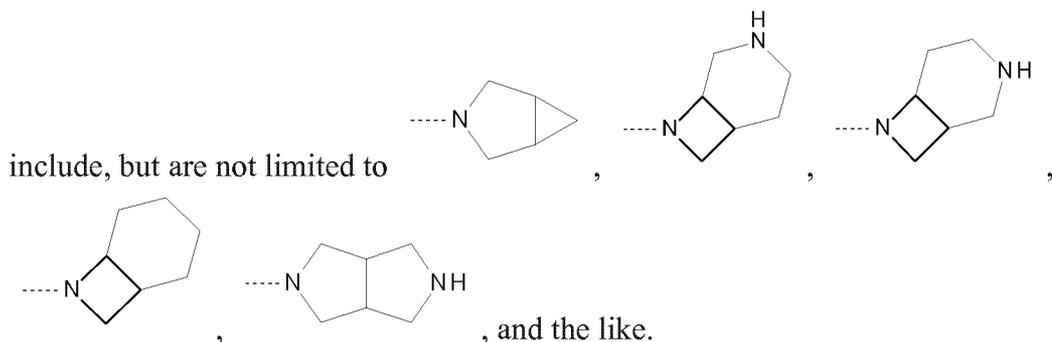
15 Within the context of this invention, bicyclic saturated heterocyclyl groups include fused, spiro and bridged saturated heterocycles.

Fused bicyclic groups are two cycles that share two atoms and the bond between these atoms.

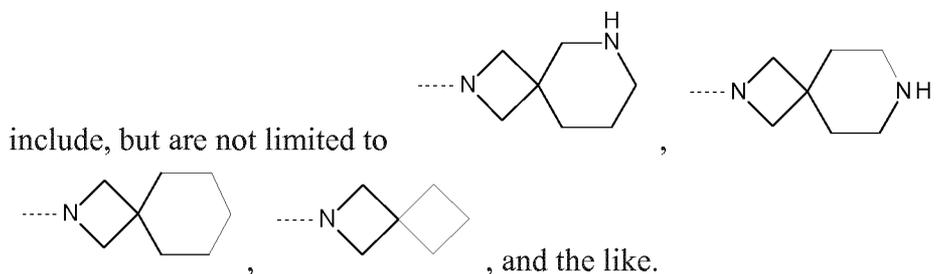
Spiro bicyclic groups are two cycles that are joined at a single atom.

20 Bridged bicyclic groups are two cycles that share more than two atoms.

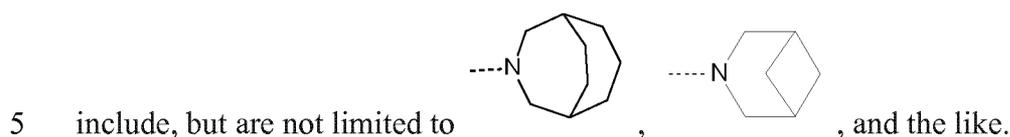
Examples of N-linked 6- to 11-membered fused bicyclic saturated heterocyclyl groups,



Examples of N-linked 6- to 11-membered spiro bicyclic saturated heterocyclyl groups,



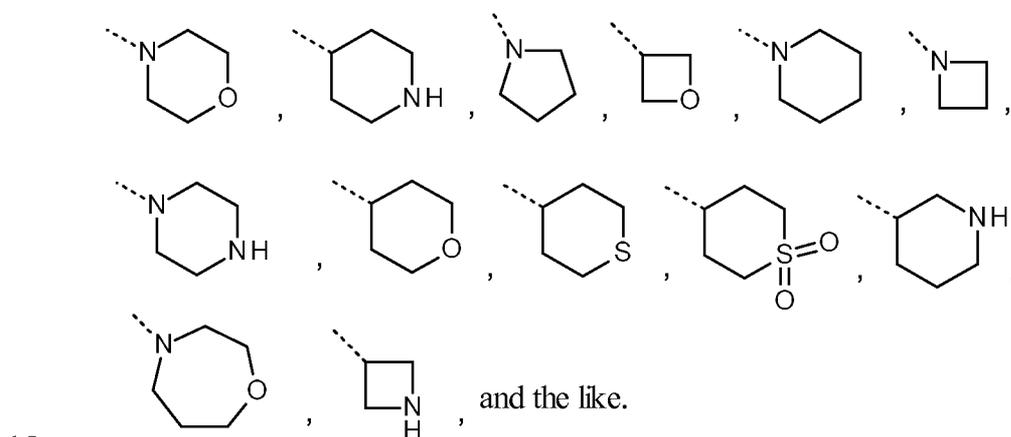
Examples of N-linked 6- to 11-membered bridged bicyclic saturated heterocyclyl groups,



The skilled person will realize that the definition of Het^{1a}, Het^{1c} and Het^{1d} also includes C-linked bicycles (attached to the remainder of the molecule of Formula (I) through any available ring carbon atom).

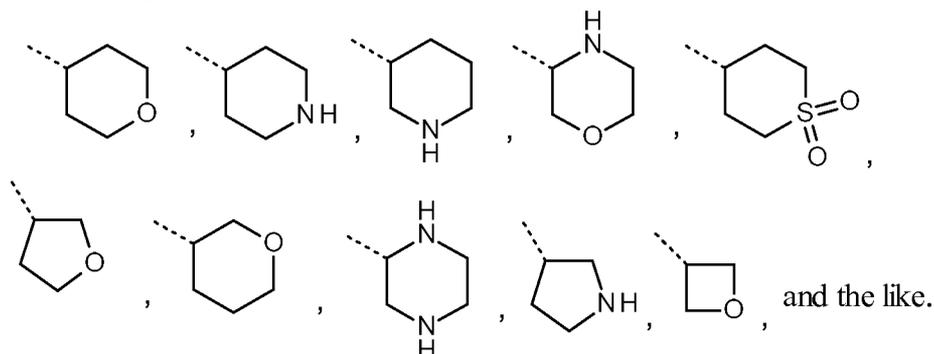
10 It should be understood that the exemplified bicyclic saturated heterocyclyl groups referred to above may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

Non-limiting examples of 4- to 7-membered monocyclic saturated heterocyclyl moieties containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N (as in the definition of Het^{1a}, Het^{1c}, and Het^{1d}) are shown below:



Each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

Non-limiting examples of 4- to 7-membered monocyclic saturated heterocyclyl moieties, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom (C-linked), and containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N (as in the definition of Het^{1b}, Het^{1e}, Het^{1g} and Het⁴) are shown below:

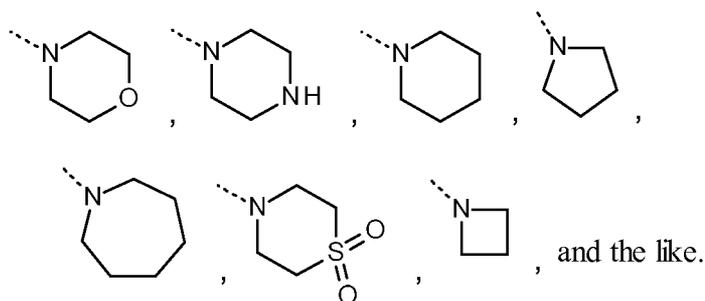


5

Each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

Non-limiting examples of N-linked 4- to 7-membered monocyclic saturated heterocyclyl moieties optionally containing one additional heteroatom selected from O, S, S(=O)_p and N (as in the definition of (b-1) and (c-1)) are shown below:

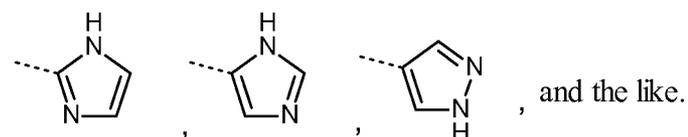
10



Each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

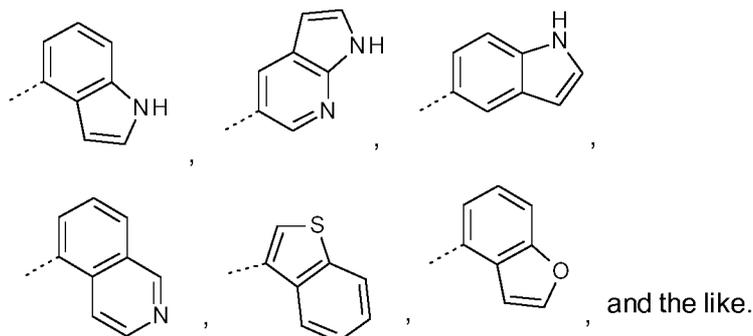
Non-limiting examples of 5-membered aromatic ring containing one, two or three N-atoms as referred to in the definition of R¹⁸ are shown below:

15



Each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

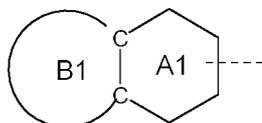
The skilled person will realize that typical fused 6- to 11-membered bicyclic heteroaromatic ring systems containing one or two heteroatoms each independently selected from O, S, and N (as in the definition of R³), will be fused 7- to 11-membered bicyclic heteroaromatic ring systems containing one or two heteroatoms each independently selected from O, S, and N. Non-limiting examples are shown below:



Each of which may optionally be substituted, where possible, on carbon atoms and/or one nitrogen atom according to any of the embodiments.

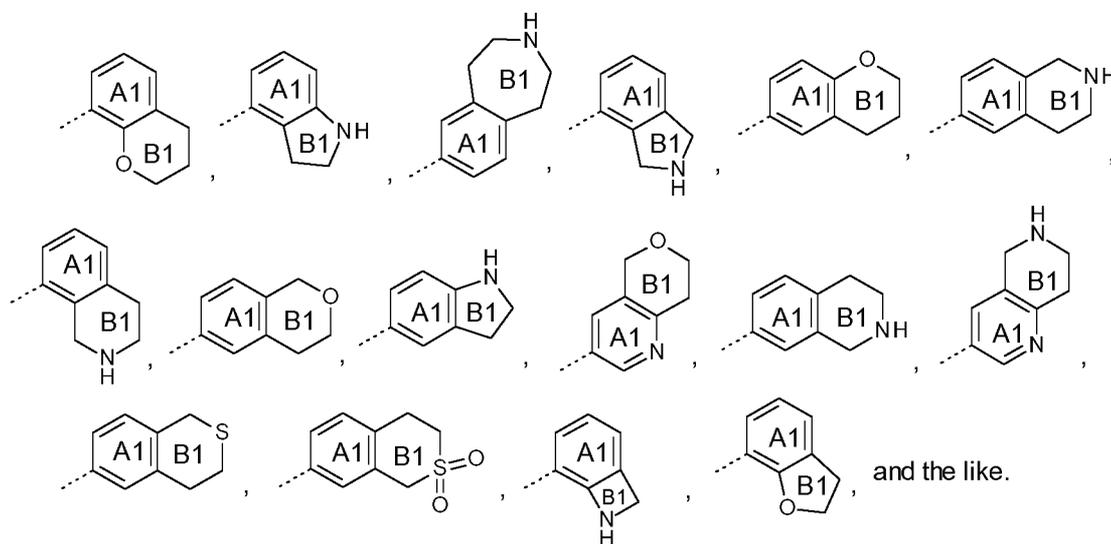
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Non-limiting examples of the fused bicyclic ring system of formula (1a-1):



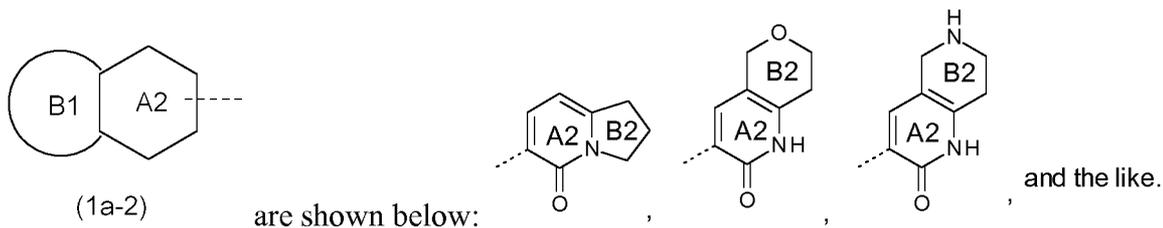
(1a-1)

are shown below:



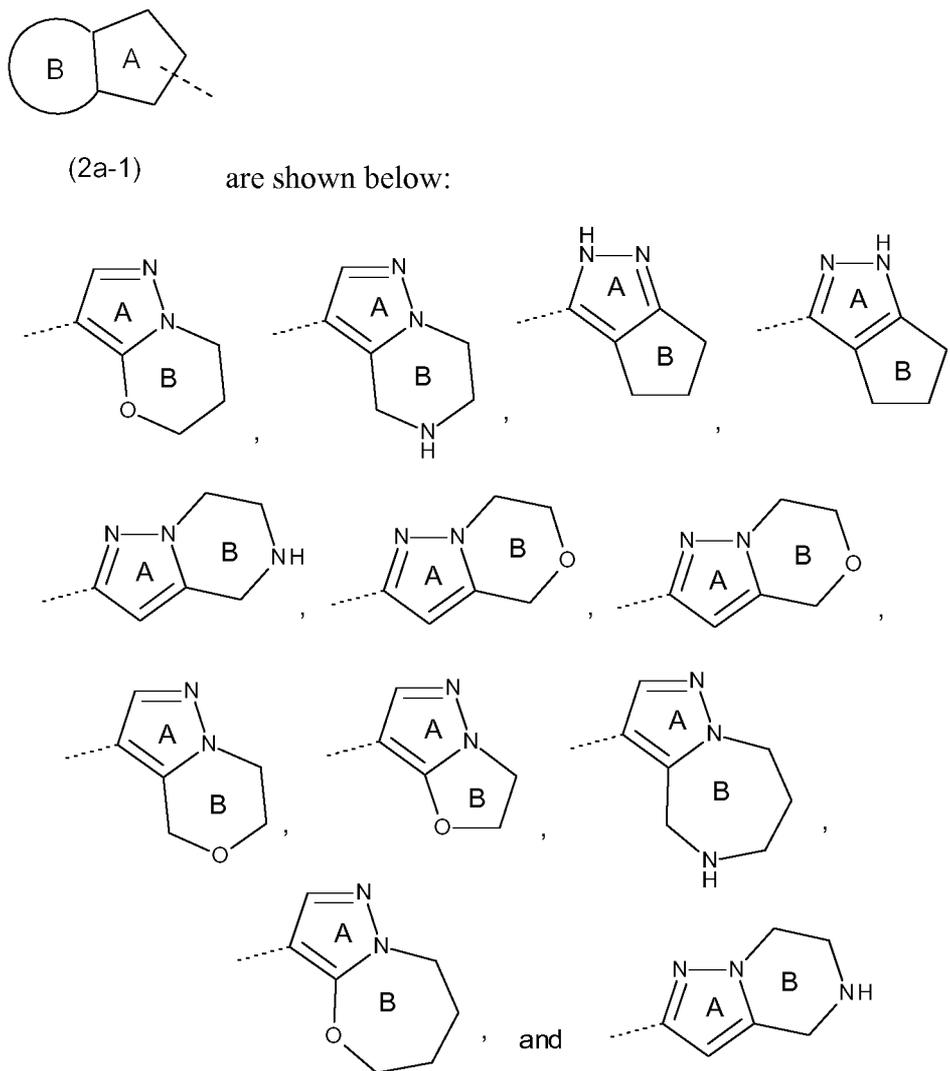
Each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

Non-limiting examples of the fused bicyclic ring system of formula (1a-2):



5 Each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

Non-limiting examples of the fused bicyclic ring system of formula (2a-1):



Each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

5 The skilled person will understand that in case R^3 represents a fused bicyclic ring system of formula (1a-1), (1a-1) is attached to the remainder of the molecule of Formula (I) (-NH-moiety) via ring A1.

The skilled person will understand that in case R^3 represents a fused bicyclic ring system of formula (1a-2), (1a-2) is attached to the remainder of the molecule of Formula (I) (-NH-moiety) via a ring carbon atom of ring A2.

10 The skilled person will understand that in case R^3 represents a fused bicyclic ring system of formula (2a-1), (2a-1) is attached to the remainder of the molecule of Formula (I) (-NH-moiety) via a ring carbon atom of ring A.

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

15 Lines (such as “---”) drawn into ring systems indicate that the bond may be attached to any of the suitable ring atoms.

When any variable occurs more than one time in any constituent, each definition is independent.

When any variable occurs more than one time in any formula (e.g. Formula (I)), each definition is independent.

20 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.

25 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.

30 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.

5 The term “compound(s) of the (present) invention” or “compound(s) according to the (present) invention” as used herein, is meant to include the compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof.

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

Hereinbefore and hereinafter, the term “compound(s) of Formula (I)” is meant to include the tautomers thereof and the stereoisomeric forms thereof.

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

15 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.

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

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
25 may be in the *E* or the *Z* configuration.

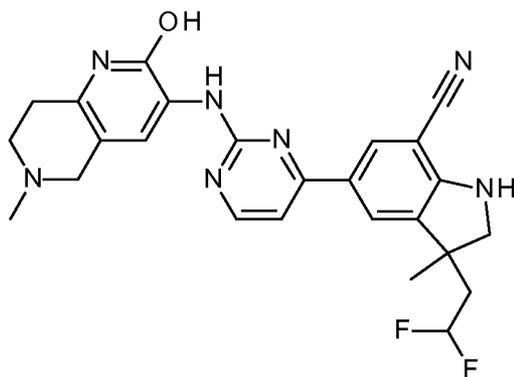
Substituents on bivalent cyclic saturated or partially saturated radicals may have either the cis- or trans-configuration; for example if a compound contains a disubstituted cycloalkyl group, the substituents may be in the cis or trans configuration.

Therefore, the invention includes enantiomers, atropisomers, diastereomers, racemates, *E*
30 isomers, *Z* isomers, cis isomers, trans isomers and mixtures thereof, whenever chemically possible.

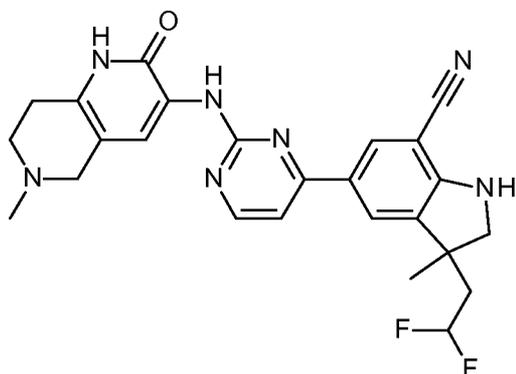
The meaning of all those terms, i.e. enantiomers, atropisomers, diastereomers, racemates, *E* isomers, *Z* isomers, cis isomers, trans isomers and mixtures thereof are known to the skilled person.

- 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.
- 10 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 according to Formula (I) may also exist in their tautomeric form. Such forms in so far as they may exist, although not explicitly indicated in the above Formula (I) are intended to be included within the scope of the present invention. It follows that a single compound may exist in both stereoisomeric and tautomeric form. For example



- 25 also covers the other tautomeric form



Pharmaceutically-acceptable addition salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

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) and solvates thereof, are able to form.

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) 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 solvent addition forms as well as the salts thereof, which the compounds of Formula (I) are able to form. Examples of such solvent addition 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 pharmaceutically acceptable addition salts, and solvates thereof, involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature (or the most abundant one found in nature).

All isotopes and isotopic mixtures of any particular atom or element as specified herein are contemplated within the scope of the compounds of the invention, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{35}S , ^{18}F , ^{36}Cl , ^{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 . In particular, deuterated compounds are intended to be included within the scope of the

present invention.

Certain isotopically-labeled compounds of the present invention (e.g., those labeled with ^3H and ^{14}C) are useful in compound and for substrate tissue distribution assays. Tritiated (^3H) and carbon-14 (^{14}C) isotopes are useful for their ease of preparation and detectability.

- 5 Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O , ^{13}N , ^{11}C and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy.

10

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

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

R^2 represents C_{1-6} alkyl, or C_{1-6} alkyl substituted with one R^5 ;

- 15 Y represents CR^4 ;

R^4 represents hydrogen or halo;

R^5 represents Het^{3a} , $-\text{NR}^{6a}\text{R}^{6b}$, or $-\text{OR}^7$;

R^{6a} represents hydrogen or C_{1-4} alkyl;

R^{6b} represents hydrogen; C_{1-4} alkyl; C_{3-6} cycloalkyl; $-\text{C}(=\text{O})-\text{C}_{1-4}$ alkyl; $-\text{C}(=\text{O})-\text{Het}^4$;

- 20 $-\text{S}(=\text{O})_2-\text{C}_{1-4}$ alkyl; $-\text{C}(=\text{O})-\text{C}_{1-4}$ alkyl substituted with one substituent selected from the group consisting of $-\text{OH}$ and $-\text{NR}^{16a}\text{R}^{16b}$; or C_{1-4} alkyl substituted with one substituent selected from the group consisting of $-\text{OH}$ and $-\text{S}(=\text{O})_2-\text{C}_{1-4}$ alkyl;

R^7 represents hydrogen, C_{1-4} alkyl, $-\text{C}_{1-4}$ alkyl- $\text{NR}^{8a}\text{R}^{8b}$, $-\text{C}(=\text{O})-\text{R}^9$, $-\text{S}(=\text{O})_2-\text{OH}$,

$-\text{P}(=\text{O})_2-\text{OH}$, $-\text{C}(=\text{O})-\text{CH}(\text{NH}_2)-\text{C}_{1-4}$ alkyl- Ar^1 , or $-\text{C}_{1-4}$ alkyl- Het^{3b} ;

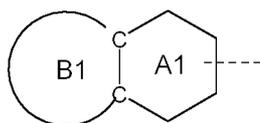
- 25 R^{8a} represents hydrogen or C_{1-4} alkyl;

R^{8b} represents hydrogen, C_{1-4} alkyl, or C_{3-6} cycloalkyl;

R^9 represents C_{1-6} alkyl, or C_{1-6} alkyl substituted with one substituent selected from the group consisting of $-\text{NH}_2$, $-\text{COOH}$, and Het^6 ;

R^{16a} and R^{16b} each independently represents hydrogen, C_{1-4} alkyl or C_{3-6} cycloalkyl;

- 30 R^3 represents a fused bicyclic ring system of formula (1a-1):



(1a-1)

ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms; ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N; wherein (1a-1) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; oxo; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -S(=O)(=N-R^{20a})-C₁₋₄alkyl; -O-C₁₋₄alkyl substituted with one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; and

wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when Het^{1a} or R¹⁸ are directly attached to the N-atom of ring B, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom;

R¹⁰ represents -OH, -O-C₁₋₄alkyl, -NR^{11a}R^{11b} or Het²;

R¹⁸ represents a 5-membered aromatic ring containing one, two or three N-atoms; wherein said 5-membered aromatic ring may optionally be substituted with one substituent selected from the group consisting of C₁₋₄alkyl and C₃₋₆cycloalkyl;

Het^{1a}, Het^{1c} and Het^{1d} each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N; or a 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, containing one, two or three heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted, where possible, on one, two or three ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and

-O-C₁₋₄alkyl; and

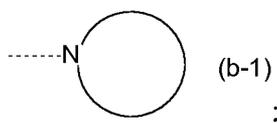
wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, oxo, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, said Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

Het² represents a heterocyclyl of formula (b-1):



(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N, or a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, optionally containing one or two additional heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein in case (b-1) contains one or two additional N-atoms, said one or two N-atoms may optionally be substituted with C₁₋₄alkyl; and

wherein (b-1) may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of halo, -OH, cyano, C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, and C₁₋₄alkyl-OH;

R^{11b} represents hydrogen; Het^{1e} ; $C_{1-4}alkyl$; $C_{1-4}alkyl-Het^5$; $C_{1-4}alkyl$ substituted with one, two or three substituents each independently selected from the group consisting of halo, –OH and –O- $C_{1-4}alkyl$; $C_{3-6}cycloalkyl$; or $C_{3-6}cycloalkyl$ substituted with one, two or three substituents each independently selected from the group consisting of halo, –OH and –O- $C_{1-4}alkyl$;

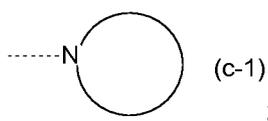
R^{13} represents –O- $C_{1-4}alkyl$, –C(=O)NR^{15a}R^{15b}, –NR^{19a}R^{19b}, $C_{3-6}cycloalkyl$, Het^{1d} , –S(=O)₂- $C_{1-4}alkyl$, –S(=O)(=N-R^{20c})- $C_{1-4}alkyl$, or –C(=O)- Het^{1f} ;

R^{12} represents –OH, –O- $C_{1-4}alkyl$, –NR^{14a}R^{14b}, –C(=O)NR^{14c}R^{14d}, –S(=O)₂- $C_{1-4}alkyl$, –S(=O)(=N-R^{20b})- $C_{1-4}alkyl$, $C_{3-6}cycloalkyl$, Ar^2 , or Het^{1c} ;

Ar^1 represents phenyl optionally substituted with one hydroxy;

Ar^2 represents phenyl optionally substituted with one $C_{1-4}alkyl$;

Het^{3a} , Het^{3b} , Het^5 , Het^6 and Het^{1f} each independently represents a heterocyclyl of formula (c-1):



(c-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N;

wherein in case (c-1) contains one additional N-atom, said additional N-atom may optionally be substituted with $C_{1-4}alkyl$ or $C_{3-6}cycloalkyl$; and

wherein (c-1) may optionally be substituted on one or two ring C-atoms atoms with one or two substituents each independently selected from the group consisting of halo, $C_{1-4}alkyl$, and $C_{3-6}cycloalkyl$;

R^{11a} , R^{14a} , R^{14c} , R^{14g} , R^{14i} , R^{14k} , R^{15a} , R^{17a} and R^{19a} each independently represents hydrogen or $C_{1-4}alkyl$;

R^{14b} , R^{14d} , R^{14h} , R^{14j} , R^{14l} , R^{15b} , R^{17b} and R^{19b} each independently represents hydrogen; $C_{1-4}alkyl$; $C_{3-6}cycloalkyl$; or $C_{1-4}alkyl$ substituted with one substituent selected from the group consisting of halo, –OH and –O- $C_{1-4}alkyl$;

R^{20a} , R^{20b} and R^{20c} each independently represents hydrogen; $C_{1-4}alkyl$; $C_{3-6}cycloalkyl$; or $C_{1-4}alkyl$ substituted with one substituent selected from the group consisting of –OH and –O- $C_{1-4}alkyl$;

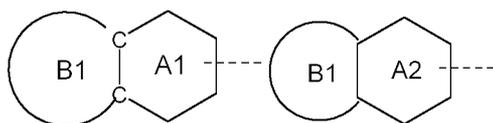
p represents 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

- 5 R¹ represents C₁₋₄alkyl;
 R² represents C₁₋₆alkyl, C₁₋₆alkyl substituted with one R⁵, or C₁₋₆alkyl substituted with one, two or three fluoro atoms;
 Y represents CR⁴ or N;
 R⁴ represents hydrogen or halo;
- 10 R⁵ represents Het^{3a}, -NR^{6a}R^{6b}, or -OR⁷;
 R^{6a} represents hydrogen or C₁₋₄alkyl;
 R^{6b} represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; -C(=O)-C₁₋₄alkyl; -C(=O)-Het⁴;
 -S(=O)₂-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -NR^{16a}R^{16b}; or C₁₋₄alkyl substituted with one substituent
 15 selected from the group consisting of -OH and -S(=O)₂-C₁₋₄alkyl;
 R⁷ represents hydrogen, C₁₋₄alkyl, -C₁₋₄alkyl-NR^{8a}R^{8b}, -C(=O)-R⁹, -S(=O)₂-OH,
 -P(=O)₂-OH, -(C=O)-CH(NH₂)-C₁₋₄alkyl-Ar¹, or -C₁₋₄alkyl-Het^{3b};
 R^{8a} represents hydrogen or C₁₋₄alkyl;
 R^{8b} represents hydrogen, C₁₋₄alkyl, or C₃₋₆cycloalkyl;
- 20 R⁹ represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one substituent selected from the group consisting of -NH₂, -COOH, and Het⁶;
 R^{16a} and R^{16b} each independently represents hydrogen, C₁₋₄alkyl or C₃₋₆cycloalkyl;
 R³ represents

a fused bicyclic ring system of formula (1a-1) or (1a-2):



25

(1a-1)

(1a-2)

ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms;

ring A2 represents 2-oxo-1,2-dihydropyridin-3-yl;

ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

30 wherein (1a-1) and (1a-2) may optionally be substituted on the ring carbon atoms with in

total one, two or three substituents each independently selected from the group consisting of halo; cyano; oxo; -OH; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -S(=O)(=N-R^{20a})-C₁₋₄alkyl; -O-C₁₋₄alkyl substituted with one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³;

wherein ring A2 may optionally be substituted, where possible, on the N-atom with a substituent selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when Het^{1a} or R¹⁸ are directly attached to the N-atom of ring A2, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom; and

wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when Het^{1a} or R¹⁸ are directly attached to the N-atom of ring B1, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom;

R¹⁰ represents -OH, -O-C₁₋₄alkyl, -NR^{11a}R^{11b} or Het²;

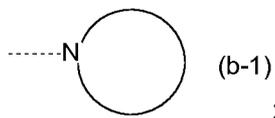
R¹⁸ represents a 5-membered aromatic ring containing one, two or three N-atoms; wherein said 5-membered aromatic ring may optionally be substituted with one substituent selected from the group consisting of C₁₋₄alkyl and C₃₋₆cycloalkyl;

Het^{1a}, Het^{1c} and Het^{1d} each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N; or a 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, containing one, two or three heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted, where possible,

on one, two or three ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and

- 5 wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, oxo, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;
- 10 Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, said Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;
- 15 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and
- 20 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;
- Het² represents a heterocyclyl of formula (b-1):



- 25 (b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N, or a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, optionally containing one or two additional heteroatoms each independently selected from O, S, S(=O)_p and N;
- 30 wherein in case (b-1) contains one or two additional N-atoms, said one or two N-atoms may optionally be substituted with C₁₋₄alkyl; and

wherein (b-1) may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of halo, -OH, cyano, C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, and C₁₋₄alkyl-OH;

R^{11b} represents hydrogen; Het^{1e}; C₁₋₄alkyl; C₁₋₄alkyl-Het⁵; C₁₋₄alkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₃₋₆cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

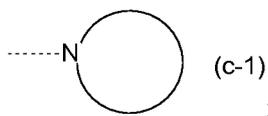
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, -S(=O)₂-C₁₋₄alkyl, -S(=O)(=N-R^{20c})-C₁₋₄alkyl, or -C(=O)-Het^{1f};

R¹² represents -OH, -O-C₁₋₄alkyl, -NR^{14a}R^{14b}, -C(=O)NR^{14c}R^{14d}, -S(=O)₂-C₁₋₄alkyl, -S(=O)(=N-R^{20b})-C₁₋₄alkyl, C₃₋₆cycloalkyl, Ar², or Het^{1c};

Ar¹ represents phenyl optionally substituted with one hydroxy;

Ar² represents phenyl optionally substituted with one C₁₋₄alkyl; or a 5- or 6-membered heteroaromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N;

Het^{3a}, Het^{3b}, Het⁵, Het⁶ and Het^{1f} each independently represents a heterocyclyl of formula (c-1):



(c-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N;

wherein in case (c-1) contains one additional N-atom, said additional N-atom may optionally be substituted with C₁₋₄alkyl or C₃₋₆cycloalkyl; and

wherein (c-1) may optionally be substituted on one or two ring C-atoms atoms with one or two substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, and C₃₋₆cycloalkyl;

R^{11a}, R^{14a}, R^{14c}, R^{14g}, R¹⁴ⁱ, R^{14k}, R^{15a}, R^{17a} and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14b}, R^{14d}, R^{14h}, R^{14j}, R^{14l}, R^{15b}, R^{17b} and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

R^{20a} , R^{20b} and R^{20c} each independently represents hydrogen; C_{1-4} alkyl; C_{3-6} cycloalkyl; or C_{1-4} alkyl substituted with one substituent selected from the group consisting of $-OH$ and $-O-C_{1-4}$ alkyl;

p represents 1 or 2;

5 and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

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

10 R^2 represents C_{1-6} alkyl, C_{1-6} alkyl substituted with one R^5 , or C_{1-6} alkyl substituted with one, two or three fluoro atoms;

Y represents CR^4 or N;

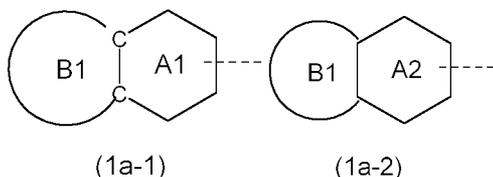
R^4 represents hydrogen or halo;

R^5 represents $-OR^7$;

15 R^7 represents hydrogen;

R^3 represents

a) a fused bicyclic ring system of formula (1a-1) or (1a-2):



ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms;

20 ring A2 represents 2-oxo-1,2-dihydropyridin-3-yl;

ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N;

wherein (1a-1) and (1a-2) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting

25 of halo; oxo; $-OH$; C_{1-6} alkyl; $-O-C_{1-4}$ alkyl; $-C(=O)-R^{10}$; $-O-C_{1-4}$ alkyl- R^{12} ; $-O-C_{3-6}$ cycloalkyl;

$-NR^{17a}R^{17b}$; C_{1-4} alkyl substituted with one, two or three $-OH$ substituents; C_{1-4} alkyl substituted with one R^{13} ; C_{2-6} alkenyl; and C_{2-6} alkenyl substituted with one R^{13} ;

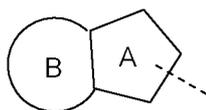
wherein ring A2 may optionally be substituted, where possible, on the N-atom with

30 a substituent selected from the group consisting of C_{1-6} alkyl; and C_{1-4} alkyl substituted with

one R¹³; and

wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l}; or

b) a fused bicyclic ring system of formula (2a-1):



(2a-1)

ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyl, and -C₁₋₄alkyl-O-C₁₋₄alkyl;

ring B represents a C₅₋₇cycloalkyl or a 5- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N;

wherein said C₅₋₇cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring carbon atoms with one or two substituents each independently selected from the group consisting of C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl and -C₁₋₄alkyl-OH, or one ring carbon atom may optionally be substituted with oxo; and wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring N-atoms with C₁₋₆alkyl; or

c) a fused 7- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N;

wherein said fused 7- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; -O-C₁₋₄alkyl; and -C(=O)-R¹⁰; and

wherein said fused 7- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; and C₁₋₄alkyl substituted with one R¹³;

R¹⁰ represents -NR^{11a}R^{11b};

Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

R^{11b} represents C₁₋₄alkyl;

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, C₃₋₆cycloalkyl, or Het^{1d};

5 R¹² represents C₃₋₆cycloalkyl;

R^{11a}, R^{14g}, R¹⁴ⁱ, R^{14k}, R^{15a}, and R^{17a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14h}, R^{14j}, R^{14l}, R^{15b}, and R^{17b} each independently represents hydrogen or C₁₋₄alkyl;

p represents 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

10

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl, C₁₋₆alkyl substituted with one R⁵, or C₁₋₆alkyl substituted with one,

15 two or three fluoro atoms;

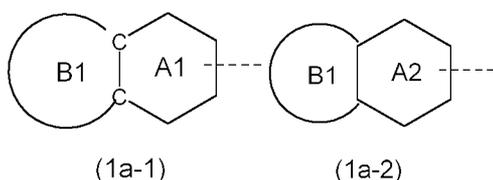
Y represents CR⁴ or N;

R⁴ represents hydrogen or halo;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

20 R³ represents a fused bicyclic ring system of formula (1a-1) or (1a-2):



ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms;

ring A2 represents 2-oxo-1,2-dihydropyridin-3-yl;

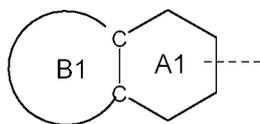
ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two

25 heteroatoms each independently selected from O and N;

wherein (1a-1) and (1a-2) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; oxo; -OH; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -O-C₁₋₄alkyl-R¹²; -O-C₃₋₆cycloalkyl;

- NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; wherein ring A2 may optionally be substituted, where possible, on the N-atom with a substituent selected from the group consisting of C₁₋₆alkyl; and C₁₋₄alkyl substituted with one R¹³; and
- 5 wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l};
- 10 R¹⁰ represents -NR^{11a}R^{11b};
- R^{11b} represents C₁₋₄alkyl;
- R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or C₃₋₆cycloalkyl;
- R¹² represents C₃₋₆cycloalkyl;
- 15 R^{11a}, R^{14g}, R¹⁴ⁱ, R^{14k}, R^{15a}, and R^{17a} each independently represents hydrogen or C₁₋₄alkyl; R^{14h}, R^{14j}, R^{14l}, R^{15b}, and R^{17b} each independently represents hydrogen or C₁₋₄alkyl; and the pharmaceutically acceptable addition salts, and the solvates thereof.

- The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein
- 20 R¹ represents C₁₋₄alkyl;
- R² represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R⁵;
- Y represents CR⁴;
- R⁴ represents hydrogen or halo;
- 25 R⁵ represents -OR⁷;
- R⁷ represents hydrogen, C₁₋₄alkyl, -C₁₋₄alkyl-NR^{8a}R^{8b}, -C(=O)-R⁹, -(C=O)-CH(NH₂)-or C₁₋₄alkyl-Ar¹;
- R^{8a} represents hydrogen or C₁₋₄alkyl;
- R^{8b} represents hydrogen, C₁₋₄alkyl, or C₃₋₆cycloalkyl;
- 30 R⁹ represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one substituent selected from the group consisting of -NH₂, and -COOH;
- R³ represents a fused bicyclic ring system of formula (1a-1):



(1a-1)

ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms; ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

- 5 wherein (1a-1) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; oxo; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -O-C₁₋₄alkyl substituted with one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; -NH-C(=O)-C₁₋₄alkyl; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three
 10 halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³;
 and

- wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; -
 15 (C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³;

R¹⁰ represents -OH, -O-C₁₋₄alkyl, or -NR^{11a}R^{11b};

- 20 R^{11b} represents hydrogen; C₁₋₄alkyl; C₁₋₄alkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₃₋₆cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

- 25 R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, or -S(=O)₂-C₁₋₄alkyl;

R¹² represents -OH, -O-C₁₋₄alkyl, -NR^{14a}R^{14b}, -C(=O)NR^{14c}R^{14d}, -S(=O)₂-C₁₋₄alkyl, C₃₋₆cycloalkyl, or Ar²;

Ar¹ represents phenyl optionally substituted with one hydroxy;

- 30 Ar² represents phenyl optionally substituted with one C₁₋₄alkyl;

R^{11a} , R^{14a} , R^{14c} , R^{14g} , R^{14i} , R^{14k} , R^{15a} , R^{17a} and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14b} , R^{14d} , R^{14h} , R^{14j} , R^{14l} , R^{15b} , R^{17b} and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

R^{20a} , R^{20b} and R^{20c} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl;

p represents 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R^1 represents C₁₋₄alkyl;

R^2 represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R^5 ;

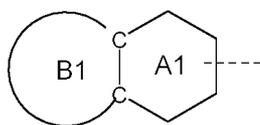
Y represents CR⁴;

R^4 represents hydrogen;

R^5 represents -OR⁷;

R^7 represents hydrogen;

R^3 represents a fused bicyclic ring system of formula (1a-1):



(1a-1)

ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms; ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N;

wherein (1a-1) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -O-C₁₋₄alkyl-R¹²; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; and

wherein ring B1 may optionally be substituted, where possible, on one or two ring N-

atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₁₋₄alkyl substituted with one R¹³; -(C=O)-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; and -C(=O)-C(=O)-NR^{14k}R^{14l};

R¹⁰ represents -NR^{11a}R^{11b};

5 R^{11b} represents C₁₋₄alkyl;

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or C₃₋₆cycloalkyl;

R¹² represents C₃₋₆cycloalkyl;

R^{11a}, R¹⁴ⁱ, R^{14k}, R^{15a}, and R^{17a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14j}, R^{14l}, R^{15b}, and R^{17b} each independently represents hydrogen or C₁₋₄alkyl;

10 and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

15 R² represents C₁₋₆alkyl substituted with one R⁵;

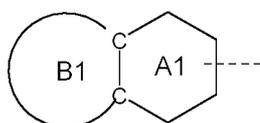
Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

20 R³ represents a fused bicyclic ring system of formula (1a-1):



(1a-1)

ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 N-atom;

ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one heteroatom selected from O and N;

25 wherein (1a-1) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of

-O-C₁₋₄alkyl; -O-C₁₋₄alkyl-R¹²; and C₁₋₄alkyl substituted with one R¹³; and

wherein ring B1 may optionally be substituted, where possible, on one N-atom with a C₁₋₆alkyl substituent;

R¹³ represents C₃₋₆cycloalkyl;

R¹² represents C₃₋₆cycloalkyl;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

5 The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents methyl;

R² represents methyl substituted with one R⁵;

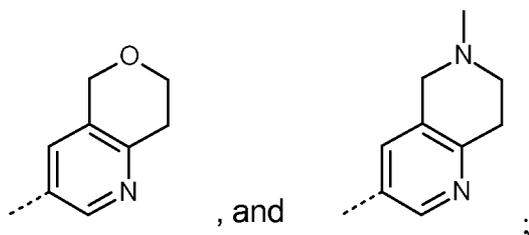
Y represents CR⁴;

10 R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents a fused bicyclic ring system selected from the following structures



15 wherein said fused bicyclic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of -O-C₁₋₄alkyl; -O-C₁₋₄alkyl-R¹²; and C₁₋₄alkyl substituted with one R¹³;

R¹³ represents C₃₋₆cycloalkyl;

R¹² represents C₃₋₆cycloalkyl;

20 and the pharmaceutically acceptable addition salts, and the solvates thereof.

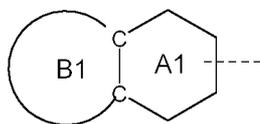
Another embodiment of the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments wherein one or more of
 25 the following restrictions apply:

(a) Y represents CR⁴; and R⁴ represents hydrogen;

(b) R⁵ represents -OR⁷;

(c) R⁷ represents hydrogen;

(d) R³ represents a fused bicyclic ring system of formula (1a-1):



(1a-1)

ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms; ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N;

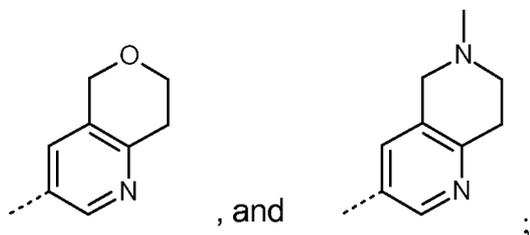
- 5 wherein (1a-1) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -O-C₁₋₄alkyl-R¹²; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; and
- 10 wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₁₋₄alkyl substituted with one R¹³; -(C=O)-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l};
- (e) R¹⁰ represents -NR^{11a}R^{11b};
- 15 (f) R^{11b} represents C₁₋₄alkyl;
- (g) R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or C₃₋₆cycloalkyl;
- (h) R¹² represents C₃₋₆cycloalkyl;
- (i) R^{11a}, R¹⁴ⁱ, R^{14k}, R^{15a}, and R^{17a} each independently represents hydrogen or C₁₋₄alkyl;
- (j) R^{14j}, R^{14l}, R^{15b}, and R^{17b} each independently represents hydrogen or C₁₋₄alkyl.

20

Another embodiment of the present invention relates to those compounds of Formula (I) and 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:

- 25 (a) R¹ represents methyl;
R² represents methyl substituted with one R⁵;
- (b) Y represents CR⁴; and R⁴ represents hydrogen;
- (c) R⁵ represents -OR⁷;
- (d) R⁷ represents hydrogen;

(e) R³ represents a fused bicyclic ring system selected from the following structures

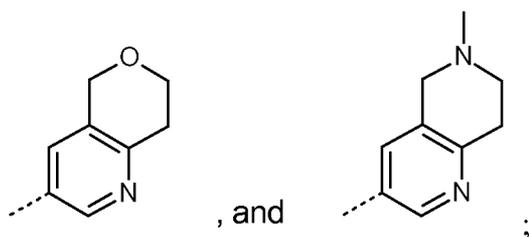


- wherein said fused bicyclic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of -O-C₁₋₄alkyl; -O-C₁₋₄alkyl-R¹²; and C₁₋₄alkyl substituted with one R¹³;
- 5 (f) R¹³ represents C₃₋₆cycloalkyl;
- (g) R¹² represents C₃₋₆cycloalkyl.

Another embodiment of the present invention relates to those compounds of Formula (I) and 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:

10

- (a) R¹ represents methyl;
- R² represents methyl substituted with one R⁵;
- 15 (b) Y represents N;
- (c) R⁵ represents -OR⁷;
- (d) R⁷ represents hydrogen;
- (e) R³ represents a fused bicyclic ring system selected from the following structures

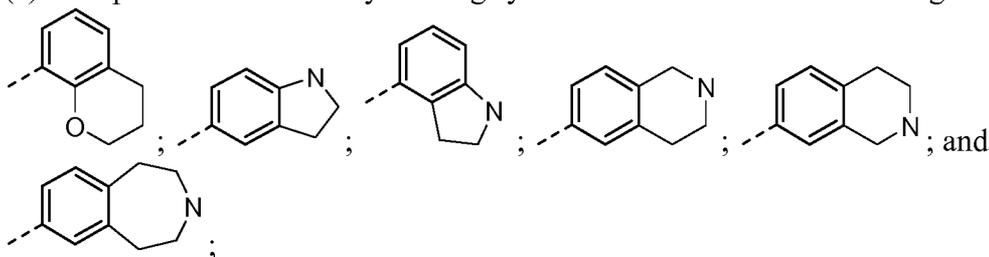


- wherein said fused bicyclic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of -O-C₁₋₄alkyl; -O-C₁₋₄alkyl-R¹²; and C₁₋₄alkyl substituted with one R¹³;
- 20 (f) R¹³ represents C₃₋₆cycloalkyl;
- (g) R¹² represents C₃₋₆cycloalkyl.

25

Another embodiment of the present invention relates to those compounds of Formula (I) and 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 (a) R^1 represents methyl;
 R^2 represents methyl substituted with one R^5 ;
 (b) Y represents CR^4 ; and R^4 represents hydrogen;
 (c) R^5 represents $-OR^7$;
 (d) R^7 represents hydrogen;
 10 (e) R^3 represents a fused bicyclic ring system selected from the following structures

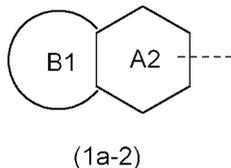


- wherein said fused bicyclic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the
 15 group consisting of halo, oxo, C_{1-6} alkyl, $-O-C_{1-4}$ alkyl; $-O-C_{1-4}$ alkyl- R^{12} ; $-NR^{17a}R^{17b}$; C_{1-4} alkyl substituted with one, two or three $-OH$ substituents; and C_{1-4} alkyl substituted with one R^{13} ; and wherein said fused bicyclic ring system may optionally be substituted on the ring N-atom with a substituent each independently selected from the group consisting of
 C_{1-6} alkyl; $-(C=O)-C_{1-4}$ alkyl; $-C(=O)-C_{1-4}$ alkyl- $NR^{14i}R^{14j}$; and $-C(=O)-C(=O)-NR^{14k}R^{14l}$;
 20 (g) R^{14i} , R^{14k} , R^{14j} , R^{14l} , R^{17a} , and R^{17b} each independently represents hydrogen or C_{1-4} alkyl;
 (h) R^{13} represents C_{3-6} cycloalkyl;
 (i) R^{12} represents C_{3-6} cycloalkyl.

- 25 The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein
 R^1 represents C_{1-4} alkyl;
 R^2 represents C_{1-6} alkyl, or C_{1-6} alkyl substituted with one R^5 ;
 Y represents CR^4 ;
 30 R^4 represents hydrogen;
 R^5 represents $-OR^7$;

R⁷ represents hydrogen;

R³ represents a fused bicyclic ring system of formula (1a-2):



ring A2 represents 2-oxo-1,2-dihydropyridin-3-yl;

- 5 ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N; wherein (1a-2) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; C₁₋₄alkyl substituted with one, two or three -OH
- 10 substituents; and C₁₋₄alkyl substituted with one R¹³;

wherein ring A2 may optionally be substituted, where possible, on the N-atom with a substituent selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; and C₁₋₄alkyl substituted with one R¹³; and

- wherein ring B1 may optionally be substituted, where possible, on one or two ring N-
- 15 atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; -(C=O)-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; and -C(=O)-C(=O)-NR^{14k}R^{14l};
- R¹⁰ represents -NR^{11a}R^{11b};

R^{11b} represents C₁₋₄alkyl;

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or C₃₋₆cycloalkyl;

- 20 R^{11a}, R¹⁴ⁱ, R^{14k}, and R^{15a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14j}, R^{14l}, and R^{15b} each independently represents hydrogen or C₁₋₄alkyl;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

- The present invention also relates in particular to compounds of Formula (I) as defined
- 25 herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R⁵;

Y represents CR⁴;

R⁴ represents hydrogen or halo;

R^5 represents Het^{3a} , $-\text{NR}^{6a}\text{R}^{6b}$, or $-\text{OR}^7$;

R^{6a} represents hydrogen or C_{1-4} alkyl;

R^{6b} represents hydrogen; C_{1-4} alkyl; C_{3-6} cycloalkyl; $-\text{C}(=\text{O})-\text{C}_{1-4}$ alkyl; $-\text{C}(=\text{O})-\text{Het}^4$;

5 $-\text{S}(=\text{O})_2-\text{C}_{1-4}$ alkyl; $-\text{C}(=\text{O})-\text{C}_{1-4}$ alkyl substituted with one substituent selected from the group consisting of $-\text{OH}$ and $-\text{NR}^{16a}\text{R}^{16b}$; or C_{1-4} alkyl substituted with one substituent selected from the group consisting of $-\text{OH}$ and $-\text{S}(=\text{O})_2-\text{C}_{1-4}$ alkyl;

R^7 represents hydrogen, C_{1-4} alkyl, $-\text{C}_{1-4}$ alkyl- $\text{NR}^{8a}\text{R}^{8b}$, $-\text{C}(=\text{O})-\text{R}^9$, $-\text{S}(=\text{O})_2-\text{OH}$,

$-\text{P}(=\text{O})_2-\text{OH}$, $-\text{C}(=\text{O})-\text{CH}(\text{NH}_2)-\text{C}_{1-4}$ alkyl- Ar^1 , or $-\text{C}_{1-4}$ alkyl- Het^{3b} ;

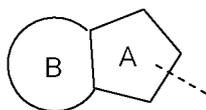
R^{8a} represents hydrogen or C_{1-4} alkyl;

10 R^{8b} represents hydrogen, C_{1-4} alkyl, or C_{3-6} cycloalkyl;

R^9 represents C_{1-6} alkyl, or C_{1-6} alkyl substituted with one substituent selected from the group consisting of $-\text{NH}_2$, $-\text{COOH}$, and Het^6 ;

R^{16a} and R^{16b} each independently represents hydrogen, C_{1-4} alkyl or C_{3-6} cycloalkyl;

R^3 represents a fused bicyclic ring system of formula (2a-1):



15 (2a-1)

ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C_{1-4} alkyl, $-\text{C}_{1-4}$ alkyl- $\text{O}-\text{C}_{1-4}$ alkyl, and C_{1-4} alkyl substituted with one, two or three halo atoms;

20 ring B represents a C_{5-7} cycloalkyl or a 5- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N;

wherein said C_{5-7} cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally be substituted on one ring carbon atom with one or two C_{1-4} alkyl substituents, or one ring carbon atom may optionally be substituted with oxo; and

25 wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring N-atoms with a substituent each independently selected from the group consisting of C_{1-6} alkyl; C_{3-6} cycloalkyl; C_{1-4} alkyl substituted with one, two or three halo atoms; C_{1-4} alkyl substituted with one, two or three $-\text{OH}$ substituents; C_{1-4} alkyl substituted with one R^{13} ; $-\text{C}(=\text{O})-\text{C}_{1-4}$ alkyl; $-\text{C}(=\text{O})\text{NR}^{14g}\text{R}^{14h}$; $-\text{C}(=\text{O})-\text{C}_{1-4}$ alkyl- $\text{NR}^{14i}\text{R}^{14j}$;

30 Het^4 represents a 4- to 7-membered monocyclic saturated heterocyclyl, attached to the remainder of the molecule of Formula (II) through any available ring carbon atom, said Het^4 containing one or two heteroatoms each independently selected from O, S, $\text{S}(=\text{O})_p$ and

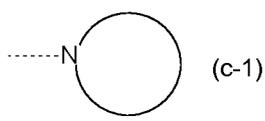
N;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, -S(=O)₂-C₁₋₄alkyl, -S(=O)(=N-R^{20c})-C₁₋₄alkyl, or -C(=O)-Het^{1f};

Ar¹ represents phenyl optionally substituted with one hydroxy;

Het^{3a}, Het^{3b}, Het⁶ and Het^{1f} each independently represents a heterocyclyl of formula (c-1):



(c-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N;

wherein in case (c-1) contains one additional N-atom, said additional N-atom may optionally be substituted with C₁₋₄alkyl or C₃₋₆cycloalkyl; and

20 wherein (c-1) may optionally be substituted on one or two ring C-atoms atoms with one or two substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, and C₃₋₆cycloalkyl;

25 Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N; or a 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, containing one, two or three heteroatoms each independently selected from O, S, S(=O)_p and N;

30 wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted, where possible, on one, two or three ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and wherein said 4- to 7-

membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, oxo, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

5 R^{14g}, R¹⁴ⁱ, R^{15a}, and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14h}, R^{14j}, R^{15b}, and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

10 R^{20c} represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl;

p represents 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

15 The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl, C₁₋₆alkyl substituted with one R⁵, or C₁₋₆alkyl substituted with one, two or three fluoro atoms;

Y represents CR⁴ or N;

20 R⁴ represents hydrogen or halo;

R⁵ represents Het^{3a}, -NR^{6a}R^{6b}, or -OR⁷;

R^{6a} represents hydrogen or C₁₋₄alkyl;

25 R^{6b} represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; -C(=O)-C₁₋₄alkyl; -C(=O)-Het⁴; -S(=O)₂-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -NR^{16a}R^{16b}; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -S(=O)₂-C₁₋₄alkyl;

R⁷ represents hydrogen, C₁₋₄alkyl, -C₁₋₄alkyl-NR^{8a}R^{8b}, -C(=O)-R⁹, -S(=O)₂-OH, -P(=O)₂-OH, -(C=O)-CH(NH₂)-C₁₋₄alkyl-Ar¹, or -C₁₋₄alkyl-Het^{3b};

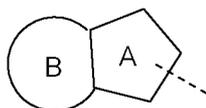
R^{8a} represents hydrogen or C₁₋₄alkyl;

30 R^{8b} represents hydrogen, C₁₋₄alkyl, or C₃₋₆cycloalkyl;

R⁹ represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one substituent selected from the group consisting of -NH₂, -COOH, and Het⁶;

R^{16a} and R^{16b} each independently represents hydrogen, C₁₋₄alkyl or C₃₋₆cycloalkyl;

R³ represents a fused bicyclic ring system of formula (2a-1):



(2a-1)

ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, and C₁₋₄alkyl substituted with one, two or three halo atoms;

ring B represents a C₅₋₇cycloalkyl or a 5- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N;

wherein said C₅₋₇cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally be substituted on one ring carbon atom with one or two substituents each independently

selected from the group consisting of C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl and

-C₁₋₄alkyl-OH, or one ring carbon atom may optionally be substituted with oxo; and

wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring N-atoms with a substituent each independently selected from the group

consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; C₁₋₄alkyl substituted with one, two or three halo

atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j};

Het⁴ represents a 4- to 7-membered monocyclic saturated heterocyclyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, said Het⁴ containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋

alkyl; and wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

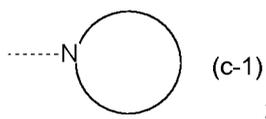
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, -S(=O)₂-C₁₋₄alkyl, -S(=O)(=N-R^{20c})-C₁₋₄alkyl, Ar² or -C(=O)-Het^{1f};

Ar¹ represents phenyl optionally substituted with one hydroxy;

Ar² represents phenyl or a 5- or 6-membered heteroaromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N;

Het^{3a}, Het^{3b}, Het⁶ and Het^{1f} each independently represents a heterocyclyl of formula

5 (c-1):



(c-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N;

wherein in case (c-1) contains one additional N-atom, said additional N-atom may

10 optionally be substituted with C₁₋₄alkyl or C₃₋₆cycloalkyl; and

wherein (c-1) may optionally be substituted on one or two ring C-atoms atoms with one or two substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, and C₃₋₆cycloalkyl;

Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or
15 two heteroatoms each independently selected from O, S, S(=O)_p and N; or a 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, containing one, two or three heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-

20 membered bicyclic saturated heterocyclyl may optionally be substituted, where possible, on one, two or three ring N-atoms with a substituent each independently selected from the

group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and wherein said 4- to 7-

membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated

25 heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, oxo, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

R^{14g}, R¹⁴ⁱ, R^{15a}, and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14h}, R^{14j}, R^{15b}, and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋

30 ₆cycloalkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

R^{20c} represents hydrogen; C_{1-4} alkyl; C_{3-6} cycloalkyl; or C_{1-4} alkyl substituted with one substituent selected from the group consisting of $-OH$ and $-O-C_{1-4}$ alkyl;

p represents 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

5

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

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

R^2 represents C_{1-6} alkyl, or C_{1-6} alkyl substituted with one R^5 ;

10 Y represents CR^4 ;

R^4 represents hydrogen or halo;

R^5 represents $-OR^7$;

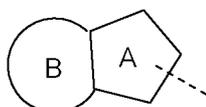
R^7 represents hydrogen, C_{1-4} alkyl, $-C_{1-4}$ alkyl- $NR^{8a}R^{8b}$, $-C(=O)-R^9$, $-(C=O)-CH(NH_2)$ -or C_{1-4} alkyl- Ar^1 ;

15 R^{8a} represents hydrogen or C_{1-4} alkyl;

R^{8b} represents hydrogen, C_{1-4} alkyl, or C_{3-6} cycloalkyl;

R^9 represents C_{1-6} alkyl, or C_{1-6} alkyl substituted with one substituent selected from the group consisting of $-NH_2$, and $-COOH$;

R^3 represents a fused bicyclic ring system of formula (2a-1):



20 (2a-1)

ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C_{1-4} alkyl, $-C_{1-4}$ alkyl- $O-C_{1-4}$ alkyl, and C_{1-4} alkyl substituted with one, two or three halo atoms;

25 ring B represents a C_{5-7} cycloalkyl or a 5- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N;

wherein said C_{5-7} cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally be substituted on one ring carbon atom with one or two C_{1-4} alkyl substituents, or one ring carbon atom may optionally be substituted with oxo; and

30 wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring N-atoms with a substituent each independently selected from the group

consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j};

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, or C₃₋₆cycloalkyl;

5 Ar¹ represents phenyl optionally substituted with one hydroxy;

R^{14g}, R¹⁴ⁱ, R^{15a}, and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14h}, R^{14j}, R^{15b}, and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

10 and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

15 R² represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R⁵;

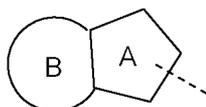
Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

20 R³ represents a fused bicyclic ring system of formula (2a-1):



(2a-1)

ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyl, and -C₁₋₄alkyl-O-C₁₋₄alkyl;

ring B represents a C₅₋₇cycloalkyl or a 5- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N;

25 wherein said C₅₋₇cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring carbon atoms with one or two substituents each independently selected from the group consisting of C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl and -C₁₋₄alkyl-OH, or one ring carbon atom may optionally be substituted with oxo; and

wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring N-atoms with C₁₋₆alkyl;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

5 The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl substituted with one R⁵;

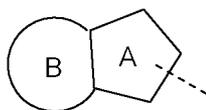
Y represents CR⁴;

10 R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents a fused bicyclic ring system of formula (2a-1):



(2a-1)

15 ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyl, and -C₁₋₄alkyl-O-C₁₋₄alkyl;

ring B represents a C₅₋₇cycloalkyl or a 5- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N;

20 wherein said C₅₋₇cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally be substituted on one ring carbon atom with one or two C₁₋₄alkyl substituents, or one ring carbon atom may optionally be substituted with oxo; and

wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring N-atoms with a C₁₋₆alkyl substituent;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

25

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl substituted with one R⁵;

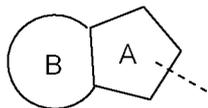
30 Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents a fused bicyclic ring system of formula (2a-1):



5 (2a-1)

ring A represents pyrazolyl;

ring B represents a 6-membered saturated heterocyclyl containing one heteroatom selected from O and N;

10 wherein said 6-membered saturated heterocyclyl may optionally be substituted on one ring carbon atom with one C₁₋₄alkyl substituent, or one ring carbon atom may optionally be substituted with oxo; and

wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one N-atom with a C₁₋₆alkyl substituent;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

15

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl substituted with one R⁵;

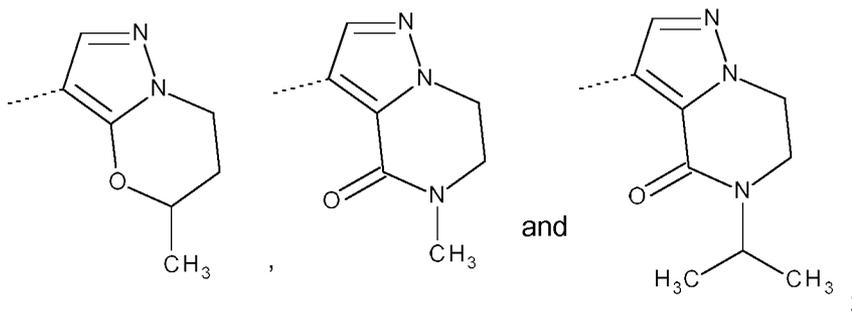
20 Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents a fused bicyclic ring system selected from the following structures:

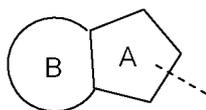


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and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

- 5 R¹ represents C₁₋₄alkyl;
 R² represents C₁₋₆alkyl substituted with one R⁵;
 Y represents CR⁴;
 R⁴ represents hydrogen;
 R⁵ represents -OR⁷;
 10 R⁷ represents hydrogen;
 R³ represents a fused bicyclic ring system of formula (2a-1):



(2a-1)

- ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyl, and -C₁₋₄alkyl-O-C₁₋₄alkyl;
 15 ring B represents a C₅₋₇cycloalkyl or a 5- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N;
 wherein said C₅₋₇cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring carbon atoms with one or two substituents each independently selected from the group consisting of C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl and -
 20 C₁₋₄alkyl-OH, or one ring carbon atom may optionally be substituted with oxo; and
 wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; and C₁₋₄alkyl
 25 substituted with one R¹³;

R¹³ represents Ar²;

Ar² represents phenyl;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl substituted with one R⁵;

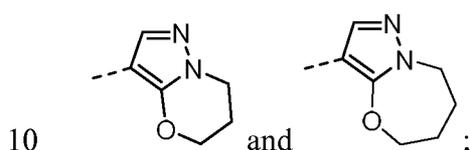
5 Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents a fused bicyclic ring system selected from the following structures:



wherein said fused bicyclic ring may optionally be substituted on one or two ring carbon atoms with one or two substituents each independently selected from the group consisting of C₁₋₄alkyl;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

15

Another embodiment of the present invention relates to those compounds of Formula (I) and 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:

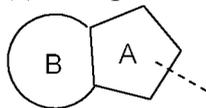
20 (a) R² represents C₁₋₆alkyl substituted with one R⁵;

(b) Y represents CR⁴; and R⁴ represents hydrogen;

(c) R⁵ represents -OR⁷;

(d) R⁷ represents hydrogen;

(e) R³ represents a fused bicyclic ring system of formula (2a-1):



25

(2a-1)

ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyl, and -C₁₋₄alkyl-O-C₁₋₄alkyl;

ring B represents a C₅₋₇cycloalkyl or a 5- to 7-membered saturated heterocyclyl containing

- one or two heteroatoms each independently selected from O and N;
 wherein said C₅₋₇cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally be substituted on one ring carbon atom with one or two C₁₋₄alkyl substituents, or one ring carbon atom may optionally be substituted with oxo; and
 5 wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring N-atoms with a C₁₋₆alkyl substituent.

- The present invention also relates in particular to compounds of Formula (I) as defined
 10 herein, tautomers and stereoisomeric forms thereof, wherein
 R¹ represents C₁₋₄alkyl;
 R² represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R⁵;
 Y represents CR⁴;
 R⁴ represents hydrogen or halo;
 15 R⁵ represents Het^{3a}, -NR^{6a}R^{6b}, or -OR⁷;
 R^{6a} represents hydrogen or C₁₋₄alkyl;
 R^{6b} represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; -C(=O)-C₁₋₄alkyl; -C(=O)-Het⁴;
 -S(=O)₂-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl substituted with one substituent selected from the
 group consisting of -OH and -NR^{16a}R^{16b}; or C₁₋₄alkyl substituted with one substituent
 20 selected from the group consisting of -OH and -S(=O)₂-C₁₋₄alkyl;
 R⁷ represents hydrogen, C₁₋₄alkyl, -C₁₋₄alkyl-NR^{8a}R^{8b}, -C(=O)-R⁹, -S(=O)₂-OH,
 -P(=O)₂-OH, -(C=O)-CH(NH₂)-C₁₋₄alkyl-Ar¹, or -C₁₋₄alkyl-Het^{3b};
 R^{8a} represents hydrogen or C₁₋₄alkyl;
 R^{8b} represents hydrogen, C₁₋₄alkyl, or C₃₋₆cycloalkyl;
 25 R⁹ represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one substituent selected from the
 group consisting of -NH₂, -COOH, and Het⁶;
 R^{16a} and R^{16b} each independently represents hydrogen, C₁₋₄alkyl or C₃₋₆cycloalkyl;
 R³ represents a fused 6- to 11-membered bicyclic heteroaromatic ring system containing
 one or two heteroatoms each independently selected from O, S, and N;
 30 wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally
 be substituted on the ring carbon atoms with in total one, two or three substituents each
 independently selected from the group consisting of halo; cyano; C₁₋₆alkyl; -O-C₁₋₄alkyl; -
 C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -S(=O)(=N-R^{20a})-C₁₋₄alkyl; -O-C₁₋₄alkyl substituted with
 one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; Het^{1a}; -

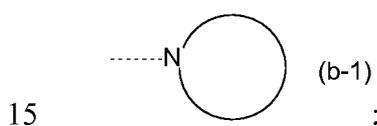
- O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; and
- 5 wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; -(C=O)-C₁₋₄alkyl; -
- 10 C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when Het^{1a} or R¹⁸ are directly attached to the N-atom of ring B, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom;
- R¹⁰ represents -OH, -O-C₁₋₄alkyl, -NR^{11a}R^{11b} or Het²;
- 15 R¹⁸ represents a 5-membered aromatic ring containing one, two or three N-atoms; wherein said 5-membered aromatic ring may optionally be substituted with one substituent selected from the group consisting of C₁₋₄alkyl and C₃₋₆cycloalkyl;
- Het^{1a}, Het^{1c} and Het^{1d} each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected
- 20 from O, S, S(=O)_p and N; or a 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, containing one, two or three heteroatoms each independently selected from O, S, S(=O)_p and N;
- wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted, where possible,
- 25 on one, two or three ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and
- O-C₁₋₄alkyl; and
- wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-
- 30 membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, oxo, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, said Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

5 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and

10 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

Het² represents a heterocyclyl of formula (b-1):



(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N, or a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, optionally containing one or two additional heteroatoms each independently selected from

20 O, S, S(=O)_p and N;

wherein in case (b-1) contains one or two additional N-atoms, said one or two N-atoms may optionally be substituted with C₁₋₄alkyl; and

wherein (b-1) may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of halo, -OH, cyano, C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, and C₁₋₄alkyl-OH;

25

R^{11b} represents hydrogen; Het^{1e}; C₁₋₄alkyl; C₁₋₄alkyl-Het⁵; C₁₋₄alkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₃₋₆cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo,

30 -OH and -O-C₁₋₄alkyl;

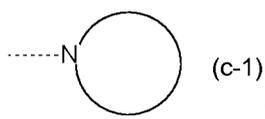
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, -S(=O)₂-C₁₋₄alkyl, -S(=O)(=N-R^{20c})-C₁₋₄alkyl, or -C(=O)-Het^{1f};

R^{12} represents $-\text{OH}$, $-\text{O}-\text{C}_{1-4}\text{alkyl}$, $-\text{NR}^{14a}\text{R}^{14b}$, $-\text{C}(=\text{O})\text{NR}^{14c}\text{R}^{14d}$, $-\text{S}(=\text{O})_2-\text{C}_{1-4}\text{alkyl}$, $-\text{S}(=\text{O})(=\text{N}-\text{R}^{20b})-\text{C}_{1-4}\text{alkyl}$, $\text{C}_{3-6}\text{cycloalkyl}$, Ar^2 , or Het^{1c} ;

Ar^1 represents phenyl optionally substituted with one hydroxy;

Ar^2 represents phenyl optionally substituted with one $\text{C}_{1-4}\text{alkyl}$;

- 5 Het^{3a} , Het^{3b} , Het^5 , Het^6 and Het^{1f} each independently represents a heterocyclyl of formula (c-1):



(c-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, $\text{S}(=\text{O})_p$ and N;

- 10 wherein in case (c-1) contains one additional N-atom, said additional N-atom may optionally be substituted with $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{3-6}\text{cycloalkyl}$; and wherein (c-1) may optionally be substituted on one or two ring C-atoms atoms with one or two substituents each independently selected from the group consisting of halo, $\text{C}_{1-4}\text{alkyl}$, and $\text{C}_{3-6}\text{cycloalkyl}$;

- 15 R^{11a} , R^{14a} , R^{14c} , R^{14g} , R^{14i} , R^{14k} , R^{15a} , R^{17a} and R^{19a} each independently represents hydrogen or $\text{C}_{1-4}\text{alkyl}$;

R^{14b} , R^{14d} , R^{14h} , R^{14j} , R^{14l} , R^{15b} , R^{17b} and R^{19b} each independently represents hydrogen; $\text{C}_{1-4}\text{alkyl}$; $\text{C}_{3-6}\text{cycloalkyl}$; or $\text{C}_{1-4}\text{alkyl}$ substituted with one substituent selected from the group consisting of halo, $-\text{OH}$ and $-\text{O}-\text{C}_{1-4}\text{alkyl}$;

- 20 R^{20a} , R^{20b} and R^{20c} each independently represents hydrogen; $\text{C}_{1-4}\text{alkyl}$; $\text{C}_{3-6}\text{cycloalkyl}$; or $\text{C}_{1-4}\text{alkyl}$ substituted with one substituent selected from the group consisting of $-\text{OH}$ and $-\text{O}-\text{C}_{1-4}\text{alkyl}$;

p represents 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

25

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

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

R^2 represents $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl}$ substituted with one R^5 , or $\text{C}_{1-6}\text{alkyl}$ substituted with one, two or three fluoro atoms;

30

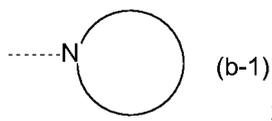
Y represents CR^4 or N;

- R⁴ represents hydrogen or halo;
- R⁵ represents Het^{3a}, -NR^{6a}R^{6b}, or -OR⁷;
- R^{6a} represents hydrogen or C₁₋₄alkyl;
- R^{6b} represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; -C(=O)-C₁₋₄alkyl; -C(=O)-Het⁴;
- 5 -S(=O)₂-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -NR^{16a}R^{16b}; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -S(=O)₂-C₁₋₄alkyl;
- R⁷ represents hydrogen, C₁₋₄alkyl, -C₁₋₄alkyl-NR^{8a}R^{8b}, -C(=O)-R⁹, -S(=O)₂-OH, -P(=O)₂-OH, -(C=O)-CH(NH₂)-C₁₋₄alkyl-Ar¹, or -C₁₋₄alkyl-Het^{3b};
- 10 R^{8a} represents hydrogen or C₁₋₄alkyl;
- R^{8b} represents hydrogen, C₁₋₄alkyl, or C₃₋₆cycloalkyl;
- R⁹ represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one substituent selected from the group consisting of -NH₂, -COOH, and Het⁶;
- R^{16a} and R^{16b} each independently represents hydrogen, C₁₋₄alkyl or C₃₋₆cycloalkyl;
- 15 R³ represents a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N;
- wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; C₁₋₆alkyl; -O-C₁₋₄alkyl; -
- 20 C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -S(=O)(=N-R^{20a})-C₁₋₄alkyl; -O-C₁₋₄alkyl substituted with one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one
- 25 R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; and
- wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋
- 30 4alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when Het^{1a} or R¹⁸ are directly attached to the N-atom of a ring, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom;

R¹⁰ represents -OH, -O-C₁₋₄alkyl, -NR^{11a}R^{11b} or Het²;

R¹⁸ represents a 5-membered aromatic ring containing one, two or three N-atoms; wherein said 5-membered aromatic ring may optionally be substituted with one substituent selected from the group consisting of C₁₋₄alkyl and C₃₋₆cycloalkyl;

- 5 Het^{1a}, Het^{1c} and Het^{1d} each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N; or a 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, containing one, two or three heteroatoms each independently selected from O, S, S(=O)_p and N;
- 10 wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted, where possible, on one, two or three ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and
- 15 -O-C₁₋₄alkyl; and wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, oxo, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -
- 20 NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;
- Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, said Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;
- 25 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and
- 30 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;
- Het² represents a heterocyclyl of formula (b-1):



(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N, or a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles,
 5 optionally containing one or two additional heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein in case (b-1) contains one or two additional N-atoms, said one or two N-atoms may optionally be substituted with C₁₋₄alkyl; and

wherein (b-1) may optionally be substituted on one, two or three ring C-atoms with one or
 10 two substituents each independently selected from the group consisting of halo, -OH, cyano, C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, and C₁₋₄alkyl-OH;

R^{11b} represents hydrogen; Het^{1e}; C₁₋₄alkyl; C₁₋₄alkyl-Het⁵; C₁₋₄alkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₃₋₆cycloalkyl substituted with one, two or three
 15 substituents each independently selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

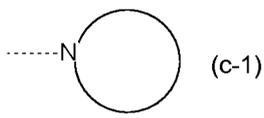
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, -S(=O)₂-C₁₋₄alkyl, -S(=O)(=N-R^{20c})-C₁₋₄alkyl, or -C(=O)-Het^{1f};

R¹² represents -OH, -O-C₁₋₄alkyl, -NR^{14a}R^{14b}, -C(=O)NR^{14c}R^{14d}, -S(=O)₂-C₁₋₄alkyl,
 20 -S(=O)(=N-R^{20b})-C₁₋₄alkyl, C₃₋₆cycloalkyl, Ar², or Het^{1c};

Ar¹ represents phenyl optionally substituted with one hydroxy;

Ar² represents phenyl optionally substituted with one C₁₋₄alkyl;

Het^{3a}, Het^{3b}, Het⁵, Het⁶ and Het^{1f} each independently represents a heterocyclyl of formula
 (c-1):



(c-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N;

wherein in case (c-1) contains one additional N-atom, said additional N-atom may optionally be substituted with C₁₋₄alkyl or C₃₋₆cycloalkyl; and

wherein (c-1) may optionally be substituted on one or two ring C-atoms atoms with one or
 30

two substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, and C₃₋₆cycloalkyl;

R^{11a}, R^{14a}, R^{14c}, R^{14g}, R¹⁴ⁱ, R^{14k}, R^{15a}, R^{17a} and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;

5 R^{14b}, R^{14d}, R^{14h}, R^{14j}, R^{14l}, R^{15b}, R^{17b} and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

R^{20a}, R^{20b} and R^{20c} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or
 10 O-C₁₋₄alkyl;

p represents 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein,
 15 tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl, C₁₋₆alkyl substituted with one R⁵, or C₁₋₆alkyl substituted with one, two or three fluoro atoms;

Y represents CR⁴ or N;

20 R⁴ represents hydrogen or halo;

R⁵ represents Het^{3a}, -NR^{6a}R^{6b}, or -OR⁷;

R^{6a} represents hydrogen or C₁₋₄alkyl;

R^{6b} represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; -C(=O)-C₁₋₄alkyl; -C(=O)-Het⁴;
 -S(=O)₂-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl substituted with one substituent selected from the
 25 group consisting of -OH and -NR^{16a}R^{16b}; or C₁₋₄alkyl substituted with one substituent
 selected from the group consisting of -OH and -S(=O)₂-C₁₋₄alkyl;

R⁷ represents hydrogen, C₁₋₄alkyl, -C₁₋₄alkyl-NR^{8a}R^{8b}, -C(=O)-R⁹, -S(=O)₂-OH,
 -P(=O)₂-OH, -(C=O)-CH(NH₂)-C₁₋₄alkyl-Ar¹, or -C₁₋₄alkyl-Het^{3b};

R^{8a} represents hydrogen or C₁₋₄alkyl;

30 R^{8b} represents hydrogen, C₁₋₄alkyl, or C₃₋₆cycloalkyl;

R⁹ represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one substituent selected from the
 group consisting of -NH₂, -COOH, and Het⁶;

R^{16a} and R^{16b} each independently represents hydrogen, C₁₋₄alkyl or C₃₋₆cycloalkyl;

- R³ represents a fused 7- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N; wherein said fused 7- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -S(=O)(=N-R^{20a})-C₁₋₄alkyl; -O-C₁₋₄alkyl substituted with one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; and wherein said fused 7- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when Het^{1a} or R¹⁸ are directly attached to the N-atom of a ring, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom;
- R¹⁰ represents -OH, -O-C₁₋₄alkyl, -NR^{11a}R^{11b} or Het²;
- R¹⁸ represents a 5-membered aromatic ring containing one, two or three N-atoms; wherein said 5-membered aromatic ring may optionally be substituted with one substituent selected from the group consisting of C₁₋₄alkyl and C₃₋₆cycloalkyl;
- Het^{1a}, Het^{1c} and Het^{1d} each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N; or a 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, containing one, two or three heteroatoms each independently selected from O, S, S(=O)_p and N;
- wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted, where possible, on one, two or three ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and

-O-C₁₋₄alkyl; and

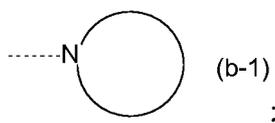
wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, oxo, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, said Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

Het² represents a heterocyclyl of formula (b-1):



(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N, or a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, optionally containing one or two additional heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein in case (b-1) contains one or two additional N-atoms, said one or two N-atoms may optionally be substituted with C₁₋₄alkyl; and

wherein (b-1) may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of halo, -OH, cyano, C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, and C₁₋₄alkyl-OH;

R^{11b} represents hydrogen; Het^{1e} ; $C_{1-4}alkyl$; $C_{1-4}alkyl-Het^5$; $C_{1-4}alkyl$ substituted with one, two or three substituents each independently selected from the group consisting of halo, –OH and –O- $C_{1-4}alkyl$; $C_{3-6}cycloalkyl$; or $C_{3-6}cycloalkyl$ substituted with one, two or three substituents each independently selected from the group consisting of halo, –OH and –O- $C_{1-4}alkyl$;

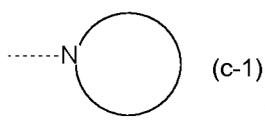
R^{13} represents –O- $C_{1-4}alkyl$, –C(=O)NR^{15a}R^{15b}, –NR^{19a}R^{19b}, $C_{3-6}cycloalkyl$, Het^{1d} , –S(=O)₂- $C_{1-4}alkyl$, –S(=O)(=N-R^{20c})- $C_{1-4}alkyl$, or –C(=O)- Het^{1f} ;

R^{12} represents –OH, –O- $C_{1-4}alkyl$, –NR^{14a}R^{14b}, –C(=O)NR^{14c}R^{14d}, –S(=O)₂- $C_{1-4}alkyl$, –S(=O)(=N-R^{20b})- $C_{1-4}alkyl$, $C_{3-6}cycloalkyl$, Ar^2 , or Het^{1c} ;

Ar^1 represents phenyl optionally substituted with one hydroxy;

Ar^2 represents phenyl optionally substituted with one $C_{1-4}alkyl$;

Het^{3a} , Het^{3b} , Het^5 , Het^6 and Het^{1f} each independently represents a heterocyclyl of formula (c-1):



(c-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N; wherein in case (c-1) contains one additional N-atom, said additional N-atom may optionally be substituted with $C_{1-4}alkyl$ or $C_{3-6}cycloalkyl$; and wherein (c-1) may optionally be substituted on one or two ring C-atoms atoms with one or two substituents each independently selected from the group consisting of halo, $C_{1-4}alkyl$, and $C_{3-6}cycloalkyl$;

R^{11a} , R^{14a} , R^{14c} , R^{14g} , R^{14i} , R^{14k} , R^{15a} , R^{17a} and R^{19a} each independently represents hydrogen or $C_{1-4}alkyl$;

R^{14b} , R^{14d} , R^{14h} , R^{14j} , R^{14l} , R^{15b} , R^{17b} and R^{19b} each independently represents hydrogen; $C_{1-4}alkyl$; $C_{3-6}cycloalkyl$; or $C_{1-4}alkyl$ substituted with one substituent selected from the group consisting of halo, –OH and –O- $C_{1-4}alkyl$;

R^{20a} , R^{20b} and R^{20c} each independently represents hydrogen; $C_{1-4}alkyl$; $C_{3-6}cycloalkyl$; or $C_{1-4}alkyl$ substituted with one substituent selected from the group consisting of –OH and –O- $C_{1-4}alkyl$;

p represents 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

- 5 R¹ represents C₁₋₄alkyl;
 R² represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R⁵;
 Y represents CR⁴;
 R⁴ represents hydrogen or halo;
 R⁵ represents -NR^{6a}R^{6b}, or -OR⁷;
- 10 R^{6a} represents hydrogen or C₁₋₄alkyl;
 R^{6b} represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or -C(=O)-C₁₋₄alkyl;
 R⁷ represents hydrogen, C₁₋₄alkyl, or -C₁₋₄alkyl-NR^{8a}R^{8b};
 R^{8a} represents hydrogen or C₁₋₄alkyl;
 R^{8b} represents hydrogen, C₁₋₄alkyl, or C₃₋₆cycloalkyl;
- 15 R³ represents a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N;
 wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; C₁₋₆alkyl; -O-C₁₋₄alkyl;
 20 C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; and
 wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the
 25 group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³;
- Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or
 30 two heteroatoms each independently selected from O, S, S(=O)_p and N;
 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and

-O-C₁₋₄alkyl; and

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, or Het^{1d};

R^{15a}, and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;

R^{15b}, and R^{19b} each independently represents hydrogen; C₁₋₄alkyl;

C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

p represents 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R⁵;

Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N;

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three halo substituents; and

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³;

Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or Het^{1d};

R^{15a} represents hydrogen or C₁₋₄alkyl;

R^{15b} represents C₁₋₄alkyl;

p represents 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

5

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R⁵;

10 Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

15 R³ represents a fused 7- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N;

wherein said fused 7- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three halo substituents; and

20 wherein said fused 7- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³;

Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

25 R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or Het^{1d};

R^{15a} represents hydrogen or C₁₋₄alkyl;

R^{15b} represents C₁₋₄alkyl;

p represents 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

30

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R⁵;

Y represents CR⁴;

R⁴ represents hydrogen;

5 R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents a fused 7- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N;

10 wherein said fused 7- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; -O-C₁₋₄alkyl; and -C(=O)-R¹⁰; and

15 wherein said fused 7- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; and C₁₋₄alkyl substituted with one R¹³;

R¹⁰ represents -NR^{11a}R^{11b};

Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

20 R^{11b} represents C₁₋₄alkyl;

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or Het^{1d};

R^{11a} and R^{15a} each independently represents hydrogen or C₁₋₄alkyl;

R^{15b} represents C₁₋₄alkyl;

p represents 1 or 2;

25 and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

30 R² represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R⁵;

Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

5 R³ represents a fused 9-membered bicyclic heteroaromatic ring system containing one or two N-atoms;
wherein said fused 9-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three halo substituents; and
wherein said fused 9-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group
10 consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³;

Het^{1d} represents morpholinyl;

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or Het^{1d};

R^{15a} represents hydrogen or C₁₋₄alkyl;

15 R^{15b} represents C₁₋₄alkyl;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

20 R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R⁵;

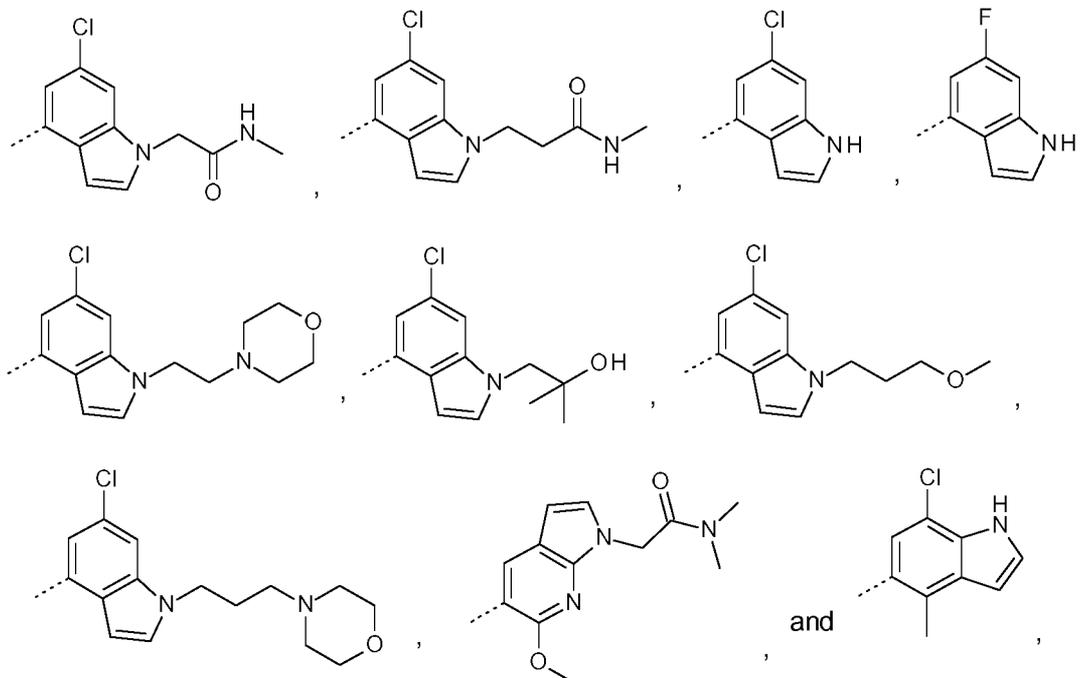
Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

25 R⁷ represents hydrogen;

R³ represents a fused 9-membered bicyclic heteroaromatic ring system selected from the following structures



and the pharmaceutically acceptable addition salts, and the solvates thereof.

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The present invention relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R⁵;

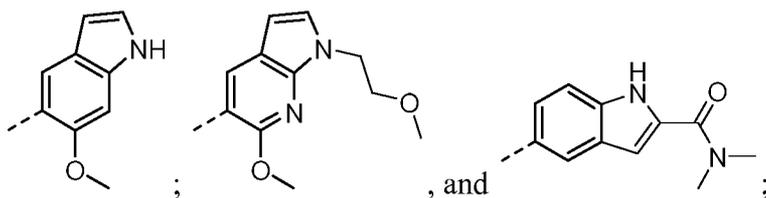
10 Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

15 R³ represents a fused 9-membered bicyclic heteroaromatic ring system selected from the following structures



and the pharmaceutically acceptable addition salts, and the solvates thereof.

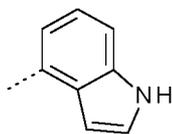
The present invention also relates in particular to compounds of Formula (I) as defined herein, tautomers and stereoisomeric forms thereof, wherein

- R¹ represents C₁₋₄alkyl;
- 5 R² represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one R⁵;
- Y represents CR⁴;
- R⁴ represents hydrogen;
- R⁵ represents -OR⁷;
- R⁷ represents hydrogen;
- 10 R³ represents a fused 9-membered bicyclic heteroaromatic ring system containing one N-atom;
- wherein said fused 9-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three halo substituents; and wherein said fused 9-membered bicyclic heteroaromatic ring system may optionally be
- 15 substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³;
- R¹³ represents -O-C₁₋₄alkyl, or -C(=O)NR^{15a}R^{15b};
- R^{15a} represents hydrogen or C₁₋₄alkyl;
- 20 R^{15b} represents C₁₋₄alkyl;
- and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present invention relates in particular to compounds of Formula (III) as defined herein, tautomers and stereoisomeric forms thereof, wherein

- 25 R¹ represents methyl;
- R² represents methyl substituted with one R⁵;
- Y represents CR⁴;
- R⁴ represents hydrogen;
- R⁵ represents -OR⁷;
- 30 R⁷ represents hydrogen;

R³ represents



optionally substituted on the ring carbon atoms with in total one, two or three halo substituents; and optionally substituted on the ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³;

R¹³ represents -O-C₁₋₄alkyl, or -C(=O)NR^{15a}R^{15b};

R^{15a} represents hydrogen or C₁₋₄alkyl;

R^{15b} represents C₁₋₄alkyl;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

10

Another embodiment of the present invention relates to those compounds of Formula (I) and 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:

15

(a) Y represents CR⁴; and R⁴ represents hydrogen;

(b) R⁵ represents -OR⁷;

(c) R⁷ represents hydrogen;

(d) R³ represents a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N;

20

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three halo substituents; and

25

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³;

(e) Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

(f) R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or Het^{1d};

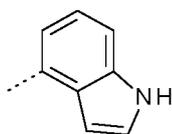
30

(g) R^{15a} represents hydrogen or C₁₋₄alkyl;

(h) R^{15b} represents C₁₋₄alkyl.

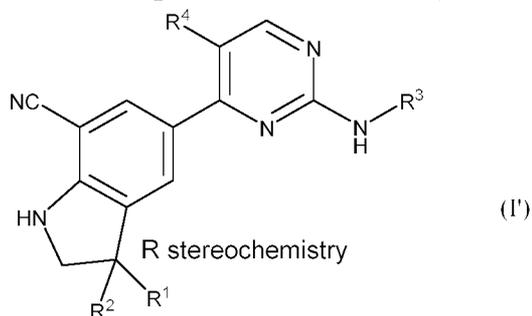
Another embodiment of the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments wherein one or more of the following restrictions apply:

- 5
10
- (a) R¹ represents methyl;
 - (b) R² represents methyl substituted with one R⁵;
 - (c) Y represents CR⁴; and R⁴ represents hydrogen;
 - (d) R⁵ represents -OR⁷;
 - (e) R⁷ represents hydrogen;
 - (f) R³ represents



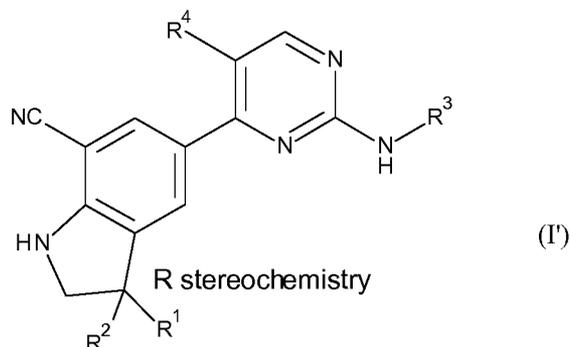
- 15
20
- optionally substituted on the ring carbon atoms with in total one, two or three halo substituents; and optionally substituted on the ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³;
 - (g) R¹³ represents -O-C₁₋₄alkyl, or -C(=O)NR^{15a}R^{15b};
 - (h) R^{15a} represents hydrogen or C₁₋₄alkyl;
 - (i) R^{15b} represents C₁₋₄alkyl.

In an embodiment, the present invention relates to a subgroup of Formula (I), hereby named compounds of Formula (I'):



wherein all variables are defined according to any of the other embodiments.

In an embodiment, the present invention relates to a subgroup of Formula (I), hereby named compounds of Formula (I'):



wherein R^1 represents C_{1-4} alkyl;

5 R^2 represents C_{1-6} alkyl substituted with one R^5 ;

in particular wherein R^1 represents C_{1-4} alkyl;

R^2 represents C_{1-6} alkyl substituted with one R^5 ;

R^5 represents $-OR^7$;

more in particular wherein R^1 represents C_{1-4} alkyl;

10 R^2 represents C_{1-6} alkyl substituted with one R^5 ;

R^5 represents $-OR^7$;

R^7 represents hydrogen;

and wherein all other variables are defined according to any of the other embodiments.

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

R^1 represents methyl;

R^2 represents methyl or $-CH_2-OH$.

20

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

R^1 represents methyl; R^2 represents $-CH_2-OH$.

25

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup

thereof as mentioned in any of the other embodiments, wherein R⁴ represents hydrogen or fluoro.

5 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R⁴ represents hydrogen.

10 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R⁷ represents hydrogen.

15 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R⁵ represents -OR⁷; and R⁷ represents hydrogen.

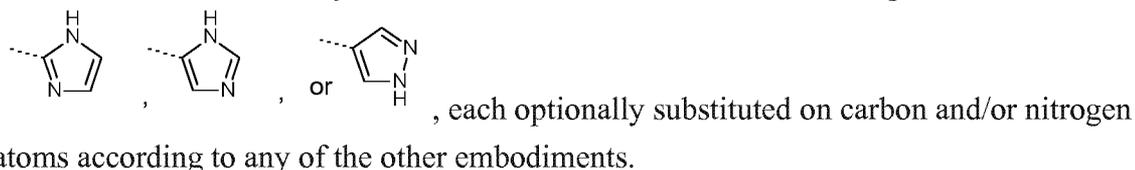
20 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R⁹ represents C₁₋₄alkyl, or C₁₋₄alkyl substituted with one substituent selected from the group consisting of -NH₂, -COOH, and Het⁶.

25 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R¹⁸ is attached to the remainder of the molecule of Formula (I) via a carbon atom.

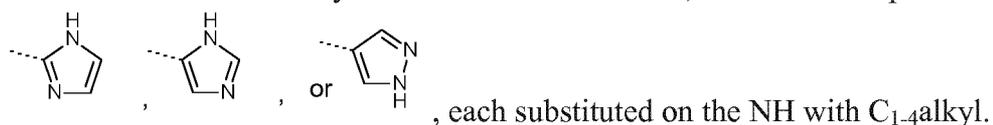
30 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein ring A represents phenyl.

