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[54] NEW SUBSTITUTED CYANOINDOLINE DERIVATIVES AS NIK INHIBITORS
作為 NIK 抑制劑的新穎的經取代的氰基吲哚啉衍生物

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(54) **NEW SUBSTITUTED CYANOINDOLINE DERIVATIVES AS NIK INHIBITORS**

NEUE N-PHENYLPYRIMIDIN-2-AMINSUBSTITUIERTE CYANOINDOLINDERIVATE ALS NIK-INHIBITOREN

NOUVEAUX DÉRIVÉS DE CYANOINDOLINE N-PHENYLPYRIMIDIN-2-AMINE SUBSTITUÉS EN TANT QU'INHIBITEURS DE NIK

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Description**FIELD OF THE INVENTION**

[0001] 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

[0002] 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. 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 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 hematological malignancies and solid tumours.

[0003] 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 (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. 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 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 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 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).

[0004] 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 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). 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).

[0005] Recently, similar mutations in the non-canonical NF κ B signaling pathway (TRAF2, TRAF3, NIK, BIRC3) were found in ibutinib-refractory mantle cell lymphoma cell lines (Rahal et al., Nat Med 2014, 1, 87-92).

[0006] 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-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 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.

[0007] 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.

[0008] 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).

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 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).

[0009] 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 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 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 *in vitro* model of oxidative stress induced cell death (as a model of COPD) to interrogate a human druggable 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).

[0010] 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). 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).

[0011] 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.

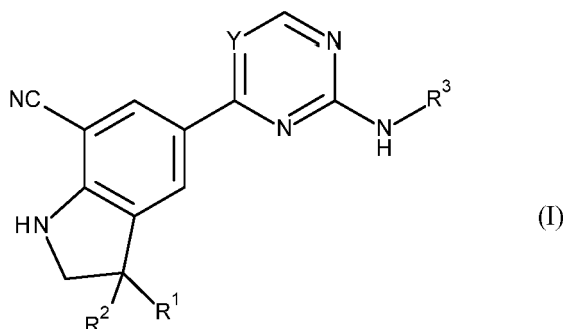
[0012] It has also been hypothesized that manipulating levels of NIK in T cells may have therapeutic value. Decreasing NIK activity in T cells might significantly ameliorate autoimmune responses and alloresponses, like GVHD (Graft Versus Host Disease) and transplant rejection, without crippling the immune system as severely as do inhibitors of canonical NF- κ B activation.

[0013] WO2010042337 and WO2009158011 disclose NIK inhibitors.

[0014] 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.

DESCRIPTION OF THE INVENTION

[0015] 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, or C_{1-6} alkyl substituted with one R^5 ;

Y represents CR^4 or N;

R^4 represents hydrogen or halo;

R^5 represents halo, 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} ;

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;

R^3 represents phenyl optionally substituted with 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; $-O-$

C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; R²¹; -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; C₂₋₆alkenyl substituted with one R¹³; C₂₋₆alkynyl; and C₂₋₆alkynyl substituted with one R¹³;

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;

R²¹ represents 3,6-dihydro-2H-pyran-4-yl or 1,2,3,6-tetrahydro-4-pyridinyl, wherein 1,2,3,6-tetrahydro-4-pyridinyl may optionally be substituted on the N-atom with C₁₋₄alkyl or 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

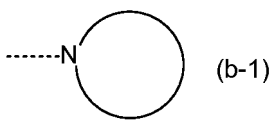
wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano,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

Het^{1b}, Het^{1e}, Het^{1g}, Het⁴, Het⁷ and Het⁸ 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}, Het⁴, Het⁷ and Het⁸ 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 a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl and Het⁷; 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-Het⁹; 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;

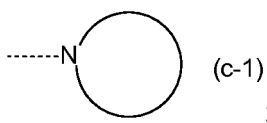
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, or -C(=O)-Het^{1f};

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;

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



10 (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

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

R^{14b}, R^{14d}, R^{15b}, R^{17b} and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; -C(=O)-C₁₋₄alkyl; C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl;

20 R^{20a} and R^{20b} 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;

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

[0016] The present invention also 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.

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

35 **[0017]** 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.

[0018] 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.

40 **[0019]** 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. 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.

45 **[0020]** 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. Additionally, it is disclosed 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.

55 **[0021]** Some of the compounds of the present invention may undergo metabolism to a more active form in vivo (prodrugs).

DETAILED DESCRIPTION OF THE INVENTION

[0022] The term 'halo' or 'halogen' as used herein represents fluoro, chloro, bromo and iodo. 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

[0023] 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.

[0024] 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.

[0025] 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.

[0026] The term "C₂₋₆alkynyl" as used herein as a group or part of a group represents a straight or branched chain hydrocarbon group having from 2 to 6 carbon atoms and containing a carbon carbon triple bond.

[0027] 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.

[0028] 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 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

[0029] 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.

[0030] 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).

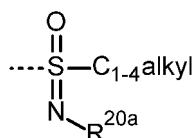
[0031] When two or more substituents are present on a moiety they may, where possible and unless otherwise is indicated or is clear from the context, replace hydrogens on the same atom or they may replace hydrogen atoms on different atoms in the moiety.

[0032] 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.

[0033] C(O) or C(=O) represents a carbonyl moiety.

[0034] S(=O)₂ or SO₂ represents a sulfonyl moiety.

[0035] The skilled person will understand that -S(=O)(=N-R^{20a})-C₁₋₄alkyl corresponds with



[0036] Within the context of this invention 'saturated' means 'fully saturated', if not otherwise specified.

[0037] 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.

[0038] 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.

[0039] 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).

[0040] 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).

[0041] 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).

[0042] 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).

[0043] 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.

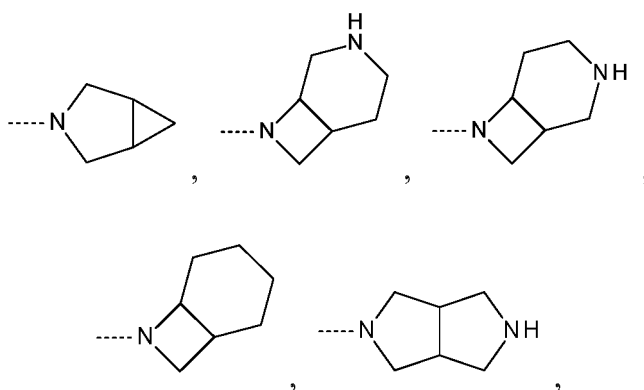
[0044] Within the context of this invention, bicyclic saturated heterocyclyl groups include fused, spiro and bridged saturated heterocycles.

[0045] Fused bicyclic groups are two cycles that share two atoms and the bond between these atoms.

[0046] Spiro bicyclic groups are two cycles that are joined at a single atom.

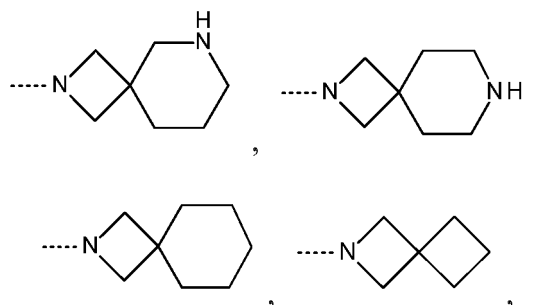
[0047] Bridged bicyclic groups are two cycles that share more than two atoms.

[0048] Examples of N-linked 6- to 11-membered fused bicyclic saturated heterocyclyl groups, include, but are not limited to



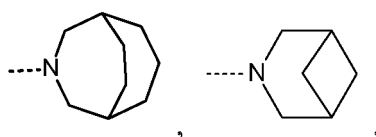
and the like.

[0049] Examples of N-linked 6- to 11-membered spiro bicyclic saturated heterocyclyl groups, include, but are not limited to



and the like.

[0050] Examples of N-linked 6- to 11-membered bridged bicyclic saturated heterocyclyl groups, include, but are not limited to

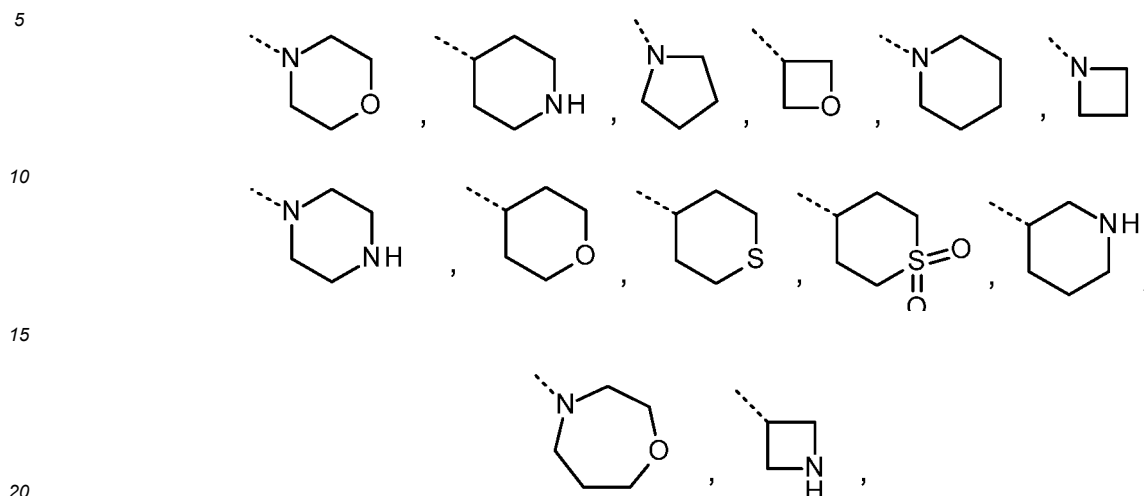


and the like.