35 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup

thereof as mentioned in any of the other embodiments, wherein R¹⁸ represents



- 5 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R¹⁸ represents



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In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1a}, Het^{1c} and Het^{1d} each independently represents morpholinyl, piperidinyl, pyrrolidinyl, oxetanyl, azetidinyl, piperazinyl, tetrahydro-2H-pyranyl, tetrahydrofuranlyl, or hexahydro-1,4-oxazepinyll, each optionally substituted on carbon and/or nitrogen atoms according to any of the other

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embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1a}, Het^{1c} and Het^{1d} each independently represents morpholinyl, piperidinyl, pyrrolidinyl, oxetanyl, azetidinyl, piperazinyl, tetrahydro-2H-pyranyl, or hexahydro-1,4-oxazepinyll, each optionally substituted on carbon and/or nitrogen atoms according to any of the other

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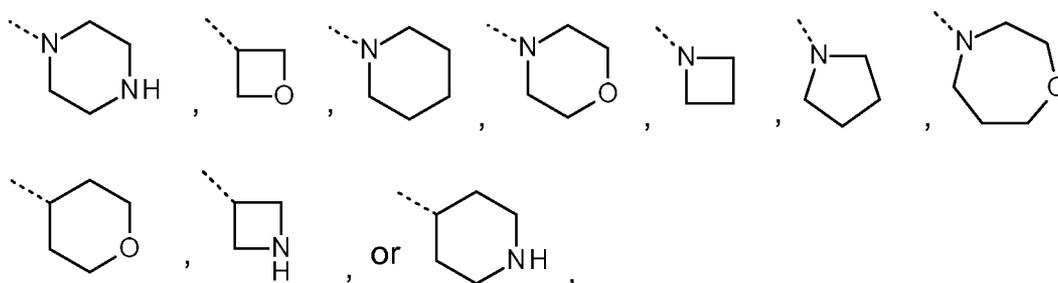
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In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1a}, Het^{1c} and Het^{1d} represent morpholinyl, in particular 1-morpholinyl, optionally substituted where possible on carbon and/or nitrogen atoms according to any of the other

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In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1d} represents morpholinyl, in particular 1-morpholinyl, optionally substituted where possible on carbon and/or nitrogen atoms according to any of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1a}, Het^{1c} and Het^{1d} each independently represents



each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and

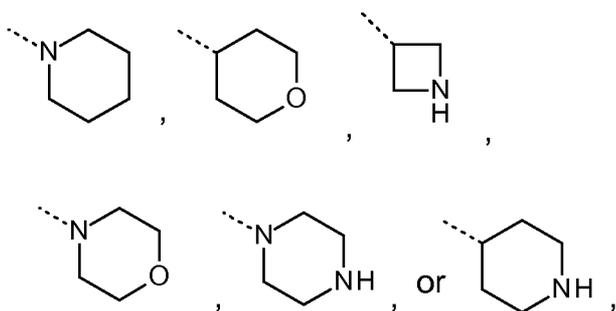
wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂.

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

- 5 Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N; or in case Het^{1d} is attached to the remainder of the molecule of Formula (I) through an N-atom, Het^{1d} may also represent a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, optionally containing one or two additional heteroatoms each independently selected from O, S, S(=O)_p and N;
- 10 wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said N-linked 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and
- 15 wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said N-linked 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂.

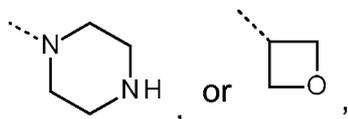
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In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1a} represents



- 25 each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

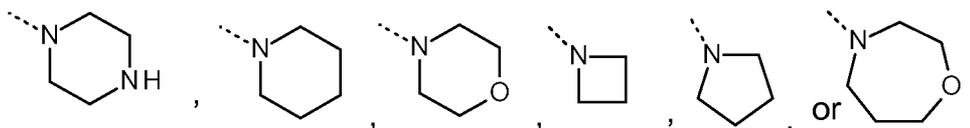
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1c} represents



- 5 each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1d} represents

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each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

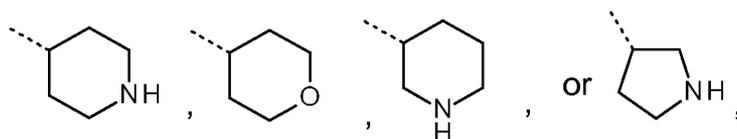
- 15 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ each independently represents morpholinyl, piperidinyl, pyrrolidinyl, oxetanyl, azetidiny, piperazinyl, tetrahydro-2H-pyranyl, tetrahydrofuranly, or hexahydro-1,4-
- 20 oxazepiny, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom,

each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

- 25 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ each independently represents piperidinyl, tetrahydro-2H-pyranly, or pyrrolidinyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon
- 30 atom,

each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ each independently represents

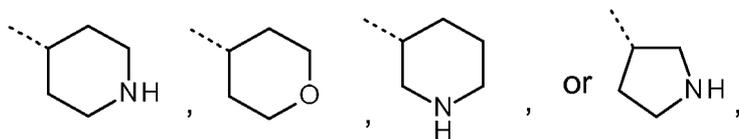


each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het⁴ represents morpholinyl, piperidinyl, pyrrolidinyl, oxetanyl, azetidiny, piperazinyl, tetrahydro-2H-pyranyl, tetrahydrofuranly, or hexahydro-1,4-oxazepinyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

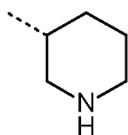
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het⁴ represents piperidinyl, tetrahydro-2H-pyranyl, or pyrrolidinyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het⁴ represents



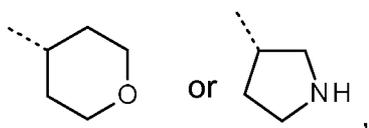
each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

- 5 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1g} represents



optionally substituted on carbon and/or nitrogen atoms according to any of the other
10 embodiments.

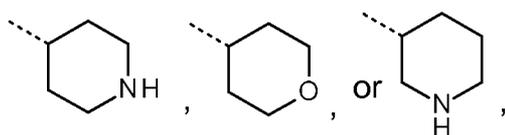
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1e} represents



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each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

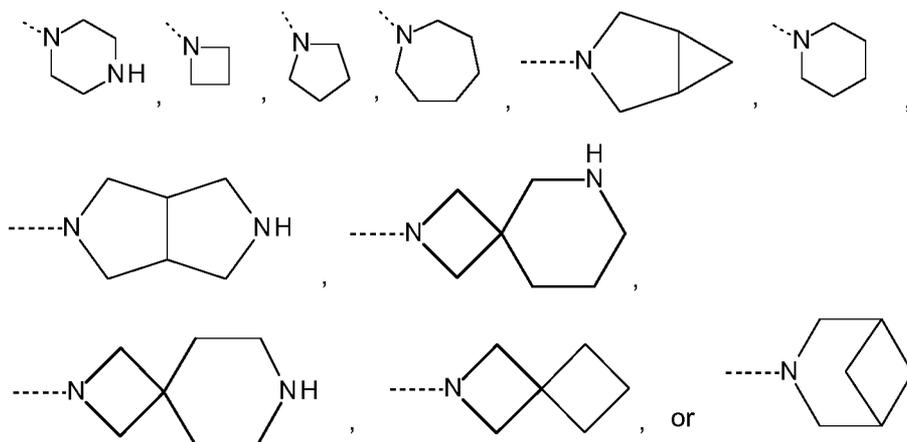
- 20 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1b} represents



each optionally substituted on carbon and/or nitrogen atoms according to any of the other
25 embodiments.

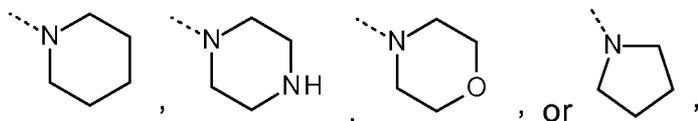
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In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het² represents



5 each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

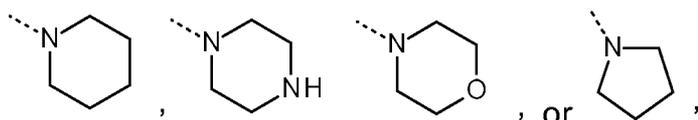
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{3a}, Het^{3b}, Het⁵, Het⁶ and Het^{1f} each independently represents



each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

15

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{3a}, Het^{3b}, Het⁶ and Het^{1f} each independently represents

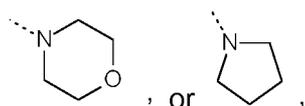


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each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

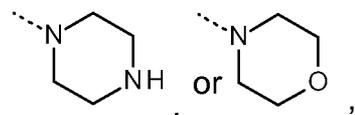
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het⁴ represents
 5 pyrrolidinyl, piperidinyl, tetrahydropyranyl, azetidiny, or 1,1-dioxidethiopyranyl;
 each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the
 10 pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het⁵ represents



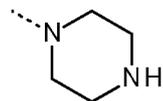
each optionally substituted according to any of the other embodiments.

15 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het⁶ represents



each optionally substituted on carbon and/or nitrogen atoms according to any of the other
 20 embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1f} represents



25 each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the
 30 pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup

thereof as mentioned in any of the other embodiments, wherein

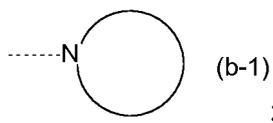
Het^{1a}, Het^{1c} and Het^{1d} each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

5 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and

10 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup

15 thereof as mentioned in any of the other embodiments, wherein Het² represents a heterocyclyl of formula (b-1):



(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N;

20 wherein in case (b-1) contains one additional N-atom, said N-atom may optionally be substituted with C₁₋₄alkyl; and

25 wherein (b-1) may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of halo, -OH, cyano, C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, and C₁₋₄alkyl-OH.

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

30 Het^{1a} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N; or a 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, containing one, two or three heteroatoms each independently selected from O, S, S(=O)_p

and N;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and

wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

Het^{1c} and Het^{1d} each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N; or in case Het^{1c} and Het^{1d} are attached to the remainder of the molecule of Formula (I) through an N-atom, Het^{1c} and Het^{1d} may also represent a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, optionally containing one or two additional heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said N-linked 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said N-linked 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂.

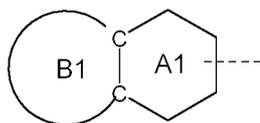
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

R⁵ represents -OR⁷;

R⁷ represents hydrogen, C₁₋₄alkyl, -C₁₋₄alkyl-NR^{8a}R^{8b}, -C(=O)-R⁹, -(C=O)-CH(NH₂)-or C₁₋₄alkyl-Ar¹;

R^9 represents C_{1-6} alkyl, or C_{1-6} alkyl substituted with one substituent selected from the group consisting of $-NH_2$, and $-COOH$;

R^3 represents a fused bicyclic ring system of formula (1a-1):



(1a-1)

5 ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms; ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, $S(=O)_p$ and N;

wherein (1a-1) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; oxo; C_{1-6} alkyl; $-O-C_{1-4}$ alkyl; $-C(=O)-R^{10}$; $-S(=O)_2-C_{1-4}$ alkyl; $-O-C_{1-4}$ alkyl substituted with one, two or three halo atoms; $-O-C_{1-4}$ alkyl- R^{12} ; C_{3-6} cycloalkyl; $-O-C_{3-6}$ cycloalkyl; $-NH-C(=O)-C_{1-4}$ alkyl; $-NR^{17a}R^{17b}$; C_{1-4} alkyl substituted with one, two or three halo atoms; C_{1-4} alkyl substituted with one, two or three $-OH$ substituents; C_{1-4} alkyl substituted with one R^{13} ; C_{2-6} alkenyl; and C_{2-6} alkenyl substituted with one R^{13} ;

15 and

wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C_{1-6} alkyl; C_{3-6} cycloalkyl; C_{1-4} alkyl substituted with one, two or three halo atoms; C_{1-4} alkyl substituted with one, two or three $-OH$ substituents; C_{1-4} alkyl substituted with one R^{13} ; $-(C=O)-C_{1-4}$ alkyl; $-C(=O)NR^{14g}R^{14h}$; $-C(=O)-C_{1-4}$ alkyl- $NR^{14i}R^{14j}$; $-C(=O)-C(=O)-NR^{14k}R^{14l}$; C_{2-6} alkenyl; and C_{2-6} alkenyl substituted with one R^{13} ;

R^{10} represents $-OH$, $-O-C_{1-4}$ alkyl, or $-NR^{11a}R^{11b}$;

R^{11b} represents hydrogen; C_{1-4} alkyl; C_{1-4} alkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, $-OH$ and $-O-C_{1-4}$ alkyl; C_{3-6} cycloalkyl; or C_{3-6} cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, $-OH$ and $-O-C_{1-4}$ alkyl;

R^{13} represents $-O-C_{1-4}$ alkyl, $-C(=O)NR^{15a}R^{15b}$, $-NR^{19a}R^{19b}$, C_{3-6} cycloalkyl, or $-S(=O)_2-C_{1-4}$ alkyl;

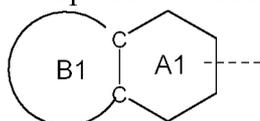
25 R^{12} represents $-OH$, $-O-C_{1-4}$ alkyl, $-NR^{14a}R^{14b}$, $-C(=O)NR^{14c}R^{14d}$, $-S(=O)_2-C_{1-4}$ alkyl, C_{3-6} cycloalkyl, or Ar^2 .

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

R⁵ represents -OR⁷;

5 R⁷ represents hydrogen;

R³ represents a fused bicyclic ring system of formula (1a-1):



(1a-1)

ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms; ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two

10 heteroatoms each independently selected from O and N;

wherein (1a-1) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -O-C₁₋₄alkyl-R¹²; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; and

15 wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₁₋₄alkyl substituted with one R¹³; -(C=O)-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; and -C(=O)-C(=O)-NR^{14k}R^{14l};

20 R¹⁰ represents -NR^{11a}R^{11b};

R^{11b} represents C₁₋₄alkyl;

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or C₃₋₆cycloalkyl;

R¹² represents C₃₋₆cycloalkyl;

R^{11a}, R¹⁴ⁱ, R^{14k}, R^{15a}, and R^{17a} each independently represents hydrogen or C₁₋₄alkyl;

25 R^{14j}, R^{14l}, R^{15b}, and R^{17b} each independently represents hydrogen or C₁₋₄alkyl.

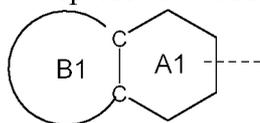
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

30 R² represents C₁₋₆alkyl substituted with one R⁵;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents a fused bicyclic ring system of formula (1a-1):



(1a-1)

ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 N-atom;

ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one heteroatom selected from O and N;

5 wherein (1a-1) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of -O-C₁₋₄alkyl; -O-C₁₋₄alkyl-R¹²; and C₁₋₄alkyl substituted with one R¹³; and wherein ring B may optionally be substituted, where possible, on one N-atom with a C₁₋

10 ₆alkyl substituent;

R¹³ represents C₃₋₆cycloalkyl;

R¹² represents C₃₋₆cycloalkyl.

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

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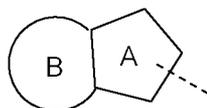
R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl substituted with one R⁵;

R⁵ represents -OR⁷;

20 R⁷ represents hydrogen;

R³ represents a fused bicyclic ring system of formula (2a-1):



(2a-1)

ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyl, and -C₁₋₄alkyl-O-C₁₋₄alkyl;

25 ring B represents a C₅₋₇cycloalkyl or a 5- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N;

wherein said C₅₋₇cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally be substituted on one ring carbon atom with one or two C₁₋₄alkyl substituents, or one ring

carbon atom may optionally be substituted with oxo; and
 wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one
 or two ring N-atoms with a C₁₋₆alkyl substituent.

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

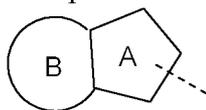
R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl substituted with one R⁵;

R⁵ represents -OR⁷;

10 R⁷ represents hydrogen;

R³ represents a fused bicyclic ring system of formula (2a-1):



(2a-1)

ring A represents pyrazolyl;

ring B represents a 6-membered saturated heterocyclyl containing one heteroatom selected
 15 from O and N;

wherein said 6-membered saturated heterocyclyl may optionally be substituted on one ring
 carbon atom with one C₁₋₄alkyl substituent, or one ring carbon atom may optionally be
 substituted with oxo; and

wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one
 20 N-atom with a C₁₋₆alkyl substituent.

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

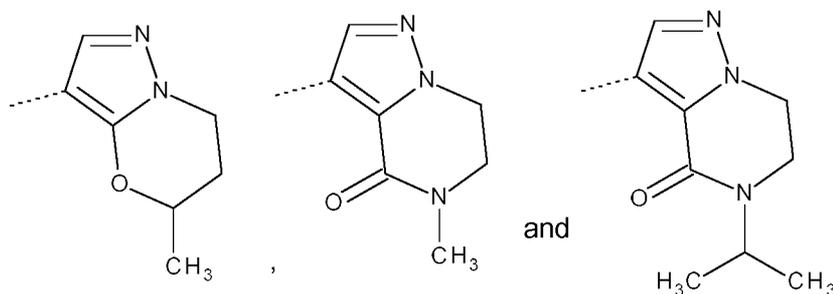
25 R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl substituted with one R⁵;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents a fused bicyclic ring system selected from the following structures:



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

- 5 R^5 represents $-NR^{6a}R^{6b}$, or $-OR^7$;
 R^{6b} represents hydrogen; C_{1-4} alkyl; C_{3-6} cycloalkyl; or $-C(=O)-C_{1-4}$ alkyl;
 R^7 represents hydrogen, C_{1-4} alkyl, or $-C_{1-4}$ alkyl- $NR^{8a}R^{8b}$;
 R^3 represents a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N;
 10 wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; C_{1-6} alkyl; $-O-C_{1-4}$ alkyl; C_{1-4} alkyl substituted with one, two or three halo atoms; C_{1-4} alkyl substituted with one, two or three $-OH$ substituents; C_{1-4} alkyl substituted with one R^{13} ; C_{2-6} alkenyl; and C_{2-6} alkenyl substituted with one R^{13} ; and
 15 wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C_{1-6} alkyl; C_{3-6} cycloalkyl; C_{1-4} alkyl substituted with one, two or three halo atoms; C_{1-4} alkyl substituted with one, two or three $-OH$ substituents; C_{1-4} alkyl substituted with one R^{13} ; C_{1-4} alkyl substituted with one R^{18} ; C_{2-6} alkenyl; and C_{2-6} alkenyl substituted with one R^{13} ;
 20 Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, $S(=O)_p$ and N;
 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, and C_{1-4} alkyl substituted with one substituent selected from the group consisting of $-OH$ and $-O-C_{1-4}$ alkyl; and

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

5 R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, or Het^{1d}.

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

R¹ represents C₁₋₄alkyl;

10 R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N;

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally
15 be substituted on the ring carbon atoms with in total one, two or three halo substituents;
and

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl
20 substituted with one R¹³;

Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or Het^{1d};

R^{15a} represents hydrogen or C₁₋₄alkyl;

25 R^{15b} represents C₁₋₄alkyl.

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

30 R¹ represents C₁₋₄alkyl;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents a fused 9-membered bicyclic heteroaromatic ring system containing one N-atom;

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three halo substituents; and

5 wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³;

R¹³ represents -O-C₁₋₄alkyl, or -C(=O)NR^{15a}R^{15b};

R^{15a} represents hydrogen or C₁₋₄alkyl;

10 R^{15b} represents C₁₋₄alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R³ represents an optionally substituted fused bicyclic ring system of formula (1a-1) or (1a-2).

15 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R³ represents an optionally substituted fused bicyclic ring system of formula (1a-1).

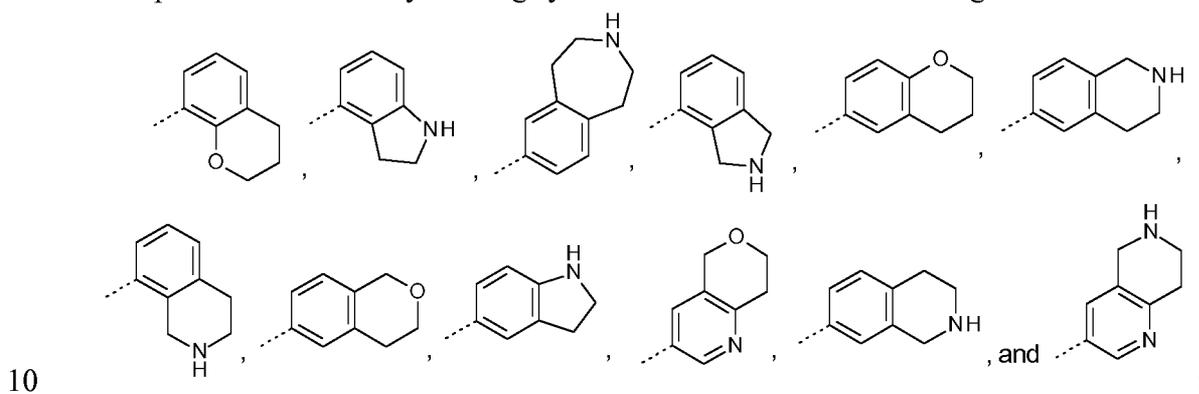
20 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R³ represents an optionally substituted fused bicyclic ring system of formula (1a-2).

25 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R³ represents an optionally substituted fused bicyclic ring system of formula (2a-1).

30 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R³ represents an optionally substituted fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^3 represents an optionally substituted fused 7- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^3 represents a fused bicyclic ring system selected from the following structures



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wherein said fused bicyclic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; C_{1-6} alkyl; $-O-C_{1-4}$ alkyl; $-C(=O)-R^{10}$; $-S(=O)_2-C_{1-4}$ alkyl; $-S(=O)(=N-R^{20a})-C_{1-4}$ alkyl; $-O-C_{1-4}$ alkyl substituted with one, two or three halo atoms; $-O-C_{1-4}$ alkyl- R^{12} ; C_{3-6} cycloalkyl; $-O-C_{3-6}$ cycloalkyl; Het^{1a} ; R^{18} ; $-P(=O)-(C_{1-4}alkyl)_2$; $-NH-C(=O)-C_{1-4}alkyl$; $-NH-C(=O)-Het^{1g}$; $-NR^{17a}R^{17b}$; $C_{1-4}alkyl$ substituted with one, two or three halo atoms; $C_{1-4}alkyl$ substituted with one, two or three $-OH$ substituents; $C_{1-4}alkyl$ substituted with one R^{13} ; $C_{1-4}alkyl$ substituted with one R^{18} ; $C_{2-6}alkenyl$; and $C_{2-6}alkenyl$ substituted with one R^{13} ; and

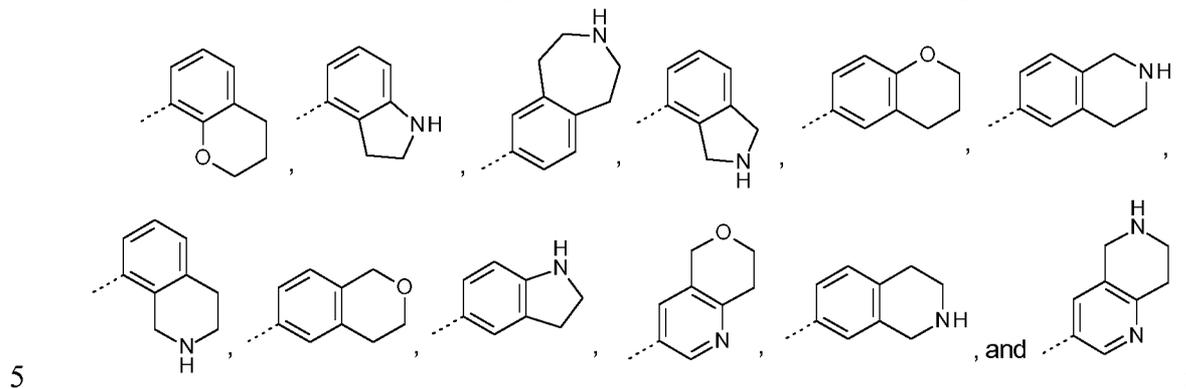
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wherein said fused bicyclic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C_{1-6} alkyl; C_{3-6} cycloalkyl; Het^{1a} ; R^{18} ; $C_{1-4}alkyl$ substituted with one, two or three halo atoms; $C_{1-4}alkyl$ substituted with one, two or three $-OH$ substituents; $C_{1-4}alkyl$ substituted with one R^{13} ; $C_{1-4}alkyl$ substituted with one R^{18} ; $-C(=O)-C_{1-4}alkyl$; $-C(=O)NR^{14g}R^{14h}$; $-C(=O)-C_{1-4}alkyl-NR^{14i}R^{14j}$; $-C(=O)-C(=O)-NR^{14k}R^{14l}$; $C_{2-6}alkenyl$; and $C_{2-6}alkenyl$ substituted with one R^{13} ; provided that when Het^{1a} or R^{18} are directly attached to a N-atom of said fused bicyclic ring system, said Het^{1a} or R^{18} are attached to the N-atom via a ring carbon atom.

25

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

R^3 represents a fused bicyclic ring system selected from the following structures



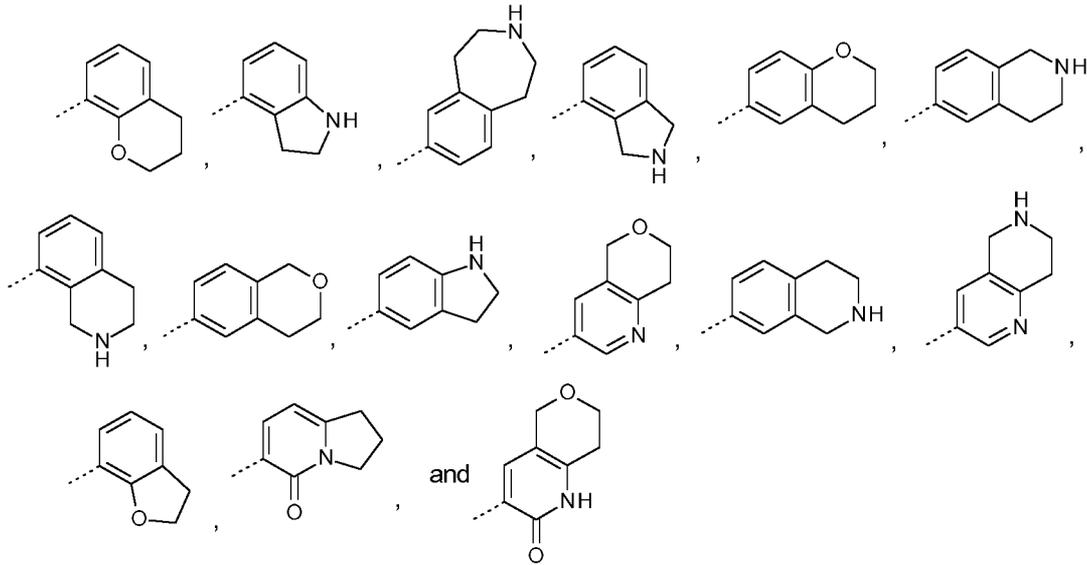
10 wherein said fused bicyclic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; C_{1-6} alkyl; $-O-C_{1-4}$ alkyl; $-C(=O)-R^{10}$; $-O-C_{1-4}$ alkyl- R^{12} ; $-NR^{17a}R^{17b}$; C_{1-4} alkyl substituted with one, two or three $-OH$ substituents; C_{1-4} alkyl substituted with one R^{13} ; C_{2-6} alkenyl; and C_{2-6} alkenyl substituted with one R^{13} ; and wherein said fused bicyclic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C_{1-6} alkyl; C_{1-4} alkyl substituted with one R^{13} ; $-C(=O)-C_{1-4}$ alkyl; $-C(=O)-C_{1-4}$ alkyl- $NR^{14i}R^{14j}$; and $-C(=O)-C(=O)-NR^{14k}R^{14l}$.

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

R^3 represents a fused bicyclic ring system selected from the following structures

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

R³ represents a fused bicyclic ring system selected from the following structures



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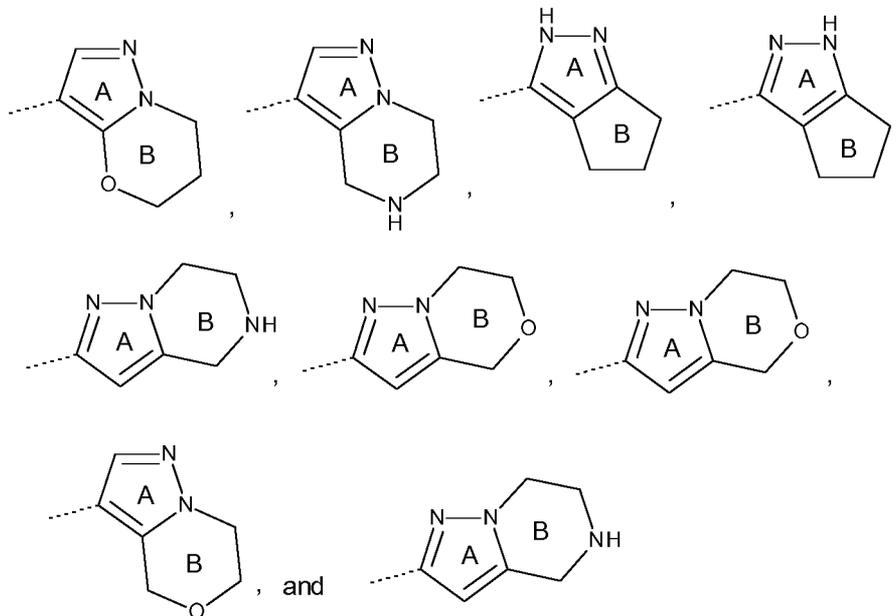
wherein said fused bicyclic ring system may optionally be substituted according to any one of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup

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thereof as mentioned in any of the other embodiments, wherein

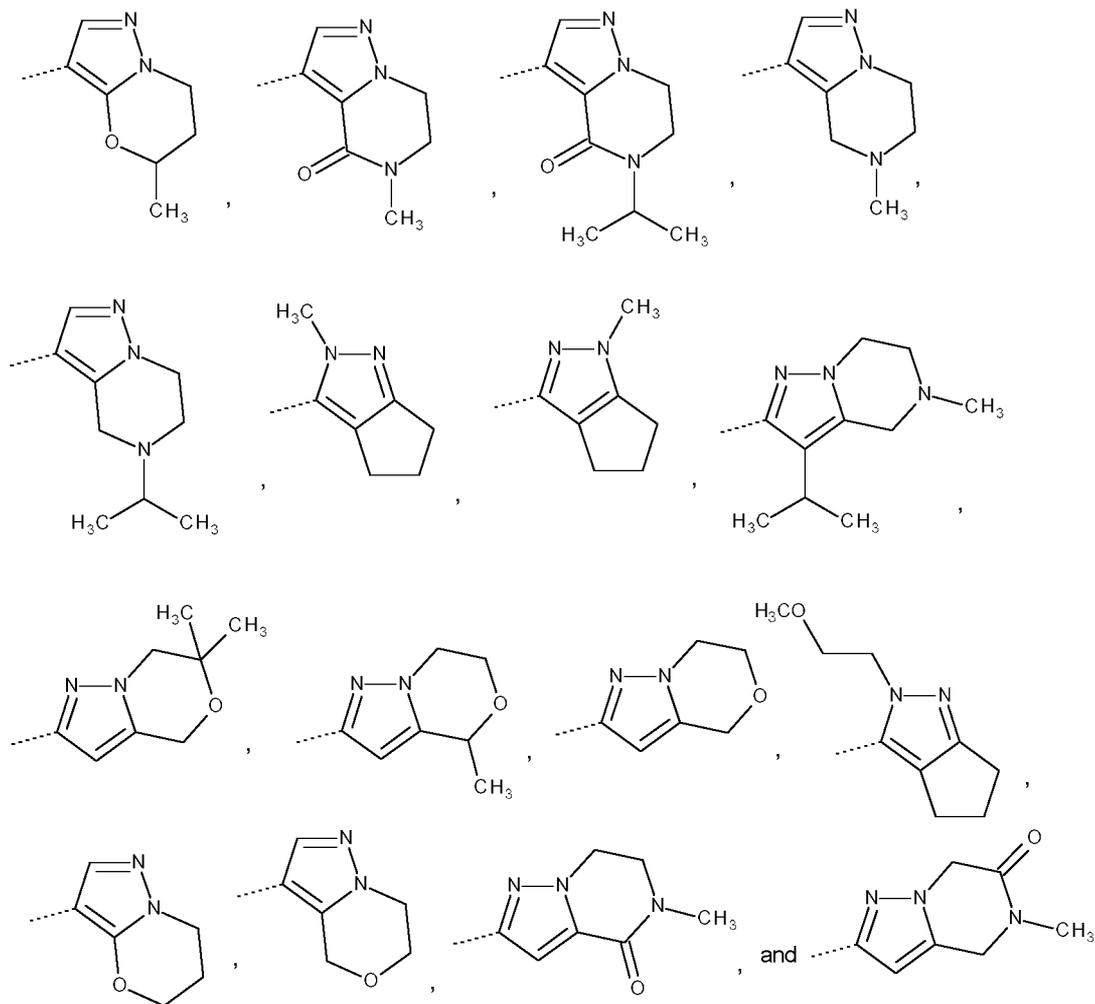
R³ represents a fused bicyclic ring system selected from the following structures



- ring A may optionally be substituted with one substituent selected from the group consisting of C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, and C₁₋₄alkyl substituted with one, two or three halo atoms;
- ring B may optionally be substituted on one ring carbon atom with one or two C₁₋₄alkyl substituents, or one ring carbon atom may optionally be substituted with oxo; and
- ring B may optionally be substituted on a ring N-atom (when containing a NH group) with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j};
- in particular ring A may optionally be substituted with one substituent selected from the group consisting of C₁₋₄alkyl, and -C₁₋₄alkyl-O-C₁₋₄alkyl;
- ring may optionally be substituted on one ring carbon atom with one or two C₁₋₄alkyl substituents, or one ring carbon atom may optionally be substituted with oxo; and
- ring B may optionally be substituted on a ring N-atom (when containing a NH group) with a C₁₋₆alkyl substituent.

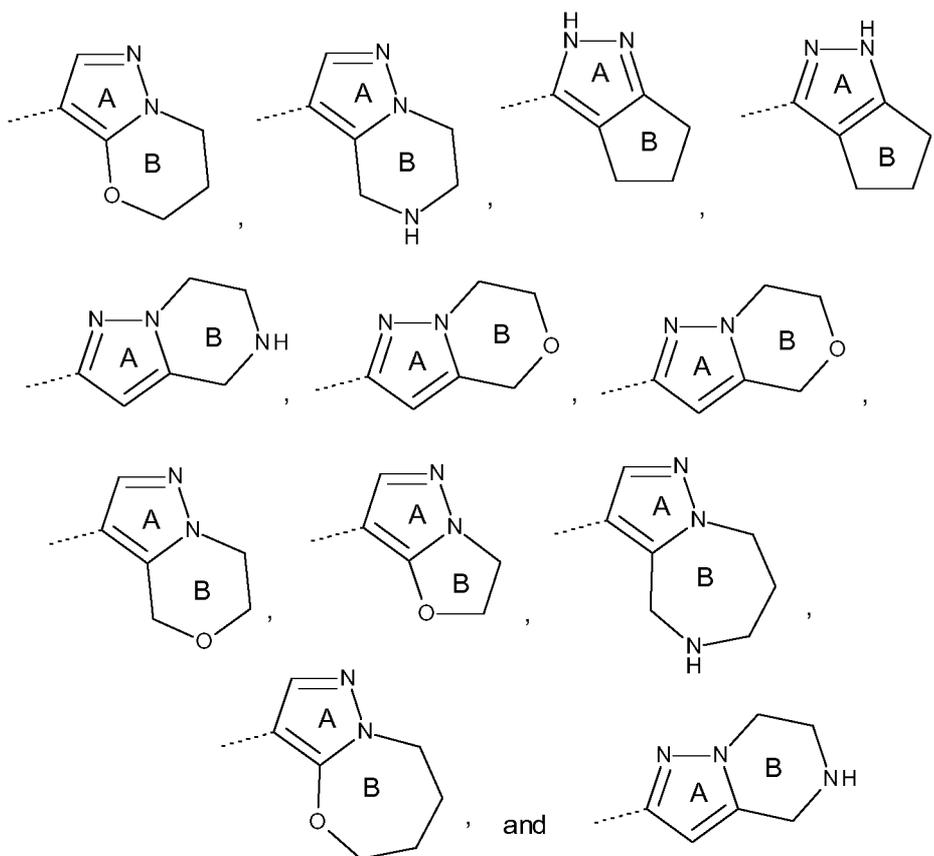
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

R³ represents a fused bicyclic ring system selected from the following structures



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

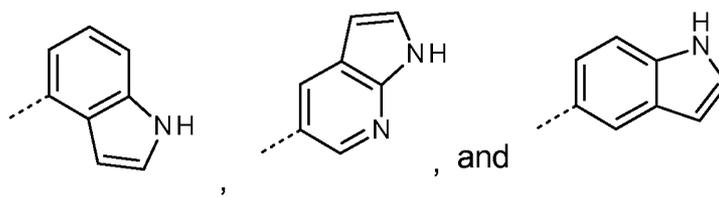
R³ represents a fused bicyclic ring system selected from the following structures



wherein said fused bicyclic ring system may optionally be substituted according to any one of the other embodiments.

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

R³ represents a fused 9-membered bicyclic heteroaromatic ring system selected from the

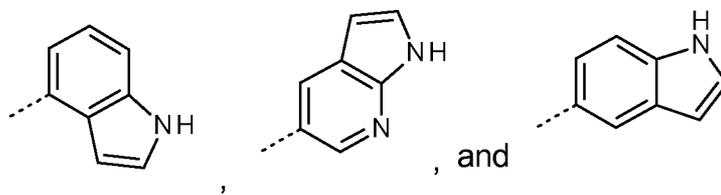


following structures

- 10 wherein said fused 9-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -S(=O)(=N-R^{20a})-C₁₋₄alkyl; -O-C₁₋₄alkyl substituted with

one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; and
 5 wherein said fused 9-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when Het^{1a} or R¹⁸ are directly attached to the N-atom of ring B, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom.

15 In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R³ represents a fused 9-membered bicyclic heteroaromatic ring system selected from the

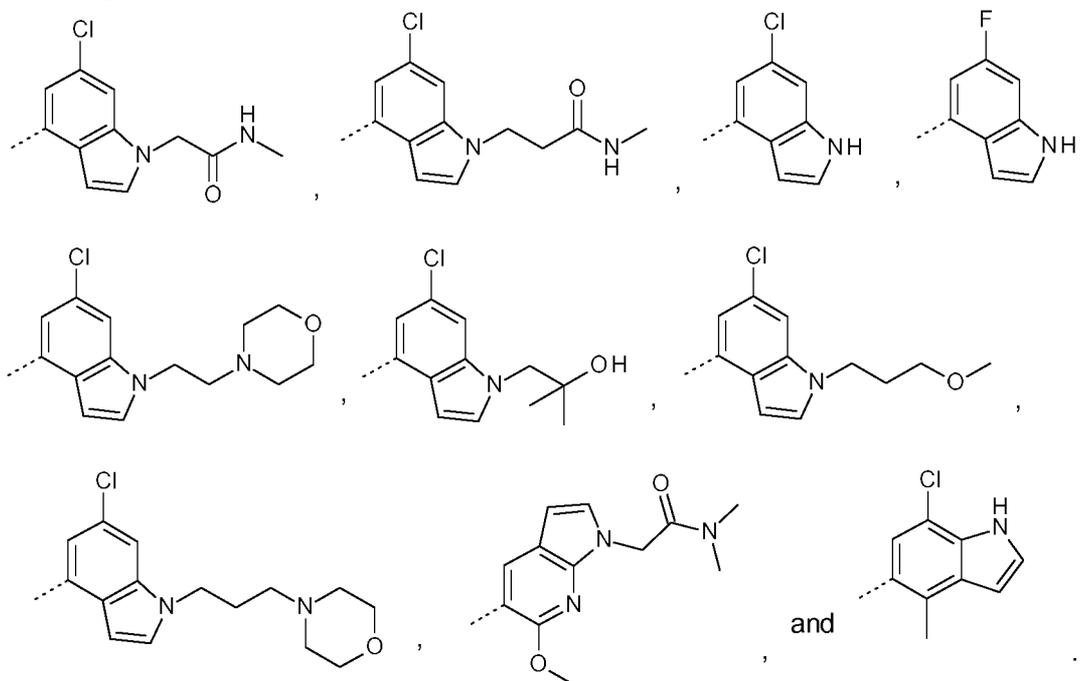


following structures

20 wherein said fused 9-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three halo substituents; and wherein said fused 9-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; and C₁₋₄alkyl substituted with one R¹³.

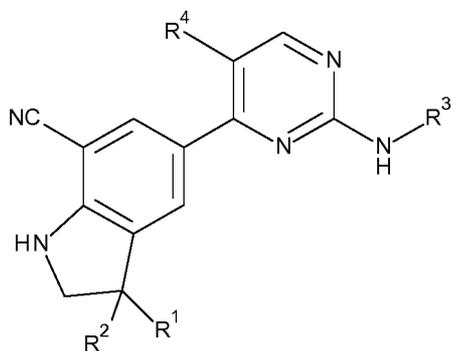
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
 30 R³ represents a fused 9-membered bicyclic heteroaromatic ring system selected from the

following structures



In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Y represents CR⁴.

In an embodiment, the present invention relates to a subgroup of Formula (I), hereby named compounds of Formula (I-x), and the pharmaceutically acceptable addition salts, and the solvates thereof:

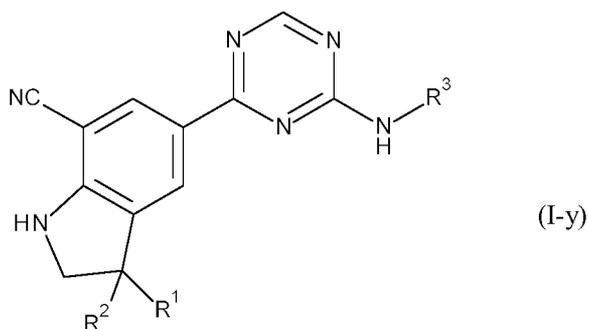


(I-x)

wherein all variables are defined according to any of the other embodiments.

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

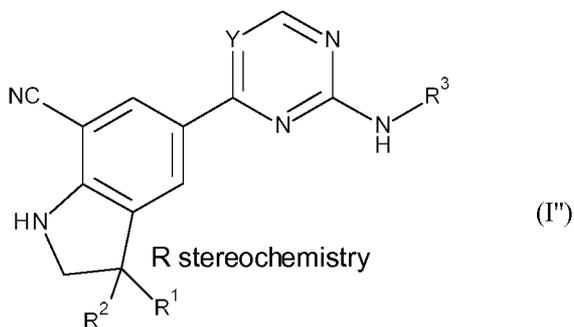
- 5 In an embodiment, the present invention relates to a subgroup of Formula (I), hereby named compounds of Formula (I-y), and the pharmaceutically acceptable addition salts, and the solvates thereof:



wherein all variables are defined according to any of the other embodiments.

10

In an embodiment, the present invention relates to a subgroup of Formula (I), hereby named compounds of Formula (I''), and the pharmaceutically acceptable addition salts, and the solvates thereof:



15 wherein all variables are defined according to any of the other embodiments.

In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 21, 25, 32, 34, 35, 1b, 2b, 3b, 17b, 3c, and 8c, tautomers and stereoisomeric forms thereof,

20 and the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 21, 25, 32, 34, 35, 1b, 2b, 3b, 17b, 3c, and 8c.

5 In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 21, 25, 32, 34, and 35, tautomers and stereoisomeric forms thereof, and the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 21, 25, 32, 34, and 35.

10 In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 1b, 2b, 3b, and 17b, tautomers and stereoisomeric forms thereof, and the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 1b, 2b, 3b, and 17b.

15

In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 3c, and 8c, tautomers and stereoisomeric forms thereof, and the pharmaceutically acceptable addition salts, and the solvates thereof.

20 In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 3c, and 8c.

In an embodiment the compound of Formula (I) is selected from the group consisting of any of the exemplified compounds, tautomers and stereoisomeric forms thereof, and the free bases, the pharmaceutically acceptable addition salts, and the solvates thereof.

25 In an embodiment, the present invention relates to a subgroup of Formula (I) as defined in the general reaction schemes.

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

30 **Methods for the Preparation of Compounds of Formula (I)**

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

The general preparation of some typical examples of the compounds of Formula (I) is described hereunder and in the specific examples, and are generally prepared from starting materials which are either commercially available or prepared by standard synthetic processes commonly used by those skilled in the art. The following schemes are only
5 meant to represent examples of the invention and are in no way meant to be a limit of the invention.

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

10 The skilled person will realise that functionalization reactions illustrated in the Schemes below for compounds of Formula (I) wherein Y is CR⁴, may also be carried out for compounds wherein Y is N. The skilled person will realise this applies, for example and without limitation, to steps 3 and 4 of scheme 2 and scheme 18.

The skilled person will realize that in the reactions described in the Schemes, although this
15 is not always explicitly shown, it may be necessary to protect reactive functional groups (for example hydroxy, amino, or carboxy groups) where these are desired in the final product, to avoid their unwanted participation in the reactions. For example in Scheme 6, the NH moiety on the pyrimidinyl or the cyanoindoline moiety can be protected with a t-butoxycarbonyl protecting group. In general, conventional protecting groups can be used
20 in accordance with standard practice. The protecting groups may be removed at a convenient subsequent stage using methods known from the art. This is illustrated in the specific examples.

The skilled person will realize that in the reactions described in the Schemes, it may be
25 advisable or necessary to perform the reaction under an inert atmosphere, such as for example under N₂-gas atmosphere.

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

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

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

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.

It will be clear for a skilled person that in case a variable in a specific general scheme is not defined, the variable is defined according to the scope of the present invention, or as defined in any one of the other general schemes.

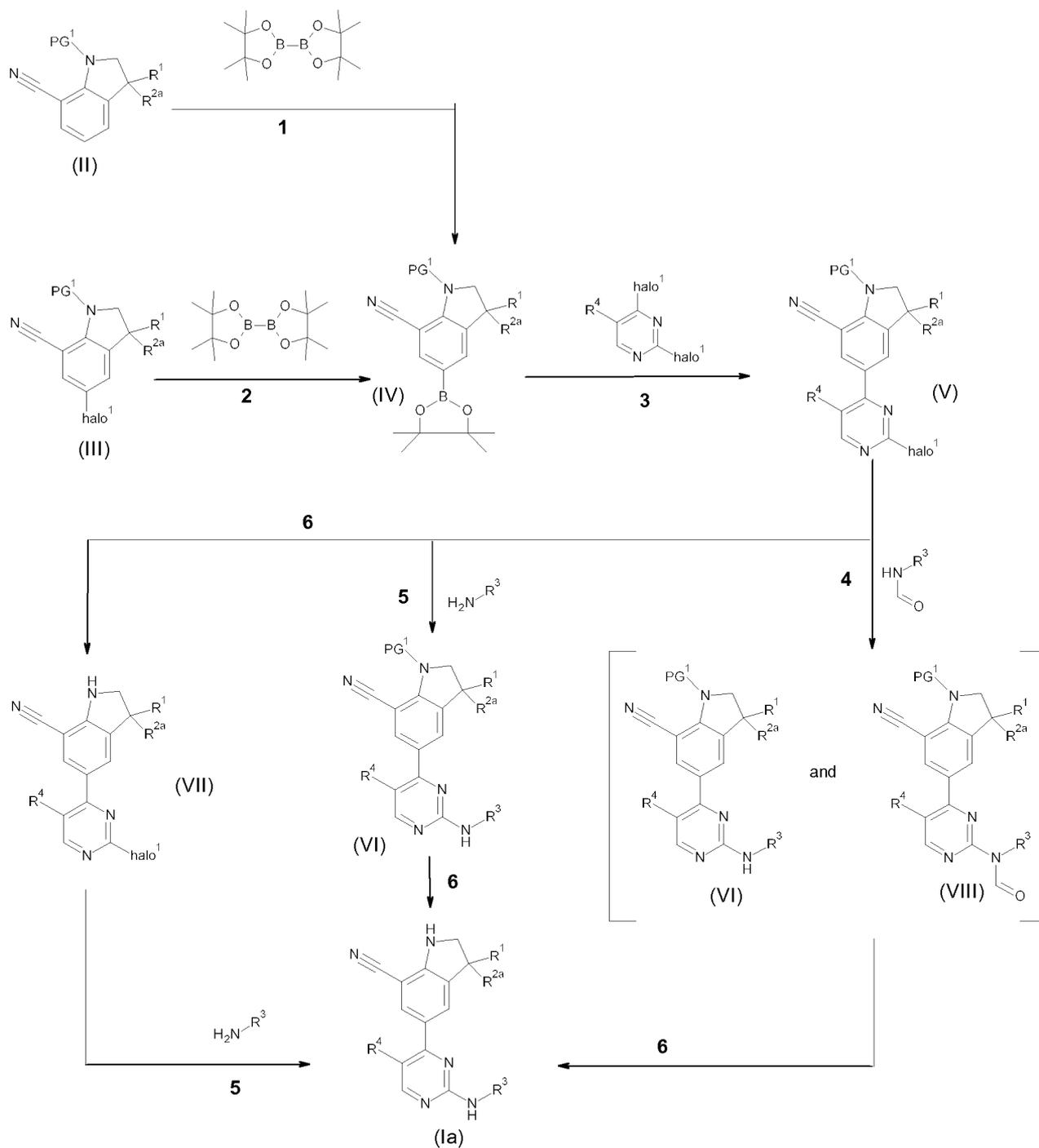
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Scheme 1

In general, compounds of Formula (I) wherein R^2 is R^{2a} being C_{1-6} alkyl, and wherein all the other variables are defined according to the scope of the present invention, hereby named compounds of Formula (Ia), can be prepared according to the following reaction Scheme 1. In Scheme 1, halo¹ is defined as Cl, Br or I; and PG¹ represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl). All other variables in Scheme 1 are defined according to the scope of the present invention.

For compounds wherein R^3 represents formula (2a-1), step 5 or 6 are preferred over step 4 in Scheme 1.

In Scheme 1, the following reaction conditions apply:



1: at a suitable temperature such as for example 80 °C, in the presence of a suitable ligand such as for example 4,4'-di-*tert*-butyl-2,2'-dipyridyl, a suitable catalyst such as for example bis(1,5-cyclooctadiene)di- μ -methoxydiiridium (I) ([Ir(OCH₃)(C₈H₁₂)₂]₂), and a suitable solvent such as for example heptane;

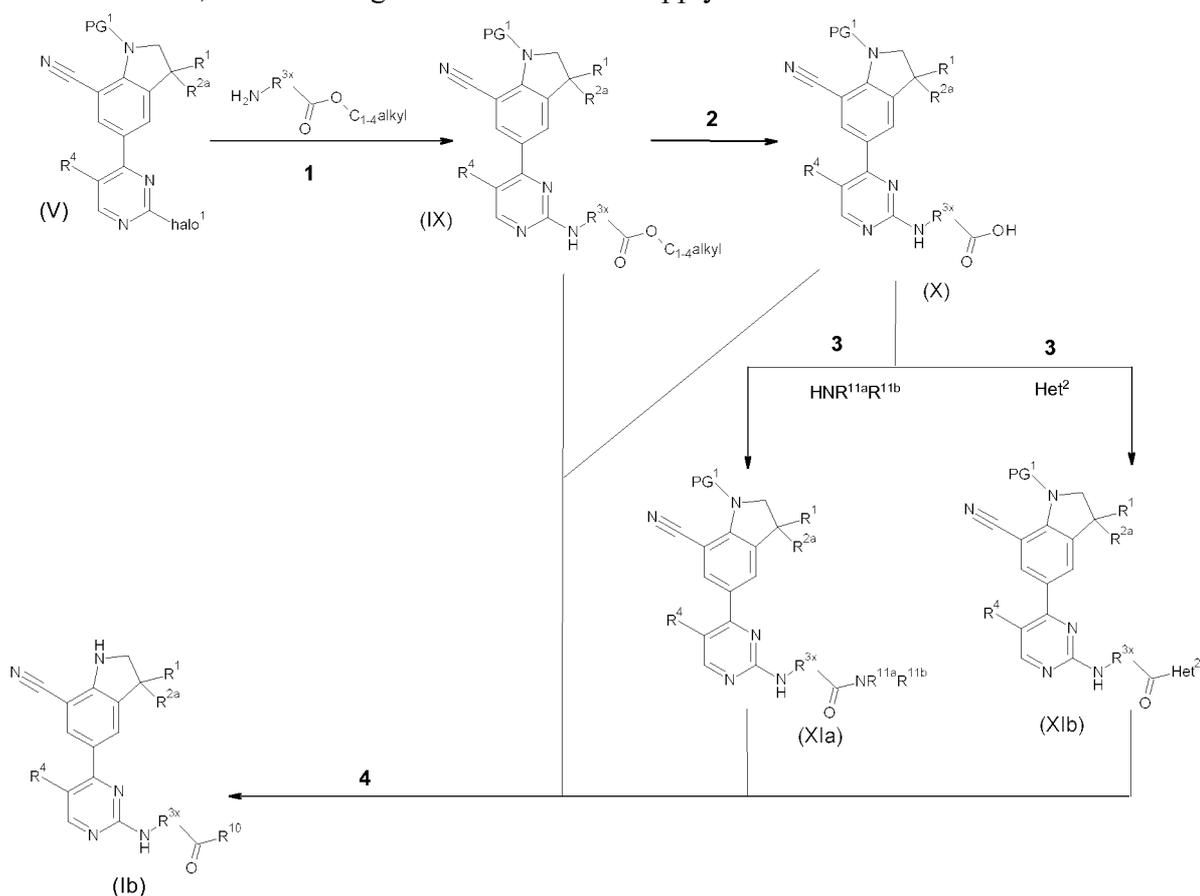
- 2: at a suitable temperature such as for example 85 °C, in the presence of a suitable catalyst such as for example [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II), optionally with dichloromethane complex, a suitable base such as for example potassium acetate and a suitable solvent such as for example 1,4-dioxane;
- 5 3: at a suitable temperature such as for example 85 °C, in the presence of a suitable catalyst such as for example palladium tetrakis (Pd(PPh₃)₄) or [1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II). Dichloromethane (Pd(dppf)Cl₂.CH₂Cl₂), a suitable base such as for example sodium carbonate, and a suitable solvent such as for example 1,4-dioxane;
- 10 4: at a suitable temperature such as for example room temperature, in presence of a suitable base such as for example sodium hydride, and a suitable solvent such as for example dimethylformamide;
- 5: at a suitable temperature such as for example ranged between 60 °C and 130°C, in the presence of a suitable catalyst such as for example palladium acetate (Pd(OAc)₂) or
- 15 Chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-tri-*i*-propyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II) (Brettphos palladacycle), a suitable ligand such as for example 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) or 2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl (Brettphos), a suitable base such as for example cesium carbonate, and a suitable solvent such as for
- 20 example 1,4-dioxane, tetrahydrofuran or , optionally under microwave irradiation; or alternatively at a suitable temperature such as for example 95 °C, in the presence of a suitable acid such as for example *p*-toluenesulfonic acid and a suitable solvent such as for example 1,4-dioxane;
- 6: at a suitable temperature such as for example 0 °C or room temperature or reflux, in
- 25 presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane or alternatively in the presence of silica in a suitable solvent such as for example toluene at a suitable temperature such as for example 125°C, and a suitable time such as for example 3 hours.
- 30 The skilled person will understand that the reactions described in Scheme 1 will also be applicable starting from an intermediate of formula (III-a) (as described in Scheme 2).

Scheme 2

In scheme 2, R^3 is limited to R^{3x} representing formula (1a-1), (1a-2) or a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N.

In general, compounds of Formula (I) wherein R^2 is R^{2a} being C_{1-6} alkyl, R^{3x} is as defined above for Scheme 2, R^{3x} is substituted with $-C(=O)-R^{10}$ and additionally optionally substituted with other substituents according to the scope of the present invention, and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Ib), can be prepared according to the following reaction Scheme 2. In Scheme 2, halo¹ is defined as Cl, Br or I; PG¹ represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl). All other variables in

In Scheme 2, the following reaction conditions apply:



15 **1:** at a suitable temperature such as for example 100 °C, in the presence of a suitable catalyst such as for example palladium acetate ($Pd(OAc)_2$), a suitable ligand such as for example 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), a suitable base such as for

example cesium carbonate, and a suitable solvent such as for example 1,4-dioxane, optionally under microwave activation;

2: at a suitable temperature such as for example 70 °C, in presence of a suitable base such as for example lithium hydroxide, and a suitable solvent such as for example a mixture of
5 tetrahydrofuran and water;

3: at a suitable temperature such as for example room temperature, in presence of a suitable coupling reagent such as for example 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), a suitable base such as for example *N,N*-diisopropylethylamine, and a suitable solvent such as for example
10 dimethylformamide;

4: at a suitable temperature such as for example 0 °C or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethylacetate, or 1,4-dioxane, and a suitable time such as for example 3 hours.

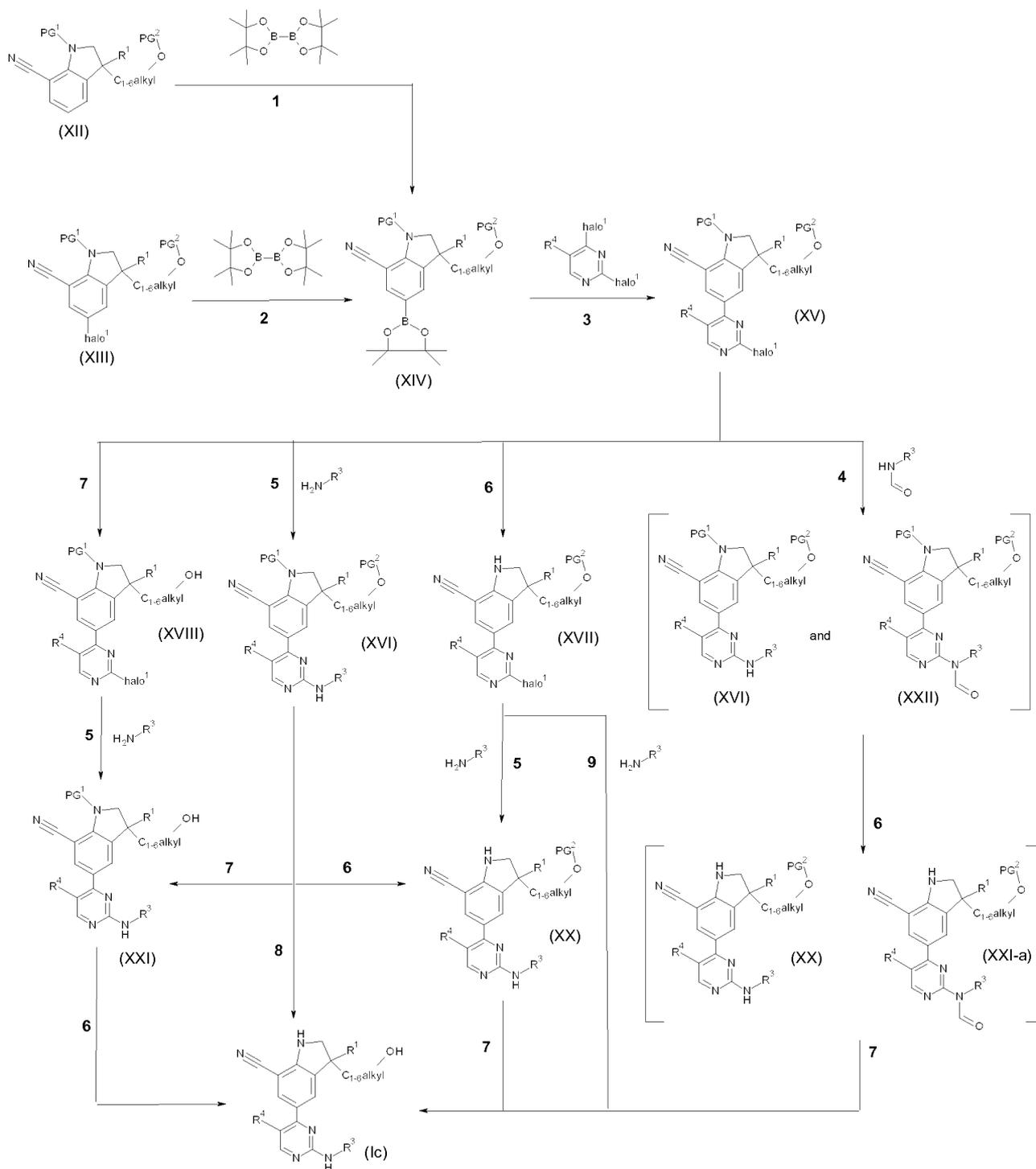
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Scheme 3

In general, compounds of Formula (I) wherein R^2 is R^{2b} being C_{1-6} alkyl substituted with one OH, and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Ic), can be prepared according to
20 the following reaction Scheme 3. In Scheme 3 halo¹ is defined as Cl, Br or I; PG¹ represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl); and PG² represents a suitable protecting group, such as for example *tert*-butyl-dimethylsilyl. All other variables in Scheme 3 are defined according to the scope of the present invention.

For compounds wherein R^3 represents formula (2a-1), step 5, 6 or 7 are preferred over step
25 4 in Scheme 3. Also for compounds wherein R^3 represents formula (2a-1), the combination of steps 5 and 7 is preferred over step 9.

In Scheme 3, the following reaction conditions apply:



1: at a suitable temperature such as for example 80 °C, in the presence of a suitable ligand such as for example 4,4'-di-*tert*-butyl-2,2'-dipyridyl, a suitable catalyst such as for

example bis(1,5-cyclooctadiene)di- μ -methoxydiiridium (I) ($[\text{Ir}(\text{OCH}_3)(\text{C}_8\text{H}_{12})]_2$), and a suitable solvent such as for example heptane;

2: at a suitable temperature such as for example 85 °C, in the presence of a suitable catalyst such as for example [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II),
5 optionally with dichloromethane complex, a suitable base such as for example potassium acetate and a suitable solvent such as for example 1,4-dioxane;

3: at a suitable temperature such as for example 85 °C, in the presence of a suitable catalyst such as for example palladium tetrakis ($\text{Pd}(\text{PPh}_3)_4$), a suitable base such as for example sodium carbonate, and a suitable solvent such as for example 1,4-dioxane;

10 4: at a suitable temperature such as for example room temperature, in presence of a suitable base such as for example sodium hydride, and a suitable solvent such as for example dimethylformamide;

5: at a suitable temperature such as for example ranged between 80 °C and 130°C, in the presence of a suitable catalyst such as for example palladium acetate ($\text{Pd}(\text{OAc})_2$) or
15 Chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-tri-*i*-propyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II) (Brettphos palladacycle), a suitable ligand such as for example 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), or 2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl (Brettphos), a suitable base such as for example cesium carbonate, and a suitable solvent such as for
20 example 1,4-dioxane, tetrahydrofuran or , optionally under microwave irradiation;

6: at a suitable temperature such as for example 0 °C or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane or alternatively in the presence of silica in a suitable solvent such as for
25 example toluene at a suitable temperature such as for example 125°C, and a suitable time such as for example 3 hours;

7: at a suitable temperature such as for example room temperature, in presence of a suitable desilylating agent such as for example *tetra-n*-butylammonium fluoride and a suitable solvent such as for example 2-methyltetrahydrofuran or tetrahydrofuran;

30 8: at a suitable temperature such as for example reflux, in presence of a suitable acid such as for example aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane, and a suitable time such as for example 6 hours;

9: at a suitable temperature such as for example 95 °C, in the presence of a suitable acid such as for example p-toluenesulfonic acid and a suitable solvent such as for example 1,4-dioxane.

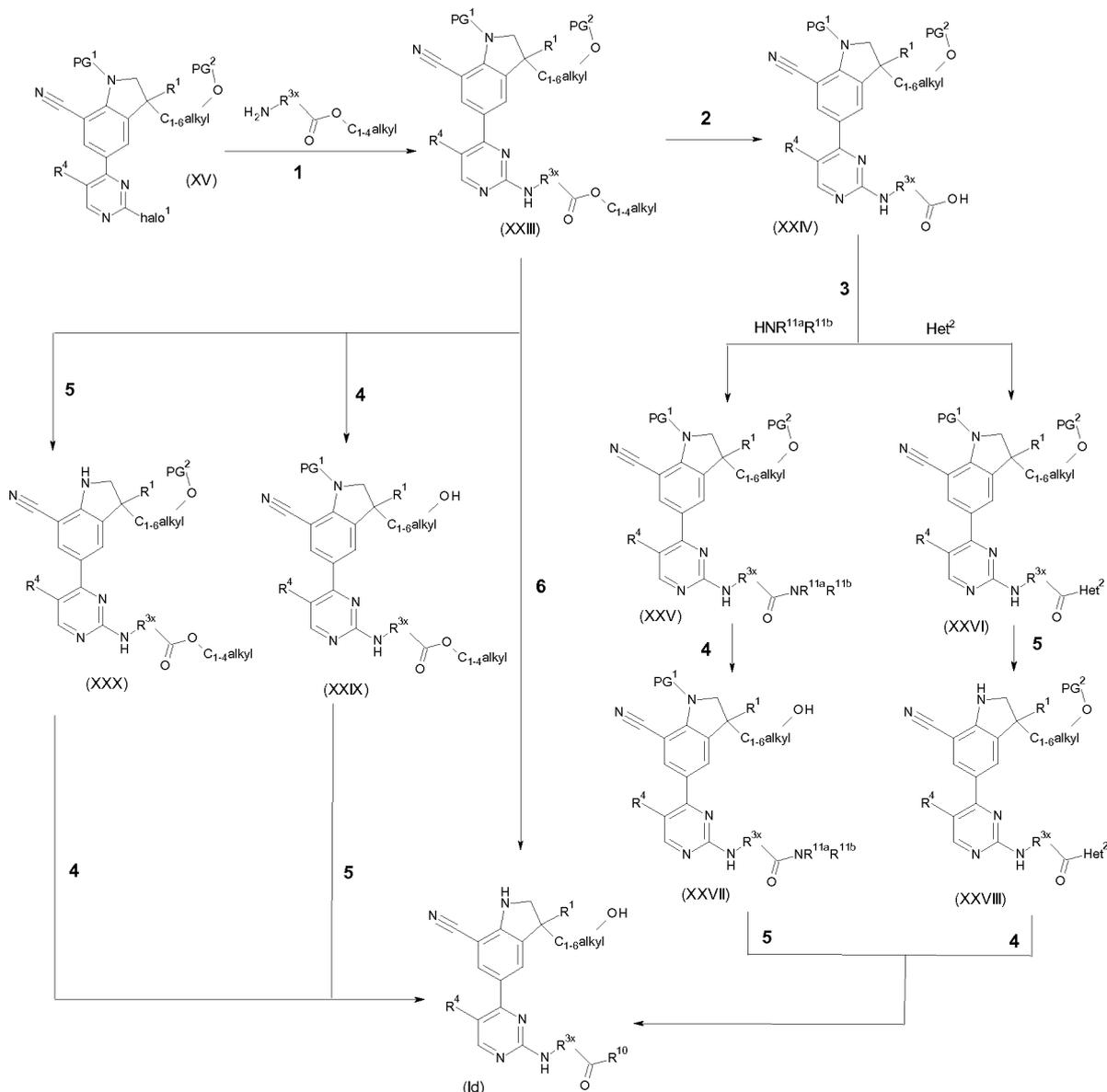
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Scheme 4

In scheme 4, R³ is limited to R^{3x} representing formula (1a-1), (1a-2) or a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N.

10 In general, compounds of Formula (I) wherein R² is R^{2b} being C₁₋₆alkyl substituted with one OH, R^{3x} is as defined above for Scheme 4, R^{3x} is substituted with -C(=O)-R¹⁰ on a carbon atom and additionally optionally substituted with other substituents according to the scope of the present invention, and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Id), can be
15 prepared according to the following reaction Scheme 4. In Scheme 4, halo¹ is defined as Cl, Br or I; PG¹ represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl) and PG² represents a suitable protecting group, such as for example *tert*-butyl-dimethylsilyl. All other variables in Scheme 4 are defined according to the scope of the present invention.

20 In Scheme 4, the following reaction conditions apply:



1: at a suitable temperature such as for example 100 °C, in the presence of a suitable catalyst such as for example palladium acetate ($\text{Pd}(\text{OAc})_2$), a suitable ligand such as for example 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), a suitable base such as for example cesium carbonate, and a suitable solvent such as for example 1,4-dioxane, optionally under microwave activation;

5

2: at a suitable temperature such as for example 70 °C, in presence of a suitable base such as for example lithium hydroxide, and a suitable solvent such as for example a mixture of tetrahydrofuran and water;

10

3: at a suitable temperature such as for example room temperature, in presence of a suitable coupling reagent such as for example 1-[bis(dimethylamino)methylene]-1H-1,2,3-

triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), a suitable base such as for example *N,N*-diisopropylethylamine, and a suitable solvent such as for example dimethylformamide;

4: at a suitable temperature such as for example room temperature, in presence of a suitable desilylating agent such as for example *tetra-n*-butylammonium fluoride and a suitable solvent such as for example 2-methyltetrahydrofuran or tetrahydrofuran;

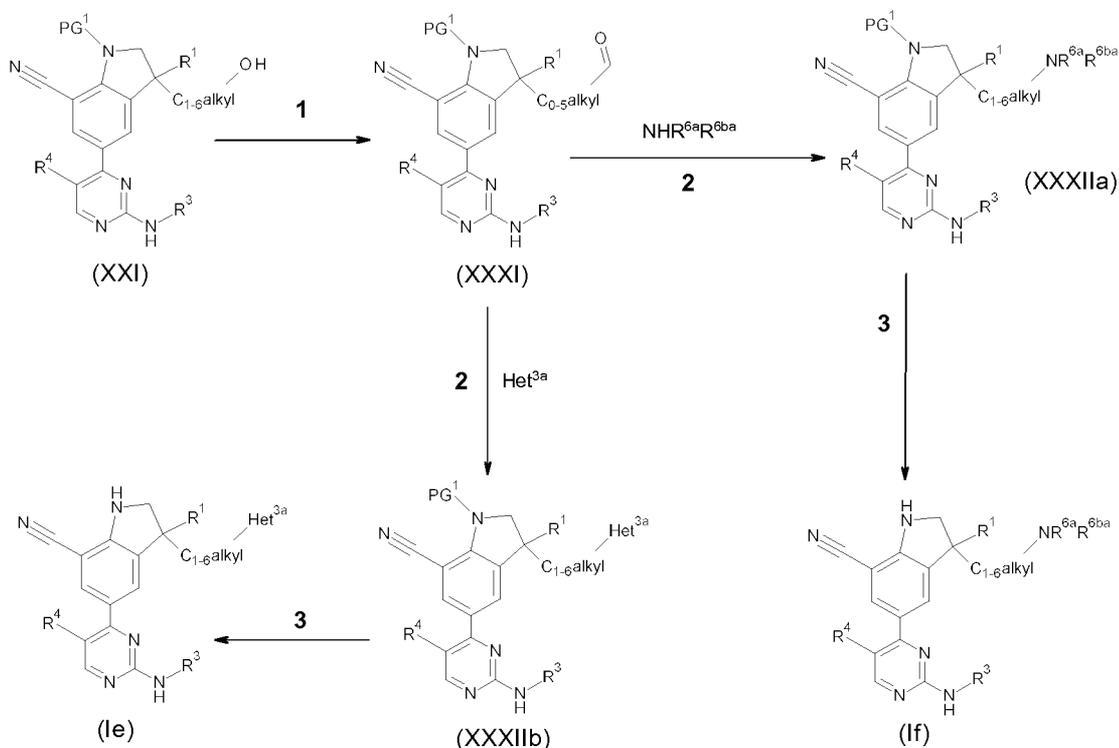
5: at a suitable temperature such as for example 0 °C or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane or alternatively in the presence of silica in a suitable solvent such as for example toluene at a suitable temperature such as for example 125°C, and a suitable time such as for example 3 hours;

6: at a suitable temperature such as for example reflux, in presence of a suitable acid such as for example aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane, and a suitable time such as for example 6 hours.

Scheme 5

In general, compounds of Formula (I) wherein R^2 is R^{2c} being C_{1-6} alkyl substituted with one Het^{3a} or $-NR^{6a}R^{6b}$, wherein R^{6b} is R^{6ba} being H, C_{1-4} alkyl and C_{3-6} cycloalkyl and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Ie) and Formula (If), can be prepared according to the following reaction Scheme 5. In Scheme 5 PG^1 represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl). All other variables in Scheme 5 are defined according to the scope of the present invention.

In Scheme 5, the following reaction conditions apply:



1: at a suitable temperature such as for example $-78\text{ }^{\circ}\text{C}$, in the presence of oxalyl chloride and dimethyl sulfoxide as reagents, a suitable base such as for example *N,N*-diisopropylethylamine, and a suitable solvent such as for example dichloromethane;

- 5 2: at a suitable temperature such as for example room temperature, in the presence of a suitable acid such as for example acetic acid, a suitable reducing agent such as for example sodium triacetoxyborohydride, and a suitable solvent such as for example dichloroethane;
- 3: at a suitable temperature such as for example $0\text{ }^{\circ}\text{C}$ or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane or alternatively in the presence of silica in a suitable solvent such as for example toluene at a suitable temperature such as for example $125\text{ }^{\circ}\text{C}$, and a suitable time such as for example 3 hours.

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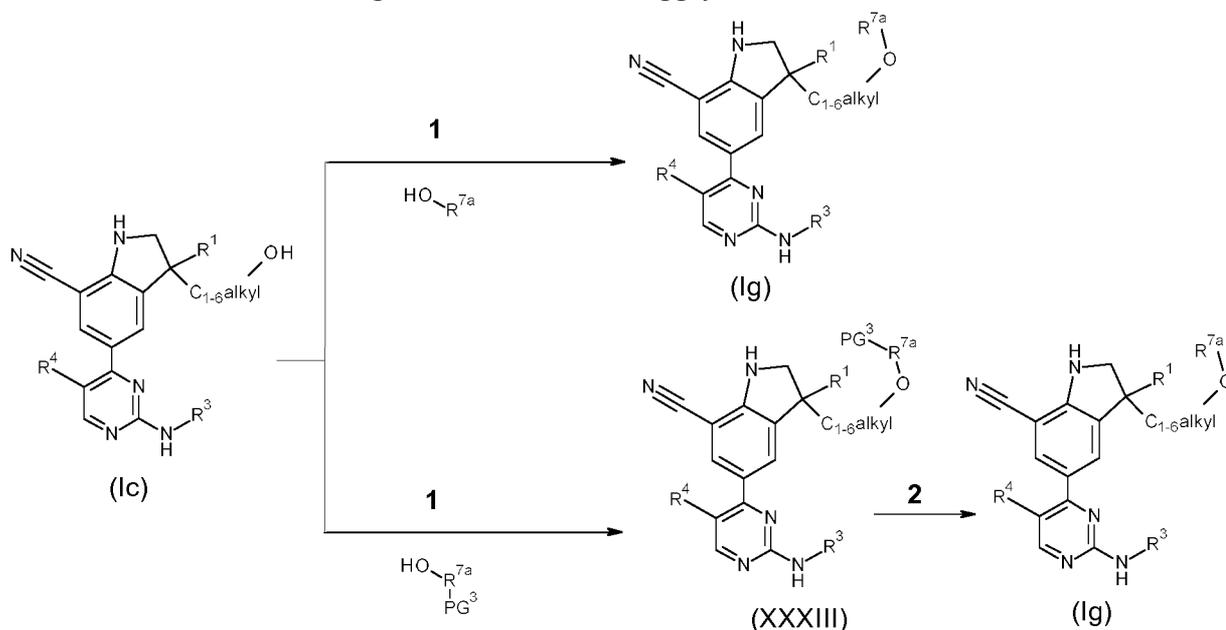
Scheme 6

In general, compounds of Formula (I) wherein R^2 is C_{1-6} alkyl substituted with one OR^{7a} , R^{7a} being $-C(=O)-R^9$ or $-(C=O)-CH(NH_2)-C_{1-4}$ alkyl- Ar^1 , and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Ig), can be prepared according to the following reaction Scheme 6. In Scheme 6 PG^3 represents a suitable protecting group, such as for example a *tert*-

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(butoxycarbonyl), a *tert*-butyl or a benzyl. All other variables in Scheme 6 are defined according to the scope of the present invention.

In Scheme 6, the following reaction conditions apply:



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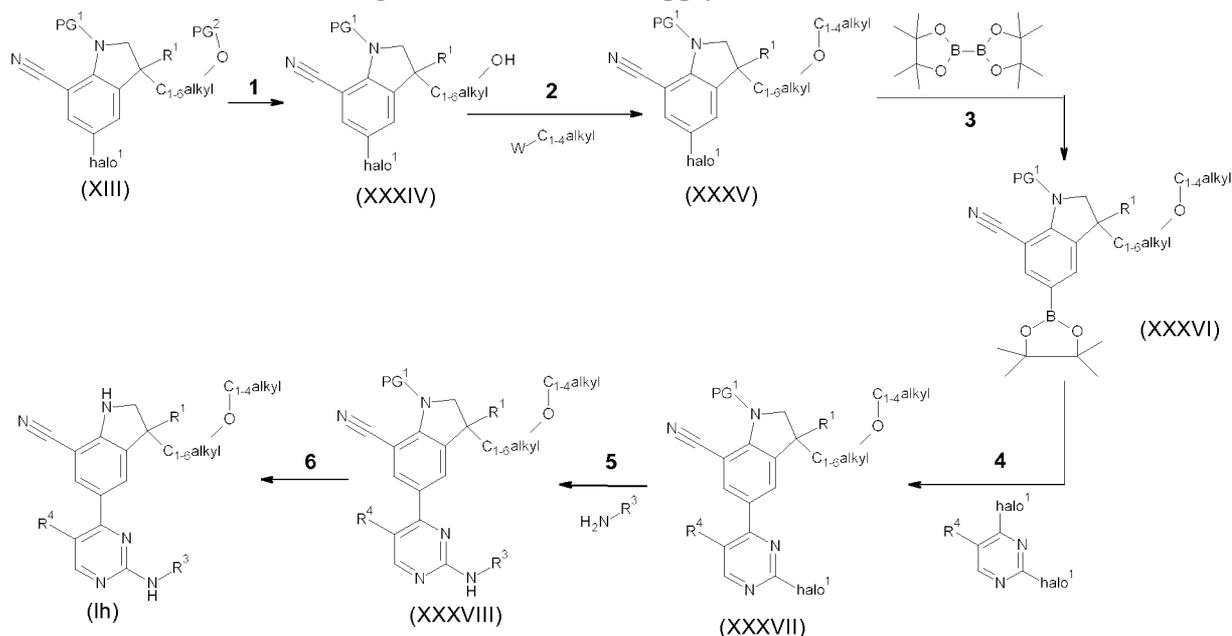
1: at a suitable temperature such as for example room temperature, in the presence of a suitable coupling reagent such as for example 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), in the presence of a suitable base as for example *N,N*-diisopropylethylamine, and a suitable solvent such as for example a mixture of tetrahydrofuran and dimethylformamide, and optionally followed by a deprotection step using a suitable acid such as for example hydrochloric acid in a suitable solvent such as for example 1,4-dioxane;

2: at a suitable temperature such as for example 0 °C or room temperature, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane or alternatively in the presence of silica in a suitable solvent such as for example toluene at a suitable temperature such as for example 125°C, and a suitable time such as for example 3 hours.

Scheme 7

In general, compounds of Formula (I) wherein R^2 is C_{1-6} alkyl substituted with one OR^{7b} , R^{7b} being C_{1-4} alkyl, and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Ih), can be prepared according to the following reaction Scheme 7. In Scheme 7 halo¹ is defined as Cl, Br or I; PG¹ represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl) and PG² represents a suitable protecting group, such as for example *tert*-butyl-dimethylsilyl; W represents a leaving group, such as for example a methane sulfonate or toluene sulfonate or an halogen (Cl, Br or I). All other variables in Scheme 7 are defined according to the scope of the present invention.

10 In Scheme 7, the following reaction conditions apply:



- 1: at a suitable temperature such as for example room temperature, in presence of a suitable desilylating agent such as for example *tetra-n*-butylammonium fluoride and a suitable solvent such as for example 2-methyltetrahydrofuran or tetrahydrofuran;
- 15 2: at a suitable temperature such as for example room temperature, in the presence of a suitable base as for example sodium hydride, and a suitable solvent such as for example dimethylformamide;
- 3: at a suitable temperature such as for example 85 °C, in the presence of a suitable catalyst
- 20 such as for example [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II), optionally with dichloromethane complex, a suitable base such as for example potassium acetate and a suitable solvent such as for example 1,4-dioxane;

4: at a suitable temperature such as for example 80 °C, in the presence of a suitable catalyst such as for example palladium tetrakis (Pd(PPh₃)₄), a suitable base such as for example sodium carbonate, and a suitable solvent such as for example 1,4-dioxane;

5: at a suitable temperature such as for example 100 °C, in the presence of a suitable catalyst such as for example palladium acetate (Pd(OAc)₂), a suitable ligand such as for example 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), a suitable base such as for example cesium carbonate, and a suitable solvent such as for example 1,4-dioxane, optionally under microwave activation;

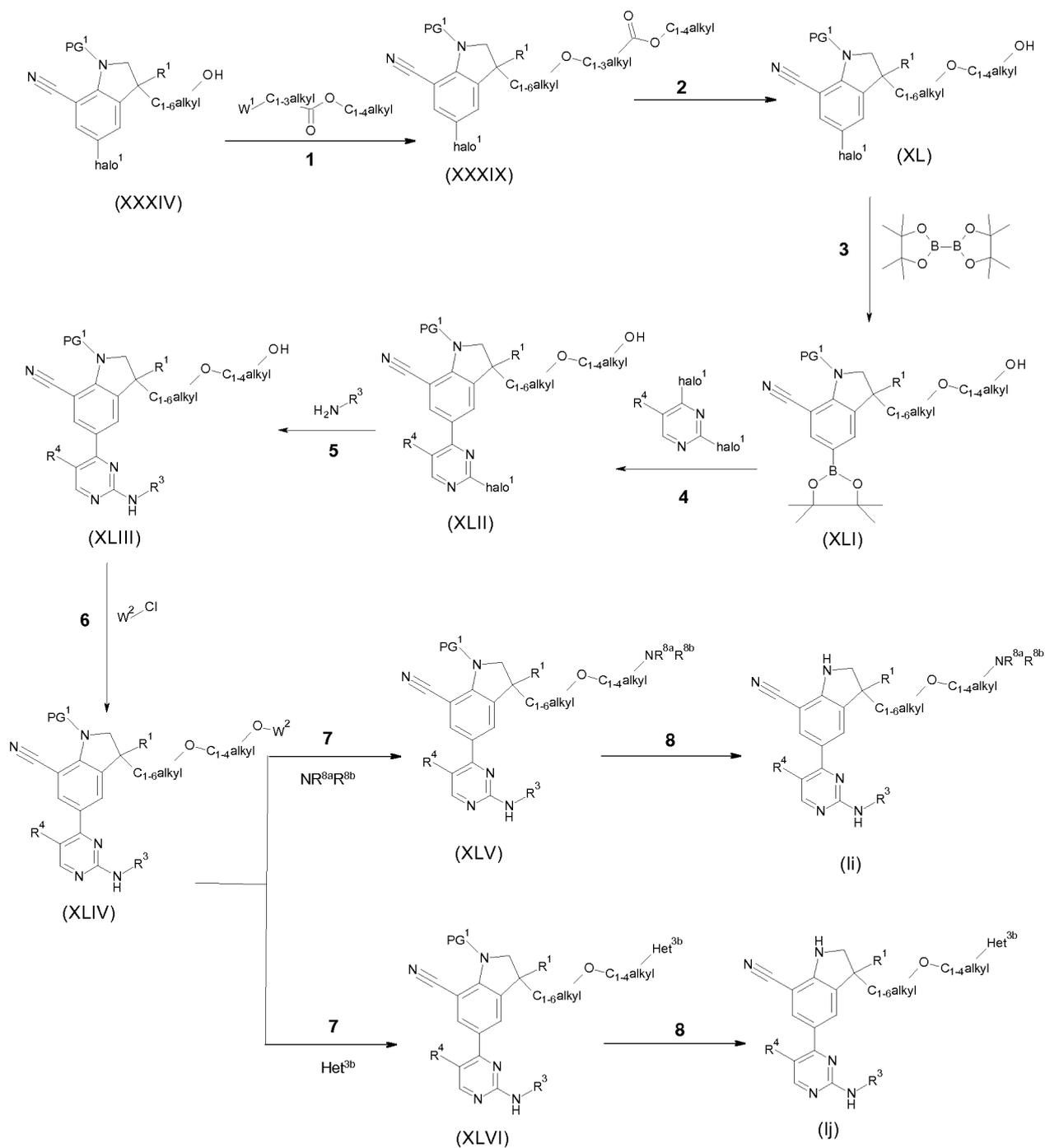
6: at a suitable temperature such as for example 0 °C or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane or alternatively in the presence of silica in a suitable solvent such as for example toluene at a suitable temperature such as for example 125°C, and a suitable time such as for example 3 hours.

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Scheme 8

In general, compounds of Formula (I) wherein R² is C₁₋₆alkyl substituted with one OR^{7c}, R^{7c} being C₁₋₄alkyl-NR^{8a}R^{8b} or C₁₋₄alkyl-Het^{3b}, and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Ii) and Formula (Ij), can be prepared according to the following reaction Scheme 8. In Scheme 8 halo¹ is defined as Cl, Br or I; PG¹ represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl); W¹ represents a leaving group, such as for example a methane sulfonate or toluene sulfonate or an halogen (Cl, Br or I); W² represents a leaving group, such as for example a mesyl or a tosyl. All other variables in Scheme 8 are defined according to the scope of the present invention.

25 In Scheme 8, the following reaction conditions apply:



1: at a suitable temperature such as for example room temperature, in the presence of a suitable base as for example sodium hydride, and a suitable solvent such as for example dimethylformamide;

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- 2: at a suitable temperature such as for example 55 °C, in presence of reducing agent such as for example sodium borohydride and a suitable solvent such as for example a mixture of tetrahydrofuran and methanol;
- 3: at a suitable temperature such as for example 100 °C, in the presence of a suitable catalyst such as for example [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II), optionally with dichloromethane complex, a suitable base such as for example potassium acetate and a suitable solvent such as for example 1,4-dioxane;
- 4: at a suitable temperature such as for example 85 °C, in the presence of a suitable catalyst such as for example palladium tetrakis (Pd(PPh₃)₄), a suitable base such as for example sodium carbonate, and a suitable solvent such as for example 1,4-dioxane;
- 5: at a suitable temperature such as for example 120 °C, in the presence of a suitable catalyst such as for example palladium acetate (Pd(OAc)₂), a suitable ligand such as for example 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), a suitable base such as for example cesium carbonate, and a suitable solvent such as for example 1,4-dioxane, optionally under microwave activation;
- 6: at a suitable temperature such as for example 5 °C, in the presence of a suitable base such as for example triethylamine, and a suitable solvent such as for example dichloromethane;
- 7: at a suitable temperature such as for example 80 °C, and a suitable solvent such as for example acetonitrile;
- 8: at a suitable temperature such as for example 0 °C or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane or alternatively in the presence of silica in a suitable solvent such as for example toluene at a suitable temperature such as for example 125°C, and a suitable time such as for example 3 hours.

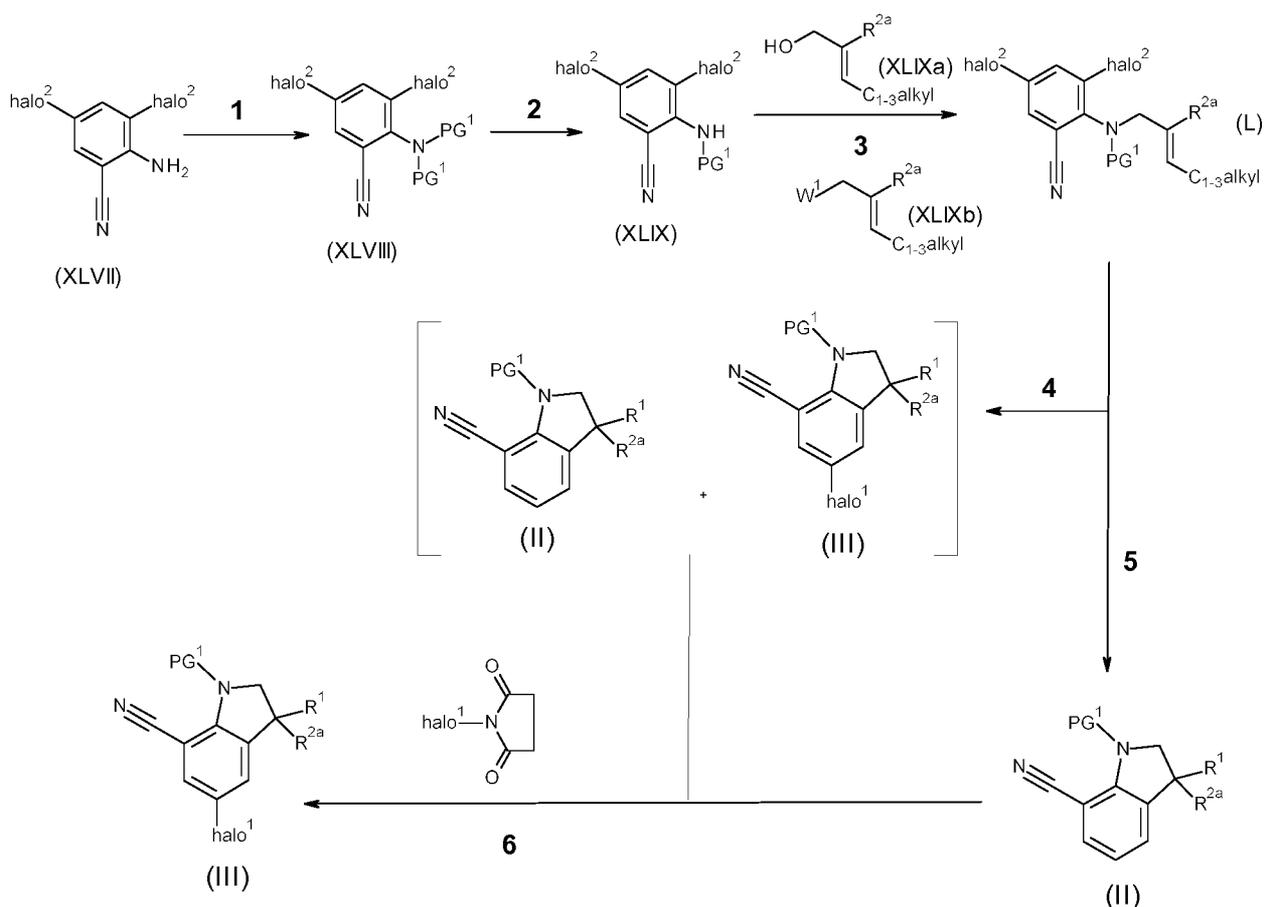
Scheme 9

In general, intermediates of Formula (II) and (III) wherein R² is R^{2a} being C₁₋₆alkyl, and wherein all the other variables are as defined according to the scope of the present

invention, hereby named compounds of Formula (II) and (III), can be prepared according to the following reaction Scheme 9. In Scheme 9 halo¹ is defined as Cl, Br, I; halo² is defined as Cl, Br, I; PG¹ represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl), W¹ represents a leaving group, such as for example a methane sulfonate or toluene sulfonate or an halogen (Cl, Br or I). All other variables in Scheme 9 are defined

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according to the scope of the present invention.
In Scheme 9, the following reaction conditions apply:



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1: at a suitable temperature such as for example 45 °C, in the presence of a suitable reagent such as for example di-*tert*-butyldicarbonate, in the presence of a suitable catalyst such as for example 4-dimethylaminopyridine (DMAP), and a suitable solvent such as for example dichloromethane;

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2: at a suitable temperature such as for example 65 °C and a suitable solvent such as for example methanol;

3: in case of (XLIXa), at a suitable temperature such as for example at room temperature, in the presence of tri-n-butylphosphine and 1,1'-(azodicarbonyl)piperidine and a suitable solvent such as for example 2-methyltetrahydrofuran;

5 In case of (XLIXb), at a suitable temperature such as for example 80°C, in the presence of a suitable base such as for example potassium carbonate, a suitable additive such as for example sodium iodide, in a suitable solvent such as for example acetonitrile;

4: at a suitable temperature such as for example 85 °C, in the presence of sodium acetate, sodium formate and tetraethylammonium chloride, a suitable catalyst such as for example palladium acetate (Pd(OAc)₂), and a suitable solvent such as for example
10 dimethylformamide;

5: at a suitable temperature such as for example 60 °C, in the presence of sodium acetate, sodium formate dehydrate and tetraethylammonium chloride, a suitable catalyst such as for example [1,1'-bis(diphenylphosphino) ferrocene] palladium, (II) chloride optionally with dichloromethane complex, and a suitable solvent such as for example
15 dimethylformamide;

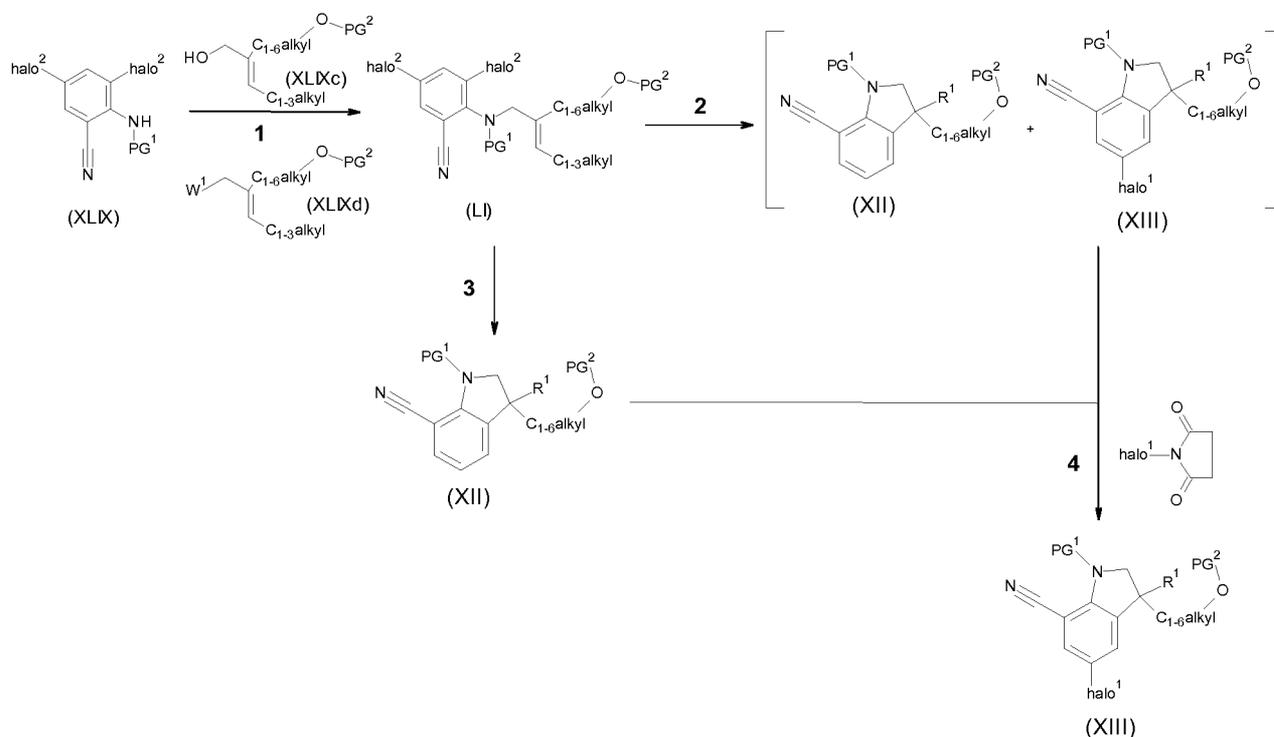
6: at a suitable temperature such as for example 40 °C, in the presence of N-halogeno-succinimide, and a suitable solvent such as for example acetonitrile. Alternatively, in the presence of a suitable reagent such as for example 1,3-dibromo-5,5-dimethylhydantoin, in a suitable solvent such as for example acetonitrile.

20

Scheme 10

In general, intermediates of Formula (XII) and (XIII) wherein R² is R^{2b} being C₁₋₆alkyl substituted with one OH, and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (XII) and (XIII), can
25 be prepared according to the following reaction Scheme 10. In Scheme 10 halo¹ is defined as Cl, Br, I; halo² is defined as Cl, Br, I; PG¹ represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl) and PG² represents a suitable protecting group, such as for example *tert*-butyl-dimethylsilyl; W¹ represents a leaving group, such as for example a methane sulfonate or toluene sulfonate or an halogen (Cl, Br or I). All other variables in
30 Scheme 10 are defined according to the scope of the present invention.

In Scheme 10, the following reaction conditions apply:



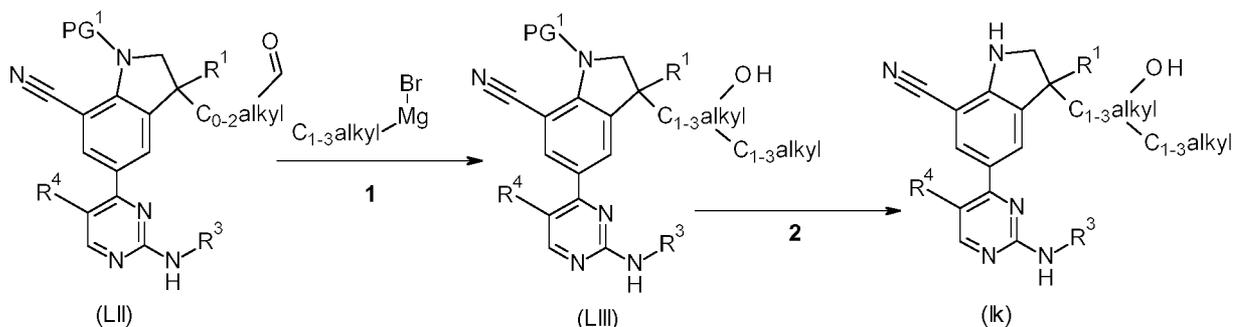
- 1: in case of (XLIXc), at a suitable temperature such as for example at room temperature, in the presence of tri-*n*-butylphosphine and 1,1'-(azodicarbonyl)piperidine and a suitable solvent such as for example 2-methyltetrahydrofuran;
- 5 In case of (XLIXb), at a suitable temperature such as for example 80°C, in the presence of a suitable base such as for example potassium carbonate, a suitable additive such as for example sodium iodide, in a suitable solvent such as for example acetonitrile;
- 2: at a suitable temperature such as for example 85 °C, in the presence of sodium acetate, sodium formate and tetraethylammonium chloride, a suitable catalyst such as for example palladium acetate (Pd(OAc)₂), and a suitable solvent such as for example dimethylformamide;
- 10 3: at a suitable temperature such as for example 60 °C, in the presence of sodium acetate, sodium formate dehydrate and tetraethylammonium chloride, a suitable catalyst such as for example [1,1'-bis(diphenylphosphino) ferrocene] palladium, (II) chloride optionally with dichloromethane complex, and a suitable solvent such as for example dimethylformamide;
- 15 4: at a suitable temperature such as for example 40 °C, in the presence of N-halogeno-succinimide, and a suitable solvent such as for example acetonitrile. Alternatively, in the

presence of a suitable reagent such as for example 1,3-dibromo-5,5-dimethylhydantoin, in a suitable solvent such as for example acetonitrile.

Scheme 11

5 In general, compounds of Formula (I) wherein R^2 is as shown in the scheme 11, and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Ik) can be prepared according to the following reaction Scheme 11. In Scheme 11 PG^1 represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl). All other variables in Scheme 11 are defined
10 according to the scope of the present invention.

In Scheme 11, the following reaction conditions apply:



1: at a suitable temperature such as for example at room temperature, and a suitable solvent
15 such as for example tetrahydrofuran;

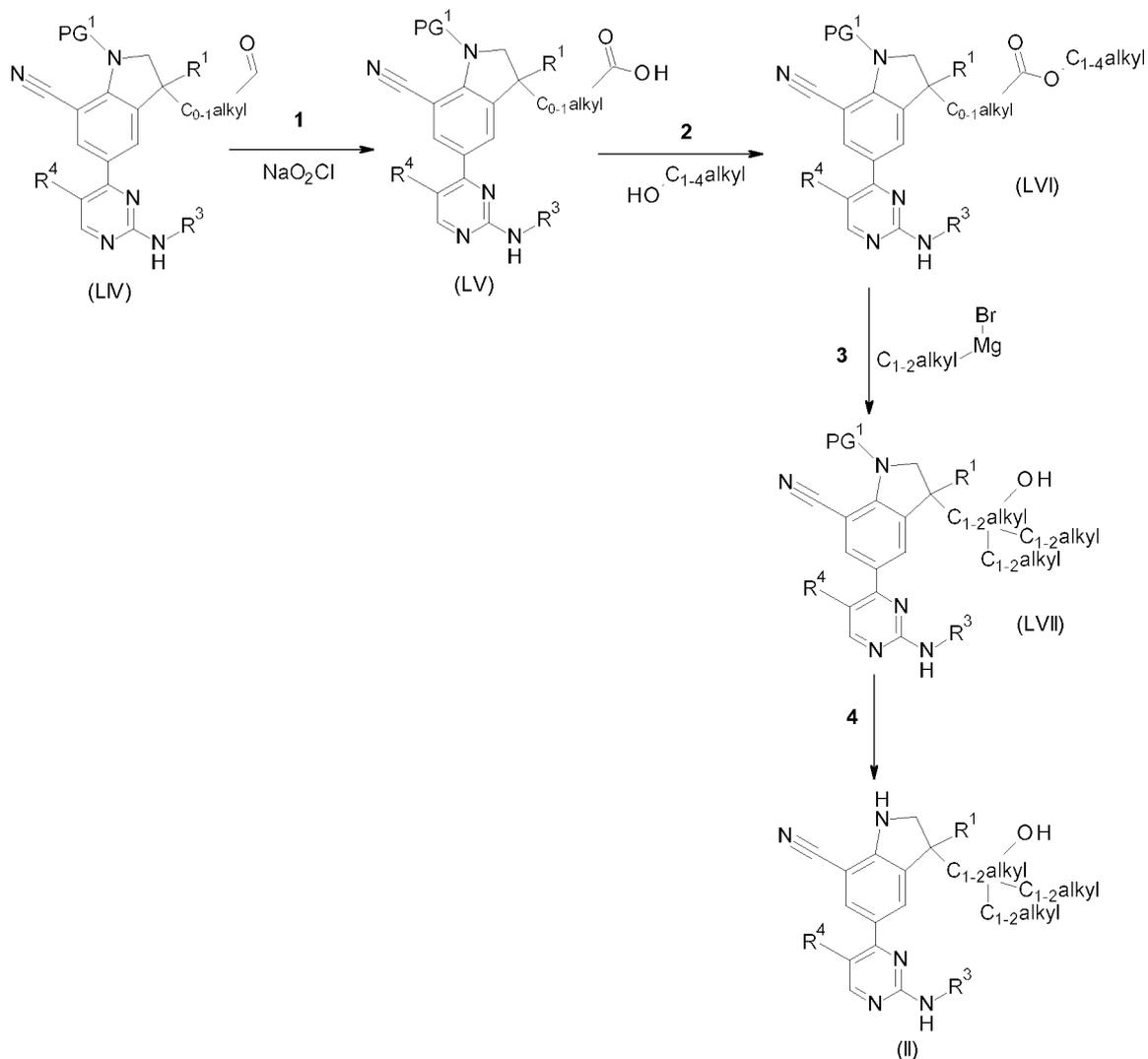
2: at a suitable temperature such as for example 0 °C or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane or alternatively in the presence of silica in a suitable solvent such as for
20 example toluene at a suitable temperature such as for example 125°C and a suitable time such as for example 3 hours.

Scheme 12

In general, compounds of Formula (I) wherein R^2 is as shown in the scheme 12, and wherein all the other variables are as defined according to the scope of the present
25 invention, hereby named compounds of Formula (II) can be prepared according to the following reaction Scheme 12. In Scheme 12 PG^1 represents a suitable protecting group,

such as for example *tert*-(butoxycarbonyl). All other variables in Scheme 12 are defined according to the scope of the present invention.

In Scheme 12, the following reaction conditions apply:



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1: at a suitable temperature such as for example at room temperature, in the presence of *tert*-butyl alcohol, 2-methyl-2-butene, sodium dihydrogenophosphate and distilled water;

2: at a suitable temperature such as for example at room temperature, in presence of 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid

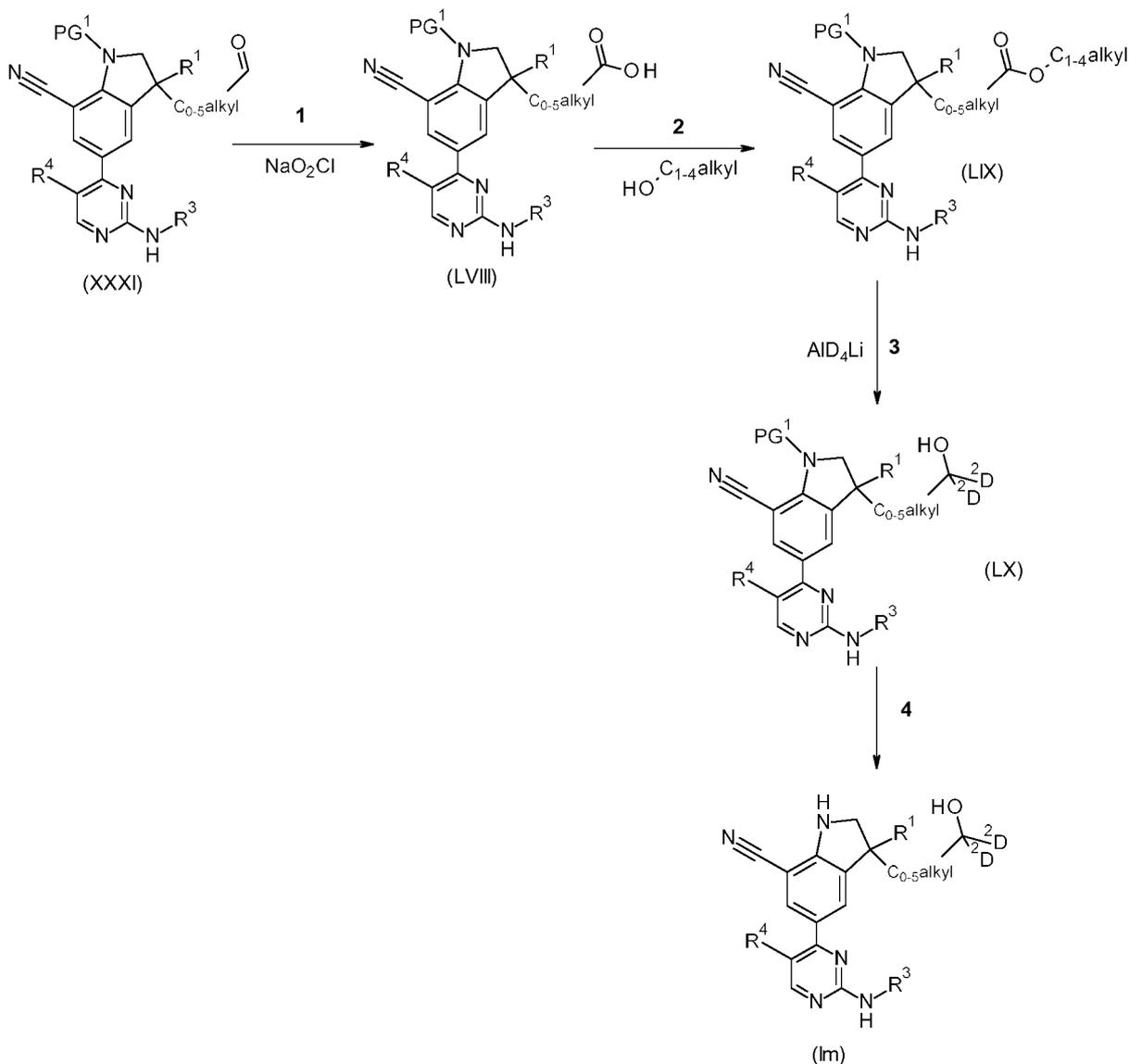
10 hexafluorophosphate (HATU) and dimethyl aminopyridine (DMAP), a suitable base such as for example DIPEA and a suitable solvent such as for example dimethylformamide;

3: at a suitable temperature such as for example at room temperature, and a suitable solvent such as for example tetrahydrofuran;

4: at a suitable temperature such as for example 0 °C or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane or alternatively in the presence of silica in a suitable solvent such as for
5 example toluene at a suitable temperature such as for example 125°C and a suitable time such as for example 3 hours.

Scheme 13

In general, compounds of Formula (I) wherein R² is as shown in the scheme 13 and
10 wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Im) can be prepared according to the following reaction Scheme 13. In Scheme 13 PG¹ represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl). All other variables in Scheme 13 are defined according to the scope of the present invention. In Scheme 13, the following reaction
15 conditions apply:



- 1: at a suitable temperature such as for example at room temperature, in the presence of *tert*-butyl alcohol, 2-methyl-2-butene, sodium dihydrogenophosphate and distilled water;
- 5 2: at a suitable temperature such as for example at room temperature, in presence of 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) and dimethyl aminopyridine (DMAP), a suitable base such as for example DIPEA and a suitable solvent such as for example dimethylformamide;
- 3: at a suitable temperature such as for example at 0 °C, and a suitable solvent such as for example tetrahydrofuran; ('AlD₄Li' means lithium aluminum deuteride)
- 10 4: at a suitable temperature such as for example 0 °C or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric

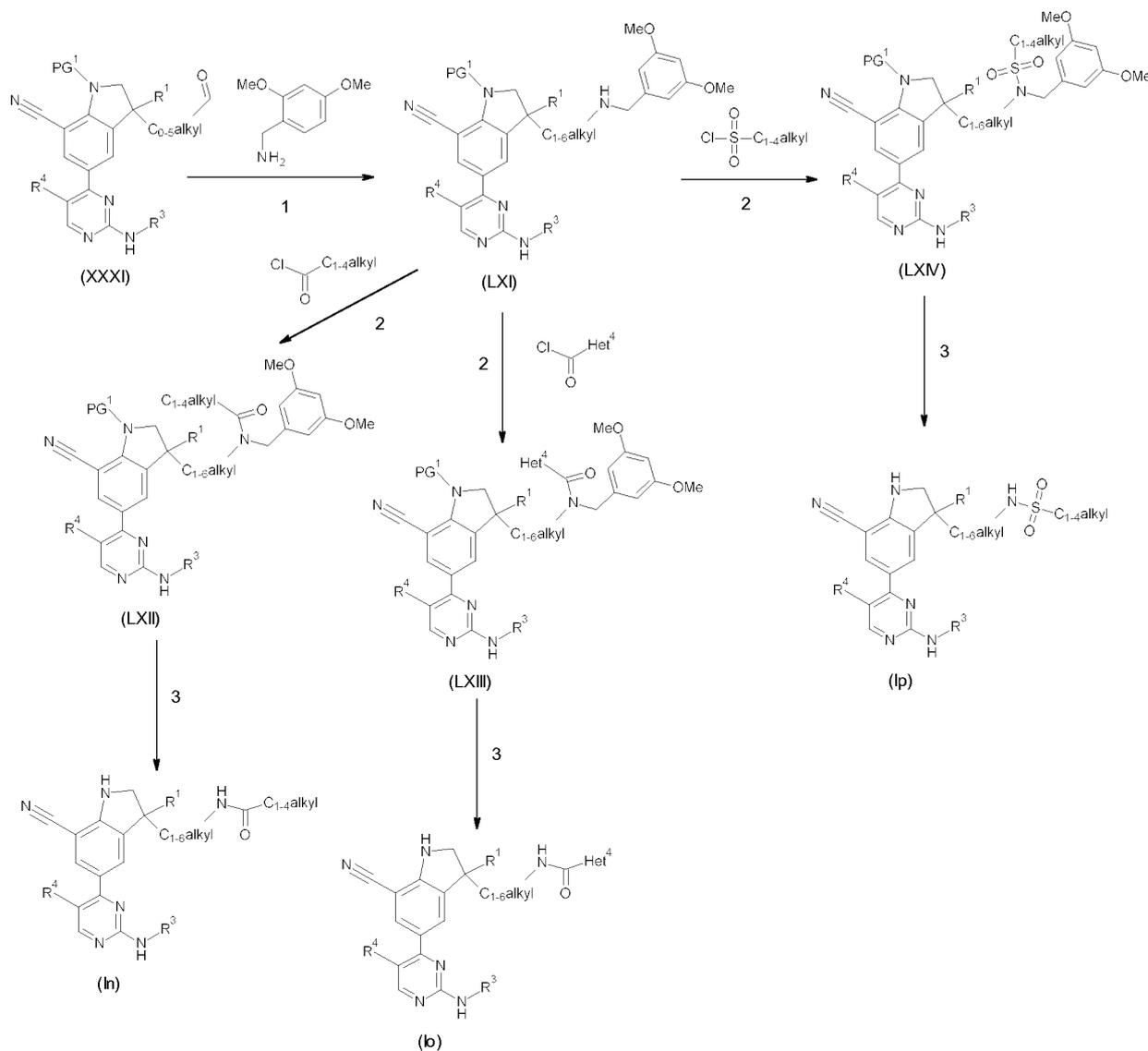
acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane or alternatively in the presence of silica in a suitable solvent such as for example toluene at a suitable temperature such as for example 125°C and a suitable time such as for example 3 hours.

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Scheme 14

In general, compounds of Formula (I) wherein R² is being C₁₋₆alkyl substituted with one Het^{3a} or -NR^{6a}R^{6b}, wherein R^{6a} is being H, R^{6b} is being -C(=O)-C₁₋₄alkyl; -C(=O)-Het⁴; -S(=O)₂-C₁₋₄alkyl and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (In), Formula (Io) and Formula (Ip), can be prepared according to the following reaction Scheme 14. In Scheme 14, PG¹ represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl). All other variables in Scheme 14 are defined according to the scope of the present invention.

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15 In Scheme 14, the following reaction conditions apply:

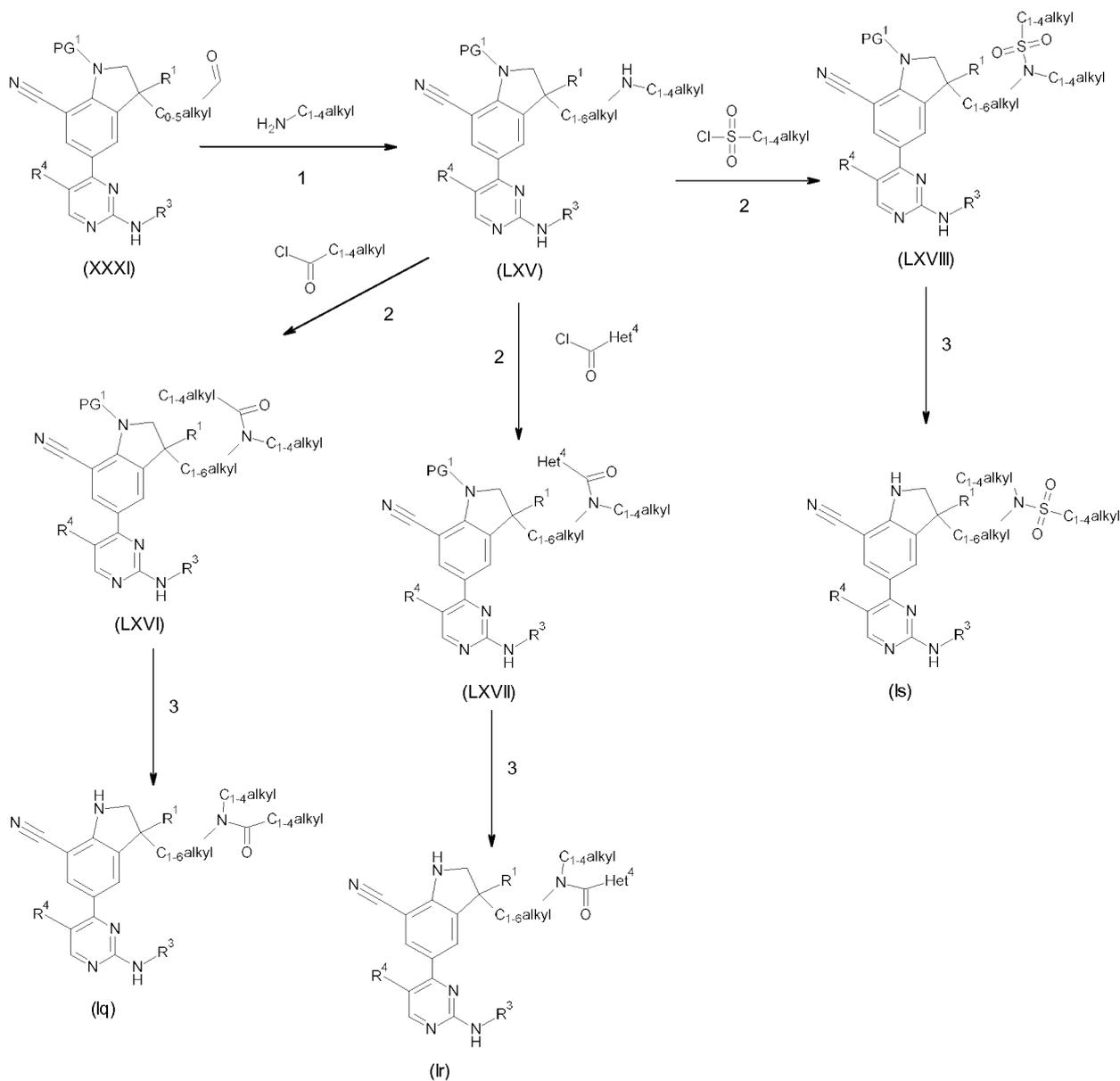


- 1: at a suitable temperature such as for example at room temperature, in the presence of a suitable acid such as for example acetic acid, in the presence of a suitable reducing agent such as for example sodium triacetoxyborohydride, in a suitable solvent such as for example dichloroethane;
- 5 2: at a suitable temperature such as for example at room temperature, in the presence of a suitable base such as for example triethylamine, in a suitable solvent such as for example tetrahydrofuran;
- 10 3: at a suitable temperature such as for example at room temperature, in the presence of a suitable acid such as for example trifluoroacetic acid, in a suitable solvent such as for example dichloromethane.

Scheme 15

In general, compounds of Formula (I) wherein R² is being C₁₋₆alkyl substituted with one Het^{3a} or -NR^{6a}R^{6b}, wherein R^{6a} is being C₁₋₄alkyl, R^{6b} is being -C(=O)-C₁₋₄alkyl; -C(=O)-
5 Het⁴; -S(=O)₂- C₁₋₄alkyl and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Iq), Formula (Ir) and Formula (Is), can be prepared according to the following reaction Scheme 15. In Scheme 15, PG¹ represents a suitable protecting group, such as for example *tert*-
10 (butoxycarbonyl). All other variables in Scheme 5 are defined according to the scope of the present invention.

In Scheme 15, the following reaction conditions apply:



- 1: at a suitable temperature such as for example at room temperature, in the presence of a suitable acid such as for example acetic acid, in the presence of a suitable reducing agent such as for example sodium triacetoxyborohydride, in a suitable solvent such as for example dichloroethane;
- 2: at a suitable temperature such as for example at room temperature, in the presence of a suitable base such as for example triethylamine, in a suitable solvent such as for example tetrahydrofuran;

3: at a suitable temperature such as for example at room temperature, in the presence of a suitable acid such as for example trifluoroacetic acid, in a suitable solvent such as for example dichloromethane.

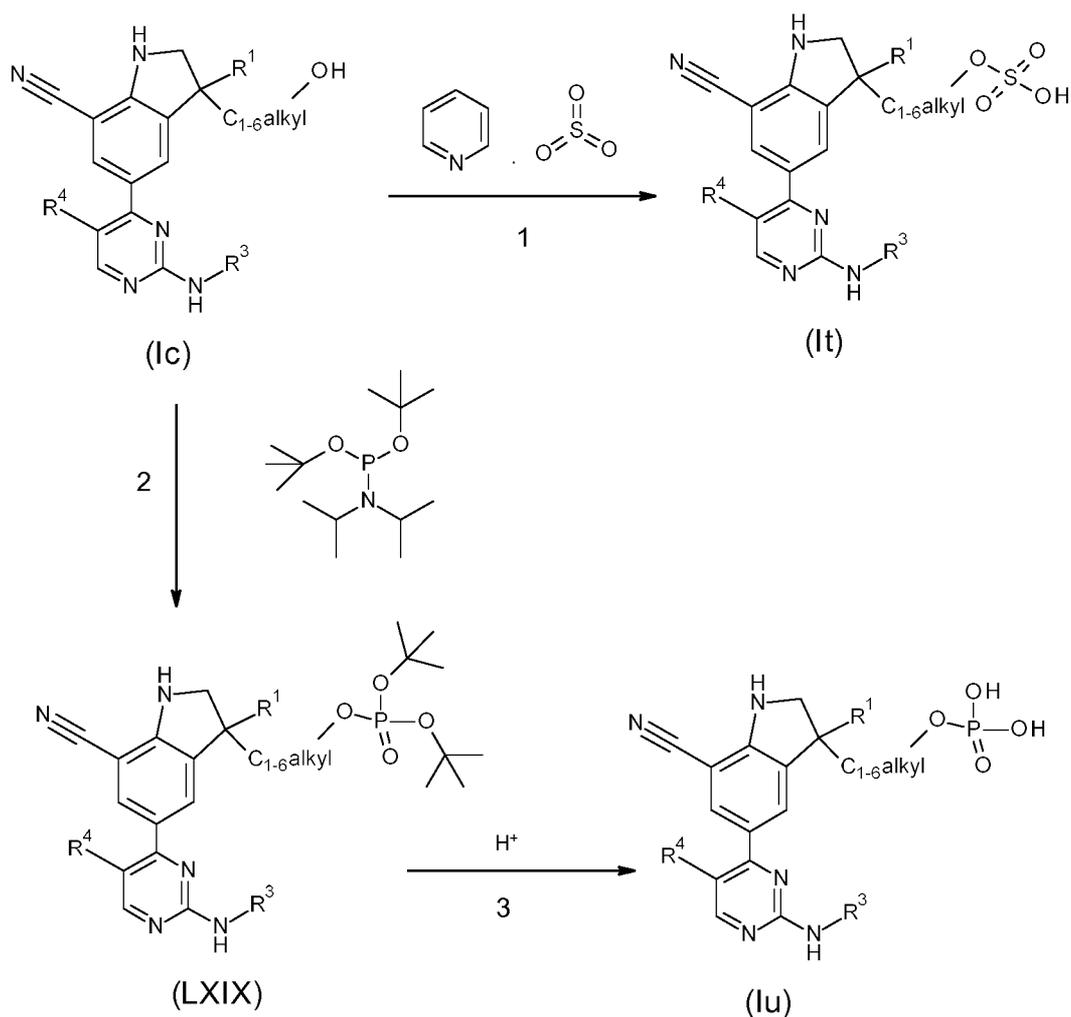
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Scheme 16

In general, compounds of Formula (I) wherein R^2 is C_{1-6} alkyl substituted with one OR^{7d} , R^{7d} being $-S(=O)_2-OH$ or $-P(=O)(OH)_2$, and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (It) and Formula (Iu), can be prepared according to the following reaction Scheme 16. All

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other variables in Scheme 16 are defined according to the scope of the present invention. In Scheme 16, the following reaction conditions apply:



1: at a suitable temperature such as for example at room temperature, in a suitable solvent such as for example tetrahydrofuran, in the presence of a suitable base such as for example sodium hydroxyde;

2: in the presence of a suitable reagent such as for example tetrazole, in the presence of a suitable oxidizing agent such as for example meta-chloroperbenzoic acid, in a suitable solvent such as for example acetonitrile;

3: at a suitable temperature such as for example at room temperature, in the presence of a suitable acid such as for example hydrochloric acid, in a suitable solvent such as for example acetonitrile.

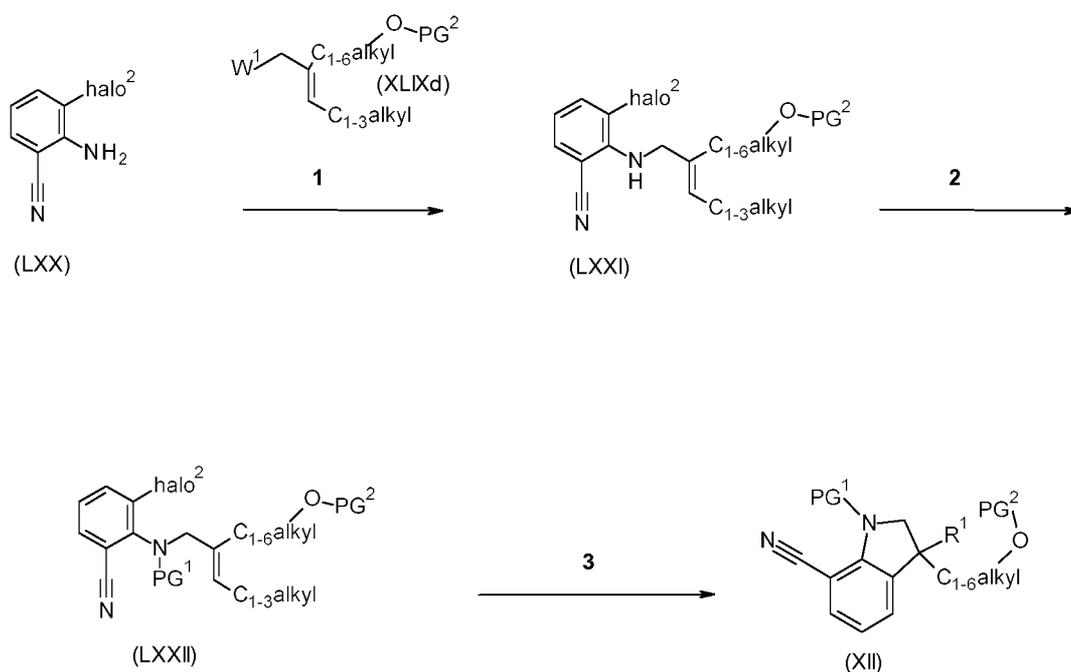
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Scheme 17

In general, intermediates of Formula (XII) wherein all the variables are as defined according to the scope of the present invention or as defined before, can be prepared according to the following reaction Scheme 17. All other variables in Scheme 17 are as defined before.

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In Scheme 17, the following reaction conditions apply:



1: At a suitable temperature range between -5°C and 5°C , in the presence of a suitable base such as for example sodium *tert*-butoxide in a suitable solvent such as for example tetrahydrofuran;

2: at a suitable temperature ranged between 65 and 70 °C, in the presence of a suitable reagent such as for example di-*tert*-butyl dicarbonate, in the presence of a suitable catalyst such as for example 4-dimethylaminopyridine (DMAP), and a suitable solvent such as for example tetrahydrofuran;

- 5 3: at a suitable temperature ranged between 45 and 50 °C, in the presence of sodium acetate, sodium formate dehydrate and tetraethylammonium chloride, a suitable catalyst such as for example palladium acetate or [1,1'-bis(diphenylphosphino) ferrocene] palladium, (II) chloride optionally with dichloromethane complex, and a suitable solvent such as for example dimethylformamide.

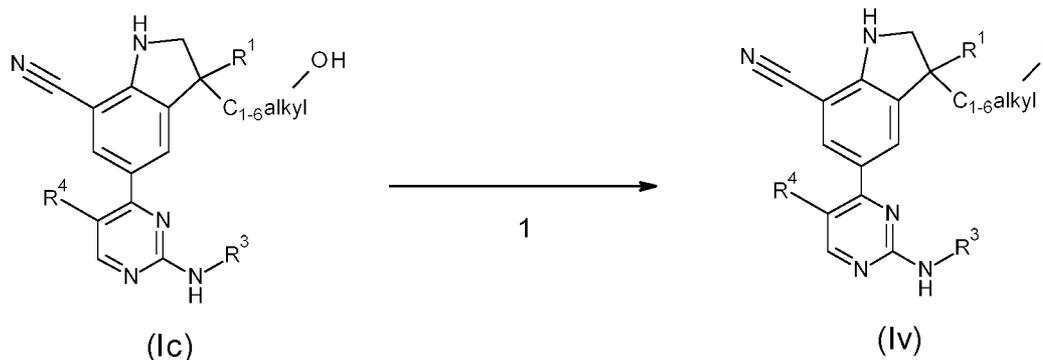
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Scheme 18

In general, compounds of Formula (I) wherein R² is R^{2d} being C₁₋₆alkyl substituted with one fluorine, Y is CR⁴, and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Iv), can be prepared

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In Scheme 18, the following reaction conditions apply:



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1: in the presence of a suitable fluorinating reagent such as for example diethylaminosulfur trifluoride, a suitable solvent such as for example dichloromethane, at a suitable temperature such as for example room temperature.

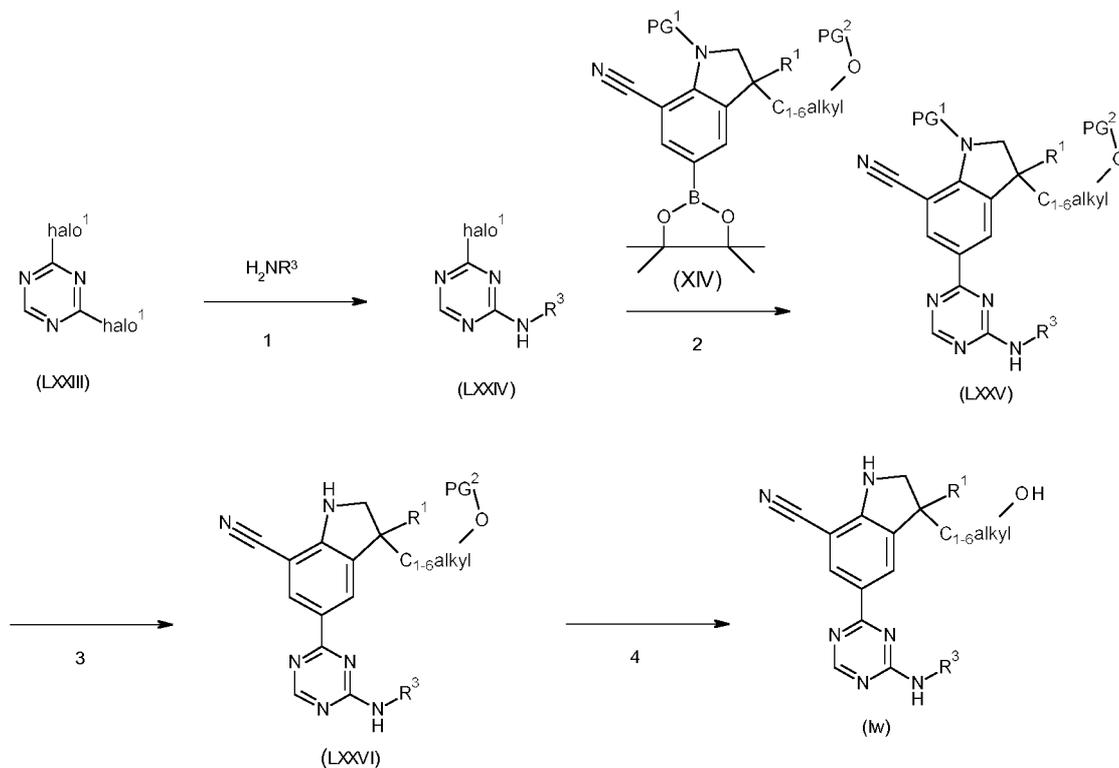
Scheme 19

In general, compounds of Formula (I) wherein R² is R^{2b} being C₁₋₆alkyl substituted with one OH, Y is N, and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Iw), can be prepared

25 according to the following reaction Scheme 19. In Scheme 19, halo¹ is defined as Cl, Br or I; PG¹ represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl) and PG² represents a suitable protecting group, such as for example *tert*-butyl-

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

In Scheme 19, the following reaction conditions apply:



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1: in the presence of a suitable base such as for example diisopropylethylamine, in a suitable solvent such as for example acetonitrile;

2: in the presence of a suitable catalyst such as for example [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II), optionally with dichloromethane complex, a suitable base such as an aqueous solution of hydrogenocarbonate at a suitable temperature such as 80°C;

10

3: at a suitable temperature such as for example 0 °C or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate

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or 1,4-dioxane or alternatively in the presence of silica in a suitable solvent such as for example toluene at a suitable temperature such as for example 125°C, and a suitable time

such as for example 3 hours;

4: at a suitable temperature such as for example room temperature, in presence of a suitable desilylating agent such as for example *tetra-n*-butylammonium fluoride and a suitable solvent such as for example 2-methyltetrahydrofuran or tetrahydrofuran.

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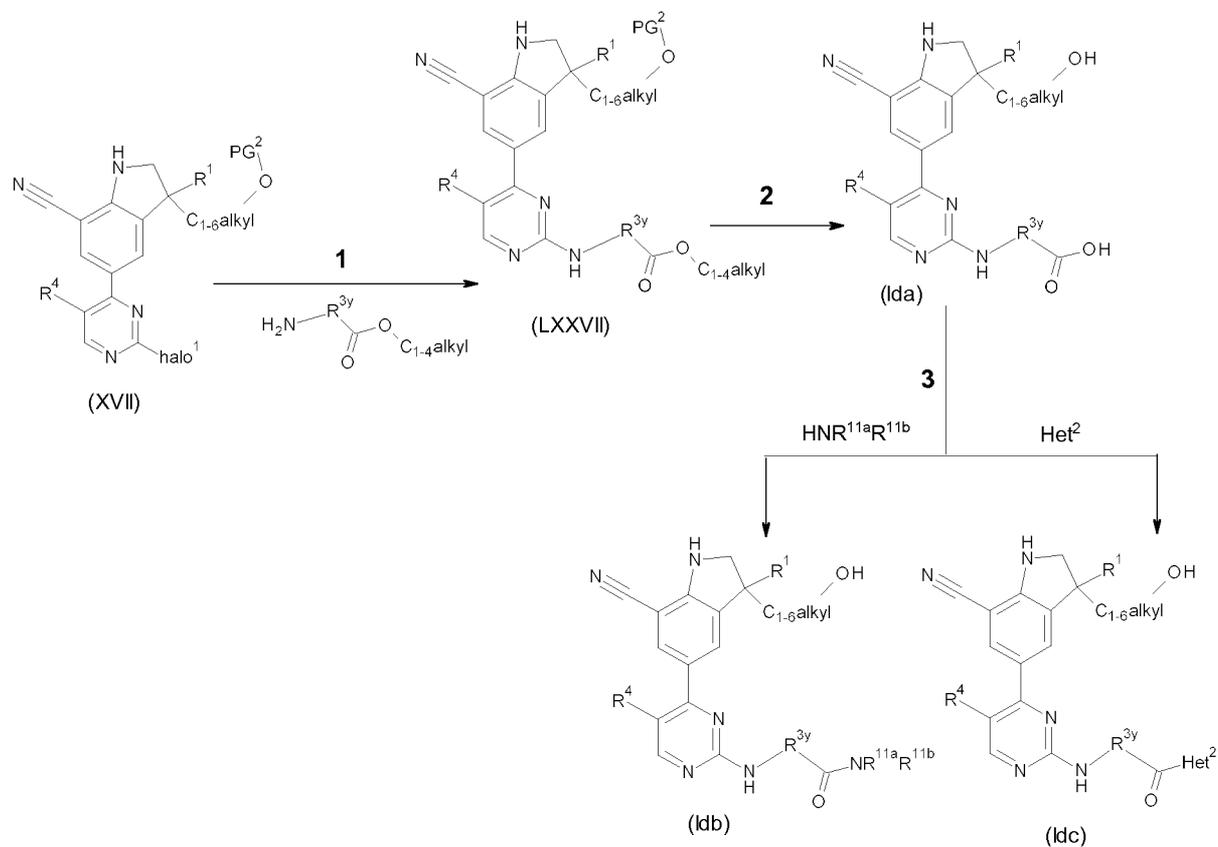
Scheme 20

In scheme 20, R³ is limited to R^{3y} representing formula (1a-1), or a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N.

In general, compounds of Formula (I) wherein R² is R^{2b} being C₁₋₆alkyl substituted with one OH, R^{3x} is defined as above for scheme 20, substituted with -C(=O)-R¹⁰ and optionally substituted with other substituents according to the scope of the present invention, Y is CR⁴, and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Ida), (Idb) and (Idc) can be prepared according to the following reaction Scheme 20. In Scheme 20, halo¹ is defined as Cl, Br or I; PG¹ represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl) and PG² represents a suitable protecting group, such as for example *tert*-butyl-dimethylsilyl. All other variables in Scheme 20 are defined according to the scope of the present invention.

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In Scheme 20, the following reaction conditions apply:

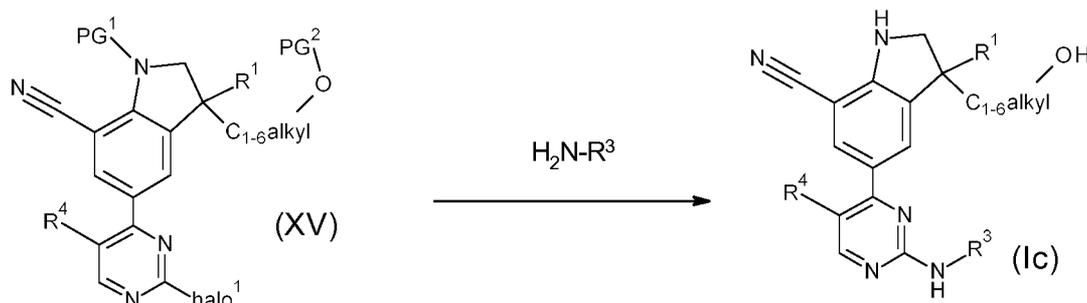


- 1: at a suitable temperature such as for example 120 °C, in the presence of a suitable catalyst such as for example palladium acetate (Pd(OAc)₂), a suitable ligand such as for example 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), a suitable base such as for example cesium carbonate, and a suitable solvent such as for example 1,4-dioxane, optionally under microwave activation;
- 5 2: at a suitable temperature such as for example 60 °C, in presence of a suitable base such as for example lithium hydroxide, and a suitable solvent such as for example a mixture of tetrahydrofuran and water;
- 10 3: at a suitable temperature such as for example room temperature, in presence of a suitable coupling reagent such as for example 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), a suitable base such as for example *N,N*-diisopropylethylamine, and a suitable solvent such as for example
- 15 dimethylformamide or dichloromethane.

Scheme 21

In general, compounds of Formula (I) wherein R^2 is R^{2b} being C_{1-6} alkyl substituted with one OH, Y is CR^4 , and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Ic), can be prepared according to the following reaction Scheme 21. All other variables in Scheme 21 are defined according to the scope of the present invention or as above.

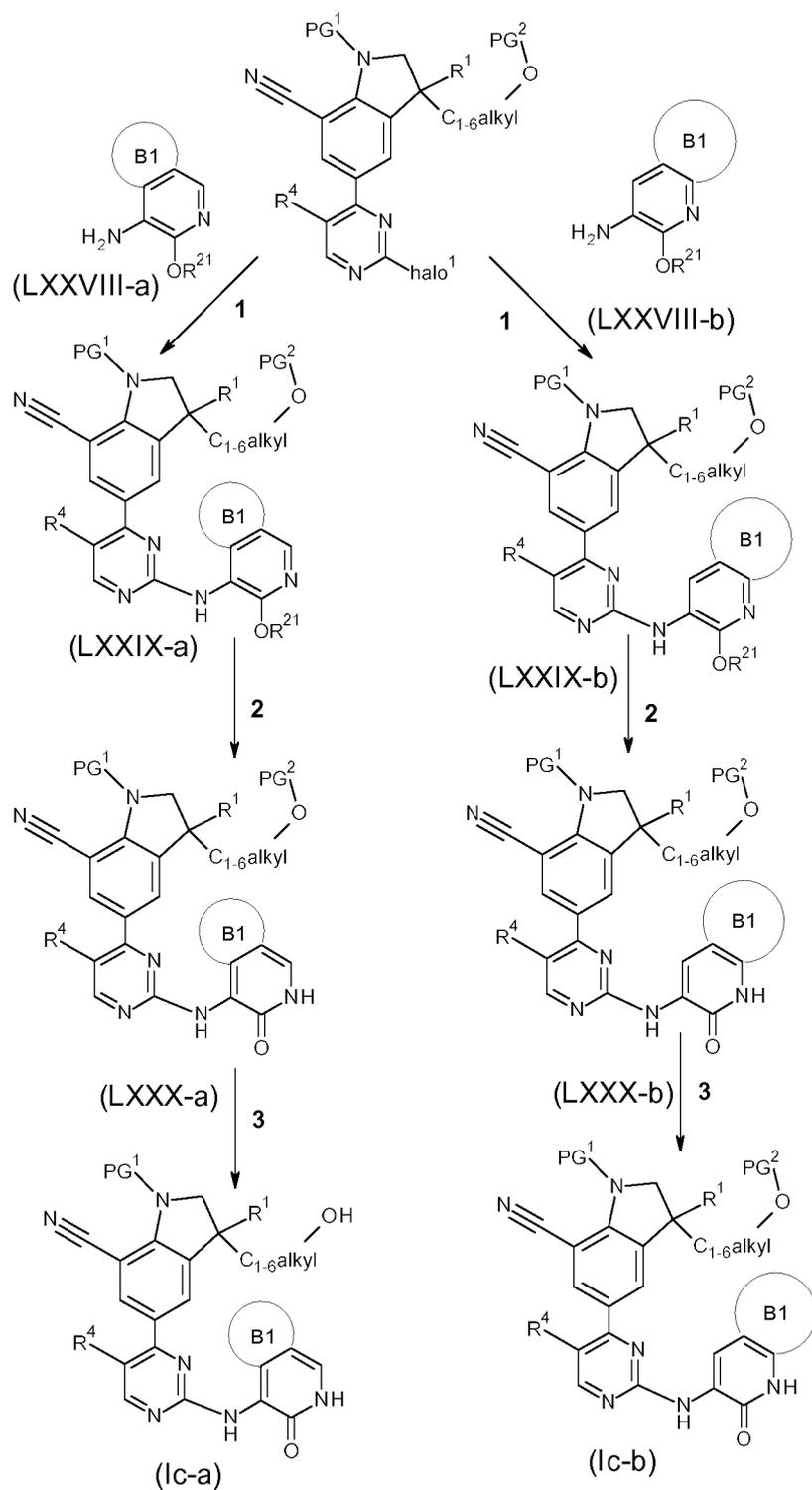
In Scheme 21, the following reaction conditions apply:



1: at a suitable temperature such as for example 90 °C, in the presence of a suitable acid such as for example p-toluenesulfonic acid and a suitable solvent such as for example 1,4-dioxane.

Scheme 22

In general, compounds of Formula (I) wherein R^3 is restricted as shown below, wherein R^{21} is for example C_{1-4} alkyl or C_{3-6} cycloalkyl, and wherein all the other variables are as defined according to the scope of the present invention, hereby named compounds of Formula (Ic-a) and (Ic-b), can be prepared according to the following reaction Scheme 22. All other variables in Scheme 22 are defined according to the scope of the present invention or as above.



In Scheme 22, the following reaction conditions apply:

- 1: at a suitable temperature such as for example 85 °C, in the presence of a suitable catalyst
 5 such as for example palladium acetate (Pd(OAc)₂), a suitable ligand such as for example

2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), a suitable base such as for example cesium carbonate, and a suitable solvent such as for example 1,4-dioxane, in sealed conditions;

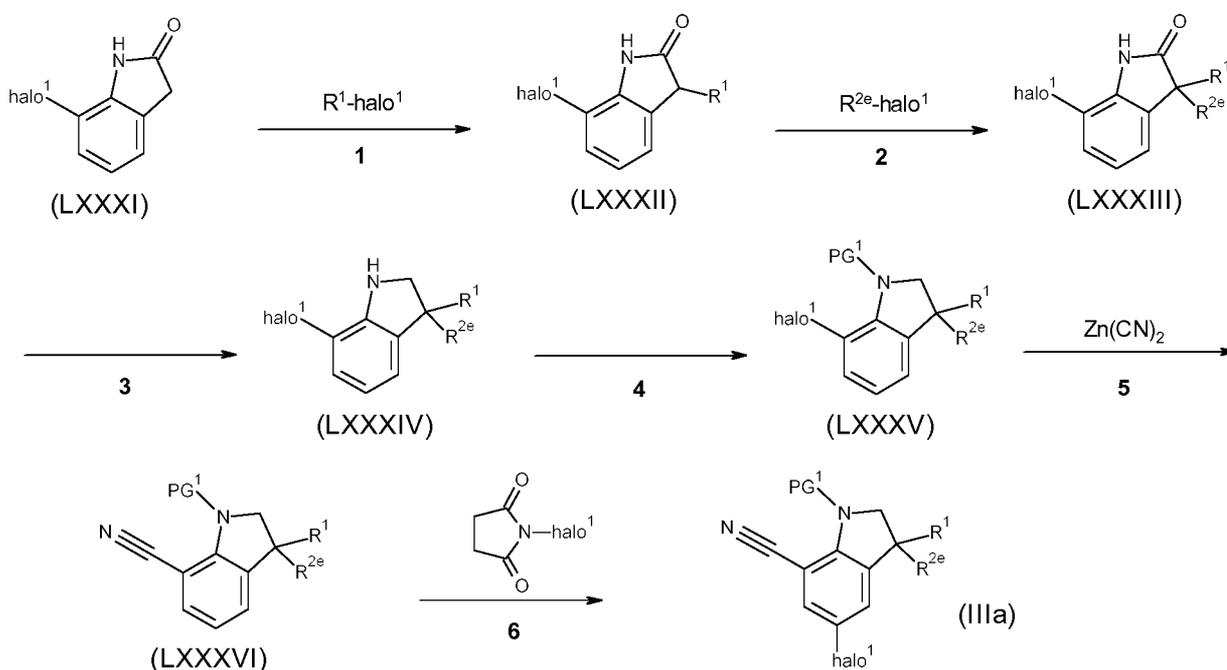
2: at a suitable temperature such as for example 0 °C or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate;

3: at a suitable temperature such as for example room temperature, in presence of a suitable desilylating agent such as for example *tetra-n*-butylammonium fluoride and a suitable solvent such as for example 2-methyltetrahydrofuran or tetrahydrofuran.

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Scheme 23

Intermediate of Formula (IIIa) wherein R² is R^{2e} being C₁₋₆alkyl or C₁₋₆alkyl substituted with one, two or three Fluoro atoms, and wherein all the other variables are defined according to the scope of the present invention, can be prepared according to the following reactions. All other variables in Scheme 23 are defined according to the scope of the present invention or as defined above.



20 In Scheme 23, the following reaction conditions apply:

1: at a suitable temperature ranged between for example -20°C and -78°C, in the presence of a chelating agent such as for example *N,N,N',N'*-tetramethylethylenediamine, a suitable

- deprotonating agent such as Butyl Lithium, in a suitable solvent such as for example tetrahydrofuran;
- 2: at a suitable temperature ranged between for example -20°C and -78°C, in the presence of a chelating agent such as for example *N,N,N',N'*-tetramethylethylenediamine, a suitable
- 5 deprotonating agent such as Butyl Lithium, in a suitable solvent such as for example tetrahydrofuran;
- 3: at a suitable temperature such as for example 70°C, in the presence of a suitable reducing agent such as for example Borane dimethyl sulfide complex, in a suitable solvent such as for example tetrahydrofuran;
- 10 4: at a suitable temperature such as for example room temperature, in the presence of a suitable reagent such as for example di-*tert*-butyldicarbonate, a suitable catalyst such as for example 4-dimethylaminopyridine (DMAP), a suitable base such as for example triethylamine and a suitable solvent such as for example tetrahydrofuran;
- 5: at a suitable temperature such as for example 100°C, in the presence of a suitable
- 15 catalyst such as for example Tetrakis(triphenylphosphine)palladium(0), and a suitable solvent such as for example anhydrous dimethylformamide;
- 6: at a suitable temperature such as for example solvent reflux, and in a suitable solvent such as for example acetonitrile.
- 20 It will be appreciated that where appropriate functional groups exist, compounds of various formulae or any intermediates used in their preparation may be further derivatised by one or more standard synthetic methods employing condensation, substitution, oxidation, reduction, or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, sulfonylation, halogenation, nitration,
- 25 formylation and coupling procedures.

The compounds of Formula (I) may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) containing a basic nitrogen atom may

30 be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali.

An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, t-butoxycarbonyl (Boc), benzyloxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 4th ed., Wiley, Hoboken, New Jersey, 2007.

Pharmacology

It has been found that the compounds of the present invention inhibit NF- κ B-inducing kinase (NIK - also known as MAP3K14). Some of the compounds of the present invention may undergo metabolism to a more active form in vivo (prodrugs). Therefore the compounds according to the invention and the pharmaceutical compositions comprising such compounds may be useful for treating or preventing diseases such as cancer, inflammatory disorders, metabolic disorders including obesity and diabetes, and autoimmune disorders. In particular, the compounds according to the present invention and the pharmaceutical compositions thereof may be useful in the treatment of a haematological malignancy or solid tumour. In a specific embodiment said haematological malignancy is selected from the group consisting of multiple myeloma, non-Hodgkin's lymphoma, Hodgkin lymphoma, T-cell leukaemia, mucosa-associated lymphoid tissue lymphoma, diffuse large B-cell lymphoma and mantle cell lymphoma, in a particular embodiment mantle cell lymphoma. In another specific embodiment of the present invention, the solid tumour is selected from the group consisting of pancreatic cancer, breast cancer, melanoma and non-small cell lung cancer.

Examples of cancers which may be treated (or inhibited) include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, urothelial, uterus,

epidermis, liver, lung (for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, squamous lung cancer), oesophagus, head and neck, gall bladder, ovary, pancreas (e.g. exocrine pancreatic carcinoma), stomach, gastrointestinal (also known as gastric) cancer (e.g. gastrointestinal stromal tumours), cervix, endometrium, thyroid, prostate, or skin (for example squamous cell carcinoma or dermatofibrosarcoma protuberans); pituitary cancer, a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, B-cell lymphoma (e.g. diffuse large B-cell lymphoma, mantle cell lymphoma), T-cell leukaemia/lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumour of myeloid lineage, for example leukemias, acute and chronic myelogenous leukemias, chronic myelomonocytic leukemia (CMML), myeloproliferative disorder, myeloproliferative syndrome, myelodysplastic syndrome, or promyelocytic leukemia; multiple myeloma; thyroid follicular cancer; hepatocellular cancer, a tumour of mesenchymal origin (e.g. Ewing's sarcoma), for example fibrosarcoma or rhabdomyosarcoma; a tumour of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma (such as glioblastoma multiforme) or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

Particular examples of cancers which may be treated (or inhibited) include B-cell malignancies, such as multiple myeloma, hodgkins lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma or chronic lymphocytic leukemia, with mutations in the non-canonical NFkB signaling pathway (eg in NIK (MAP3K14), TRAF3, TRAF2, BIRC2 or BIRC3 genes).

Hence, the invention relates to compounds of Formula (I), the tautomers and the stereoisomeric forms thereof, and the pharmaceutically acceptable addition salts, and the solvates thereof, for use as a medicament.

The invention also relates to the use of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable addition salt, or a solvate thereof, or a pharmaceutical composition according to the invention, for the manufacture of a medicament.

The present invention also relates to a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable addition salt, or a solvate thereof, or a pharmaceutical composition according to the invention, for use in the treatment, prevention, amelioration, control or reduction of the risk of disorders associated

with NF- κ B-inducing kinase dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by inhibition of NF- κ B-inducing kinase. Also, the present invention relates to the use of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable addition salt, or a solvate thereof, or a pharmaceutical composition according to the invention, for the manufacture of a medicament for treating, preventing, ameliorating, controlling or reducing the risk of disorders associated with NF- κ B-inducing kinase dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by inhibition of NF- κ B-inducing kinase.

10 The invention also relates to a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable addition salt, or a solvate thereof, for use in the treatment or prevention of any one of the diseases mentioned hereinbefore.

The invention also relates to a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable addition salt, or a solvate thereof, for use in treating or preventing any one of the diseases mentioned hereinbefore.

15 The invention also relates to the use of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable addition salt, or a solvate thereof, for the manufacture of a medicament for the treatment or prevention of any one of the disease conditions mentioned hereinbefore.

20 The compounds of the present invention can be administered to mammals, preferably humans, for the treatment or prevention of any one of the diseases mentioned hereinbefore.

In view of the utility of the compounds of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable addition salt, or a solvate thereof, there is provided a method of treating warm-blooded animals, including humans, suffering from any one of the diseases mentioned hereinbefore.

25 Said method comprises the administration, i.e. the systemic or topical administration, preferably oral administration, of a therapeutically effective amount of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable addition salt, or a solvate thereof, to warm-blooded animals, including humans.

30 Therefore, the invention also relates to a method for the treatment of any one of the diseases mentioned hereinbefore comprising administering a therapeutically effective amount of compound according to the invention to a patient in need thereof.

One skilled in the art will recognize that a therapeutically effective amount of the compounds of the present invention is the amount sufficient to have therapeutic activity and that this amount varies *inter alias*, depending on the type of disease, the concentration of the compound in the therapeutic formulation, and the condition of the patient.

5 Generally, the amount of a compound of the present invention to be administered as a therapeutic agent for treating the disorders referred to herein will be determined on a case by case by an attending physician.

Those of skill in the treatment of such diseases could determine the effective therapeutic daily amount from the test results presented hereinafter. An effective therapeutic daily
10 amount would be from about 0.005 mg/kg to 50 mg/kg, in particular 0.01 mg/kg to 50 mg/kg body weight, more in particular from 0.01 mg/kg to 25 mg/kg body weight, preferably from about 0.01 mg/kg to about 15 mg/kg, more preferably from about 0.01 mg/kg to about 10 mg/kg, even more preferably from about
15 0.01 mg/kg to about 1 mg/kg, most preferably from about 0.05 mg/kg to about 1 mg/kg body weight. A particular effective therapeutic daily amount might be from about 10 mg/kg body weight to 40 mg/kg body weight. A particular effective therapeutic daily amount might be 1 mg/kg body weight, 2 mg/kg body weight, 4 mg/kg body weight, or 8 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
20 effect may vary on case-by-case basis, for example with the particular compound, the route of administration, the age and condition of the recipient, and the particular disorder or disease being treated. A method of treatment may also include administering the active ingredient on a regimen of between one and four intakes per day. In these methods of treatment the compounds according to the invention are preferably formulated prior to
25 administration. As described herein below, suitable pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

The present invention also provides compositions for preventing or treating the disorders referred to herein. Said compositions comprising a therapeutically effective amount of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a
30 pharmaceutically acceptable addition salt, or a solvate thereof, and a pharmaceutically acceptable carrier or diluent.

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 compound according to the present

invention, together with a pharmaceutically acceptable carrier or diluent. 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.

The pharmaceutical compositions of this invention may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro et al. Remington's Pharmaceutical Sciences (18th ed., Mack Publishing Company, 1990, see especially Part 8 : Pharmaceutical preparations and their Manufacture). A therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as oral, percutaneous or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. 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 and solutions; or solid carriers such as starches, sugars, kaolin, 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 form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects 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 or as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions

in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The present compounds can be used for systemic administration such as oral, percutaneous or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. The compounds are preferably orally administered. The exact dosage and frequency of administration depends on the particular compound of Formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient 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 said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

The compounds of the present invention may be administered alone or in combination with one or more additional therapeutic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound according to the present invention and one or more additional therapeutic agents, as well as administration of the compound according to the present invention and each additional therapeutic agent in its own separate pharmaceutical dosage formulation. For example, a compound according to the present invention 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.

Therefore, an embodiment of the present invention relates to a product containing as first active ingredient a compound according to the invention and as further active ingredient one or more medicinal agent, more particularly, with one or more anticancer agent or adjuvant, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

Accordingly, for the treatment of the conditions mentioned hereinbefore, the compounds of the invention may be advantageously employed in combination with one or more other

medicinal agents (also referred to as therapeutic agents), more particularly, with other anti-cancer agents or adjuvants in cancer therapy. Examples of anti-cancer agents or adjuvants (supporting agents in the therapy) include but are not limited to:

- 5 - 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;
- topoisomerase I inhibitors such as camptothecin compounds for example irinotecan, SN-38, topotecan, topotecan hcl;
- 10 - topoisomerase II inhibitors such as anti-tumour epipodophyllotoxins or podophyllotoxin derivatives for example etoposide, etoposide phosphate or teniposide;
- anti-tumour vinca alkaloids for example vinblastine, vincristine or vinorelbine;
- anti-tumour nucleoside derivatives for example 5-fluorouracil, leucovorin, gemcitabine, gemcitabine hcl, capecitabine, cladribine, fludarabine, nelarabine;
- 15 - alkylating agents such as nitrogen mustard or nitrosourea for example cyclophosphamide, chlorambucil, carmustine, thiotepa, mephalan (melphalan), lomustine, altretamine, busulfan, dacarbazine, estramustine, ifosfamide optionally in combination with mesna, pipobroman, procarbazine, streptozocin, temozolomide, uracil;
- anti-tumour anthracycline derivatives for example daunorubicin, doxorubicin
- 20 optionally in combination with dexrazoxane, doxil, idarubicin, mitoxantrone, epirubicin, epirubicin hcl, valrubicin;
- molecules that target the IGF-1 receptor for example picropodophilin;
- tetracarcin derivatives for example tetrocarcin A;
- glucocorticoiden for example prednisone;
- 25 - antibodies for example trastuzumab (HER2 antibody), rituximab (CD20 antibody), gemtuzumab, gemtuzumab ozogamicin, cetuximab, pertuzumab, bevacizumab, alemtuzumab, eculizumab, ibritumomab tiuxetan, nofetumomab, panitumumab, tositumomab, CNTO 328;
- estrogen receptor antagonists or selective estrogen receptor modulators or inhibitors
- 30 of estrogen synthesis for example tamoxifen, fulvestrant, toremifene, droloxifene, faslodex, raloxifene or letrozole;
- aromatase inhibitors such as exemestane, anastrozole, letrozole, testolactone and vorozole;
- differentiating agents such as retinoids, vitamin D or retinoic acid and retinoic acid
- 35 metabolism blocking agents (RAMBA) for example accutane;

- DNA methyl transferase inhibitors for example azacytidine or decitabine;
- antifolates for example pemetrexed disodium;
- antibiotics for example antinomycin D, bleomycin, mitomycin C, dactinomycin, carminomycin, daunomycin, levamisole, plicamycin, mithramycin;
- 5 - antimetabolites for example clofarabine, aminopterin, cytosine arabinoside or methotrexate, azacytidine, 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;
- 10 - kinase inhibitors (e.g. EGFR (epithelial growth factor receptor) inhibitors, MTKI (multi target kinase inhibitors), mTOR inhibitors) for example flavoperidol, imatinib mesylate, erlotinib, gefitinib, dasatinib, lapatinib, lapatinib ditosylate, sorafenib, sunitinib, sunitinib maleate, temsirolimus;
- farnesyltransferase inhibitors for example tipifarnib;
- 15 - histone deacetylase (HDAC) inhibitors for example sodium butyrate, suberoylanilide hydroxamic acid (SAHA), depsipeptide (FR 901228), NVP-LAQ824, R306465, quisinostat, trichostatin A, vorinostat;
- Inhibitors of the ubiquitin-proteasome pathway for example PS-341, Velcade (MLN-341) or bortezomib;
- 20 - Yondelis;
- Telomerase inhibitors for example telomestatin;
- Matrix metalloproteinase inhibitors for example batimastat, marimastat, prinostat or metastat;
- Recombinant interleukins for example aldesleukin, denileukin diftitox, interferon
- 25 alfa 2a, interferon alfa 2b, peginterferon alfa 2b;
- MAPK inhibitors;
- Retinoids for example alitretinoin, bexarotene, tretinoin;
- Arsenic trioxide;
- Asparaginase;
- 30 - Steroids for example dromostanolone propionate, megestrol acetate, nandrolone (decanoate, phenpropionate), dexamethasone;
- Gonadotropin releasing hormone agonists or antagonists for example abarelix, goserelin acetate, histrelin acetate, leuprolide acetate;
- Thalidomide, lenalidomide;
- 35 - Mercaptopurine, mitotane, pamidronate, pegademase, pegaspargase, rasburicase;

- BH3 mimetics for example ABT-199;
- 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; 5 oprelvekin; zoledronate, zoledronic acid; fentanyl; bisphosphonate; palifermin;
- a steroidal cytochrome P450 17alpha-hydroxylase-17,20-lyase inhibitor (CYP17), e.g. abiraterone, abiraterone acetate.

The one or more other medicinal agents and the compound according to the present 10 invention may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two or more compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for 15 each component of the combination will depend on the particular other medicinal agent and compound of the present invention being administered, their route of administration, the particular tumour being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the 20 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 25 on the particular compound according to the invention and the other anticancer agent(s) used, the particular condition being treated, the severity of the condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective daily amount may be lowered or increased depending on the response of the 30 treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. A particular weight ratio for the present compound of Formula (I) and another anticancer agent may range from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

The platinum coordination compound is advantageously administered in a dosage of 1 to 500 mg per square meter (mg/m²) of body surface area, for example 50 to 400 mg/m², particularly for cisplatin in a dosage of about 75 mg/m² and for carboplatin in about 300 mg/m² per course of treatment.

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The taxane compound is advantageously administered in a dosage of 50 to 400 mg per square meter (mg/m²) of body surface area, for example 75 to 250 mg/m², 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.

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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.

15

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 250 mg/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.

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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.

25

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.

30

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

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in a dosage of about 150 to 200 mg/m² , and for lomustine in a dosage of about 100 to 150 mg/m² per course of treatment.

5 The anti-tumour anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter (mg/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 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.

10 The antiestrogen agent is advantageously administered in a dosage of about 1 to 100 mg daily depending on the particular agent and the condition being treated. Tamoxifen is advantageously administered orally in a dosage of 5 to 50 mg, preferably 10 to 20 mg twice a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Toremifene is advantageously administered orally in a dosage of about
15 60 mg 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 20-100 mg once a day. Raloxifene is advantageously administered orally in a dosage of about 60 mg once a day. Exemestane is advantageously administered orally in a dosage of
20 about 25 mg once a day.

Antibodies are advantageously administered in a dosage of about 1 to 5 mg per square meter (mg/m²) of body surface area, or as known in the art, if different. Trastuzumab is
25 advantageously administered in a dosage of 1 to 5 mg per square meter (mg/m²) of body surface area, particularly 2 to 4 mg/m² 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 further illustrate the present invention.

30

Examples

Several methods for preparing the compounds of this invention are illustrated in the following examples. All starting materials were obtained from commercial suppliers and

used without further purification, or alternatively, can be easily prepared by a skilled person according to well-known methods.

Hereinafter, the terms : 'AcOH' or 'HOAc' means acetic acid, 'AcCl' means acetyl
5 chloride, 'BOC' or 'Boc' means tert-butyloxycarbonyl, 'Ar' means Argon, 'Boc₂O' means di-tert-butyl dicarbonate, 'BrettPhos' or 'BRETTPHOS' means 2-(Dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl, 'Brettphos Palladacycle' means Chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4', 6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II), 'celite[®]' means
10 diatomaceous earth, 'CV' means column volumes, 'DCE' means 1,2-dichloroethene, 'DCM' means dichloromethane, 'DiPE' means diisopropylether, 'DIBAL-H' means diisobutylaluminium hydride, 'DIPEA' means diisopropylethylamine, 'DMAP' means dimethylaminopyridine, 'DMF' means dimethylformamide, 'ee' means enantiomeric excess, 'eq.' or 'equiv.' means equivalent(s), 'Et' means ethyl, 'Me' means methyl, 'Et₂O'
15 means diethyl ether, 'EtOAc' or 'AcOEt' means ethyl acetate, 'EtOH' means ethanol, 'h' means hours(s), 'HATU' means 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, 'HBTU' means N,N,N',N'-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate, 'HPLC' means High-performance Liquid Chromatography, 'iPrOH' or 'IPA' means isopropyl alcohol, 'LC/MS' means Liquid
20 Chromatography/Mass Spectrometry, 'Me-THF' means 2-methyl-tetrahydrofuran, 'MeOH' means methanol, 'MgSO₄' means magnesium sulfate 'mn' or 'min' means minute(s), 'MsCl' means methanesulfonyl chloride, 'M.P.' or 'm.p.' means melting point, 'NaBH(OAc)₃' means sodium triacetoxyborohydride, 'NBS' means N-bromosuccinimide, 'NIS' means N-iodosuccinimide, 'NMR' means Nuclear Magnetic Resonance, 'OR'
25 means optical rotation, 'Pd/C 10%' means palladium on carbon loading 10%, 'PdCl₂(PPh₃)₂' means Bis(triphenylphosphine)palladium chloride, 'Pd(dppf)Cl₂' means [1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II), 'Pd(dppf)Cl₂.CH₂Cl₂' means [1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II). dichloromethane, 'Pd(OAc)₂' means palladium (II) acetate, 'PtO₂' means platinum oxide, 'Quant.' means
30 quantitative, 'RaNi' means Raney Nickel, 'rt' means room temperature, 'R_t' means retention time, 'SFC' means supercritical fluid chromatography, 'SOCl₂' means thionyl chloride, 'T' means temperature, 'TBAF' means tetrabutylammonium fluoride, 'TBD' means triazabicyclodecene, 'TBDMS' or 'SMDBT' means tert-butyldimethylsilyl, 'TEA' means triethylamine, 'TFA' means trifluoroacetic acid, 'THF' means tetrahydrofuran,

'Me-THF' means 2-methyltetrahydrofuran, 'TLC' means thin layer chromatography, 'Ti(OiPr)₄' means titanium isopropoxide, 'HCl' means hydrochloric acid, 'LiAlH₄' means lithium aluminium hydride, 'K₂CO₃' means potassium carbonate, 'NaHCO₃' means sodium hydrogenocarbonate, 'NaOH' means potassium hydroxide, 'CuI' means copper (I) iodide, 'H₂SO₄' means sulfuric acid, 'MeCN', 'CH₃CN' or 'ACN' means acetonitrile, 'iPrNH₂' means isopropylamine, 'v.' means volume, 'NaH' means sodium hydride, 'Na₂SO₄' means sodium sulfate, 'NaBH₄' means sodium borohydride, 'BH₃.THF' means borane.tetrahydrofuran complex, 'COMU®' means (1-Cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate, 'Na₂CO₃' means sodium carbonate, 'NH₄OH' means ammonium hydroxide, 'Cs₂CO₃' means cesium carbonate, 'Pd(PPh₃)₄' means palladium tetrakis(triphenylphosphine) (also tetrakis(triphenylphosphine)palladium (0)), 'NH₄Cl' means ammonium chloride, 'XPhos' means 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 'Xphos palladacycle' or 'XPhos precatalyst' means (2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) chloride, 'BINAP', '(±)-BINAP' or 'rac-BINAP' means (±)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (also [1,1'-Binaphthalene]-2,2'-diylbis[diphenylphosphine] or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), 'RuPhos Palladacycle Gen. 1' means Chloro(2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II), methyl-t-butylether adduct.

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

For intermediates that were used in a next reaction step as a crude or as a partially purified intermediate, theoretical mol amounts are indicated in the reaction protocols described below.

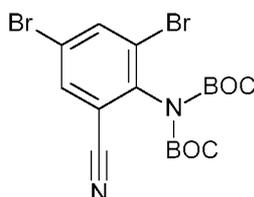
It is well known to one skilled in the art that protecting groups such as TBDMS can routinely be removed with TBAF in a variety of solvents such as for example THF. Similarly, conditions for removal of BOC protecting groups are well known to one skilled in the art, commonly including for example TFA in a solvent such as for example DCM, or HCl in a solvent such as for example dioxane.

The skilled person will realize that in some cases where an organic layer was obtained at the end of an experimental protocol, it was necessary to dry the organic layer with a typical

drying agent such as for example MgSO_4 , or by azeotropic distillation, and to evaporate the solvent before using the product as a starting material in the next reaction step.

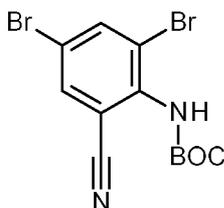
A. Preparation of the intermediates

5 Example A1



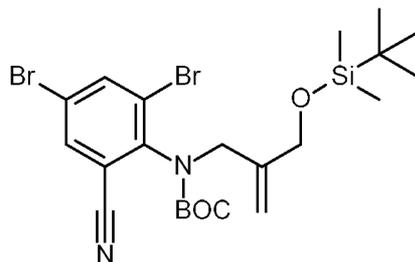
Preparation of intermediate 1:

To a solution of 2,4-dibromo-6-cyanoaniline (200.00 g, 724.82 mmol) and DMAP (17.71 g, 144.96 mmol) in DCM (3 L), Boc_2O (474.58 g, 2.17 mol) was added and the reaction mixture was stirred at 45 °C for 4 h. The crude mixture was successively washed with saturated NaHCO_3 (2 x 1 L) and brine (2 x 1 L), dried over MgSO_4 , filtered and concentrated under vacuum to give 323 g of intermediate 1 (56% yield, yellow solid, 86% purity evaluated by LC/MS). The product was used in the next step without any further purification.



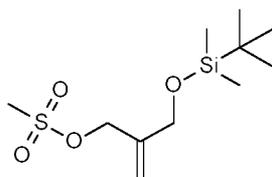
15 Preparation of intermediate 2:

A mixture of intermediate 1 (620.00 g, 1.30 mol) and K_2CO_3 (539.02 g, 3.90 mol) in MeOH (6 L) was stirred at 65 °C for 3 h. The reaction mixture was cooled to 25 °C filtered and concentrated under vacuum. Then, the residue was dissolved in EtOAc (4 L) and the organic layer was washed with brine (2 L), dried over MgSO_4 , and filtered. The filtrate was evaporated under vacuum to 1/8 solvent, filtered to collect the solid and dried under reduced pressure to give 300 g of intermediate 2 (60% yield, yellow solid). The product was used in the next step without any further purification.



Preparation of intermediate 3:

Intermediate 2 (100.00 g, 265.93 mmol), 2-(((*tert*-butyl-dimethyl-silanyl)oxy)methyl)prop-2-en-1-ol (80.72 g, 398.90 mmol) and tributylphosphane (107.61 g, 531.86 mmol) were dissolved in THF (2 L) and cooled to 0 °C. A solution of 1,1'-(azodicarbonyl)-dipiperidine (147.61 g, 585.05 mmol) in THF (50 mL) was added dropwise under N₂ and stirred at 0 °C for 1 h, then 25 °C for 12 h. The resulting mixture was triturated with petroleum ether (3 L), filtered and concentrated under vacuum. Then, the residue was dissolved in EtOAc (6 L), washed successively with water (2 x 2 L) and brine (2 x 2 L), dried over MgSO₄, filtered and concentrated under vacuum. Three reactions (each 100 g) were carried out in parallel. The resulting residues were purified by column chromatography on silica gel (SiO₂, mobile phase: petroleum ether/EtOAc, 10:1). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 350 g of intermediate 3 (78% yield, yellow oil).



15 Preparation of intermediate 3a:

Triethylamine (196.3 mL; 1.408 mol) was added to a solution of 2-(((*tert*-butyl-dimethyl-silanyl)oxy) methyl) prop-2-en-1-ol (114 g, 563.3 mmol) in DCM (1L) at 0 °C. Methanesulfonylchloride (56.0 mL; 704.2 mmol) was added slowly to the mixture and this mixture was stirred for 2 h at 0 °C. The reaction was quenched with saturated aqueous solution of NaHCO₃ (100 ml) and extracted with DCM (500ml*2). The organic layer was dried over MgSO₄, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (Petroleum ether/ethyl acetate from 0/100 to 5/1) to give 50g (32%; light yellow oil) of intermediate 3a.

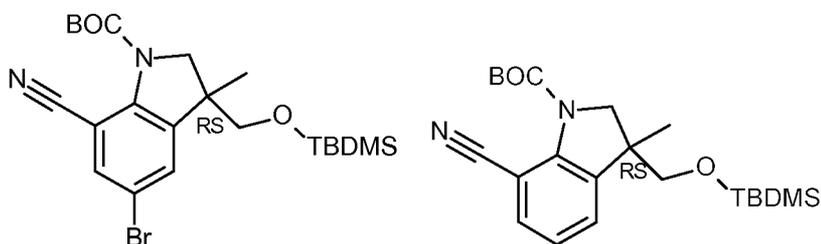
25 Alternative preparation of intermediate 3a:

A solution of 1,3-Hydroxy-2-methylenepropane (100 g) in dry THF (200 mL) was added dropwise at 0 °C to a suspension of sodium hydride (0.95 eq.) in dry THF (600 mL). After 30 min a solution of *tert*-butyldimethylsilylchloride (0.95 eq.) in dry THF (200 mL) was added dropwise to the mixture. After approximately 18 hours at 0-5 °C, water (500 mL) was added slowly keeping the temperature between 0-5 °C. After phase separation, the aqueous layer was back-extracted with ethyl acetate (500 mL) and the combined organic layers were washed with water (500 mL). The organic phase was concentrated to a residue which was azeotropically dried by co-evaporation with THF affording 252.7 g of the crude monoTBDMS-protected diol. A portion of the crude monoTBDMS-protected diol (152.4 g) was dissolved in dry dichloromethane (610 mL) and triethylamine (1.4 eq.) was added. The mixture was then stirred at 0 °C for 30 min and methanesulfonic anhydride (1.2 eq.) was added as a solution in dichloromethane (950 mL) and the mixture was stirred for 1 h between -5 and 5 °C. An additional aliquot of methanesulfonic anhydride (0.1 eq.) and triethylamine (0.2 eq.) were added and, after 1 additional hour, water (500 mL) was added. After phase separation, the organic layer was washed twice with water (500 mL) and concentrated to a residue, which was re-diluted with THF and partially concentrated to obtain a solution of intermediate 3a (311.1 g, 57 weight % intermediate 3a in the solution).

20 Alternative preparation of intermediate 3:

Intermediate 2 (140g; 372.3 mmol) was dissolved in acetonitrile (1.3L). Intermediate 3a (104.4g; 372.3 mmol), potassium carbonate (128.6 g; 930.7 mmol), and sodium iodide (5.58 g; 37.2 mmol) were added. The mixture was stirred at 80 °C for 12 h, cooled and concentrated under reduced pressure. The residue was dissolved in water (1 L) and extracted with ethyl acetate (1 L x2). The combined organic phase was washed with brine (1 L), dried over Na₂SO₄ and filtered. The filtrate was concentrated under vacuum to give a crude product. The residue was purified by silica gel chromatography (Petroleum ether/ethyl acetate from 100/0 to 40/1) to give 180g (86%; clear oil) of intermediate 3.

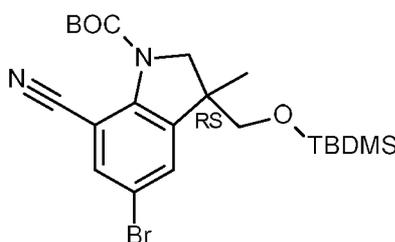
30 Preparation of intermediate 4 and intermediate 4':



intermediate 4

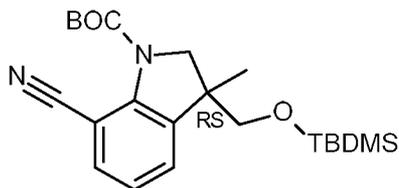
intermediate 4'

A suspension of intermediate 3 (120.00 g, 214.14 mmol), sodium acetate (45.67 g, 556.76 mmol), sodium formate (37.86 g, 556.76 mmol), Pd(OAc)₂ (4.81 g, 21.41 mmol) and tetraethylammonium chloride (44.35 g, 267.67 mmol) in DMF (1.26 L) was degassed under vacuum, purged with Ar three times, and stirred at 85 °C for 2 h. The resulting mixture was filtered through a pad of celite[®] and the solid was washed with DCM (2 L). The filtrate was concentrated under vacuum. The residue was dissolved in ethyl acetate (4 L), washed successively with water (2 x 2 L) and brine (2 x 2 L), dried over MgSO₄, filtered and concentrated under vacuum. Then, the residue was purified by column chromatography on silica gel (SiO₂, mobile phase: petroleum ether/EtOAc, 15:1). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give a mixture of intermediates 4 and 4'. Three reactions (each on 100-120 g of intermediate 3) were carried out in parallel which gave in total 160 g of a mixture of intermediates 4 and 4' (38:62).

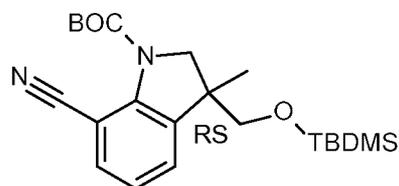


15 Alternative preparation of intermediate 4:

To a solution of intermediates 4 and 4' in CH₃CN (1.60 L), 1-bromopyrrolidine-2,5-dione (212.20 g, 1.19 mol) was added and the resulting mixture was stirred at 40 °C for 16 h. The solvent was removed by evaporation under reduced pressure. The residue was dissolved in ethyl acetate (2 L), washed successively with NaHCO₃ (2 x 1 L) and brine (2 x 1 L), dried over MgSO₄ and filtered. The filtrate was evaporated under vacuum and purified by column chromatography on silica gel (SiO₂, mobile phase: petroleum ether/EtOAc, 50:1). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 110 g of intermediate 4 (56% yield, yellow oil, 97% purity evaluated by LC/MS).

Alternative preparation A of intermediate 4':

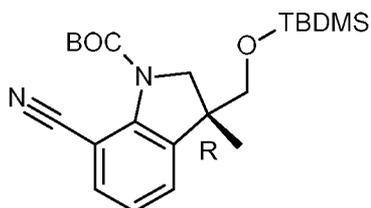
To a solution of intermediate 3 (295.00 g, 473.70 mmol), sodium acetate (101.05 g, 1.23 mol), sodium formate dihydrate (128.15 g, 1.23 mol) and [1,1'-bis(diphenylphosphino)ferrocene] palladium, (II) chloride complex with dichloromethane (19.34 g, 23.70 mmol) in DMF (2 L) was added *tetra-N*-butylammonium chloride (164.60 g, 592.20 mmol) under N₂ at rt. The reaction mixture was stirred overnight at 60 °C, then, filtered through a pad of celite[®] and the solid was washed with DCM (400 mL). The filtrate was concentrated under vacuum. The resulting residue was dissolved in EtOAc (4 L) and the organic layer was washed successively with water (2 L) and brine (2 L), dried over Na₂SO₄, filtered and concentrated to give the crude product as black oil. This residue was purified by column chromatography on silica gel (SiO₂, mobile phase: petroleum ether/EtOAc, gradient from 100:0 to 10:1). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 155 g of intermediate 4' (70% yield, yellow oil).

Alternative preparation B of intermediate 4':

Intermediate 242 (50.0 g) was dissolved in DMF (250 mL). Sodium formate dehydrate (2.6 eq.), sodium acetate (2.6 eq.), tetraethylammonium chloride (1.25 eq.) and palladium acetate (0.05 eq.) were added. The mixture was degassed with nitrogen (3 times) and was then warmed at 45-50 °C until complete conversion (typically 24 hours monitored by HPLC). Water (350 mL) was then added followed by heptane (350 mL). The mixture was filtered and, after phase separation, the aqueous layer was extracted with heptane (350 mL). The combined organic layers were washed with water (250 mL) and then filtered on a diatomite pad (25 g; diatomaceous earth). The filtrate was concentrated to 100-150 mL, cooled to -10 to -5 °C for 2 hours and filtered to afford 37.6 g of intermediate 4'. An additional amount of intermediate 4' could be recovered by filtering the mother liquors on

a silica gel pad to remove impurities, and subsequently cool down the filtrate to -10 °C to crystallize out an additional amount of intermediate 4'.

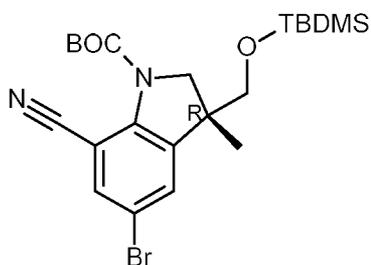
Preparation of intermediate 4'R



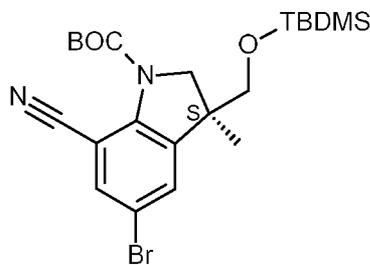
5 Intermediate 4'R

Intermediate 4'R was obtained from a chiral chromatography separation of intermediate 4' (column CHIRALPAK IC 5cm *25 cm; mobile phase: hexane/EtOH:80/20; Flow rate: 60.0mL/min; Wavelength: UV 254 nm; Temperature: 35°C).

10 Preparation of intermediate 4R and intermediate 4S:



intermediate 4R



intermediate 4S

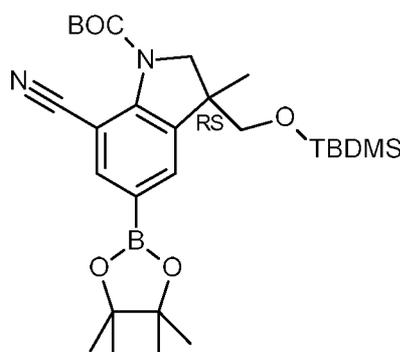
Intermediate 4 (500.00 g) was purified via Normal Phase Chiral separation (Stationary phase: Daicel Chiralpak IC 2000 gram 10 microhm, mobile phase: heptane/EtOH, Isocratic 80% heptane, 20% EtOH). The fractions containing the products were mixed and concentrated to afford 266 g of intermediate 4R (53% yield, ee > 98 %) and 225 g of intermediate 4S (45% yield, ee > 98 %).

Alternatively, intermediate 4 (10.00 g) was purified by chiral SFC (Stationary phase: CHIRALPAK IC 5 μm 250 x 30 mm, mobile phase: 85% CO₂, 15% iPrOH). The pure fractions were collected and evaporated to dryness yielding 4.3 g of intermediate 4R (43% yield, ee = 100%) and 4.5 g of intermediate 4S (45% yield, ee = 100%).

Alternative preparation of intermediate 4R:

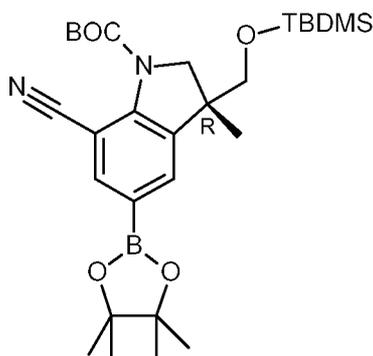
To a solution of intermediate 4'R (10.0 g) in ACN (100 mL) 1,3-dibromo-5,5-dimethylhydantoin (0.75 eq.) was added and the mixture was stirred at 20 °C for 24-28 hours, monitoring the conversion by HPLC. After complete conversion aqueous 5% NaHCO₃ was added (250 mL) and the mixture was stirred for 30 minutes. Toluene (250 mL) was then added and, after 30 min stirring at room temperature, the mixture was allowed to settle and the layers were separated. The organic layer was washed twice with water (100 mL) and used directly in the next step (conversion 99.6%) .

Example A2a



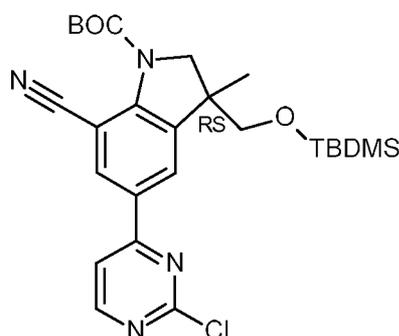
10 Preparation of intermediate 5:

To a solution of intermediate 4 (127.00 g, 234.70 mmol) in 1,4-dioxane (1.2 L), bis(pinacolato)diboron (74.50 g, 293.40 mmol) and potassium acetate (69.11 g, 704.24 mmol) were added. Then, [1,1'-bis(diphenylphosphino) ferrocene] palladium (II) chloride (8.59 g, 11.74 mmol) was added and stirred for 4 h at 85 °C under N₂ atmosphere. The mixture was cooled, partitioned between EtOAc (2 L) and water (500 mL) and filtered through a pad of celite[®]. The organic and aqueous layers were separated. The organic layer was washed successively with water (300 mL), brine (300 mL), dried over Na₂SO₄ and concentrated under vacuum. The residue was dissolved in a mixture of DCM/EtOAc (90:10, 600 mL), filtered through a plug of flash silica gel and washed with DCM/EtOAc (90:10, 3 L). The filtrate was evaporated to give 125 g of crude intermediate 5 (brown oil) which was directly engaged in the next step.



Preparation of intermediate 5R:

To a solution of intermediate 4R (20.00 g, 41.50 mmol) in 1,4-dioxane (200 mL), bis(pinacolato)diboron (13.20 g, 51.90 mmol) and potassium acetate (12.20 g, 124.60 mmol) were added. Then, [1,1'-bis(diphenylphosphino) ferrocene] palladium (II) chloride complex with dichloromethane (1.70 g, 2.08 mmol) was added and stirred for 4 h at 85 °C under N₂. The mixture was cooled, partitioned between EtOAc (200 mL) and water (100 mL), and filtered through a pad of celite[®]. The organic and aqueous layers were separated. The organic layer was washed successively with water (100 mL) and brine (100 mL), dried over Na₂SO₄, and concentrated under vacuum. The residue was dissolved in a mixture of DCM/EtOAc (90:10, 200 mL), filtered through a plug of flash silica gel and washed with a mixture of DCM/EtOAc (90:10, 1 L). The filtrate was evaporated to give 25 g of crude intermediate 5R (brown oil) which was directly engaged in the next step.



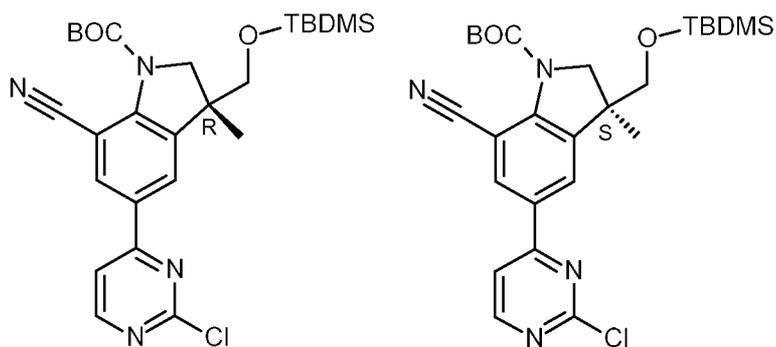
Preparation of intermediate 6:

A solution of intermediate 5 (160.00 g, 302.70 mmol) in 1,4-dioxane (1.2 L) was treated with a solution of NaHCO₃ (76.30 g, 908.10 mmol) in water (400 mL). Then, 2,4-dichloropyrimidine (67.64 g, 545.06 mmol) and Pd(PPh₃)₄ (17.50 g, 15.13 mmol) were added under N₂. The reaction mixture was stirred at 80 °C under N₂. The mixture was cooled, partitioned between EtOAc (2 L) and water (800 mL), and filtered through a pad of celite[®]. The organic and aqueous layers were separated. The organic layer was washed successively with water (800 mL) and brine (500 mL), dried over Na₂SO₄ and

concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (SiO₂, mobile phase: petroleum ether/EtOAc, gradient from 100:0 to 10:1). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 100 g of intermediate 6 (71% yield in 2 steps, yellow solid).