[0051] 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).

[0052] 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.

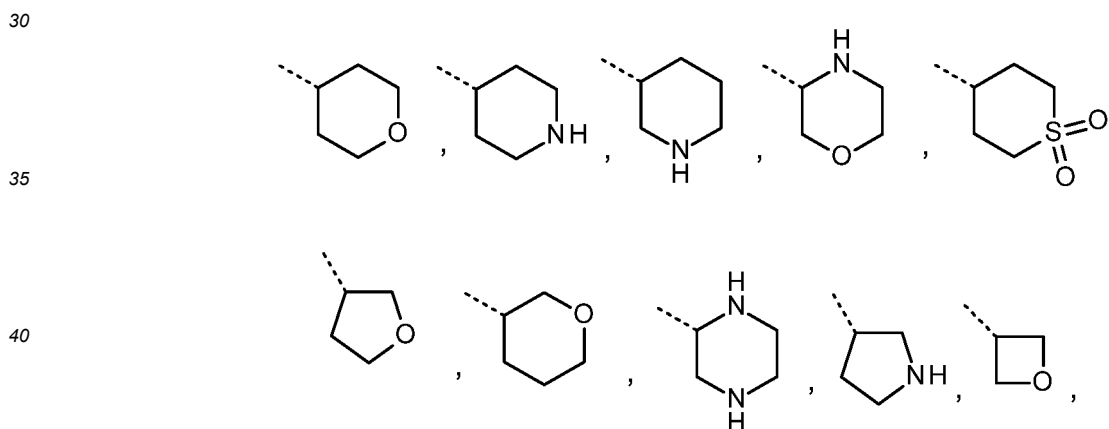
[0053] Non-limiting examples of 4- to 7-membered monocyclic saturated heterocyclyl moieties containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N (as in the definition of Het^{1a}, Het^{1c}, and Het^{1d}) are shown below:



and the like.

[0054] Each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

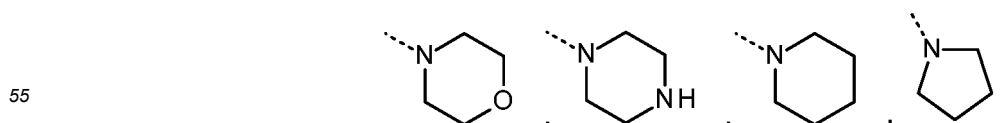
[0055] Non-limiting examples of 4- to 7-membered monocyclic saturated heterocyclyl moieties, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom (C-linked), and containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N (as in the definition of Het^{1b}, Het^{1e}, Het^{1g}, Het⁴, Het⁷ and Het⁸) are shown below:

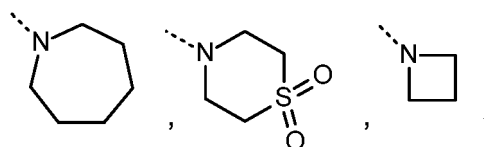


and the like.

[0056] Each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

[0057] 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:

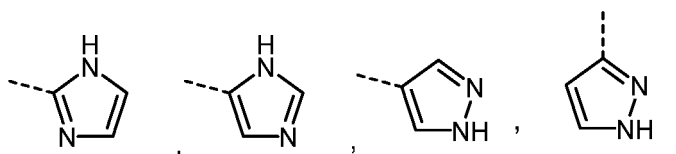




and the like.

[0058] Each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

[0059] 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:



and the like.

[0060] Each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

[0061] Whenever substituents are represented by chemical structure, "----" represents the bond of attachment to the remainder of the molecule of Formula (I).

[0062] Lines (such as "----") drawn into ring systems indicate that the bond may be attached to any of the suitable ring atoms.

[0063] When any variable occurs more than one time in any constituent, each definition is independent.

[0064] When any variable occurs more than one time in any formula (e.g. Formula (I)), each definition is independent.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] As used herein, any chemical formula with bonds shown only as solid lines and not as solid wedged or hashed wedged bonds, or otherwise indicated as having a particular configuration (e.g. *R*, *S*) around one or more atoms, contemplates each possible stereoisomer, or mixture of two or more stereoisomers.

[0071] Hereinbefore and hereinafter, the term "compound(s) of Formula (I)" is meant to include the tautomers thereof and the stereoisomeric forms thereof.

[0072] The terms "stereoisomers", "stereoisomeric forms" or "stereochemically isomeric forms" hereinbefore or hereinafter are used interchangeably.

[0073] 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.

[0074] 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.

[0075] Atropisomers (or atropoisomers) are stereoisomers which have a particular spatial configuration, resulting from a restricted rotation about a single bond, due to large steric hindrance. All atropisomeric forms of the compounds of Formula (I) are intended to be included within the scope of the present invention.

[0076] Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, i.e. they are not related as

mirror images. If a compound contains a double bond, the substituents may be in the *E* or the *Z* configuration.

[0077] 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.

[0078] Therefore, the invention includes enantiomers, atropisomers, diastereomers, racemates, *E* isomers, *Z* isomers, *cis* isomers, *trans* isomers and mixtures thereof, whenever chemically possible.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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.

[0090] 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).

[0091] 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.

[0092] 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. 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.

[0093] 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 $\text{C}_{1-6}\text{alkyl}$, or $\text{C}_{1-6}\text{alkyl}$ substituted with one R^5 ;

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

R^{6b} represents hydrogen; $\text{C}_{1-4}\text{alkyl}$; $\text{C}_{3-6}\text{cycloalkyl}$; $-\text{C}(=\text{O})-\text{C}_{1-4}\text{alkyl}$; $-\text{C}(=\text{O})-\text{Het}^4$; $-\text{S}(=\text{O})_2-\text{C}_{1-4}\text{alkyl}$; $-\text{C}(=\text{O})-\text{C}_{1-4}\text{alkyl}$ substituted with one substituent selected from the group consisting of $-\text{OH}$ and $-\text{NR}^{16a}\text{R}^{16b}$; or $\text{C}_{1-4}\text{alkyl}$ substituted with one substituent selected from the group consisting of $-\text{OH}$ and $-\text{S}(=\text{O})_2-\text{C}_{1-4}\text{alkyl}$;

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

R^{8a} represents hydrogen or $\text{C}_{1-4}\text{alkyl}$;

R^{8b} represents hydrogen, $\text{C}_{1-4}\text{alkyl}$, or $\text{C}_{3-6}\text{cycloalkyl}$;

R^9 represents $\text{C}_{1-6}\text{alkyl}$, or $\text{C}_{1-6}\text{alkyl}$ 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, $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{3-6}\text{cycloalkyl}$;

R^3 represents phenyl optionally substituted with one, two or three substituents each independently selected from the group consisting of halo; cyano; $\text{C}_{1-6}\text{alkyl}$; $-\text{O}-\text{C}_{1-4}\text{alkyl}$; $-\text{C}(=\text{O})-\text{R}^{10}$; $-\text{S}(=\text{O})_2-\text{C}_{1-4}\text{alkyl}$; $-\text{S}(=\text{O})(=\text{N}-\text{R}^{20a})-\text{C}_{1-4}\text{alkyl}$; $-\text{O}-\text{C}_{1-4}\text{alkyl}$ substituted with one, two or three halo atoms; $-\text{O}-\text{C}_{1-4}\text{alkyl}-\text{R}^{12}$; $\text{C}_{3-6}\text{cycloalkyl}$; $-\text{O}-\text{C}_{3-6}\text{cycloalkyl}$; Het^{1a} ; $-\text{O}-\text{Het}^{1b}$; R^{18} ; R^{21} ; $-\text{P}(=\text{O})-(\text{C}_{1-4}\text{alkyl})_2$; $-\text{NH}-\text{C}(=\text{O})-\text{C}_{1-4}\text{alkyl}$; $-\text{NH}-\text{C}(=\text{O})-\text{Het}^{19}$; $-\text{NR}^{17a}\text{R}^{17b}$; $\text{C}_{1-4}\text{alkyl}$ substituted with one, two or three halo atoms; $\text{C}_{1-4}\text{alkyl}$ substituted with one, two or three $-\text{OH}$ substituents; $\text{C}_{1-4}\text{alkyl}$ substituted with one R^{13} ; $\text{C}_{1-4}\text{alkyl}$ substituted with one R^{18} ; $\text{C}_{2-6}\text{alkenyl}$; and $\text{C}_{2-6}\text{alkenyl}$ substituted with one R^{13} ;

R^{10} represents $-\text{OH}$, $-\text{O}-\text{C}_{1-4}\text{alkyl}$, $-\text{NR}^{11a}\text{R}^{11b}$ or Het^2 ;

R^{18} 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 $\text{C}_{1-4}\text{alkyl}$ and $\text{C}_{3-6}\text{cycloalkyl}$;

R^{21} represents 3,6-dihydro-2H-pyran-4-yl or 1,2,3,6-tetrahydro-4-pyridinyl, wherein 1,2,3,6-tetrahydro-4-pyridinyl may optionally be substituted on the N-atom with $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{3-6}\text{cycloalkyl}$;

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, $\text{S}(=\text{O})_p$ 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, $\text{S}(=\text{O})_p$ 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 $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{3-6}\text{cycloalkyl}$, and $\text{C}_{1-4}\text{alkyl}$ substituted with one substituent selected from the group consisting of $-\text{OH}$ and $-\text{O}-\text{C}_{1-4}\text{alkyl}$; 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

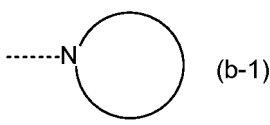
independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl, -O-C₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)₂;

Het^{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}; 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;

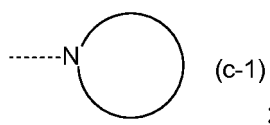
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, or -C(=O)-Het^{1f},

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;

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^{15a}, R^{17a} and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14b}, R^{14d}, 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} and R^{20b} 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.