5

Preparation of intermediate 6R and intermediate 6S:



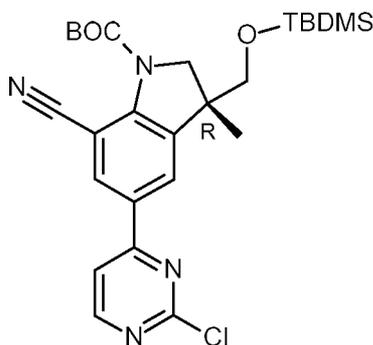
intermediate 6R

intermediate 6S

Intermediate 6 (52.00 g) was purified by chiral SFC (stationary phase: CHIRALPAK IC 5 μm 250 x 30 mm, mobile phase: 60% CO₂, 40% MeOH). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 25 g of intermediate 6R (48% yield) and 25.1 g of intermediate 6S (48% yield).

10

Intermediate 6R (50.10 g) was further purified by chiral SFC (stationary phase: CHIRALPAK IA 5 μm 250 * 20 mm, mobile phase: 87.5% CO₂, 12.5% MeOH). The pure fractions were mixed and the solvent was evaporated to afford 49.10 g of intermediate 6R.



15 Alternative preparation of intermediate 6R:

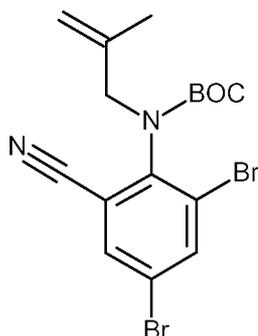
A solution of intermediate 5R (25.00 g, 41.90 mmol) in 1,4-dioxane (1.2 L) was treated with a solution of NaHCO₃ (10.50 g, 125.72 mmol) in water (80 mL). Then, 2,4-dichloropyrimidine (9.36 g, 62.86 mmol) and Pd(PPh₃)₄ (2.42 g, 2.09 mmol) were added under N₂. The reaction mixture was stirred at 80 °C under N₂. The mixture was cooled,

partitioned between EtOAc (300 mL) and water (100 mL), and filtered through a pad of celite[®]. The organic layer was washed with water (100 mL), brine (100 mL), dried over Na₂SO₄ and concentrated under vacuum. The resulting residue was combined with 3 other batches coming from reactions performed on 25 g of intermediate 5R. The residue was purified by flash column chromatography on silica gel (SiO₂, mobile phase: petroleum ether/EtOAc, gradient from 100:0 to 10:1). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 63 g of intermediate 6R (70% yield over 2 steps, yellow solid).

10 Alternative preparation of intermediate 6R:

To a solution of intermediate 4R (50.0 g) in toluene (400 mL) was added bis(pinacolato)diboron (1.3 eq.), potassium acetate (3.0 eq.) and Pd(dppf)Cl₂ (0.05 eq.). The mixture was degassed 3 times with nitrogen and heated to 90 °C for 12-14 hours. Subsequently, the mixture was cooled to room temperature and filtered on a celite pad which was washed with toluene (150 mL). The filtrate was washed with water (250 mL) and was then filtered on a silica pad (10 g) to afford a toluene solution containing 49g of intermediate 5R. To this solution was added 2,4-dichloropyrimidine (1.5 eq.), NaHCO₃ (3.0 eq.), water (25 mL) and Pd(PPh₃)₄ (0.05 eq.). After degassing three times with nitrogen, the mixture was stirred at 90 °C monitoring the conversion by HPLC. After complete conversion (24-48 hours), the mixture was cooled to room temperature, filtered on a celite pad and washed with water (250 mL). To the organic layer was added silica thiol scavenging resin (10 g) and the mixture was stirred at 90 °C for 3 hours, then cooled to room temperature and filtered. The solvent was switched completely to isopropanol by repeated distillation until about 100 mL of isopropanol solution remained. The solution was warmed to 50°C and 250 mL of methanol were added. After stirring at 50 °C for 4 hours, the mixture was cooled to 0°C in 4h, held at the same temperature for 16 hours and finally filtered to obtain 26g of intermediate 6R.

Example A2b

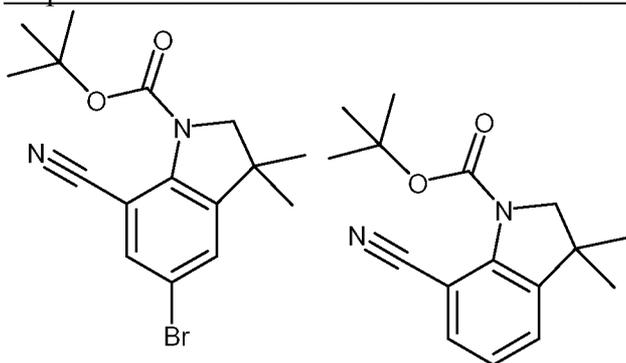


Preparation of intermediate 158b:

A solution of intermediate 2 (10.00 g, 26.59 mmol) and 2-methyl-2-propen-1-ol (4.50 mL, 53.69 mmol) in Me-THF (200 mL) was cooled with EtOH/ice bath under N₂ to an internal temperature of -5 °C. Tri-n-butylphosphine (13.30 mL, 53.19 mmol) was added. Then a solution of 1,1'-(azodicarbonyl)piperidine (14.80 g, 58.62 mmol) in Me-THF (120 mL) was added dropwise over 25 min. The solution was stirred for 5 min more at this temperature then the cooling bath was removed and the solution stirred at rt for 18 h. The reaction mixture was poured onto a 10% aqueous solution of K₂CO₃ and extracted with DCM. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue (20 g) was taken up with heptane and the insoluble material was removed by filtration. The filtrate was concentrated to 20 mL and purified by column chromatography on silica gel (irregular SiOH, 80 g, mobile phase: heptane/EtOAc, gradient from 100:0 to 88:12). The pure fractions were collected and evaporated to dryness to give 10.80 g of intermediate 158b (94% yield).

15

Preparation of intermediate 159b and intermediate 159b':

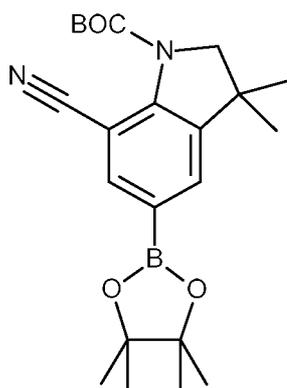


intermediate 159b intermediate 159b'

A mixture of intermediate 158b (10.80 g, 25.11 mmol), sodium acetate (5.35 g, 65.28 mmol), sodium formate (4.44 g, 65.28 mmol) and tetraethylammonium chloride (5.20 g, 31.38 mmol) in DMF (100 mL) was de-gassed by sonication for 10 min under a stream of

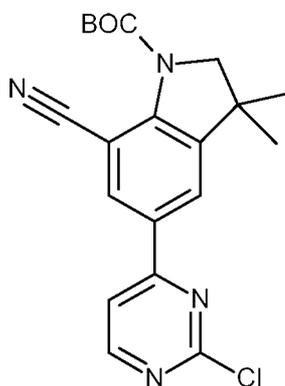
20

Ar. Pd(OAc)₂ (563.00 mg, 2.51 mmol) was added and the resulting orange suspension was then stirred at 85 °C (block temperature) for 4 h. The residue was diluted with EtOAc and water, then filtered through a plug of celite[®]. The organic layer was decanted, washed successively with a saturated aqueous solution of NaHCO₃ and brine, dried over MgSO₄,
5 filtered and evaporated to dryness. The residue (8.3 g, mixture of intermediates 159b and 159b') was dissolved in CH₃CN (230 mL) and NBS (4.47 g, 25.11 mmol) was added. The reaction mixture was heated at 55 °C (block temp) for 18 h. The reaction mixture was evaporated to dryness and the residue was taken up with heptane/DCM. The precipitate was filtered off (1 g derivative) and the filtrate (10 g) was purified by column
10 chromatography on silica gel (irregular SiOH, 120 g, injection in DCM, mobile phase: heptane/EtOAc, gradient from 100:0 to 80:20). The pure fractions were collected and evaporated to dryness to give 4 g of intermediate 159b (45% yield).



Preparation of intermediate 160b:

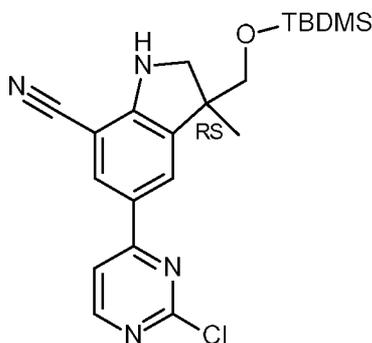
15 [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (243.00 mg, 0.30 mmol) was added to a solution of intermediate 159b (2.09 g, 5.95 mmol), bis(pinacolato)diboron (1.90 g, 7.44 mmol) and potassium acetate (1.75 g, 17.85 mmol) in 1,4-dioxane (45 mL) and the reaction mixture was heated for 18 h at 85 °C. The reaction mixture was diluted with EtOAc and filtered through a pad of
20 celite[®]. The filtrate was washed with water, and the organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue was crystallized from DiPE and the precipitate was filtered and dried to give 1.85 g of intermediate 160b (78% yield).



Preparation of intermediate 161b:

A degassed suspension of intermediate 160b (1.12 g, 2.81 mmol), 2,4-dichloropyridine (502.00 mg, 3.37 mmol), Pd(PPh₃)₄ (162.00 mg, 0.14 mmol) and a solution of Na₂CO₃ 2M (4.20 mL, 8.14 mmol) in 1,4-dioxane (24 mL) was heated to 85 °C for 18 h. The reaction mixture was partitioned between DCM and saturated aqueous NaHCO₃. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue (2 g) was purified by column chromatography on silica gel (irregular SiOH, 40 g, mobile phase: heptane/EtOAc, gradient from 70:30 to 50:50). The pure fractions were collected and evaporated to dryness to give 933 mg of intermediate 161b (86% yield, 85% purity based on LC/MS).

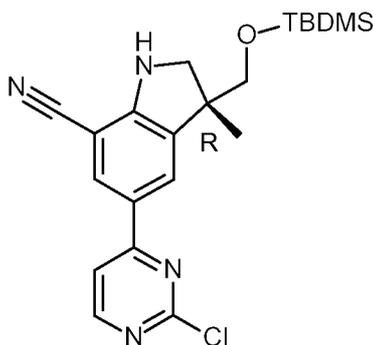
Example A3a



Preparation of intermediate 7:

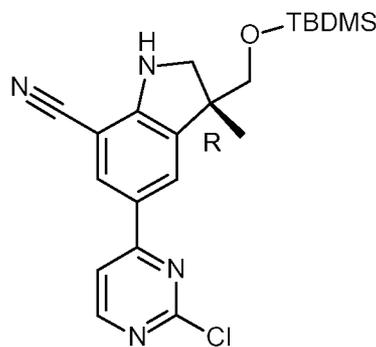
To a solution of intermediate 6 (1.50 g, 2.91 mmol) in DCM (30 mL), TFA (7 mL, 91.50 mmol) was added at 0-5 °C and the resulting mixture was stirred at 0-5 °C for 1 h, then at rt for 1 h. The crude product was poured in a mixture of crushed ice and a saturated aqueous solution of NaHCO₃. After extraction with DCM (twice), the organic layers were combined, washed with saturated solution of NaHCO₃, dried over MgSO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (Irregular SiOH, 40 μm, mobile phase: NH₄OH/MeOH/DCM, gradient from 0%

NH₄OH, 0% MeOH, 100% DCM to 0.1% NH₄OH, 2% MeOH, 98% DCM). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 524 mg of intermediate 7 (65% yield).



5 Preparation of intermediate 7R:

In a three neck round bottom flask, SiO₂ (35-70 μm) (200 g) was added to a solution of intermediate 6R (45.00 g, 87.36 mmol) in toluene (640 mL) at rt. The reaction mixture was refluxed (bath temperature 125 °C) for 6 h under mechanical agitation. Then, SiO₂ (35-70 μm) was filtered off, washed successively with THF and EtOAc, and the filtrate was
 10 evaporated to dryness to give 37.2 g of crude intermediate 7R which was directly engaged in the next steps.

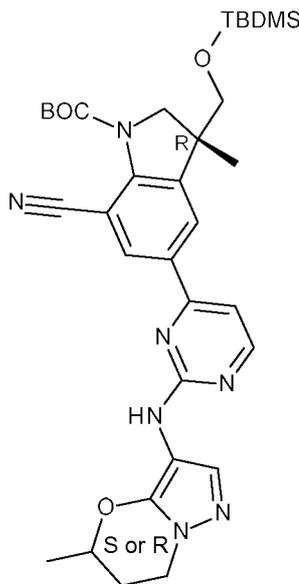


Alternative preparation of intermediate 7R:

TFA (135 mL, 1.76 mol) was added dropwise at -10 °C (over 50 min) to a solution of intermediate 6R (20.00 g, 38.82 mmol) in DCM (550 mL). The reaction mixture was
 15 stirred below 0 °C for 15 min more, then poured in a mixture of crushed ice and a saturated aqueous solution of K₂CO₃. After extraction with DCM (twice), the organic layers were combined, washed with an aqueous solution of K₂CO₃, dried over MgSO₄ and evaporated to dryness. The residue (17.40 g) was purified by chromatography on silica gel (irregular SiOH, 80 g, mobile phase: NH₄OH/MeOH/DCM, gradient from 0% NH₄OH, 0% MeOH,
 20 100% DCM to 0.2% NH₄OH, 2% MeOH, 98% DCM). The desired fractions were

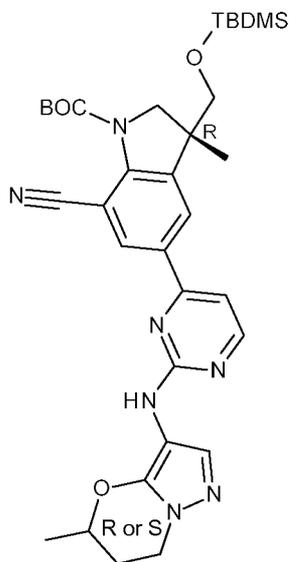
collected and the solvent was concentrated to dryness under vacuum to give 12.1 g of intermediate 7R (75% yield).

Example A3b



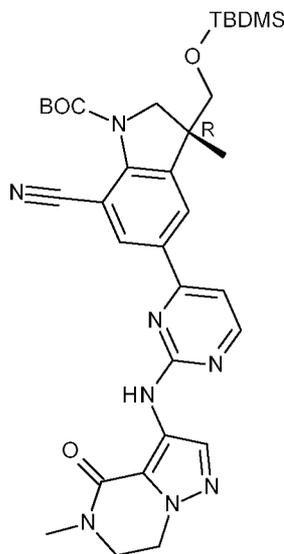
5 Preparation of intermediate 10b:

Intermediate 6R (224.83 mg, 0.44 mmol), intermediate 9b (117.00 mg, 0.764 mmol), Pd(OAc)₂ (9.80 mg, 43.65 μmol), BINAP (27.18 mg, 43.65 μmol) and Cs₂CO₃ (426.61 mg, 1.31 mmol) in 1,4-dioxane (7.19 mL) in a sealed tube were 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. The reaction mixture was poured into water and DCM. The mixture was filtered over celite[®], decanted and the organic layer was dried over MgSO₄, filtered and evaporated under vacuum. The residue was purified by silica gel chromatography (Irregular SiOH 40 μm 80 g, mobile phase gradient: from 100% DCM to 96% DCM, 4% MeOH, 0.5% NH₄OH). The pure fractions were combined and the solvent was evaporated to give 170 mg of intermediate 10b (62% yield).



Preparation of intermediate 12b:

Intermediate 6R (224.83 mg, 0.446 mmol), intermediate 9a (117.00 mg, 0.76 mmol), Pd(OAc)₂ (9.80 mg, 43.65 μmol), BINAP (27.18 mg, 43.65 μmol) and Cs₂CO₃ (426.61 mg, 1.31 mmol) in 1,4-dioxane (7.19 mL) in a sealed tube were stirred at 120 °C using one
5 single mode microwave (Biotage Initiator EXP 60[®]) with a power output ranging from 0 to 400 W for 30 min.. The reaction mixture was poured into water and DCM. The mixture was filtered over celite[®], decanted and the organic layer was dried over MgSO₄, filtered and evaporated under vacuum. The residue was purified by silica gel chromatography
10 (Irregular SiOH 40 μm 40 g, mobile phase gradient: from 100% DCM to 96% DCM, 4% MeOH, 0.5% NH₄OH). The pure fractions were combined and the solvent was evaporated to give 300 mg of intermediate 12b (quant. yield).

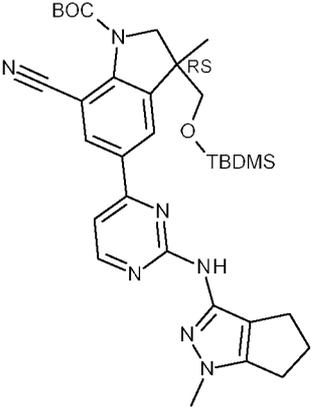
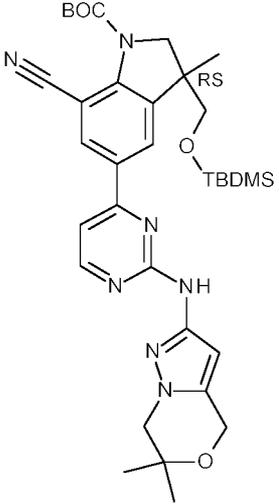
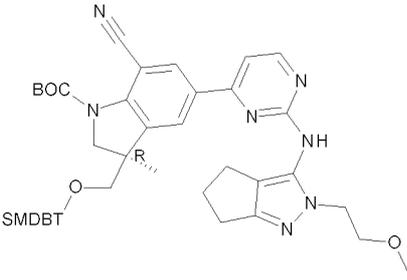


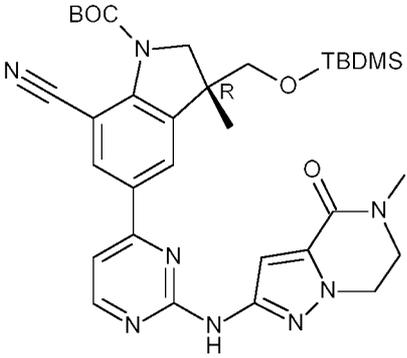
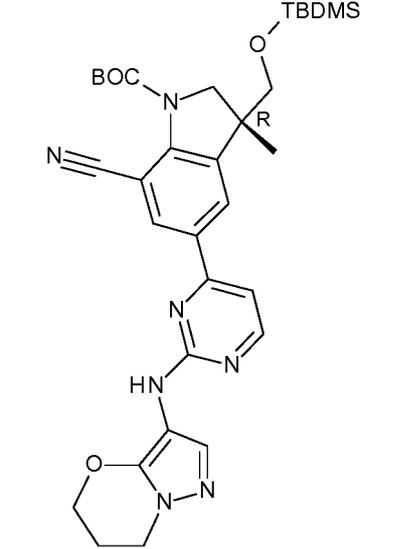
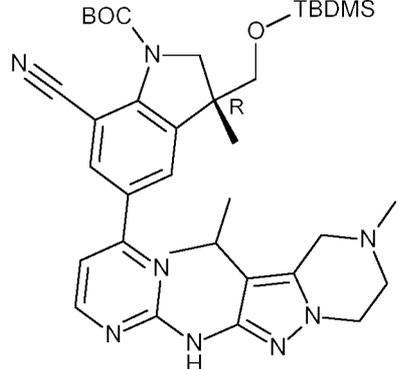
Preparation of intermediate 16b:

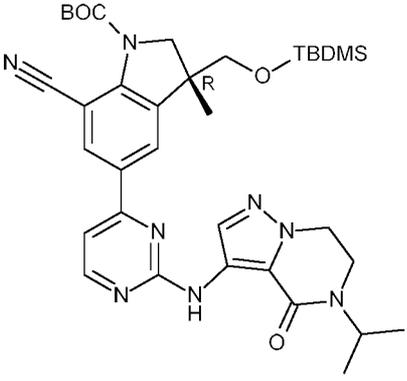
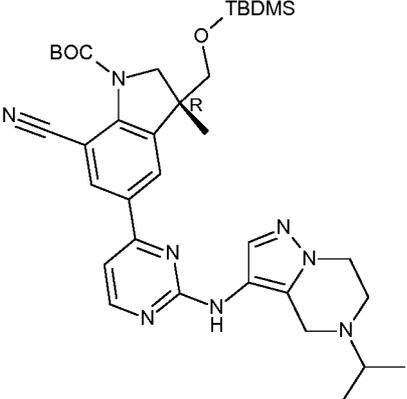
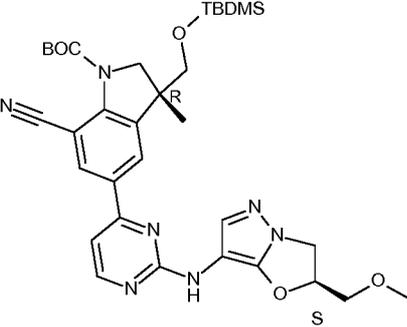
A mixture of intermediate 6R (600.00 mg, 1.17 mmol), intermediate 15b (0.25 g, 1.50 mmol), Cs₂CO₃ (0.90 g, 2.76 mmol), Pd(OAc)₂ (0.022 g, 0.10 mmol) and BINAP (0.059 g, 0.10 mmol) in 1,4-dioxane (14.00 mL) was stirred in a sealed tube at 120 °C using one
 5 single mode microwave (Anton Paar monowave 300[®]) with a power output ranging from 0 to 850 W for 30 min. The reaction was cooled down to room temperature. Water was added and the mixture was extracted twice with DCM. The organic layers were combined, dried over Na₂SO₄, filtered and the solvent was evaporated until dryness. The crude
 10 residue was purified by silica gel chromatography (Irregular SiOH 40 μm, 80 g, mobile phase gradient: from 69% Heptane, 29% EtOAc, 2% MeOH (+10% NH₄OH) to 40% Heptane, 52% EtOAc, 8% MeOH (+10% NH₄OH)). The pure fractions were collected and the solvent was evaporated to dryness to give 580 mg of intermediate 16b (77% yield).

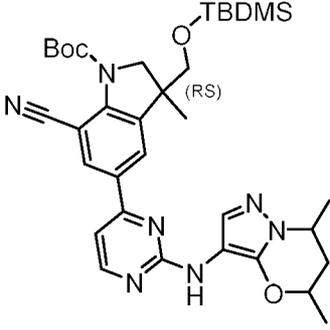
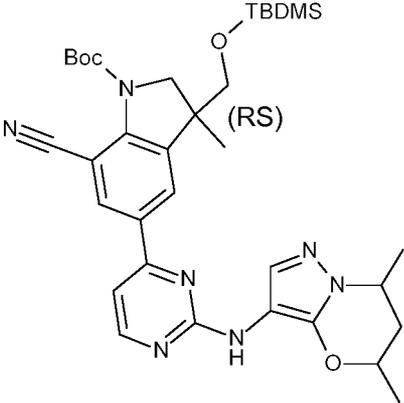
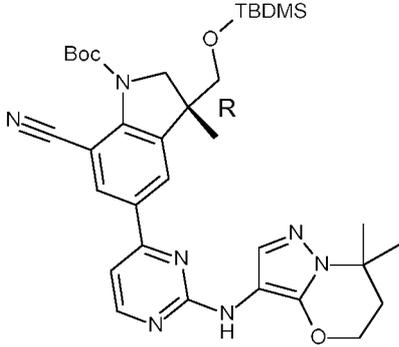
The intermediates in the table below were prepared by using an analogous method as
 15 described for the preparation of intermediate 10b, starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

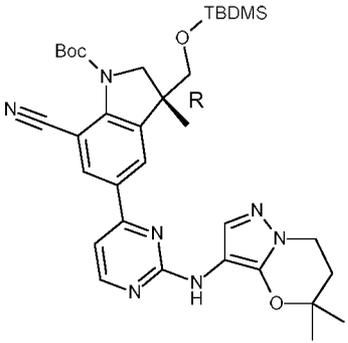
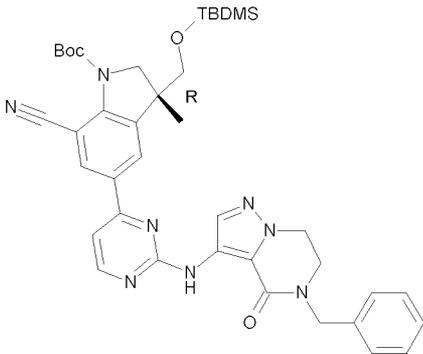
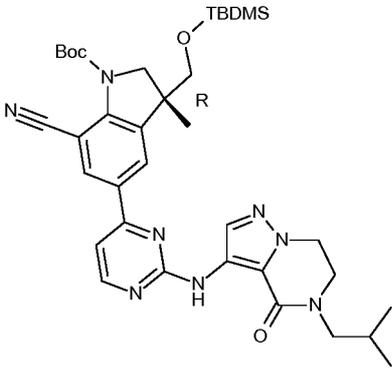
Intermediate number	Structure	Mass (mg)	Yield (%)
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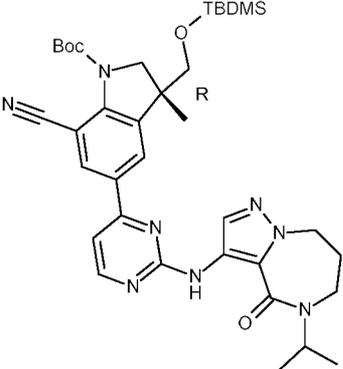
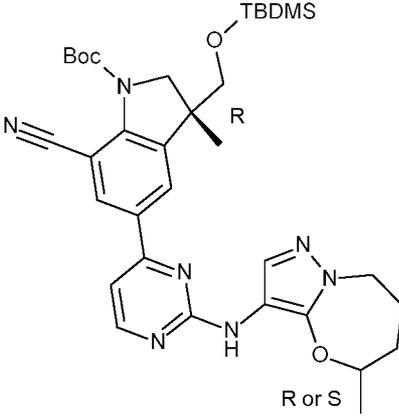
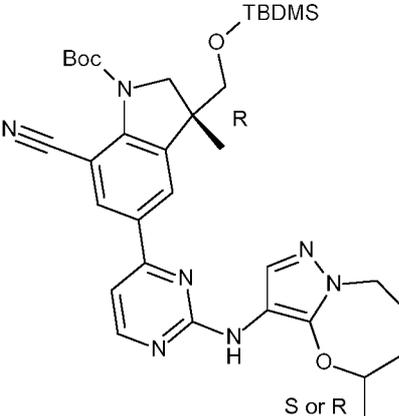
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 22b	 <p>From intermediates 6b and 18b</p>	410	69
Intermediate 56b	 <p>From intermediates 6b and 55b</p>	520	83 Procedure with 2.5 equiv. of Cs ₂ CO ₃
Intermediates 59b	 <p>From intermediate 6R and a mixture of intermediates 58b and 58b' (86/14)</p>	187	29

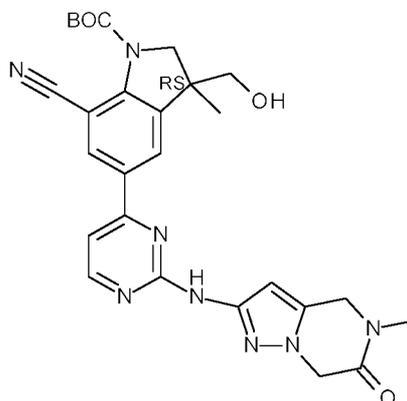
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 73b	 <p>From intermediates 6R and 72b</p>	307	57
Intermediate 78b	 <p>From intermediates 6R and 77b</p>	650	78 Procedure with dioxane/DMF: 11/1
Intermediate 87b	 <p>From intermediates 6R and 86b</p>	430	85

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 92b	 <p>From intermediates 6R and 91b</p>	627	93 Procedure with 2.5 equiv. of Cs ₂ CO ₃
Intermediate 99b	 <p>From intermediates 6R and 98b</p>	400	73
Intermediate 104b	 <p>From intermediates 6R and 103b</p>	1000	quant Procedure with 3 equiv. of Cs ₂ CO ₃

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 109b (methyl groups are <i>cis</i> in bicyclic pyrazole)	 <p>methyl groups <i>CIS</i>: mixture of (R,S) and (S,R)</p> <p>From intermediates 6 and 108b</p>	530	94 Procedure with 3 equiv. of Cs ₂ CO ₃
Intermediate 113b (methyl groups are <i>trans</i> in bicyclic pyrazole)	 <p>methyl groups <i>TRANS</i>: mixture of (S,S) and (R,R)</p> <p>From intermediates 6 and 112b</p>	194	85 Procedure with 3 equiv. of Cs ₂ CO ₃
Intermediate 127b	 <p>From intermediates 6R and 126b</p>	565	99.9 Procedure with 3 equiv. of Cs ₂ CO ₃

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 131b	 <p data-bbox="603 763 1031 797">From intermediates 6R and 130b</p>	705	81.7 Procedure with 3 equiv. of Cs ₂ CO ₃
Intermediate 135b	 <p data-bbox="603 1234 1031 1267">From intermediates 6R and 134b</p>	1300	66.7 Procedure with 2.5 equiv. of Cs ₂ CO ₃
Intermediate 139b	 <p data-bbox="603 1671 1031 1704">From intermediates 6R and 138b</p>	281	78 Procedure with 2.5 equiv. of Cs ₂ CO ₃

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 143b	 <p>From intermediates 6R and 142b</p>	740	34 Procedure with 2.5 equiv. of Cs ₂ CO ₃
Intermediate 150b Isomer separation performed <i>via</i> chiral SFC (Stationary phase: Chiralpak AS-H 5μm 250*20mm, Mobile phase: 90% CO ₂ , 10% EtOH)	 <p>From intermediates 6R and 149b</p>	180	16 Procedure with 3 equiv. of Cs ₂ CO ₃
Intermediate 152b Isomer separation performed <i>via</i> chiral SFC (Stationary phase: Chiralpak AS-H 5μm 250*20mm, Mobile phase: 90% CO ₂ , 10% EtOH)	 <p>From intermediates 6R and 149b</p>	180	16 Procedure with 3 equiv. of Cs ₂ CO ₃

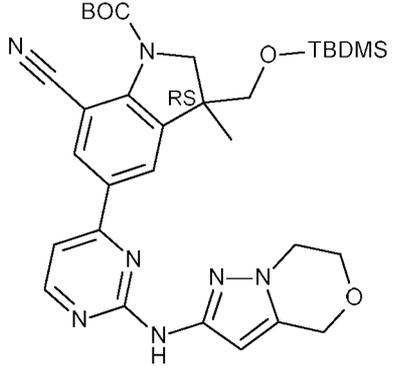
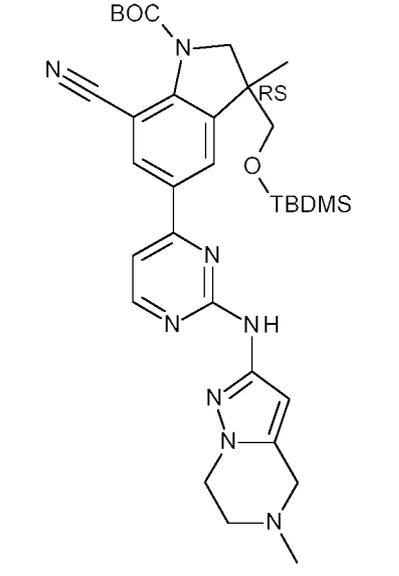
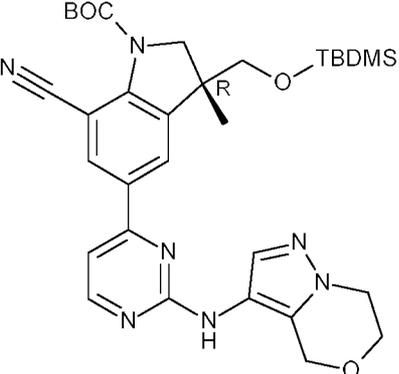


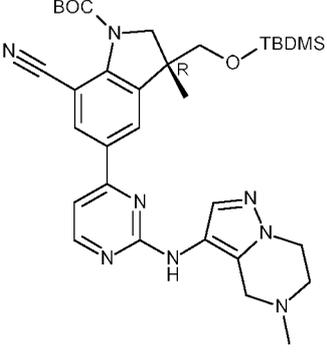
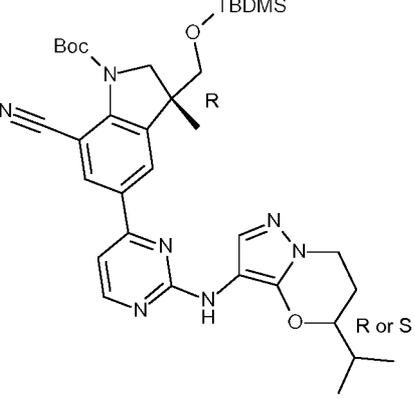
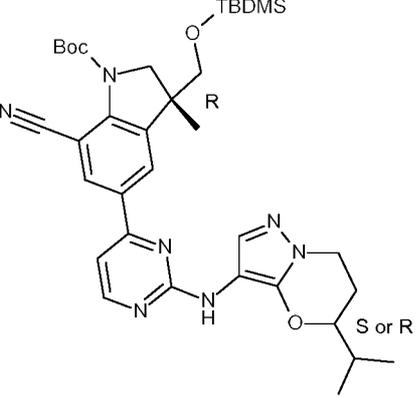
Preparation of intermediate 47b:

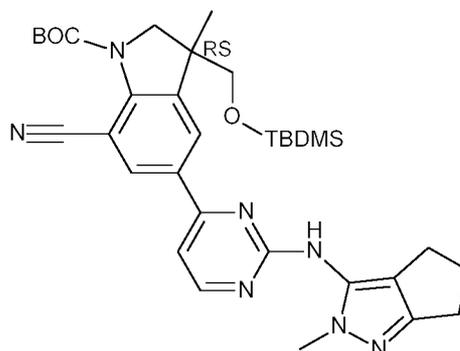
A mixture of intermediate 46b (180 mg, 0.45 mmol), intermediate 45b (82.08 mg, 0.494 mmol) and Cs_2CO_3 (365.75 mg, 1.123 mmol) in 1,4-dioxane (4 mL) was purged with nitrogen. A catalytic amount of $\text{Pd}(\text{OAc})_2$ (8.065 mg, 35.922 μmol) and BINAP (22.37 mg, 35.922 μmol) were then added. The reaction mixture was purged with nitrogen and stirred at 95°C for 2 hours. Water and DCM were added. The organic layer was separated, dried over MgSO_4 , filtered and evaporated. The residue (210 mg) was purified by silica gel chromatography (Irregular SiOH 40 μm 40g, mobile phase from 100% DCM to 95% DCM, 5% MeOH, 0.5% NH_4OH). The pure fractions were combined and the solvent was evaporated to give 87 mg of intermediate 47b (37%).

The intermediates in the table below were prepared by using an analogous method as described for the preparation of intermediate 47b, starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 32b	<p>From intermediates 6 and 31b</p>	160	43 Procedure with 2.5 equiv. of Cs_2CO_3 and R-BINAP

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 39b	 <p>From intermediates 6 and 38b</p>	120 63% purity based on LC/MS	63 Procedure with 1.5 equiv. of Cs ₂ CO ₃ and R- BINAP
Intermediate 51b	 <p>From intermediates 6 and 50b</p>	140	23 Procedure with 2.5 equiv. of Cs ₂ CO ₃
Intermediate 67b	 <p>From intermediates 6R and 66b</p>	570 <i>Yellow foam</i>	Quant. Procedure with 2 equiv. of Cs ₂ CO ₃

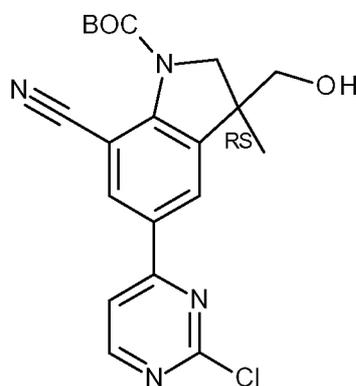
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 82b	 <p style="text-align: right;">From intermediates 6R and 81b</p>	300	25 Procedure with 2.5 equiv. of Cs ₂ CO ₃ at 120°C
Intermediate 120 Isomer separation performed <i>via</i> achiral SFC (Stationary phase: CHIRALPAK IC 5μm 250x30mm, Mobile phase: 50% CO ₂ , 50% EtOH(0.3% ⁱ PrNH ₂))	 <p style="text-align: right;">From intermediates 6R and 119b</p>	244	16 Procedure at 120°C; sealed tube; 4hrs; with 3 equiv. of Cs ₂ CO ₃
Intermediate 121b Isomer separation performed <i>via</i> achiral SFC (Stationary phase: CHIRALPAK IC 5μm 250x30mm, Mobile phase: 50% CO ₂ , 50% EtOH(0.3% ⁱ PrNH ₂))	 <p style="text-align: right;">From intermediates 6R and 119b</p>	210	14 Procedure at 120°C; sealed tube; 4hrs; with 3 equiv. of Cs ₂ CO ₃



Preparation of intermediate 20b:

Intermediate 6 (500.00 mg, 0.97 mmol), intermediate 19b (266.31 mg, 1.94 mmol), Brettphos Palladacycle (77.54 mg, 97.06 μmol), Brettphos (52.10 mg, 97.06 μmol) and
 5 Cs_2CO_3 (0.95 g, 2.91 mmol) in THF (15.80 mL) in a sealed tube were stirred at 140 °C for 7 hours. The reaction mixture was poured into water and DCM, filtered over celite[®] and decanted. The organic layer was separated, dried over MgSO_4 , filtered and evaporated. The residue was purified by silica gel chromatography (Irregular SiOH 40 μm , mobile phase: 97% DCM, 3% MeOH, 0.1% NH_4OH). The pure fractions were combined and the solvent
 10 was evaporated. The crude residue was purified by silica gel chromatography (Irregular SiOH 40 μm , mobile phase: 60% Heptane, 5% MeOH (+ 10% NH_4OH), 35% EtOAc) to give 145 mg of intermediate 20b (24% yield).

Example A4a

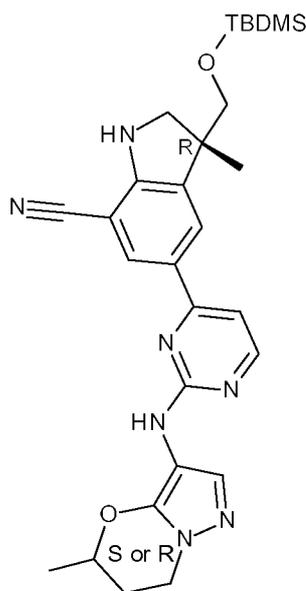


15 Preparation of intermediate 8:

A solution of intermediate 6 (500.00 mg, 0.97 mmol) in THF (5.71 mL) was treated with TBAF (1M in THF) (1.16 mL, 1.16 mmol) and stirred at rt for 12 h. The reaction mixture was poured in EtOAc. The organic layers were washed with water and brine, dried over MgSO_4 and evaporated in vacuo. The residue (483 mg) was purified by column
 20 chromatography on silica gel (Irregular SiOH, 40 μm , 40 g, mobile phase:

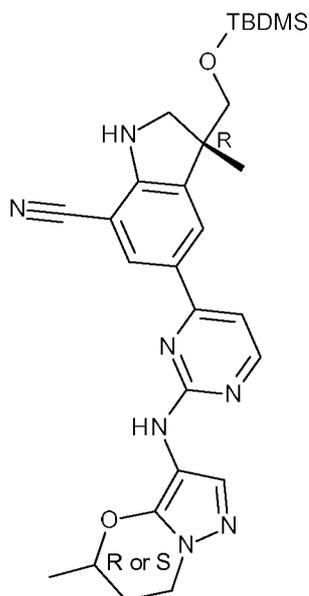
DCM/MeOH/NH₄OH, gradient from 100% DCM to 98% DCM, 2% MeOH, 0.2% NH₄OH). The pure fractions were combined and the solvent was evaporated to give 358 mg of intermediate 8 (92% yield).

5 Example A4b



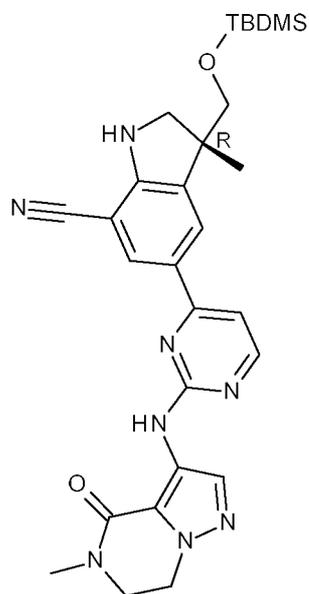
Preparation of intermediate 11b:

SiO₂ (35-70 μm) (1.00 g) was added to a solution of intermediate 10b (170.00 mg, 0.27 mmol) in toluene (8.58 mL) at rt. The reaction mixture was stirred at reflux for 4 hours. After cooling down to rt, SiO₂ was filtered off, washed with DCM/MeOH (80/20) and the filtrate was evaporated to give 140 mg of intermediate 11b (98% yield).



Preparation of intermediate 13b:

SiO₂ (35-70 μm) (1.40 g) was added to a solution of intermediate 12b (300.00 mg, 0.48 mmol) in toluene (8.58 mL) at rt. The reaction mixture was stirred at reflux for 4 hours. After cooling down to rt, SiO₂ was filtered off, washed with DCM/MeOH (80/20) and the filtrate was evaporated to give 252 mg of intermediate 13b (quantitative yield).

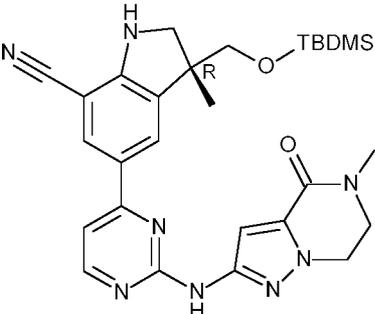
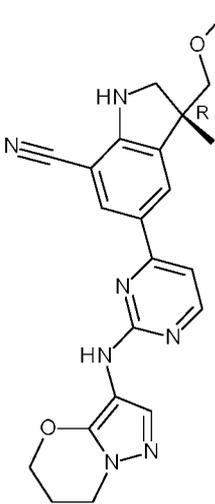


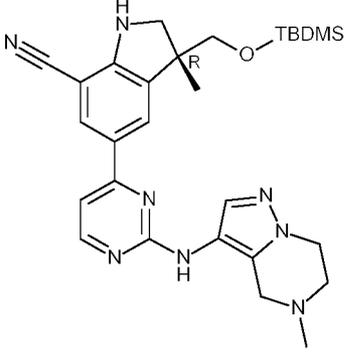
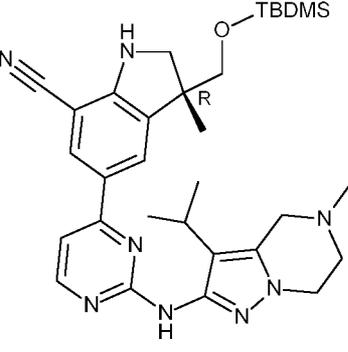
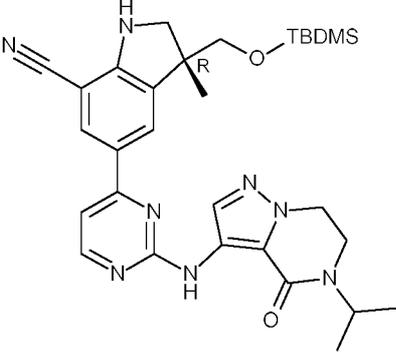
Preparation of intermediate 17b:

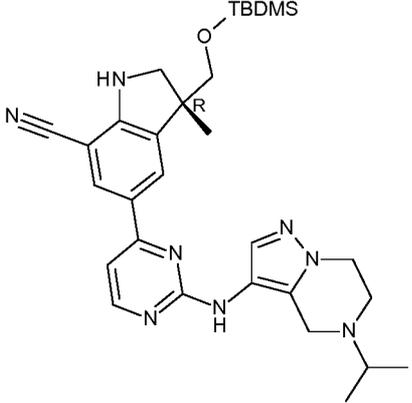
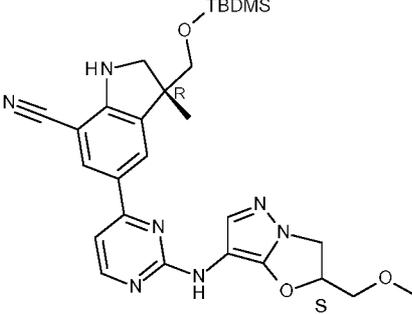
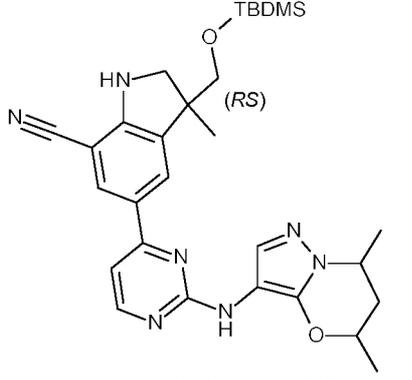
A mixture of intermediate 16b (0.58 g, 0.90 mmol) and SiO₂ (35-70 μm) (700.00 mg) in toluene (8 mL) was stirred at 120 °C for 4 hours. Another amount of SiO₂ (35-70 μm) (0.55 g) was added and the reaction mixture was stirred at 120 °C for 2 hours. The hot mixture was filtered, washed with a solution of EtOAc/MeOH (80/20) (twice) then with a

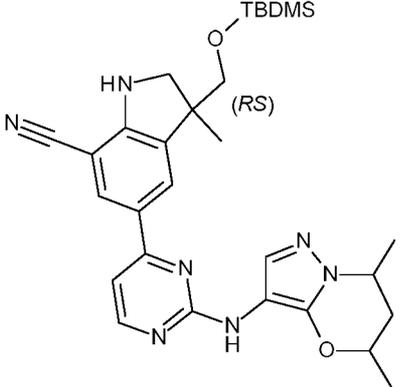
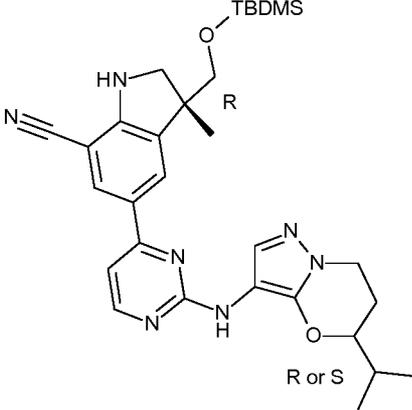
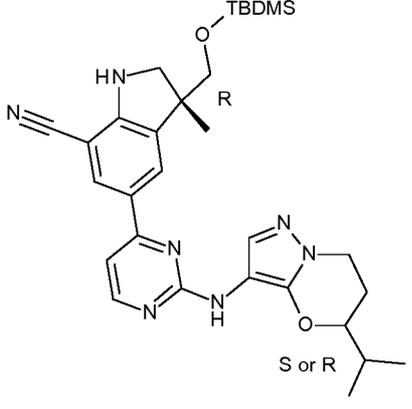
solution of DCM/MeOH (80/20) (twice) and the solvent was evaporated until dryness. The crude residue was purified by silica gel chromatography (Irregular SiOH 15-40 μ m, 40 g, mobile phase gradient: from 98% DCM, 2% MeOH (+10% NH_4OH) to 92% DCM, 8% MeOH (+10% NH_4OH)). The pure fractions were collected and the solvent was evaporated until dryness to give 311 mg of intermediate 17b (64% yield).

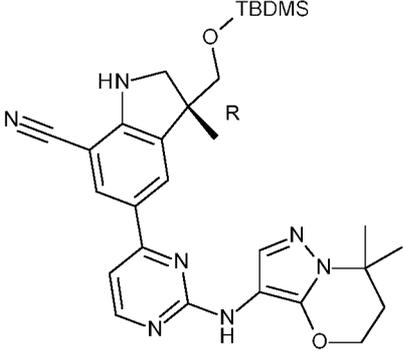
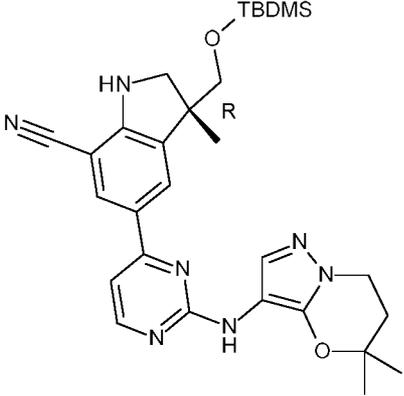
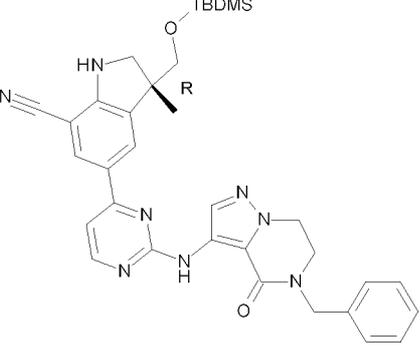
The intermediates in the table below were prepared by using an analogous method as described for the preparation of intermediate 11b, starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

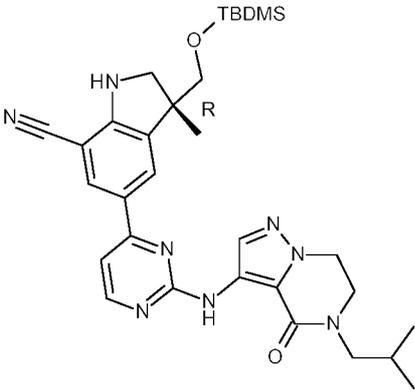
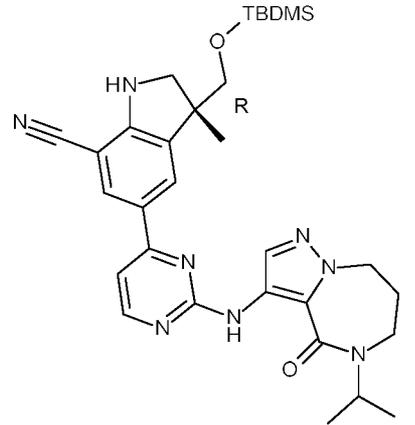
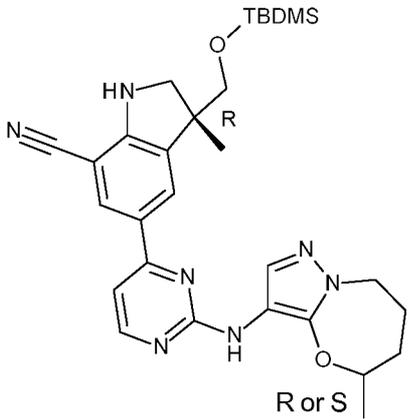
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 74b	 <p>From intermediate 73b</p>	154	59
Intermediate 79b	 <p>From intermediate 78b</p>	543	Quant.

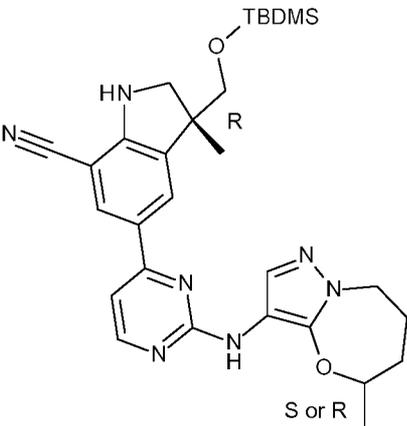
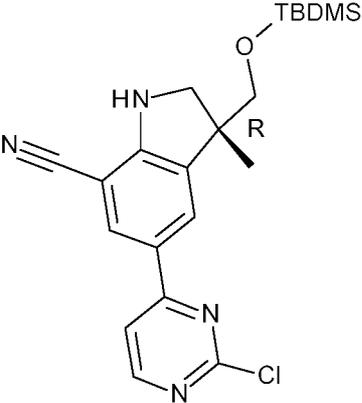
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 83b	 <p data-bbox="667 779 967 813">From intermediate 82b</p>	78	31
Intermediate 88b	 <p data-bbox="667 1202 967 1236">From intermediate 87b</p>	367	Quant.
Intermediate 93b	 <p data-bbox="667 1619 967 1653">From intermediate 92b</p>	450 <i>Yellow oil</i>	84 Procedure with SiO ₂ 40-63 μm

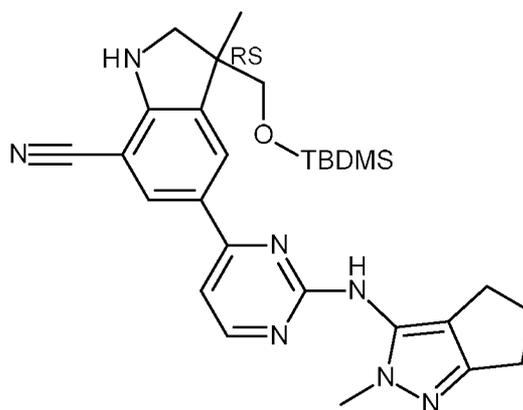
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 100b	 <p data-bbox="667 831 965 864">From intermediate 99b</p>	358 <i>Yellow oil</i>	Quant. Procedure with SiO ₂ 40-63 μm
Intermediate 105b	 <p data-bbox="667 1211 965 1245">From intermediate 104b</p>	760	90
Intermediate 110b (methyl groups <i>cis</i> in bicyclic pyrazole)	 <p data-bbox="746 1637 1029 1697">methyl groups CIS: mixture of (R,S) and (S,R)</p> <p data-bbox="667 1704 965 1738">From intermediate 109b</p>	437	98

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 114b (methyl groups <i>trans</i> in bicyclic pyrazole)	 <p style="text-align: center;">methyl groups TRANS: mixture of (S,S) and (R,R)</p> <p style="text-align: center;">From intermediate 113b</p>	194	Quant
Intermediate 122b	 <p style="text-align: center;">R or S</p> <p style="text-align: center;">From intermediate 120b</p>	205	Quant.
Intermediate 123b	 <p style="text-align: center;">S or R</p> <p style="text-align: center;">From intermediate 121b</p>	178	Quant.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 128b	 <p data-bbox="660 779 971 815">From intermediate 127b</p>	435	91
Intermediate 132b	 <p data-bbox="660 1249 971 1285">From intermediate 131b</p>	595	99.9
Intermediate 136b	 <p data-bbox="660 1720 971 1756">From intermediate 135b</p>	1470	Quant (used directly in next step)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 140b	 <p style="text-align: center;">From intermediate 139b</p>	146	Quant (used directly in next step)
Intermediate 144b	 <p style="text-align: center;">From intermediate 143b</p>	798	Quant (used directly in next step)
Intermediate 151b	 <p style="text-align: center;">From intermediate 150b</p>	152	Quant

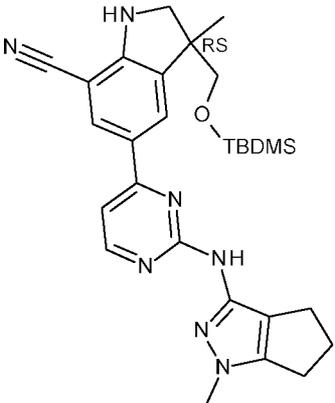
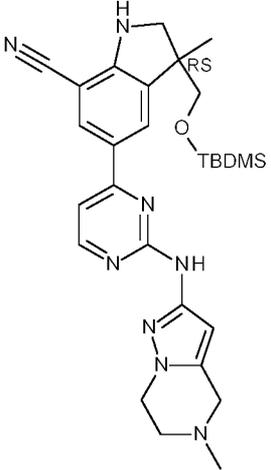
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 153b	 <p>From intermediate 152b</p>	152	Quant
Intermediate 154b	 <p>From intermediate 6R</p>	3450	83 18 hrs at 125°C under mechanical agitation

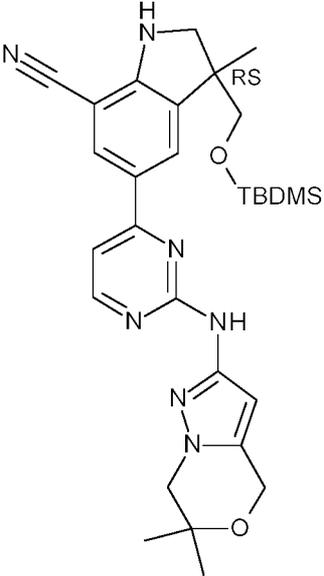
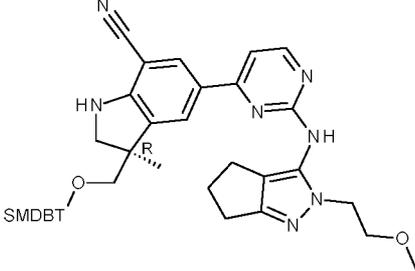
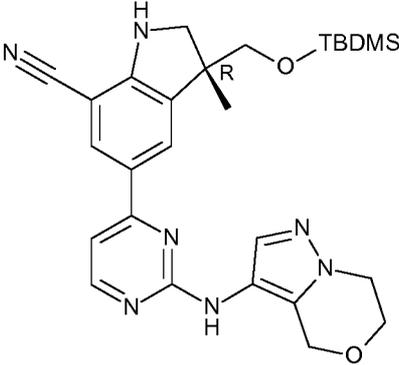


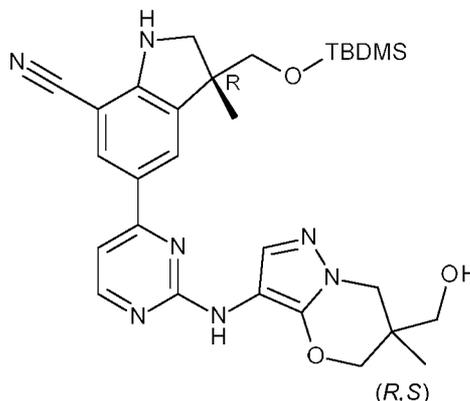
Preparation of intermediate 21b:

A solution of intermediate 20b (145.00 mg, 0.24 mmol) and TFA (0.36 mL) in DCM (1.49 mL) was stirred at 0 °C for 30 minutes. The reaction mixture was poured into a mixture of ice, water and NH₄OH. The mixture was extracted with EtOAc, dried over MgSO₄, filtered and evaporated to give 122 mg of intermediate 21b (quantitative yield) which was used in the next step without any further purification.

The intermediates in the table below were prepared by using an analogous method as described for the preparation of intermediate 21b, starting from the respective starting materials. Minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 23b	 <p>From intermediate 22b</p>	344	Quant.
Intermediate 52b	 <p>From intermediate 51b</p>	84	49 Procedure with TFA/DCM: 1/6, v/v

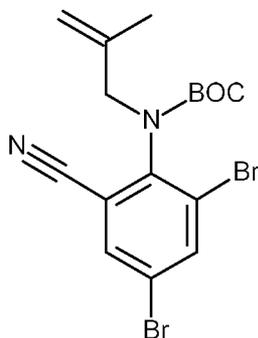
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 57b	 <p data-bbox="651 1010 944 1039">From intermediate 56b</p>	240	55 Procedure with TFA/DCM: 1/6, v/v
Intermediate 60b	 <p data-bbox="651 1359 944 1388">From intermediate 59b</p>	172	97 Procedure with TFA/DCM: 1/10, v/v
Intermediate 68b	 <p data-bbox="651 1800 944 1830">From intermediate 67b</p>	420 <i>Yellow foam</i>	93 Procedure with TFA/DCM: 1/12, v/v



Preparation of intermediate 157b:

A mixture of intermediate 156b (0.300 g; 1.64 mmol), intermediate 154b (0.500 g; 1.21 mmol), Pd(OAc)₂ (0.024 g; 0.11 mmol), BINAP (0.066 g; 0.11 mmol) and Cs₂CO₃ (0.780 g; 2.39 mmol) in 1,4-dioxane (15.00 mL) was stirred in a sealed tube at 120°C using one
 5 single mode microwave (Antoon Parr Monowave300) with a power output ranging from 0 to 850 W for 30 min.(fixed hold time). The reaction mixture was cooled to room temperature. Water was added and the mixture was extracted twice with DCM. The organic layer was decanted and the solvent was evaporated until dryness. The resultant crude material was purified by preparative LC (Irregular SiOH 15-40µm 80g
 10 GraceResolv®, mobile phase Gradient from : 99% DCM, 1% MeOH, 0.1% NH₄OH to 93% DCM, 7% MeOH, 0.7% NH₄OH). The pure fractions were collected and the solvent was evaporated until dryness to give 286 mg (42%) of intermediate 157b.

Example A5a

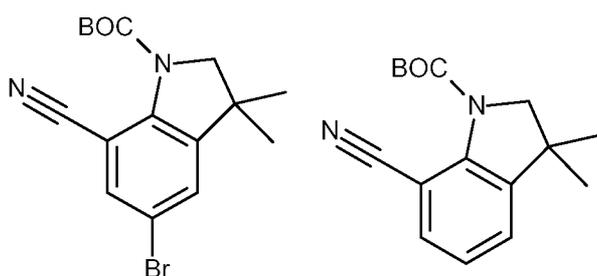


15 Preparation of intermediate 9:

A solution of intermediate 2 (10.00 g, 26.59 mmol) and 2-methyl-2-propen-1-ol (4.50 mL, 53.69 mmol) in Me-THF (200 mL) was cooled with EtOH/ice bath under N₂ to an internal temperature of -5 °C. Tri-n-butylphosphine (13.30 mL, 53.19 mmol) was added. Then, a solution of 1,1'-(azodicarbonyl)piperidine (14.80 g, 58.62 mmol) in Me-THF (120 mL)
 20 was added dropwise over 25 min and the solution was stirred for 5 min more at this temperature. The cooling bath was removed and the solution was stirred at rt for 18 h. The

reaction mixture was poured onto a 10% aqueous solution of K_2CO_3 and extracted with DCM. The organic layer was decanted, dried over $MgSO_4$, filtered and evaporated to dryness. The residue (20 g) was taken up with heptane and the insoluble material was removed by filtration. The filtrate was concentrated to 20 mL and purified by column chromatography on silica gel (irregular SiOH, 80 g, mobile phase: heptane/EtOAc, gradient from 100:0 to 88:12). The pure fractions were collected and evaporated to dryness to give 10.80 g of intermediate 9 (94% yield).

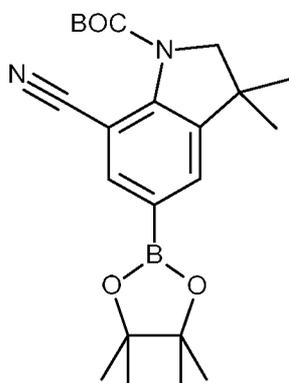
Preparation of intermediate 10 and intermediate 10':



intermediate 10 intermediate 10'

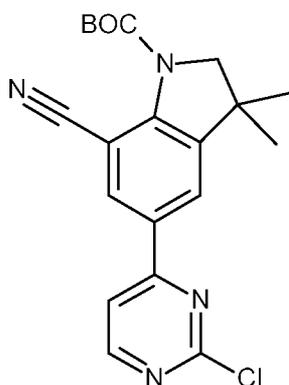
A mixture of intermediate 9 (10.80 g, 25.11 mmol), sodium acetate (5.35 g, 65.28 mmol), sodium formate (4.44 g, 65.28 mmol) and tetraethylammonium chloride (5.20 g, 31.38 mmol) in DMF (100 mL) was degassed by sonication for 10 min under a stream of Ar. $Pd(OAc)_2$ (563.00 mg, 2.51 mmol) was added and the resulting orange suspension was stirred at 85 °C for 4 h. The residue was diluted with EtOAc and water, then filtered through a pad of celite[®]. The organic layer was decanted, washed successively with a saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The resulting residue (8.3 g) was dissolved in CH_3CN (230 mL) and NBS (4.47 g, 25.11 mmol) was added. The reaction mixture was heated at 55 °C for 18 h.

The reaction mixture was evaporated to dryness and the residue was taken up with heptane/DCM. The precipitate was filtered off and the filtrate (10 g) was purified by silica gel chromatography (irregular SiOH, 120 g, injection in DCM, mobile phase: heptane/EtOAc, gradient from 100:0 to 80:20). The pure fractions were collected and evaporated to dryness to give 4 g of intermediate 10 (45% yield).



Preparation of intermediate 11:

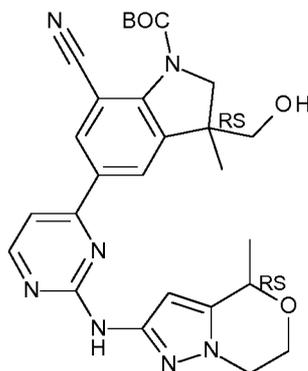
[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (243.00 mg, 0.30 mmol) was added to a solution of intermediate 10 (2.09 g, 5.95 mmol), bis(pinacolato)diboron (1.90 g, 7.44 mmol) and potassium acetate (1.75 g, 17.85 mmol) in 1,4-dioxane (45 mL) and the reaction mixture was heated for 18 h at 85 °C. The reaction mixture was diluted with EtOAc and filtered through a pad of celite®. The filtrate was washed with water, and the organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue was crystallized from DiPE and the precipitate was filtered and dried to give 1.85 g of intermediate 11 (78% yield).



Preparation of intermediate 12:

A degassed suspension of intermediate 11 (1.12 g, 2.81 mmol), 2,4-dichloropyridine (502.00 mg, 3.37 mmol), Pd(PPh₃)₄ (162.00 mg, 0.14 mmol) and a 2M solution of Na₂CO₃ (4.20 mL, 8.14 mmol) in 1,4-dioxane (24 mL) was heated to 85 °C for 18 h. The reaction mixture was partitioned between DCM and saturated aqueous NaHCO₃. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue (2 g) was purified by column chromatography on silica gel (irregular SiOH, 40 g, mobile phase: heptane/EtOAc, gradient from 70:30 to 50:50). The pure fractions were collected and evaporated to dryness to give 933 mg of intermediate 12 (86% yield, 85% purity based on LC/MS).

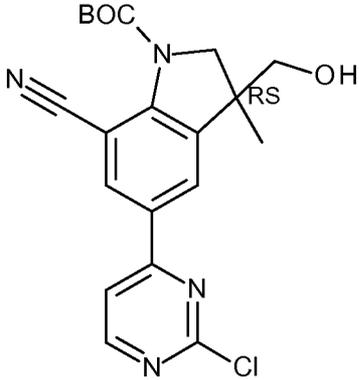
Example A5b

Preparation of intermediate 33b:

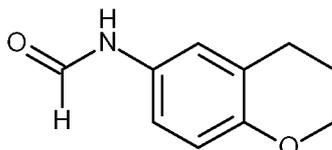
TBAF (1M in THF) (0.28 mL, 0.28 mmol) was added to a solution of intermediate 32b (180.00 mg, 0.14 mmol) in THF (1 mL). The mixture was stirred at rt for 17 h. The reaction mixture was poured into EtOAc (5 mL) and water (5 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The organic layers were combined, dried over Na₂SO₄, filtered and evaporated under vacuo to give 100 mg of intermediate 33b (61% yield; mixture of 4 diastereoisomers) which was used in the next step without any further purification.

The intermediates in the table below were prepared by using an analogous method as described for the preparation of intermediate 33b starting from the respective starting materials. Minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

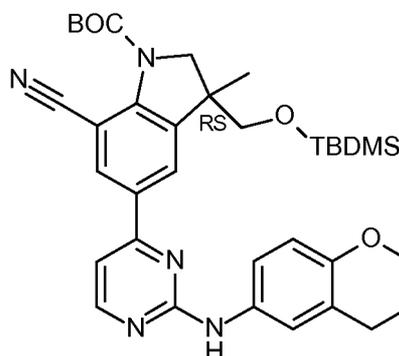
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 40b	<p>From intermediate 39b</p>	180	50
		30% purity based on LC/MS	Procedure with 1.2 equiv. of TBAF

Intermediate 46b	 <p data-bbox="686 712 949 745">From intermediate 6</p>	2100	90 Procedure with 1.2 equiv. of TBAF
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Example A6a

Preparation of intermediate 13:

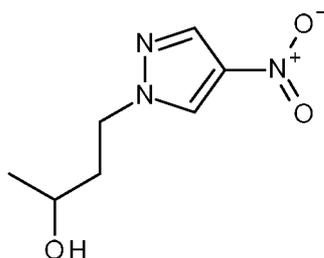
Phenyl formate (405.00 μ L, 3.71 mmol) was added dropwise to a stirred solution of 3,4-dihydro-2H-1-benzopyran-6-amine (369.00 mg, 2.47 mmol) in DCM (7.2 mL) at rt. After addition, the reaction mixture was stirred at room temperature for 18 h. The solution was purified by silica gel chromatography (Irregular SiOH 40 μ m, mobile phase gradient: from 100% DCM, 0% MeOH, 0.1% NH_4OH to 94% DCM, 6% MeOH, 0.1% NH_4OH). The pure fractions were combined and the solvent was evaporated under vacuum to give 445 mg of intermediate 13 (quant. yield).

Preparation of intermediate 14:

NaH (60% dispersion in mineral oil) (81.53 mg, 2.04 mmol) was added portionwise to a stirred solution of intermediate 13 (120.40 mg, 0.68 mmol) in DMF (6.6 mL) under N_2 atmosphere at rt. The mixture was stirred at rt for 20 min. This suspension was added to a solution of intermediate 6 (280.00 mg, 0.54 mmol) in DMF (3.30 mL). The mixture was

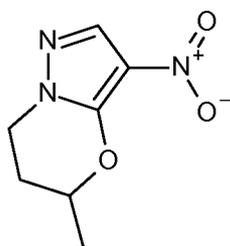
stirred at rt for 1.5 h. The reaction mixture was poured onto ice and 10% NH₄Cl aqueous solution, stirred for 30 min and the precipitate was filtered off and dried under vacuum. The precipitate was purified by chromatography on silical gel (Irregular SiOH, 40 μm, mobile phase: 70% Heptane, 30% EtOAc). The pure fractions were combined and the solvent was evaporated to dryness under vacuum to give 129 mg of intermediate 14 (38% yield).

Example A6b



Preparation of intermediate 7b:

10 In a sealed tube, 4-nitro-1H-pyrazole (3.31 g, 29.25 mmol) and methyl vinyl ketone (4.10 g, 58.495 mmol) in EtOH (34.16 mL) were stirred at 140 °C for 12 h. NaBH₄ (2.21 g, 58.50 mmol) was added dropwise to the previous solution at rt. The reaction mixture was stirred for 1 hour and poured into ice and water. The solution was acidified with 3N aqueous solution of HCl and the aqueous layer was extracted twice with DCM. The
15 combined organic layers were combined, dried over MgSO₄, filtered and evaporated. The crude residue was purified via silica gel chromatography (Stationary phase: irregular SiOH 15-40 μm, 120 g, mobile phase gradient: from 100% DCM to 95% DCM, 5% MeOH (2% NH₄OH)) to give 4.7 g of intermediate 7b (87% yield).



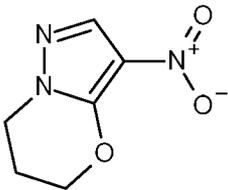
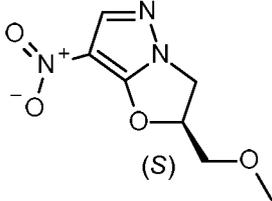
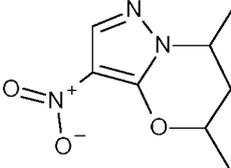
20 Preparation of intermediate 8b:

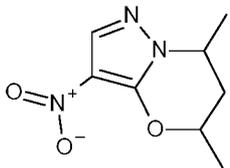
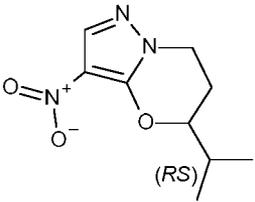
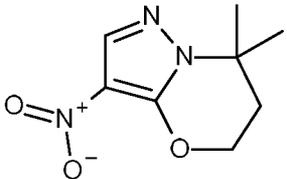
Lithium bis(trimethylsilyl)amide (1M in THF) (12.31 mL, 12.31 mmol) was added dropwise to a stirred solution of intermediate 7b (950.00 mg, 5.13 mmol) in THF (15.39 mL) at -70 °C under nitrogen. The reactive mixture was stirred at -70 °C for 2 hours and hexachloroethane (1.46 g, 6.16 mmol) in THF (3.08 mL) was added dropwise. The
25 reactive mixture was allowed to stir at rt for 20 h. Water and NH₄Cl were added and the

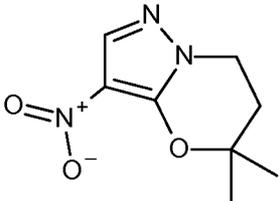
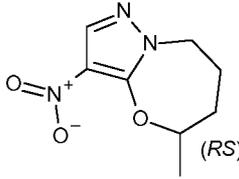
solution was extracted with DCM. The organic layer was dried over MgSO₄, filtered and evaporated. The crude residue was purified via silica gel chromatography (Stationary phase: irregular SiOH 15-40 μm, 24 g, mobile phase: 100% DCM) to give 363 mg of intermediate 8b (39% yield).

5

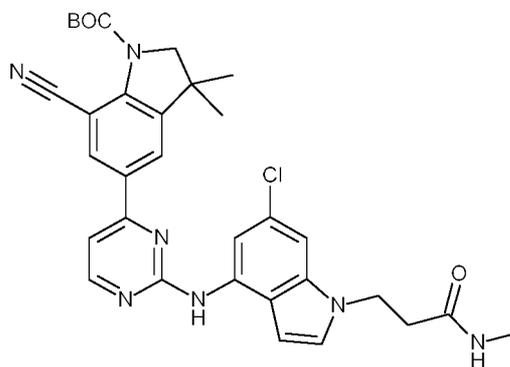
The intermediates in the table below were prepared by using an analogous method as described for the preparation of intermediate 8b, starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 76b	 <p>From intermediate 75b</p>	737	50
Intermediate 102b	 <p>From intermediate 101b</p>	540	32
Intermediate 107b (<i>cis</i>) isolation via achiral SFC (Stationary phase: DIETHYLAMIN OPROPYL 5μm 150x21.2mm, Mobile phase: 97.5% CO ₂ , 2.5% MeOH)	 <p>CIS (mixture of (R,S) and (S,R)) From intermediate 106b</p>	610	37

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 111b <i>(trans)</i> isolation via achiral SFC (Stationary phase: DIETHYLAMIN OPROPYL 5 μ m 150x21.2mm, Mobile phase: 97.5% CO ₂ , 2.5% MeOH)	 <p>TRANS (mixture of (R,R) and (S,S))</p> <p>From intermediate 106b</p>	120	7
Intermediate 118b	 <p>(RS)</p> <p>From intermediate 117b</p>	1000	72
Intermediate 125b Isolation via preparative LC (Stationary phase: irregular SiOH 15-40 μ m 40g Grace, Mobile phase: gradient from 80% heptane, 20% AcOEt to 50% heptane, 50% AcOEt)	 <p>From intermediate 124b + 124b'</p>	294	50

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 129b Isolation via preparative LC (Stationary phase: irregular SiOH 15-40 μ m 40g Grace, Mobile phase: gradient from 80% heptane, 20% AcOEt to 50% heptane, 50% AcOEt)	 <p>From intermediate 124b + 124b'</p>	115	19
Intermediate 148b	 <p>From intermediate 147b</p>	590	60

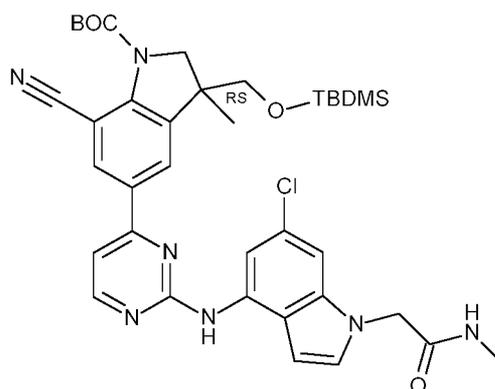
Example A6c

Preparation of intermediate 15c:

A degassed suspension of intermediate 12 (100.00 mg, 0.26 mmol), intermediate 14 (81.81 mg, 0.29 mmol based on 88% purity determined by LC/MS), Pd(OAc)₂ (5.84 mg, 0.026 mmol), BINAP (16.19 mg, 0.026 mmol) and Cs₂CO₃ (254.14 mg, 0.70 mmol) in 1,4-

dioxane (3 mL) was heated to 85 °C for 30 min. The reaction mixture was partitioned between DCM and water. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness to give 156 mg of intermediate 15c (quantitative yield, brown oil) which was directly engaged in the next step without any further purification.

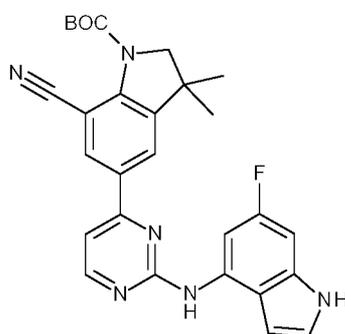
5



Preparation of intermediate 21c:

To a solution of intermediate 6 (0.66 g, 1.28 mmol), intermediate 20c (0.34 g, 1.41 mmol), Pd(OAc)₂ (0.029 g, 0.128 mmol) and Cs₂CO₃ (1.25 g, 3.84 mmol) in 1,4-dioxane (24 mL) was added BINAP (79.80 mg, 0.128 mmol) and the reaction mixture was heated for 3 h at 95 °C. The reaction mixture was then diluted with ethyl acetate and washed with water and brine. The organic layer was dried with sodium sulfate and concentrated under vacuo. The residue was purified by chromatography over silica gel (15-40 μm, 40 g, eluent: DCM/MeOH: 100/0 to 99/1). The pure fractions were combined and the solvent was evaporated to give 817 mg of intermediate 21c (89% yield).

15



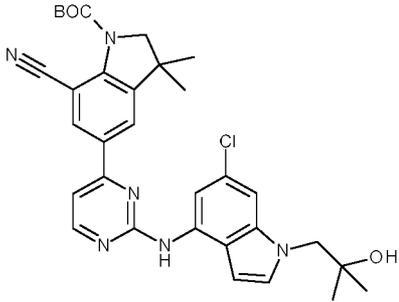
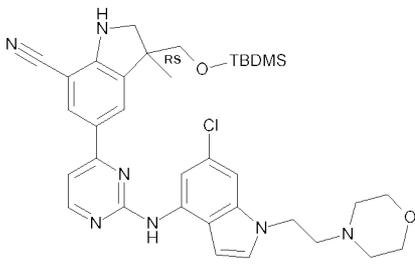
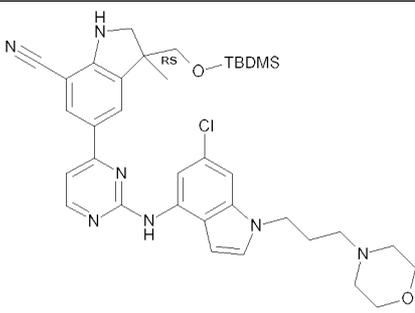
Preparation of intermediate 35c:

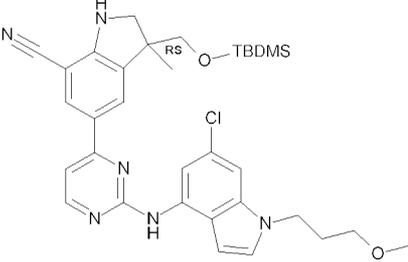
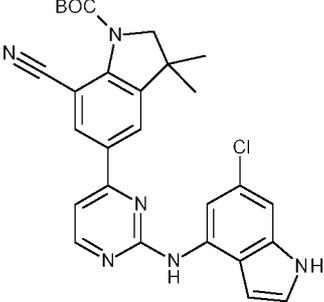
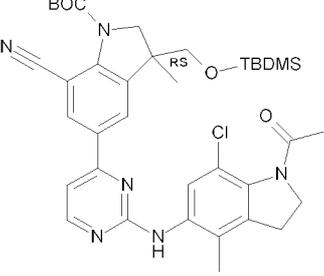
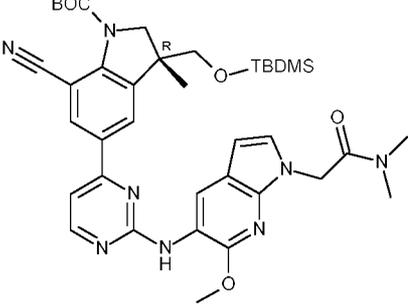
To a solution of intermediate 12 (233.00 mg, 0.61 mmol), intermediate 34c (100.00 mg, 0.67 mmol), Pd(OAc)₂ (137.00 mg, 0.061 mmol) and Cs₂CO₃ (592.00 mg, 1.82 mmol) in 1,4-dioxane (5 mL) was added BINAP (38.00 mg, 0.061 mmol) and the reaction mixture was heated for 3 h at 95 °C. The reaction mixture was then diluted with ethyl acetate and washed with water and brine. The organic layer was dried with sodium sulfate and

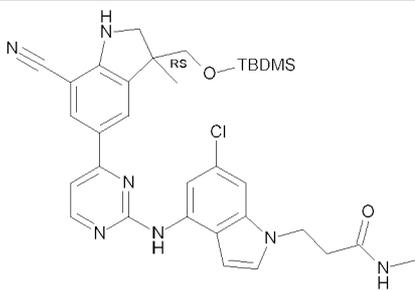
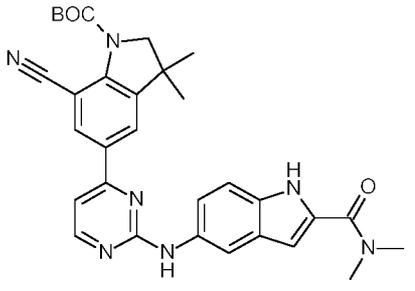
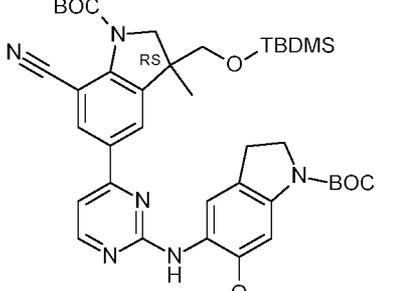
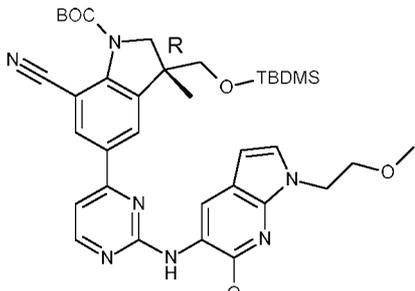
20

concentrated in vacuo to give 397 mg of intermediate 35c (quant. yield, 76% purity based on LC/MS, dark black foam) which was used in the next step without any further purification.

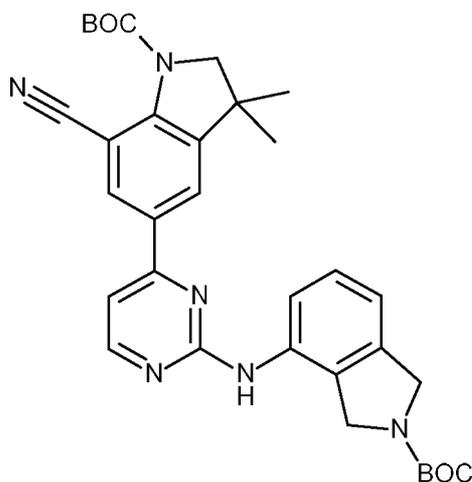
5 The intermediates in the table below were prepared by using an analogous method starting from the respective starting materials. Minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 18c	 <p>From intermediate 12 and 17c</p>	153 (79% purity based on LC/MS) <i>brown oil</i>	Quant. with T = 85 °C for 30 mn
Intermediate 25c	 <p>From intermediate 7 and intermediate 24c</p>	70 (90% purity based on LC/MS) <i>yellow solid</i>	34
Intermediate 28c	 <p>From intermediate 7 and intermediate 27c</p>	465 (85% purity based on LC/MS) <i>yellow solid</i>	96 Heat time: 1h00

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 31c	 <p data-bbox="544 734 863 819">From intermediate 7 and intermediate 30c</p>	470	51 Heat time: 1h30
Intermediate 33c	 <p data-bbox="544 1160 935 1205">From intermediate 12 and 32c</p>	384 (73% purity based on LC/MS)	Quant. <i>dark black foam</i>
Intermediate 40c	 <p data-bbox="544 1518 919 1554">From intermediate 6 and 39c</p>	1250 (76% purity)	Quantitative <i>brown foam</i>
Intermediate 45c	 <p data-bbox="544 1899 887 1991">From intermediate 6R and intermediate 44c</p>	690 (95% purity based on ¹ H NMR)	80 Procedure with T = 100 °C and 2.0 equiv. of Cs ₂ CO ₃ <i>white solid</i>

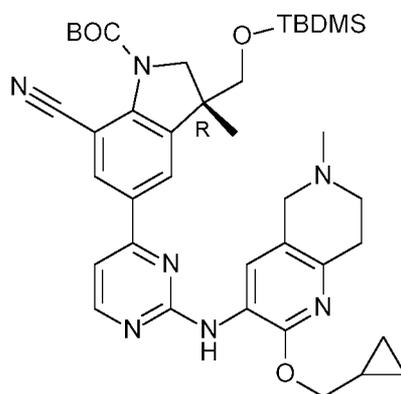
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 47c	 <p>From intermediate 7 and 14c</p>	510 (55% purity based on ¹ H NMR)	44
Intermediate 50c	 <p>From intermediate 12 and 49c</p>	200	3 Based on a purity of 21% evaluated by LC/MS Procedure with 2.5 equiv. of Cs ₂ CO ₃
Intermediate 53c	 <p>From intermediate 6 and 52c</p>	440	69 Procedure with 2.5 equiv. of Cs ₂ CO ₃
Intermediate 57c	 <p>From intermediate 6R and 56c</p>	250	77 Procedure with 2 equiv. of Cs ₂ CO ₃ and T = 100°C

Example A7a

Preparation of intermediate 16:

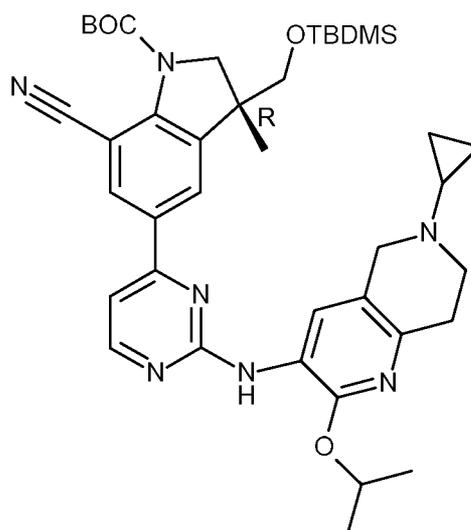
In a sealed tube, BINAP (40.45 mg, 0.07 mmol) was added to a solution of intermediate 12 (250.00 mg, 0.65 mmol), tert-butyl 4-aminoisindoline-2-carboxylate (228.29 mg, 0.97 mmol), Pd(OAc)₂ (14.58 mg, 0.065 mmol) and Cs₂CO₃ (635.94 mg, 1.95 mmol) in 1,4-dioxane (12.5 mL) and the reaction mixture was heated at 110 °C using one single mode microwave (biotage[®] Initiator EXP 60) with a power output ranging from 0 to 400 W for 20 min. The reaction mixture was cooled to rt, diluted with DCM and poured onto water. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (Irregular SiOH, 40 g, mobile phase gradient: from 0% NH₄OH, 0% MeOH, 100% DCM to 0.5% NH₄OH, 5% MeOH, 95% DCM). The pure fractions were collected and evaporated to dryness to give 378 mg of intermediate 16 (quant. yield).

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Preparation of intermediate 148:

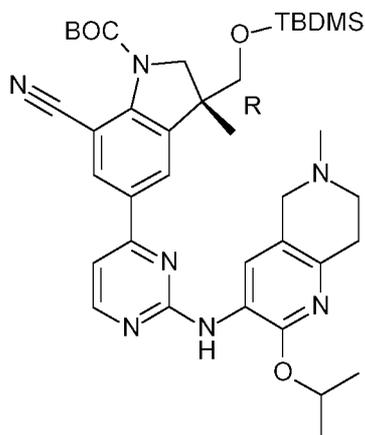
In a sealed tube, intermediate 6R (291.04 mg, 0.57 mmol), intermediate 147 (145.00 mg, 0.62 mmol), Pd(OAc)₂ (12.68 mg, 56.50 μmol), BINAP (35.18 mg, 56.50 μmol) and

Cs₂CO₃ (0.46 g, 1.41 mmol) in 1,4-dioxane (9.31 mL) were 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. The mixture in a sealed tube was then stirred at 125 °C using one single mode microwave (biotage[®] Initiator EXP 60) with a power output ranging from 0 to 400 W for 45 min. The reaction mixture was poured onto water and DCM. The mixture was filtered over celite[®], decanted and the organic layer was dried over MgSO₄, filtered and evaporated under vacuum. The residue was purified by chromatography on silical gel (Irregular SiOH 40 μm, 40 g, mobile phase gradient: from 100% DCM to 95% DCM, 5% MeOH, 0.5% NH₄OH). The pure fractions were combined and the solvent was evaporated to give 85 mg of intermediate 148 (21% yield).



Preparation of intermediate 194:

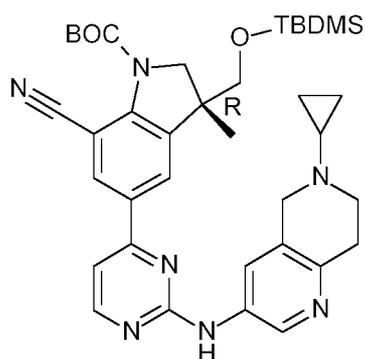
Intermediate 6R (132.5 mg, 0.257 mmol), intermediate 193 (70 mg, 0.283 mmol), Pd(OAc)₂ (5.78 mg, 25.73 μmol), BINAP (16 mg, 25.73 μmol) and Cs₂CO₃ (209 mg, 0.64 mmol) in 1,4-dioxane (4.24 mL, 49.72 mmol) in a sealed tube were stirred at 120°C using one single mode microwave (Anton Paar) with a power output ranging from 0 to 900 W for 30 min. The reaction mixture was poured onto water and DCM. The mixture was filtered over a pad of celite[®], decanted and the organic layer was dried over MgSO₄, filtered and evaporated. The residue (203mg) was purified by silica gel chromatography (Irregular SiOH 40μm 24g; Mobile phase from 100% DCM to 95% DCM, 5% MeOH, 0.5% NH₄OH). The fractions containing the product were combined and the solvent was evaporated to give 130mg (70%) of intermediate 194.



Preparation of intermediate 198:

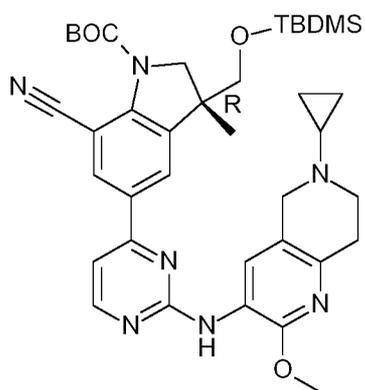
Intermediate 198 was

prepared using a similar protocol to the one used for the preparation of intermediate 148 starting from intermediate 6R and intermediate 197 (900 mg; 83%).



5 Preparation of intermediate 202:

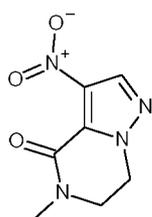
Intermediate 202 was prepared using a similar protocol to the one used for the preparation of intermediate 194 starting from intermediate 6R and intermediate 201 (130 mg; 43%).



10 Preparation of intermediate 206:

Intermediate 206 was prepared using a similar protocol to that used for the preparation of intermediate 194 starting from intermediate 6R and intermediate 205 (93 mg; 49%).

5 Example A7b

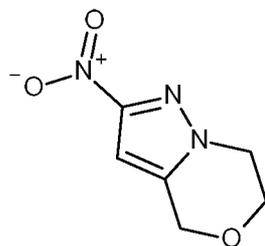


Preparation of intermediate 14b:

2-(methylamino)ethanol (2.00 g, 26.63 mmol) and 4-nitro-1H-pyrazole-3-carboxylic acid (3.54 g, 22.52 mmol) in toluene (24.44 mL) were stirred at 15 °C. SOCl₂ (4.52 mL, 62.28 mmol) was slowly added followed by DMF (171.44 μL, 2.21 mmol). The reaction mixture was stirred at 55 °C for 10 minutes then 70 °C for 18 h. Solvents were evaporated. The residue was taken up into DMF (20.62 mL) and TEA (16.66 mL) was added slowly. The reaction mixture was stirred at rt for 12 h. Water was added and the mixture was extracted twice with EtOAc, dried over MgSO₄, filtered and evaporated. The crude residue was purified via silica gel chromatography (Stationary phase: irregular SiOH 15-40 μm, 80 g, mobile phase gradient: from 100% DCM to 97% DCM, 3% MeOH (+ 10% NH₄OH)) to give 1.96 g of intermediate 14b (38% yield).

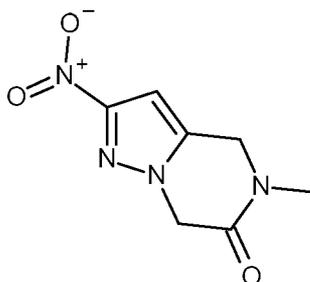
The intermediates in the table below were prepared by using an analogous method as described for the preparation of intermediate 14b, starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 48b	<p>From 2-(methylamino)ethanol and 3-nitro-1H-pyrazole-5-carboxylic acid</p>	743	50



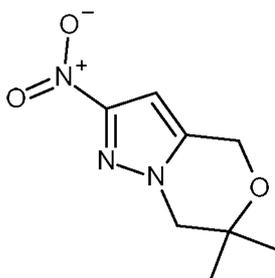
Preparation of intermediate 37b:

5 K_2CO_3 (579.60 mg, 4.20 mmol) was added into a mixture of intermediate 36b (500.00 mg, 1.60 mmol) in CH_3CN (3 mL) and the resulting solution was stirred at 80 °C for 8 h. The mixture was filtered and evaporated under vacuo to give 400 mg of intermediate 37b (66% yield, 45% purity based on LC/MS) which was used in the next step without further purification.



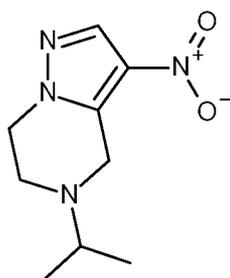
Preparation of intermediate 44b:

10 Intermediate 43b (3.60 g, 7.58 mmol) and methylamine (2M in THF) (37.9 mL, 75.8 mmol) in a sealed tube were stirred at 75 °C for 12 h. The reaction mixture was evaporated. The residue was taken up into water, extracted with DCM and evaporated. The residue was purified by silica gel chromatography (Irregular SiOH 40 μ m, mobile phase gradient: from 0% NH_4OH , 100% DCM, 0% MeOH to 0.1% NH_4OH , 97% DCM, 3% MeOH). The pure fractions were combined and the solvent was evaporated. The crude residue was taken up into Et_2O . The solid was filtered and dried under vacuo to give 420 mg of intermediate 44b (28% yield).



Preparation of intermediate 54b:

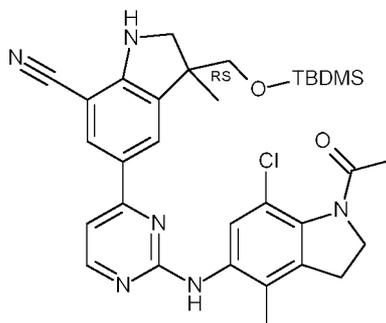
Intermediate 53b (2.15 g, 9.99 mmol) in H₂SO₄ (14.00 mL, 262.64 mmol) was stirred at 45 °C for 16 hours. The reaction mixture was cooled down to room temperature and was poured onto a mixture of ice/water and basified with K₂CO₃ powder. This mixture was extracted with DCM. The organic layer was decanted, dried over MgSO₄, filtered and the solvent was evaporated until dryness to give 1.12 g of intermediate 54b (57% yield).



Preparation of intermediate 97b:

Intermediate 96b (1.30 g, 3.96 mmol), 2-aminopropane (2.02 mL, 23.77 mmol) and TEA (1.10 mL, 7.92 mmol) in DCM (20.3 mL) were stirred at 60 °C for 6 hours. Solvent was evaporated and the crude residue was purified by silica gel chromatography (solid deposit) (Irregular SiOH 40 μm 40 g, mobile phase gradient: from 80% Heptane, 20% EtOAc to 50% Heptane, 50% EtOAc). The pure fractions were combined and the solvent was evaporated under vacuo to give 640 mg of intermediate 97b (77% yield).

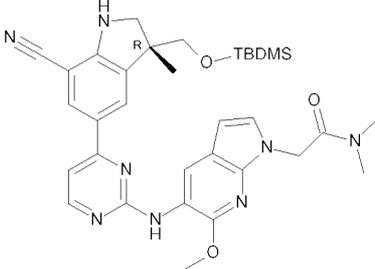
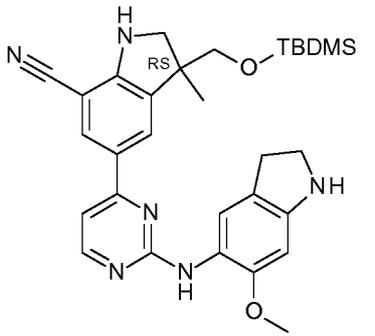
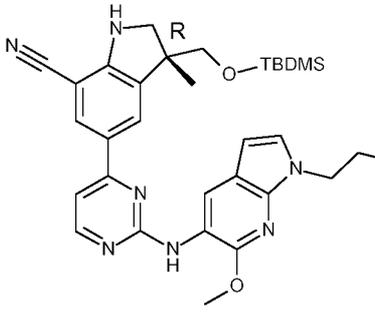
Example A7c



Preparation of intermediate 41c:

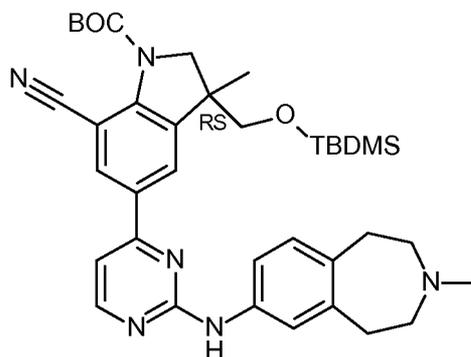
A solution of intermediate 40c (1.25 g, 1.35 mmol based on 76%) in a mixture of TFA (1 mL) and DCM (7 mL) was stirred at rt for 1 h. The mixture was basified with saturated aqueous NaHCO₃ solution. An extraction was performed with DCM. The organic layer was washed with brine, dried over MgSO₄, evaporated and purified by column chromatography on silica gel (irregular SiOH 15-40 μm, 120 g, liquid injection with DCM, mobile phase: heptane/EtOAc, gradient from 100:0 to 0:100 in 15 CV). The product containing fractions were combined and concentrated under vacuum to give 521 mg of intermediate 41c (64% yield, off-white solid).

The intermediate in the table below was prepared by using an analogous method starting from the respective starting materials. Minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 46c	 <p>From intermediate 45c</p>	390	66 <i>Yellow foam</i> Procedure with DCM/TFA (11:1, v/v)
Intermediate 54c	 <p>From intermediate 53c</p>	321	Quant. Procedure with DCM/TFA (3:1, v/v)
Intermediate 58c	 <p>From intermediate 57c</p>	96	50 Procedure with DCM/TFA (11:1, v/v) and reaction time: 30mn

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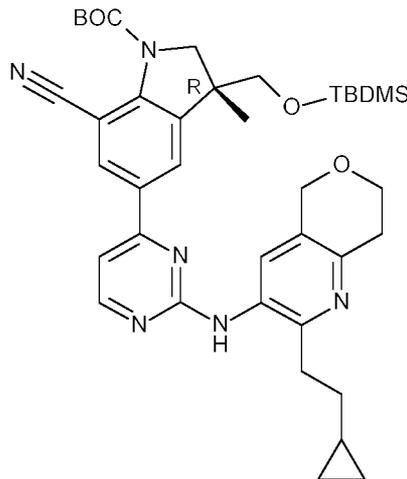
Example A8a



Preparation of intermediate 21:

In a sealed tube, a mixture of intermediate 6 (500.00 mg, 0.97 mmol), intermediate 20 (188.19 mg, 1.07 mmol) and Cs_2CO_3 (948.75 mg, 2.91 mmol) in dry 1,4-dioxane (10 mL) was purged with N_2 . Then $\text{Pd}(\text{OAc})_2$ (21.79 mg, 97.10 μmol) and BINAP (60.44 mg, 97.10 μmol) were added. The mixture was purged with N_2 and stirred at 95 °C for 17 h. The reaction mixture was diluted with EtOAc and water, and the layers were separated. The organic layer was washed with brine, dried over MgSO_4 , filtered and evaporated under reduced pressure to give 635 mg of intermediate 21 (quant. yield) which was directly engaged in the next step without further purification.

10



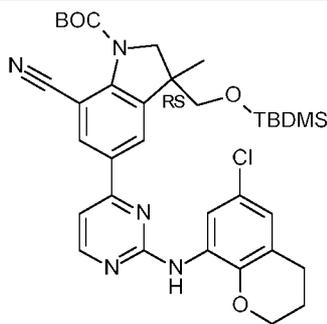
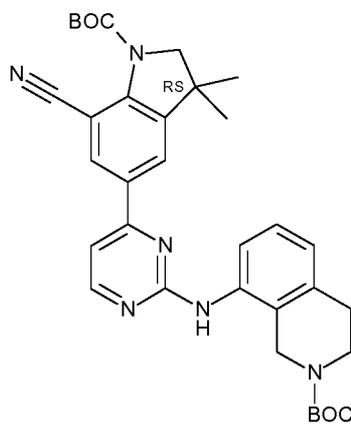
Preparation of intermediate 105:

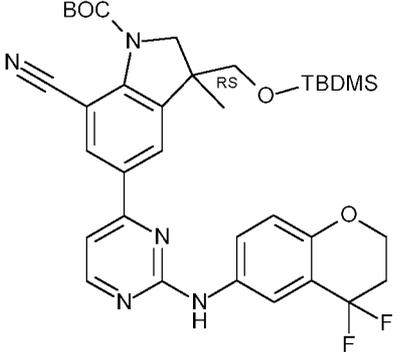
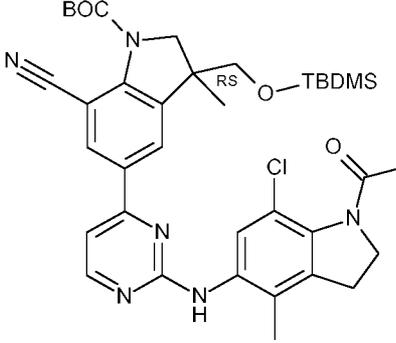
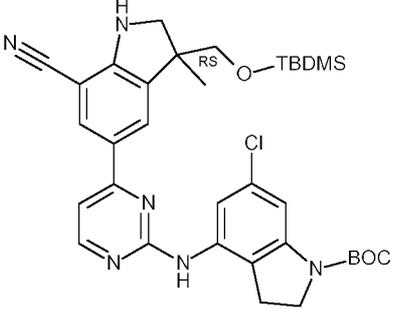
In a sealed tube, a mixture of intermediate 6R (475.61 mg, 0.79 mmol), intermediate 104 (260.00 mg, 1.19 mmol) and Cs_2CO_3 (1.03 g, 3.18 mmol) in dry 1,4-dioxane (20.2 mL) was purged with N_2 . Then $\text{Pd}(\text{OAc})_2$ (17.83 mg, 0.079 mmol) and BINAP (49.44 mg, 0.079 mmol) were added. The mixture was purged with N_2 and stirred at 90 °C for 16 h. The reaction mixture was diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc (twice). The combined organic layers were dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The crude

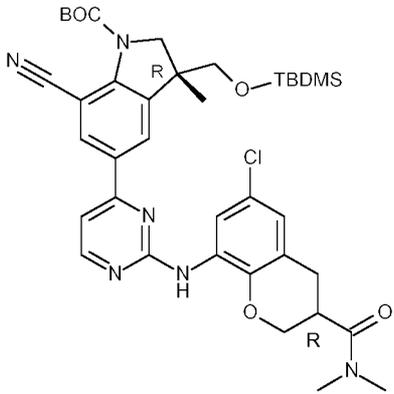
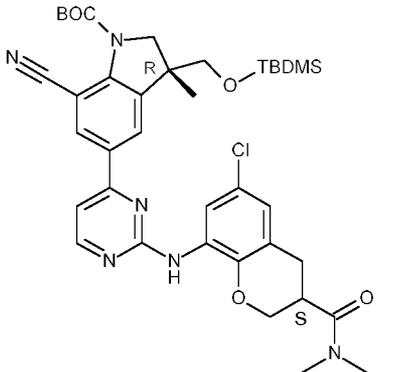
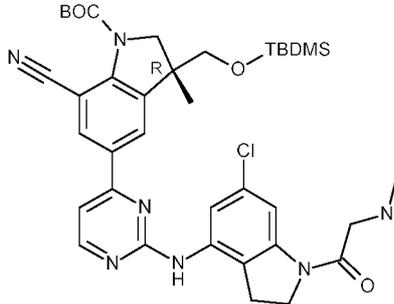
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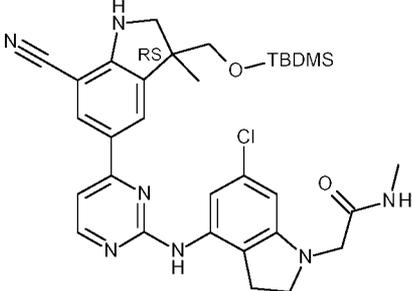
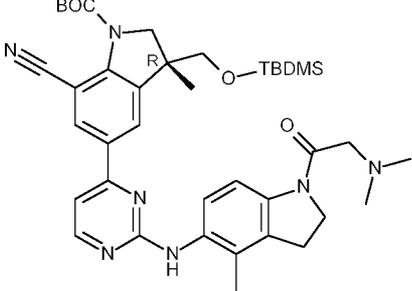
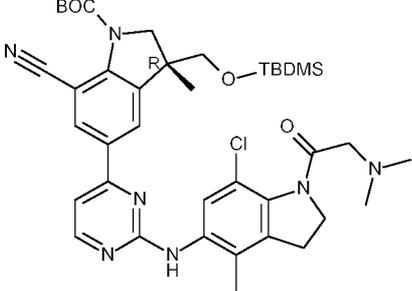
residue was purified by chromatography on silica gel (irregular SiOH, 15-40 μm , 24 g, dry loading on celite[®], mobile phase gradient: from heptane/EtOAc 95/5 to 60/40) to give 450 mg of intermediate 105 (81% yield, yellow residue).

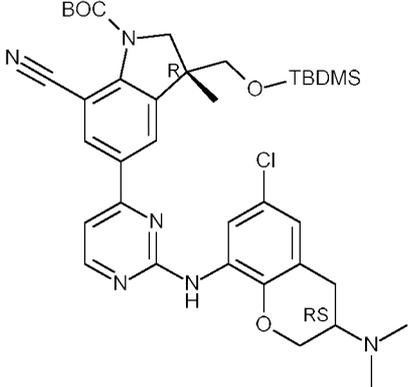
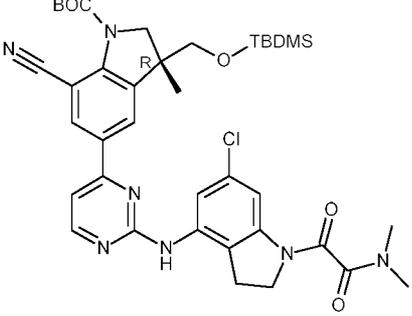
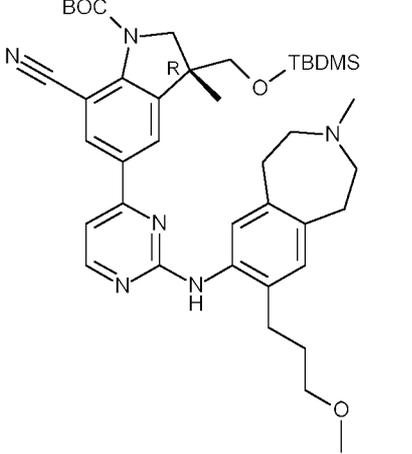
- 5 The intermediates in the table below were prepared by using an analogous method starting from the respective starting materials. The most relevant minor deviations to the referencemethod are indicated as additional information in the column 'Yield (%)'.

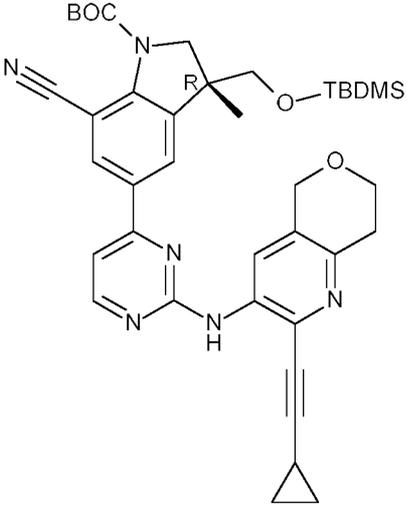
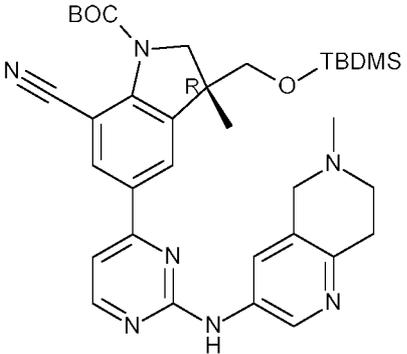
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 26	 <p>From intermediate 6 and intermediate 25</p>	688 <i>brown solid</i>	Quant.
Intermediate 36	 <p>From intermediate 12 and 2-Boc-8-amino-3,4-dihydroisoquinoline</p>	142	57

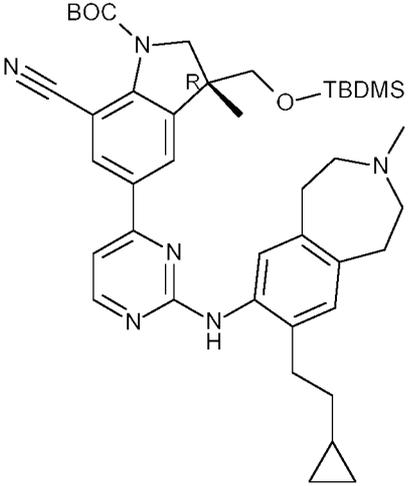
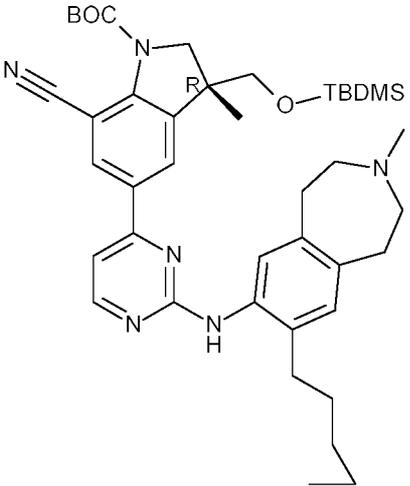
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 39	 <p data-bbox="600 786 919 869">From intermediate 6 and intermediate 38</p>	139	22 Procedure with 2.5 equiv. of Cs ₂ CO ₃
Intermediate 46	 <p data-bbox="600 1249 919 1335">From intermediate 6 and intermediate 45</p>	1250 (76% purity based on LC/MS)	Quant. <i>brown foam</i>
Intermediate 51	 <p data-bbox="600 1682 919 1760">From intermediate 7 and intermediate 50</p>	486	59 <i>brown solid</i>

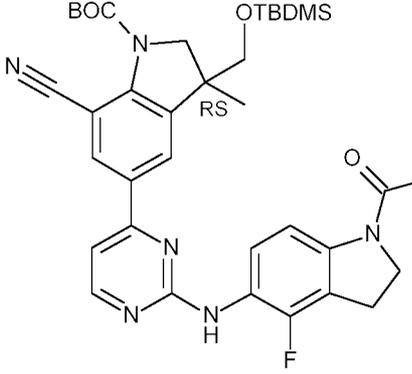
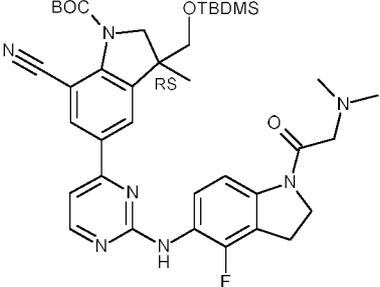
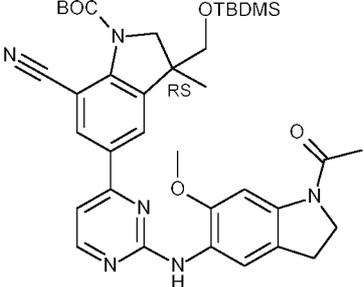
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 58	 <p data-bbox="600 815 943 898">From intermediate 6R and intermediate 57</p>	440 <i>yellow oil</i>	Quant.
Intermediate 61	 <p data-bbox="600 1301 943 1384">From intermediate 6R and intermediate 60</p>	530 <i>yellow oil</i>	Quant.
Intermediate 65	 <p data-bbox="600 1771 943 1854">From intermediate 6R and intermediate 64</p>	214 <i>yellow solid</i>	60

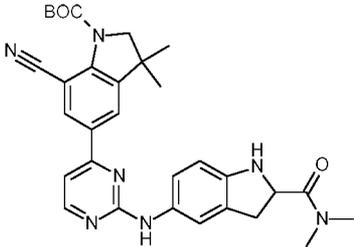
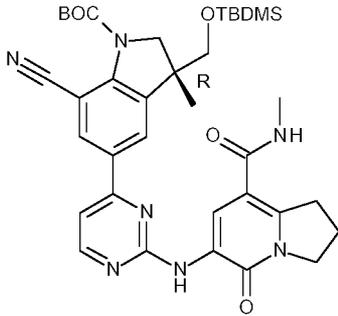
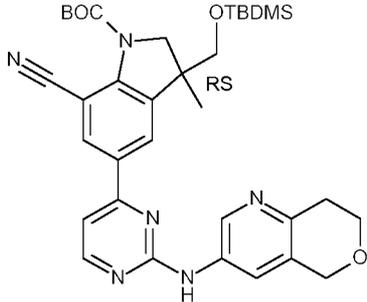
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 70	 <p data-bbox="600 725 919 801">From intermediate 7 and intermediate 69</p>	254 <i>orange solid</i>	77
Intermediate 75	 <p data-bbox="600 1189 943 1265">From intermediate 6R and intermediate 74</p>	365 (74% purity based on LC/MS) <i>brown solid</i>	Quant.
Intermediate 81	 <p data-bbox="600 1653 943 1729">From intermediate 6R and intermediate 80</p>	756 (67% purity based on LC/MS) <i>brown foam</i>	Quant.

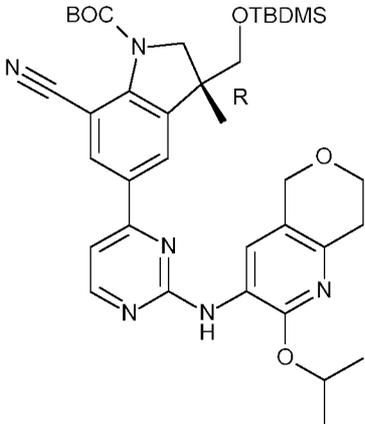
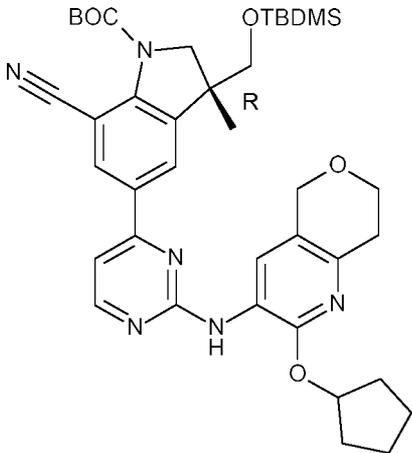
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 86	 <p>From intermediate 6R and intermediate 85</p>	860 <i>yellow oil</i>	Quant.
Intermediate 92	 <p>From intermediate 6R and intermediate 91</p>	260 <i>brown oil</i>	88
Intermediate 98	 <p>From intermediate 6R and intermediate 97</p>	1040 <i>brown oil</i>	82 With T = 90 °C

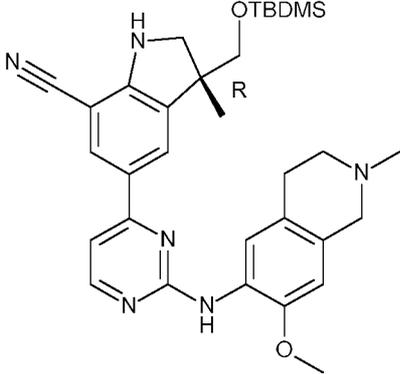
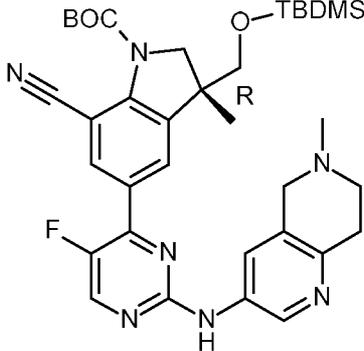
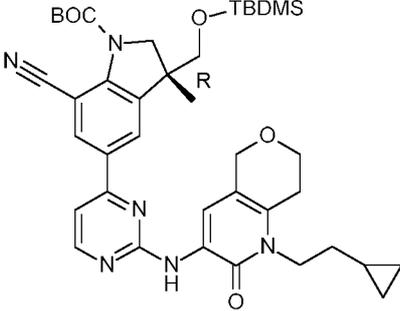
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 107	 <p data-bbox="600 987 943 1061">From intermediate 6R and intermediate 103</p>	270 <i>yellow oil</i>	62 With T = 90 °C Procedure with 4 equiv. of Cs ₂ CO ₃
Intermediate 130	 <p data-bbox="600 1464 943 1538">From intermediate 6R and intermediate 129</p>	620 <i>beige foam</i>	Quant. With T = 90 °C Procedure with 2.5 equiv. of Cs ₂ CO ₃

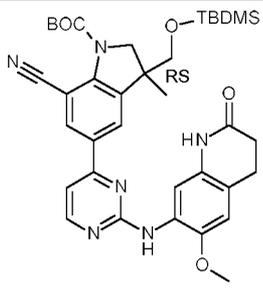
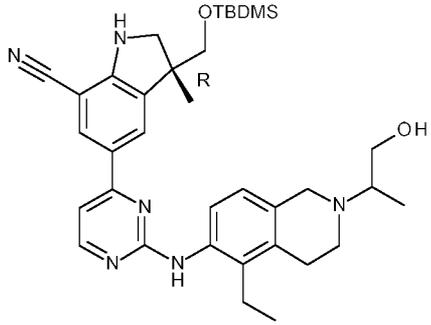
Intermediate number	Structure	Mass (mg)	Yield (%)
Mixture of intermediate 123c and 123'		1530 <i>yellow solid</i>	Quant. With T = 90°C Procedure with 4 equiv. of Cs ₂ CO ₃
	<p data-bbox="600 967 943 1043">From intermediate 6R and intermediate 122</p> <p data-bbox="600 1061 619 1088">+</p>  <p data-bbox="600 1671 943 1747">From intermediate 6R and intermediate 122'</p>	130 <i>yellow solid</i>	9

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 151	 <p data-bbox="600 853 919 931">From intermediate 6 and intermediate 150</p>	800	85 With T = 80°C
Intermediate 156	 <p data-bbox="600 1261 919 1341">From intermediate 6 and intermediate 155</p>	500	38
Intermediate 159	 <p data-bbox="600 1671 919 1751">From intermediate 6 and intermediate 158</p>	480	58 Procedure with 2.5 equiv. of Cs ₂ CO ₃

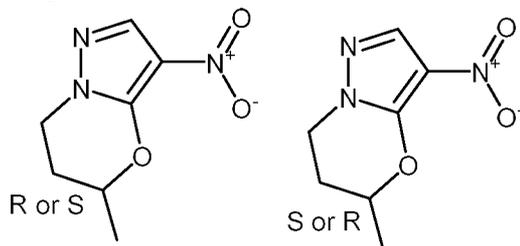
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 173	 <p data-bbox="600 719 943 797">From intermediate 12 and intermediate 172</p>	500	22% based on a purity of 59% evaluated by LC/MS Procedure with 2.5 equiv. of Cs ₂ CO ₃
Intermediate 178	 <p data-bbox="600 1361 943 1440">From intermediate 6R and intermediate 177</p>	290	92 Procedure with 2.5 equiv. of Cs ₂ CO ₃
Intermediate 180	 <p data-bbox="600 1783 919 1861">From intermediate 6 and intermediate 102</p>	978	Quant. Based on a purity of 74% evaluated by LC/MS

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 183	 <p data-bbox="600 853 943 936">From intermediate 6R and intermediate 182</p>	160	67% 78% of purity based on LC/Ms Procedure with 2 equiv. of Cs_2CO_3 and $T = 120^\circ\text{C}$
Intermediate 186	 <p data-bbox="600 1603 943 1686">From intermediate 6R and intermediate 185</p>	190	68 Procedure with 2 equiv. of Cs_2CO_3 and $T = 120^\circ\text{C}$

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 210	 <p data-bbox="600 808 943 887">From intermediate 7R and intermediate 209</p>	81	33 Procedure with 2 equiv. of Cs ₂ CO ₃ and T = 120°C
Intermediate 212	 <p data-bbox="600 1288 954 1366">From intermediate 211 and intermediate 129</p>	160	86 Procedure with 2 equiv. of Cs ₂ CO ₃ and T = 120°C
Intermediate 228	 <p data-bbox="600 1727 943 1805">From intermediate 6R and intermediate 227</p>	236	54 Procedure with 2 equiv. of Cs ₂ CO ₃ and T = 100°C

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 233	 <p>From intermediate 6 and intermediate 232</p>	980	86 Based on a purity of 86% evaluated by LC/Ms Procedure with 2.5 equiv. of Cs ₂ CO ₃
Intermediate 240	 <p>From intermediate 7R and intermediate 239</p>	39	19 Procedure with 2 equiv. of Cs ₂ CO ₃ and T = 120°C

Example A8b

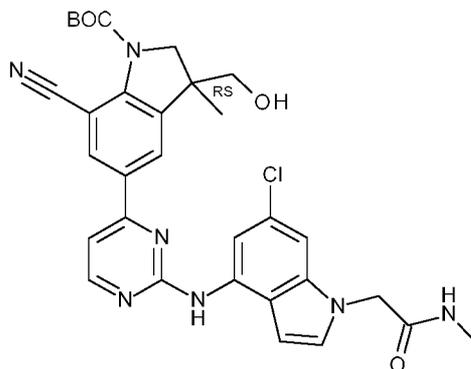
Preparation of intermediate 8b' and intermediate 8b'':

intermediate 8b' intermediate 8b''

- 5 Intermediate 8b (363 mg) was purified via chiral SFC (Stationary phase: Whelk O1 (S,S) 5 μ m 250*21.1 mm, mobile phase: 85% CO₂, 15% iPrOH). Pure fractions were collected

and evaporated to give 140 mg of intermediate 8b' (39% yield) and 145 mg of intermediate 8b'' (40% yield).

Example A8c



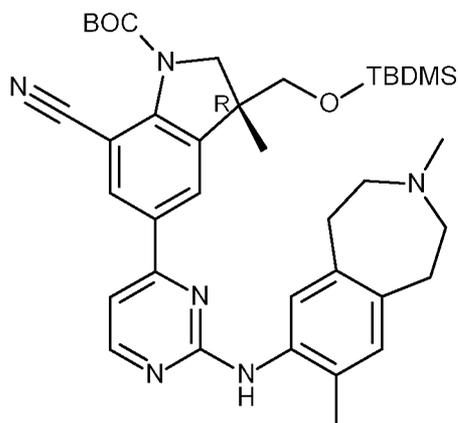
5 Preparation of intermediate 22c:

A solution of intermediate 21c (266.00 mg, 0.26 mmol based on 70% purity determined by LC/MS) and TBAF (1M in THF) (0.26 mL, 0.26 mmol) in THF (3 mL) was stirred at rt for 0.5 h. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried with Na₂SO₄ and concentrated under vacuum to give 240 mg of
 10 intermediate 22c (99% yield, 65% purity based on LC/MS, dark oil) which was directly engaged in the next step without further purification.

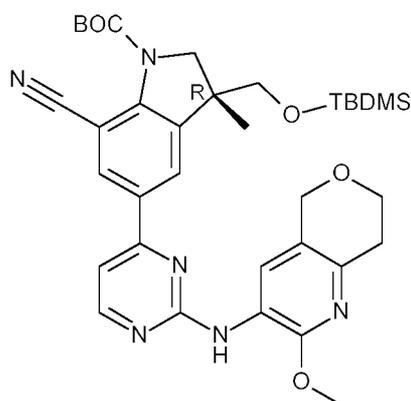
The intermediate in the table below was prepared by using an analogous method starting from the respective starting materials. Minor deviations to the referenced method are
 15 indicated as additional information in the column 'Yield (%)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 42c	<p>From intermediate 41c</p>	299	71
		<i>Off-white solid</i>	Procedure with Me-THF as solvent and 1.16 equiv. of TBAF

Example A9a

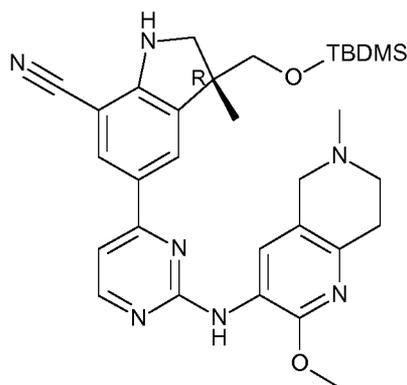
Preparation of intermediate 111:

In a sealed tube, a mixture of intermediate 6R (400.00 mg, 0.77 mmol), intermediate 110
 5 (265.97 mg, 1.40 mmol), Pd(OAc)₂ (17.43 mg, 77.65 μmol), BINAP (48.35 mg, 77.65 μmol) and Cs₂CO₃ (632.50 mg, 1.94 mmol) was purged with N₂ (three times). Dry Me-THF (8 mL) was added and the reaction mixture was degassed under N₂ for 5 min and then heated at 90 °C for 18 h. The reaction mixture was concentrated under vacuum and purified by silica gel chromatography (Irregular SiOH 15-40 μm, 40 g, dry loading on celite[®], mobile phase gradient: from DCM/MeOH (+5% aq. NH₃) 100/0 to 85/15). The
 10 pure fractions were collected and evaporated under vacuum to give 371 mg of intermediate 111 (71% yield, orange powder).

Preparation of intermediate 118:

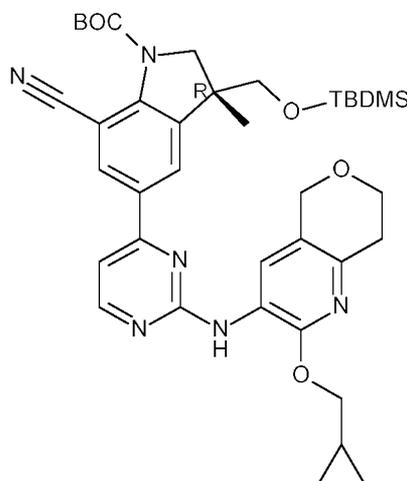
In a sealed tube, a solution of intermediate 6R (500.00 mg, 0.97 mmol), intermediate 117
 15 (279.86 mg, 1.55 mmol) and Cs₂CO₃ (790.63 mg, 2.43 mmol) in dry Me-THF (9.70 mL) was purged with N₂. Pd(OAc)₂ (21.79 mg, 97.06 μmol) and BINAP (60.44 mg, 97.06 μmol) were added and the mixture was purged with N₂ and heated at 85 °C for 3 h. After cooling down to rt, the crude was filtered on a pad of celite[®]. The cake was washed with

EtOAc and the filtrate was evaporated in vacuo. The crude residue was purified by silica gel chromatography (Irregular SiOH, 15-40 μm , 50g, liquid loading (DCM), mobile phase gradient: from Heptane 95%, EtOAc/MeOH (9:1) 5% to Heptane 70%, EtOAc/MeOH (9:1) 30%) to give 692 mg of intermediate 118 (88% yield, 81% purity based on ^1H NMR, pale brown solid).



Preparation of intermediate 139:

In a sealed tube, a suspension of intermediate 7R (300.00 mg, 0.68 mmol based on 94% purity determined by LC/MS), intermediate 138 (196.97 mg, 1.02 mmol), $\text{Pd}(\text{OAc})_2$ (15.26 mg, 0.068 mmol), BINAP (42.31 mg, 0.068 mmol) and Cs_2CO_3 (664.18 mg, 2.04 mmol) was purged with N_2 . Me-THF (6 mL) was added and the mixture was purged with N_2 and stirred at 85 $^\circ\text{C}$ overnight. The mixture was filtered on a pad of celite[®]. The cake was washed with EtOAc and the filtrate was evaporated in vacuo. The crude residue was purified by silica gel chromatography (irregular SiOH, 15-40 μm , 40 g, liquid loading (DCM), mobile phase gradient: from Heptane 75%, EtOAc/MeOH (9:1) 25% to Heptane 20%, EtOAc/MeOH (9:1) 80%) to give 340 mg of intermediate 139 (88% yield, 89% purity based on LC/MS, beige foam).

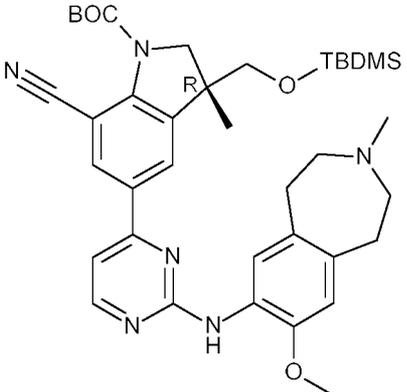
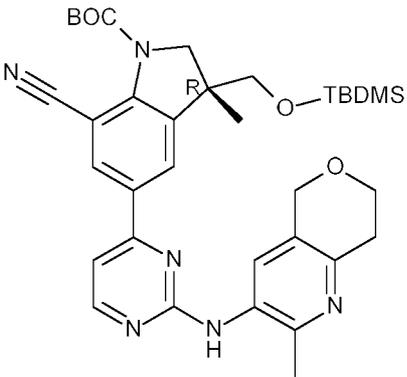
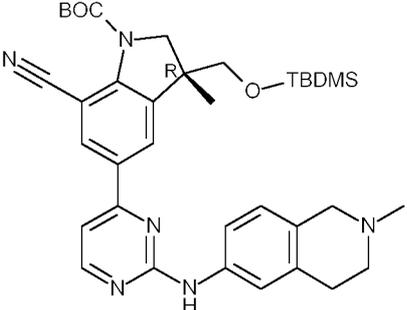


Preparation of intermediate 145:

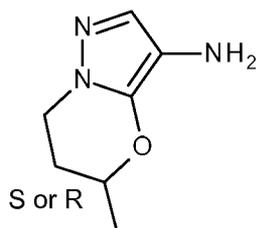
In a sealed tube, a solution of intermediate 6R (300.00 mg, 0.58 mmol), intermediate 144 (205.25 mg, 0.93 mmol) and Cs_2CO_3 (474.37 mg, 1.46 mmol) in dry Me-THF (5.80 mL) was purged with N_2 . $\text{Pd}(\text{OAc})_2$ (13.08 mg, 58.24 μmol) and BINAP (36.26 mg, 58.24 μmol) were added and the mixture was purged with N_2 and heated at 85 °C for 3 h. After cooling down to rt, the crude was filtered on a pad of celite[®]. The cake was washed with EtOAc and the filtrate was evaporated in vacuo. The crude residue was purified by silica gel chromatography (Irregular SiOH, 15-40 μm , 24g, liquid loading (DCM), mobile phase gradient: from heptane 95%, EtOAc/MeOH (9:1) 5% to heptane 70%, EtOAc/MeOH (9:1) 30%) to give 348 mg of intermediate 145 (59% yield, 69% purity based on ^1H NMR, yellow oil) which was used in the next step without further purification.

The intermediates in the table below were prepared by using an analogous method starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

15

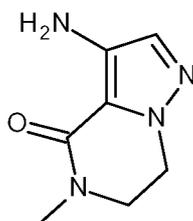
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 115	 <p data-bbox="598 828 941 907">From intermediate 6R and intermediate 114</p>	416 <i>yellow powder</i>	78 With T = 90°C
Intermediate 126	 <p data-bbox="598 1332 941 1411">From intermediate 6R and intermediate 125</p>	607 (81% purity based on LC/MS) <i>pale brown solid</i>	79
Intermediate 133	 <p data-bbox="598 1769 941 1848">From intermediate 6R and intermediate 132</p>	680 <i>yellow oil</i>	89 With T = 90°C Procedure with 4 equiv. of Cs ₂ CO ₃

A mixture of intermediate 8b' (140.00 mg, 0.76 mmol) in MeOH (8.54 mL) was hydrogenated at room temperature at atmospheric pressure for 12 h with Pd/C (10% wt) (18.04 mg, 16.95 μ mol) as catalyst. The catalyst was filtered over a pad of celite[®] which was washed with DCM and MeOH. The filtrate was evaporated to afford 117 mg of intermediate 9a (quantitative yield) which was used directly in the next reaction step.



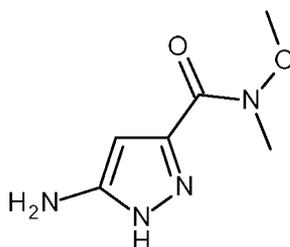
Preparation of intermediate 9b:

A mixture of intermediate 8b'' (140.00 mg, 0.76 mmol) in MeOH (8.54 mL) was hydrogenated at room temperature at atmospheric pressure for 12 h with Pd/C (10% wt) (18.04 mg, 16.95 μ mol) as a catalyst. The catalyst was filtered over a pad of celite[®] which was washed with DCM and MeOH. The filtrate was evaporated to afford 117 mg of intermediate 9b (quantitative yield) which was used directly in the next reaction step.



Preparation of intermediate 15b:

Intermediate 14b (1.16 g, 5.91 mmol) in MeOH (23.96 mL) was hydrogenated at rt with Pd/C (10% wt.) (167.74 mg, 0.16 mmol) as a catalyst under atmospheric pressure for 12 hours. The catalyst was filtered o a pad of Celite[®] and the filtrate was evaporated under reduced pressure to give 983 mg of intermediate 15b (quantitative yield).

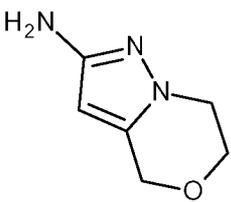
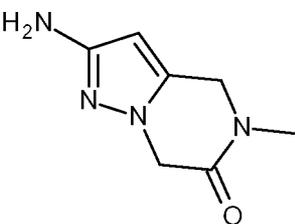
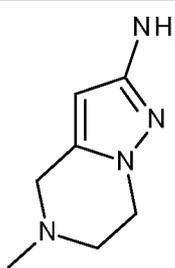


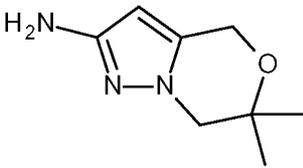
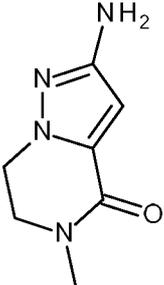
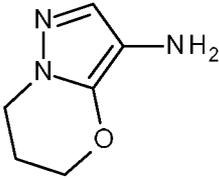
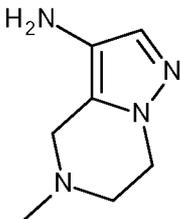
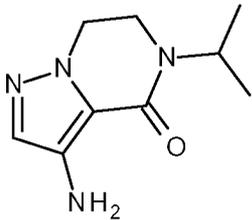
Preparation of intermediate 25b:

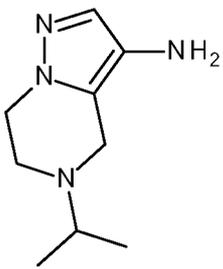
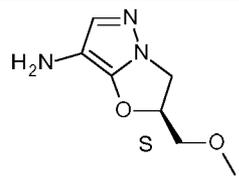
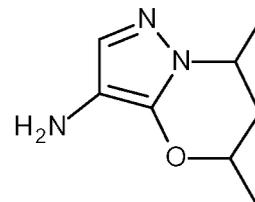
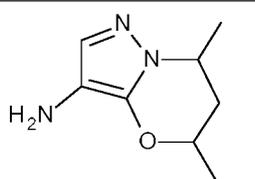
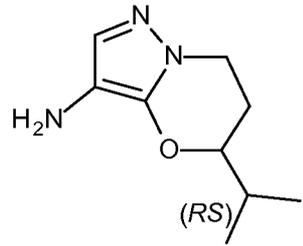
A mixture of intermediate 24b (6.20 g, 30.98 mmol) in MeOH (250 mL) and THF (250 mL) was hydrogenated (1 bar) at rt with Pd/C (10% wt) (220 mg) as a catalyst for 12 h.

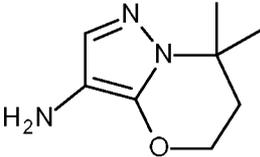
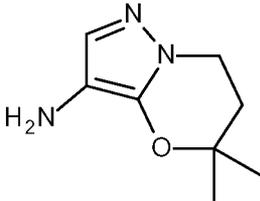
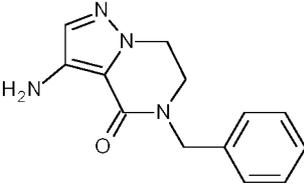
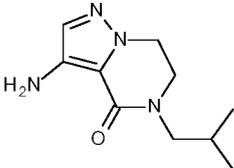
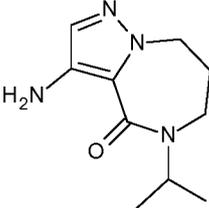
The catalyst was filtered off and the filtrate was concentrated under reduce pressure to give 4.7 g of intermediate 25b (89% yield) which was used in the next step without any further purification.

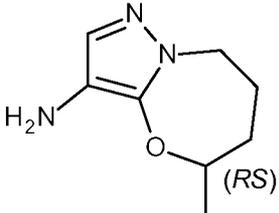
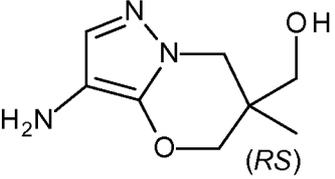
- 5 The intermediates in the table below were prepared by using an analogous method as described for the preparation of intermediate 9a, starting from the respective starting materials. Minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

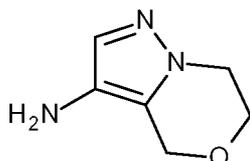
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 38b	 <p>From intermediate 37b</p>	60 88% purity based on LC/MS	36 Procedure with MeOH as solvent
Intermediate 45b	 <p>From intermediate 44b</p>	331	93 Procedure with MeOH/EtOAc, 1:1 as solvent
Intermediate 50b	 <p>From intermediate 49b</p>	576	Quantitative Procedure with MeOH as solvent

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 55b	 <p>From intermediate 54b</p>	930	98 Procedure with MeOH/EtOAc, 1:1 as solvent
Intermediate 72b	 <p>From intermediate 71b</p>	153	38 Procedure with MeOH as solvent
Intermediate 77b	 <p>From intermediate 76b</p>	329	Quantitative Procedure with MeOH as solvent
Intermediate 81b	 <p>From intermediate 80b</p>	320	87 Procedure with MeOH as solvent
Intermediate 91b	 <p>From intermediate 90b</p>	238	Quantitative With MeOH as solvent

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 98b	 <p>From intermediate 97b</p>	225	42 Procedure with MeOH as solvent
Intermediate 103b	 <p>From intermediate 102b</p>	420	92 Procedure with EtOAc as solvent
Intermediate 108b (<i>cis</i>)	 <p>CIS: mixture of (R,S) and (S,R)</p> <p>From intermediate 107b</p>	305	Quant Procedure with MeOH as solvent
Intermediate 112b (<i>trans</i>)	 <p>TRANS: mixture of (R,R) and (S,S)</p> <p>From intermediate 111b</p>	101	99 Procedure with MeOH as solvent
Intermediate 119b	 <p>(RS)</p> <p>From intermediate 118b</p>	705	86 Procedure with EtOAc as solvent at 5 bars for 48hrs

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 126b	 <p>From intermediate 125b</p>	305	99.9 Procedure with ⁱ PrOH; THF as solvent
Intermediate 130b	 <p>From intermediate 129b</p>	382	Quant Procedure with ⁱ PrOH; THF as solvent
Intermediate 134b	 <p>From intermediate 133b</p>	738	Quant Procedure for 2 hrs, with EtOH; Me-THF as solvent
Intermediate 138b	 <p>From intermediate 137b</p>	120	27 Procedure for 2 hrs, with EtOH; Me-THF as solvent
Intermediate 142b	 <p>From intermediate 141b</p>	758	Quant Procedure for 2 hrs at 3 bars, with EtOH; Me-THF as solvent

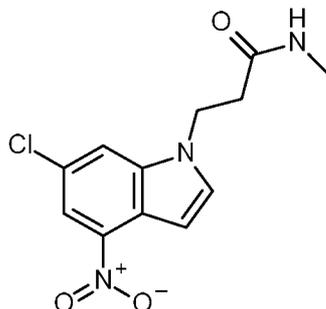
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 149b	 <p>From intermediate 148b</p>	500	Quant Procedure with ⁱ PrOH; THF as solvent
Intermediate 156b	 <p>From intermediate 155b</p>	313	Quant Procedure for 5 hrs, with ⁱ PrOH; THF as solvent



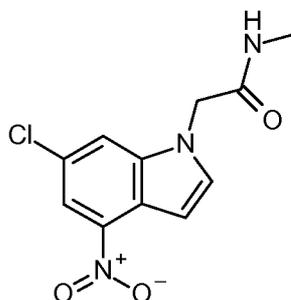
Preparation of intermediate 66b:

A mixture of intermediate 65b (750.00 mg, 4.43 mmol), iron powder (1.24 g, 22.17 mmol) and NH₄Cl (0.95 g, 18 mmol) in EtOH (26 mL) and water (26 mL) was heated at 80 °C for 2 h. The reaction mixture was cooled down to room temperature, diluted with DCM and filtered through a pad of celite. The solution was washed twice with a 10% aqueous solution of K₂CO₃. The organic layer was dried over MgSO₄, filtered and evaporated to dryness yielding to 386 mg of a first batch of crude intermediate 66b which was combined with 106 mg of another batch of crude intermediate 66v. The resulting residue was purified by silica gel chromatography (irregular silica, 15-40 μm, 40 g, liquid loading (DCM), mobile phase gradient: from 100% DCM, 0% MeOH/aq. NH₃ (9:1) to 95% DCM, 5% MeOH/aq. NH₃ (9:1), in 10 CV). The fractions containing the product were combined and evaporated to give 209 mg of intermediate 66b (23% yield, yellow brown solid).

Example A9c

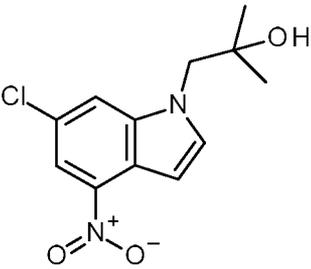
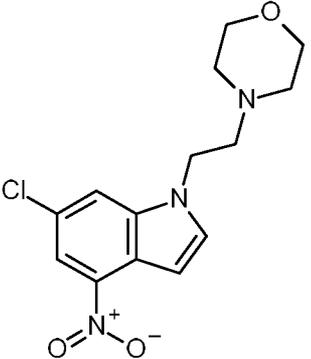
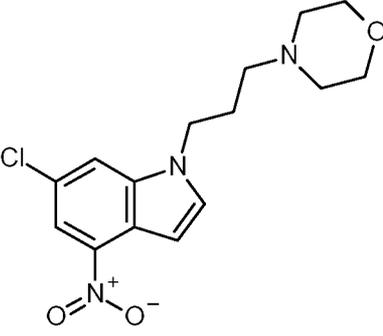
Preparation of intermediate 13c:

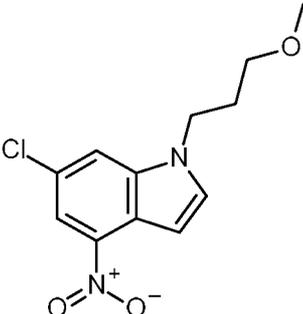
To a solution of 6-chloro-4-nitro-1H-indole (500.00 mg, 2.54 mmol) and Cs₂CO₃ (1.24 g, 3.81 mmol) in DMF (5 mL) was added 3-chloro-*N*-methylpropanamide (464.00 mg, 3.81 mmol) under N₂ and the reaction mixture was stirred at 90 °C for 0.5 h. The reaction mixture was then partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated to dryness under vacuum. The residue was triturated with cyclohexane and the solid was collected by filtration and dried under vacuum to give 687 mg of crude intermediate 13c (96% yield) which was used in the next step without any further purification.

Preparation of intermediate 19c:

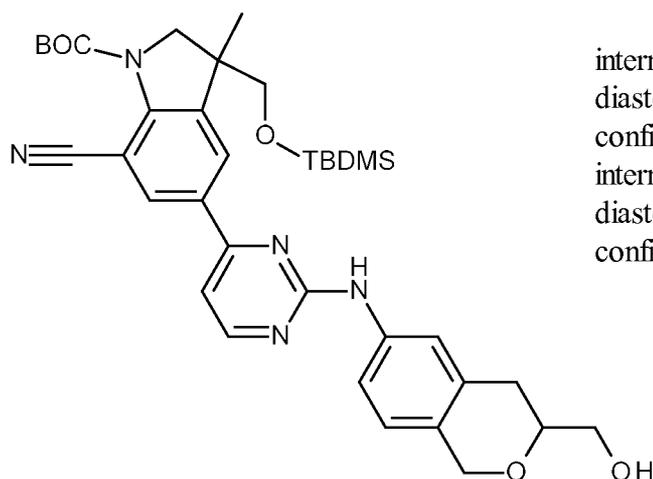
To a solution of 6-chloro-4-nitro-1H-indole (500.00 mg, 2.54 mmol) and Cs₂CO₃ (1.24 g, 3.82 mmol) in DMF (5 mL) was added 2-chloro-*N*-methylacetamide (410.00 mg, 3.82 mmol) under nitrogen and the reaction mixture was stirred at 90 °C for 0.5 h. The reaction mixture was then partitioned between ethyl acetate and water, and layers were separated. The organic layer was washed with brine, dried over sodium sulfate and concentrated in vacuo. The yellow solid residue was triturated with cyclohexane and the solid was collected by filtration and dried in vacuo to give 541 mg of intermediate 19c (79% yield, yellow solid) which was used in the next step without any further purification.

The intermediates in the table below were prepared by using an analogous method starting from the respective starting materials. Minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 16c	 <p>From 6-chloro-4-nitro-1H-indole and 1-chloro-2-methyl-propan-2-ol</p>	1860	68
Intermediate 23c	 <p>From 6-chloro-4-nitro-1H-indole and 4-(2-chloroethyl)morpholine hydrochloride</p>	108	69
Intermediate 26c	 <p>From 6-chloro-4-nitro-1H-indole and 4-(3-chloropropyl)morpholine</p>	417	Quant.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 29c	 <p>From 6-chloro-4-nitro-1H-indole and 1-chloro-3-methoxy-propane</p>	470	86
		<i>brown solid</i>	Procedure with 2.5 equiv. of Cs ₂ CO ₃

Example A10a

Preparation of intermediate 33 and intermediate 34:

intermediate 33: mixture of two diastereoisomers with unknown configuration (DIA A)
intermediate 34: mixture of two diastereoisomers with unknown configuration (DIA B)

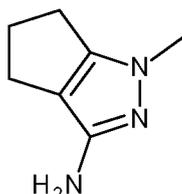
5

In a sealed tube, a mixture of intermediate 6 (547.86 mg, 1.12 mmol), intermediate 31 (400.00 mg, 2.23 mmol), Cs₂CO₃ (1.09 g, 3.35 mmol), chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl] palladium (II) (89.14 mg, 111.59 μmol) and BRETTPHOS (59.90 mg, 111.59 μmol) in THF (18 mL) was stirred at 140 °C using one single mode microwave (biotage[®] Initiator EXP 60) with a power output ranging from 0 to 400 W for 2 h. The reaction mixture was poured onto water and DCM. The mixture was filtered over celite[®], decanted and the organic layer was dried over MgSO₄, filtered and evaporated under vacuum. The residue was purified by chromatography on silical gel (Irregular SiOH 40 μm, mobile phase: 97% DCM, 3%

10

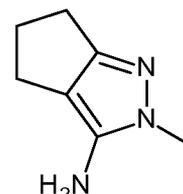
MeOH, 0.1% NH₄OH). The pure fractions were combined and the solvent was evaporated under vacuum. Another purification was performed via silica gel chromatography (Irregular bare silica 40 g, mobile phase: 60% Heptane, 5% MeOH (+10% NH₄OH), 35% EtOAc). The pure fractions were combined and the solvent was evaporated under vacuum to give 350 mg of a mixture of 4 diastereoisomers (48% yield) which was further purified by achiral SFC (Stationary phase: Chiralcel OD-H 5 μm 250*4.6 mm, mobile phase: 65% CO₂, 35% MeOH (0.3% iPrNH₂)). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 131 mg of intermediate 33 (37% yield, eluted in the first position from the column) and 146 mg of intermediate 34 (42% yield, eluted in the second position from the column).

Example A10b

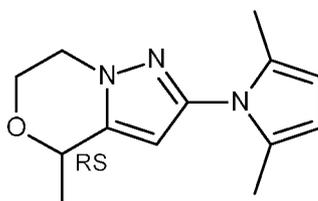


Preparation of intermediate 18b:

and intermediate 19b:



Cyclopentanone-2-carbonitrile (4.00 g, 36.65 mmol), methylhydrazine (2.12 mL, 40.32 mmol) and TEA (7.07 mL, 50.89 mmol) in toluene (26.76 mL) were heated to 120 °C for 16 hours. The reaction was cooled down to room temperature and the solvent was evaporated. The residue was taken up into Et₂O, filtered and dried under vacuo. The filtrate was evaporated and the crude residue was purified via silica gel chromatography (Stationary phase: Irregular SiOH 20-45 μm, 450 g, mobile phase gradient: from 44% Heptane, 6% MeOH (+10% NH₄OH), 50% EtOAc to 42% Heptane, 8% MeOH (+10% NH₄OH), 50% EtOAc). The pure fractions were collected and evaporated to give 205 mg of intermediate 18b (4% yield) and 545 mg of intermediate 19b (11% yield).

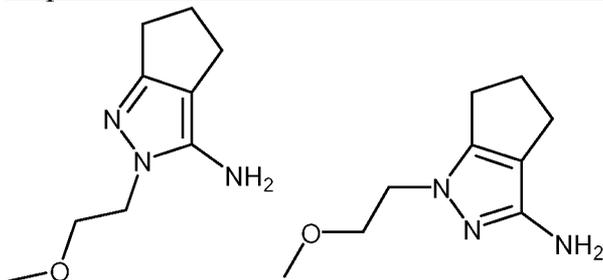


Preparation of intermediate 30b:

To a solution of intermediate 29b (2.60 g, 8.33 mmol) in CH₃CN (100 mL) was added K₂CO₃ (2.30 g, 16.67 mmol) and the mixture was refluxed for 5 h. The reaction mixture was then cooled and filtered. The filtrate was concentrated under reduced pressure. The

residue was purified by silica gel chromatography (petroleum ether/ EtOAc, 5/1) to give 683 mg of intermediate 30b (71% yield, yellow oil).

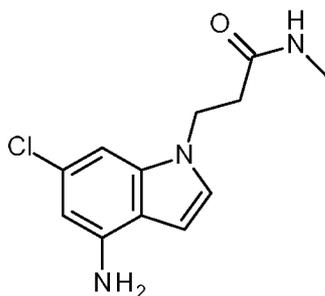
Preparation of intermediate 58b and intermediate 58b':



5 intermediate 58b intermediate 58b'

A mixture of 2-oxocyclopentanecarbonitrile (1.00 g, 9.16 mmol) and 2-methoxyethylhydrazine hydrochloride (1.50 g, 11.85 mmol) in EtOH (10.00 mL) was stirred at 90 °C for 5 hours. The reaction was cooled down to room temperature and the solvent was evaporated until dryness. The crude residue was purified by silica gel chromatography (Irregular SiOH 40 μm, 40 g, mobile phase gradient: from 99% DCM, 1% MeOH (+10% NH₄OH) to 93% DCM, 7% MeOH (+ 10% NH₄OH)). The pure fractions were collected and the solvent was evaporated until dryness to give 570 mg of intermediate 58b and intermediate 58b' mixture (86/14 evaluated by LC/MS).

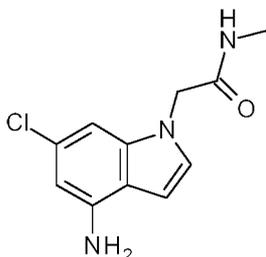
15 Example A10c



Preparation of intermediate 14c:

A suspension of intermediate 13c (687.00 mg, 2.43 mmol), ammonium chloride (521.53 mg, 9.75 mmol) and iron powder (680.81 mg, 12.19 mmol) in EtOH (10 mL) and water (10 mL) was heated at 75 °C for 2 h. The reaction mixture was filtered through celite[®] and the filtrate was concentrated to dryness under vacuum. The residue was partitioned between EtOAc and water. The organic layer was dried with Na₂SO₄ and concentrated

under vacuum to give 437 mg of crude intermediate 14c (63%, 88% purity based on LC/MS, dark foam) which was directly engaged in the next step.



Preparation of intermediate 20c:

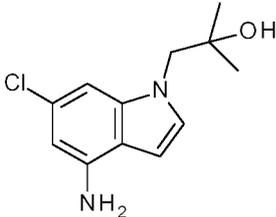
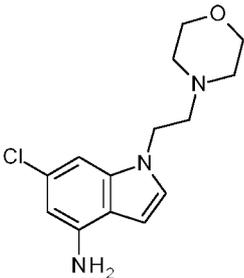
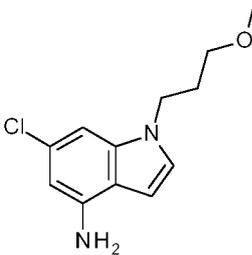
- 5 A suspension of intermediate 19c (541.00 mg, 2.02 mmol), ammonium chloride (432.00 mg, 8.08 mmol) and iron powder (564 mg, 10.11 mmol) in EtOH (10 mL) and water (10 mL) was heated at 75 °C for 1 h. The reaction mixture was filtered through celite[®] and the filtrate was concentrated in vacuo. The residue was partitioned between ethyl acetate and water. Layers were separated and the organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to give 476 mg of intermediate 20c (quant. yield) which was used in the next step without any further purification.

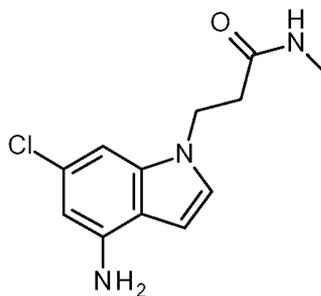


Preparation of intermediate 34c:

- 15 A suspension of 6-fluoro-4-nitro-1H-indole (1.00 g, 5.55 mmol), ammonium chloride (1.19 g, 22.21 mmol) and iron powder (1.55 g, 27.76 mmol) in EtOH (16 mL) and water (16 mL) was heated at 75 °C for 1 h. The reaction mixture was filtered through celite[®] and the filtrate was concentrated in vacuo. The residue was partitioned between ethyl acetate and water. Layers were separated and the organic layer was dried over sodium sulfate and concentrated in vacuo to give 842 mg of intermediate 34c (quant. yield, purple solid) which was used in the next step without any further purifications.

The intermediates in the table below were prepared by using an analogous method starting from the respective starting materials. Minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 17c	 <p>From intermediate 16c</p>	720 <i>brown oil</i>	88
Intermediate 24c	 <p>From intermediate 23c</p>	95 <i>orange oil</i>	97 Procedure with 4 equiv. of Iron powder and T = 90 °C
Intermediate 30c	 <p>From intermediate 29c</p>	394 <i>brown oil</i>	94 With T = 85 °C
Intermediate 32c	 <p>From 6-chloro-4-nitro-1H-indole</p>	454 <i>off-white solid</i>	Quantitative

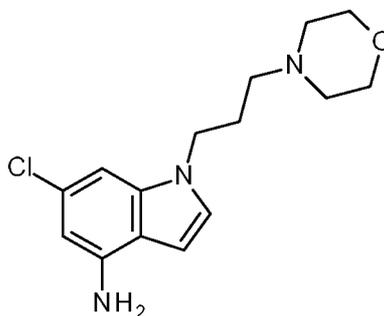


Alternative preparation of intermediate 14c:

A mixture of intermediate 13c (410.00 mg, 1.45 mmol) in titanium trichloride (18.7 mL, 21.8 mmol) and THF (40 mL) was stirred at rt for 2 h. The mixture was mixed with another reaction performed on 180mg of intermediate 13c, diluted with water, basified by addition of K₂CO₃ powder at 0 °C and then, diluted with EtOAc. The organic layer was separated, dried over MgSO₄, filtered and evaporated under vacuum. The crude product was purified by silica gel chromatography (irregular SiOH 15-40 μm, 24 g, liquid injection with DCM, mobile phase gradient: from DCM/MeOH 100/0 to 80/20). The product containing fractions were combined and concentrated under vacuum to give 280 mg of intermediate 14c (53% yield based on 590 mg of intermediate 13, yellow residue).

The intermediates in the table below were prepared by using an analogous method starting from the respective starting materials. Minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

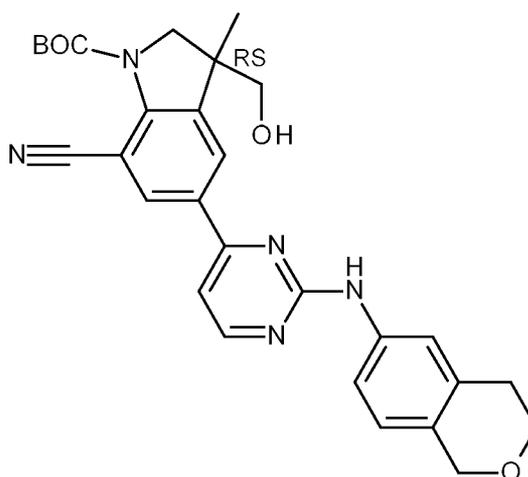
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 30c	<p>From intermediate 29c</p>	400 <i>brown solid</i>	90 Procedure with 20 equiv. of TiCl ₃
Intermediate 32c	<p>From 6-chloro-4-nitro-1H-indole</p>	118 <i>brown oil</i>	Quant. Procedure with 20 equiv. of TiCl ₃



Preparation of intermediate 27c:

In a sealed tube, a mixture of intermediate 26c (639.68 mg, 1.97 mmol) and iron powder (441.34 mg, 7.90 mmol) in 10% aqueous NH_4Cl solution (6.2 mL), EtOH (11.3 mL) and EtOAc (27.8 mL) was stirred at 90 °C for 18 h. Further Iron powder (441.34 mg, 7.90 mmol) was added and the mixture was stirred at 90 °C for 4 h. The mixture was filtered over a pad of celite[®] and was washed with EtOAc. The organic layer was washed with a saturated aqueous solution of NaHCO_3 and brine, dried over MgSO_4 , filtered and the solvent was removed under reduced pressure to give 460 mg of intermediate 27c (79%, orange oil) which was directly engaged in the next step.

Example A11a

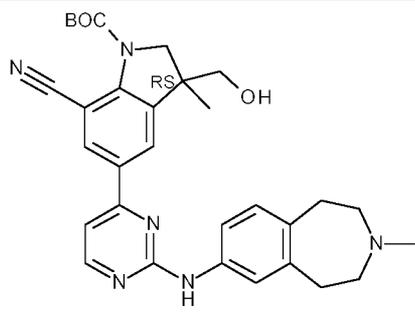
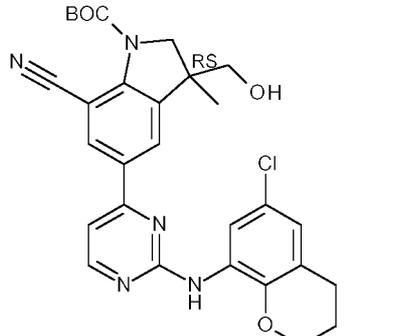
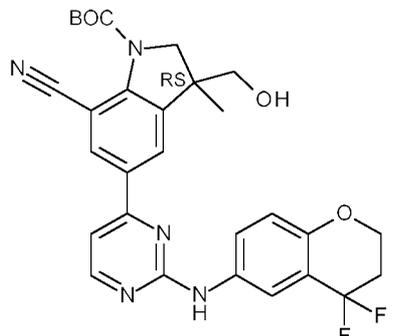


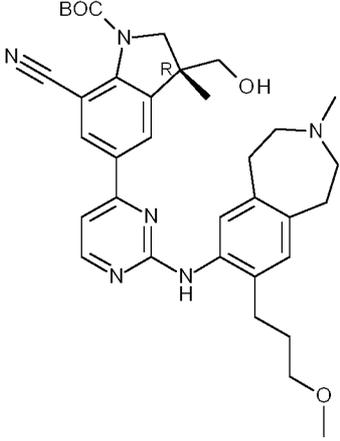
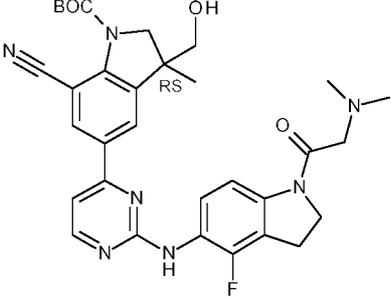
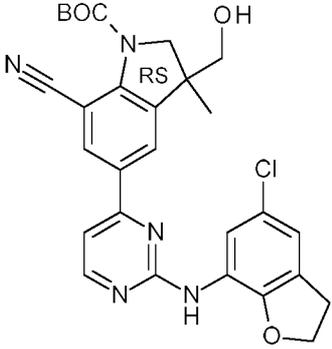
Preparation of intermediate 15:

A mixture of intermediate 14 (175.00 mg, 0.28 mmol) and TBAF (1M in THF) (0.56 mL, 0.56 mmol) in THF (2.4 mL) was stirred at rt for 48 h. The reaction mixture was diluted with EtOAc and water. The layers were separated and the organic layer was dried over MgSO_4 , filtered and the solvent was removed under reduced pressure.

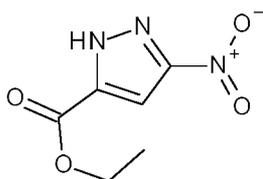
The residue was taken up into Et₂O, filtered and dried under vacuum to give 126 mg of intermediate 15 (88% yield) which was directly engaged in the next step without further purification.

- 5 The intermediates in the table below were prepared by using an analogous method starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 22	 <p>From intermediate 21</p>	524 <i>Brown solid</i>	Quant. Procedure with 2.2 equiv. of TBAF
Intermediate 27	 <p>From intermediate 26</p>	201 <i>brown oil</i>	32 Procedure with 2.2 equiv. of TBAF
Intermediate 40	 <p>From intermediate 39</p>	77	67 Procedure with 1.2 equiv. of TBAF

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 99	 <p data-bbox="600 869 879 902">From intermediate 98</p>	620 <i>yellow oil</i>	71 Procedure with 1.1 equiv. of TBAF
Intermediate 157	 <p data-bbox="600 1238 895 1272">From intermediate 156</p>	400	68 Procedure without solvent
Intermediate 167	 <p data-bbox="600 1659 895 1693">From intermediate 166</p>	300	99 Based on a purity of 64% evaluated by LC/MS Procedure with 1.05 equiv. of TBAF

mixture was refluxed overnight. The precipitate was collected by filtration and suspended in DCM (82.5 mL). N,O-dimethylhydroxylamine hydrochloride (3.74 g, 38.34 mmol) and TEA (13.35 mL, 95.99 mmol) were added and the mixture was stirred at rt overnight. The mixture was poured into water (100 mL) and extracted with DCM (3 x 60 mL) and
 5 DCM/MeOH (9/1, 60 mL). The organic layers were combined, dried over Na₂SO₄, filtered and concentrated in vacuo to give 6.2 g of intermediate 24b (97% yield).



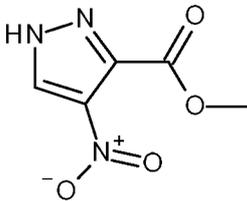
Preparation of intermediate 34b:

To a solution of 5-nitro-3-pyrazolecarboxylic acid (4.00 g, 25.46 mmol) in EtOH (80 mL)
 10 was added SOCl₂ (25 mL) and the mixture was stirred at 70 °C overnight. The mixture was evaporated under vacuo and the residue was added into water (20 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated under reduced pressure to give 4 g of intermediate 34b (68% yield, 80% purity based on LC/MS) which was used in the next step without any further
 15 purification.

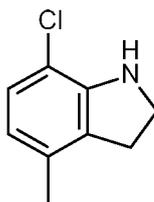
The intermediates in the table below were prepared by using an analogous method as reported for the preparation of intermediate 34b, starting from the respective starting materials.

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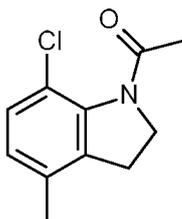
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 69b	<p>From 5-nitro-3-pyrazolecarboxylic acid and MeOH</p>	1600	Quant.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 89b	 <p>From 4-nitro-3-pyrazolecarboxylic acid and MeOH</p>	9500	87

Example A11c

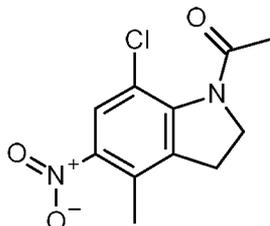
Preparation of intermediate 36c:

Sodium cyanoborohydride (759.86 mg, 12.1 mmol) was added slowly to a solution of 7-chloro-4-methyl-1H-indole (1.00 g, 6.04 mmol) in AcOH (10 mL). The mixture was stirred at rt for 3 h. The mixture was poured into a mixture of ice and 3M aqueous NaOH solution. An extraction was performed with EtOAc. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure to give 1.15 g of intermediate 36c (quant. yield, 88% purity, orange oil) which was directly engaged in the next step.

Preparation of intermediate 37c:

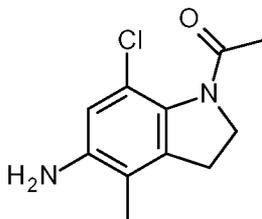
A mixture of intermediate 36c (1.15 g, 6.04 mmol based on 88% purity), acetyl chloride (0.64 mL, 9.06 mmol) and triethylamine (1.34 mL, 9.66 mmol) in DCM (20 mL) was stirred under N₂ at rt for 6 h. An extraction was performed with DCM and brine. The organic layer was dried over MgSO₄, evaporated and purified by silica gel chromatography (irregular SiOH 15-40 μm, 40 g, liquid injection with DCM, mobile phase gradient: from DCM/MeOH 100/0 to 95/05 in 10 CV). The fractions containing the product were

combined and concentrated under vacuum to give 1.13 g of intermediate 37c (89%, light yellow solid).



Preparation of intermediate 38c:

5 A mixture of intermediate 37c (1.13 g, 5.39 mmol) and NaNO₃ (503.87 mg, 5.93 mmol) in TFA (20 mL) was stirred at rt for 18 h. The mixture was poured in a mixture of ice and aqueous NaHCO₃ and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, evaporated and purified by silica gel chromatography (irregular SiOH 15-40 μm, 120 g, liquid injection with DCM, mobile phase gradient: from DCM/MeOH 100/0 to 95/05 in 10 CV). The fractions containing the product were combined and concentrated under vacuum to give 1.01 g of intermediate 38c (73%, brown solid).



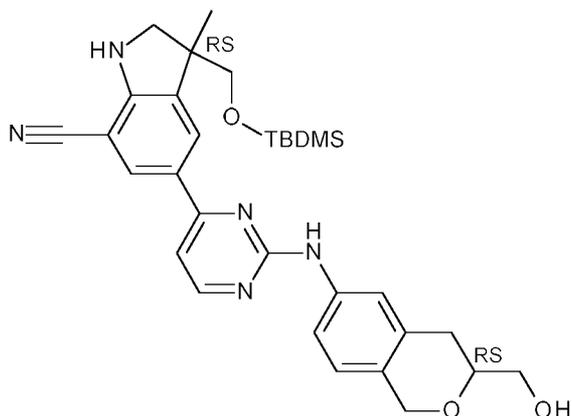
Preparation of intermediate 39c:

15 A mixture of intermediate 38c (1.00 g, 3.93 mmol), Zinc (2.57 g, 39.27 mmol) and AcOH (42.25 mL, 39.27 mmol) in MeOH (25 mL) was stirred at rt for 2.5 h. The mixture was filtered over a pad of celite[®] and an extraction was performed with EtOAc. The organic layer was washed with HCl 1N. The aqueous layer was basified with NaOH 1N and extracted with EtOAc (twice). The organic layers were combined, washed with brine, dried over MgSO₄ and evaporated to dryness to give 550 mg of intermediate 39c (62%, light brown foam) which was directly engaged in the next step.

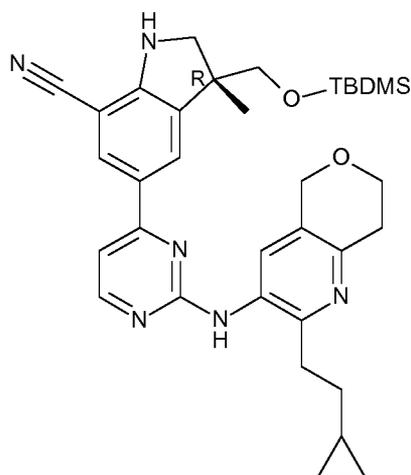
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Example A12a

Preparation of intermediate 35 (mixture of 2 diastereoisomers with unknown configuration (DIA A)):

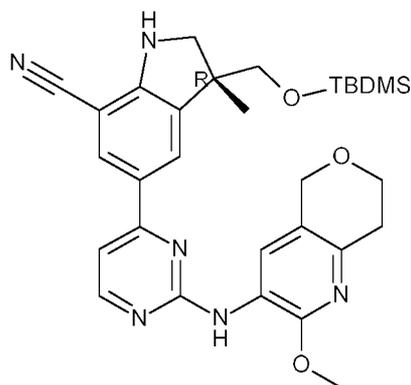


A solution of intermediate 33 (131.00 mg, 0.20 mmol) in a mixture of TFA (305.00 μ L) and DCM (1.3 mL) was stirred at 0 °C for 30 min. The reaction mixture was poured onto ice, water and NH_4OH . The mixture was extracted with EtOAc and the organic layer was dried over MgSO_4 , filtered and concentrated under vacuum to give 70 mg of intermediate 35 (72% yield) which was directly engaged in the next step without further purification.



Preparation of intermediate 106:

To a solution of intermediate 105 (450.00 mg, 0.65 mmol) in DCM (15 mL) was added TFA (1.46 mL, 19.0 mmol) and the mixture was stirred at rt for 20 min. The mixture was poured into a saturated solution of NaHCO_3 solution and stirred for 10 min. The layers were separated and the aqueous layer was extracted with DCM (twice). The combined organic layers were dried over MgSO_4 , filtered and evaporated in vacuo. The crude residue was purified by silica gel chromatography (irregular SiOH , 15-40 μm , 24 g, liquid injection (DCM), mobile phase gradient: from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100/0 to 95/5) to give 260 mg of intermediate 106 (67% yield, yellow solid).

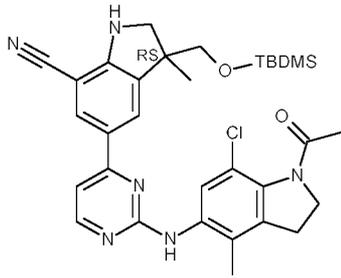
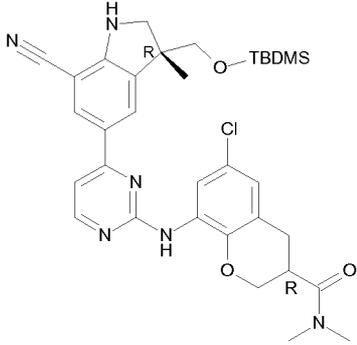
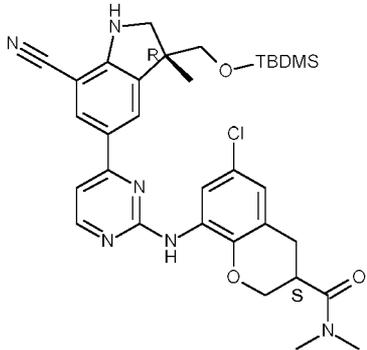
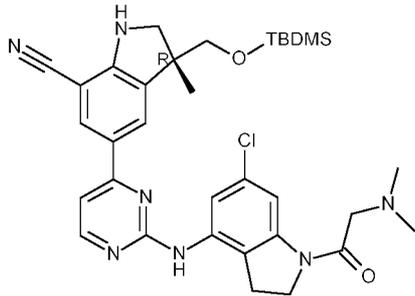


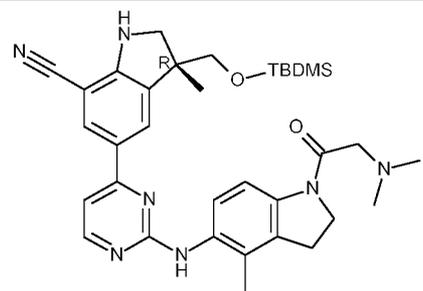
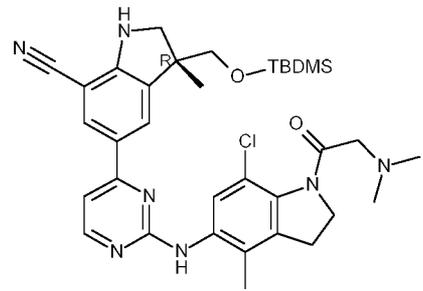
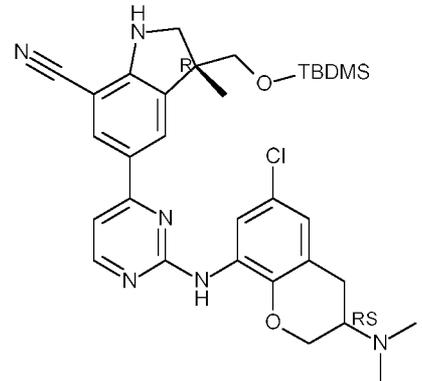
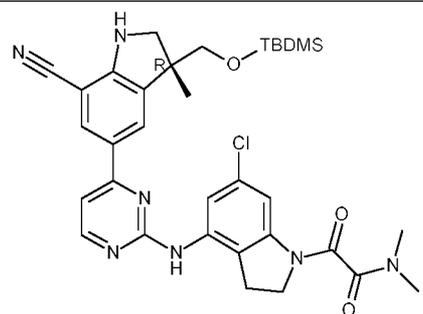
Preparation of intermediate 119:

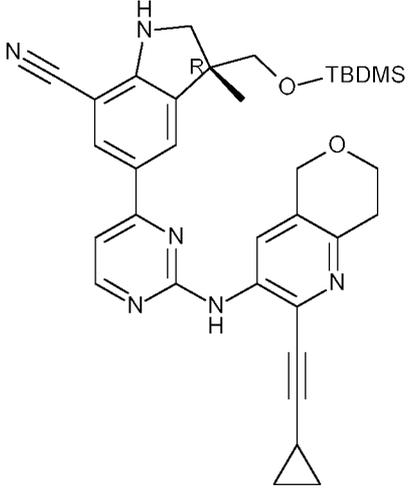
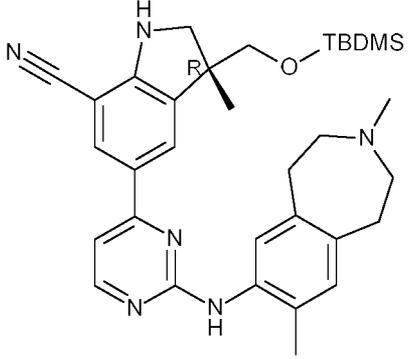
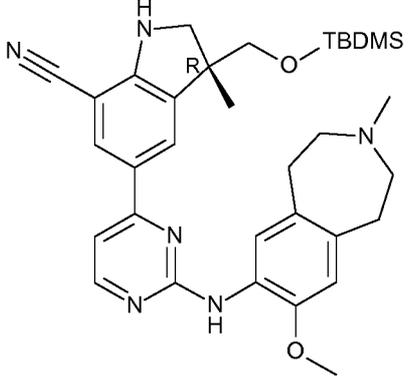
TFA (3.26 mL, 42.54 mmol) was added to a solution of intermediate 118 (692.00 mg, 0.85 mmol, 81% purity based on $^1\text{H NMR}$) in dry DCM (12 mL) at 0 °C. The solution was allowed to warm to rt and stirred for 1 h. The solution was quickly poured into a saturated aqueous solution of NaHCO_3 and DCM was added. The layers were separated and the organic layer was dried over MgSO_4 , filtered and evaporated in vacuo. The crude residue was purified by silica gel chromatography (Irregular SiOH 15-40 μm , 24 g, liquid loading (DCM), mobile phase gradient: from heptane 90%, EtOAc 10% to heptane 70%, EtOAc 30%) to give 338 mg of intermediate 119 (59% yield, 83% purity based on $^1\text{H NMR}$, yellow oil).

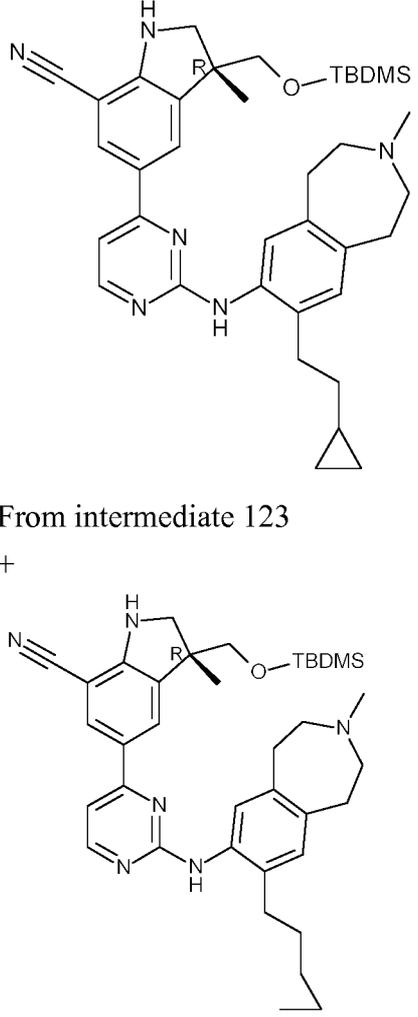
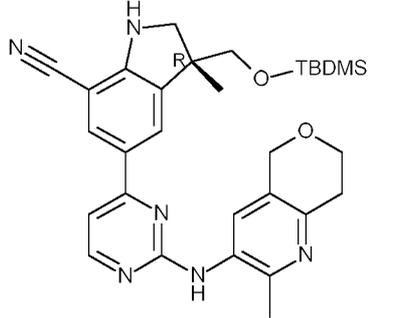
The intermediates in the table below were prepared by using an analogous method starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

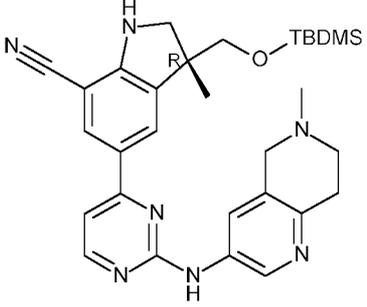
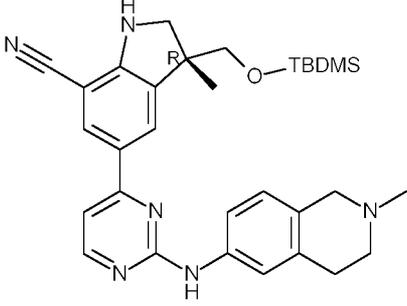
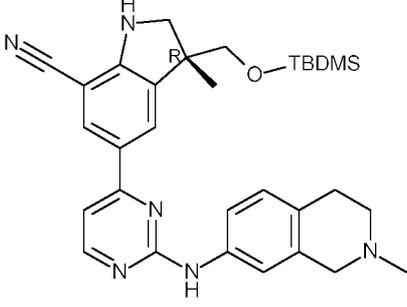
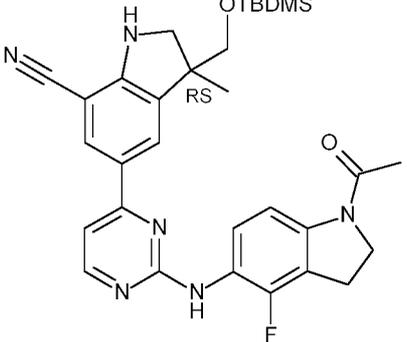
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 41 (Mixture of 2 diastereoisomers with unknown configuration (DIA B))		124	Quantitative
	From intermediate 34		

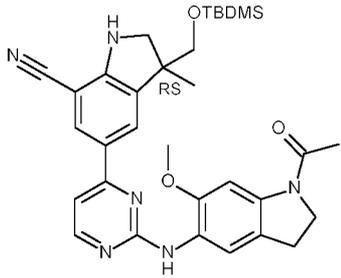
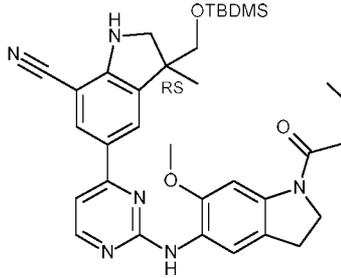
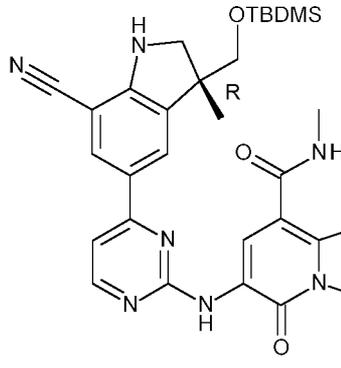
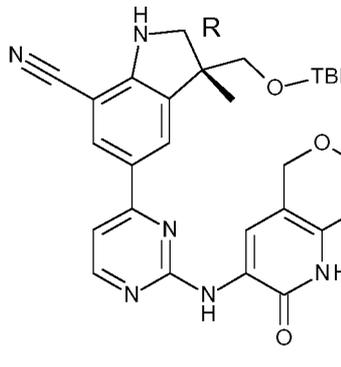
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 47	 <p data-bbox="587 696 863 728">From intermediate 46</p>	521	64 <i>Off-white solid</i> Procedure with DCM/TFA (8:1, eq./eq.)
Intermediate 59	 <p data-bbox="587 1108 863 1140">From intermediate 58</p>	379	Quant. <i>brown solid</i> Procedure with DCM/TFA (3:1, eq./eq.)
Intermediate 62	 <p data-bbox="587 1523 863 1554">From intermediate 61</p>	250	68 <i>yellow solid</i> Procedure with DCM/TFA (3:1, eq./eq.)
Intermediate 66	 <p data-bbox="587 1933 863 1964">From intermediate 65</p>	137	74 <i>yellow oil</i> Procedure with DCM/TFA (6:1, eq./eq.)

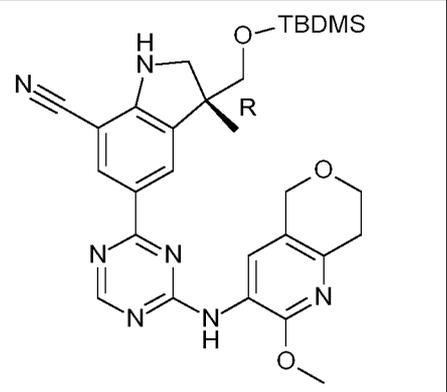
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 76	 <p>From intermediate 75</p>	94	40
Intermediate 82	 <p>From intermediate 81</p>	219	50
Intermediate 87	 <p>From intermediate 86</p>	570	77
Intermediate 93	 <p>From intermediate 92</p>	135	60

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 108	 <p>From intermediate 107</p>	160 <i>Yellow residue</i>	69 Procedure with DCM/TFA (12:1, eq./eq.)
Intermediate 112	 <p>From intermediate 111</p>	241 <i>Yellow solid</i>	79 Procedure with DCM/TFA (12:1, eq./eq.)
Intermediate 116	 <p>From intermediate 115</p>	306 <i>Yellow solid</i>	90 Procedure with DCM/TFA (12:1, eq./eq.)

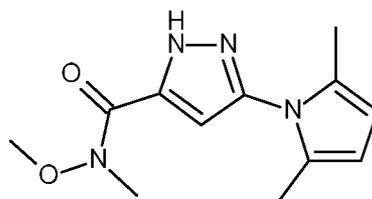
Intermediate number	Structure	Mass (mg)	Yield (%)
Mixture of intermediate 124 and 124'	 <p>From intermediate 123 +</p> <p>From intermediate 123'</p>	840 <i>yellow solid</i>	64 Procedure with DCM/TFA (10:1 eq./eq.)
Intermediate 127	 <p>From intermediate 126</p>	378 (75% purity based on LC/MS) <i>Off-white solid</i>	68

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 131	 <p>From intermediate 130</p>	523 <i>Orange foam</i>	Quant. Procedure with DCM/TFA (8:1, eq./eq.)
Intermediate 134	 <p>From intermediate 133</p>	310 <i>Yellow solid</i>	54 Procedure with DCM/TFA (6:1, eq./eq.)
Intermediate 136	 <p>From intermediate 135</p>	235	81 Procedure with DCM/TFA (6:1, eq./eq.)
Intermediate 152	 <p>From intermediate 151</p>	700	Quant.

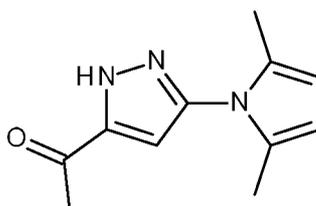
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 160	 <p>From intermediate 159</p>	538	Quant. Procedure with DCM/TFA (2:1, v./v.)
Intermediate 165	 <p>From intermediate 164</p>	260	Quant. Procedure with DCM/TFA (4:1, v./v.)
Intermediate 178	 <p>From intermediate 178</p>	192	79 Procedure with DCM/TFA (10:1, v./v.)
Intermediate 188	 <p>From intermediate 145</p>	177	66 Procedure with DCM/TFA (3:1, v./v.)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 216	 <p>From intermediate 215</p>	350	58 50% of purity evaluated by LC/MS Procedure with DCM/TFA (4:1, v/v.)

Example A12b

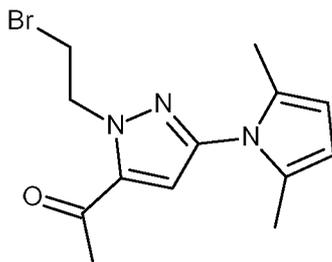
Preparation of intermediate 26b:

Intermediate 25b (4.40 g, 25.86 mmol) and 2,5-hexanedione (3.25 g, 28.43 mmol) were dissolved in acetic acid (30 mL) and toluene (90 mL). The mixture was refluxed for 2 h, then washed with water and DCM and layers were separated. The organic phase was dried over Na₂SO₄, filtered and concentrated under vacuo. The crude residue was purified by silica gel chromatography (elution: petroleum ether/ EtOAc, 5/1). The desired fractions were collected and concentrated under vacuum to give 4.8 g of intermediate 26b (75% yield).

Preparation of intermediate 27b:

Intermediate 26b (4.80 g, 19.33 mmol) was dissolved in THF (140 mL) under N₂. Methylmagnesium bromide (3M in Et₂O) (16 mL, 48 mmol) was added dropwise at 0 °C and the resulting mixture was stirred at room temperature for 4 h. The mixture was

quenched with an aqueous NH_4Cl solution (25 mL) and extracted with EtOAc (2 x 100 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by silica gel chromatography (elution: petroleum ether/ EtOAc, 4/1) to give 3.6 g of intermediate 27b (92% yield).