[0094] 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 or N;

R⁴ represents hydrogen or halo;

R⁵ represents halo, 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;

-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;

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

R⁹ represents C₁₋₄alkyl, or C₁₋₄alkyl 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 phenyl optionally substituted with 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; R²¹; -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; C₂₋₆alkenyl substituted with one R¹³; C₂₋₆alkynyl; and C₂₋₆alkynyl substituted with one R¹³;

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;

R²¹ represents 3,6-dihydro-2H-pyran-4-yl or 1,2,3,6-tetrahydro-4-pyridinyl, wherein 1,2,3,6-tetrahydro-4-pyridinyl may optionally be substituted on the N-atom with C₁₋₄alkyl or 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;

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;

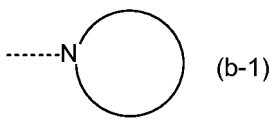
Het^{1b}, Het^{1e}, Het^{1g}, Het⁷ and Het⁸ each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, said Het^{1b}, Het^{1e}, Het^{1g}, Het⁷ and Het⁸ containing one or two heteroatoms 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 a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl and Het⁷; 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-Het⁸; 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;

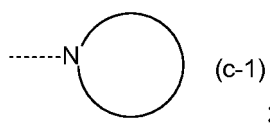
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, or -C(=O)-Het^{1f},

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^{21b})-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 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^{15a}, R^{17a} and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14b}, R^{14d}, R^{15b}, R^{17b} and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; -C(=O)-C₁₋₄alkyl; C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl;

R^{20a} and R^{20b} 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.

[0095] 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 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;

-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;

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

R⁹ represents C₁₋₄alkyl, or C₁₋₄alkyl 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 phenyl optionally substituted with 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; R²¹; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het¹⁹; -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;

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;

R²¹ represents 3,6-dihydro-2H-pyran-4-yl or 1,2,3,6-tetrahydro-4-pyridinyl, wherein 1,2,3,6-tetrahydro-4-pyridinyl may optionally be substituted on the N-atom with C₁₋₄alkyl or 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;

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;

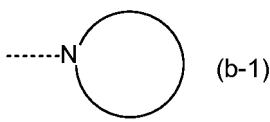
Het^{1b}, Het^{1e}, and Het^{1g} each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, said Het^{1b}, Het^{1e}, and Het^{1g} containing one or two heteroatoms each independently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

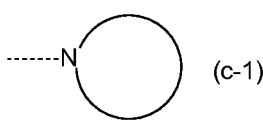
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, or -C(=O)-Het^{1f},

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^{21b})-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 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^{15a}, R^{17a} and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14b}, R^{14d}, 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} and R^{20b} 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.

[0096] 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 or N;

R⁴ represents hydrogen or halo;

R⁵ represents halo, 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 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;

R⁹ represents C₁₋₄alkyl, or C₁₋₄alkyl 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 phenyl optionally substituted with 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; R²¹; -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; C₂₋₆alkenyl substituted with one R¹³; C₂₋₆alkynyl; and C₂₋₆alkynyl substituted with one R¹³;

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;

R²¹ represents 3,6-dihydro-2H-pyran-4-yl or 1,2,3,6-tetrahydro-4-pyridinyl, wherein 1,2,3,6-tetrahydro-4-pyridinyl may optionally be substituted on the N-atom with C₁₋₄alkyl or 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

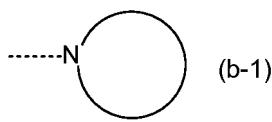
wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one substituent each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl,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

Het^{1b}, Het^{1e}, Het^{1g}, Het⁴, Het⁷ and Het⁸ 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}, Het⁴, Het⁷ and Het⁸ 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 substituent 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 a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl and Het⁷; and

wherein (b-1) may optionally be substituted on one, two or three ring C-atoms with one substituent 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-Het⁸; 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;

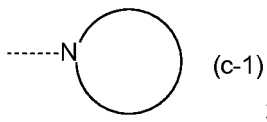
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, or -C(=O)-Het^{1f};

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^{21b})-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 with one substituent each independently selected from the group consisting of halo, C₁₋₄alkyl, and C₃₋₆cycloalkyl;

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

R^{14b}, R^{14d}, R^{15b}, R^{17b} and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; -C(=O)-C₁₋₄alkyl; C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl;

R^{20a} and R^{20b} 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.

[0097] 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 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 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;

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

R⁹ represents C₁₋₄alkyl, or C₁₋₄alkyl 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 phenyl optionally substituted with 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; R²¹; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het¹⁹; -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;

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;

R²¹ represents 3,6-dihydro-2H-pyran-4-yl or 1,2,3,6-tetrahydro-4-pyridinyl, wherein 1,2,3,6-tetrahydro-4-pyridinyl may optionally be substituted on the N-atom with C₁₋₄alkyl or 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

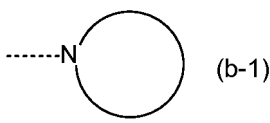
wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said 6- to 11-membered bicyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one substituent each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, cyano, -C(=O)-C₁₋₄alkyl,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

Het^{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 substituent 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 substituent 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;

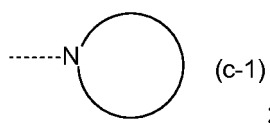
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, or -C(=O)-Het^{1f},

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;

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 with one substituent each independently selected from the group consisting of halo, C₁₋₄alkyl, and C₃₋₆cycloalkyl;

R^{11a}, R^{14a}, R^{14c}, R^{15a}, R^{17a} and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;
 R^{14b}, R^{14d}, 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} and R^{20b} 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.

[0098] 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 or N;
 R⁴ represents hydrogen or halo;
 R⁵ represents halo, -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; -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, or -(C=O)-CH(NH₂)-C₁₋₄alkyl-Ar¹;
 R^{8a} represents hydrogen or C₁₋₄alkyl;
 R^{8b} represents hydrogen, C₁₋₄alkyl, or C₃₋₆cycloalkyl;
 R⁹ represents C₁₋₄alkyl, or C₁₋₄alkyl substituted with one substituent selected from the group consisting of -NH₂ and -COOH;
 R^{16a} and R^{16b} each independently represents hydrogen, C₁₋₄alkyl or C₃₋₆cycloalkyl;
 R³ represents phenyl optionally substituted with 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; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -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; C₂₋₆alkenyl; C₂₋₆alkenyl substituted with one R¹³; C₂₋₆alkynyl; and C₂₋₆alkynyl substituted with one R¹³;
 R¹⁰ represents -OH, -O-C₁₋₄alkyl, or -NR^{11a}R^{11b};
 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;
 R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, or C₃₋₆cycloalkyl;
 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, or Ar²;
 Ar¹ represents phenyl optionally substituted with one hydroxy;
 Ar² represents phenyl optionally substituted with one C₁₋₄alkyl;
 R^{11a}, R^{14a}, R^{14c}, R^{15a}, R^{17a} and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;
 R^{14b}, R^{14d}, R^{15b}, R^{17b} and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; -C(=O)-C₁₋₄alkyl; C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl;
 R^{20a} and R^{20b} 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;
 and the pharmaceutically acceptable addition salts, and the solvates thereof.