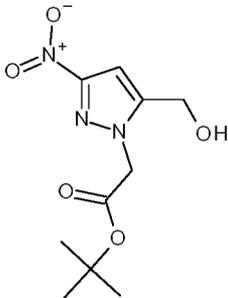
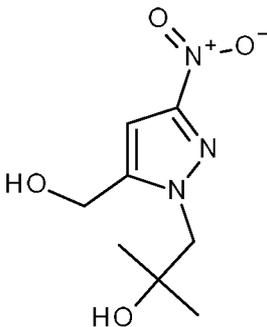
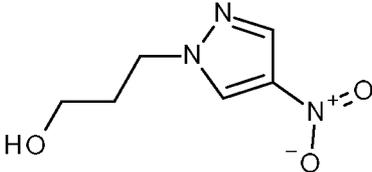
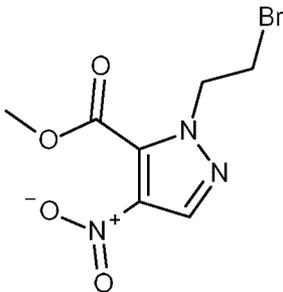


5 Preparation of intermediate 28b:

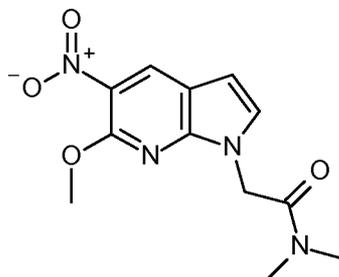
Intermediate 27b (2.00 g, 9.84 mmol) was dissolved in CH_3CN (50 mL). 1,2-dibromoethane (7.4 g, 39.39 mmol) and K_2CO_3 (2.72 g, 19.71 mmol) were added and the mixture was refluxed for 2 h. The mixture was cooled to room temperature and filtered. The filtrate was concentrated and the crude residue was purified by silica gel chromatography (elution: Petroleum ether/ EtOAc, 5/1). The desired fractions were collected and concentrated to give 2.8 g of intermediate 28b (92% yield).

The intermediates in the table below were prepared by using an analogous method as described in the preparation of intermediate 28b, starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

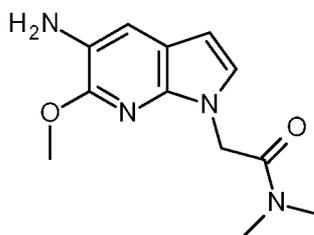
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 35b	<p>From intermediate 34b and 1,2-dibromoethane</p>	500	14
		90% purity based on LC/MS	Procedure with acetone as solvent

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 42b	 <p>From intermediate 41b and tert-butyl bromoacetate</p>	1970	44
Intermediate 53b	 <p>From intermediate 41b and 2,2-dimethyloxirane</p>	2150	89
Intermediate 75b	 <p>From 4-nitro-1H-pyrazole and 3-bromo-1-propanol</p>	2200	58
Intermediate 94b	 <p>From intermediate 89b and 1,2-dibromoethane</p>	2310	18

Example A12c

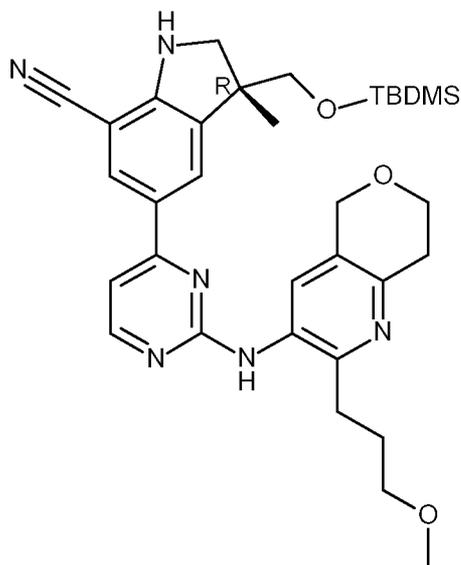
Preparation of intermediate 43c:

To a solution of 6-methoxy-5-nitro-1H-pyrrolo[2,3-b]pyridine (412.00 mg, 2.13 mmol) in
5 dry DMF (10 mL) was added NaH (60% dispersion in mineral oil) (93.84 mg, 2.35 mmol)
and the mixture was stirred at rt for 10 min. Then, 2-chloro-*N,N*-dimethylacetamide (241
 μ L, 2.35 mmol) was added and the reaction mixture was stirred at rt for 18 h. Celite[®] was
added and a dry load was prepared under vacuum. The resulting crude product was
purified by silica gel chromatography (regular SiOH 30 μ m, 40 g, dry load with celite[®],
10 mobile phase gradient: from DCM/MeOH 100/0 to 98/02 in 10 CV). The fractions
containing the product were combined and concentrated under vacuum to give 530 mg of
intermediate 43c (89% yield, yellow solid).

Preparation of intermediate 44c:

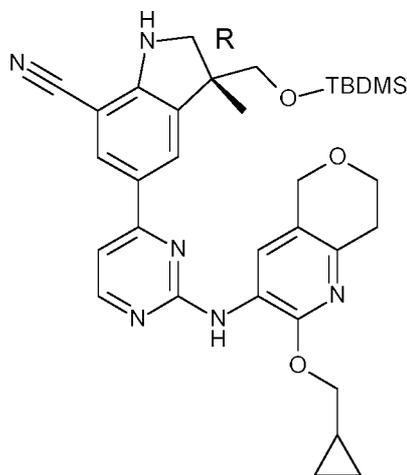
15 A suspension of intermediate 43c (530.00 mg, 1.91 mmol) and Pd/C (10%) (0.10 g, 0.09
mmol) in Me-THF (30 mL) and EtOH (40 mL) was stirred in the dark at rt for 20 h under
H₂ atmosphere (1 bar). The mixture was then diluted with DCM, filtered over celite[®] and
the filtrate was evaporated to dryness under vacuum to give 490 mg of intermediate 44c
20 (quant. yield, greenish residue) which was used as it in the next step.

Example A13a



Preparation of intermediate 143:

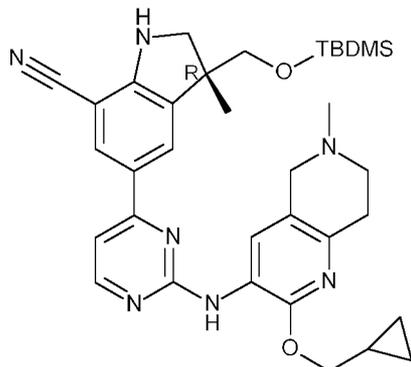
SiO₂ (40-63 μm) (1.57 g) was added to a solution of intermediate 142 (313.00 mg, 0.45 mmol) in toluene (4 mL) and the mixture was refluxed for 2 h. After cooling down to rt, the mixture was diluted with EtOAc and filtered on a glass frit. The filtrate was evaporated under vacuum to give 287 mg of intermediate 143 (quant. yield, yellow oil) which was directly engaged in the next step without further purification.



Preparation of intermediate 146:

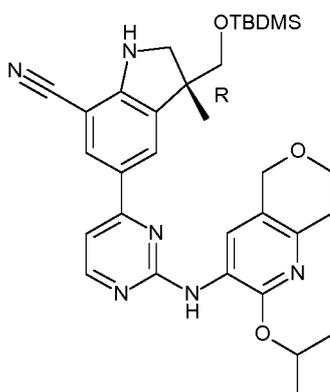
SiO₂ (1.74 g, 5 equiv. wt) was added to a solution of intermediate 145 (348.00 mg, 0.34 mmol, 69% of purity based on ¹H NMR) in toluene (3 mL) and the mixture was refluxed for 2 h. After cooling down to rt, the mixture was diluted with EtOAc and filtered on a glass frit. The filtrate was evaporated in vacuo. The crude residue was purified by silica gel chromatography (Irregular SiOH 15-40 μm, 12 g, liquid loading (DCM), mobile phase gradient: from heptane 95%, EtOAc/MeOH (9:1) 5% to heptane 70%, EtOAc/MeOH (9:1)

30%) to give 255 mg of intermediate 146 (86% yield, 69% purity based on ¹H NMR, yellow oil).



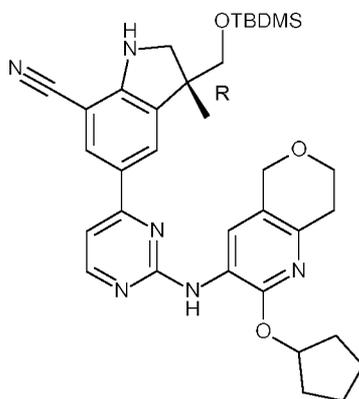
Preparation of intermediate 149:

- 5 SiO₂ (40-63 μm) (0.43 g) was added to a solution of intermediate 148 (85.00 mg, 0.12 mmol) in toluene (1.04 mL) and the mixture was refluxed for 2 h. After cooling down to rt, the mixture was diluted with DCM and MeOH and filtered on a glass frit. The filtrate was evaporated in vacuo to give 65 mg of intermediate 149 (89% yield, yellow oil) which was used in the next step without further purification.



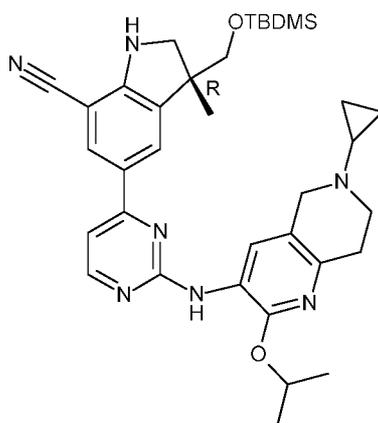
- 10 Preparation of intermediate 184:

- SiO₂ was added to a solution of intermediate 183 (160 mg; 0.233 mmol) in toluene (2.3 mL). The mixture was heated to 90 °C for two days. The mixture was filtered and washed with ethyl acetate. The filtrate was evaporated and the crude was purified by silica gel chromatography (Eluent: Heptane-EtOAc: 8/2). The fractions containing the product were
15 mixed and concentrated to give 136 mg (99%) of intermediate 184.



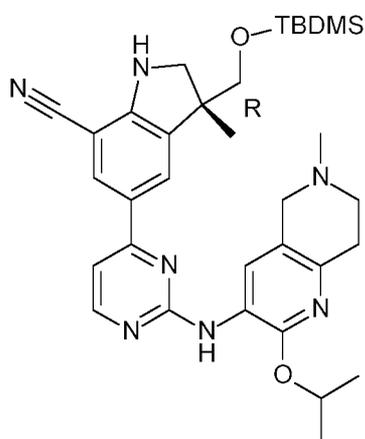
Preparation of intermediate 187:

Intermediate 187 was prepared accordingly to intermediate 184 starting from intermediate 186 (152mg; 93%).



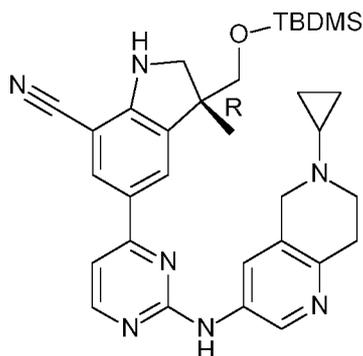
5 Preparation of intermediate 195:

Intermediate 195 was prepared accordingly to intermediate 143 starting from intermediate 194 (120mg).



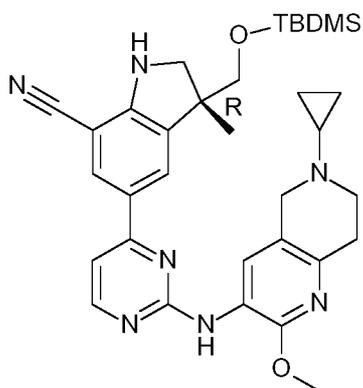
Preparation of intermediate 199:

Intermediate 199 was prepared accordingly to intermediate 143 starting from intermediate 198 (664mg; 81%).



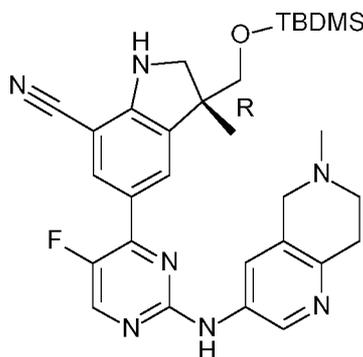
Preparation of intermediate 203:

- 5 Intermediate 203 was prepared accordingly to intermediate 143 starting from intermediate 202 (110mg; 99%).



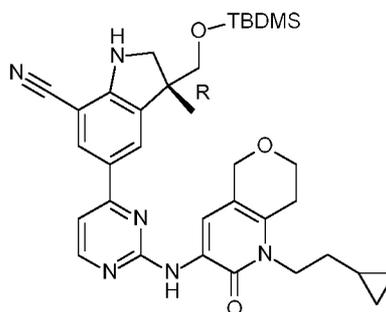
Preparation of intermediate 207:

- 10 Intermediate 207 was prepared accordingly to intermediate 143 starting from intermediate 206 (120mg, purity 68% based evaluated by LC/MS).



Preparation of intermediate 213:

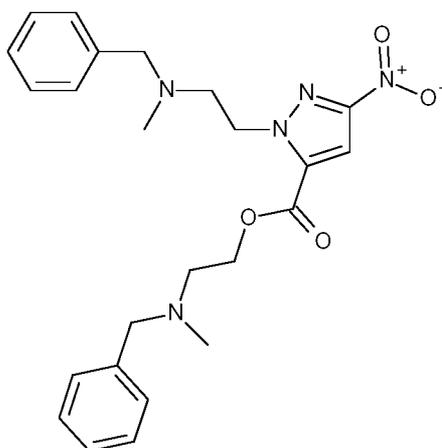
Intermediate 213 was prepared accordingly to intermediate 143 starting from intermediate 212 (130mg, 95%).



Preparation of intermediate 229:

- 5 Intermediate 229 was prepared accordingly to intermediate 184 starting from intermediate 228 (135mg; 96%).

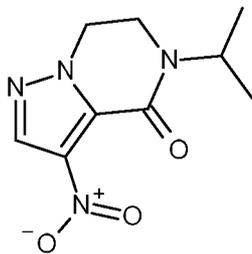
Example A13b



Preparation of intermediate 70b:

- 10 Cyanomethylenetriethylphosphorane (2.91 mL, 11.10 mmol) was added to a stirred solution of intermediate 69b (950.00 mg, 5.55 mmol) and *N*-benzyl-*N*-methylethanolamine (1.36 mL, 8.33 mmol) in toluene (24.78 mL) at rt. The reaction mixture was stirred at rt for 9 h. Solvent was evaporated and the crude residue was purified via silica gel chromatography (Stationary phase: irregular SiOH 15-40 μ m, 80 g, mobile phase gradient: 15 from 80% Heptane, 20% EtOAc to 50% Heptane, 50% EtOAc) to give 1.3 g of intermediate 70b (52% yield).

Preparation of intermediate 90b:



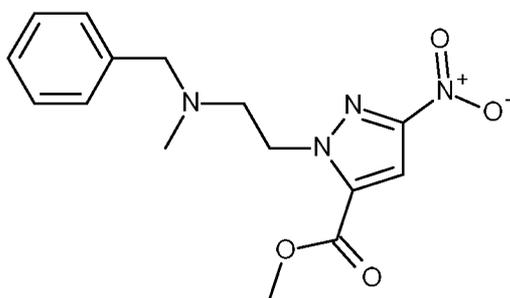
The reaction was performed twice the same quantities of intermediate 89b (0.5 g, 2.922 mmol):

- 5 Cyanomethylenetriethylphosphorane (1.41 mL, 5.38 mmol) was added to a solution of intermediate 89b (0.5 g, 2.92 mmol) and 2-(isopropylamino)ethanol (468.63 μ L, 4.075 mmol) in toluene (14 mL) in a sealed tube were stirred at 110°C using one single mode microwave (Masterwave BTR Anton Paar[®]) with a power output ranging from 0 to 1700 W for 30 min. The reaction mixtures were diluted with EtOAc, mixed and washed with a
- 10 10% aqueous solution of K_2CO_3 , water and a solution of saturated NaCl. The layers were separated and the organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure.

The crude (3.8g) was purified by silica gel chromatography (Irregular SiOH 40 μ m 80g; Mobile phase 100% DCM to 97% DCM, 3% MeOH, 0.3% NH_4OH). The pure fractions

15 were combined and the solvent was evaporated to give 458mg of an intermediate fraction which was purified again by silica gel chromatography (Irregular SiOH 40 μ m 40g; Mobile phase from 80% Heptane, 20% AcOEt to 40% Heptane, 50% AcOEt, 10% MeOH, 0.1% NH_4OH). The pure fractions were combined and the solvent was evaporated to give 249 mg (19%) of intermediate 90b.

20

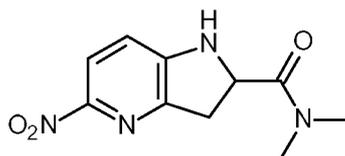


Preparation of intermediate 71b:

A mixture of intermediate 70b (1.10 g, 2.44 mmol) in MeOH (7.37 mL) was stirred at 100 °C in a sealed tube using one single mode microwave (Anton Paar monowave 300[®]) with a

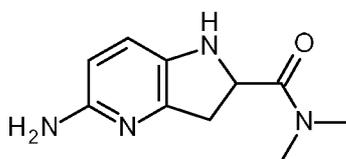
power output ranging from 0 to 850 W for 10 min. The solution was evaporated under reduced pressure to give 775 mg of intermediate 71b (quant. yield) which was used in the next step without further purification.

5 Example A13c



Preparation of intermediate 48c:

A mixture of 5-nitro-indoline-2-carboxylic acid (1.8g; 8.65 mmol), dimethylamine hydrochloride (1.41g; 17.30 mmol), Propylphosphonic acid anhydride (13.8g; 21.62 mmol; 50% in EtOAc) and TEA (5 mL; 34.6 mmol) in DCM (100 mL) was stirred at room temperature overnight. The mixture was poured into water and extracted with DCM (50 mL*3). The organic layers were combined and washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated. The intermediate product was washed with EtOH and dried under vacuo to give 1.8 g (88%) of intermediate 171c as a yellow solid.

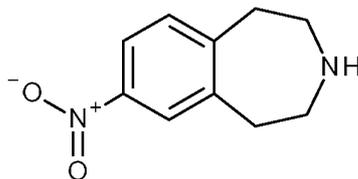


15 Preparation of intermediate 49c:

A mixture of intermediate 48c (1.8g; 7.65 mmol) in EtOH (100 mL) was hydrogenated at room temperature (atmospheric pressure) with Pd/C 10% as a catalyst under 1 atmosphere of hydrogen. After overnight stirring, the reaction mixture was filtered and the solvent was removed to give 1.3 g (83%) of intermediate 49c as a brown sticky oil.

20 It was directly used for next step.

Example A14a



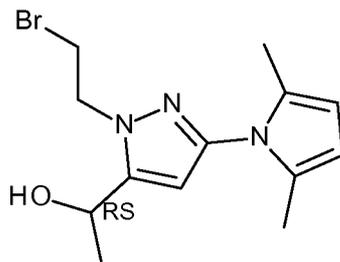
Preparation of intermediate 17:

In a round bottom flask, potassium nitrate (3.60 g, 35.66 mmol) was added portionwise at 5 °C to a solution of 2,3,4,5-tetrahydro-1H-3-benzazepine (5.00 g, 33.96 mmol) in H₂SO₄ (34 mL). The reaction mixture was stirred for 10 min. Then, the reaction mixture was

poured into ice water and carefully basified with solid K_2CO_3 . The aqueous layer was extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated to dryness to give 4.65 g of intermediate 17 (71% yield, brown oil) which was directly engaged in the next step without further purification.

5

Example A14b

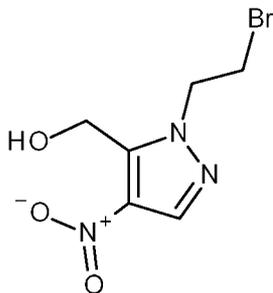


Preparation of intermediate 29b:

To a solution of intermediate 28b (2.80 g, 9.03 mmol) in MeOH (50 mL) was added $NaBH_4$. The reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with water, extracted with DCM. The organic phase was washed with brine, dried over Na_2SO_4 , filtered and concentrated in vacuo to give 2.6 g of intermediate 29b (92% yield) which was used in the next step without any further purification.

The intermediate in the table below was prepared by using an analogous method as described for the preparation of intermediate 29b, starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 36b	<p>From intermediate 35b</p>	500	94
		80% purity based on LC/MS	Procedure with EtOH as solvent

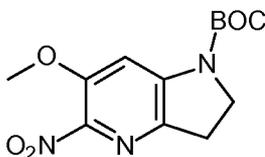


Preparation of intermediate 95b:

Diisobutylaluminium hydride in DCM (1M) (5.92 mL, 33.23 mmol) was added dropwise to a dry solution of intermediate 94b (2.31 g, 8.31 mmol) in DCM (22.35 mL) at rt under nitrogen (syringe pump, 20 mL/h). The reaction mixture was stirred at rt for 4 h.

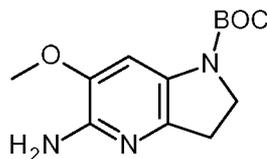
- 5 Additional diisobutylaluminium hydride in DCM (5.922 mL, 0.798 g/mL, 33.23 mmol) was added dropwise (syringe pump, 20 mL/h) and the resulting solution was stirred at rt for 16 h. The reactive mixture was poured onto ice and water. The mixture was acidified with a 3N aqueous solution of HCl, extracted twice with DCM, filtered over celite[®] and the layers were separated. The organic layer was dried over MgSO₄, filtered and evaporated.
- 10 The crude residue was purified by silica gel chromatography (Irregular SiOH 40 μm, 80 g, mobile phase gradient: from 80% Heptane, 20% EtOAc to 50% Heptane, 50% EtOAc). The pure fractions were combined and the solvent was evaporated to give 1.04 g of intermediate 95b (50% yield).

15 Example A14c



Preparation of intermediate 51c:

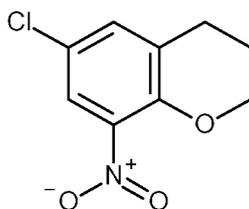
- To a stirred solution of 6-(methoxy)-5-nitro-2,3-dihydro-1-*H*-indole (300mg; 1.33 mmol) in DCM (5 mL) was added trimethylamine (463μL; 3.32 mmol), di-*tert*-butyldicarbonate (319mg; 1.46mmol) and 4-dimethylaminopyridine (16mg; 0.13 mmol). The reaction mixture was stirred at room temperature overnight. Then, the mixture was stirred for 12hrs at 40°C. Water (10 mL) was added and the mixture was extracted with DCM (3 *20 mL). The combined organic layers were washed brine and dried over Na₂SO₄ and the solvent was removed under vacuum. The resulting residue (500 mg) was purified by flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 60/40).
- 25 The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 340 mg (87%) of intermediate 51c.



Preparation of intermediate 52c:

A mixture of intermediate 51c (340 mg; 1.15 mmol) in MeOH (5 mL) and EtOAc (5 mL) was hydrogenated overnight at room temperature (25 psi of hydrogen) with Pd/C 10% as catalyst. The catalyst was filtered off and the filtrate was evaporated under reduced pressure to afford 240 mg (79%) of intermediate 52c.

Example A15a



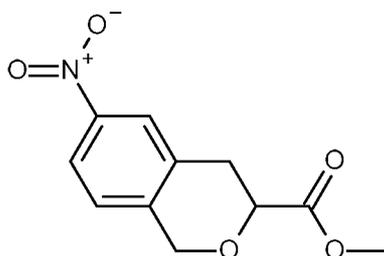
Preparation of intermediate 24:

Sodium nitrite (479.00 mg, 6.95 mmol) was added to a solution of intermediate 23 (1.00 g, 5.94 mmol) in TFA (36 mL) and the mixture was stirred at rt for 4 h. The reaction mixture was diluted with EtOAc and a 10% aqueous solution of Na₂CO₃. The layers were separated and the organic layer was dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography (irregular SiOH 15-40 μm, 40 g, dry loading on celite[®], mobile phase gradient: from heptane/EtOAc 100/0 to 40/60) to give 340 mg of intermediate 24 (27% yield, off-white solid).

The intermediate in the table below was prepared by using an analogous method starting from the respective starting materials.

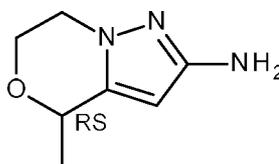
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 54	<p>From intermediate 53</p>	732	56

Example A15aa

Preparation of intermediate 29:

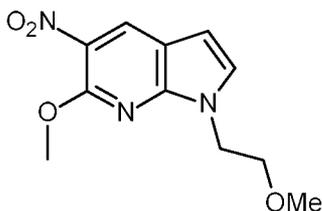
To fuming nitric acid (19.48 mL, 426.61 mmol) previously cooled between -40 and -50 °C
5 was added dropwise intermediate 28 (4.10 g, 21.33 mmol) in AcOH (8.2 mL, 143.24
mmol). The reaction mixture was stirred between -40 and -50 °C for 40 min, poured onto
ice and extracted with DCM. The organic layer was dried over MgSO₄, filtered and
evaporated under vacuum. The residue was purified by silica gel chromatography
(spherical SiOH 30 μm, mobile phase: DCM 100%). The pure fractions were combined
10 and the solvent was removed in vacuo to give 5.2 g of intermediate 29 (quant. yield).

Example A15b

Preparation of intermediate 31b:

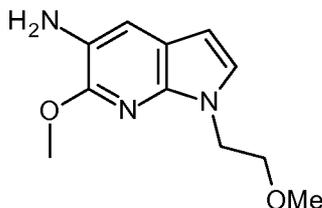
To a solution of intermediate 30b (913.00 mg, 3.95 mmol) in EtOH (3 mL) was added a
15 mixture of KOH (664.00 mg, 11.86 mmol) and hydroxylamine hydrochloride (1.65 g,
23.71 mmol) in H₂O (6 mL) and EtOH (6 mL). The resulting mixture was refluxed
overnight. The solution was concentrated under reduced pressure and the crude residue
was dissolved in EtOAc (10 mL), washed with water and brine, dried over Na₂SO₄, filtered
and concentrated in vacuo. The crude residue was purified by silica gel chromatography
20 (eluent: 100% EtOAc) to give 200 mg of intermediate 31b (33% yield).

Example A15c



Preparation of intermediate 55c:

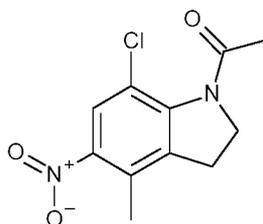
To a solution of 6-methoxy-5-nitro-7-azaindole (144 mg; 0.745 mmol) in dry DMF (4 mL) was added sodium hydride (33 mg; 0.82 mmol; 60% dispersion in oil) and the mixture was stirred at room temperature for 30 min. Then 2-bromoethylmethyl ether (77 μ L ; 0.82 mmol) was added, and the reaction mixture was stirred at room temperature for 16h , then evaporated, taken up with a mixture of DCM/MeOH (3:1) and combined 2 other reactions respectively performed on 10mg and 50mg of 6-methoxy-5-nitro-7-azaindole.. Celite was added and a dry load was prepared under vacuum. The resulting residue was purified by silica gel chromatography (regular silica 30 μ m, 25 g, dry load (Celite), mobile phase gradient: from heptane 100% to heptane 70%, EtOAc/MeOH (90:10) 30% in 10 CV) to afford, after evaporation in vacuo, 190 mg (71%, combined yield) of intermediate 55c as an orange oil.



15 Preparation of intermediate 56c:

Intermediate 56c was prepared accordingly to intermediate 49c starting from intermediate 55c (110 mg; 67%).

Example A16a

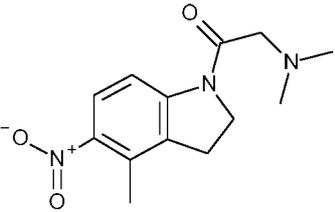
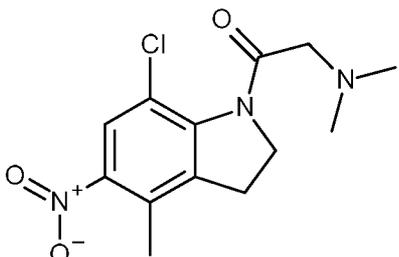
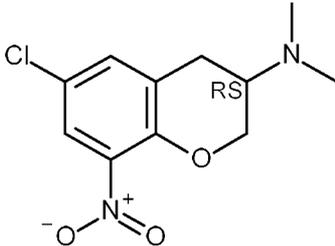


20 Preparation of intermediate 44:

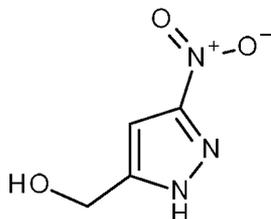
A mixture of intermediate 43 (1.13 g, 5.39 mmol) and sodium nitrate (503.87 mg, 5.93 mmol) in TFA (20 mL) was stirred at rt for 18 h. The mixture was poured into a mixture of ice and aqueous NaHCO₃ and extracted with EtOAc. The organic layer was washed with

brine, dried over MgSO₄, filtered and evaporated under reduced pressure. The crude residue was purified by silica gel chromatography (irregular SiOH 15-40 μm, 120 g, liquid injection with DCM, mobile phase gradient: DCM/MeOH from 100:0 to 95:05 in 10 CV). The pure fractions were combined and the solvent was removed in vacuo to give 1.01 g of intermediate 44 (74% yield, brown solid).

The intermediates in the table below were prepared by using an analogous method starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 73	 <p>From intermediate 72</p>	180	19
Intermediate 79	 <p>From intermediate 78</p>	378	72
Intermediate 84	 <p>From intermediate 83</p>	470	79

10 Example A16b



Preparation of intermediate 41b:

BH₃.THF (1M) (166.46 mL, 166.46 mmol) was added dropwise to a stirred solution of 3-nitro-1H-pyrazol-5-carboxylic acid (8.70 g, 55.38 mmol) in THF (131 mL) at 0 °C under nitrogen. The reaction mixture was stirred at rt for 16 h. HCl (2M in H₂O) (43.5 mL, 87 mmol) was added and the reaction mixture was stirred at reflux for 1 h. The reaction mixture was cooled down to rt and concentrated under reduce pressure to a volume of approximately 30 mL. The aqueous layer was extracted 3 times with EtOAc, dried over MgSO₄, filtered and evaporated under vacuo to give 8 g of intermediate 41b (quantitative yield) which was used in the next step without any further purification.

10

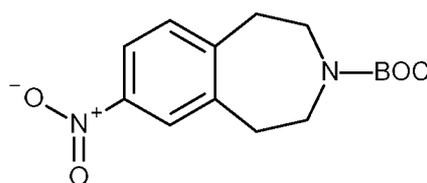
The intermediates in the table below were prepared by using an analogous method as reported for the preparation of intermediate 41b, starting from the respective starting materials. The most important minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

15

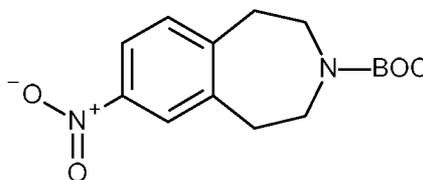
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 49b	<p>From intermediate 48b</p>	690	Quant. Procedure with 2 equivalent of BH ₃ .THF
Intermediate 80b		439	16 Procedure with 2 equivalent of

Intermediate number	Structure	Mass (mg)	Yield (%)
	From intermediate 14b		BH ₃ .THF

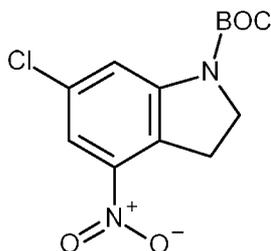
Example A17a

Preparation of intermediate 18:

Boc₂O (2.00 g, 9.16 mmol) was added portionwise to a solution of intermediate 17 (880.00 mg, 4.58 mmol) in CH₃CN (30 mL) and the reaction mixture was stirred at rt for 15 h. The reactive mixture was poured into H₂O and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by silical gel chromatography (irregular SiOH 35-40 μm, 40 g, mobile phase gradient: from 100% heptane, 0% EtOAc to 60% heptane, 40% EtOAc). The pure fractions were collected and evaporated to dryness to give 1.07 g of intermediate 18 (80% yield).

Alternative preparation of intermediate 18:

To a solution of intermediate 17 (5.28 g, 27.46 mmol) in TEA (8.77 mL, 63.15 mmol) and DCM (274 mL) were added at rt Boc₂O (14.98 g, 68.64 mmol) and DMAP (0.67 g, 5.49 mmol). The reaction mixture was stirred at rt for 13 h. The solvent was evaporated in vacuo and the crude residue was dissolved in EtOAc and washed with sat. NaHCO₃ solution and brine. The organic layer was dried over MgSO₄, filtered and concentrated under vacuo. The crude product was purified by silical gel chromatography (SiO₂, mobile phase gradient: 95% hexane, 5% EtOAc to 50% hexane, 50% EtOAc). The pure fractions were collected and evaporated to dryness to give 7.3 g of intermediate 18 (91% yield).

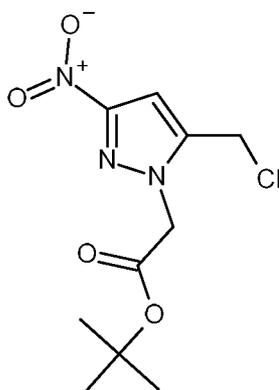


Preparation of intermediate 49:

Boc₂O (356.04 mg, 1.63 mmol) was added to a solution of intermediate 48 (270.00 mg, 1.36 mol) in THF (11 mL) and the solution was stirred at rt for 3 days. DMAP (16.61 mg, 0.14 mmol) and additional Boc₂O (356.04 mg, 1.63 mmol) were added and the mixture was stirred at 60 °C in a sealed tube for 3 h. The reaction mixture was cooled to rt and was diluted with EtOAc and water. The organic layer was dried over MgSO₄, filtered and the solvent was removed under reduced pressure to give 400 mg of intermediate 49 (98% yield, yellow solid) which was directly engaged in the next step without further purification.

10

Example A17b



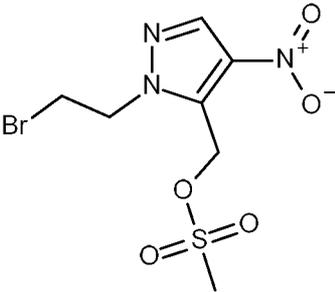
Preparation of intermediate 43b:

MsCl (1.17 mL, 15.16 mmol) was added dropwise to a stirred solution of intermediate 42b (1.95 g, 7.58 mmol) and TEA (1.58 mL, 11.37 mmol) in DCM (34.8 mL) at rt. The reaction mixture was stirred at rt for 2 h. MsCl (1.17 mL, 15.16 mmol) was added dropwise and the reaction mixture was stirred at rt for 24 hours. Water was added and the residue was extracted with DCM, dried over MgSO₄, filtered and evaporated under vacuum to give 3.6 g of intermediate 43b (quant. yield) which was used in the next step without any further purification.

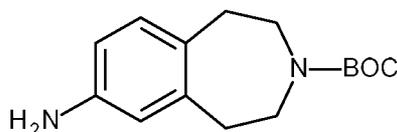
20

The intermediate in the table below was prepared by using an analogous method as reported for the preparation of intermediate 43b, starting from the respective starting

materials. The most important minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

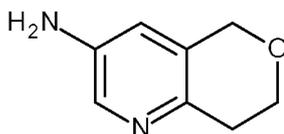
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 96b	 <p>From intermediate 95b</p>	1310	Quantitative. Procedure with 3 equiv. of MsCl and 3 equiv. of TEA

5 Example A18a



Preparation of intermediate 19:

Intermediate 18 (7.30 g, 24.97 mmol) was dissolved in MeOH (300 mL) and the solution was purged using vacuum and nitrogen. Pd/C (10 wt. %, 1.00 g, 1.00 mmol) was added and the reaction mixture was purged with hydrogen and stirred at rt under an atmosphere of hydrogen (1 bar) for 15 h. The reaction mixture was filtered through celite[®] and washed with MeOH. The filtrate was concentrated to dryness and the residue was purified by silica gel chromatography (mobile phase: DCM/MeOH/NH₃). The pure fractions were collected and evaporated to dryness to give 6.6 g of intermediate 19 (quant. yield).

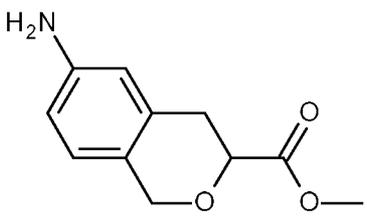
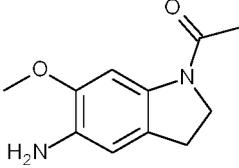
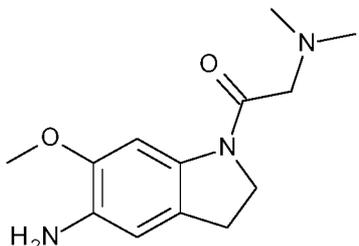
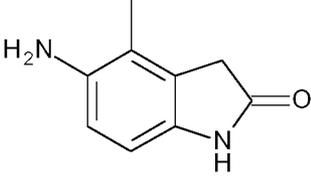


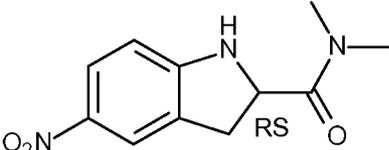
15 Preparation of intermediate 101:

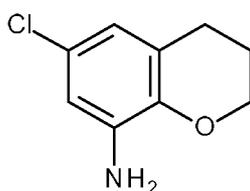
Intermediate 100 (1.30 g, 7.22 mmol) was dissolved in MeOH (77 mL) and the solution was degassed by N₂ bubbling. Pd/C (10% wt, 767.89 mg, 0.72 mmol) was added and the mixture was hydrogenated under an atmosphere of H₂ (1 bar) at rt for 16 h. The reaction mixture was filtered on a pad of celite[®] and the solvent was removed under reduced

pressure to give 1.03 g of intermediate 101 (95% yield, brown solid) which was used in the next step without further purification.

5 The intermediate in the table below was prepared by using an analogous method starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

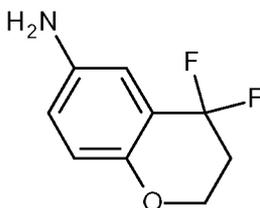
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 30	 <p>From intermediate 29</p>	1060	23
Intermediate 158	 <p>From Indoline, 1-acetyl-6-methoxy</p>	320	96 Procedure with MeOH/EtOAc: 1/1 as solvent
Intermediate 163	 <p>From intermediate 162</p>	850	Quant. Procedure with EtOH as solvent
Intermediate 169	 <p>From intermediate 168</p>	350	55 Based on a purity of 80% evaluated by

			LC/MS Procedure with EtOH as solvent
Intermediate 172	 <p>From intermediate 171</p>	1300	83 Procedure with EtOH as solvent



Preparation of intermediate 25:

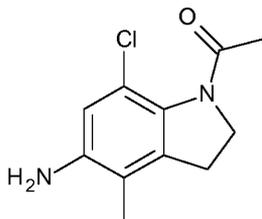
Zinc (10.41 mg, 0.16 mmol) was added to a solution of intermediate 24 (340.00 mg, 1.59 mmol) in AcOH (25 mL) and the mixture was stirred at rt for 20 h. The solvent was removed under reduced pressure. The residue was taken up with EtOAc and was basified with an aqueous saturated solution of NaHCO₃. The layers were separated and the organic layer was dried over MgSO₄, filtered and the solvent was removed under reduced pressure to give 250 mg of intermediate 25 (86% yield, brown oil).



10 Preparation of intermediate 38:

A solution of intermediate 37 (0.78 g, 3.62 mmol) in MeOH (29.37 mL, 725.05 mmol) was hydrogenated at rt with RaNi (0.79 g, 13.54 mmol) under 3 bars pressure for 12 h. The catalyst was filtered over a pad of celite[®] and the filtrate was evaporated to dryness. The residue was purified by silica gel chromatography (Irregular SiOH 40 μm, mobile phase:

100% DCM). The pure fractions were evaporated to give 515 mg of intermediate 38 (77% yield).



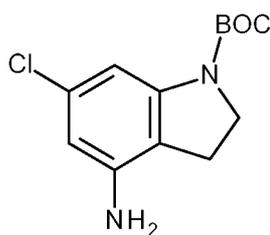
Preparation of intermediate 45:

5 A mixture of intermediate 44 (1.00 g, 3.93 mmol), Zinc (2.57 g, 39.26 mmol) and AcOH (42.25 mL, 39.26 mmol) in MeOH (25 mL) was stirred at rt for 2.5 h. The mixture was filtered over a pad celite[®]. Then, an extraction was performed with EtOAc and HCl 1N. The aqueous layer was basified with NaOH 1N and extracted with EtOAc (twice). The organic layers were washed with brine, dried with MgSO₄, filtered and evaporated under vacuum to give 550 mg of intermediate 45 (62% yield, light brown foam) which was
10 directly engaged in the next step without any further purification.

The intermediates in the table below were prepared by using an analogous method starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 74	<p>From intermediate 73</p>	116	73
Intermediate 80	<p>From intermediate 79</p>	271	63

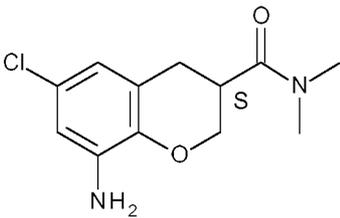
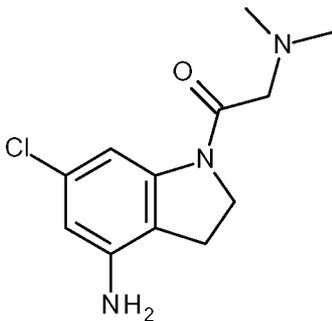
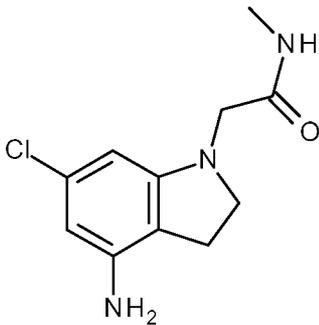
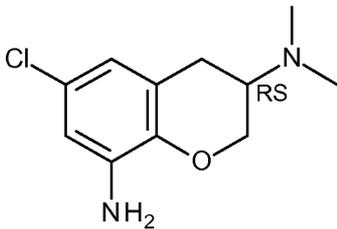
Intermediate number	Structure	Mass (mg)	Yield (%)
		<i>solid</i>	

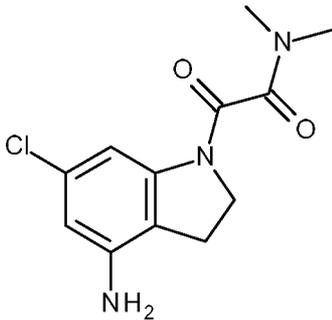
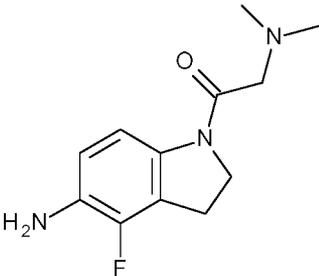
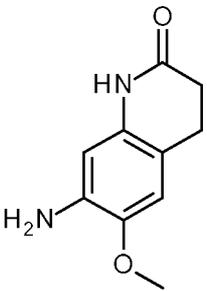


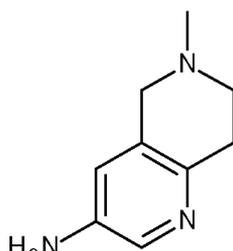
Preparation of intermediate 50:

- In a sealed tube, a suspension of intermediate 49 (390.00 mg, 1.31 mmol), NH₄Cl (279.33 mg, 5.22 mmol) and iron powder (364.54 mg, 6.53 mmol) in EtOH (7 mL) and water (7 mL) was stirred at 85 °C for 2 h. The reaction mixture was diluted with EtOAc and water and, the layers were separated. The organic layer was dried over MgSO₄, filtered and the solvent was removed under reduced pressure to give 390 mg of intermediate 50 (90% yield, 83% purity based on ¹H NMR, yellow oil) which was directly engaged in the next step without further purification.
- 10 The intermediates in the table below were prepared by using an analogous method starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 57	<p>From intermediate 55</p>	222	Quant.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 60	 <p>From intermediate 56</p>	230	99
Intermediate 64	 <p>From intermediate 63</p>	152	70
Intermediate 69	 <p>From intermediate 68</p>	192	58
Intermediate 85	 <p>From intermediate 84</p>	320	77

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 91	 <p>From intermediate 90</p>	129	43
Intermediate 155	 <p>From intermediate 154</p>	350	63 Procedure in an open vessel with MeOH as solvent
Intermediate 232	 <p>From intermediate 231</p>	600	63 in an open vessel with MeOH as solvent



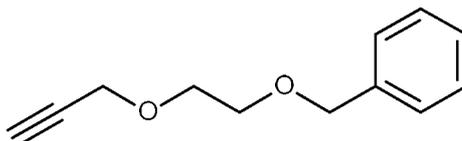
Preparation of intermediate 129:

To a solution of intermediate 128 (1.50 g, 7.76 mmol) in EtOH (35 mL) and Me-THF (35 mL) was added Pd/C (10 wt. %) (826.24 mg, 0.77 mmol) and the mixture was stirred

under H₂ atmosphere for 2 h. The mixture was filtered over a pad of celite[®] and the cake was washed with EtOH. The filtrate was evaporated in vacuo to give 1.33 g of intermediate 129 which crystallized upon standing (quant. yield, 95% purity based on ¹H NMR, yellow oil).

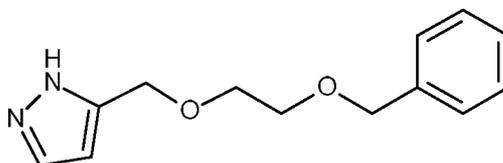
5

Example A18b

Preparation of intermediate 61b:

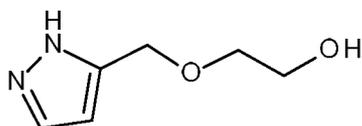
In a 500 mL triple-neck flask under N₂, NaH (95%) (7.91 g, 313 mmol) was suspended at 0 °C in dry Me-THF (200 mL). 2-benzyloxyethanol (31.75 g, 209 mmol) was added dropwise at 0-5 °C over 30 min, and the mixture was stirred at rt for 30 min. Propargyl bromide (80% in toluene) (45.35 mL, 417 mmol) was then added dropwise at 0-5 °C over 30 min and the mixture was allowed to reach rt, then refluxed (oil bath temperature: 85 °C) for 16 h and cooled down to rt. A 10% aqueous solution of NH₄Cl (~100 mL) was added dropwise to the reaction mixture at 0-5 °C over 30 min under stirring, and the resulting mixture was extracted with EtOAc (5 x 200 mL), dried over MgSO₄, filtered and evaporated in vacuo. The crude residue was then suspended in 500 mL of a mixture heptane/EtOAc (9:1). Irregular silica was added and the suspension was stirred for 30 min, then filtered. The plug of silica was washed with heptane/EtOAc (9:1, 3 x 500 mL). The solvent was evaporated to give 38.6 g of intermediate 61b (97% yield, clear yellow oil).

20

Preparation of intermediate 62b:

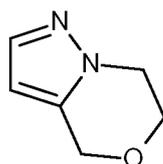
In a 300 mL-sealed tube, intermediate 61b (32.32 g, 170 mmol) and (trimethylsilyl)diazomethane (2M in hexane) (87.50 mL, 175 mmol) were mixed and the tube was sealed and stirred at 135 °C for 20 h. After cooling down to rt, the mixture was evaporated under vacuum to give 51 g of intermediate 62b (quant. yield, yellow-brown oil) which was used in the next step without any further purification.

25



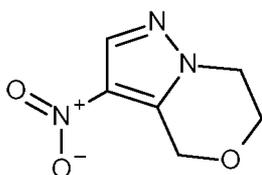
Preparation of intermediate 63b:

In a 1L autoclave, Pd(OH)₂ on carbon (9.25 g, 6.6 mmol) was added to a solution of intermediate 62b (51.00 g, 0.22 mol) in EtOH (400 mL). The mixture was hydrogenated during 18 h at 100 °C under 10 bar. The mixture was cooled down to rt and filtered with DCM and EtOH on celite[®]. The solvents were evaporated under vacuum and the resulting residue was dried under vacuum to give 25.7 g of intermediate 63b (82% yield, colorless oil).



Preparation of intermediate 64b:

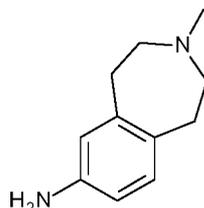
To a mixture of intermediate 63b (3.27 g, 23.0 mmol) in dry DCM (on amylene, EtOH free) (490 mL) was added cyanomethylenetriethylphosphorane (7.23 mL, 28 mmol). The mixture was then stirred for 60 hours at 40 °C. The solvent was evaporated and the mixture was purified via silica gel chromatography (Stationary phase: irregular bare silica 150 g, mobile phase: 30% heptane, 70% EtOAc) to afford, after evaporation, 1.57 g of intermediate 64b (55% yield, clear brown oil).



Preparation of intermediate 65b:

Intermediate 64b (1.57 g, 12.6 mmol) was dissolved in sulfuric acid (98%) (20 mL) and the reaction mixture was cooled to 0 °C. A mixture of nitric acid (63%) (10.4 mL) in sulfuric acid (98%) (12 mL) was added dropwise and the reaction mixture was stirred at room temperature for 3.5 hours. The reaction was then poured into ice/water and extracted with DCM (5 x 200 mL). The combined organic layers were washed with a saturated solution of NaHCO₃ (twice), dried over MgSO₄, filtered, and evaporated in vacuo to give 1.4 g of intermediate 65b (65% yield, off-white solid).

Example A19a

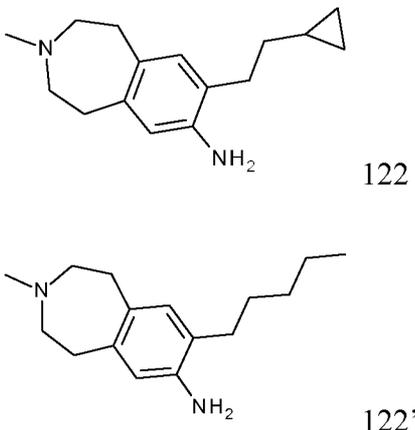
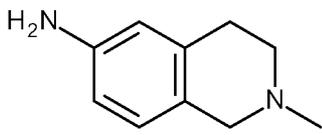


Preparation of intermediate 20:

In a schlenk flask, LiAlH_4 (4.34 g, 114.35 mmol) was added to a solution of intermediate 19 (5.00 g, 19.1 mmol) in dry THF (400 mL). The reaction mixture was heated at 60 °C for 6 h, then quenched with addition of water (4.34 mL, very slow addition), 3N solution of NaOH (4.34 mL) and water (13 mL). The mixture was stirred at rt for 5 min, diluted with EtOAc and water. The layers were separated and the organic layer was dried over MgSO_4 , filtered and the solvent was removed under reduced pressure to give 3.43 g of intermediate 20 (quant. yield, orange oil).

10 The intermediates in the table below were prepared by using an analogous method starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column ‘Yield (%)’.

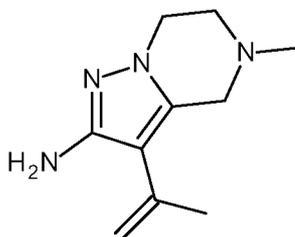
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 97	<p>From intermediate 96</p>	450 <i>Yellow oil</i>	Quant.
Intermediate 110	<p>From intermediate 109</p>	346 <i>Yellow solid</i>	74
Intermediate 114	<p>From intermediate 113</p>	278 <i>Yellow oil</i>	72

Intermediate number	Structure	Mass (mg)	Yield (%)
Mixture of intermediate 122 and intermediate 122'	 <p>122</p> <p>122'</p> <p>From a mixture of intermediate 121 and 121'</p>	917	91
Intermediate 132	 <p>From 6-amino-2-N-Boc-1,2,3,4-tetrahydro-isoquinoline</p>	320	98

Example A19b

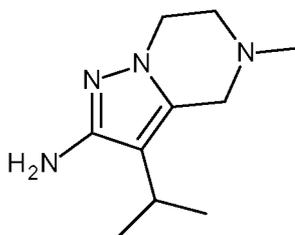
Preparation of intermediate 84b:

5 NBS (1.93 g, 10.81 mmol) was added portionwise to a solution of intermediate 50b (1.50 g, 9.86 mmol) in DCM (85.22 mL). The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was poured onto ice and water and basified with K_2CO_3 powder. The mixture was extracted with DCM, dried over $MgSO_4$, filtered and evaporated under vacuum to give 2.15 g of intermediate 84b (94% yield).



Preparation of intermediate 85b:

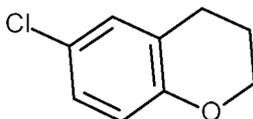
Intermediate 84b (600.00 mg, 2.60 mmol), 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (683.24 μ L, 3.635 mmol), XPhos precatalyst (153.21 mg, 0.20 mmol) and potassium phosphate (0,5 M aqueous solution) (10.39 mL, 5.19 mmol) in THF (5.28 mL) were stirred in a sealed tube at 130 °C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 15 min. Water was added and the reaction mixture was filtered over a pad of celite[®] which was washed with DCM. The filtrate was decanted and The organic layer was separated, dried over MgSO₄, filtered and evaporated. The residue was purified by silica gel chromatography (Stationary phase: Irregular SiOH 40 g, mobile phase gradient: from 100% DCM to 94% DCM, 6% MeOH (2% NH₄OH)). The pure fractions were combined and the solvent was evaporated to give 220 mg of intermediate 85b (44% yield).



Preparation of intermediate 86b:

Intermediate 85b (220.00 mg, 1.14 mmol) in MeOH (15.87 mL) and EtOAc (9.1 mL) was hydrogenated at room temperature with Pd/C (10%) (31.74 mg, 0.030 mmol) as a catalyst in a pressure vessel reactor (3 bars) for 12 h. The catalyst was filtered off on a pad of celite and the solvent was evaporated to give 220 mg of intermediate 86b (quant. yield).

20 Example A20a



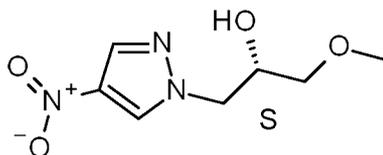
Preparation of intermediate 23:

To a solution of 6-chlorochroman-4-one (3.00 g, 16.43 mmol) in AcOH (105 mL), degassed with N₂ bubbling, was added Pd/C (10 wt. %, 1.75 g, 1.64 mmol) and the mixture

was hydrogenated under an atmosphere of H₂ (1 bar) at rt for 16 h. The mixture was filtered over a pad of celite[®] and the solvent was removed under reduced pressure. The residue was coevaporated with toluene (twice) to give 2.87 g of intermediate 23 (quant. yield, off-white solid).

5

Example A20b



Preparation of intermediate 101b:

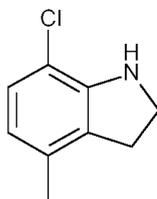
In a sealed tube, 4-nitro-1H-pyrazole (1.5 g, 13.265 mmol), (S)-glycidyl methyl ether (1.753 g, 19.898 mmol) and K₂CO₃ (2.75 g, 19.898 mmol) in DMF (14.38 mL) were stirred at 130°C using one single mode microwave (Masterwave BTR Anton Paar) with a power output ranging from 0 to 1700 W for 5 min. [fixed hold time].

10

The reaction mixture was poured into water, acidified with 3N HCl (aq), extracted twice with EtOAc and the combined organic layers were washed with water, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by normal phase flash chromatography (Irregular SiOH 40µm 40g GraceResolv[®]). Mobile phase gradient from 80% heptane, 20% EtOAc to 60% heptane, 40% EtOAc. The pure fractions were combined and the solvent was evaporated *in vacuo* to afford the product (1.7 g, yield 63.7%).

15

20 Example A21a

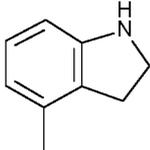


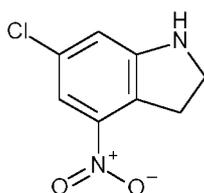
Preparation of intermediate 42:

Sodium cyanoborohydride (758.86 mg, 12.08 mmol) was added slowly to a solution of 7-chloro-4-methyl-1H-indole (1.00 g, 6.04 mmol) in AcOH (10 mL). The mixture was stirred at rt for 3 h. The mixture was poured in ice and aqueous NaOH 3M. An extraction was performed with EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to give 1.15 g of intermediate 42 (quant. yield, 88% purity based on ¹H NMR, orange oil) which was directly engaged in the next step without any further purification.

25

The intermediate in the table below was prepared by using an analogous method starting from the respective starting materials.

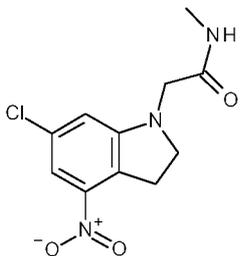
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 71	 From 4-methylindole	912	90
		<i>Colorless oil</i>	



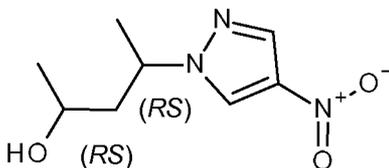
5 Preparation of intermediate 48:

In a sealed tube, a mixture of 6-chloro-4-nitro-indoline (1.00 g, 5.09 mmol) and triethylsilane (2.11 mL, 13.22 mmol) in TFA (16 mL) was stirred at 60 °C for 2 h. The reaction mixture was diluted with EtOAc and was treated with an aqueous saturated solution of NaHCO₃. The layers were separated and the organic layer was dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography (irregular SiOH 15-40 μm, 40 g, dry loading on celite[®], mobile phase gradient: from Heptane/EtOAc 100/0 to 60/40) to give 650 mg of intermediate 48 (64% yield, red solid).

15 The intermediate in the table below was prepared by using an analogous method starting from the respective starting materials.

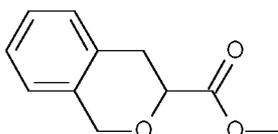
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 68	 From intermediate 67	<i>Yellow solid</i>	Quant.

Example A21b

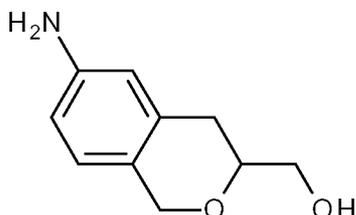
Preparation of intermediate 106b:

- In a sealed tube, 4-nitro-1*H*-pyrazole (3.898 g, 34.475 mmol) and 3-penten-2-one (6.729 mL, 0.862 g/mL, 68.951 mmol) in EtOH (40.26 mL) were stirred at 140°C for 4 hours.
- 5 After cooling down to rt, sodium borohydride (2.609 g, 68.951 mmol) was added portionwise. The reaction mixture was stirred at rt overnight. The reaction mixture was poured onto ice water, acidified with 3N HCl(aq), extracted with DCM twice, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified *via*
- 10 preparative LC (Stationary phase: irregular SiOH 15-40µm 80g Grace, Mobile phase: gradient from 80% heptane, 20% EtOAc to 40% heptane, 60% EtOAc, 10% MeOH (2% NH₄OH)) to afford intermediate 106b (5.3 g, yield 77.2%)

Example A22a

15 Preparation of intermediate 28:

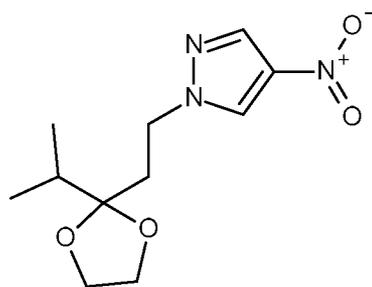
- In a sealed tube, a mixture of DL-Phenyllactic acid (5.00 g, 30.09 mmol) and paraformaldehyde (903.44 mg, 30.09 mmol) in trifluoroacetic acid (17.5 mL) were purged by N₂. The reaction mixture was stirred at 150 °C using one single mode microwave (Biotage[®] Initiator EXP 60) with a power output ranging from 0 to 400 W for 5 min. The
- 20 reaction mixture was evaporated and dissolved in MeOH (62.5 mL) and a catalytic amount of H₂SO₄ (80.19 µL, 1.50 mmol). The reaction mixture was refluxed for 4 h. The reaction mixture was diluted with DCM and washed with sat. NaHCO₃. The organic layer was dried over MgSO₄, filtered and evaporated to dryness. A purification was performed *via* silica gel chromatography (Irregular SiOH 20-45 µm, 80 g, mobile phase gradient: from
- 25 90% Heptane, 10% EtOAc to 70% Heptane, 30% EtOAc) to give 5.2 g of intermediate 28 (90% yield).



Preparation of intermediate 31:

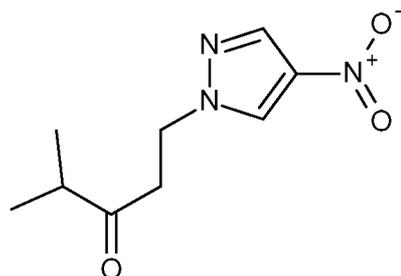
LiAlH₄ (2.4 M in THF) (2.54 mL, 6.11 mmol) was added dropwise to a stirred solution of intermediate 30 (530.00 mg, 2.56 mmol) in THF (16.6 mL) at -40 °C under nitrogen. The reaction mixture was stirred at -40 °C for 45 min. Water was carefully added. The reaction mixture was stirred at rt for 15 min and filtered over a pad of celite[®]. The celite[®] was washed with DCM. The organic layer was separated, dried over MgSO₄, filtered and evaporated to give 470 mg of intermediate 31 (quantitative yield).

Example A22b



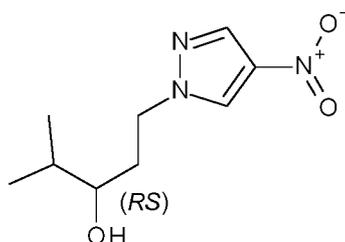
10 Preparation of intermediate 115b:

In a sealed tube, (cyanomethylene)tributylphosphorane (CMBP) (5.141 mL, 0.92 g/mL, 19.596 mmol) was added to a solution of 4-nitro-1*H*-pyrazole (1.153 g, 10.195 mmol) and 2-(2-isopropyl-1,3-dioxolan-2-yl)ethanol (2.45 g, 15.292 mmol) in toluene (45.352 mL). The mixture was heated at 60°C for 12 hours. The solvent was evaporated. The residue was purified by preparative LC (Irregular SiOH 20-45μm 120g GraceResolv[®], mobile phase Gradient from 100% DCM to 99% DCM, 1% MeOH (2% NH₄OH))
 15 The pure fractions were combined and the solvent was concentrated in vacuo to afford intermediate 115b (2.6 g, yield 99.9 %).



Preparation of intermediate 116b:

Intermediate 115b (2.6 g, 10.185 mmol) in HCl (1M in H₂O) (40.741 mL, 1 M, 40.741 mmol) and ACN (49.553 mL) was stirred at rt for 12 hours. Water was added. The reaction mixture was extracted twice with DCM, dried over MgSO₄, filtered and concentrated *in vacuo* to afford intermediate 116b (2.15 g, yield 99.9 %).

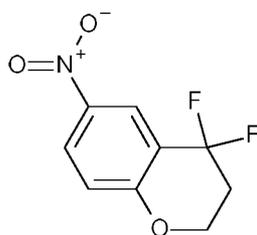


Preparation of intermediate 117b:

Sodium borohydride (752.279 mg, 19.884 mmol) was added to intermediate 116b (2.1 g, 9.942 mmol) in EtOH (17.416 mL) at rt. The reaction mixture was stirred for 3 hours, poured out onto ice and water and made acidic with 3N HCl(aq). The aqueous layer was extracted twice with DCM, dried over MgSO₄, filtered and concentrated *in vacuo*. A purification was performed *via* preparative LC (Stationary phase: irregular SiOH 15-40 μ m 80g GRACE, Mobile phase: 100% DCM) to afford intermediate 117b (1.53 g, yield 72.2%).

15

Example A23a



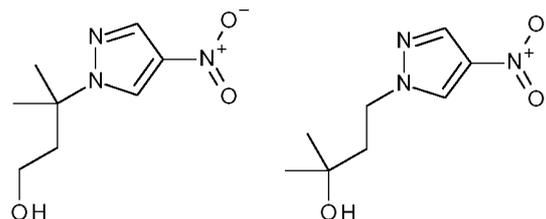
Preparation of intermediate 37:

To a solution of 6-nitrochroman-4-one (2.00 g, 10.35 mmol) in DCM (1.99 mL) was added at rt (diethylamino)sulfur trifluoride (2.5 mL). The mixture was stirred at 60 °C for 7 h. The reaction mixture was carefully quenched with MeOH. The solvents were evaporated

20

under vacuum and the residue was purified by silica gel chromatography (Irregular SiOH 40 μ m, mobile phase 100% DCM) to give 680 mg of intermediate 37 (31% yield).

Example A23b

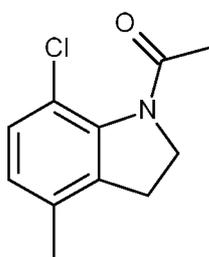


5 Preparation of intermediate 124b and 124b':

In a sealed tube, (cyanomethylene)tributylphosphorane (CMBP) (15.608 mL, 0.92 g/mL, 59.496 mmol) was added dropwise to a solution of 4-nitro-1*H*-pyrazole (3.5 g, 30.953 mmol) and 3-methyl-1,3-butanediol (4.836 g, 46.429 mmol) in toluene (137.696 mL). The mixture was heated at 60°C for 12 hours. The solvent was evaporated. The residue was purified by preparative LC (Irregular SiOH 20-45 μ m 220g GraceResolv®, mobile phase Gradient from 90% heptane, 10% AcOEt to 40% heptane, 60% AcOEt)

The pure fractions were combined and the solvent was evaporated to afford a residue (3.3 g, yield 53.5%). The residue was purified by preparative LC (Irregular SiOH 20-45 μ m 80g GraceResolv®, mobile phase Gradient from 100% DCM to 97% DCM, 3% MeOH (2% NH₄OH)). The pure fractions were combined and the solvent was evaporated to afford a 55/45 mixture of intermediate 124b and 124b' (620 mg, yield 10 %).

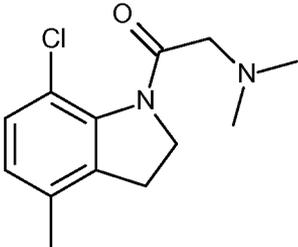
Example A24a

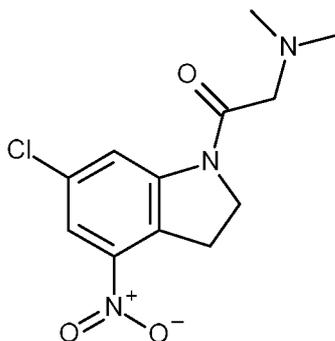


Preparation of intermediate 43:

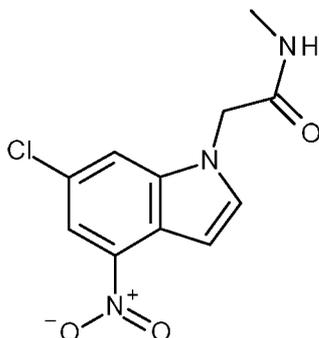
20 A mixture of intermediate 42 (1.15 g, 6.04 mmol based on 88% purity based on ¹H NMR), acetyl chloride (0.64 mL, 9.06 mmol) and TEA (1.34 mL, 9.66 mmol) in DCM (20 mL) was stirred under N₂ at rt for 6 h. An extraction was performed with DCM and brine. The organic layer was dried over MgSO₄, filtered and evaporated under reduced pressure. The crude residue was purified by silica gel chromatography (irregular SiOH 15-40 μ m, 40 g ,
25 liquid injection with DCM, mobile phase gradient: DCM/MeOH from 100:0 to 95:05 in 10 CV) to give 1.13 g of intermediate 43 (89% yield, light yellow solid).

The intermediate in the table below was prepared by using an analogous method starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 78	 <p>From intermediate 42 and dimethylaminoacetyl chloride hydrochloride</p>	442 <i>Brown oil</i>	41 Procedure with DCM/TEA (10:1, eq/eq)

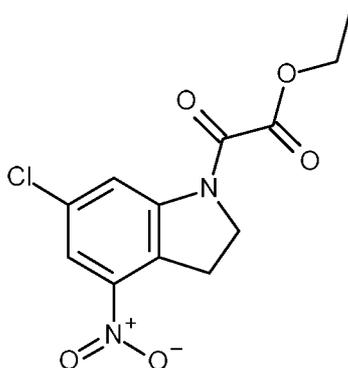


- 5 Preparation of intermediate 63:
 Bromoacetyl bromide (264 μ L, 3.02 mmol) was added to a stirred suspension of intermediate 48 (500 mg, 2.52 mmol) and triethylamine (770 μ L, 5.54 mmol) in dry DCM (6.7 mL) at 0 °C under N₂. The mixture was stirred at 0°C under N₂ for 17h. Then, dimethylamine (1.9 mL, 3.78 mmol) was added to the mixture under N₂. The reaction
- 10 mixture was stirred at 0°C under N₂ and allowed to warm to room temperature for 20h. The reaction mixture was diluted with EtOAc and water and the layers were separated. The organic layer was dried over MgSO₄, filtered off and evaporated under reduced pressure to give 572 mg of a brown oil. This residue was purified by silica gel chromatography (irregular SiOH 15-40 μ m, 30 g, dry loading on celite[®], mobile phase gradient: from DCM
- 15 100% to DCM 90%, MeOH 10%) to give 243 mg of intermediate 63 (34%).



Preparation of intermediate 67:

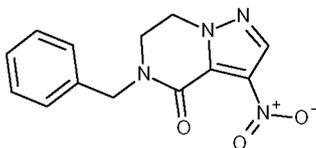
In a sealed tube, intermediate 77 (287.19 mg, 2.67 mmol) was added to a solution of 6-chloro-4-nitroindole (350.00 mg, 1.78 mmol) and Cs_2CO_3 (870.11 mg, 2.67 mmol) in dry DMF (3.5 mL) under N_2 . The mixture was stirred at 90 °C for 17 h. The reaction mixture was diluted with EtOAc and water and the layers were separated. The organic layer was washed with brine, dried over MgSO_4 and filtered. The solvent was removed under reduced pressure to give 378 mg of intermediate 67 (79% yield, brown solid) which was directly engaged in the next step without further purification.



Preparation of intermediate 88:

A solution of intermediate 48 (510.00 mg, 2.57 mmol) and DIPEA (1.33 mL, 7.70 mmol) in dry DCM (8 mL) was cooled in an ice bath. Then, ethyl oxalyl chloride (345 μL , 3.08 mmol) was added dropwise. The reaction was stirred and allowed to warm to room temperature for 17 h. The reaction mixture was diluted with EtOAc and washed with water, a saturated aqueous solution of NaHCO_3 and brine. The organic layer was dried over MgSO_4 , filtered and the solvent was removed under reduced pressure to give 752 mg of intermediate 88 (98% yield, brown residue) which was directly engaged in the next step without further purification.

Example A24b

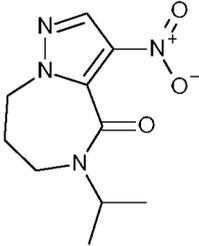


Preparation of intermediate 133b:

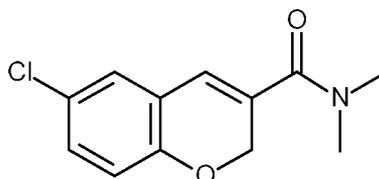
N-Benzylthanalamine (2.147 mL, 1.06 g/mL, 15.052 mmol) and 4-nitro-1*H*-pyrazole-3-carboxylic acid (2 g, 12.732 mmol) in toluene (13.814 mL) were stirred at 15°C. SOCl₂ (2.554 mL, 1.64 g/mL, 35.206 mmol) was slowly added followed by DMF (96.907 μL, 0.944 g/mL, 1.252 mmol). The reaction mixture was stirred at 55°C for 10 minutes then 70°C for 18h. The reaction was allowed to cool to room temperature and then the solvents were evaporated *in vacuo*. The residue was taken up into DMF (11.655 mL) and triethylamine (9.415 mL, 0.728 g/mL, 67.732 mmol) was added slowly. The reaction mixture was stirred at rt for 12h. Water was added. The mixture was extracted twice with EtOAc, dried over MgSO₄, filtered and concentrated *in vacuo* to give 4.4g of crude material. A purification was performed *via* preparative LC (Stationary phase: irregular SiOH 15-40μm 120g Grace, Mobile phase: gradient from 100% DCM to 97% DCM, 3% MeOH, 0.3%NH₄OH) to give 1.7g of intermediate 133b (41%).

The intermediates in the table below were prepared by using an analogous method as described for the preparation of intermediate 133b, starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

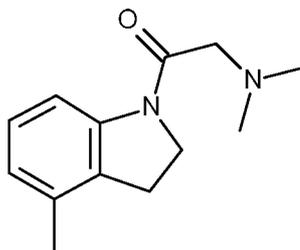
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 137b	<p>From 4-nitro-1<i>H</i>-pyrazole-3-carboxylic acid and 2-(Isobutylamino)ethanol Hydrochloride</p>	500	44

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 141b	 <p>From 4-nitro-1<i>H</i>-pyrazole-3-carboxylic acid and 3-(Isopropylamino)propanol</p>	850	9

Example A25a

Preparation of intermediate 52:

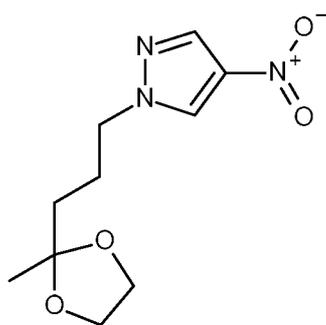
To a solution of 6-chloro-2*H*-chromene-3-carboxylic acid (1.00 g, 4.75 mmol) in dry DMF (50 mL) were added DIPEA (2.07 mL, 11.87 mmol) and HBTU (1.80 g, 4.75 mmol). The mixture was stirred at rt for 15 min and dimethylamine (2.0 M in THF) (3.56 mL, 7.12 mmol) was added. The mixture was stirred at rt for 16 h and evaporated in vacuo. The residue was taken-up in EtOAc and a mixture of a saturated aqueous solution of NaHCO₃ and water (50:50) was added. The aqueous layer was separated and extracted with EtOAc (three times). The combined organic layers were washed with a saturated aqueous solution of NaCl (three times), dried over MgSO₄, filtered off and evaporated in vacuo to give 1.45 g of intermediate 52 (quantitative yield, brown oil) which was directly engaged in the next step without further purification.

Preparation of intermediate 72:

A solution of intermediate 71 (912.00 mg, 6.85 mmol), HATU (3.12 g, 8.22 mmol), DIPEA (2.37 mL, 13.7 mmol) and *N,N*-dimethylglycine hydrochloride (955.74 mg, 6.85

mmol) in dry DMF (80 mL) was stirred for 3 h at rt under nitrogen. The mixture was evaporated to dryness and extracted with EtOAc and aqueous NaOH 1N. The organic layer was washed with brine, dried over MgSO₄, filtered and evaporated. Another extraction was performed using DCM and water. The organic layer was washed with brine, dried over
 5 MgSO₄, filtered, evaporated and purified by silica gel chromatography (irregular SiOH 15-40 μm, 80 g, liquid injection with DCM, mobile phase gradient: DCM/MeOH from 100:0 to 95:05 in 10 CV) to give 0.9 g of intermediate 72 (60% yield, white solid).

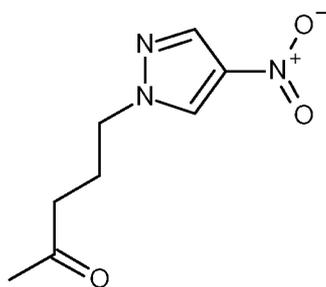
Example A25b



10 Preparation of intermediate 145b:

5-Chloro-2-pentanone ethylene ketal (8.014 mL, 1.09 g/mL, 53.062 mmol) was added to a suspension of 4-nitro-1H-pyrazole (4 g, 35.375 mmol) and K₂CO₃ (7.333 g, 53.062 mmol) in DMF (40.198 mL) at rt. The reaction mixture was stirred at 50°C for 3h.

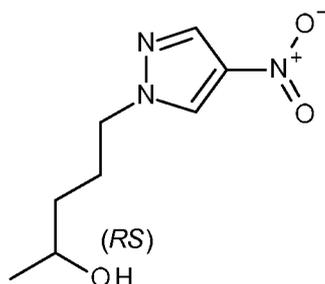
The reaction mixture was partitioned between water and DCM. The aqueous layer was
 15 extracted with DCM. The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. A purification was performed *via* preparative LC (Stationary phase: irregular SiOH 15-40μm 80g Grace, Mobile phase: gradient from 80% heptane, 20% EtOAc to 60% heptane, 40% EtOAc) to afford intermediate 145b (5.1 g, yield 59.8%)



Preparation of intermediate 146b:

20 HCl(aq) 3M (1.326 mL, 3 M, 3.979 mmol) was added to intermediate 145b (240 mg, 0.995 mmol) in ACN (4.84 mL) and distilled water (2.65 mL) and the reaction mixture stirred at rt for 12hours. Water was added. The reaction mixture was extracted twice with DCM,

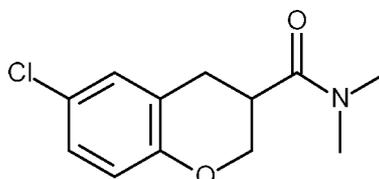
dried over MgSO_4 , filtered and concentrated *in vacuo* to afford intermediate 146b (230 mg, yield 117 %) which was used directly in the next step.



Preparation of intermediate 147b:

- 5 Sodium borohydride (1496.468 mg, 39.555 mmol) was added to intermediate 146b (3.9 g, 19.778 mmol) in EtOH (34.644 mL) at rt. The reaction mixture was stirred for 5 hours, poured out onto ice and water and made acidic with 3N HCl(aq). The aqueous layer was extracted twice with DCM, dried over MgSO_4 , filtered and concentrated *in vacuo*. A purification was performed *via* preparative LC (Stationary phase: irregular SiOH 15-40 μm
- 10 80g GRACE, Mobile phase: gradient from 100% DCM to 98% DCM, 2% MeOH(2% NH_4OH)) to afford intermediate 147b (3360 mg, yield 85.3 %).

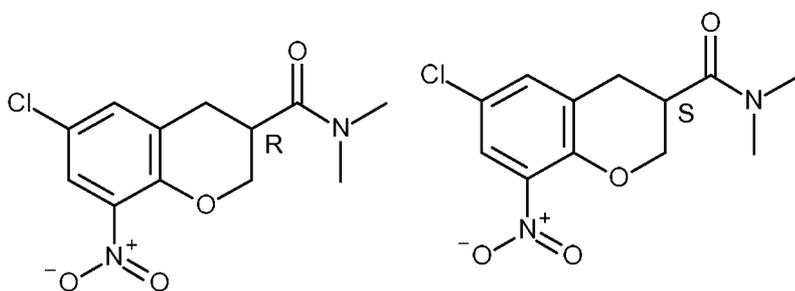
Example A26a



Preparation of intermediate 53:

- 15 To a solution of intermediate 52 (2.08 g, 8.75 mmol) in MeOH (103 mL) degassed with N_2 was added PtO_2 (198.72 mg, 0.87 mmol) and the mixture was hydrogenated under an atmosphere of H_2 (1 bar) at rt for 16 h. The mixture was filtered over a pad of celite[®] and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography (irregular SiOH 15-40 μm , 120 g, dry loading on celite[®], mobile phase
- 20 gradient: from Heptane/EtOAc 80/20 to 20/80) to give 1.28 g of intermediate 53 (61% yield, colourless oil).

Preparation of intermediate 55 and intermediate 56:

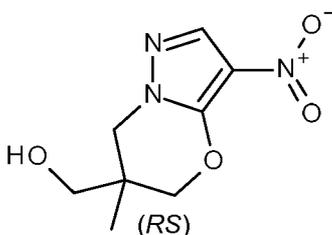


intermediate 55

intermediate 56

Intermediate 54 (732.00 mg) was purified by chiral SFC (Chiralcel OD-H 5 μ m 250*30 mm, mobile phase: 85% CO₂, 15% EtOH). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 250 mg of intermediate 55 as a white solid (34%) and 260 mg of intermediate 56 as a white solid (36%).

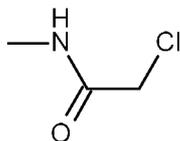
Example A26b

Preparation of intermediate 155b:

At 0°C under N₂, NaH (60% dispersion in mineral oil) (440 mg, 11.00 mmol) was added portionwise to a solution of 3-methyl-3-oxetanemethanol (1.10 mL, 11.03 mmol) in methyl-THF (40 mL). The reaction mixture was stirred at 0°C for 15 minutes. The reaction mixture was cooled to -78°C, and a solution of 1,4-dinitro-1H-pyrazole (2.60 g; 16.45 mmol) in methyl-THF (5.00 mL) was added dropwise. The reaction was diluted with Methyl-THF (15.00 mL) and stirred at -78 °C for 45 minutes. The reaction was quenched with water/ice and acidified with 3N HCl (aq), before being extracted with EtOAc. The organic layer was decanted and the solvent was evaporated until dryness. The product was taken up in DCM, triturated and the precipitate was filtered, dried under vacuum to give 0.46 g of intermediate 155b (20%). The material was used directly in the next step.

20

Example A27a

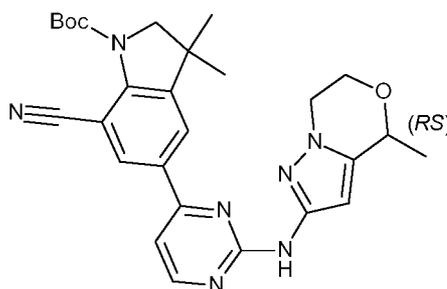


Preparation of intermediate 77:

In a sealed tube, under N₂, methylamine (13 mL, 26.0 mmol) was added dropwise to a solution of chloroacetyl chloride (1 mL, 12.6 mmol) in dry DCM (20 mL) at 0 °C and the mixture was allowed to warm to rt and was stirred at this temperature for 16 h. The reaction mixture was diluted with CH₂Cl₂ and water. The layers were separated and the organic layer was washed with a saturated aqueous solution of NaHCO₃. The organic layer was dried over MgSO₄, filtered and the solvent was removed under reduced pressure to give 993 mg of intermediate 77 (73% yield, colorless oil) which was directly engaged in the next step without further purification.

10

Example A27b

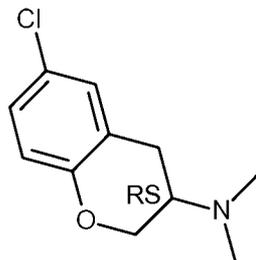


Preparation of intermediate 162b:

To a mixture of intermediate 31b (100 mg, 0.564 mmol), intermediate 161b (238.66 mg, 0.62 mmol) and Cs₂CO₃ (459.2, 1.409 mmol) in 1,4-dioxane (5 ml) was added Pd(OAc)₂ (12.657 mg, 0.0564 mmol) and BINAP (35.103 mg, 0.0564 mmol). The mixture was stirred for 2hrs at 95°C. The mixture was filtered and evaporated *in vacuo* to give a crude product. This residue was purified by flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate =1:1). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give the product intermediate 162b as a yellow solid (200 mg, 34.7%).

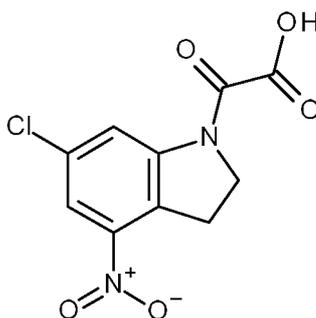
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Example A28

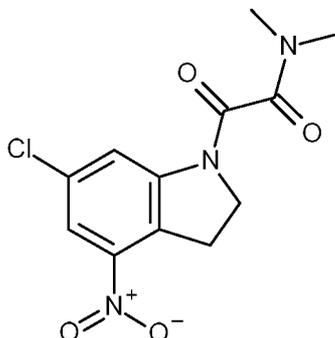
Preparation of intermediate 83:

In a sealed tube, a mixture of 6-chlorochroman-3-one (350.00 mg, 1.92 mmol),
 5 dimethylamine (2.88 mL, 5.75 mmol) and $\text{Ti}(\text{OiPr})_4$ (1.70 mL, 5.75 mmol) in Me-THF (18 mL) in presence of activated molecular sieve 4\AA was stirred at $60\text{ }^\circ\text{C}$ for 3 h. $\text{NaBH}(\text{OAc})_3$ (2.03 g, 9.58 mmol) and HOAc (3.28 mL) were added and the mixture was stirred at rt for 20 h. The reaction mixture was diluted with EtOAc and water. The layers were separated and the organic layer was washed with brine, dried over MgSO_4 , filtered and the solvent
 10 was removed under reduced pressure. The crude residue was purified by silica gel chromatography (irregular SiOH 15-40 μm , 24 g, dry loading on celite[®], mobile phase gradient: from heptane/EtOAc 100/0 to 40/60) to give 265 mg of intermediate 83 (65% yield, brown oil).

15 Example A29

Preparation of intermediate 89:

A mixture of intermediate 88 (514.00 mg, 1.72 mmol) and LiOH monohydrate (108.32 mg, 2.58 mmol) in Me-THF (12 mL) and distilled water (5 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with water and washed (twice) with
 20 DCM. The aqueous layer was acidified with 3N HCl and extracted with DCM (three times). The combined organic layers were dried over MgSO_4 , filtered and evaporated under reduced pressure to give 198 mg of intermediate 89 (43% yield, brown oil) which was directly engaged in the next step without any further purification.



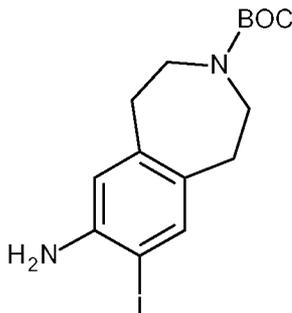
Preparation of intermediate 90:

In a sealed glassware, Triazabicyclo[4.4.0]dec-5-ene (23.78 mg, 167.40 μmol) and dimethylamine (0.50 mL, 1.00 mmol) were added to a stirred solution of intermediate 88 (100.00 mg, 0.33 mmol) in dry toluene (6.5 mL) at room temperature. The mixture was stirred at 50 $^{\circ}\text{C}$ for 17 h. The reaction mixture was diluted with EtOAc and water and the layers were separated. The organic layer was dried over MgSO_4 , filtered and the solvent was removed under reduced pressure to give 77 mg of intermediate 90 (77% yield, brown oil) which was directly engaged in the next step without any further purification.

10 Alternative preparation of intermediate 90:

In a sealed tube, intermediate 89 (198.00 mg, 0.73 mmol) and dimethylamine (438.98 μL , 0.88 mmol) were diluted in DMF (8.5 mL). Then, HATU (612.02 mg, 1.61 mmol) and DIPEA (319.46 μL , 1.83 mmol) were added and the mixture was stirred at 70 $^{\circ}\text{C}$ for 17 h. The reaction mixture was diluted with EtOAc and water and an extraction was performed (three times). The organic layer was washed with brine, dried over MgSO_4 and filtered. The solvent was removed under reduced pressure to give 354 mg of intermediate 90 (quant. yield, brown residue) which was directly engaged in the next step without any further purification.

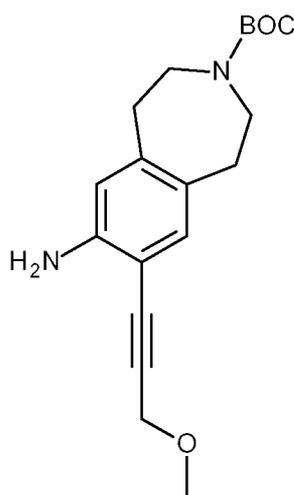
Example A30



20 Preparation of intermediate 94:

N-iodosuccinimide (4.72 g, 20.96 mmol) in MeCN (80 mL) was added via a dropping funnel to a solution of intermediate 19 (5.00 g, 19.1 mmol) in MeCN (170 mL) at 0 $^{\circ}\text{C}$

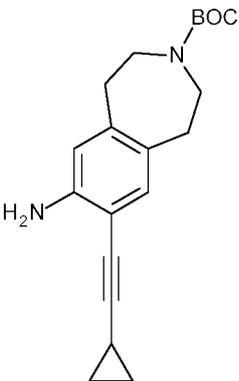
over 30 min and the mixture was stirred from 0 °C to room temperature for 16 h. The reaction mixture was diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography (irregular SiOH 15-40 μm, 220 g, dry loading on celite[®], mobile phase gradient: from Heptane/EtOAc 90/10 to 60/40) to give 6.00 g of intermediate 94 (82% yield, yellow solid).

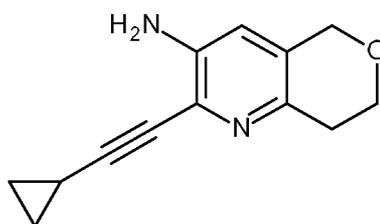


Preparation of intermediate 95:

In a Schlenk flask, a mixture of intermediate 94 (1.00 g, 2.58 mmol), methyl propargyl ether (218.00 μL, 2.58 mmol) and TEA (1.79 mL, 12.9 mmol) in dry Me-THF (13 mL) was purged with N₂. Then, PdCl₂(PPh₃)₂ (90.40 mg, 0.13 mmol) and copper(I) iodide (49.05 mg, 0.26 mmol) were added. The mixture was purged with N₂ and stirred at rt for 16 h. The mixture was then diluted with EtOAc and an aqueous saturated solution of NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc (once). Organic layer was dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography (irregular SiOH 15-40 μm, 40 g, dry load on celite[®], mobile phase gradient: from DCM/MeOH 100/0 to 95/5) to give 1.6 g of intermediate 95 (94% yield, yellow oil).

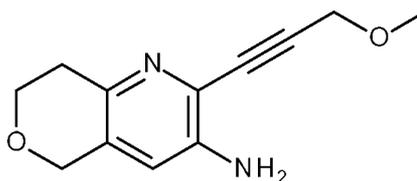
The intermediate in the table below was prepared by using an analogous method starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 120	 <p>From intermediate 94 and cyclopropylacetylene</p>	1560	88



Preparation of intermediate 103:

In a sealed tube, a mixture of intermediate 102 (0.89 g, 3.89 mmol), ethynylcyclopropane (0.51 g, 7.77 mmol) and TEA (2.70 mL, 19.4 mmol) in dry DMF (19 mL) was purged with N₂. PdCl₂(PPh₃)₂ (136.35 mg, 0.19 mmol) and CuI (73.99 mg, 0.39 mmol) were added. The mixture was purged with N₂ and stirred at 60 °C for 1 h. The reaction mixture was diluted with EtOAc and treated with an aqueous saturated solution of NaHCO₃. The organic layer was washed with brine (twice), dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography (irregular SiOH 15-40 μm, 24 g, dry load on celite[®], mobile phase gradient: from Heptane/EtOAc 90/10 to 30/70) to give 740 mg of intermediate 103 (89% yield, yellow solid).

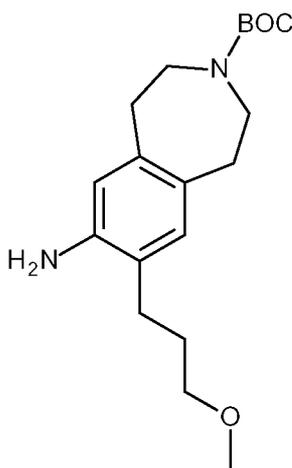


Preparation of intermediate 140:

In a sealed tube, a mixture of intermediate 102 (385.00 mg, 1.68 mmol), methyl propargyl ether (170.31 μL, 2.02 mmol), CuI (16.00 mg, 84.0 μmol) and piperidine (498.86 μL, 5.04

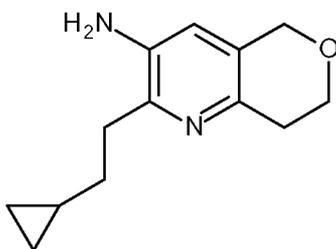
mmol) in Me-THF (8 mL) was purged with N₂. PdCl₂(PPh₃)₂ (117.97 mg, 0.17 mmol) was added and the mixture was purged with N₂ and stirred at rt for 18 h. The crude product was combined with another batch coming from a reaction performed on 30 mg of intermediate 102 and EtOAc and water were added. The organic layer was separated, dried over
 5 MgSO₄, filtered off and evaporated in vacuo. The crude residue was purified by silica gel chromatography (Irregular SiOH 15-40 μm, 24 g, mobile phase gradient: from DCM 100% to DCM 95%, iPrOH 5%) to give 283 mg of intermediate 140 (72% yield, brown solid).

Example A31



10 Preparation of intermediate 96:

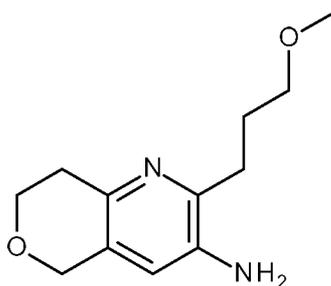
Intermediate 95 (0.50 g, 1.51 mmol) was diluted in MeOH (12 mL) and was purged with N₂. Pd/C (10 wt. %, 161.03 mg, 0.15 mmol) was added and the mixture was hydrogenated under an atmosphere of H₂ (1 bar) at rt for 16 h. The mixture was filtered on a pad of celite[®] and the solvent was removed under reduced pressure. The crude residue was
 15 purified by silica gel chromatography (irregular SiOH 15-40 μm, 24 g, dry load, mobile phase gradient: from Heptane/EtOAc 90/10 to 60/40) to give 352 mg of intermediate 96 (70% yield, yellow oil).



Preparation of intermediate 104:

CoCl₂ (89.72 mg, 0.69 mmol) was added to a solution of intermediate 103 (740.00 mg, 3.45 mmol) in dry MeOH (13.4 mL) and the mixture was stirred at rt for 30 min under N₂.
 20 Then NaBH₄ (522.64 mg, 13.81 mmol) in dry DMF (7.4 mL) was added and the mixture

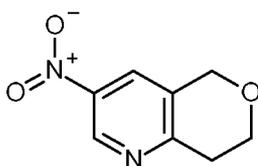
was stirred at rt for 15 min under N₂. The reaction mixture was diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc (twice). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography (irregular SiOH, 15-40 μm, 24 g, dry load on celite[®], mobile phase gradient: from Heptane/EtOAc 90/10 to 50/50) to give 260 mg of intermediate 104 (34% yield, yellow solid).