[0099] 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 or halo;

R⁵ represents -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; -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, or -(C=O)-CH(NH₂)-C₁₋₄alkyl-Ar¹;

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

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

R⁹ represents C₁₋₄alkyl, or C₁₋₄alkyl substituted with one substituent selected from the group consisting of -NH₂ and -COOH;

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

R³ represents phenyl optionally substituted with 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; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -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; C₂₋₆alkenyl; and C₂₋₆alkenyl substituted with one R¹³;

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

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;

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

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, or Ar²;

Ar¹ represents phenyl optionally substituted with one hydroxy;

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

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

R^{14b}, R^{14d}, 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} and R^{20b} 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;

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

[0100] 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 or N;

R⁴ represents hydrogen or halo;

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

R^{6a} represents hydrogen;

R^{6b} represents -C(=O)-C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl;

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

R^{8a} represents hydrogen;

R^{8b} represents C₃₋₆cycloalkyl;

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

R³ represents phenyl optionally substituted with 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; -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; C₂₋₆alkenyl substituted with one R¹³; and C₂₋₆alkynyl substituted with one R¹³;

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

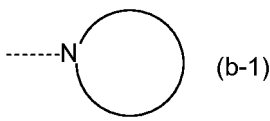
R¹⁸ represents a 5-membered aromatic ring containing one, two or three N-atoms; wherein said 5-membered aromatic ring may optionally be substituted with one substituent selected from the group consisting of C₁₋₄alkyl; Het^{1a}, Het^{1c} and Het^{1d} each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O 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 -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, -O-C₁₋₄alkyl, and -N(C₁₋₄alkyl)₂;

Het^{1b}, Het^{1e}, Het^{1g}, Het⁷ and Het⁸ 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}, Het⁷ and Het⁸ containing one or two heteroatoms each independently selected from O 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 and C₃₋₆cycloalkyl; 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, and halo;

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 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 N-atoms;

wherein in case (b-1) contains one or two additional N-atoms, said one or two N-atoms may optionally be substituted with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl and Het⁷; 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 -OH, cyano, C₁₋₄alkyl, and C₁₋₄alkyl-OH;

R^{11b} represents Het^{1e}; C₁₋₄alkyl; -C₁₋₄alkyl-Het⁵; -C₁₋₄alkyl-Het⁸, C₁₋₄alkyl substituted with one, two or three OH substituents; or C₃₋₆cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo and -OH;

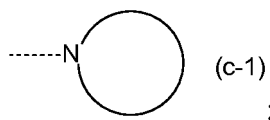
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, or -C(=O)-Het^{1f};

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

Ar¹ represents phenyl;

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

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 and N;

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

C₁₋₄alkyl;

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

R^{14b}, R^{14d}, R^{15b}, R^{17b} and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; -C(=O)-C₁₋₄alkyl; C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl;

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

[0101] 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 or halo;

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

R^{6a} represents hydrogen;

R^{6b} represents -C(=O)-C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl;

R⁷ represents hydrogen, -C(=O)-R⁹, -S(=O)₂-OH, or -(C=O)-CH(NH₂)-C₁₋₄alkyl-Ar¹;

R⁹ represents C₁₋₄alkyl, or C₁₋₄alkyl substituted with one substituent selected from the group consisting of -NH₂, -COOH, and Het⁶;

R³ represents phenyl optionally substituted with 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; -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}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; and C₁₋₄alkyl substituted with one R¹³

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; 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 and N;

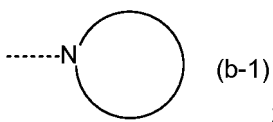
wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one -O-C₁₋₄alkyl; and

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, -O-C₁₋₄alkyl, and -N(C₁₋₄alkyl)₂;

Het^{1b}, Het^{1e}, and Het^{1g} 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} and Het^{1g} containing one or two heteroatoms each independently selected from O 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 and C₃₋₆cycloalkyl; 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 -OH substituents;

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 N-atom, or a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, optionally containing one or two additional N-atoms;

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 -OH, cyano, and C₁₋₄alkyl-OH;

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

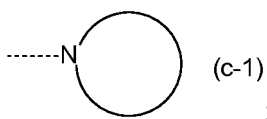
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, or -C(=O)-Het^{1f},

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

Ar¹ represents phenyl;

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

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 and N;

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

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

R^{14b}, R^{14d}, R^{15b}, and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one -O-C₁₋₄alkyl;

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

[0102] 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 or halo;

R⁵ represents -OR⁷;

R⁷ represents hydrogen or -C(=O)-R⁹;

R⁹ represents C₁₋₄alkyl;

R³ represents phenyl optionally substituted with 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; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het^{1g}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; and C₁₋₄alkyl substituted with one R¹³;

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

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 and N;

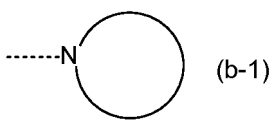
wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl substituted with one -O-C₁₋₄alkyl; and

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, C₁₋₄alkyl, -O-C₁₋₄alkyl, and -N(C₁₋₄alkyl)₂;

Het^{1b}, Het^{1e}, and Het^{1g} 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} and Het^{1g} containing one or two heteroatoms each independently selected from O and N;

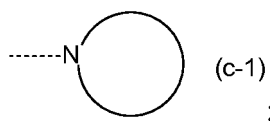
wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected from the group consisting of C₁₋₄alkyl and C₃₋₆cycloalkyl; and wherein said 4- to 7-membered monocyclic saturated heterocyclyl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

stituted on one, two or three ring C-atoms with one or two -OH substituents;
Het² represents a heterocyclyl of formula (b-1):



10 (b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional N-atom, or a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, optionally containing one or two additional N-atoms;
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
15 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 -OH, cyano, and C₁₋₄alkyl-OH;

R^{11b} represents Het^{1e}; C₁₋₄alkyl; C₁₋₄alkyl substituted with one, two or three OH substituents; or C₃₋₆cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo and -OH;
20 R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, C₃₋₆cycloalkyl, Het^{1d}, 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, C₃₋₆cycloalkyl, Ar², or Het^{1c};
Ar² represents phenyl optionally substituted with one C₁₋₄alkyl;
Het^{1f} represents a heterocyclyl of formula (c-1):



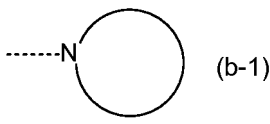
30 (c-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O and N;
wherein in case (c-1) contains one additional N-atom, said additional N-atom may optionally be substituted with C₁₋₄alkyl;
35 R^{11a}, R^{14a}, R^{14c}, and R^{15a} each independently represents hydrogen or C₁₋₄alkyl;
R^{14b}, R^{14d}, and R^{15b} each independently represents hydrogen; C₁₋₄alkyl; or C₃₋₆cycloalkyl;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

40 **[0103]** 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;
45 R⁴ represents hydrogen;
R⁵ represents -OR⁷;
R⁷ represents hydrogen or -C(=O)-R⁹;
R⁹ represents C₁₋₄alkyl; or C₁₋₄alkyl substituted with one -NH₂ substituent;
R³ represents phenyl substituted with one, two or three substituents each independently selected from the group
50 consisting of halo; cyano; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -O-C₁₋₄alkyl-R¹²; -O-C₃₋₆cycloalkyl;
-O-Het^{1b}; -NH-C(=O)-Het^{1g}; and C₁₋₄alkyl substituted with one R¹³;
R¹⁰ represents -NR^{11a}R^{11b} or Het²;
Het^{1g} 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^{1g} containing one or two N-atoms;
55 wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible,
on one or two ring N-atoms with a C₁₋₄alkyl substituent;
Het^{1b} 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} containing one or two N-atoms;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a C₁₋₄alkyl substituent; and wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one ring C-atom with one halo substituent;

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



(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl wherein (b-1) may optionally be substituted on one C-atom with one -OH substituent;

R^{11b} represents C₁₋₄alkyl;

R¹³ represents -O-C₁₋₄alkyl;

R¹² represents -O-C₁₋₄alkyl;

R^{11a} represents hydrogen;

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

[0104] 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 or -C(=O)-R⁹;

R⁹ represents C₁₋₄alkyl;

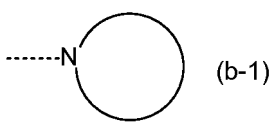
R³ represents phenyl substituted with one, two or three substituents each independently selected from the group consisting of halo; cyano; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -O-C₁₋₄alkyl-R¹²; -NH-C(=O)-Het¹⁹; and C₁₋₄alkyl substituted with one R¹³;

R¹⁰ represents -NR^{11a}R^{11b} or Het²;

Het¹⁹ 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 Het¹⁹ containing one or two N-atoms;

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a C₁₋₄alkyl substituent;

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



(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl wherein (b-1) may optionally be substituted on one C-atom with one -OH substituent;

R^{11b} represents C₁₋₄alkyl;

R¹³ represents -O-C₁₋₄alkyl;

R¹² represents -O-C₁₋₄alkyl;

R^{11a} represents hydrogen;

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

[0105] 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 or -C(=O)-R⁹;

R⁹ represents C₁₋₄alkyl; or C₁₋₄alkyl substituted with one -NH₂ substituent;

R³ represents phenyl substituted with 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; -O-C₁₋₄alkyl-R¹²; -O-C₃₋₆cycloalkyl; and C₁₋₄alkyl substituted with one R¹³;

R¹⁰ represents -NR^{11a}R^{11b};

R^{11b} represents C₁₋₄alkyl;

R¹³ represents -O-C₁₋₄alkyl;

R¹² represents -O-C₁₋₄alkyl;

R^{11a} represents hydrogen;

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

[0106] 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 or -C(=O)-R⁹;

R⁹ represents C₁₋₄alkyl;

R³ represents phenyl substituted with 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; -O-C₁₋₄alkyl-R¹²; -O-C₃₋₆cycloalkyl; and C₁₋₄alkyl substituted with one R¹³;

R¹⁰ represents -NR^{11a}R^{11b};

R^{11b} represents C₁₋₄alkyl;

R¹³ represents -O-C₁₋₄alkyl;

R¹² represents -O-C₁₋₄alkyl;

R^{11a} represents hydrogen;

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

[0107] 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;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen or -C(=O)-R⁹;

R⁹ represents C₁₋₄alkyl; or C₁₋₄alkyl substituted with one -NH₂ substituent;

R³ represents phenyl substituted with one, two or three substituents each independently selected from the group consisting of halo; cyano; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -O-C₃₋₆cycloalkyl; and -O-Het^{1b};

R¹⁰ represents -NR^{11a}R^{11b};

Het^{1b} 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} containing one or two N-atoms; wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a C₁₋₄alkyl substituent; and

wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one ring C-atom with one halo substituent;

R^{11b} represents C₁₋₄alkyl;

R^{11a} represents hydrogen;

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

[0108] 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 C₁₋₄alkyl substituted with one R⁵;

Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents phenyl substituted with 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; -O-C₁₋₄alkyl-R¹²; -O-C₃₋₆cycloalkyl; -O-Het^{1b}; -NH-C(=O)-Het^{1g}; and C₁₋₄alkyl substituted with one R¹³;

R¹⁰ represents -NR^{11a}R^{11b};

Het^{1b} represents a pyrrolidine attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, wherein the N-atom is substituted with methyl and one ring C-atom is substituted with one halo substituent;

Het^{1g} represents 4-piperidinyI wherein the N-atom is substituted with methyl;

R^{11b} represents C₁₋₄alkyl;

R¹³ represents -O-C₁₋₄alkyl;

R¹² represents -O-C₁₋₄alkyl;

R^{11a} represents hydrogen;

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

[0109] 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 C₁₋₄alkyl substituted with one R⁵;

Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen;

R³ represents phenyl substituted with 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; -O-C₁₋₄alkyl-R¹²; -NH-C(=O)-Het^{1g}; and C₁₋₄alkyl substituted with one R¹³;

in particular R³ represents phenyl substituted with 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; -O-C₁₋₄alkyl-R¹²; and C₁₋₄alkyl substituted with one R¹³;

R¹⁰ represents -NR^{11a}R^{11b};

Het^{1g} represents 4-piperidinyI wherein the N-atom is substituted with methyl;

R^{11b} represents C₁₋₄alkyl;

R¹³ represents -O-C₁₋₄alkyl;

R¹² represents -O-C₁₋₄alkyl;

R^{11a} represents hydrogen;

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

[0110] 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;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen or -C(=O)-R⁹;

R⁹ represents C₁₋₄alkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of -NH₂ and -COOH;

R³ represents phenyl substituted with one, two or three substituents each independently selected from the group

consisting of halo; cyano; and C₁₋₆alkyl;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

[0111] 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;
R⁴ represents hydrogen;
R⁵ represents -OR⁷;
R⁷ represents hydrogen;
R³ represents phenyl substituted with one, two or three substituents each independently selected from the group consisting of halo; cyano; and C₁₋₆alkyl;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

[0112] 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;
R⁴ represents hydrogen;
R⁵ represents -OR⁷;
R⁷ represents hydrogen or -C(=O)-R⁹;
R⁹ represents C₁₋₄alkyl substituted with one -NH₂ substituent;
R³ represents phenyl substituted with one, two or three substituents each independently selected from the group consisting of cyano; and C₁₋₆alkyl;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

[0113] 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;
R⁴ represents hydrogen;
R⁵ represents -OR⁷;
R⁷ represents hydrogen;
R³ represents phenyl substituted with one, two or three substituents each independently selected from the group consisting of cyano; and C₁₋₆alkyl;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

[0114] 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 -NR^{6a}R^{6b}, or -OR⁷;
R^{6b} represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; -C(=O)-C₁₋₄alkyl; -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, or -C(=O)-CH(NH₂)-C₁₋₄alkyl-Ar¹.

[0115] 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 Y represents CR⁴ or N, in particular wherein Y represents CR⁴; and wherein one or more of the following restrictions apply:

(a) R⁵ represents halo, -NR^{6a}R^{6b}, or -OR⁷; in particular R⁵ represents -NR^{6a}R^{6b}, or -OR⁷;

(b) R^{6a} represents hydrogen;

(c) R^{6b} represents -C(=O)-C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl;

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

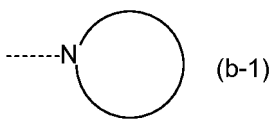
(e) R³ represents phenyl optionally substituted with one, two or three substituents each independently selected from the group consisting of halo; cyano; C₁₋₆alkyl; -O-C₁₋₄alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄alkyl; -O-C₁₋₄alkyl-R¹²; C₃₋₆cycloalkyl; -O-C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄alkyl)₂; -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; C₂₋₆alkenyl substituted with one R¹³; and C₂₋₆alkynyl substituted with one R¹³; in particular R³ represents phenyl optionally substituted with 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; -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}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; and C₁₋₄alkyl substituted with one R¹³;

(f) 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;

(g) 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 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 -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, -O-C₁₋₄alkyl, and -N(C₁₋₄alkyl)₂;

(h) Het^{1b}, Het^{1e}, Het^{1g}, Het⁷ and Het⁸ 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}, Het⁷ and Het⁸ containing one or two heteroatoms each independently selected from O 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 and C₃₋₆cycloalkyl; 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, and halo; in particular Het^{1b}, Het^{1e}, and Het^{1g} 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} and Het^{1g} containing one or two heteroatoms each independently selected from O 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 and C₃₋₆cycloalkyl; 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 -OH substituents;

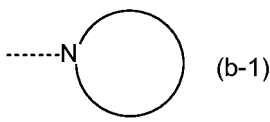
(i) Het² represents a heterocyclyl of formula (b-1):



(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional heteroatom selected from O 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 N-atoms;
 wherein in case (b-1) contains one or two additional N-atoms, said one or two N-atoms may optionally be
 substituted with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl
 and Het⁷; 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 -OH, cyano, C₁₋₄alkyl, and C₁₋₄alkyl-OH;

in particular 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 N-atom, or a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and
 bridged cycles, optionally containing one or two additional N-atoms;
 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 -OH, cyano, and C₁₋₄alkyl-OH;

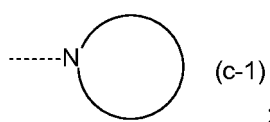
(j) R^{11b} represents Het^{1e}; C₁₋₄alkyl; -C₁₋₄alkyl-Het⁵; -C₁₋₄alkyl-Het⁸, C₁₋₄alkyl substituted with one, two or three OH
 substituents; or C₃₋₆cycloalkyl substituted with one, two or three substituents each independently selected from the
 group consisting of halo and -OH; in particular R^{11b} represents Het^{1e}; C₁₋₄alkyl; -C₁₋₄alkyl-Het⁵; C₁₋₄alkyl substituted
 with one, two or three OH substituents; or C₃₋₆cycloalkyl substituted with one, two or three substituents each inde-
 pendently selected from the group consisting of halo and -OH;

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

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

(m) Ar¹ represents phenyl;

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

(o) R^{14b}, R^{14d}, R^{15b}, R^{17b} and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl;
 -C(=O)-C₁₋₄alkyl; C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-
 C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl; in particular R^{14b}, R^{14d}, R^{15b}, and R^{19b} each independently represents hydrogen;
 C₁₋₄alkyl; C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one -O-C₁₋₄alkyl.

[0116] Another embodiment of the present invention relates to those compounds of Formula (I) and the pharmaceu-
 tically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other
 embodiments wherein Y represents CR⁴ or N, in particular wherein Y represents CR⁴; and wherein one or more of the
 following restrictions apply:

(a) R⁴ represents hydrogen;

(b) R^5 represents $-OR^7$;

(c) R^7 represents hydrogen or $-C(=O)-R^9$;

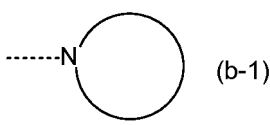
(d) R^9 represents C_{1-4} alkyl;

(e) R^3 represents phenyl substituted with 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; $-O-C_{1-4}$ alkyl- R^{12} ; $-NH-C(=O)-Het^{19}$; and C_{1-4} alkyl substituted with one R^{13} ;

(f) R^{10} represents $-NR^{11a}R^{11b}$ or Het^2 ;

(g) Het^{19} 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^{19} containing one or two N-atoms; wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a C_{1-4} alkyl substituent;

(h) Het^2 represents a heterocyclyl of formula (b-1):



(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl wherein (b-1) may optionally be substituted on one C-atom with one $-OH$ substituent;

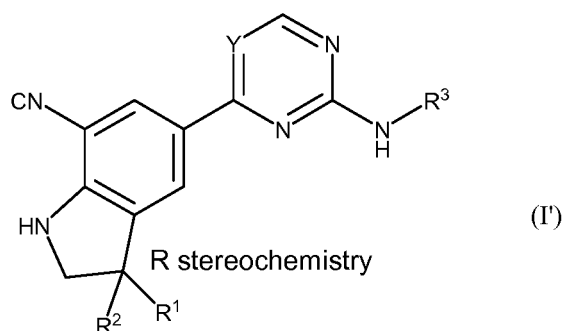
(i) R^{11b} represents C_{1-4} alkyl;

(j) R^{13} represents $-O-C_{1-4}$ alkyl;

(k) R^{12} represents $-O-C_{1-4}$ alkyl;

(l) R^{11a} represents hydrogen.