Preparation of intermediate 141:

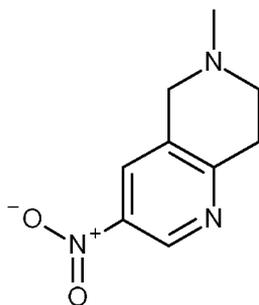
To a solution of intermediate 140 (250.00 mg, 1.15 mmol) in EtOH (5.50 mL) were added TEA (111.45 μL, 802 μmol) and PtO₂ (10.40 mg, 45.8 μmol). The mixture was stirred under H₂ atmosphere (1 bar) for 24 h and filtered on a pad of celite[®]. The celite[®] was washed with EtOH and the filtrate was evaporated in vacuo. The crude residue was purified by silica gel chromatography (Irregular SiOH 15-40 μm, 10 g, mobile phase gradient: from heptane 95%, EtOAc/MeOH (9:1) 5% to heptane 50%, EtOAc/MeOH (9:1) 50%) to give 173 mg of intermediate 141 (68% yield, pale brown solid).

Example A32



Preparation of intermediate 100:

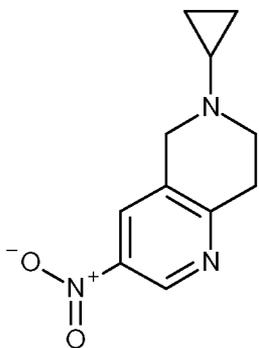
In a sealed tube, a solution of tetrahydro-4H-pyran-4-one (2.00 g, 19.98 mmol) and 1-methyl-3,5-dinitro-1H-pyridin-2-one (3.98 g, 19.98 mmol) in ammonia (7N in MeOH) (34 mL) was stirred at 50 °C for 18 h. After cooling down to rt, the mixture was diluted with DCM and a saturated aqueous solution of NaHCO₃ was added. The aqueous layer was separated and extracted with DCM (three times). The combined organic layers were dried over MgSO₄, filtered off and evaporated in vacuo to give 1.70 g of intermediate 100 (47% yield, red solid).



Preparation of intermediate 128:

In a schlenk reactor, a solution of 1-methyl-3,5-dinitro-1H-pyridin-2-one (5.00 g, 25.11 mmol) and 1-methyl-4-piperidone (3.13 g, 27.62 mmol) in ammonia (7N in MeOH) (43 mL) was stirred overnight at 50 °C. After cooling down to rt, the mixture was evaporated in vacuo, taken-up in DCM and a saturated aqueous solution of NaHCO₃ was added. The layers were separated and the aqueous layer was extracted with DCM (three times). The combined organic layers were dried over MgSO₄, filtered off and evaporated in vacuo to give 2.32 g of intermediate 128 (48% yield, reddish solid) which was used in the next step without further purification.

10

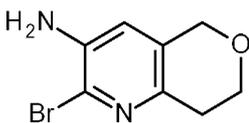


Preparation of intermediate 200:

Intermediate 200 was prepared following a similar protocol than the one used for the preparation of intermediate 128 starting from 1-methyl-3,5-dinitro-1H-pyridin-2-one and 1-cyclopropyl-4-piperidinone as reagents (111mg; 50%).

15

Example A33



Preparation of intermediate 102:

Bromine (351.40 μL, 6.86 mmol) was added to a solution of intermediate 101 (1.03 g, 6.86 mmol) and sodium acetate (1.13 g, 13.7 mmol) in AcOH (25 mL) and the mixture was

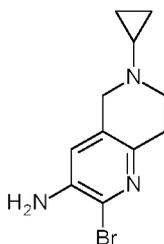
20

stirred at rt for 2 h. The mixture was diluted in EtOAc and water and treated with an aqueous saturated solution of NaHCO₃ and a 10% aqueous solution of sodium thiosulfate. The organic layer was dried over MgSO₄, filtered, evaporated in vacuo and purified by silica gel chromatography (irregular SiOH 15-40 μm, 40 g, dry load on celite[®], mobile phase gradient: from Heptane/EtOAc 90/10 to 30/70) to give 890 mg of intermediate 102 (57% yield, pale brown solid).

Alternative preparation of intermediate 102:

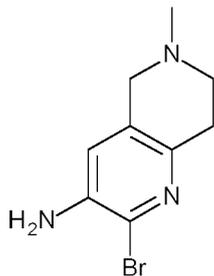
10 A solution of intermediate 101 (550mg; 3.66 mmol) in ACN (20 mL) was cooled to 0°C. Then, a solution of *N*-bromosuccinimide (652 mg; 3.66 mmol) in ACN (20mL) was added dropwise and the reaction mixture was stirred for 1h at room temperature. The mixture was concentrated in vacuo and the residue was diluted with ethyl acetate and washed with a solution of NaHCO₃. The aqueous layer was extracted with ethyl acetate.

15 The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure to give a crude that was purified by flash chromatography eluting with heptane and Ethyl Acetate. The fractions containing the product were mixed to give, after removal of the solvent, 780 mg (93%) of intermediate 102



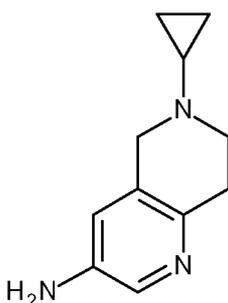
20 Preparation of intermediate 204:

Intermediate 204 was prepared following the alternative procedure used for the preparation of intermediate 102 starting from intermediate 201 (477 mg; 75%).



Preparation of intermediate 137:

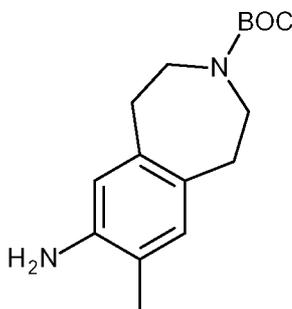
Bromine (665.49 μ L, 12.99 mmol) was added to a solution of intermediate 129 (2.12 g, 12.99 mmol) and sodium Acetate (2.13 g, 25.98 mmol) in AcOH (40 mL) at rt and the mixture was stirred at rt for 1 h. The mixture was diluted in DCM and water and treated with NaHCO_3 slowly. The organic layer was dried over MgSO_4 , filtered and evaporated in vacuo to give 2.2 g of intermediate 137 (70% yield, brown solid) which was used in the next step without further purification.



Preparation of intermediate 201:

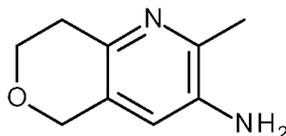
Intermediate 201 was prepared following a similar protocol than the one used for the preparation of intermediate 129 starting from intermediate 200 (94mg; 98%).

Example A34



Preparation of intermediate 109:

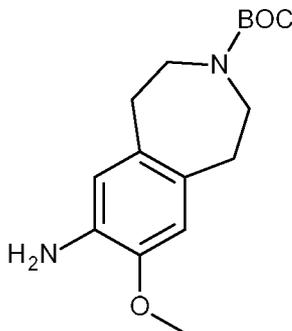
A sealed tube was charged with intermediate 94 (1.50 g, 3.86 mmol), methylboronic acid (693.81 mg, 11.6 mmol), CsF (315.51 mg, 386 μ mol) and $\text{Pd(dppf)Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (2.05 g, 13.5 mmol). The system was degassed and filled with N_2 (three times) before addition of 1,4-dioxane (34 mL). The reaction mixture was degassed with N_2 for 5 min and heated at 90 $^\circ\text{C}$ for 16 h. The reaction mixture was diluted with water, the layers were separated and the aqueous layer was extracted with EtOAc (three times). The combined organic layers were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (Irregular SiOH 15-40 μm , 40 g, liquid loading in DCM, mobile phase gradient: from heptane/EtOAc 90/10 to 60/40 over 10 CV) to give 711 mg of intermediate 109 (67% yield, yellow solid).



Preparation of intermediate 125:

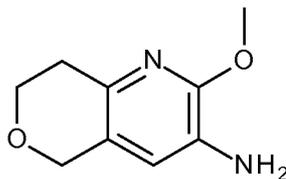
In a microwave vial, a solution of intermediate 102 (250.00 mg, 1.09 mmol), dimethylzinc (546 μ L, 1.09 mmol) and Pd(dppf)Cl₂.CH₂Cl₂ (89.35 mg, 0.11 mmol) in 1,4-dioxane (10 mL) was purged with N₂ and heated at 100 °C using one single mode microwave Biotage[®] Initiator EXP 60 with a power output ranging from 0 to 400 W for 10 min. This reaction was performed in two batches from 500 mg of intermediate 102 each. The 2 batches were combined, diluted with EtOAc and water was slowly added. The mixture was filtered on a pad of celite[®] and the filtrate was transferred in a separatory funnel. The organic layer was separated, dried over MgSO₄, filtered off and evaporated in vacuo. The crude residue was purified by silica gel chromatography (Irregular SiOH 15-40 μ m, 24 g, liquid loading with DCM, mobile phase gradient: from Heptane 90%, EtOAc 10% to Heptane 70%, EtOAc 30%) to give 164 mg of intermediate 125 (46% yield, yellow oil).

Example A35



Preparation of intermediate 113:

In a sealed tube, a mixture of intermediate 94 (1.50 g, 3.86 mmol), CuI (73.58 mg, 386 μ mol), 1,10-phenanthroline (139.25 mg, 773 μ mol) and Cs₂CO₃ (2.52 g, 7.73 mmol) in MeOH (10.4 mL) 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 2 h. The reaction mixture was diluted with MeOH and EtOAc. The mixture was passed through a celite[®] pad and the black filtrate was concentrated. The crude residue was purified by silica gel chromatography (Irregular SiOH 15-40 μ m, 80 g, dry loading on celite[®], mobile phase gradient: from Heptane/EtOAc 90/10 to 60/40) to give 576 mg of intermediate 113 (51% yield, orange solid).

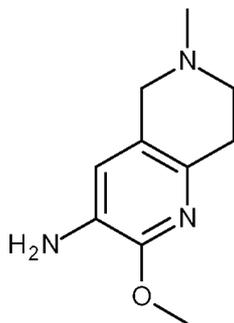


Preparation of intermediate 117:

In a microwave vial, a mixture of intermediate 102 (480.00 mg, 2.10 mmol) and Cs₂CO₃ (1.37 g, 4.19 mmol) in MeOH (5 mL) was purged with N₂. CuI (39.91 mg, 209.54 μmol) and 1,10-phenanthroline (75.52 mg, 419.08 μmol) were added and the mixture was purged 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 2 h. The crude was diluted with EtOAc, filtered through a pad of celite[®] which was rinsed with MeOH. The black filtrate was concentrated in vacuo. The crude residue was purified by silica gel chromatography (Irregular SiOH 15-40 μm, 50 g, liquid injection (DCM), mobile phase gradient: from heptane 95%, EtOAc/MeOH (9:1) 5% to heptane 70%, EtOAc/MeOH (9:1) 30%) to give 303 mg of intermediate 117 (80% yield, beige solid).

Alternative preparation of intermediate 117: A mixture of intermediate 102 (2g; 8.73mmol), CuI (166.3mg; 0.87mmol), 1,10-phenanthroline (314.7mg; 1.75mmol), Cs₂CO₃ (5.7g; 17.5mmol) in MeOH (20 mL) was heated to 100°C for 18 hours under nitrogen atmosphere in a sealed tube. The mixture was extracted with DCM (100 mL*3) and the organic layer was dried (MgSO₄) and concentrated.

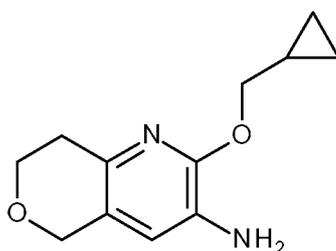
The residue (4g, dark solid) was purified by column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 0/100). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 950 mg (60%) of intermediate 117.



Preparation of intermediate 138:

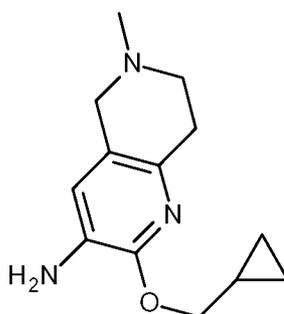
In a microwave vial, a mixture of intermediate 137 (500.00 mg, 2.07 mmol) and Cs₂CO₃ (1.35 g, 4.13 mmol) in MeOH was purged with N₂. CuI (39.33 mg, 0.21 mmol) and 1,10-

phenanthroline (74.43 mg, 0.41 mmol) were added and the mixture was purged with N₂ and heated at 100 °C using one single mode microwave Biotage[®] Initiator EXP 60 with a power output ranging from 0 to 400 W for 2 h. The mixture was evaporated in vacuo. The crude residue was purified by silica gel chromatography (irregular SiOH, 15-40 μm, 120 g, dry loading (celite[®]), mobile phase gradient: from DCM 98%, MeOH/aq. NH₃ (95:5) 2% to DCM 85%, MeOH/aq. NH₃ (95:5) 15%). The residue was further purified by silica gel chromatography (irregular SiOH, 15-40 μm, 24 g, liquid loading (DCM), mobile phase gradient: from DCM 100% to DCM 90%, MeOH/aq. NH₃ (95:5) 10%) to give 230 mg of intermediate 138 (58% yield, yellow solid).



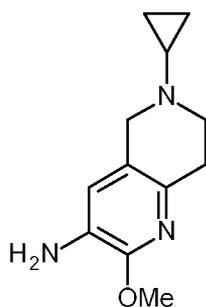
10 Preparation of intermediate 144:

In a microwave vial, a mixture of intermediate 102 (500.00 mg, 2.18 mmol), cyclopropyl carbinol (11.83 mL), 1,10-phenanthroline (78.67 mg, 436.51 μmol) and Cs₂CO₃ (1.42 g, 4.37 mmol) was purged with N₂. CuI (41.57 mg, 218.27 μmol) was added and the mixture was purged 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 4 h. After cooling down to rt, the crude was diluted with EtOAc and water and filtered on a pad of celite[®]. The filtrate was transferred in a separatory funnel. The organic layer was separated, washed with water (three times), dried over MgSO₄, filtered off and evaporated in vacuo. The crude residue was purified by silica gel chromatography (Irregular SiOH 15-40 μm, 10 g, liquid loading (DCM), mobile phase gradient: from heptane 95%, EtOAc/MeOH (9:1) 5% to heptane 70%, EtOAc/MeOH (9:1) 30%) to give 206 mg of intermediate 144 (43% yield, colorless oil).



Preparation of intermediate 147:

In a microwave vial, a mixture of intermediate 137 (415 mg, 1.71 mmol) and Cs₂CO₃ (1.12 g, 3.43 mmol) in cyclopropylmethanol (8.30 mL) was purged with N₂. CuI (32.64 mg, 0.17 mmol) and 1,10-phenanthroline (61.78 mg, 0.34 mmol) were added and the mixture was purged with N₂ and heated at 100 °C using one single mode microwave Biotage[®] Initiator EXP 60 with a power output ranging from 0 to 400 W for 2 h. After cooling down to rt, the crude was diluted with EtOAc and filtered on a pad of celite[®]. The celite[®] was rinsed with MeOH and the filtrate was evaporated in vacuo to give a brown residue. The residue was diluted in EtOAc, washed with water (three times), dried over MgSO₄, filtered off and evaporated in vacuo. The crude residue was purified via silica gel chromatography (Stationary phase: irregular SiOH 15-40 μm, 220 g, Mobile phase gradient: from 100% DCM to 97% DCM, 3% MeOH (10% NH₄OH)) to give 145 mg of intermediate 147 (24% yield, 66% purity based on LC/MS).

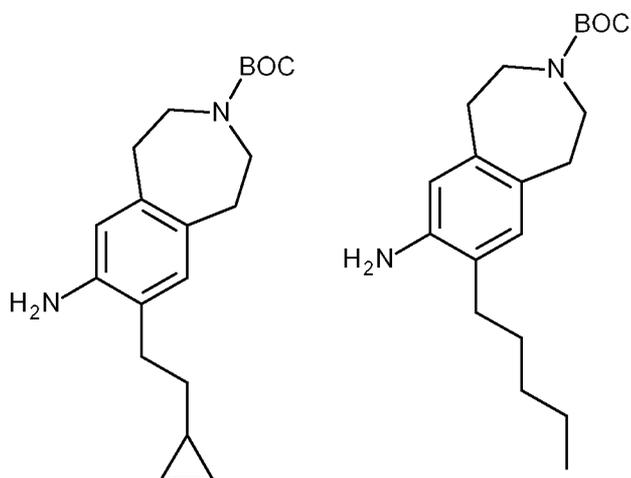


Preparation of intermediate 205:

Intermediate 205 was prepared via a similar protocole (T = 100°C and time = 1 hour) than the one used for the preparation of intermediate 113 starting from intermediate 204 (65 mg; 17%).

Example A36

Preparation of a mixture of intermediate 121 and intermediate 121':



intermediate 121

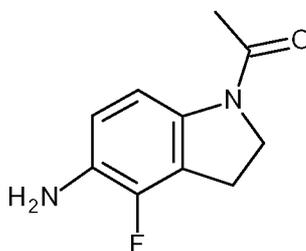
intermediate 121'

In a Schlenk reactor, a solution of intermediate 120 (1.02 g, 3.13 mmol), ammonium formate (11.82 g, 187.48 mmol) and Pd/C (10 wt. %) (1.99 g, 1.88 mmol) in isopropanol (25.5 mL) and Me-THF (12.75 mL) was purged with N₂ and stirred at 70 °C for 35 min.

- 5 The reaction mixture was filtered on a pad of celite[®] and the filtrate was diluted with EtOAc and water. The layers were separated and the organic layer was dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure to give 981 mg of a mixture of intermediate 121 and 121' (95% yield, brown oil) which was directly engaged in the next step without any further purification.

10

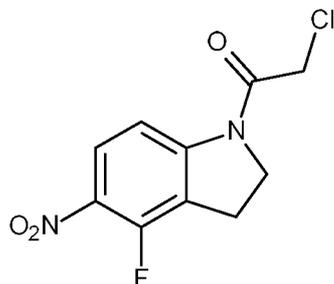
Example A37



Preparation of intermediate 150:

- 15 A mixture of 1-(4-Fluoro-5-nitroindolin-1-yl)ethanone (600 mg; 2.676 mmol) was hydrogenated in a pressure vessel reactor at room temperature in ethanol (30 mL) and THF (20 mL) with Pd/C 10% (275 mg) as a catalyst under a 3 bars pressure of hydrogen for 3h00. The catalyst was filtered off on a pad of Celite[®] which was further washed with DCM and MeOH. The solvent was removed until dryness to give 470mg (90%) of intermediate 150.

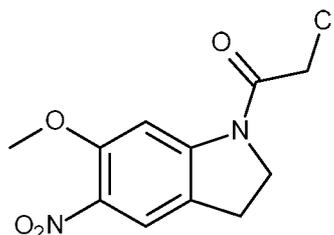
Example A38



Preparation of intermediate 153:

Chloroacetic acid chloride (0.7 mL; 8.78 mmol) and potassium carbonate (1.33g; 9.66 mmol) in DCM (15 ml) was stirred under ice-bath. Then, 4-fluoro-5-nitro-2,3-dihydroindole in DCM (5 ml) was added dropwise. The mixture was stirred at room temperature for 4 hours. Water (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (20 mL*2). The organic layers were combined, dried over MgSO₄, filtered and evaporated to give 700 mg (59%) of intermediate 153 as a yellow solid which was directly used in the next step.

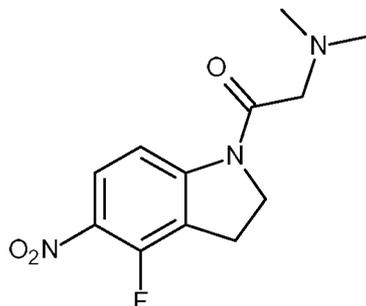
10



Preparation of intermediate 161:

Intermediate 161 was prepared following a similar procedure that the one used for the preparation of intermediate 153 starting from 6-(methoxy)-5-nitro-2,3-dihydro-1H-indole (1.08g)

15

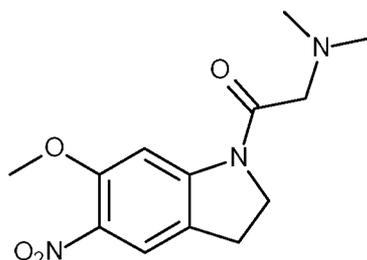


Preparation of intermediate 154:

Intermediate 153 (700 mg; 2.7 mmol), diethylamine (366 mg; 8.12 mmol) and K₂CO₃ (1.12g; 8.12 mmol) in THF (40 mL) and water (20 mL) was stirred at room temperature

for 16 hours. Water (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (50 mL*2). The organic layers were combined, dried over MgSO₄, filtered and evaporated to give 600 mg (83%) of intermediate 154 as a yellow solid which was directly used in the next step.

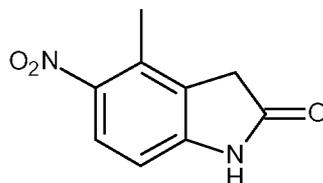
5



Preparation of intermediate 162:

Intermediate 162 was prepared following a similar procedure that the one used for the preparation of intermediate 154 starting from intermediate 161 (950 mg; 85%)

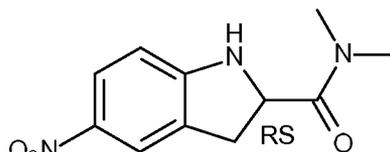
10 Example A39



Preparation of intermediate 168:

4-methyloxindole (1.23 g; 8.36 mmol) was dissolved in concentrated sulfuric acid at -10°C. Potassium nitrate (844 mg; 8.36 mmol) was added and the mixture was stirred at 0°C for 1h. The mixture was poured into ice water and extracted with EtOAc (30 mL*3).
 15 The organic layer were combined and washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated. For the purification, the crude (1.93 g) was combined with another crude (1.57 g) coming from a reaction performed on 1.2 g of 4-methyloxindole. The combined mixture was purified by silica gel chromatography (Eluent: Petroleum ether/ EtOAc 3/1). The desired fractions were collected and the solvent
 20 was removed to give 650 mg (20%) of intermediate 168 as a white solid white solid.

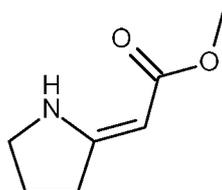
Example A40



Preparation of intermediate 171:

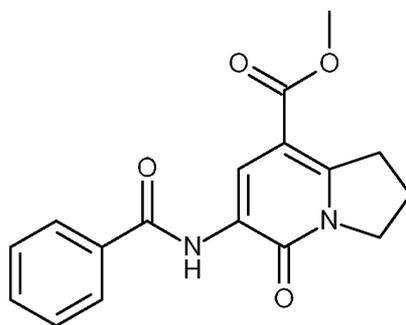
A mixture of 5-nitro-indoline-2-carboxylic acid (1.8 g; 8.65 mmol), dimethylamine hydrochloride (1.41 g; 17.30 mmol), Propylphosphonic acid anhydride (13.8 g; 21.62 mmol; 50% in EtOAc) and TEA (5 mL; 34.6 mmol) in DCM (100 mL) was stirred at room temperature overnight. The mixture was poured into water and extracted with DCM (50 mL*3). The organic layers were combined and washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated. The intermediate product was washed with EtOH and dried under vacuo to give 1.8 g (88%) of intermediate 171 as yellow solid.

Example A41



10 Preparation of intermediate 174:

To a solution of sodium methoxide (1.17 g, 21.6 mmol) in dry MeOH (25 mL) under N₂ was added a suspension of 2,2-Dimethyl-5-(2-pyrrolidinylidene)-1,3-dioxane-4,6-dione (4.57 g, 21.6 mmol) in dry MeOH (25 mL). The resulting suspension was heated at 70 °C overnight. The reaction mixture was diluted with H₂O (50 mL). Aqueous 1N HCl was added until pH = 6 and the mixture was extracted with DCM (3x). The combined organic layers were dried over MgSO₄ and concentrated to give a white solid which was purified by silica gel chromatography (Irregular SiOH 15-40 μm, 120 g, dry loading on Celite[®], mobile phase gradient: from Heptane/EtOAc 70/30 to 50/50). The fractions containing the product were mixed and concentrated to give 2.77 g (91%) of intermediate 174 as a white solid.

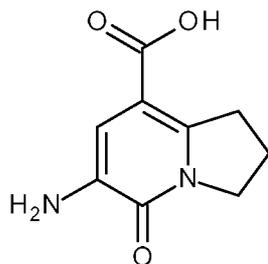


Preparation of intermediate 175:

The reaction was performed twice on 500 mg of intermediate 174.

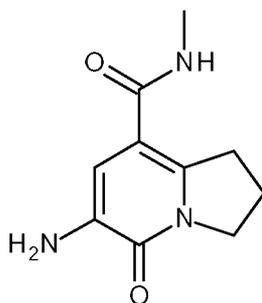
25 Typical procedure for one batch on 500 mg of intermediate 174 :

- A tube was charged with intermediate 174 (500 mg, 3.54 mmol) and 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (769 mg, 3.54 mmol). Then, ACN (15 mL) and Bismuth(III) nitrate pentahydrate (172 mg, 354 μ mol) were added. The tube was sealed and the reaction mixture was heated at 130 °C using one single mode microwave Biotage Initiator EXP 60 with a power output ranging from 0 to 400 w for 25 min. The batches, coming from the 2 reactions performed on 500 mg of intermediate 174, were combined and concentrated to give a dark red residue which was purified by silica gel chromatography (Irregular SiOH 15-40 μ m, 12 g, dry loading on Celite[®], mobile phase gradient: from DCM/MeOH 100/0 to 95/5) to give 2 fractions of intermediate 175:
- 5
- 10 - 618 mg (30%; 82% of purity evaluated by LC/MS) of intermediate 175 as a beige solid
- 710 mg (32%; 85% of purity evaluated by LC/MS) of intermediate 175 as an orange solid



Preparation of intermediate 176:

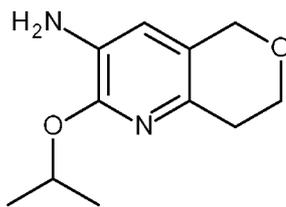
- A mixture of intermediate 175 (625 mg, 2.00 mmol) and sodium hydroxide (1.60 g, 40.0 mmol) in 1,4-dioxane (8 mL) and water (8 mL) was heated at 100 °C over the weekend. The reaction mixture was concentrated and then, acidified with 1N aqueous HCl until pH = 4. The resulting mixture was extracted with DCM/iPrOH (3/1) (8x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by silica gel chromatography (irregular SiOH 15-40 μ m, 24 g, dry loading on celite[®], mobile phase gradient: from DCM/MeOH 95/5 to 85/15) to give 278 mg (72%) of intermediate 176 as a beige solid.
- 15
- 20



Preparation of intermediate 177:

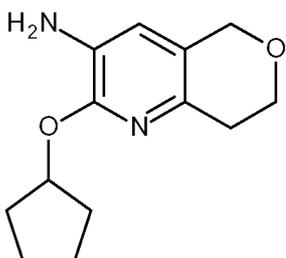
To a solution of intermediate 176 (278 mg, 1.43 mmol) in DMF (14 mL) were added DIPEA (740 μ L, 4.30 mmol), methylamine (2.86 mL, 5.73 mmol) and COMU[®] (1.53 g, 3.58 mmol). The solution was stirred at room temperature for 4 hours and then, concentrated. The resulting residue was purified by silica gel chromatography (irregular SiOH 15-40 μ m, 40 g, dry loading (celite[®]), mobile phase gradient: DCM/MeOH from 95:5 to 85:15) to give 168 mg (57%) of intermediate 177 as a white solid.

Example A42



Preparation of intermediate 182:

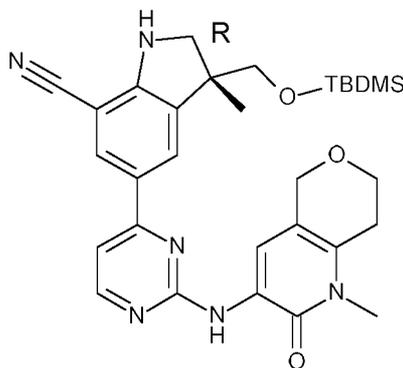
10 Isopropyl alcohol (10 mL) was added to NaH (419 mg; 10.5mmol, 60% purity, previously washed with anhydrous heptane) and intermediate 102 (300 mg; 1.31 mmol) was added. The mixture was heated to 220 °C in a steel vessel for 2 h. The reaction mixture was treated with ethyl acetate and washed with aqueous 10% K₂CO₃ and brine. The organic layer was separated and dried over MgSO₄ and the solvent was removed under reduced pressure to give a crude that was purified by flash column chromatography eluting with DCM-MeOH to yield 85 mg (31%) of intermediate 182



Preparation of intermediate 185:

20 Intermediate 185 was prepared using a similar procedure than the one used for the preparation of intermediate 182 starting from intermediate 102 (100 mg; 65%).

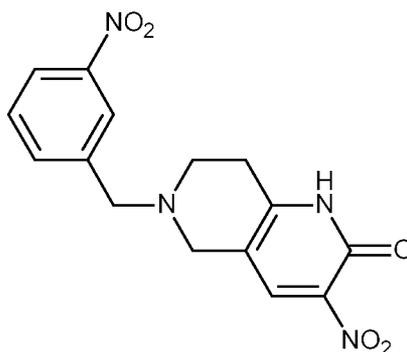
Example A43



Preparation of intermediate 189:

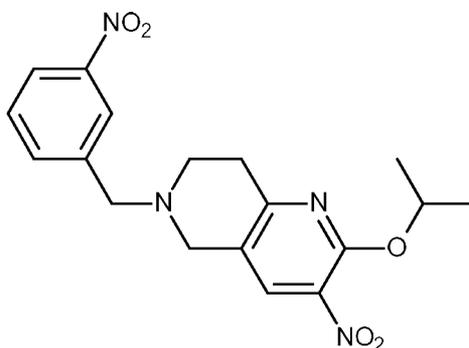
To a solution of intermediate 188 (91.0 mg; 167 μmol) and K_2CO_3 (46.2 mg; 0.334 mmol) in DMF (910 μL) at room temperature was added iodomethane (12.4 μL ; 200 μmol). The mixture was stirred at room temperature for 18h. Then, EtOAc and water were added. The organic layer was separated, dried over MgSO_4 , filtered off and evaporated in vacuo to give an orange oil which was purified by silica gel chromatography (Irregular SiOH 15-40 μm , 10 g, liquid loading (DCM), mobile phase gradient: from DCM 100% to DCM 97%, MeOH 3%) to give 74 mg (73%) of intermediate 189 as a pale brown solid.

10 Example A44



Preparation of intermediate 190:

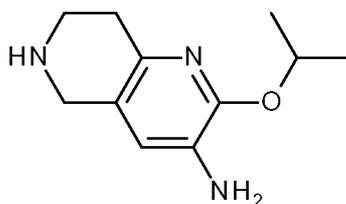
6-benzyl-5,6,7,8-tetrahydro-[1,6]-naphthyridin-2(1H)-one (1.48 g, 6.16 mmol) was dissolved into sulfuric acid (7.93 mL) and the solution was stirred for 15 minutes at 0°C . Then, nitric acid (8.72 mL) was added dropwise and this reaction was stirred at rt for 18 hours. The reaction mixture was poured onto ice and water, basified with K_2CO_3 powder and extracted with DCM. The organic layer was dried over MgSO_4 , filtered and evaporated. The resulting residue was purified by silica gel chromatography (Stationary phase: irregular SiOH 15-40 μm 12g, Mobile phase: gradient from 100% DCM to 98% DCM, 2% MeOH (2% NH_4OH)). The fractions containing the product were mixed and concentrated to afford 660mg (32%) of intermediate 190.



Preparation intermediate 191:

Intermediate 190 (600 mg, 1.82 mmol), iPrOH (278 μ L) and cyanomethylenetributylphosphorane (1.2 mL) in toluene (8.71 mL) in a sealed tube were stirred at 90°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 20 min. The volatiles were evaporated and the resulting residue was purified by silica gel chromatography (Stationary phase: irregular SiOH 15-40 μ m 40g, Mobile phase: from 90% Heptane, 10% EtOAc to 60% Heptane, 40% EtOAc). The fractions containing the product were mixed and concentrated to afford 298 mg (44%) of intermediate 191.

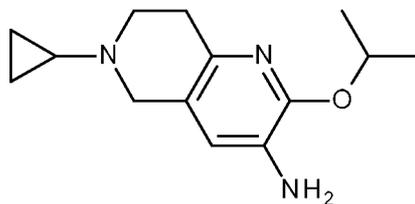
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Preparation of intermediate 192:

A mixture of intermediate 191 (290 mg, 0.78 mmol) in EtOH (6.82 mL) was hydrogenated at 60°C under 10 bars pressure for 12h with palladium hydroxide (26 mg, 0.185 mmol) as a catalyst. The catalyst was filtered off on a pad of celite[®] which was with DCM and MeOH. The filtrate was evaporated to give 200 mg of of an intermediate residue which was purified by silica gel chromatography (Irregular SiOH 40 μ m 24g; Mobile phase 93% DCM, 7% MeOH, 0.7% NH₄OH to 88% DCM, 12% MeOH, 1.2% NH₄OH. The fractions containing the product were combined and the solvent was evaporated to give 100 mg (62%) of intermediate 192.

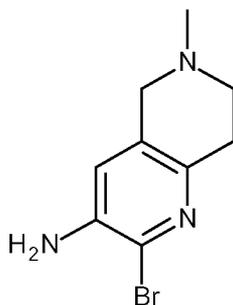
20



Preparation of intermediate 193:

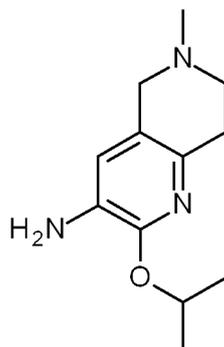
In a sealed tube, a mixture of intermediate 192 (100 mg, 0.482 mmol), (1-ethoxycyclopropoxy) trimethylsilane (0.1 mL, 0.493 mmol) and sodiumcyanoborohydride (0.043 g, 0.69 mmol) in MeOH (1.26 mL, 31.16 mmol) and AcOH (0.04 mL, 0.69 mmol) was stirred at 60°C overnight. The reaction was cooled down to room temperature. An aqueous solution of NaOH 1N was added and this mixture was extracted twice with DCM. The organic layers were decanted, mixed and evaporated until dryness. The crude product (123 mg) was purified by silica gel chromatography (Irregular SiOH 40µm 80g; Mobile phase 99% DCM, 1% MeOH, 0.1% NH₄OH to 93% DCM, 7% MeOH, 0.7% NH₄OH. The fractions containing the product were combined and the solvent was evaporated to give a first fraction of 80 mg (67%) of intermediate 193 and a second fraction of 20 mg (18%) intermediate 193.

Example A45a



Preparation of intermediate 196:

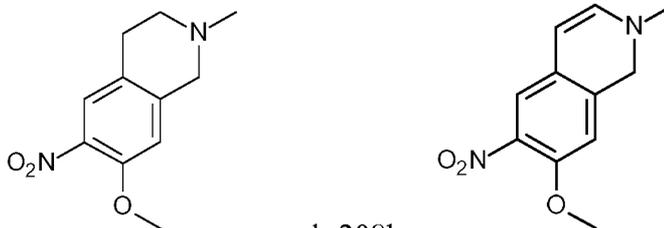
Bromine (665 µL, 12.99 mmol) was added to a solution of 6-methyl-5,6,7,8-tetrahydronaphthyridine-3-amine (2.12 g, 12.99 mmol) and sodium Acetate (2.13 g, 25.98 mmol) in AcOH (40 mL) at room temperature and the mixture was stirred at this temperature for 1h. The mixture was diluted in DCM and water and treated with NaHCO₃ slowly. The organic layer was separated, dried over MgSO₄, filtered and evaporated in vacuo to give 2.2 g of intermediate 196 as a brown solid.



Preparation of intermediate 197:

Intermediate 196 (2 g, 8.26 mmol) and sodium isopropoxide (5.42 g, 66.08 mmol) in iPrOH (15.2 mL) in an autoclave were stirred at 220°C 10h. The reaction mixture was diluted with EtOAc, washed with a 10% aqueous solution of K₂CO₃, water. The layers were separated and the organic layer was dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residue (6.6g) was purified by silica gel chromatography (Irregular SiOH 40µm 330g, Mobile phase from 100% DCM to 95% DCM, 5% MeOH, 0.5% NH₄OH). The pure fractions were combined and the solvent was evaporated to give 720 mg of a mixture of intermediate 196 and intermediate 197 (as the major product) and 80 mg (4%) of intermediate 197. The mixture of 720 mg of intermediate 196 and intermediate 197 was purified via reverse phase chromatography (Stationary phase: YMC-actus Triart-C18 10µm 30*150mm, Mobile phase: Gradient from 75% NH₄HCO₃ 0.2% , 25% ACN to 35% NH₄HCO₃ 0.2% , 65% ACN). The fractions containing the product were mixed and concentrated to afford 377 mg (21%) of intermediate 197.

Example A45b

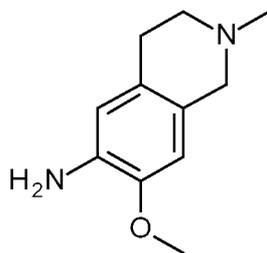


Preparation of intermediate 208a

and 208b

Sodium hydride (91 mg; 2.26 mmol; 60% dispersion in mineral oil) was added portionwise in anhydrous MeOH (1 mL; 24.69 mmol) at 0°C. Then, a solution of 7-fluoro-2-methyl-6-nitro-1,2,3,4-tetrahydroisoquinoline (238 mg; 1.13 mmol) in MeTHF (2 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured onto iced water and extracted with DCM. The organic layer was decanted, washed with water,

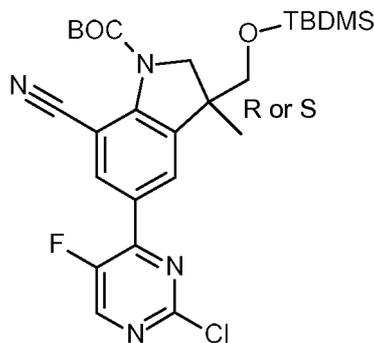
dried over MgSO_4 , filtered and evaporated to give 265 mg of a mixture of intermediate 208a and 208b as a brown solid which was directly engaged in the next step without any further purification.



Preparation of intermediate 209

- 5 A mixture of intermediate 208a and 208b (265 mg; 1.19 mmol) and Pd/C 10% (55 mg; 0.51 mmol) in MeOH (27 mL) was hydrogenated at rt in a pressure vessel reactor (3bar) for 4h. The catalyst was filtered through a pad of Celite[®] which was washed with DCM/MeOH and the filtrate was evaporated 212 mg of brown oil. This residue was purified by chromatography over silica gel (SiO_2 , 12 g, eluent: from 97% DCM, 3% MeOH, 0.3% NH_4OH to 90% DCM, 10% MeOH, 1% NH_4OH).
- 10 The fractions containing the product were collected and the solvent was evaporated to give 133 mg (58%) of intermediate 209 as an orange solid.

Example A46



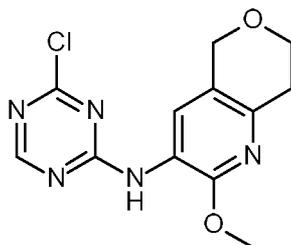
- 15 Preparation of intermediate 211:
To a solution of intermediate 5R (3.33 g; 4.92 mmol), 5-fluoro-2,4-dichloropyrimidine (0.89 g; 5.32 mmol) and Cs_2CO_3 (4.03 g; 12.3 mmol) in 1,4-dioxane (21 mL) and water (2 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (0.237 g; 0.205 mmol) and the reaction mixture was heated overnight at 95°C . The mixture was poured into ice and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO_4 , filtered and the solvent was evaporated.
- 20

The residue was purified by chromatography over silica gel (240 g, 15-40 μm , eluent: heptane/EtOAc: 1/0 to 0/1). The pure fractions were mixed and the solvent was evaporated affording 1.82 g (83%) of intermediate 211.

5 Alternative preparation of intermediate 211 A solution in sealed tube of intermediate 5 (1.1 g; 2.1 mmol) in MeTHF (10 mL) was treated with Na_2CO_3 (0.4 g; 3.8 mmol) in water (1 mL), 5-fluoro-2,4-dichloropyrimidine (332 mg; 2 mmol), triphenylphosphine (20 mg; 0.076 mmol) and $\text{Pd}(\text{OAc})_2$ (8.5 mg; 0.04 mmol) and the mixture evacuated and purged with nitrogen and then heated to 90°C overnight. The reaction mixture was poured into a mixture of K_2CO_3 in water and extracted with EtOAc. The organic layer was dried over
10 MgSO_4 , filtered and evaporated until dryness.

The residue was purified by silica gel chromatography (24 g of SiOH 15 μm , gradient from 90% heptane 10% EtOAc to 50% heptane 50% EtOAc). The fractions were collected and evaporated until dryness to afford 830 mg (78%) of intermediate 211.

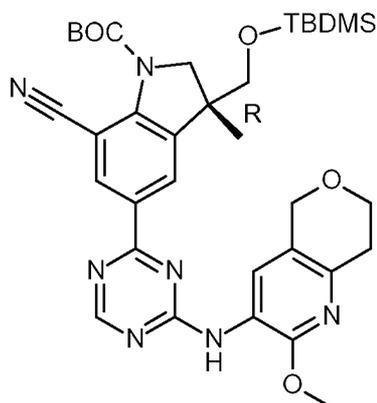
15 Example A47



Preparation of intermermediate 214:

Intermediate 117 (900 mg; 4.99 mmol) was dissolved in acetone (20 mL). Dichlorotriazine (749 mg; 4.99 mmol) and DIEA (2.61 mL; 14.98 mmol) were added and the mixture was stirred overnight at room temperature. The reaction mixture was combined
20 with another reaction performed on 50 mg of intermediate 102.

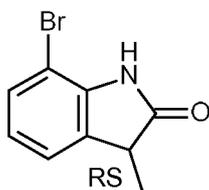
The solid was filtered and was dried under vacuum to give 950 mg of intermediate 214.



Preparation of intermermediate 215:

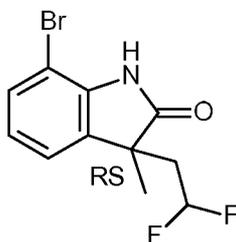
A mixture of intermediate 5R (590 mg; 1.12 mmol), intermediate 214 (453.4 mg; 1.45 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (91 mg; 0.11 mmol) and a saturated aqueous solution of NaHCO₃ in dioxane was stirred at 80°C overnight under N₂. The reaction mixture was
 5 combined another reaction performed on 50 mg of intermediate 5R. The mixture was evaporated under vacuum. The crude compound was stirred in ethyl acetate (50 mL), and then filtered through celite[®]. The filtrate was evaporated under vacuum.
 The resulting residue was purified by silica gel chromatographie (eluent: petroleum ether/ethyl acetate from 100/0 to 70/30). The desired fractions were collected and the
 10 solvent was concentrated to dryness under vacuum to give 460 mg of intermediate 215 as yellow solid.

Example A48



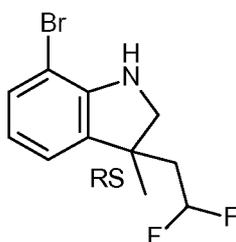
Preparation of intermediate 217:

15 To a cooled (-78°C) solution of 7-bromooxindole (4.7g; 22.16 mmol) and *N,N,N', N'*-tetramethylethylenediamine (10.97 mL; 73.17 mmol) in dry THF (230 mL) was slowly added n-butyllithium solution (19.5 mL; 48.76 mmol; 2.5 M in hexane). The solution was stirred for 30 minutes at the same temperature and then, iodomethane (1.65 mL; 26.6 mmol) was added slowly. The reaction mixture was stirred at -20°C for 1.5h, then,
 20 quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc.
 The organic layer was sried over MgSO₄, filtered and concentrated in vacuo. The resulting crude material was purified by silica gel chromatography (mobile phase: heptane/EtOAc) to afford, after solvent evaporation, 1.3 g (22%) of intermediate 217.



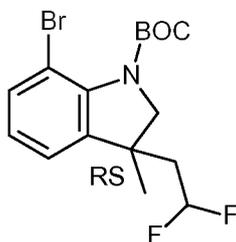
Preparation of intermediate 218:

To a cooled (-78°C) solution of intermediate 218 (1 g; 4.42 mmol) and *N,N,N', N'*-tetramethylethylenediamine (2.19 mL; 14.60 mmol) in dry THF (50 mL) was slowly added *n*-butyllithium solution (3.89 mL; 9.73 mmol; 2.5 M in hexane). The solution was stirred for 30 minutes at the same temperature and then, 1,1-difluoro-2-iodoethane (0.467 mL; 5.31 mmol) was added slowly. The reaction mixture was stirred at -20°C for 1.5h, then, quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography over silica gel (mobile phase: *n*-heptane/ethyl acetate from 100/0 to 50/50%). The desired fractions were collected and the solvents were evaporated in vacuo to give 650 mg (50%) of intermediate 218 as a white solid.



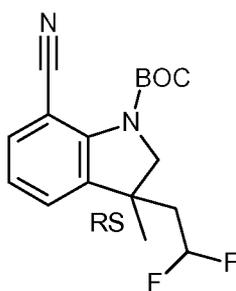
Preparation of intermediate 219:

Borane dimethyl sulfide complex (2.12 mL; 22.40 mmol) was added to a solution of intermediate 218 (650 mg; 2.24 mmol) in THF (20 mL). The reaction mixture was stirred at 70°C for 3 hours. The reaction was cooled to room temperature and MeOH was carefully added. The resulting solution was heated at reflux for 2 hours. The solvents were removed in vacuo and the residue was purified by flash column chromatography over silica gel (mobile phase: *n*-heptane/ethyl acetate from 100/0 to 80/20%). The desired fractions were collected and the solvents were removed in vacuo to give 605 mg (88%) of intermediate 219 as a colorless oil.



Preparation of intermediate 220:

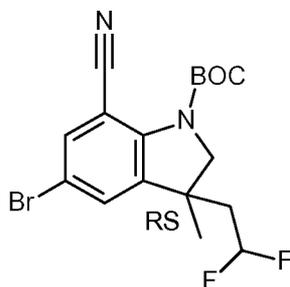
To a solution of intermediate 219 (605 mg; 2.19 mmol) in THF (20 mL) were added trimethylamine (305 μ L; 2.19 mmol), 4-dimethylaminopyridine (267.7 mg; 2.19 mmol) and di-*tert*-butyldicarbonate (717.3 mg; 3.29 mmol) and the solution was stirred at room temperature overnight. The solvents were evaporated in vacuo and the crude residue was purified by flash column chromatography over silica gel (mobile phase: n-heptane/Ethyl acetate from 100/0 to 50/50%). The desired fractions were collected and the solvents were evaporated in vacuo to give 750 mg (90%) of intermediate 220 as a colorless oil.



10 Preparation of intermediate 221:

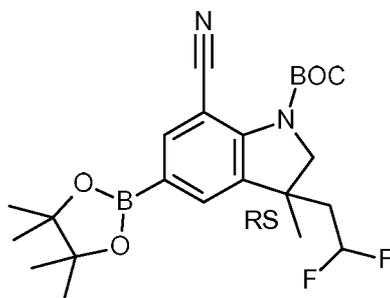
In a sealed tube a mixture intermediate 220 (700 mg; 1.86 mmol), zinc cyanide (437 mg; 3.72 mmol), Pd(PPh₃)₄ (430 mg; 0.372 mmol) in anhydrous DMF was degassed with N₂ for 10 minutes and then, warmed at 100°C and stirred overnight. After cooling, the reaction was diluted with a saturated aqueous solution of NH₄Cl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel chromatography eluted with 20 % ethyl acetate in n-heptane. The fractions containing the product were combined and the solvent was concentrated in vacuo to afford 316 mg (42% based on a purity of 80% evaluated by LC/MS) of intermediate 221.

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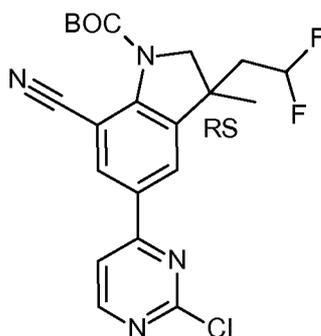
Preparation of intermediate 222

A mixture of intermediate 221 (320 mg; 0.99 mmol) and N-bromosuccinimide (176.7 mg; 0.99 mmol) in ACN (10 mL) was refluxed overnight. The solvent was evaporated in vacuo and the crude was purified by flash column chromatography over silica gel (mobile phase: n-heptane/ethyl acetate from 100/0 to 80/20%). The desired fractions were collected and the solvents were evaporated in vacuo to give 227 mg (46% based on a purity of 80% evaluated by LC/MS) of intermediate 222 as a brown solid.



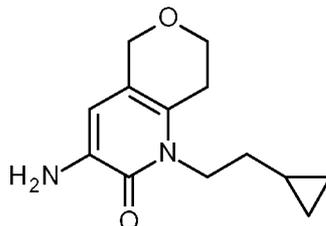
Preparation of intermediate 223:

To a mixture of intermediate 222 (200 mg; 0.4 mmol) in dioxane (5 mL) was added bis(pinacolato)diboron (253 mg; 1 mmol) and potassium acetate (117.4 mg; 1.2 mmol). After 5 minutes of bubbling nitrogen, Pd(dppf)Cl₂.CH₂Cl₂ (8.1 mg; 0.01 mmol) and XPhos (9.5 mg; 0.02 mmol) were added. The reaction mixture was heated at 60°C overnight. The solvent was removed in vacuo and the crude was used in the next step without any further purification.



Preparation of intermediate 224:

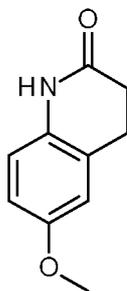
removed until dryness and the crude was directly engaged in the next step without further purification.



Preparation of intermediate 227:

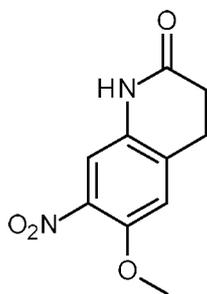
5 Cs₂CO₃ (2.3g; 7.08 mmol) was added to a solution of intermediate 226 (530 mg; 2.14 mmol) in anhydrous DMF (12 mL) under N₂ atmosphere. The mixture was stirred at room temperature for 15 minutes and (2-iodoethyl)cyclopentane was added. The reaction was stirred at room temperature overnight and was diluted with water. The precipitate was filtered off, washed with water and dried in vacuo. The resulting crude was purified by silica gel chromatography (mobile phase: gradient 100% DCM 0% DCM/MeOH (9/1) to 10 0% DCM 100% DCM/MeOH (9/1)). The fractions containing the product were mixed and the solvent was concentrated to afford 153 mg (30%) of intermediate 227.

Example A50



Preparation of intermediate 230:

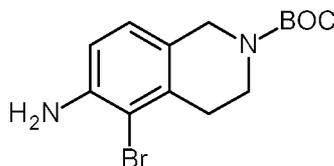
15 To a solution of 3,4-dihydro-6-hydroxycarbostyryl (4.89 g; 30 mmol) in acetone (40 mL) was added of dimethyl sulfate (4.67 g; 45 mmol) and K₂CO₃ (12.44g; 90 mmol). The reaction mixture was stirred at ambient temperature for 16 hours. The mixture was concentrated in vacuo. The residue was partitioned between a saturated aqueous solution of bicarbonate (10 ml) and methylene chloride (20 mL*2). The organic layer was dried over 20 sodium sulfate and evaporated to give 4 g (75%) of intermediate 230 as an off-white solid.



Preparation of intermediate 231:

To a solution of intermediate 230 (2 g; 11.3 mmol) in TFA (16 mL) was added sodium nitrite (934.5 mg; 13.54 mmol) at 0°C. The temperature was raised to 25°C and the mixture was stirred for 4 hours. The mixture was poured into ice and the yellow precipitate was collected affording 1.2 g (41%; 85% of purity evaluated by LC/MS) of intermediate 131.

Example A51



Preparation of intermediate 235:

10

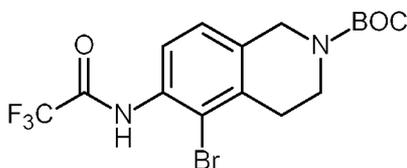
Preparation of intermediate 235 was performed via 2 reactions as reported below.

Reaction 1: *N*-bromosuccinimide (716 mg; 4.03 mmol) was added portionwise at 0°C to a solution of *t*-Butyl-6-amino-3,4-dihydroisoquinoline-2-carboxylate (1 g; 4.03 mmol) in DCM (20 mL). The reaction mixture was stirred at room temperature for 2 hours, poured onto a 10% aqueous solution of K₂CO₃ and extracted with DCM.

Reaction 2: *N*-bromosuccinimide (2.08 g; 11.68 mmol) was added portionwise at 0°C to a solution of *t*-Butyl-6-amino-3,4-dihydroisoquinoline-2-carboxylate (2.9 g; 11.68 mmol) in C (60 mL). The reaction mixture was stirred at room temperature for 2 hours, poured onto a 10% aqueous solution of K₂CO₃ and extracted with DCM.

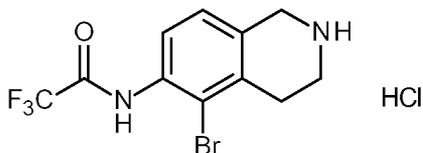
The two residues were combined and purified by chromatography over silica gel (irregular SiOH, 80g; mobile phase: gradient from 20% EtOAc, 80% heptane to 40% EtOAc, 60% heptane). The pure fractions were collected and evaporated to dryness yielding 2.8 g (54%) of intermediate 235.

25



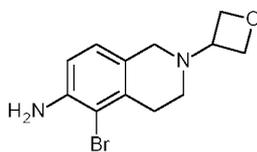
Preparation of intermediate 236:

Trifluoroacetic anhydride (1.03 mL; 7.43 mmol) was added dropwise to a solution of intermediate 235 (2.21 g; 6.75 mmol) and triethylamine (3.76 mL; 27.02 mmol) in DCM (35.4 mL) and the reaction mixture was stirred at room temperature for 18h. Additional trifluoroacetic anhydride (0.1 eq.; 94 μ L; 0.68 mmol) was added and the reaction mixture was stirred at room temperature for 2h. Additional trifluoroacetic anhydride (0.5 eq.; 469 μ L; 3.38 mmol) was added and the reaction mixture was stirred at room temperature for 30h. Water was added and the reaction mixture was extracted with DCM (3X). The organic layer was decanted, dried over MgSO₄, filtered and the solvent was evaporated to give 3.18 g of intermediate 236 as a yellow solid.

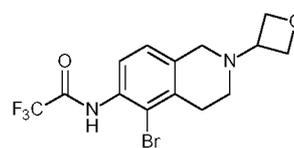


Preparation of intermediate 237:

HCl 4M in dioxane (74 mL; 295 mmol) was added dropwise to a solution of intermediate 236 (3.18 g; 7.51 mmol) in 1,4-dioxane (25 mL) and the reaction mixture was stirred at room temperature for 3h. The reaction mixture was evaporated to dryness and the solid was suspended in ACN. The precipitate was filtered, washed with ACN and dried to give 2.21 g (82%) of intermediate 237 as a white solid.



and 238b



Preparation intermediate 238a

3-oxetanone (942 μ L; 15.69 mmol) was added to a solution of intermediate 237 (1.41 g; 3.92 mmol) in MeOH (40 mL). The reaction mixture was heated at reflux for 1h. The reaction mixture was cooled to room temperature then sodium cyanoborohydride (739 mg; 11.76 mmol) was added. The reaction mixture was refluxed for 2h. The reaction mixture was cooled to room temperature and allow to stand overnight. The mixture was poured onto a 10% solution of K₂CO₃ and diluted with DCM. The mixture was extracted with DCM (3X). NaCl solid was added into the aqueous layer and the product was extracted

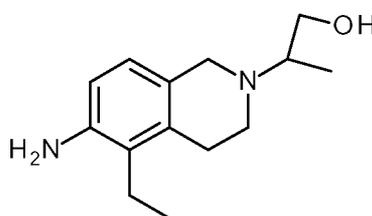
with EtOAc (twice). The organic layers were combined, then dried over MgSO_4 , filtered and the solvent was evaporated. The yellow solid residue (2.6 g) was purified by chromatography over silica gel (SiO_2 , Grace, 80 g, solid deposit; eluent: 96% DCM, 4% MeOH, 0.4% NH_4OH). The fractions containing the product were collected and the solvent was evaporated to give 1.25 g of an impure fraction which was purified again by chromatography over silica gel (SiO_2 , Grace, 40 g; gradient: from 100% DCM to 98% DCM, 2% MeOH, 0.2% NH_4OH). The fractions containing the product were collected and the solvent was evaporated to give 363 mg (33%) of intermediate 238a as a pale yellow solid and 694 mg (47%) of intermediate 238b as a yellow solid.

10

Alternative preparation of intermediate 238a:

Sodium hydroxide (407 mg; 7.25 mmol) was added to a mixture of intermediate 238b (687 mg; 1.81 mmol) in MeOH (14 mL). The reaction mixture was stirred at reflux for 5h. The solvent was evaporated, then water and DCM were added onto the residue. The mixture was extracted with DCM (3X) and decanted. The organic layer was dried over MgSO_4 , filtered and the solvent was evaporated to give 538 mg of intermediate 238a as a yellow oil which crystallized upon standing.

15



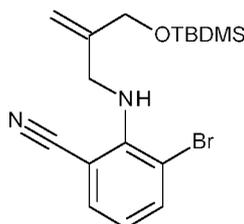
20 Preparation of intermediate 239:

In a sealed tube, triethylborane 1M in hexanes (4 mL; 4 mmol) was added dropwise at room temperature to a previously degassed mixture of intermediate 238a (374 mg; 1.32 mmol), Cs_2CO_3 (861 mg; 2.64 mmol) and RuPhos Palladacycle Gen. 1 (108 mg; 0.13 mmol) in THF (9 mL). The reaction mixture was stirred at 60°C (pre-heated bath) overnight and the reaction was combined with another reaction performed on 50 mg of intermediate 238a. The reaction mixture was then cooled to room temperature, poured onto water and extracted with EtOAc (3x). The organic layer was decanted, washed with brine, dried over MgSO_4 , filtered through a pad of celite[®] and the solvent was evaporated. The resulting residue (590 mg) was purified by chromatography over silica gel (irregular bare silica 40 g, mobile phase: 94% DCM, 6% MeOH, 0.5% NH_4OH). The fractions containing

30

the product were collected and the solvent was evaporated to give 122 mg (39%) of intermediate 239 as a yellow oil.

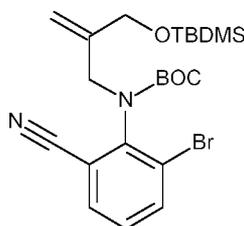
Example A52



5 Preparation of intermediate 241:

To a solution of 2-Amino-3-bromobenzonitrile (30.0 g) in THF (240 mL) was added sodium *tert*-butoxide (1.1 eq.) and the mixture was stirred at -5 to 5°C for 1 hour. A solution of intermediate 3a in THF (85.0 g) was then added dropwise and the mixture was stirred for 2-4 hours monitoring the conversion by HPLC. Water (210 mL) was then added dropwise and the mixture was concentrated to remove most of THF. Heptane (300 mL) was then added and the mixture was stirred for 30 min. After phase separation, the organic layer was washed with water (210 mL), concentrated to 2-3 volumes and filtered through a pad of silica gel (60 g), washing the pad with heptane (300 mL), affording 63.3 g of intermediate 241.

15



Preparation of intermediate 242:

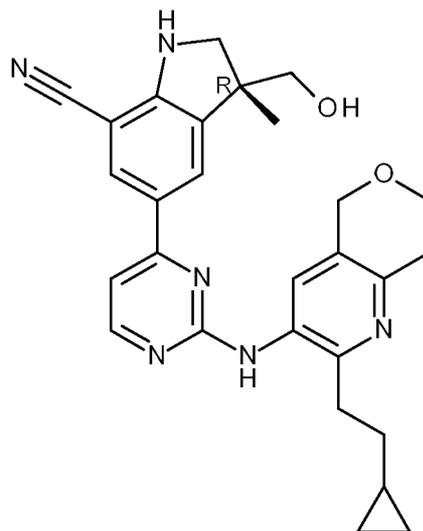
To a solution of intermediate 241 (50.0 g) in dry THF (500 mL) was added dimethylaminopyridine (0.5 eq.) and the temperature was adjusted to 65-70 °C. Di-*tert*-butyldicarbonate (2.2 eq.) was then added and the mixture was stirred for 2 hours monitoring the conversion by HPLC. Water (350 mL) was added and the mixture was concentrated to 350-400 mL. Heptane (500 mL) was added and the pH was adjusted by addition of 20% aqueous AcOH to 4-6. The layers were separated and water (350 mL) was added. After pH adjustment to 7-8 with aqueous 8% NaHCO₃, the layers were separated and the organic layer was washed with water (350 mL) and concentrated to afford 64g (quantitative) of intermediate 242.

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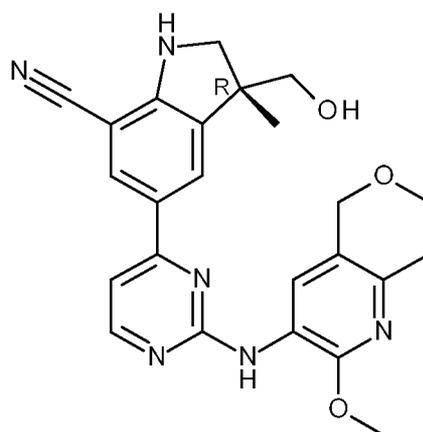
25

B. Preparation of the final compounds

Example B1

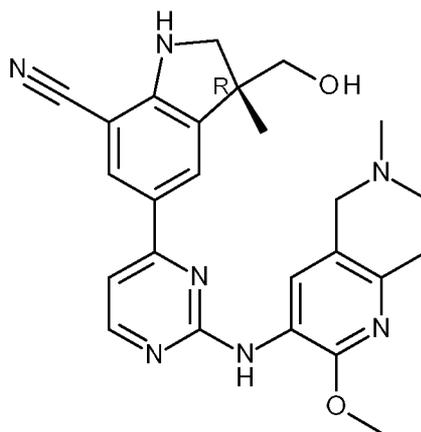
Preparation of compound 21:

To a solution of intermediate 106 (260.00 mg, 0.44 mmol) in Me-THF (5 mL) was added
5 TBAF (1M in THF) (0.50 mL, 0.50 mmol) and the mixture was stirred at rt for 20 h. The
reaction mixture was diluted with EtOAc and water. The layers were separated and the
organic layer was dried over MgSO₄, filtered, and the solvent was removed under reduced
pressure. The crude residue was purified by silica gel chromatography (irregular SiOH 15-
40 μm, 12 g, dry load on celite[®], mobile phase gradient: from DCM/iPrOH 100/0 to 90/10)
10 to give 161 mg of an off-white solid. This product was solubilized in MeCN (1 mL),
extended with water (9 mL) and freeze-dried to give 161 mg of compound 21 (77% yield,
white solid).

Preparation of compound 25:

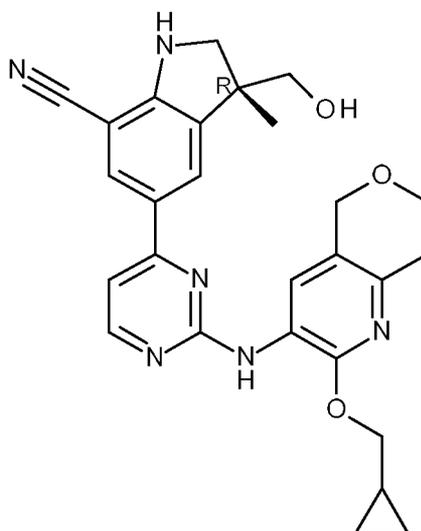
To a solution of intermediate 119 (338.00 mg, 0.50 mmol) in Me-THF (5 mL) was added
15 TBAF (1M in THF) (540.00 μL, 0.54 mmol). The solution was stirred at rt for 3 h and

evaporated in vacuo. The crude residue was purified by silica gel chromatography (Irregular SiOH 15-40 μm , 24 g, mobile phase gradient: from DCM 100% to DCM 97%, MeOH 3%). The pure fractions were collected and evaporated to dryness and the residue was triturated in Et₂O, the solid was filtered on a glass frit and dried under high vacuum (50 °C, 18 h) to give 172 mg of compound 25 (40% yield, white solid).



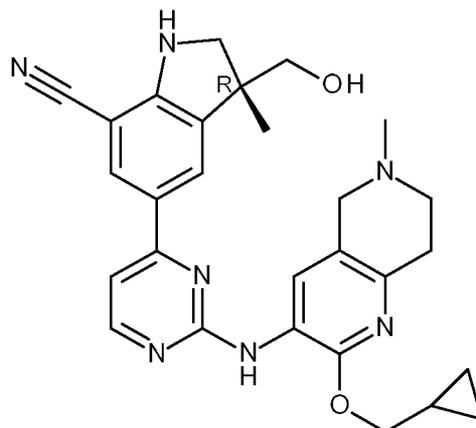
Preparation of compound 32:

To a solution of intermediate 139 (382.00 mg, 0.67 mmol) in Me-THF (7.5 mL) was added TBAF (1M in THF) (0.75 mL, 0.75 mmol) and the mixture was stirred at rt overnight. The mixture was evaporated in vacuo and purified by silica gel chromatography (irregular SiOH, 15-40 μm , 30 g, liquid loading with DCM, mobile phase gradient: from DCM 98%, MeOH/aq. NH₃ (95:5) 2% to DCM 92%, MeOH/aq. NH₃ (95:5) 8%) to give a yellow oil which crystallized upon standing. The residue was then triturated in diethylether. The precipitate was filtered on glass-frit and dried under vacuum (50 °C, 16 h) to give 143 mg of compound 32 (39% yield, white solid).



15 Preparation of compound 34:

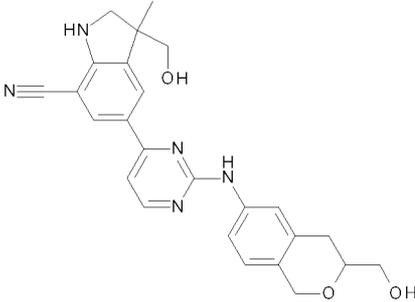
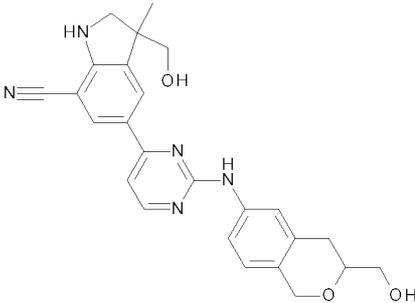
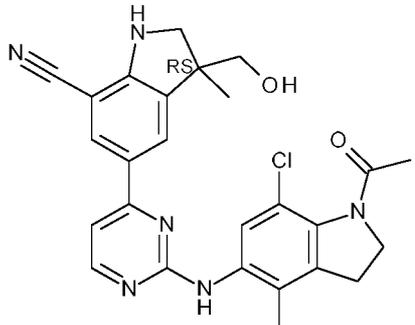
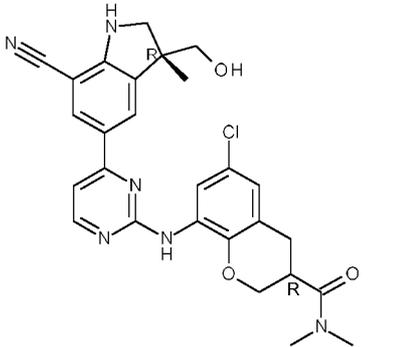
To a solution of intermediate 146 (255.00 mg, 0.29 mmol based on 69% purity ¹H NMR) in Me-THF (3 mL) was added TBAF (1M in THF) (320.00 μL, 0.32 mmol). The solution was stirred at rt for 18 h then evaporated in vacuo. The crude residue was sonicated in MeOH, and the filtrate was evaporated in vacuo. The crude residue was further sonicated in DCM. The solid was filtered on a glass frit and dried in vacuo to give 104 mg of compound 34 (35% yield, off-white solid).

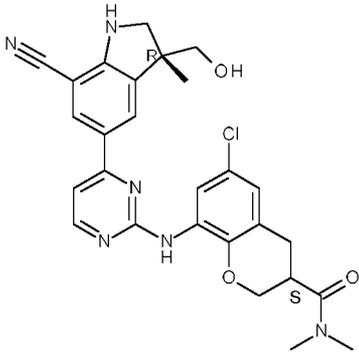
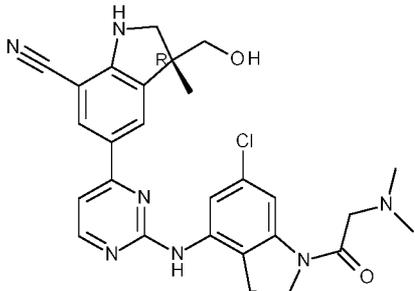
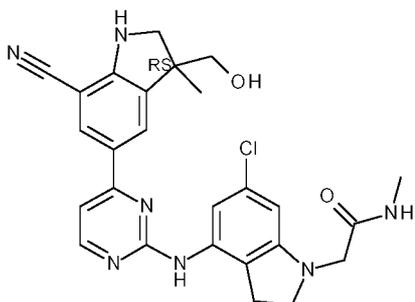
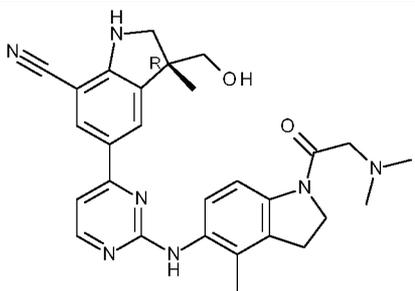


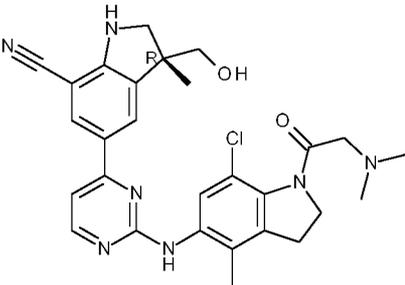
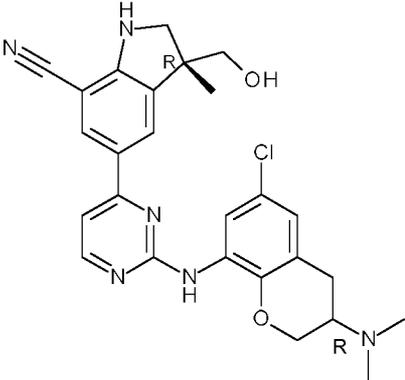
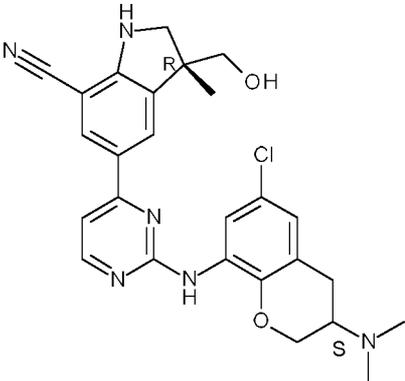
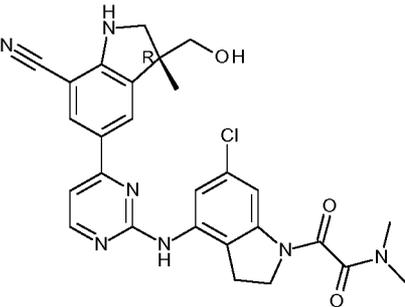
Preparation of compound 35:

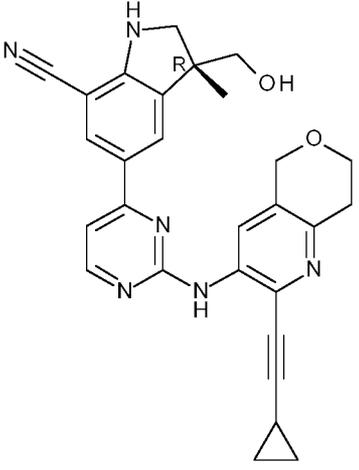
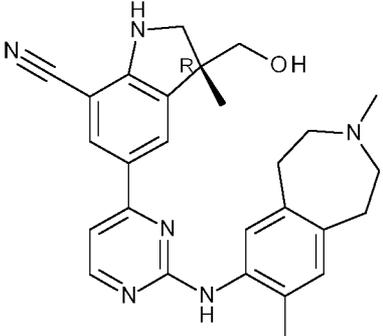
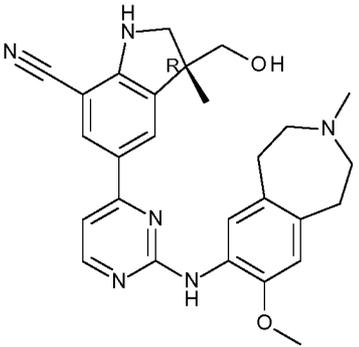
A mixture of intermediate 149 (65.00 mg, 0.11 mmol) and TBAF (1M in THF) (212.47 μL, 0.21 mmol) in Me-THF (1.06 mL, 10.62 mmol) was stirred at rt for 3 h. The reaction mixture was diluted with EtOAc, washed with an aqueous solution of K₂CO₃ (10%), water (twice) and a saturated solution of NaCl (twice). The layers were separated and the organic layer was dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography (Irregular SiOH 40 μm, 40 g, mobile phase gradient: 98% DCM, 2% MeOH, 0.2% NH₄OH to 88% DCM, 12% MeOH, 1.2% NH₄OH). The pure fractions were combined and the solvent was evaporated under reduced pressure. The residue was freeze-dried with CH₃CN to give 33 mg of compound 35 (62% yield).

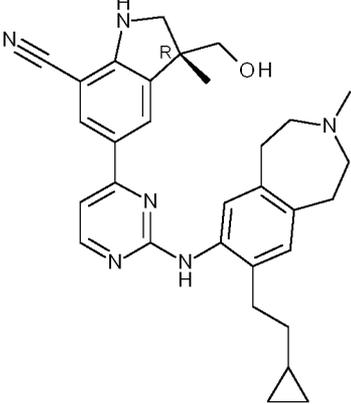
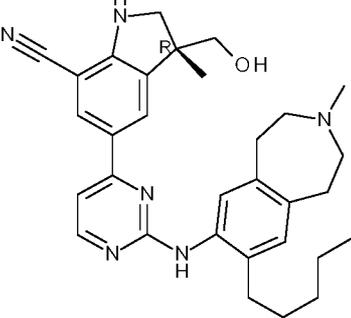
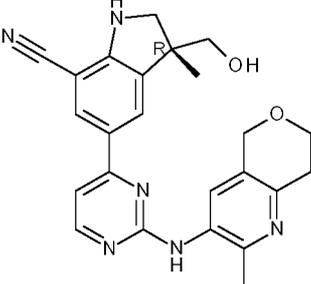
The compounds in the table below were prepared by using an analogous method starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

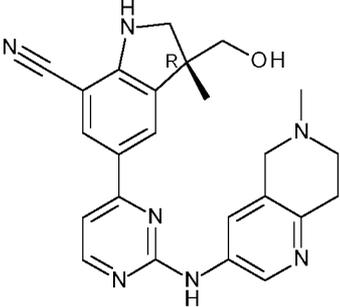
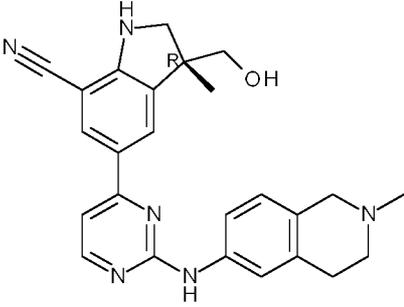
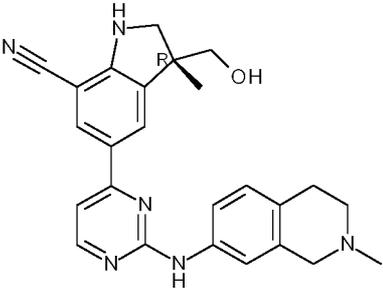
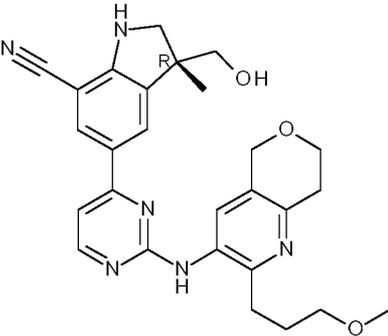
Compound number	Structure	Mass (mg)	Yield (%)
Compound 5 (mixture of two diastereomers with unknown configuration (DIA A))	 <p>From intermediate 35</p>	40	45 Procedure with 1.5 equiv. of TBAF
Compound 8 (mixture of two diastereomers with unknown configuration (DIA B))	 <p>From intermediate 41</p>	98	55 Procedure with 1.5 equiv. of TBAF
Compound 9	 <p>From intermediate 47</p>	299 <i>Off-white solid</i>	71 Procedure with 1.2 equiv. of TBAF
Compound 11	 <p>From intermediate 59</p>	115 <i>yellow solid</i>	37 Procedure with 1.1 equiv. of TBAF

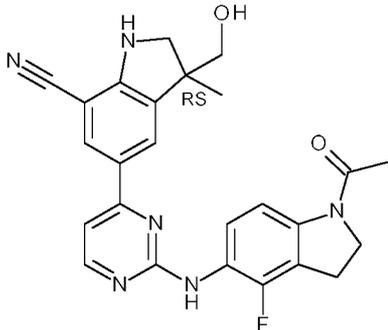
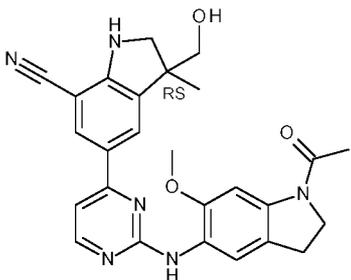
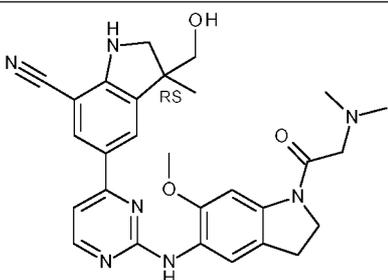
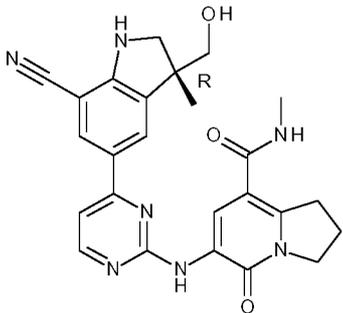
Compound number	Structure	Mass (mg)	Yield (%)
Compound 12	 <p>From intermediate 62</p>	126 <i>Pale yellow solid</i>	61 Procedure with 1.1 equiv. of TBAF
Compound 13	 <p>From intermediate 66</p>	76 <i>White solid</i>	68 Procedure with 1.1 equiv. of TBAF
Compound 14	 <p>From intermediate 70</p>	26 <i>White solid</i>	13 Procedure with 1.1 equiv. of TBAF
Compound 15	 <p>From intermediate 76</p>	65 <i>Pale yellow solid</i>	77 Procedure with 1.3 equiv. of TBAF

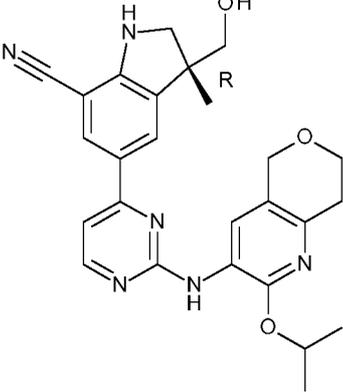
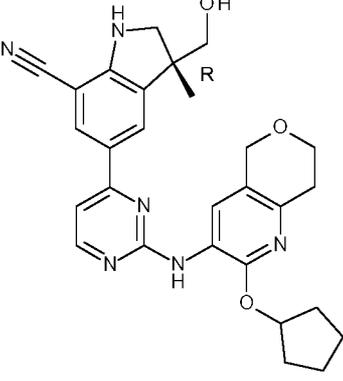
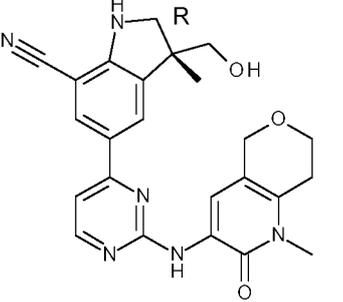
Compound number	Structure	Mass (mg)	Yield (%)
Compound 16	 <p>From intermediate 82</p>	82 <i>Off-white solid</i>	45 Procedure with 1.5 equiv. of TBAF
Compound 17	 <p>From intermediate 87</p>	100 <i>white solid</i>	34 Procedure with 1.1 equiv. of TBAF
Compound 18	 <p>From intermediate 87</p>	86 <i>white solid</i>	29 Procedure with 1.1 equiv. of TBAF
Compound 19		41 <i>Off-white solid</i>	37 Procedure with 1.1 equiv. of TBAF

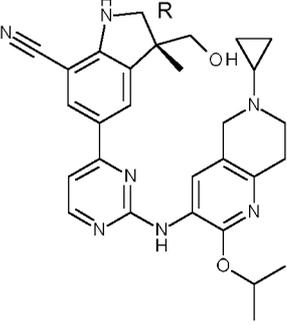
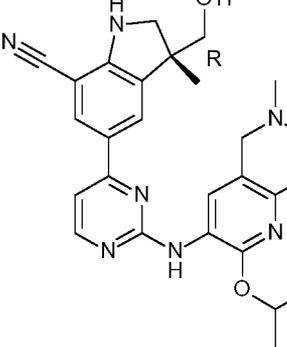
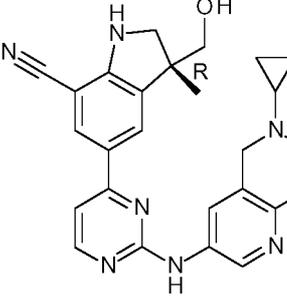
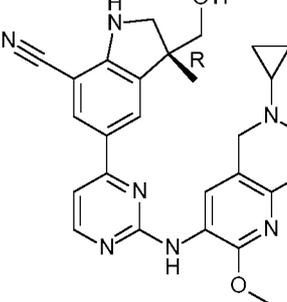
Compound number	Structure	Mass (mg)	Yield (%)
	From intermediate 93		
Compound 22	 <p>From intermediate 108</p>	85 <i>white fluffy solid</i>	65 Procedure with 1.15 equiv. of TBAF
Compound 23	 <p>From intermediate 112</p>	126 <i>yellow solid</i>	65 Procedure with 1.1 equiv. of TBAF
Compound 24	 <p>From intermediate 116</p>	132 <i>yellow solid</i>	54 Procedure with 1.1 equiv. of TBAF

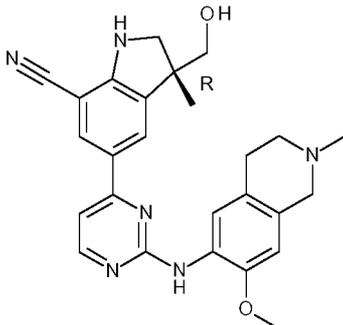
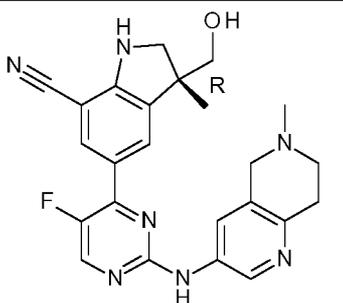
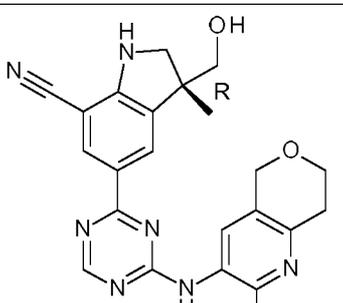
Compound number	Structure	Mass (mg)	Yield (%)
Compound 26	 <p data-bbox="544 835 948 913">From a mixture of intermediate 124 and 124'</p>	155 <i>Pale yellow solid</i>	23 Procedure with 1.1 equiv. of TBAF
Compound 27	 <p data-bbox="544 1283 948 1361">From a mixture of intermediate 124 and 124'</p>	36 <i>white solid</i>	5 Procedure with 1.1 equiv. of TBAF
Compound 28	 <p data-bbox="544 1697 836 1736">From intermediate 127</p>	202 <i>Yellow solid</i>	49 Procedure with 1.1 equiv. of TBAF

Compound number	Structure	Mass (mg)	Yield (%)
Compound 29	 <p>From intermediate 131</p>	263 <i>Pale yellow solid</i>	64 Procedure with 1.1 equiv. of TBAF
Compound 30	 <p>From intermediate 134</p>	167 <i>Pale yellow solid</i>	68 Procedure with 1.1 equiv. of TBAF
Compound 31	 <p>From intermediate 136</p>	72 <i>White fluffy solid</i>	39 Procedure with 1.1 equiv. of TBAF
Compound 33	 <p>From intermediate 143</p>	133 <i>Yellow solid</i>	57 Procedure with 1.05 equiv. of TBAF

Compound number	Structure	Mass (mg)	Yield (%)
Compound 36	 <p>From intermediate 152</p>	170	31 Procedure with 2.5 equiv. of TBAF and THF as solvent
Compound 39	 <p>From intermediate 160</p>	44	16 Procedure with 1.5 equiv. of TBAF and THF as solvent
Compound 40	 <p>From intermediate 165</p>	80	37 Procedure with 4 equiv. of TBAF and THF as solvent
Compound 44	 <p>From intermediate 179</p>	122	79

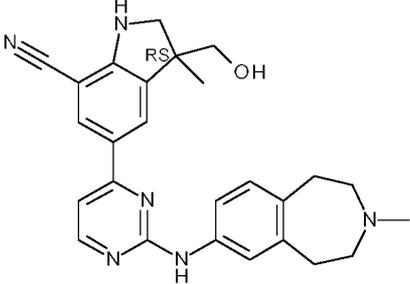
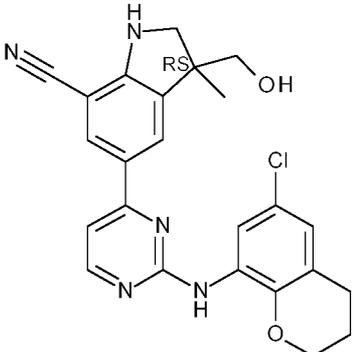
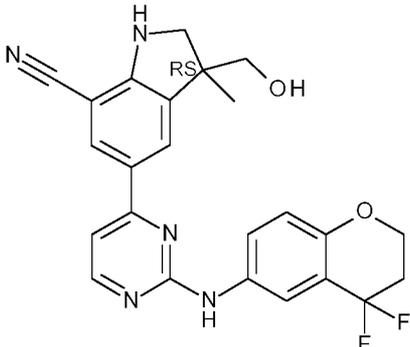
Compound number	Structure	Mass (mg)	Yield (%)
Compound 46	 <p data-bbox="544 831 839 857">From intermediate 184</p>	62	57 Procedure with 1.2 equiv. of TBAF
Compound 47	 <p data-bbox="544 1279 839 1305">From intermediate 187</p>	57	41
Compound 48	 <p data-bbox="544 1653 839 1675">From intermediate 189</p>	43	57 Procedure with 1.05 equiv. of TBAF

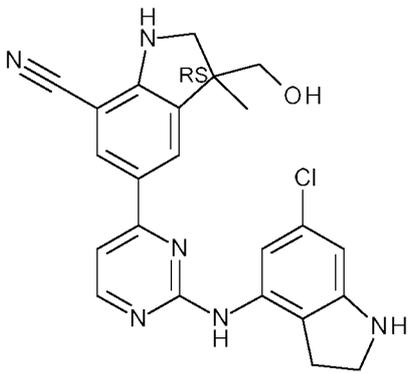
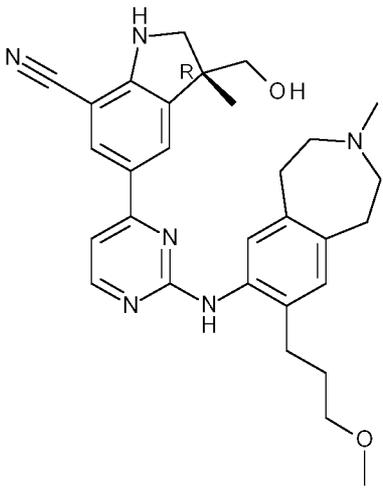
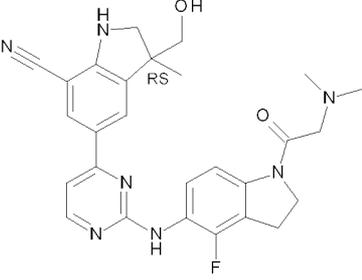
Compound number	Structure	Mass (mg)	Yield (%)
Compound 49	 <p data-bbox="544 757 837 790">From intermediate 195</p>	47	48 Procedure with 2 equiv. of TBAF
Compound 50	 <p data-bbox="544 1193 837 1227">From intermediate 199</p>	296	55 Procedure with 2 equiv. of TBAF
Compound 51	 <p data-bbox="544 1563 837 1597">From intermediate 203</p>	53	60 Procedure with 2 equiv. of TBAF
Compound 52		36	37 Procedure with 2 equiv. of TBAF

Compound number	Structure	Mass (mg)	Yield (%)
	From intermediate 207		
Compound 53	 <p>From intermediate 210</p>	43	67 Procedure with 2 equiv. of TBAF
Compound 54	 <p>From intermediate 213</p>	97	94 Procedure with 4 equiv. of TBAF and THF as solvent
Compound 55	 <p>From intermediate 216</p>	48	31 Procedure with 1.6 equiv. of TBAF and THF as solvent

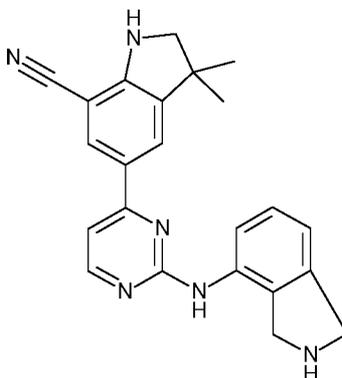
The compounds in the table below were prepared by using an analogous method starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

5

Compound number	Structure	Mass (mg)	Yield (%)
Compound 3	 <p>From intermediate 22</p>	120 <i>yellow solid</i>	28 Procedure with DCM/TFA (3:1, eq./eq.)
Compound 4	 <p>From intermediate 27</p>	104 <i>Pale yellow solid</i>	63 Procedure with DCM/TFA (3:1, eq./eq.)
Compound 7	 <p>From intermediate 40</p>	25	29

Compound number	Structure	Mass (mg)	Yield (%)
Compound 10	 <p>From intermediate 51</p>	28 <i>Pale green solid</i>	22 Procedure with DCM/TFA (4:1, eq./eq.)
Compound 20	 <p>From intermediate 99</p>	241 <i>White fluffy solid</i>	46 Procedure with DCM/TFA (3:1, eq./eq.)
Compound 38	 <p>From intermediate 157</p>	20	6 Procedure with DCM/TFA (10:1, v./v.)

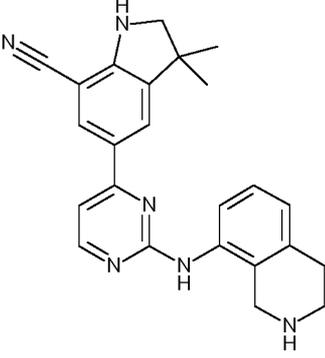
Example B3

Preparation of compound 2:

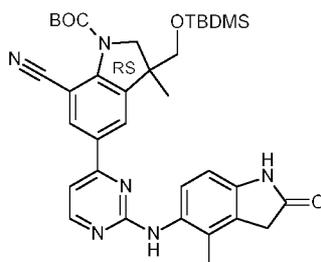
HCl (3M in H₂O) (3 mL, 9 mmol) was added to a solution of intermediate 16 (378.76 mg, 0.65 mmol) in MeOH (10 mL) and the reaction mixture was stirred 5 h at 65 °C. The reaction mixture was cooled to room temperature, poured onto a 10% aqueous solution of K₂CO₃ and extracted with DCM. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue was taken up with DCM/MeOH (90/10) and the precipitate was filtered, washed with DCM and dried. The filtrate was evaporated and dissolved in DCM/MeOH (330 mL, 10% MeOH) and a 10% aqueous solution of K₂CO₃ was added. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 25 g + 5 g solid deposit, mobile phase gradient: from 0.5% NH₄OH, 5% MeOH, 95% DCM to 1% NH₄OH, 10% MeOH, 90% DCM). The pure fractions were collected and evaporated to dryness. The residue was further purified by reverse phase chromatography (X-Bridge-C18 5 μm 30*150 mm, mobile phase gradient: from 60% NH₄HCO₃ (0.5%), 40% MeOH to 20% NH₄HCO₃ (0.5%), 80% MeOH). The pure fractions were collected and evaporated to dryness. The residue was crystallized from CH₃CN and the precipitate was filtered and dried to give 53 mg of compound 2 (21% yield).