[0117] 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:



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

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;

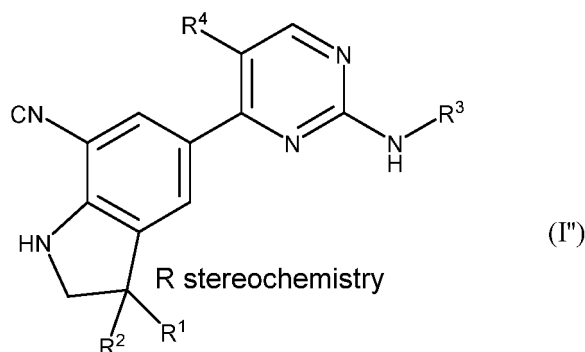
R^2 represents C_{1-6} alkyl substituted with one R^5 ;

R^5 represents $-OR^7$;

R^7 represents hydrogen;

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

[0118] 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:



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

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;

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.

[0119] 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 $-CH_2-OH$.

[0120] 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 $-CH_2-OH$.

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 phenyl which is substituted with one, two or three substituents according to any of the other embodiments.

[0121] 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 phenyl optionally substituted with one, two or three substituents according to any of the other embodiments, provided however that the substituents are not selected from the group consisting of $-S(=O)_2-C_{1-4}$ alkyl; $-S(=O)(=N-R^{20a})-OC_{1-4}$ alkyl; and $-P(=O)-(C_{1-4}$ alkyl) $_2$.

[0122] 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^4 is hydrogen or fluoro.

[0123] 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^4 is hydrogen.

[0124] 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^7 represents hydrogen.

[0125] 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

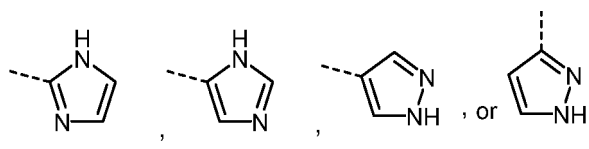
R^5 represents $-OR^7$; and

R^7 represents hydrogen.

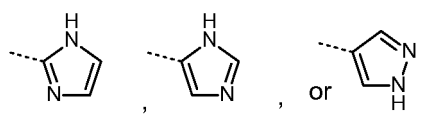
[0126] In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^9 represents C_{1-4} alkyl, or C_{1-4} alkyl substituted with one substituent selected from the group consisting of $-NH_2$, $-COOH$, and Het⁶.

[0127] 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^{18} is attached to the remainder of the molecule of Formula (I) via a carbon atom.

[0128] 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^{18} represents

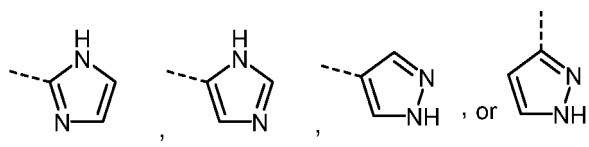


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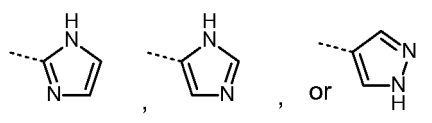


each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

[0129] 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^{18} represents



in particular



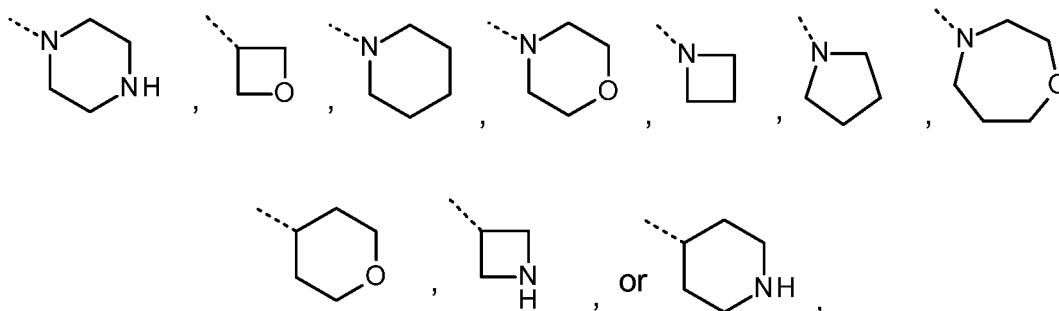
each substituted on the NH with C_{1-4} alkyl.

[0130] 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, azetidiny, piperazinyl, tetrahydro-2H-pyranyl, tetrahydrofuranyl, or hexahydro-1,4-oxazepinyl,

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

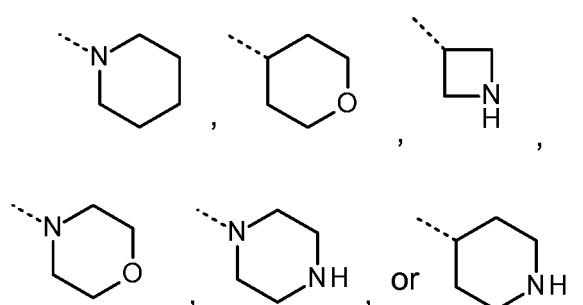
[0131] In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1a}, Het^{1c} and Het^{1d} each independently represents morpholinyl, piperidinyl, pyrrolidinyl, oxetanyl, azetidiny, piperazinyl, tetrahydro-2H-pyranyl, or 1-exahydro-1,4-oxazepinyl, each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

[0132] 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



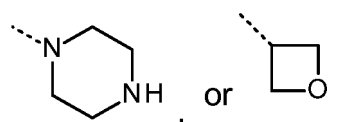
each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

[0133] 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



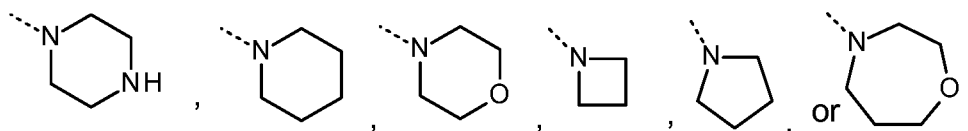
each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

[0134] 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



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

[0135] 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



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

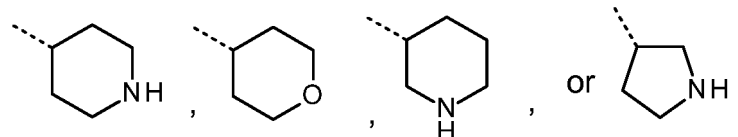
[0136] In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ each independently represents morpholinyl, piperidinyl, pyrrolidinyl, oxetanyl, azetidinyl, piperazinyl, tetrahydro-2H-pyranyl, tetrahydrofuranyl, 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.

[0137] 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,

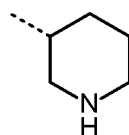
wherein Het^{1b}, Het^{1e}, Het^{1g} and Het⁴ each independently represents piperidinyl, tetrahydro-2H-pyranyl, or pyrrolidinyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

[0138] 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



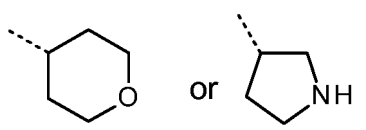
each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

[0139] 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



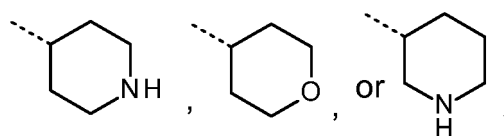
optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

[0140] 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



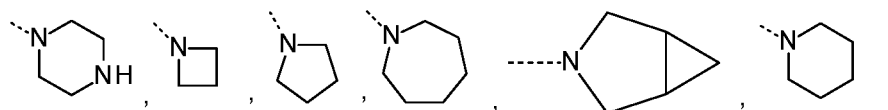
each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

[0141] 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

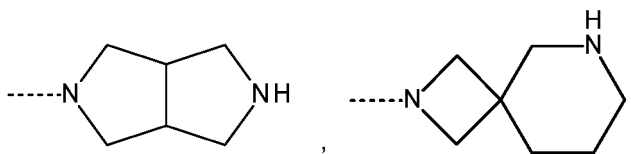


each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

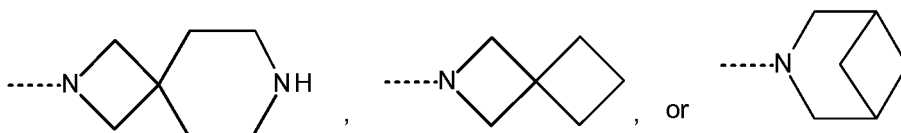
[0142] In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het² represents



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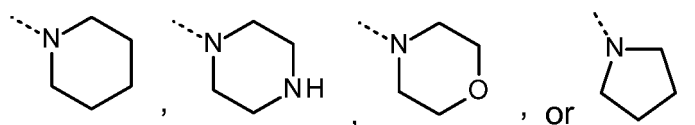


each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

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[0143] 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

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

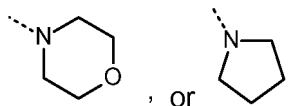
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[0144] In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het⁴ represents pyrrolidinyl, piperidinyl, tetrahydropyranyl, azetidinyl, or 1,1-dioxidethiopyranyl; each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

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[0145] 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 Het⁵ represents

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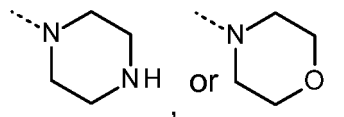


each optionally substituted according to any of the other embodiments.

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[0146] 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

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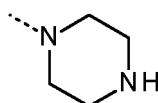


each optionally substituted on carbon and/or nitrogen atoms according to any of the other embodiments.

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[0147] 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

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

[0148] 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 Het⁷ and Het⁸ each independently represent

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10 optionally substituted on carbon atoms according to any of the other embodiments.

[0149] 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

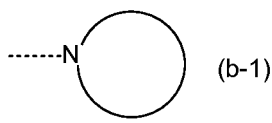
15 Het^{1a}, Het^{1c} and Het^{1d} each independently represents a 4- to 7-membered monocyclic saturated heterocyclyl containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

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.

25 **[0150]** 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 a heterocyclyl of formula (b-1):

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35 (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; wherein in case (b-1) contains one additional N-atom, said N-atom 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. 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

40 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;

45 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;

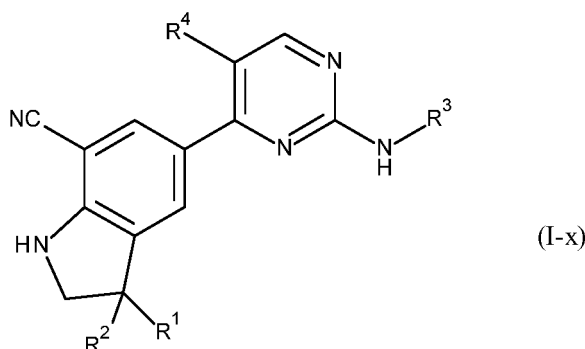
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wherein said 4- to 7-membered monocyclic saturated heterocyclyl or said N-linked 6-to 11-membered bicyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a substituent each independently selected 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.

[0151] 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.

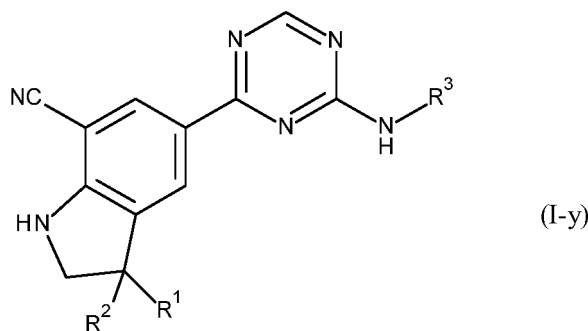
[0152] In an embodiment, the present invention relates to a subgroup of Formula (I), hereby named compounds of Formula (I-x), and the pharmaceutically acceptable addition salts, and the solvates thereof:



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

[0153] 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.

[0154] 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.

[0155] In an embodiment, the present invention relates to a subgroup of Formula (I) as defined in the general reaction schemes.

[0156] In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 1, 4, 45, 66, 68, 73, 74, 110, 125, 138, 155, 156 and 232, tautomers and stereoisomeric forms thereof, and the free bases, any pharmaceutically acceptable addition salts, and the solvates thereof.

[0157] In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 1, 4, 45, 66, 68, 73, 74, 110, 125, 138, 155, 156 and 232.

[0158] In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 1, 138, 155, 156 and 232, tautomers and stereoisomeric forms thereof, and the free bases, any pharmaceutically acceptable addition salts, and the solvates thereof.

[0159] In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 1, 138, 155, 156 and 232.

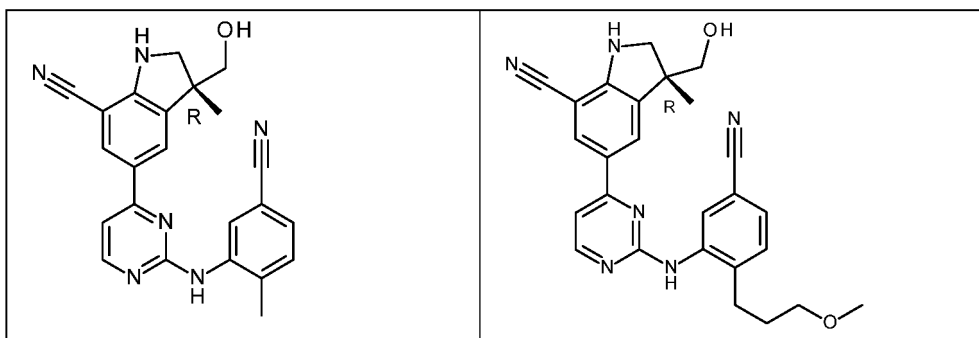
[0160] In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 1, 4, 45, 66, 68, 73, 74, 110, and 125, tautomers and stereoisomeric forms thereof, and the pharmaceutically acceptable addition salts, and the solvates thereof.

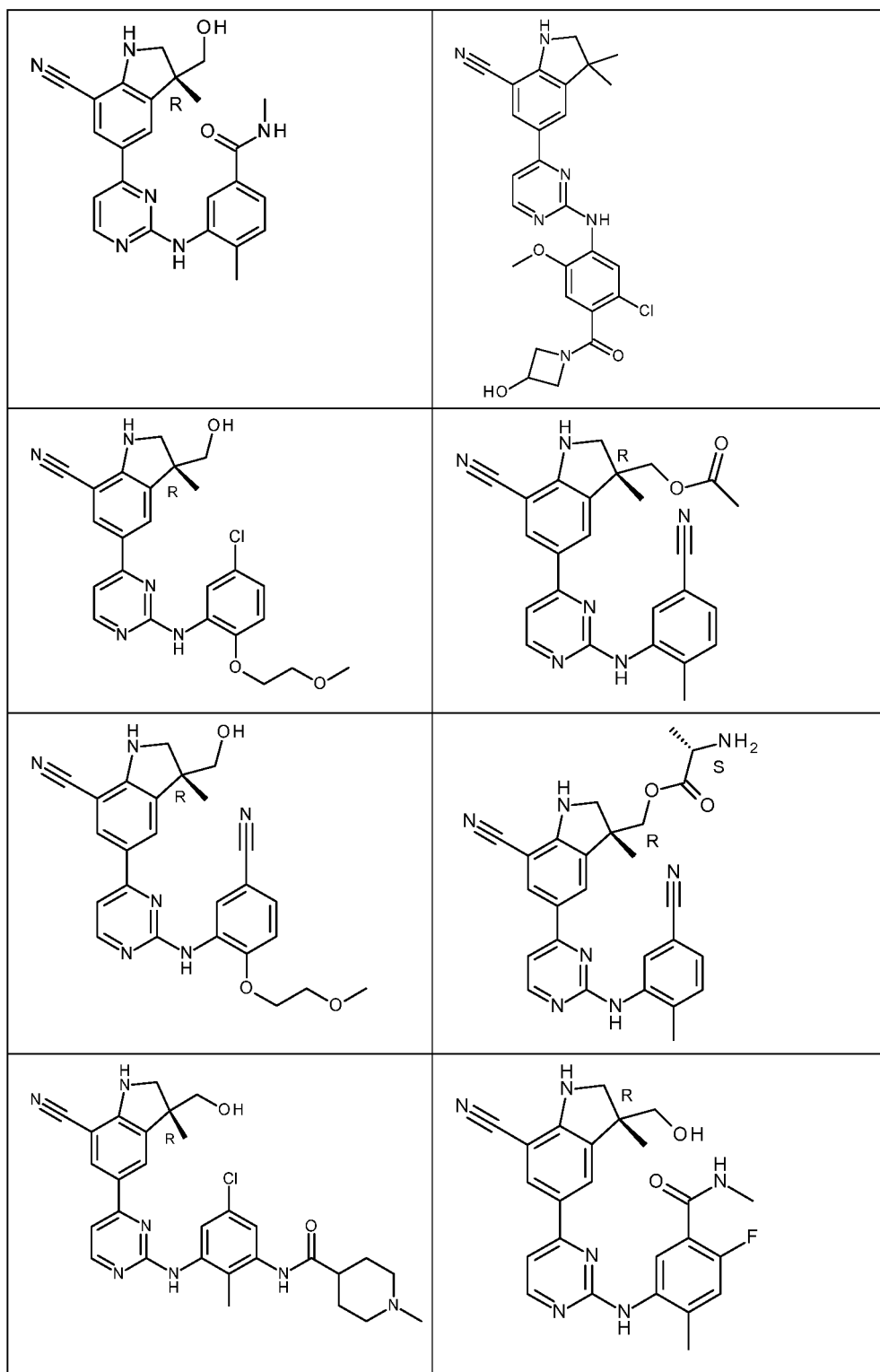
[0161] In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 1, 4, 45, 66, 68, 73, 74, 110, and 125.