The compound in the table below was prepared by using an analogous method starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

Compound number	Structure	Mass (mg)	Yield (%)

Compound 6	 <p data-bbox="555 689 836 716">From intermediate 36</p>	26	28 Procedure with MeOH/HCl (3M in H ₂ O) (28:1, eq./eq.)
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Example B4

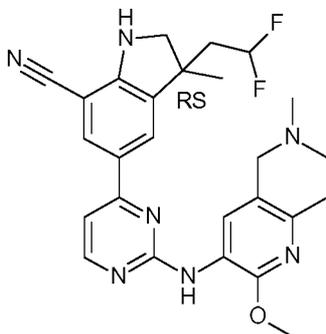


Preparation of compound 42:

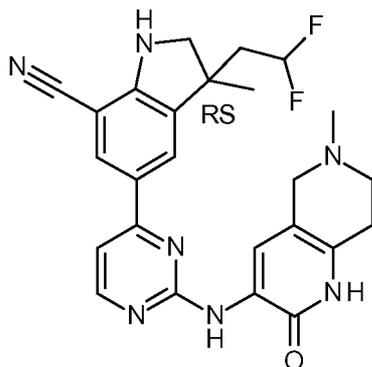
Intermediate 170 (200 mg; 0.15 mmol) in TFA (5 mL) and DCM (20 mL) was stirred for 1 hour. Then, aqueous NaHCO₃ was added to the mixture until pH superior to 7. The organic layer was separated, dried over MgSO₄, filtered and evaporated to give a sticky gum which was diluted in THF (5 mL) and treated with TBAF 1M in THF (2.5 mL; 2.5 mmol). The solvent was removed, and the reaction mixture was partitioned between DCM (20 mL) and water (20 mL). The organic layer was separated, dried over MgSO₄, filtered and evaporated.

The residue was purified by high-performance liquid chromatography (column: Phenomenex Synergi C18 150*30mm*4um, eluent: 0.1% aqueous TFA-ACN from 20% to 30%, v/v). The desired fraction was collected and the solvent was concentrated. The intermediate fraction was basified by aqueous NaHCO₃ (5 mL) and extracted with DCM (10 mL *3). The organic layers were combined, dried over MgSO₄, filtered and evaporated to give 10 mg (15%) of compound 42 as a yellow solid.

Example B5



Preparation of compound 56



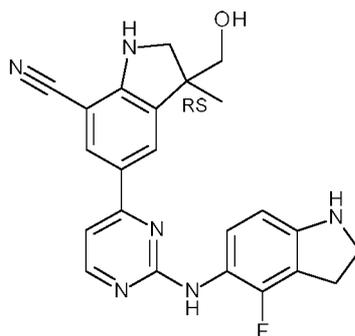
and compound 57

To a mixture of intermediate 225 (153 mg; 0.259 mmol) in DCM (4 mL) was added TFA (2 mL) and the reaction was stirred at room temperature for 2 hours. The solvents were evaporated in vacuo and the crude was purified by reverse phase (Stationary phase: Phenomenex- Gemini C18 (5 μ m) 21.2*100mm; mobile phase: from 90 % of H₂O (0.1% HCOOH)- 10 % (MeOH) till 54% of H₂O (0.1% HCOOH)- 46 % (MeOH). The desired fractions were collected, washed with a saturated solution of NaHCO₃ and extracted with ethyl acetate to afford 2 fractions. The respective organic layers were dried over MgSO₄, filtered and the solvent was evaporated in vacuo to afford - fraction A (clear oil) which was dissolved in a mixture of ACN-Diethyl Ether and evaporated until precipitation. The white solid was filtered to afford 30 mg (23%) of compound 56.

Fraction B (impure compound 57) which was purified again via reverse phase (Stationary phase: Phenomenex- Gemini C18 (5 μ m) 21.2*100mm; mobile phase: from 95 % of H₂O (0.1% HCOOH)- 5 % (MeOH) till 63% of H₂O (0.1% HCOOH)- 37 % (MeOH) followed by a third reverse phase purification (Stationary phase: Phenomenex- Gemini C18 (5 μ m) 21.2*100mm; mobile phase: from 70 % of H₂O (25mM NH₄HCO₃)- 30 % (ACN: MeOH 1:1) till 27% of H₂O (25mM NH₄HCO₃)- 73 % (ACN: MeOH 1:1). The desired tubes were collected and the solvents were evaporated in vacuo. The resulting yellow solid was dissolved three times in ACN and then, the solvent was concentrated under vacuum to give 22 mg (18%) of compound 57.

Conversion

Conversion C1:

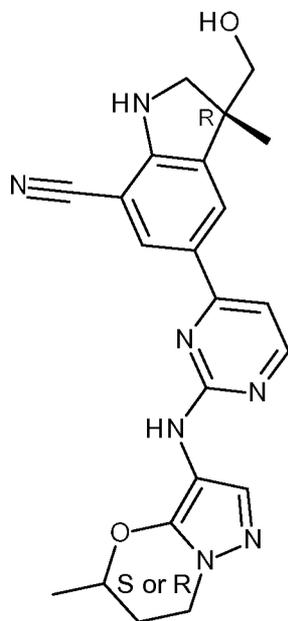


5 Preparation of compound 37:

A mixture of compound 36 (300 mg; 35% of purity), HCl 3M (5 mL) in MeOH (10 mL) was heated to reflux for 1h. Then, the solvent was removed. The reaction mixture was basified by aqueous solution of NaHCO₃ and of a solid (300 mg) was collected.

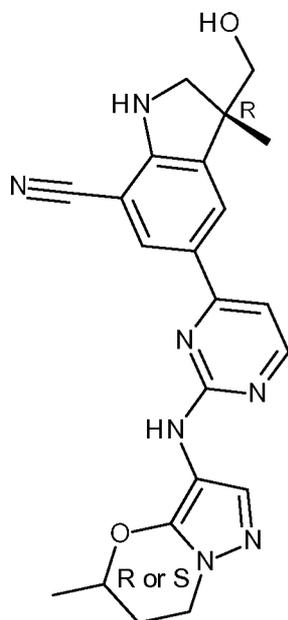
It was then purified by preparative high-performance liquid chromatography (column: Gemini 150*25 5u, eluent: 0.05%HCl-ACN from 0%/100% to 25%/75%, v/v). The desired fraction was collected and the solvent was removed to give 120 mg of an impure intermediate fraction A. Fraction A was further purified by preparative high-performance liquid chromatography (column: Phenomenex Gemini 150*25mm*10um, eluent: water (0.05% ammonium hydroxide, v/v) - ACN from 35%/65% to 65%/35%, v/v). The desired fraction was collected and the solvent was removed to give 40 mg (14%) of compound 37.

Example B1b



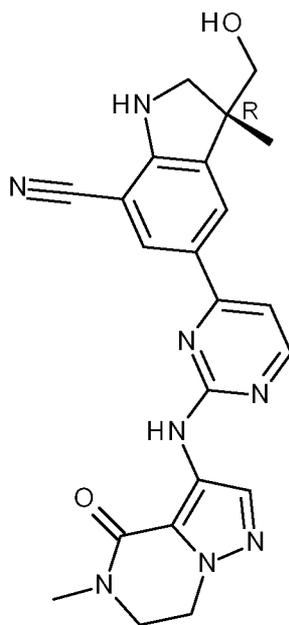
Preparation of compound 1b:

A mixture of intermediate 11b (140.00 mg, 0.26 mmol) and TBAF (1M in THF) (0.53 mL, 0.53 mmol) in Me-THF (2.64 mL) was stirred at rt for 8h. The crude residue was purified via silica gel chromatography (Stationary phase: irregular SiOH 15-40 μ m, 80 g, mobile phase gradient: from 100% DCM to 90% DCM, 10% MeOH, 0.1% NH_4OH). Product containing fractions were collected and concentrated under reduced pressure. The residue was taken up into CH_3CN . The precipitate was filtered and dried under vacuum to give 44 mg of compound 1b (40% yield).



Preparation of compound 2b:

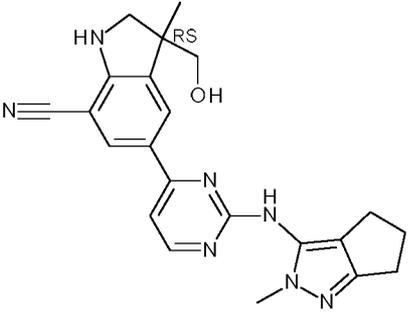
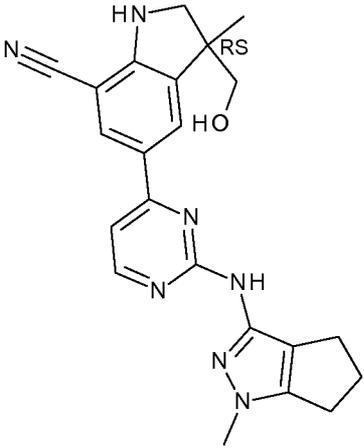
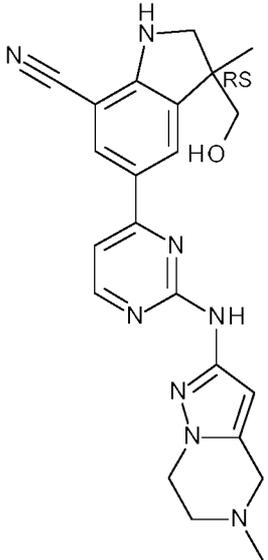
- A mixture of intermediate 13b (252.00 mg, 0.47 mmol) and TBAF (1M in THF) (0.95 mL, 0.95 mmol) in Me-THF (4.75 mL) was stirred at rt for 8 h. The crude residue was purified via silica gel chromatography (Stationary phase: irregular SiOH 15-40 μ m, 80 g, mobile phase gradient: from 100% DCM to 90% DCM, 10% MeOH, 0,1% NH₄OH). Pure fractions were collected and evaporated to give 77 mg of compound 2b (39% yield).

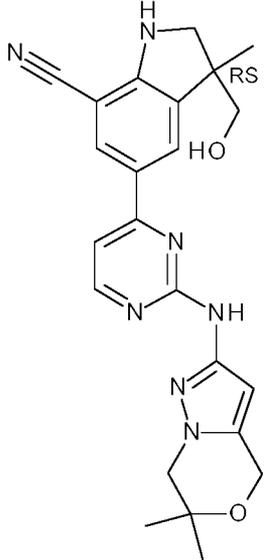
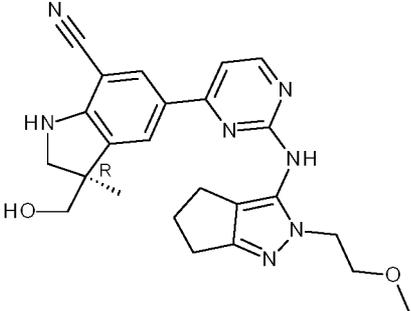
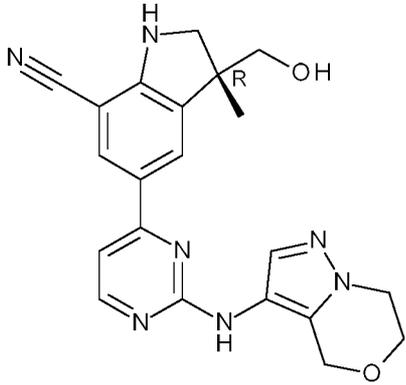


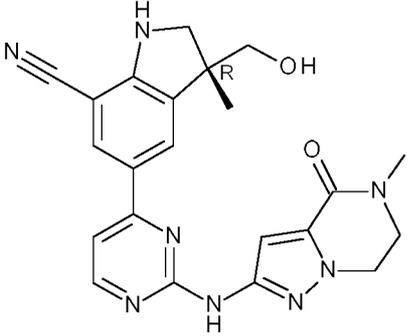
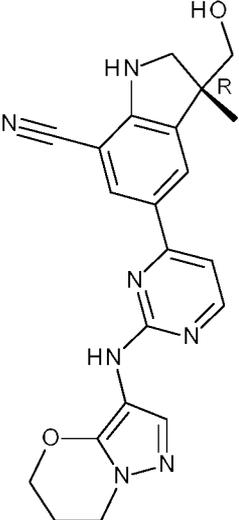
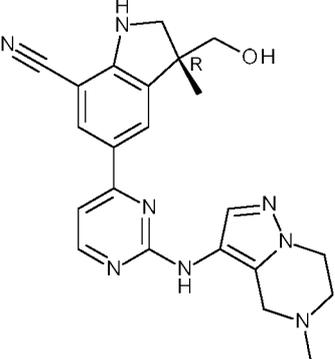
Preparation of compound 3b:

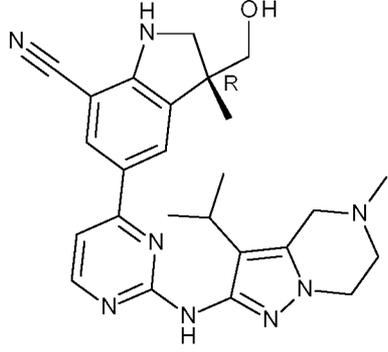
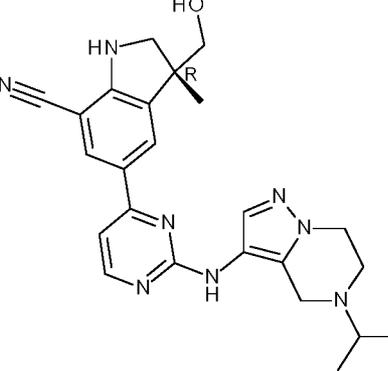
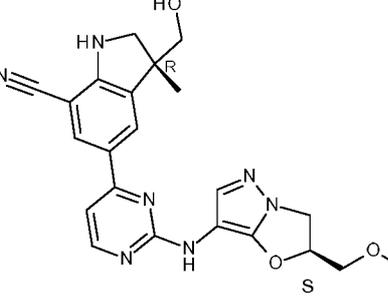
- TBAF (1M in THF) (0.35 mL, 0.35 mmol) was added to a solution of intermediate 17b (0.13 g, 0.23 mmol) in THF (4.00 mL) and the solution was stirred at room temperature overnight. Water and a 10% aqueous solution of K₂CO₃ were added and this mixture was extracted twice with EtOAc. The organic layers were combined, dried over Na₂SO₄, filtered and the solvent was evaporated until dryness. The residue was taken up into CH₃CN, triturated and filtered. The precipitate was washed once with DCM and dried until dryness to give 77 mg of compound 3 (77% yield).
- The compounds in the table below were prepared by using an analogous method as described for the preparation of compound 3b, starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

Compound number	Structure	Mass (mg)	Yield (%)

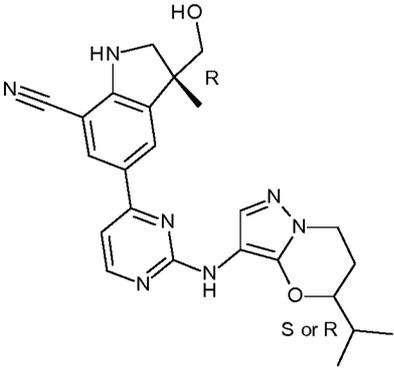
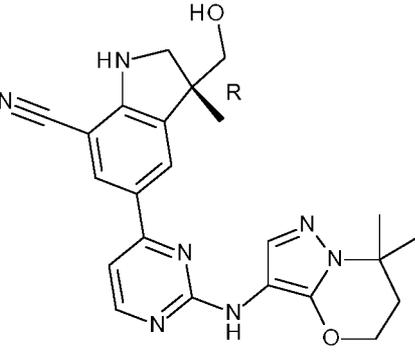
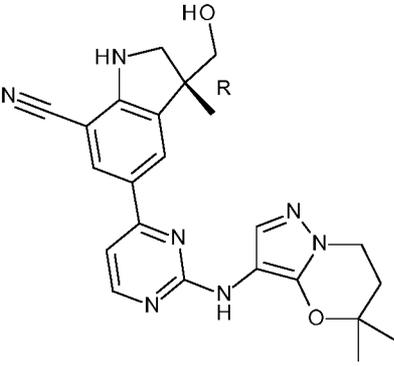
Compound number	Structure	Mass (mg)	Yield (%)
Compound 4b	 <p data-bbox="667 741 965 775">From intermediate 21b</p>	66	71 Procedure with 1.1 equiv. of TBAF
Compound 5b	 <p data-bbox="667 1261 965 1296">From intermediate 23b</p>	198	74
Compound 9b	 <p data-bbox="667 1895 965 1933">From intermediate 52b</p>	44	68 Procedure with Me-THF as solvent

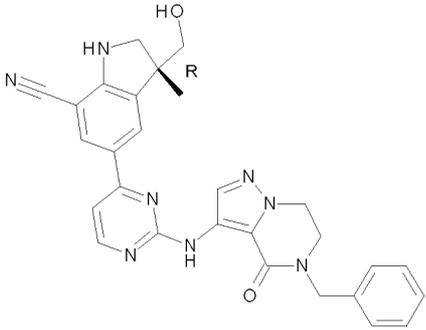
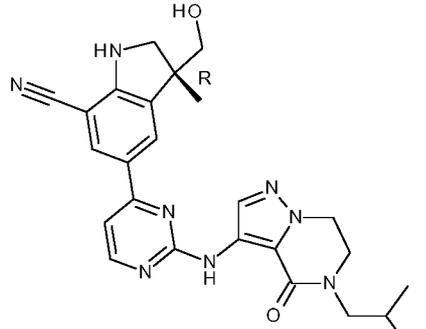
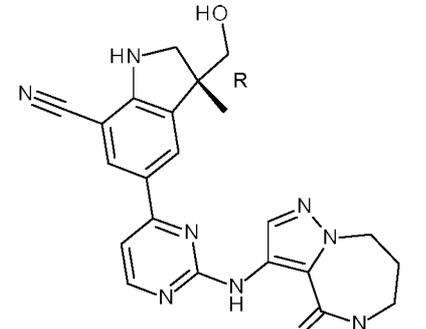
Compound number	Structure	Mass (mg)	Yield (%)
Compound 10b	 <p data-bbox="667 992 967 1025">From intermediate 57b</p>	44	23 Procedure with Me-THF as solvent
Compound 11b	 <p data-bbox="667 1429 967 1460">From intermediate 60b</p>	65	67 Procedure with 1.6 equiv. of TBAF and Me-THF as solvent
Compound 12b	 <p data-bbox="667 1888 967 1919">From intermediate 68b</p>	12 <i>Off-white solid</i>	4 Procedure with 1.1 equiv. of TBAF and Me-THF as solvent

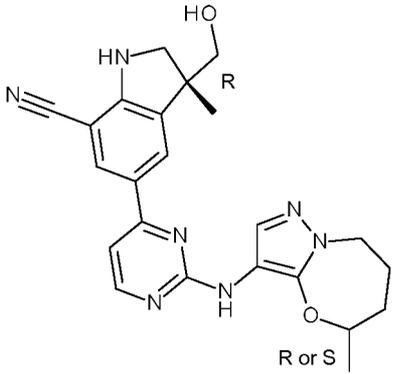
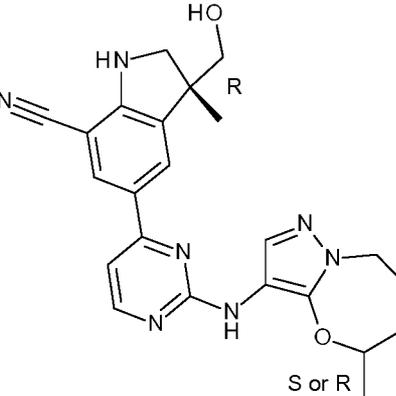
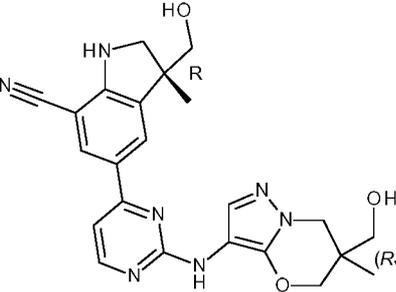
Compound number	Structure	Mass (mg)	Yield (%)
Compound 13b	 <p data-bbox="667 815 965 848">From intermediate 74b</p>	30	25 Procedure with 2 equiv. of TBAF and Me-THF as solvent
Compound 14b	 <p data-bbox="667 1413 965 1447">From intermediate 79b</p>	76	18 Procedure with 2 equiv. of TBAF and Me-THF as solvent
Compound 15b	 <p data-bbox="667 1852 965 1886">From intermediate 83b</p>	95	68 Procedure with 2 equiv. of TBAF and Me-THF as solvent

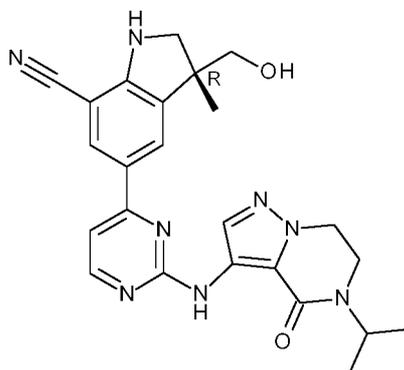
Compound number	Structure	Mass (mg)	Yield (%)
Compound 16b	 <p data-bbox="667 779 959 813">From intermediate 88b</p>	136	46 Procedure with 2 equiv. of TBAF and Me-THF as solvent
Compound 18b	 <p data-bbox="667 1234 959 1267">From intermediate 100b</p>	62	23 Procedure with 2 equiv. of TBAF and Me-THF as solvent
Compound 19b	 <p data-bbox="667 1597 959 1630">From intermediate 105b</p>	297	50 Procedure with 2 equiv. of TBAF and Me-THF as solvent

Compound number	Structure	Mass (mg)	Yield (%)
Compound 20b (methyl groups <i>cis</i> in bicyclic pyrazole)	<p style="text-align: center;">methyl groups <i>CIS</i>: mixture of (R,S) and (S,R)</p> <p style="text-align: center;">From intermediate 110b</p>	185	56 Procedure with 2 equiv. of TBAF and Me-THF as solvent
Compound 21b (methyl groups <i>trans</i> in bicyclic pyrazole)	<p style="text-align: center;">methyl groups <i>TRANS</i>: mixture of (R,R) and (S,S)</p> <p style="text-align: center;">From intermediate 114b</p>	54	35 Procedure with 2 equiv. of TBAF and Me-THF as solvent
Compound 22b	<p style="text-align: center;">From intermediate 122b</p>	92	64 Procedure with 2 equiv. of TBAF and Me-THF as solvent

Compound number	Structure	Mass (mg)	Yield (%)
Compound 23b	 <p data-bbox="662 790 970 824">From intermediate 123b</p>	24	15 Procedure with 2 equiv. of TBAF and Me-THF as solvent
Compound 24b	 <p data-bbox="662 1256 970 1290">From intermediate 128b</p>	157	46 Procedure with 2 equiv. of TBAF and Me-THF as solvent
Compound 25b	 <p data-bbox="662 1688 970 1722">From intermediate 132b</p>	185	39 Procedure with 2 equiv. of TBAF and Me-THF as solvent

Compound number	Structure	Mass (mg)	Yield (%)
Compound 26b	 <p data-bbox="660 797 975 831">From intermediate 136b</p>	486	53 Procedure with 2 equiv. of TBAF and Me-THF as solvent
Compound 27b	 <p data-bbox="660 1218 975 1252">From intermediate 140b</p>	63	62 Procedure with 2 equiv. of TBAF and Me-THF as solvent
Compound 28b	 <p data-bbox="660 1693 975 1727">From intermediate 144b</p>	320	63 Procedure with 2 equiv. of TBAF and Me-THF as solvent

Compound number	Structure	Mass (mg)	Yield (%)
Compound 29b	 <p data-bbox="660 792 973 831">From intermediate 151b</p>	77	65 Procedure with 2 equiv. of TBAF and Me-THF as solvent
Compound 30b	 <p data-bbox="660 1317 973 1350">From intermediate 153b</p>	42	35 Procedure with 2 equiv. of TBAF and Me-THF as solvent
Compound 31b	 <p data-bbox="660 1675 973 1709">From intermediate 157b</p>	111	46 Procedure with 1.9 equiv. of TBAF and Me-THF as solvent

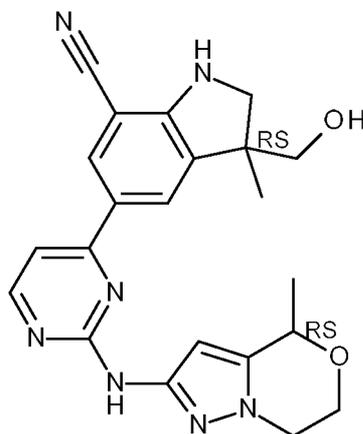


Preparation of compound 17b:

A mixture of intermediate 93 (450 mg, 0.786 mmol) and TBAF (1M in THF) (1.57 mL, 1.57 mmol) in Me-THF (7.87 mL) was stirred at rt for 3h. The reaction mixture was diluted with EtOAc, washed with a 10% aqueous solution of K_2CO_3 , water and a saturated solution of NaCl. The layers were separated and the organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure.

The crude product (460 mg) was purified by silica gel chromatography (Irregular SiOH 40 μ m 40 g; Mobile phase 99% DCM, 1% MeOH, 0.1% NH_4OH to 93% DCM, 7% MeOH, 0.7% NH_4OH). The pure fractions were combined and the solvent was evaporated to give 272 mg of an intermediate compound which was crystallized from ACN to give 183mg (51%) of compound 17. M.P= 212°C (Kofler).

Example B2b



Preparation of compound 6b:

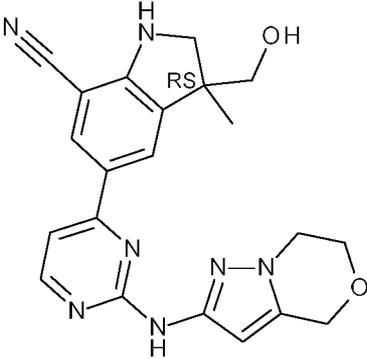
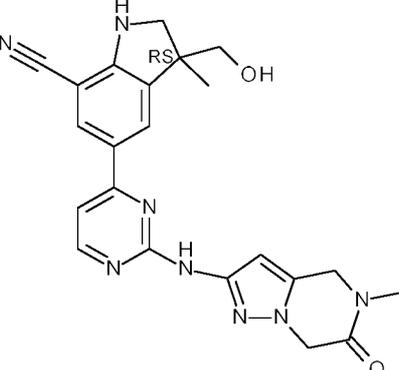
TFA (2 mL) was added to a solution of intermediate 33b (100.00 mg, 0.084 mmol) in DCM (5 mL) and the mixture was stirred at room temperature for 17 h. The reaction mixture was evaporated under vacuum and the resulting residue was combined with another batch carried out on 0.040 mmol of intermediate 33b. The resulting mixture was purified by high-performance liquid chromatography (gradient elution: acetonitrile / 0.05%

ammonia in purified water). The desired fractions were collected and the solvent was concentrated under vacuum. The crude residue was further purified by preparative TLC plates (eluent: EtOAc/MeOH: 9/1) to give 14 mg of compound 6b (38% yield; mixture of 4 diastereoisomers).

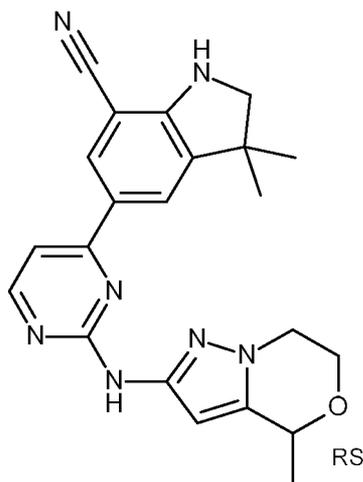
5

The compounds in the table below were prepared by using an analogous method as reported for the preparation of compound 6b, starting from the respective starting materials. Minor deviations to the referenced method are indicated as additional information in the column 'Yield (%)'.

10

Compound number	Structure	Mass (mg)	Yield (%)
Compound 7b	 <p>From intermediate 40b</p>	38	84
Compound 8b	 <p>From intermediate 47b</p>	28	40 Procedure with TFA/DCM 1:4, v/v

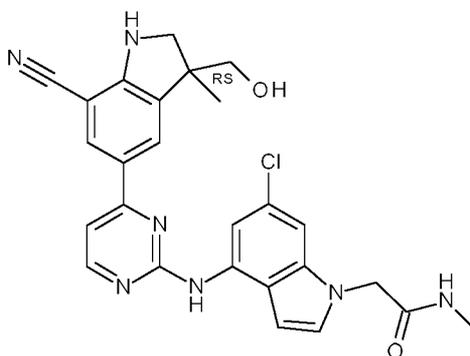
Example B3b



Preparation of compound 32b:

TFA (1 mL) was added to a solution of intermediate 162b (200.00 mg, 0.196 mmol) in DCM (5 ml) at 0°C. The mixture was stirred at 0°C for 1 hour. The reaction was concentrated to give the crude product. The crude product was purified by preparative high-performance liquid chromatography. (Column: Waters Xbridge 150*25 5u. Condition: A: water(10mM NH₄HCO₃); B: MeCN; at the beginning: A (60%) and B (40%); at the end: A: (30%) and B (70%); Gradient Time(min) 12; 100%B Hold Time(min) 2; Flow Rate(ml/min) 25.) The pure fractions were collected and the solvent was evaporated under vacuum. Water was added and lyophilized to dryness to give compound 32b as yellow solid (45 mg; 57.2%).

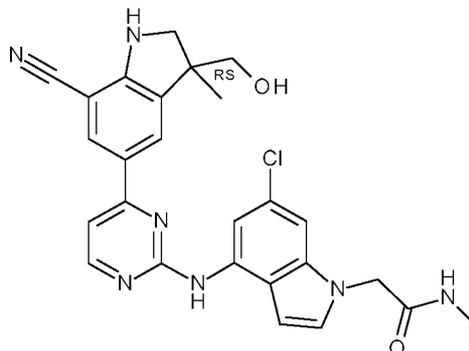
Example B1c



Preparation of compound 3c:

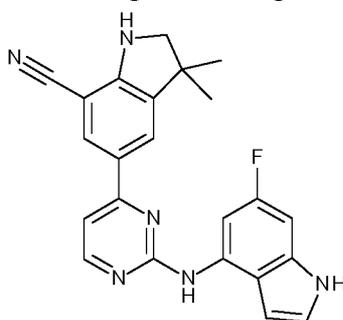
A solution of intermediate 22c (241.00 mg, 0.26 mmol based on 65% purity determined by LC/MS) in TFA (3 mL) and DCM (3 mL) was stirred at rt for 0.5 h. The reaction mixture was concentrated under vacuum and coevaporated with toluene. The residue was purified by reverse phase semi-preparative HPLC (Stationary phase: X-Bridge-C18, 10 μm, 30 x 150 mm, mobile phase gradient from 10% CH₃CN, 90% H₂O, 0.1% NH₄OH to 98%

CH₃CN, 2% H₂O, 0.1% NH₄OH). The relevant fractions were freeze dried overnight to give 43.7 mg of compound 3c (34% yield, pale orange solid).



Alternative preparation of compound 3c:

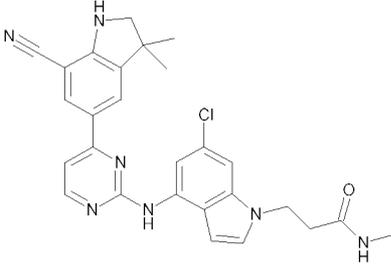
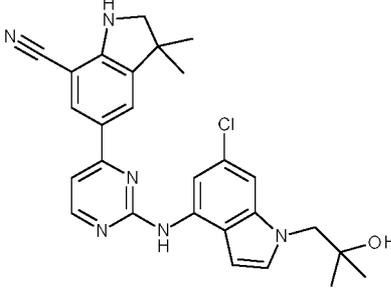
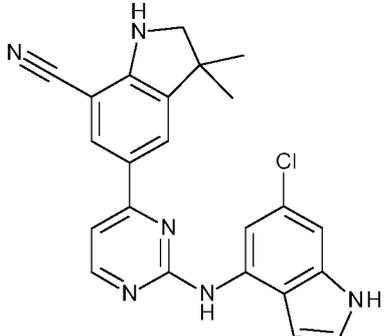
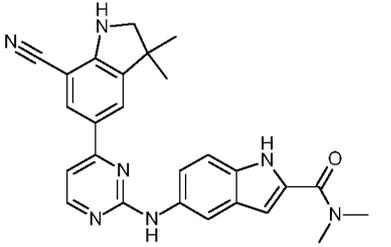
A solution of intermediate 21c (817.00 mg, 1.14 mmol) in TFA (12.2 mL) and DCM (12.2 mL) was stirred at rt overnight. The reaction mixture was poured into ice, basified with K₂CO₃, filtered and extracted with DCM. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent was concentrated under vacuum. The residue was crystallized from ACN, filtered and dried under vacuum to give crude compound 3c. The residue was purified by reverse phase (stationary phase: X-Bridge-C18, 5 μm, 30 x 150 mm, mobile phase gradient from 50% aq. NH₄HCO₃ (0.5%), 50% MeOH to 0% aq. NH₄HCO₃ (0.5%), 100% MeOH). The fractions containing the product were combined and evaporated to dryness under vacuum to give 130 mg of compound 3c (23% yield).



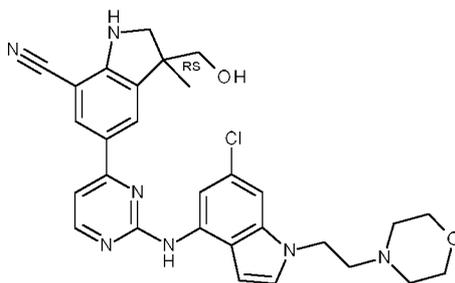
Preparation of compound 8c:

A solution of intermediate 35c (397.00 mg, 0.605 mmol based on 76% purity determined by LC/MS) in TFA (3 mL) and DCM (3 mL) was stirred at rt for 1 h. The reaction mixture was concentrated under vacuum and coevaporated with toluene. The residue was triturated with cyclohexane and a minimum of ethyl acetate and the solid was collected by filtration, washed with cyclohexane and dried under vacuum. The crude product was purified by a Mass Directed Auto Purification system (basic column) to give 31 mg of compound 8c (10% yield, beige solid).

The compounds in the table below were prepared by using an analogous method starting from the respective starting materials.

Compound number	Structure	Mass (mg)	Yield (%)
Compound 1c	 <p>From intermediate 15c</p>	35	28
Compound 2c	 <p>From intermediate 18c</p>	45	35
Compound 7c	 <p>From intermediate 33c</p>	2.2	1
Compound 12c	 <p>From intermediate 50c</p>	20	54

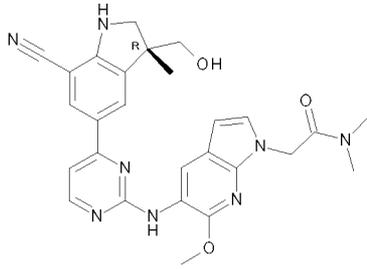
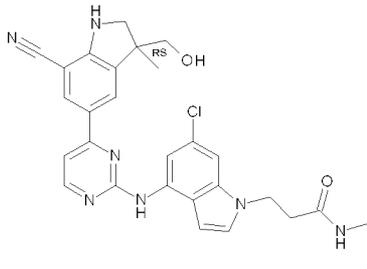
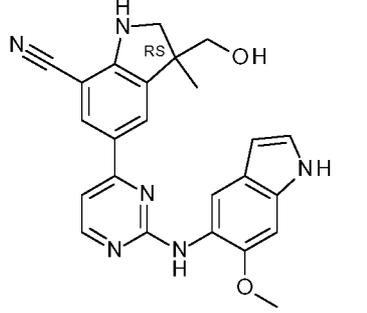
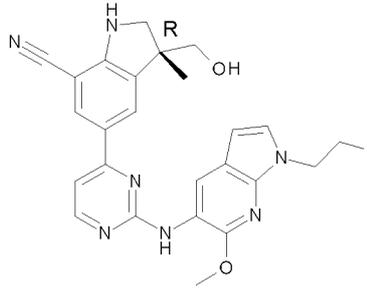
Example B2c

Preparation of compound 4c:

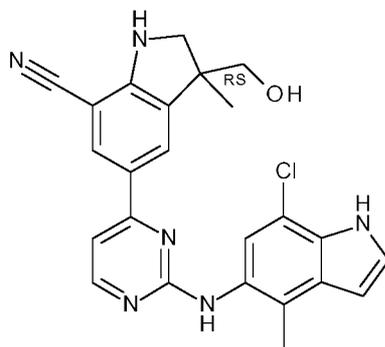
A mixture of intermediate 25c (77.00 mg, 0.117 mmol) and TBAF (1M in THF) (0.129 mL, 0.129 mmol) in Me-THF (2 mL) was stirred at rt for 2 h. The residue was directly purified by silica gel chromatography (irregular SiOH 15-40 μ m, 24g, liquid injection with DCM, mobile phase gradient: from DCM/MeOH (+ 10% aq. NH₃) 100/0 to 80/20). The product containing fractions were combined and evaporated to dryness. The residue (35 mg) was recrystallized from EtOH, filtered on a glass frit and washed with EtOH. The solid was collected and was dried at 50 °C under reduced pressure for 16 h to give 24 mg of compound 4c (38% yield, pale yellow solid).

The compounds in the table below were prepared by using an analogous method starting from the respective starting materials.

Compound number	Structure	Mass (mg)	Yield (%)
Compound 5c	<p>From intermediate 28c</p>	192	45 <i>yellow green solid</i> (over 2 steps)
Compound 6c	<p>From intermediate 31c</p>	132	34 <i>brown solid</i>

Compound number	Structure	Mass (mg)	Yield (%)
Compound 10c	 <p>From intermediate 46c</p>	180	56
Compound 11c	 <p>From intermediate 47c</p>	1127	30
Compound 13c	 <p>From intermediate 54c</p>	6.7	2
Compound 14c	 <p>From intermediate 58c</p>	48	62

Example B3c

Preparation of compound 9c:

A solution of intermediate 42c (155.00 mg, 0.317 mmol) in sodium ethanolate (20% in EtOH) (30 mL) was stirred at 40 °C for 1.5 h. The mixture was neutralized (pH: 7) with HCl 1N and extracted with EtOAc. The organic layer was dried over MgSO₄, concentrated under vacuum and purified by silica gel chromatography (irregular SiOH 15-40 μm, 40 g, liquid injection with DCM, mobile phase gradient: from DCM/MeOH (+ 10% aq. NH₃) 100/0 to 90/10 in 10 CV). The pure fractions were combined and the solvent was evaporated. The residue (45 mg) was purified again by reverse phase (Stationary phase: X-Bridge-C18, 5 μm, 30 x 150 mm, mobile phase: gradient from 60% NH₄HCO₃ (0.2% in H₂O), 40% MeOH to 20% NH₄HCO₃ (0.2% in H₂O), 80% MeOH). The product containing fractions were combined and evaporated to dryness to give 26 mg of compound 9c (18%, light yellow solid).

15 **Analytical Part****LCMS** (Liquid chromatography/Mass spectrometry)

The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.

Compounds are described by their experimental retention times (R_t) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the $[M+H]^+$ (protonated molecule) and/or $[M-H]^-$ (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. $[M+NH_4]^+$, $[M+HCOO]^-$, etc...). For molecules with multiple isotopic patterns (Br, Cl.), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

Hereinafter, "SQD" means Single Quadrupole Detector, "RT" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, "HSS" High Strength Silica, "DAD" Diode Array
10 Detector.

Table: LCMS Method codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes).

Method code	Instrument	Column	Mobile phase	gradient	Flow (mL/min)	Run time
					T (° C)	
Method 1	Waters: Acquity UPLC® -DAD and Quattro Micro™	Waters: BEH C18 (1.7 µm, 2.1 x 100 mm)	A: 95% CH ₃ COONH ₄ 7mM / 5% CH ₃ CN, B: CH ₃ CN	84.2% A for 0.49 min, to 10.5% A in 2.18 min, held for 1.94 min, back to 84.2% A in 0.73 min, held for 0.73 min.	0.343	6.2
					40	
Method 2	Waters: Acquity UPLC® H-Class – DAD and SQD 2	Waters: BEH C18 (1.7 µm, 2.1 x 100 mm)	A: 95% CH ₃ COONH ₄ 7mM / 5% CH ₃ CN, B: CH ₃ CN	From 84.2% A to 10.5% A in 2.18 min, held for 1.94 min, back to 84.2% A in 0.73 min, held for 0.73 min.	0.343	6.1
					40	
Method 3	Agilent 1200 equip with MSD 6110	Agilent TC-C18 (5 µm, 2.1 x 50 mm)	A: H ₂ O (0.1% TFA), B: CH ₃ CN (0.05% TFA)	90% A held for 0.80 min, then from 90% A to 20% A in 3.7 min, held for 3.00 min, back to 90% A in 2.00 min.	0.8	10
					50	
Method 4	Agilent 1200, MSD 6110	Agilent TC-C18 (5 µm, 2.1 x 50 mm)	A: water (+ 0.1% TFA), B: CH ₃ CN (+ 0.1% TFA)	From 100% A for 1 min, to 40% A in 4 min, to 15% A in 2.5 min, back to 100% A in 2 min, held for 0.5 min.	0.8	10
					50	
Method 5	Agilent: 1100-DAD and MSD	YMC: Pack ODS-AQ (3µm, 4.6x50mm)	A: HCOOH 0.1% in water, B: CH ₃ CN	95% A to 5% A in 4.8min, held for 1min, back to 95% A in 0.2min.	2.6	6
					35	

Method code	Instrument	Column	Mobile phase	gradient	Flow (mL/min)	Run time
					T (° C)	
Method 6	Agilent 1290 Infinity DAD TOF-LC/MS G6224A	YMC-pack ODS-AQ C18 (50 x 4.6 mm, 3 µm)	A: 0.1% HCOOH in H ₂ O B: ACN	From 95% A to 5% A in 4.8 min, held for 1.0 min, to 95% A in 0.2 min.	2.6	6.0
					35	
Method 7	Agilent 1200 equip with MSD 6110	Phenomenex Luna-C18, 50×2mm, 5µm	A : H ₂ O (0.1 %TFA, B: ACN (0.0 5% TFA)	100% A held for 1 mn then 100% A to 40% A in 4 mn then 40% A to 15 % A in 2.5 mn then back to 100% A in 2 mn held for 0.5 min.	0.8	10
					50	
Method 8	Agilent 1260 series equip with an Agilent G2120B ESI-SQD set in positive mode	ACE C18 (50 x 3 mm, 3 µm)	A: 0.05% TFA in H ₂ O B: ACN	From 95% A to 0% A in 1.3 min	2.2 — 50	1.3
Method 9	Waters: Acquity UPLC® - PDA and SQD	Waters: BEH C18 (1.7 µm, 2.1 x 100 mm)	A: H ₂ O+ 0.1% HCOOH / B: CH ₃ CN + 0.1% HCOOH	From 95% A for 0.40 min, to 5% A in 5.2 min, held for 0.80 min.	0.40 — 40	6.4
Method 10	Agilent 1200 equip with MSD 6110	XBridge Shield RP18(5 µm, 2.1 x 50 mm)	A: H ₂ O (0.05% NH ₃ .H ₂ O), B: CH ₃ CN	100% A held for 1.00 min, then from 100% A to 40% A in 4.00 min, then from 40% A to 5% A in 2.50 min, back to 100% A in 2.00 min.	0.8 — 50	10

Melting point (DSC, MP50, or K)

For a number of compounds, melting points (MP) were determined with a DSC1 (Mettler-Toledo) (indicated with DSC in the analytical table). Melting points were measured with a temperature gradient of 10 °C/minute. Maximum temperature was 350 °C. Values are peak values.

For a number of compounds, melting points were obtained with a Kofler (K) hot bench, consisting of a heated plate with linear temperature gradient, a sliding pointer and a temperature scale in degrees Celsius (indicated with K in the analytical table).

For a number of compounds, melting points were obtained with a Mettler Toledo MP50 apparatus (indicated with MP50 in the analytical table). Melting points were measured with a temperature gradient of 10°C per minute starting from 50°C (waiting time 10 seconds) to a maximum value of 300°C.

Table: N°. means compound number; MP means melting point (°C); R_t means retention time (min)

N°	MP (°C)	MP Method	R _t	[M + H] ⁺	LC/MS Method
1	221	K	2.73	414	Method 1
2	230	K	2.42	383	Method 1
3	171	DSC	2.10	441	Method 1
4	235	DSC	3.30	448	Method 2
5	152	K	1.97	444	Method 2
6	-	-	2.19	397	Method 2
7	245	K	2.45	450	Method 2
8	168	K	1.96	444	Method 2
9	221	DSC	2.52	489	Method 1
10	196	DSC	2.67	433	Method 1
11	205	DSC	2.81	519	Method 1
12	153	DSC	2.80	519	Method 1
13	225	DSC	2.44	518	Method 1
14	265	DSC	2.43	504	Method 1
15	-	-	2.13	498	Method 1
16	-	-	2.43	532	Method 1

N°	MP (°C)	MP Method	Rt	[M + H] ⁺	LC/MS Method
17	224	DSC	2.98	491	Method 1
18	224	DSC	2.97	491	Method 1
19	278	DSC	2.56	532	Method 1
20	-	-	2.29	513	Method 1
21	-	-	2.64	483	Method 1
22	-	-	2.64	479	Method 1
23	-	-	2.21	455	Method 1
24	296	DSC	2.29	471	Method 1
25	136	DSC	2.81	445	Method 1
26	-	-	2.69	509	Method 1
27	-	-	2.86	511	Method 1
28	202	DSC	2.20	429	Method 1
29	-	-	2.07	428	Method 1
30	232	DSC	2.19	427	Method 1
31	-	-	2.24	427	Method 1
32	139	DSC	2.52	458	Method 1
33	122	DSC	2.37	487	Method 1
34	219	DSC	3.22	485	Method 1
35	-	-	3.00	498	Method 1
36	-	-	3.98	459	Method 4
37	-	-	2.54	417	Method 3
38	-	-	2.53	502	Method 3
39	-	-	4.06	471	Method 4
40	-	-	3.63	514	Method 4
41	-	-	4.73	434	Method 4
42	-	-	3.51	427	Method 4
43	-	-	2.87	454	Method 3
44	-	-	2.04	472	Method 1
45	253	DSC	2.19	415	Method 1
46	199	MP50	2.99	473	Method 6
47	170	MP50	3.21	499	Method 6
48	-	-	2.31	445	Method 1
49	138	Kofler	3.63	512	Method 1

N°	MP (°C)	MP Method	Rt	[M + H] ⁺	LC/MS Method
	(gum)				
50	199	K	2.96	486	Method 1
51	176 (gum)	K	2.33	454	Method 2
52	>260	K	3.02	484	Method 2
53	159 (gum)	K	2.35	457	Method 1
54	-	-	0.68	447	Method 8
55	-	-	4.91	466	Method 7
56	156	MP50	2.72	492	Method 5
57	238	MP50	2.34	478	Method 5
58	166	MP50	4.13	499	Method 5
59	-	-	4.00	457	Method 4
60	-	-	2.16	499	Method 2
1b	> 250	K	2.01	418	Method 2
2b	gum at 244	K	2.02	418	Method 2
3b	315	DSC	2.27	431	Method 1
4b	-	-	402	2.27	Method 1
5b	>260	K	2.23	402	Method 2
6b	-	-	3.86	418	Method 4
7b	-	-	3.70	404	Method 4
8b	>260	K	2.02	431	Method 1
9b	162	K	2.08	417	Method 1
10b	212	K	2.36	432	Method 1
11b	-	-	2.42	446	Method 1
12b	201	DSC	2.04	404	Method 1
13b	>260	K	2.09	431	Method 1
14b	>250	K	2.03	404	Method 1
15b	258	K	2.00	417	Method 1
16b	235	K	2.33	459	Method 1
17b	212	K	2.42	459	Method 2
18b	247	K	2.21	445	Method 1
19b	233	DSC	1.92	434	Method 2

N°	MP (°C)	MP Method	Rt	[M + H] ⁺	LC/MS Method
20b	246	K	2.14	432	Method 2
21b	279	DSC	2.11	432	Method 2
22b	>260	K	2.28	446	Method 2
23b	>260	K	2.28	446	Method 2
24b	209	DSC	2.24	432	Method 1
25b	>260	DSC	2.09	432	Method 2
26b	174 (gum)	K	2.67	507	Method 2
27b	164 (gum)	K	2.60	473	Method 2
28b	173	DSC	2.40	473	Method 2
29b	266	DSC	2.36	432	Method 1
30b	258	DSC	2.36	432	Method 1
31b	179	DSC	1.95	448	Method 1
32b	-	-	3.94	402	Method 4
1c	-	-	4.54	500	Method 9
2c	-	-	5.07	487	Method 9
3c	>250	K	2.24	502	Method 2
4c	216	DSC	2.73	544	Method 2
5c	220	DSC	2.88	558	Method 1
6c	182	DSC	3.06	503	Method 1
7c	-	-	4.95	413	Method 9
8c	-	-	4.69	399	Method 9
9c	217	DSC	2.67	445	Method 1
10c	260	DSC	2.58	513	Method 1
11c	217	DSC	2.51	516	Method 1
12c	-	-	5.15		Method 10
13c	-	-	2.74	427	Method 3
14c	209	DSC	2.85	486	Method 1

NMR

The NMR experiments were carried out using a Bruker Avance 500 III using internal deuterium lock and equipped with reverse triple-resonance (¹H, ¹³C, ¹⁵N TXI) probe head or using a Bruker Avance DRX 400 spectrometer at ambient temperature, using internal

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deuterium lock and equipped with reverse double-resonance (^1H , ^{13}C , SEI) probe head with z gradients and operating at 400 MHz for the proton and 100MHz for carbon. Chemical shifts (δ) are reported in parts per million (ppm). J values are expressed in Hz.

5 Compound 21:

^1H NMR (400 MHz, DMSO- d_6): δ 8.79 (s, 1 H) 8.31 (d, $J=5.1\text{Hz}$, 1 H) 8.02 (s, 1 H) 7.88 (s, 1 H) 7.61 (s, 1 H) 7.35 (s, 1 H) 7.25 (d, $J=5.6\text{ Hz}$, 1 H) 4.94 - 5.00 (m, 1 H) 4.69 (s, 2 H) 3.97 (br t, $J=5.6\text{ Hz}$, 2 H) 3.67 (br d, $J=9.6\text{ Hz}$, 1 H) 3.39 - 3.46 (m, 1 H) 3.32 - 3.38 (m, 1 H) 3.23 - 3.28 (m, 1 H, partially obscured by solvent peak) 2.79 - 2.89 (m, 4 H) 1.46 - 1.56 (m, 2 H) 1.26 (s, 3 H) 0.60 - 0.76 (m, 1 H) 0.27 - 0.35 (m, 2 H) -0.09 - 0.00 (m, 2 H).

10 Compound 25:

^1H NMR (400 MHz, DMSO- d_6): δ 8.42 (d, $J=5.6\text{ Hz}$, 1 H) 8.26 (s, 1 H) 8.08 - 8.12 (m, 1 H) 8.07 (s, 1 H) 7.95 - 7.98 (m, 1 H) 7.41 (s, 1 H) 7.37 (d, $J=5.6\text{ Hz}$, 1 H) 5.00 (t, $J=5.3\text{ Hz}$, 1 H) 4.68 (s, 2 H) 3.94 - 3.98 (m, 2 H) 3.93 (s, 3 H) 3.68 (d, $J=9.6\text{ Hz}$, 1 H) 3.42 - 3.49 (m, 1 H) 3.36 - 3.42 (m, 1 H) 3.28 - 3.30 (m, 1 H, partially obscured by solvent peak) 2.76 (br t, $J=5.6\text{ Hz}$, 2 H) 1.29 (s, 3 H).

15 Compound 32:

^1H NMR (400 MHz, DMSO- d_6): δ 8.41 (d, $J=5.1\text{ Hz}$, 1 H) 8.26 (s, 1 H) 8.08 - 8.13 (m, 1 H) 8.05 (s, 1 H) 7.92 - 8.00 (m, 1 H) 7.42 (s, 1 H) 7.36 (d, $J=5.6\text{ Hz}$, 1 H) 5.00 (t, $J=5.6\text{ Hz}$, 1 H) 3.91 (s, 3 H) 3.69 (d, $J=9.6\text{ Hz}$, 1 H) 3.49 (s, 2 H) 3.42 - 3.47 (m, 1 H) 3.36 - 3.41 (m, 1 H) 3.27 - 3.30 (m, 1 H, partially obscured by solvent peak) 2.74 - 2.81 (m, 2 H) 2.65 - 2.70 (m, 2 H) 2.36 (s, 3 H) 1.30 (s, 3 H).

20 Compound 34:

^1H NMR (400 MHz, DMSO- d_6): δ 8.43 (d, $J=5.1\text{ Hz}$, 1 H) 8.29 (s, 1 H) 8.04 - 8.12 (m, 1 H) 7.90 - 8.00 (m, 2 H) 7.42 (s, 1 H) 7.39 (d, $J=5.6\text{ Hz}$, 1 H) 5.01 (t, $J=5.3\text{ Hz}$, 1 H) 4.68 (s, 2 H) 4.18 (d, $J=7.1\text{ Hz}$, 2 H) 3.95 (t, $J=5.6\text{ Hz}$, 2 H) 3.68 (d, $J=9.6\text{ Hz}$, 1 H) 3.42 - 3.49 (m, 1 H) 3.36 - 3.42 (m, 1 H) 3.31 - 3.34 (m, 1 H, partially obscured by solvent peak) 2.73 (br t, $J=5.1\text{ Hz}$, 2 H) 1.25 - 1.35 (m, 4 H) 0.50 - 0.59 (m, 2 H) 0.29 - 0.44 (m, 2 H).

25 Compound 35:

^1H NMR (500 MHz, DMSO- d_6): δ 8.43 (d, $J=5.4\text{ Hz}$, 1 H) 8.29 (s, 1 H) 8.07 - 8.13 (m, 1 H) 7.96 (d, $J=8.2\text{ Hz}$, 2 H) 7.45 (s, 1 H) 7.38 (d, $J=5.4\text{ Hz}$, 1 H) 5.02 (t, $J=5.4\text{ Hz}$, 1 H) 4.15 (d, $J=7.3\text{ Hz}$, 2 H) 3.69 (d, $J=9.8\text{ Hz}$, 1 H) 3.51 (br s, 2 H) 3.43 - 3.48 (m, 1 H) 3.37 - 3.41 (m, 1 H) 3.29 - 3.32 (m, 1 H, partially obscured by solvent peak) 2.73 - 2.78 (m, 2 H) 2.65 - 2.72 (m, 2 H) 2.37 (s, 3 H) 1.25 - 1.35 (m, 4 H) 0.51 - 0.59 (m, 2 H) 0.35 (q, $J=4.8\text{ Hz}$, 2 H).

35

Compound 56:

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.44 (br d, *J*=5.4 Hz, 1H) 8.26 (s, 1H) 8.14 (s, 1H) 8.07 (br d, *J*=3.8 Hz, 2H) 7.51 (s, 1H) 7.39 (br d, *J*=5.1 Hz, 1H) 5.90 - 6.43 (m, 1H) 3.91 (s, 3H) 3.69 (br d, *J*=10.2 Hz, 1H) 3.48 (br s, 2H) 3.41 (br d, *J*=10.7 Hz, 1H) 2.65 - 2.86 (m, 4H) 2.18 - 2.43 (m, 5H) 1.37 (s, 3H).

Compound 1b:

¹H NMR (500 MHz, DMSO-*d*₆): δ 8.14 - 8.30 (m, 2 H) 8.04 (br s, 1 H) 7.89 (br s, 1 H) 7.27 - 7.36 (m, 2 H) 7.13 (d, *J*=5.0 Hz, 1 H) 5.00 (t, *J*=5.4 Hz, 1 H) 4.33 - 4.46 (m, 1 H) 4.00 - 4.19 (m, 2 H) 3.66 (d, *J*=9.8 Hz, 1 H) 3.39 - 3.46 (m, 1 H) 3.34 - 3.37 (m, 1 H, partially obscured by solvent peak) 3.28 (d, *J*=10.1 Hz, 1 H) 2.16 - 2.28 (m, 1 H) 1.91 - 2.05 (m, 1 H) 1.35 (d, *J*=6.3 Hz, 3 H) 1.26 (s, 3 H).

Compound 2b:

¹H NMR (500 MHz, DMSO-*d*₆): δ 8.17 - 8.31 (m, 2 H) 8.04 (br s, 1 H) 7.89 (br s, 1 H) 7.27 - 7.38 (m, 2 H) 7.13 (d, *J*=5.4 Hz, 1 H) 5.01 (t, *J*=5.4 Hz, 1 H) 4.34 - 4.45 (m, 1 H) 4.02 - 4.15 (m, 2 H) 3.67 (d, *J*=9.8 Hz, 1 H) 3.39 - 3.46 (m, 1 H) 3.35 - 3.39 (m, 1 H, partially obscured by solvent peak) 3.28 (br d, *J*=9.8 Hz, 1 H) 2.16 - 2.27 (m, 1 H) 1.92 - 2.07 (m, 1 H) 1.36 (d, *J*=6.3 Hz, 3 H) 1.27 (s, 3 H).

Compound 3b:

¹H NMR (500 MHz, DMSO-*d*₆): δ 8.61 (s, 1 H) 8.47 (d, *J*=5.4 Hz, 1 H) 8.24 (s, 1 H) 8.10 (s, 1 H) 8.00 (s, 1 H) 7.46 (s, 1 H) 7.39 (d, *J*=5.4 Hz, 1 H) 5.04 (br s, 1 H) 4.36 (t, *J*=6.0 Hz, 2 H) 3.81 (t, *J*=6.0 Hz, 2 H) 3.69 (d, *J*=9.8 Hz, 1 H) 3.44 - 3.51 (m, 1 H) 3.37 - 3.43 (m, 1 H) 3.29 - 3.33 (m, 1 H, partially obscured by solvent peak) 3.04 (s, 3 H) 1.31 (s, 3 H).

Compound 17b:

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.65 (s, 1H), 8.46 (d, *J*=5.4 Hz, 1H), 8.23 (s, 1H), 8.10 (s, 1H), 7.99 (s, 1H), 7.46 (s, 1H), 7.38 (d, *J*=5.4 Hz, 1H), 5.03 (t, *J*=5.2 Hz, 1H), 4.77 (spt, *J*=6.7 Hz, 1H), 4.33 (t, *J*=6.0 Hz, 2H), 3.65 - 3.76 (m, 3H), 3.43 - 3.51 (m, 1H), 3.36 - 3.43 (m, 1H), 3.31 (d, *J*=9.8 Hz, 1H), 1.30 (s, 3H), 1.18 (d, *J*=6.6 Hz, 6H).

Compound 3c: ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.44 (s, 1 H) 8.50 (d, *J*=5.0 Hz, 1 H) 8.15 - 8.21 (m, 2 H) 7.98 - 8.07 (m, 2 H) 7.39 - 7.46 (m, 2 H) 7.26 (d, *J*=3.2 Hz, 1 H) 7.14 (s, 1 H) 7.00 (d, *J*=3.2 Hz, 1 H) 5.00 (t, *J*=5.4 Hz, 1 H) 4.79 (s, 2 H) 3.73 (d, *J*=9.8 Hz, 1 H) 3.44 - 3.52 (m, 1 H) 3.37 - 3.43 (m, 1 H) 3.31 (d, *J*=9.8 Hz, 1 H) 2.63 (d, *J*=4.7 Hz, 3 H) 1.31 (s, 3 H).

Compound 8c:

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.13 (br s, 1 H) 9.38 (s, 1 H) 8.50 (d, *J*=5.6 Hz, 1 H) 8.16 (s, 1 H) 8.10 (s, 1 H) 7.97 (br d, *J*=12.1 Hz, 1 H) 7.37 - 7.52 (m, 2 H) 7.23 (br s, 1 H) 6.96 (br s, 1 H) 6.83 (br d, *J*=8.6 Hz, 1 H) 3.44 (s, 2 H) 1.31 (s, 6 H).

5 **OR**

Optical Rotation is measured with a polarimeter such as e.g. 341 Perkin Elmer, an Autopol IV automatic polarimeter (Rodolph research analytical) or a P-2000 (Jasco).

Specific rotation (OR): $[\alpha]_{\lambda}^{\theta} = (100 * \alpha) / (c * l)$

10 α (measured rotation) is the angle through which plane polarized light is rotated by a solution of mass concentration *c* and path length *l*. Concentration is in grams per 100 mL; path length *l* is in decimeters and is 1.000 decimeter.

θ is the temperature (°C) and λ the wavelength of the light used.

Unless otherwise indicated, temperature is 20 °C, and the sodium D line is used (589 nanometer).

15

OR data: Solvent : DMF (unless otherwise indicated); temperature : 20 °C (unless otherwise indicated); wavelength : 589 nm (unless otherwise indicated); Concentration of the sample in grams per 100 mL; 'OR' means optical rotation (specific rotation); 'N°' means compound number

N°	OR (°)	Concentration (g / 100 mL)
11	+ 58.08	0.260
12	- 11.38	0.290
13	+ 19.80	0.227
16	+ 19.04	0.236
17	+ 63.93	0.280
18	- 5.00	0.260
19	+ 18.93	0.280
20	+ 6.15	0.260
21	+ 9.95	0.342
22	- 19.03	0.242
23	+ 11.28	0.293
24	+ 9.62	0.312
25	+ 11.78	0.221
26	+ 12.44	0.225
27	+ 9.78	0.225
28	+ 9.92	0.222
29	+ 10.87	0.230
30	+ 15.71	0.280
31	+ 17.04	0.270

N°	OR (°)	Concentration (g / 100 mL)
32	+ 18.71	0.278
33	+ 12.37	0.291
34	+ 10.73	0.261
35	+ 22.40	0.250
44	+17.69	0.39
46	+18.6	0.10 (MeOH; 23°C)
47	+13.3	0.06 (MeOH; 23°C)
48	+8.52	0.27
49	+37.83	0.23
50	+23.33	0.24
51	+11.2	0.25
52	+33.85	0.26
53	+13.62	0.257
58	-2.3	0.18 (DMSO; 23°C)

N°	OR (°)	Concentration (g / 100 mL)
3b	+ 23.73	0.295
11b	+ 16.46	0.243
12b	+ 14.55	0.275
13b	+ 16.80	0.250
14b	+ 9.55	0.220

N°	OR (°)	Concentration (g / 100 mL)
15b	+ 6.80	0.250
16b	+ 6.40	0.250
17b	+ 16.97	0.330
18b	+ 9.60	0.250
19b	- 18.75	0.240

N°	OR (°)	Concentration (g / 100 mL)
22b	- 34.34	0.335
24b	+ 10.83	0.240
25b	+ 15.00	0.200
26b	+ 17.41	0.270

N°	OR (°)	Concentration (g / 100 mL)
27b	+ 18.57	0.210
28b	+ 22.31	0.260
10c	+ 14.55	0.220
14c	+16.3	0.227

Pharmacological Part

Biological assay A

Inhibition of auto-phosphorylation of recombinant human NF-kappaB-inducing kinase (NIK/MAP3K14) activity (AlphaScreen®)

- 5 NIK/MAP3K14 auto-phosphorylation activity was measured using the AlphaScreen® (αscreen) format (Perkin Elmer). All compounds tested were dissolved in dimethyl sulfoxide (DMSO) and further dilutions were made in assay buffer. Final DMSO concentration was 1% (v/v) in assays. Assay buffer was 50 mM Tris pH 7.5 containing 1 mM EGTA (ethylene glycol tetraacetic acid), 1 mM DTT (dithiothreitol), 0.1 mM
- 10 Na₃VO₄, 5 mM MgCl₂, 0.01% Tween® 20. Assays were carried out in 384 well Alphaplates (Perkin Elmer). Incubations consisted of compound, 25 microM Adenosine-5'-triphosphate (ATP), and 0.2 nM NIK/MAP3K14. Incubations were initiated by addition of GST-tagged NIK/MAP3K14 enzyme, carried out for 1h at 25 °C and terminated by addition of stop buffer containing anti-phospho-IKK Ser176/180
- 15 antibody. Protein A Acceptor and Glutathione-Donor beads were added before reading using an EnVision® Multilabel Plate Reader (Perkin Elmer). Signal obtained in the wells containing blank samples was subtracted from all other wells and IC₅₀'s were determined by fitting a sigmoidal curve to % inhibition of control versus Log₁₀ compound concentration.

20 Biological assay B

Effect of compounds on P-IKKα levels in L363 (NIK translocated multiple myeloma) cells

- All compounds tested were dissolved in DMSO and further dilutions were made in culture medium. Final DMSO concentration was 1% (v/v) in cell assays. The human
- 25 L363 cells (ATCC) were cultured in RPMI 1640 medium supplemented with GlutaMax and 10% fetal calf serum (PAA). Cells were routinely maintained at densities of 0.2x10⁶ cells per ml – 1x10⁶ cells per ml at 37°C in a humidified 5% CO₂ atmosphere. Cells were passaged twice a week splitting back to obtain the low density. Cells were seeded in 96 well plates (Nunc 167008) at 2x10⁶ per ml media in a volume of 75 µl per

well plus 25 μ l 1 μ g/ml recombinant human B-cell activating factor (BAFF/BLyS/TNFSF13B). Seeded cells were incubated at 37°C in a humidified 5% CO₂ atmosphere for 24 hr. Drugs and/or solvents were added (20 μ l) to a final volume of 120 μ l. Following 2 hr treatment plates were removed from the incubator and cell

5 lysis was achieved by the addition of 30 μ l 5x lysis buffer followed by shaking on a plate shaker at 4°C for 10 min. At the end of this incubation lysed cells were centrifuged at 800 x g for 20 min at 4°C and the lysate was assessed for P-IKK α levels by sandwich immuno-assay carried out in anti-rabbit antibody coated Mesoscale plates. Within an experiment, the results for each treatment were the mean of 2 replicate wells.

10 For initial screening purposes, compounds were tested using an 8 point dilution curve (serial 1:3 dilutions). For each experiment, controls (containing MG132 and BAFF but no test drug) and a blank incubation (containing MG132 and BAFF and 10 μ M ADS125117, a test concentration known to give full inhibition) were run in parallel. The blank incubation value was subtracted from all control and sample values. To

15 determine the IC₅₀ a sigmoidal curve was fitted to the plot of % inhibition of control P-IKK α levels versus Log₁₀ compound concentration.

Biological assay C

Determination of antiproliferative activity on JJN-3 (NIK translocated) and KMS12-BM (NIK WT) multiple myeloma cells

20 All compounds tested were dissolved in DMSO and further dilutions were made in culture medium. Final DMSO concentration was 0.3% (v/v) in cell proliferation assays. Viability was assessed using CellTiter-Glo cell viability assay kit (Promega). The human JJN-3 and KMS12-BM cells (DSMZ) were cultured in RPMI 1640 medium supplemented with 2 mM L-glutamine, and 10% fetal calf serum (PAA). Cells were

25 routinely kept as suspension cells at 37°C in a humidified 5% CO₂ atmosphere. Cells were passaged at a seeding density of 0.2x10⁶ /ml twice a week. Cells were seeded in black tissue culture treated 96-well plates (Perkin Elmer). Densities used for plating ranged from 15000 (JJN3) to 20000 (KMS12BM) cells per well in a total volume of 135 μ l medium. Drugs and/or solvents were added (15 μ l) to a final volume of 150 μ l.

30 Following 96 hr of treatment, plates were removed from the incubator and allowed to equilibrate to room temperature for approx 10 min. 75 μ l CellTiter-Glo reagent was added to each well that was then covered (Perkin Elmer Topseal) and shaken on plate shaker for 10 min. Luminescence was measured on a HTS Topcount (Perkin Elmer). Within an experiment, the results for each treatment were the mean of 2 replicate wells.

35 For initial screening purposes, compounds were tested using a 9 point dilution curve (serial 1:3 dilutions). For each experiment, controls (containing no drug) and a blank incubation (containing cells read at the time of compound addition) were run in

parallel. The blank value was subtracted from all control and sample values. For each sample, the mean value for cell growth (in relative light units) was expressed as a percentage of the mean value for cell growth of the control.

- Data for the compounds of the invention in the above assays are provided in Table A
 5 (the values in Table are averaged values over all measurements on all batches of a compound). ('n.c.' means not calculated)

Table A:

Compound	Auto-phosphorylation inhibition of NIK (IC50 (nM))	Inhibition of pIKK α _L-363 (IC50 (nM))	KMS-12 Proliferation inhibition (IC50 (nM))	JJN-3 Proliferation inhibition (IC50 (nM))
45	2.7	n.c.	~186	~60
1	5.9	n.c.	550	96
2	4.3	n.c.	~177	112
3	1.4	n.c.	85	~24
4	26.9	n.c.	>10000	107
5	1.9	n.c.	151	21
6	12.6	n.c.	794	263
7	5.9	n.c.	525	48
8	2.0	n.c.	162	41
39	2.5	3	n.c.	n.c.
36	3.7	16	n.c.	n.c.
41	11.8	3	>10000	138
9	2.0	n.c.	~2754	25
10	4.9	n.c.	~5754	42
11	9.1	n.c.	1175	36
12	14.1	n.c.	~6606	22
37	4.3	9	n.c.	n.c.
13	1.3	n.c.	~3548	18
14	3.0	n.c.	251	54
40	4.3	3	n.c.	n.c.
42	8.9	36	n.c.	n.c.
15	2.5	n.c.	96	89
43	6.6	5	n.c.	n.c.
16	1.6	n.c.	~339	26
17	3.3	n.c.	182	5
18	4.1	16	9	1
19	5.0	n.c.	~692	6
38	3.4	12	n.c.	n.c.
59	12.9	37	n.c.	n.c.
20	20.4	n.c.	1479	372

Compound	Auto-phosphorylation inhibition of NIK (IC50 (nM))	Inhibition of pIKK α _L-363 (IC50 (nM))	KMS-12 Proliferation inhibition (IC50 (nM))	JJN-3 Proliferation inhibition (IC50 (nM))
21	3.0	21	3890	81
22	2238.7	>10000	n.c.	n.c.
23	4.8	~79	~550	162
24	3.0	~74	~288	~214
25	1.7	10	>10000	174
26	5.1	501	~525	692
27	7.1	~1202	1380	871
28	1.1	14	>10000	851
29	3.4	16	51	~27
30	0.8	2	10	4
44	4.5	35	>10000	>10000
31	1.4	2	~31	4
32	1.7	10	525	195
33	8.1	17	>10000	776
34	10.5	23	>10000	1738
48	1.6	31	>10000	~2344
35	4.3	69	n.c.	n.c.
50	3.4	56	3981	240
46	13.0	20	>10000	778
51	3.4	4	~174	52
53	1.8	1	~468	12
47	35.5	51	n.c.	n.c.
49	34.7	115	n.c.	n.c.
54	4.2	2	~9	~7
52	7.8	20	>10000	200
58	35.5	204	>10000	2399
56	12.0	76	~5754	3236
57	17.4	n.c.	>10000	11220
55	3.8	11	>10000	107
60	4.8	17	603	100
1b	2.8	2	~2818	58
2b	2.0	4	>10000	93
3b	1.0	3	>10000	91
4b	8.5	n.c.	~6456	1905
5b	20.4	n.c.	>10000	468
6b	5.9	n.c.	~851	398
7b	11.8	n.c.	6310	1698
8b	4.0	n.c.	6166	1148
9b	6.8	n.c.	1660	204
10b	9.6	n.c.	2399	1023
11b	39.8	n.c.	~1820	1585
12b	1.5	4	~549	251
13b	2.0	29	~1862	457

Compound	Auto-phosphorylation inhibition of NIK (IC50 (nM))	Inhibition of pIKK α _L-363 (IC50 (nM))	KMS-12 Proliferation inhibition (IC50 (nM))	JJN-3 Proliferation inhibition (IC50 (nM))
14b	2.0	6	3981	155
15b	3.5	11	~4467	200
16b	363.1	n.c.	n.c.	n.c.
17b	3.0	3	>10000	309
18b	6.2	7	~5495	288
19b	11.7	19	~5495	316
20b	6.2	2	n.c.	n.c.
21b	5.9	5	2512	269
22b	7.1	3	>10000	166
23b	6.9	2	~2239	45
24b	4.9	28	~5888	676
25b	8.1	7	>10000	3020
26b	9.5	25	~9550	1698
27b	4.47	13	>10000	1585
28b	17.0	251	>10000	3388
29b	3.9	6	>10000	85
30b	5.2	13	>10000	263
31b	5.0	63	~7762	~2138
32b	5.9	8	n.c.	n.c.
1c	30.2	23	1380	26
2c	87.1	78	~6026	123
3c	4.3	4	204	12
4c	9.6	n.c.	~1023	9
5c	12.0	n.c.	~692	23
6c	34.8	n.c.	1622	10
7c	148.0	72	>10000	537
8c	38.0	n.c.	>10000	85
9c	10.5	n.c.	5623	1175
10c	4.3	n.c.	>10000	63
11c	4.3	n.c.	427	16
12c	10.5	14	n.c.	n.c.
13c	6.2	3	n.c.	n.c.
14c	5.6	n.c.	>10000	63

Prophetic composition examples

- “Active ingredient” (a.i.) as used throughout these examples relates to a compound of Formula (I), including any tautomer or stereoisomeric form thereof, or a 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
5	Lactose	30 mg
	Talcum	10 mg
	Magnesium stearate	5 mg
	Potato starch	ad 200 mg

2. Suspension

- 10 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

- 15 A parenteral composition is prepared by stirring 1.5 % (weight/volume) of active ingredient in 0.9 % NaCl solution or in 10 % by volume propylene glycol in water.

4. Ointment

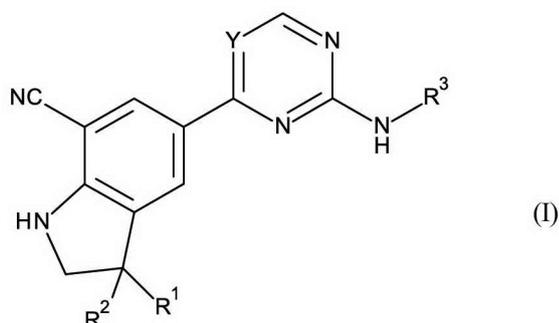
	Active ingredient	5 to 1000 mg
	Stearyl alcohol	3 g
	Lanoline	5 g
20	White petroleum	15 g
	Water	ad 100 g

In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

25

CLAIMS

1. A compound of Formula (I):



5 a tautomer or a stereoisomeric form thereof, wherein

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

R^2 represents C_{1-6} alkyl, C_{1-6} alkyl substituted with one R^5 , or C_{1-6} alkyl substituted with one, two or three fluoro atoms;

Y represents CR^4 or N;

10 R^4 represents hydrogen or halo;

R^5 represents Het^{3a}, $-NR^{6a}R^{6b}$, or $-OR^7$;

R^{6a} represents hydrogen or C_{1-4} alkyl;

R^{6b} represents hydrogen; C_{1-4} alkyl; C_{3-6} cycloalkyl; $-C(=O)-C_{1-4}$ alkyl; $-C(=O)-Het^4$;

15 $-S(=O)_2-C_{1-4}$ alkyl; $-C(=O)-C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of $-OH$ and $-NR^{16a}R^{16b}$; or C_{1-4} alkyl substituted with one substituent selected from the group consisting of $-OH$ and $-S(=O)_2-C_{1-4}$ alkyl;

R^7 represents hydrogen, C_{1-4} alkyl, $-C_{1-4}$ alkyl- $NR^{8a}R^{8b}$, $-C(=O)-R^9$, $-S(=O)_2-OH$,

$-P(=O)_2-OH$, $-C(=O)-CH(NH_2)-C_{1-4}$ alkyl- Ar^1 , or $-C_{1-4}$ alkyl- Het^{3b} ;

R^{8a} represents hydrogen or C_{1-4} alkyl;

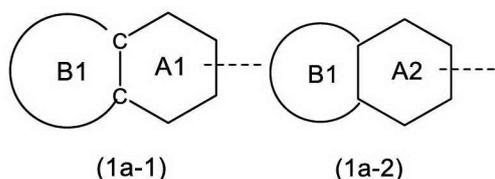
20 R^{8b} represents hydrogen, C_{1-4} alkyl, or C_{3-6} cycloalkyl;

R^9 represents C_{1-6} alkyl, or C_{1-6} alkyl substituted with one substituent selected from the group consisting of $-NH_2$, $-COOH$, and Het^6 ;

R^{16a} and R^{16b} each independently represents hydrogen, C_{1-4} alkyl or C_{3-6} cycloalkyl;

R^3 represents

25 a) a fused bicyclic ring system of formula (1a-1) or (1a-2):



ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms;

ring A2 represents 2-oxo-1,2-dihydropyridin-3-yl;

ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

5 wherein (1a-1) and (1a-2) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; oxo; -OH; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -S(=O)(=N-R^{20a})-C₁₋₄alkyl; -O-C₁₋₄alkyl substituted with one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³;

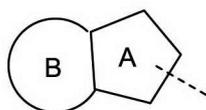
15 wherein ring A2 may optionally be substituted, where possible, on the N-atom with a substituent selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when

20 Het^{1a} or R¹⁸ are directly attached to the N-atom of ring A2, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom; and

wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when Het^{1a} or R¹⁸ are directly attached to the N-atom of ring B1, said Het^{1a} or R¹⁸ are attached to the N-atom via a

30 ring carbon atom; or

b) a fused bicyclic ring system of formula (2a-1):



(2a-1)

ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, and C₁₋₄alkyl substituted with one, two or three halo atoms;

ring B represents a C₅₋₇cycloalkyl or a 5- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N;

wherein said C₅₋₇cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring carbon atoms with one or two substituents each independently selected from the group consisting of C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl and -C₁₋₄alkyl-OH, or one ring carbon atom may optionally be substituted with oxo;

and

wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl

substituted with one R¹³; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h};

-C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; or

c) a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N;

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may

optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano;

C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -S(=O)(=N-R^{20a})-C₁₋₄alkyl;

-O-C₁₋₄alkyl substituted with one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²;

C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄alkyl)₂;

-NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one,

two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents;

C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and

C₂₋₆alkenyl substituted with one R¹³; and

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may

optionally be substituted, where possible, on one ring N-atom with a substituent

selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or

three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with

one R¹⁸; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j};

-C(=O)-C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³;

provided that when Het^{1a} or R¹⁸ are directly attached to a N-atom, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom;

R¹⁰ represents -OH, -O-C₁₋₄alkyl, -NR^{11a}R^{11b} or Het²;

R¹⁸ represents a 5-membered aromatic ring containing one, two or three N-atoms;

5 wherein said 5-membered aromatic ring may optionally be substituted with one substituent selected from the group consisting of C₁₋₄alkyl and C₃₋₆cycloalkyl;

Het^{1a}, Het^{1c} and Het^{1d} each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N; or a 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, containing one, two or three heteroatoms each independently selected from O, S, S(=O)_p and N;

10 wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted, where possible, on one, two or three ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and

15 wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, oxo, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

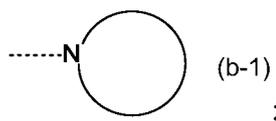
20 Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, said Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

25 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and

30 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each

independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

Het² represents a heterocyclyl of formula (b-1):



- 5 (b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N, or a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, optionally containing one or two additional heteroatoms each independently selected from O, S, S(=O)_p and N;
- 10 wherein in case (b-1) contains one or two additional N-atoms, said one or two N-atoms may optionally be substituted with C₁₋₄alkyl; and wherein (b-1) may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of halo, -OH, cyano, C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, and C₁₋₄alkyl-OH;

- 15 R^{11b} represents hydrogen; Het^{1e}; C₁₋₄alkyl; C₁₋₄alkyl-Het⁵; C₁₋₄alkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₃₋₆cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

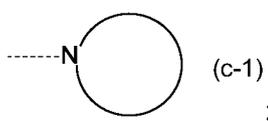
- 20 R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, -S(=O)₂-C₁₋₄alkyl, -S(=O)(=N-R^{20c})-C₁₋₄alkyl, or -C(=O)-Het^{1f};

R¹² represents -OH, -O-C₁₋₄alkyl, -NR^{14a}R^{14b}, -C(=O)NR^{14c}R^{14d}, -S(=O)₂-C₁₋₄alkyl, -S(=O)(=N-R^{20b})-C₁₋₄alkyl, C₃₋₆cycloalkyl, Ar², or Het^{1c};

Ar¹ represents phenyl optionally substituted with one hydroxy;

- 25 Ar² represents phenyl optionally substituted with one C₁₋₄alkyl;

Het^{3a}, Het^{3b}, Het⁵, Het⁶ and Het^{1f} each independently represents a heterocyclyl of formula (c-1):



- (c-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O, S, S(=O)_p and N;
- 30 wherein in case (c-1) contains one additional N-atom, said additional N-atom may

optionally be substituted with C₁₋₄alkyl or C₃₋₆cycloalkyl; and wherein (c-1) may optionally be substituted on one or two ring C-atoms with one or two substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, and C₃₋₆cycloalkyl;

5 R^{11a}, R^{14a}, R^{14c}, R^{14g}, R¹⁴ⁱ, R^{14k}, R^{15a}, R^{17a} and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;

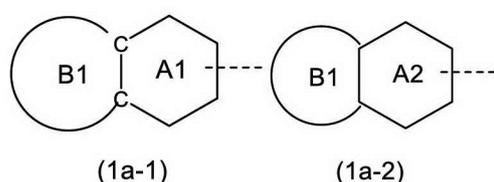
R^{14b}, R^{14d}, R^{14h}, R^{14j}, R^{14l}, R^{15b}, R^{17b} and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl;

10 R^{20a}, R^{20b} and R^{20c} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl;

p represents 1 or 2;

15 and the pharmaceutically acceptable addition salts, and the solvates thereof.

2. The compound according to claim 1, wherein R³ represents a fused bicyclic ring system of formula (1a-1) or (1a-2):



20 ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms;

ring A2 represents 2-oxo-1,2-dihydropyridin-3-yl;

ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

25 wherein (1a-1) and (1a-2) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; oxo; -OH; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -S(=O)(=N-R^{20a})-C₁₋₄alkyl; -O-C₁₋₄alkyl substituted with one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³;

wherein ring A2 may optionally be substituted, where possible, on the N-atom with a substituent selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when Het^{1a} or R¹⁸ are directly attached to the N-atom of ring A2, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom; and

wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when Het^{1a} or R¹⁸ are directly attached to the N-atom of ring B1, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom.

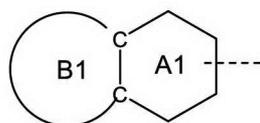
3. The compound according to claim 1 or 2, wherein

R⁵ represents -OR⁷;

R⁷ represents hydrogen, C₁₋₄alkyl, -C₁₋₄alkyl-NR^{8a}R^{8b}, -C(=O)-R⁹, -(C=O)-CH(NH₂)- or C₁₋₄alkyl-Ar¹;

R⁹ represents C₁₋₆alkyl, or C₁₋₆alkyl substituted with one substituent selected from the group consisting of -NH₂, and -COOH;

R³ represents a fused bicyclic ring system of formula (1a-1):



(1a-1)

ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms;

ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

wherein (1a-1) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; oxo; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -O-C₁₋₄alkyl substituted with one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋

C_6 cycloalkyl; $-\text{NH}-\text{C}(=\text{O})-\text{C}_{1-4}$ alkyl; $-\text{NR}^{17a}\text{R}^{17b}$; C_{1-4} alkyl substituted with one, two or three halo atoms; C_{1-4} alkyl substituted with one, two or three $-\text{OH}$ substituents; C_{1-4} alkyl substituted with one R^{13} ; C_{2-6} alkenyl; and C_{2-6} alkenyl substituted with one R^{13} ; and

- 5 wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C_{1-6} alkyl; C_{3-6} cycloalkyl; C_{1-4} alkyl substituted with one, two or three halo atoms; C_{1-4} alkyl substituted with one, two or three $-\text{OH}$ substituents; C_{1-4} alkyl substituted with one R^{13} ; $-\text{C}(=\text{O})-\text{C}_{1-4}$ alkyl; $-\text{C}(=\text{O})\text{NR}^{14g}\text{R}^{14h}$; $-\text{C}(=\text{O})-\text{C}_{1-4}$ alkyl- $\text{NR}^{14i}\text{R}^{14j}$; $-\text{C}(=\text{O})-\text{C}(=\text{O})-\text{NR}^{14k}\text{R}^{14l}$; C_{2-6} alkenyl; and C_{2-6} alkenyl substituted with one R^{13} ;

R^{10} represents $-\text{OH}$, $-\text{O}-\text{C}_{1-4}$ alkyl, or $-\text{NR}^{11a}\text{R}^{11b}$;

- R^{11b} represents hydrogen; C_{1-4} alkyl; C_{1-4} alkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, $-\text{OH}$ and $-\text{O}-\text{C}_{1-4}$ alkyl; C_{3-6} cycloalkyl; or C_{3-6} cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, $-\text{OH}$ and $-\text{O}-\text{C}_{1-4}$ alkyl;

R^{13} represents $-\text{O}-\text{C}_{1-4}$ alkyl, $-\text{C}(=\text{O})\text{NR}^{15a}\text{R}^{15b}$, $-\text{NR}^{19a}\text{R}^{19b}$, C_{3-6} cycloalkyl, or $-\text{S}(=\text{O})_2-\text{C}_{1-4}$ alkyl;

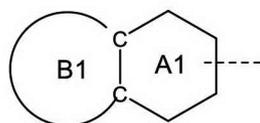
- R^{12} represents $-\text{OH}$, $-\text{O}-\text{C}_{1-4}$ alkyl, $-\text{NR}^{14a}\text{R}^{14b}$, $-\text{C}(=\text{O})\text{NR}^{14c}\text{R}^{14d}$, $-\text{S}(=\text{O})_2-\text{C}_{1-4}$ alkyl, C_{3-6} cycloalkyl, or Ar^2 .

4. The compound according to claim 1 or 2, wherein

R^5 represents $-\text{OR}^7$;

R^7 represents hydrogen;

- 25 R^3 represents a fused bicyclic ring system of formula (1a-1):



(1a-1)

ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 or 2 N-atoms;

- 30 ring B1 represents a 4- to 7-membered saturated heterocycle containing one or two heteroatoms each independently selected from O and N;

wherein (1a-1) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo;

C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -O-C₁₋₄alkyl-R¹²; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; and

5 wherein ring B1 may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₁₋₄alkyl substituted with one R¹³; -(C=O)-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; and -C(=O)-C(=O)-NR^{14k}R^{14l};

R¹⁰ represents -NR^{11a}R^{11b};

R^{11b} represents C₁₋₄alkyl;

10 R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or C₃₋₆cycloalkyl;

R¹² represents C₃₋₆cycloalkyl;

R^{11a}, R¹⁴ⁱ, R^{14k}, R^{15a}, and R^{17a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14j}, R^{14l}, R^{15b}, and R^{17b} each independently represents hydrogen or C₁₋₄alkyl.

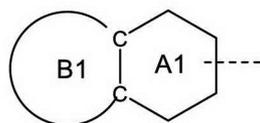
15 5. The compound according to claim 1 or 2, wherein

R² represents C₁₋₆alkyl substituted with one R⁵;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents a fused bicyclic ring system of formula (1a-1):



20 (1a-1)

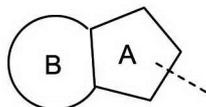
ring A1 represents phenyl or a 6-membered heteroaromatic ring containing 1 N-atom; ring B1 represents a 4- to 7-membered saturated heterocyclyl containing one heteroatom selected from O and N;

25 wherein (1a-1) may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of -O-C₁₋₄alkyl; -O-C₁₋₄alkyl-R¹²; and C₁₋₄alkyl substituted with one R¹³; and wherein ring B may optionally be substituted, where possible, on one N-atom with a C₁₋₆alkyl substituent;

R¹³ represents C₃₋₆cycloalkyl;

30 R¹² represents C₃₋₆cycloalkyl.

6. The compound according to claim 1, wherein R³ represents a fused bicyclic ring system of formula (2a-1):



(2a-1)

5 ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, and C₁₋₄alkyl substituted with one, two or three halo atoms;

ring B represents a C₅₋₇cycloalkyl or a 5- to 7-membered saturated heterocyclyl containing one or two heteroatoms each independently selected from O and N; wherein said C₅₋₇cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally
10 be substituted on one or two ring carbon atoms with one or two substituents each independently selected from the group consisting of C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl and -C₁₋₄alkyl-OH, or one ring carbon atom may optionally be substituted with oxo; and

wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on
15 one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}.

20 7. The compound according to claim 6, wherein

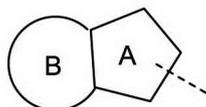
R¹ represents C₁₋₄alkyl;

R² represents C₁₋₆alkyl substituted with one R⁵;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

25 R³ represents a fused bicyclic ring system of formula (2a-1):



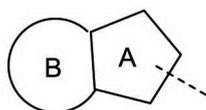
(2a-1)

ring A represents pyrazolyl optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyl, and -C₁₋₄alkyl-O-C₁₋₄alkyl;

ring B represents a C₅₋₇cycloalkyl or a 5- to 7-membered saturated heterocyclyl
30 containing one or two heteroatoms each independently selected from O and N;

wherein said C₅₋₇cycloalkyl or 5- to 7-membered saturated heterocyclyl may optionally be substituted on one ring carbon atom with one or two C₁₋₄alkyl substituents, or one ring carbon atom may optionally be substituted with oxo; and
 5 wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one or two ring N-atoms with a C₁₋₆alkyl substituent.

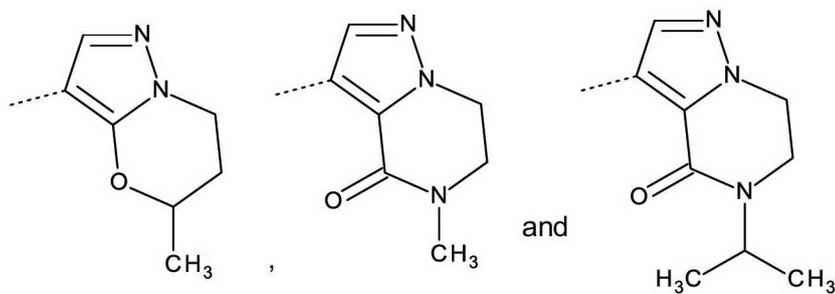
8. The compound according to claim 6, wherein
 R¹ represents C₁₋₄alkyl;
 R² represents C₁₋₆alkyl substituted with one R⁵;
 10 R⁵ represents -OR⁷;
 R⁷ represents hydrogen;
 R³ represents a fused bicyclic ring system of formula (2a-1):



(2a-1)

- ring A represents pyrazolyl;
 15 ring B represents a 6-membered saturated heterocyclyl containing one heteroatom selected from O and N;
 wherein said 6-membered saturated heterocyclyl may optionally be substituted on one ring carbon atom with one C₁₋₄alkyl substituent, or one ring carbon atom may optionally be substituted with oxo; and
 20 wherein said 5- to 7-membered saturated heterocyclyl may optionally be substituted on one N-atom with a C₁₋₆alkyl substituent.

9. The compound according to claim 8, wherein
 R³ represents a fused bicyclic ring system selected from the following structures:



- 25 10. The compound according to claim 1, wherein R³ represents a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each

independently selected from O, S, and N;

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -S(=O)(=N-R^{20a})-C₁₋₄alkyl; -O-C₁₋₄alkyl substituted with one, two or three halo atoms; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; and

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; Het^{1a}; R¹⁸; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; -(C=O)-C₁₋₄alkyl; -C(=O)NR^{14g}R^{14h}; -C(=O)-C₁₋₄alkyl-NR¹⁴ⁱR^{14j}; -C(=O)-C(=O)-NR^{14k}R^{14l}; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; provided that when Het^{1a} or R¹⁸ are directly attached to a N-atom, said Het^{1a} or R¹⁸ are attached to the N-atom via a ring carbon atom.

11. The compound according to claim 10, wherein

R⁵ represents -NR^{6a}R^{6b}, or -OR⁷;

R^{6b} represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or -C(=O)-C₁₋₄alkyl;

R⁷ represents hydrogen, C₁₋₄alkyl, or -C₁₋₄alkyl-NR^{8a}R^{8b};

R³ represents a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N; wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three substituents each independently selected from the group consisting of halo; cyano; C₁₋₆alkyl; -O-C₁₋₄alkyl; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³; and

wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₆alkyl; C₃₋₆cycloalkyl; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH

substituents; C₁₋₄alkyl substituted with one R¹³; C₁₋₄alkyl substituted with one R¹⁸; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³;

Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

5 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; and

10 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, or Het^{1d}.

15

12. The compound according to claim 10, wherein

R¹ represents C₁₋₄alkyl;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

20 R³ represents a fused 6- to 11-membered bicyclic heteroaromatic ring system containing one or two heteroatoms each independently selected from O, S, and N; wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three halo substituents; and

25 wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³;

30 Het^{1d} represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, or Het^{1d};

R^{15a} represents hydrogen or C₁₋₄alkyl;

R^{15b} represents C₁₋₄alkyl.

13. The compound according to claim 10, wherein
R¹ represents C₁₋₄alkyl;
R⁵ represents -OR⁷;
R⁷ represents hydrogen;
- 5 R³ represents a fused 9-membered bicyclic heteroaromatic ring system containing one N-atom;
wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted on the ring carbon atoms with in total one, two or three halo substituents; and
- 10 wherein said fused 6- to 11-membered bicyclic heteroaromatic ring system may optionally be substituted, where possible, on one ring N-atom with a substituent selected from the group consisting of C₁₋₄alkyl substituted with one, two or three -OH substituents; C₁₋₄alkyl substituted with one R¹³;
- R¹³ represents -O-C₁₋₄alkyl, or -C(=O)NR^{15a}R^{15b};
- 15 R^{15a} represents hydrogen or C₁₋₄alkyl;
R^{15b} represents C₁₋₄alkyl.
14. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 13 and a pharmaceutically acceptable carrier or diluent.
- 20
15. A compound as claimed in any one of claims 1 to 13 for use as a medicament.
16. A compound as claimed in any one of claims 1 to 13, or a pharmaceutical composition as claimed in claim 14, for use in the prevention or treatment of cancer.
- 25
17. A method of treating or preventing cancer wherein the cancer is modulated by the NIK pathway and wherein the method comprises administering an effective amount of a compound as claimed in any one of claims 1 to 13 or a pharmaceutical composition as claimed in claim 14.
- 30
18. Use of a compound as claimed in any one of claims 1 to 13, or a pharmaceutical composition as claimed in claim 14, in the manufacture of a medicament for treating or preventing cancer wherein the cancer is modulated by the NIK pathway.

19. A method of treating or preventing a cell proliferative disease modulated by the NIK pathway in a warm-blooded animal which comprises administering to the said animal an effective amount of a compound as claimed in any one of claims 1 to 13, or a pharmaceutical composition as claimed in claim 14.

5

20. Use of a compound as claimed in any one of claims 1 to 13, or a pharmaceutical composition as claimed in claim 14, in the manufacture of a medicament for treating or preventing a cell proliferative disease modulated by the NIK pathway in a warm-blooded animal.

10