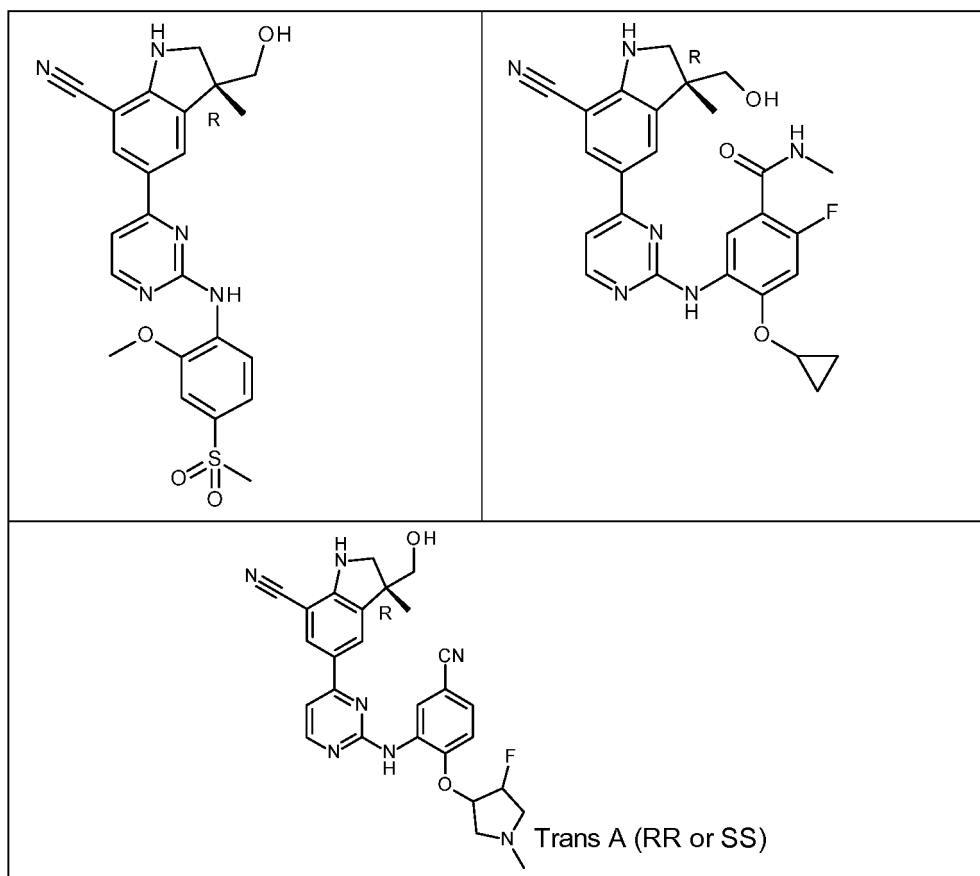
[0162] In an embodiment the compound of Formula (I) is selected from the group consisting of any of the exemplified compounds,

tautomers and stereoisomeric forms thereof, and the free bases, any pharmaceutically acceptable addition salts, and the solvates thereof.

[0163] In an embodiment the compound of Formula (I) is selected from the group consisting of

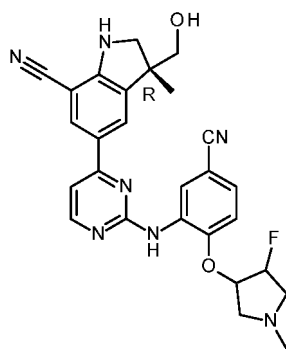






tautomers and stereoisomeric forms thereof,
and the pharmaceutically acceptable addition salts, and the solvates thereof.

[0164] In an embodiment the compound of Formula (I) is selected from the group consisting of



tautomers and stereoisomeric forms thereof,
and the pharmaceutically acceptable addition salts, and the solvates thereof.

[0165] All possible combinations of the above-indicated embodiments are considered to be embraced within the scope of this invention.

Methods for the Preparation of Compounds of Formula (I)

[0166] 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.

[0167] The general preparation of some typical examples of the compounds of Formula (I) is described hereunder and in the specific examples, and are generally prepared from starting materials which are either commercially available

or prepared by standard synthetic processes commonly used by those skilled in the art. The following schemes are only meant to represent examples of the invention and are in no way meant to be a limit of the invention.

[0168] 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.

[0169] 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.

[0170] The skilled person will realize that in the reactions described in the Schemes, although this is not always explicitly shown, it may be necessary to protect reactive functional groups (for example hydroxy, amino, or carboxy groups) where these are desired in the final product, to avoid their unwanted participation in the reactions. For example in Scheme 6, the NH moiety on the pyrimidinyl can be protected with a t-butoxycarbonyl protecting group. In general, conventional protecting groups can be used in accordance with standard practice. The protecting groups may be removed at a convenient subsequent stage using methods known from the art. This is illustrated in the specific examples.

[0171] The skilled person will realize that in the reactions described in the Schemes, it may be advisable or necessary to perform the reaction under an inert atmosphere, such as for example under N₂-gas atmosphere.

[0172] 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).

[0173] 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.

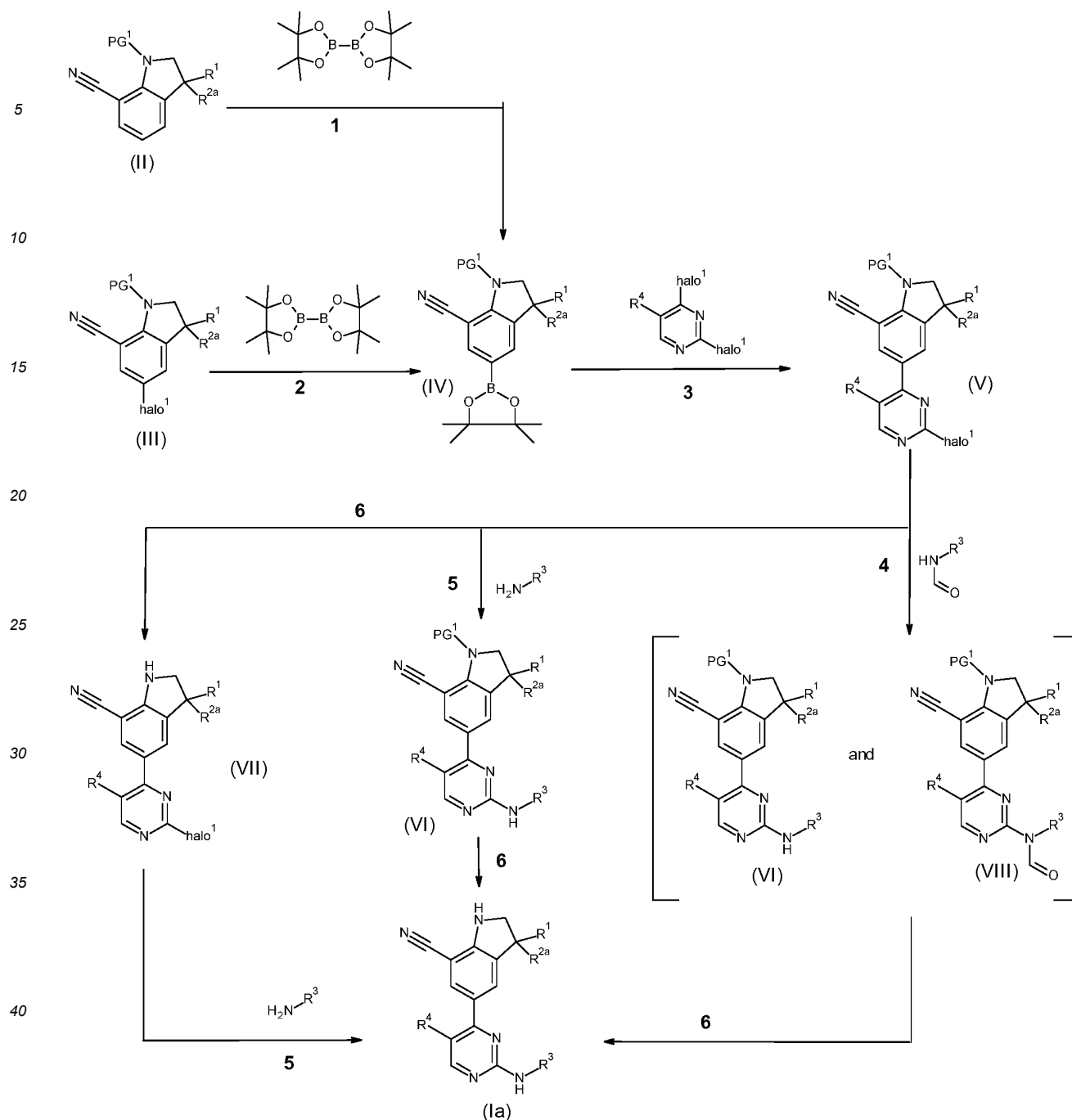
[0174] The skilled person will realize that another sequence of the chemical reactions shown in the Schemes below, may also result in the desired compound of formula (I).

[0175] 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.

Scheme 1

[0176] In general, compounds of Formula (I) wherein R² is R^{2a} being C₁₋₆alkyl, Y is CR⁴, 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.

[0177] 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) $[\text{Ir}(\text{OCH}_3)(\text{C}_8\text{H}_{12})_2]_2$, 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;

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;

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 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;

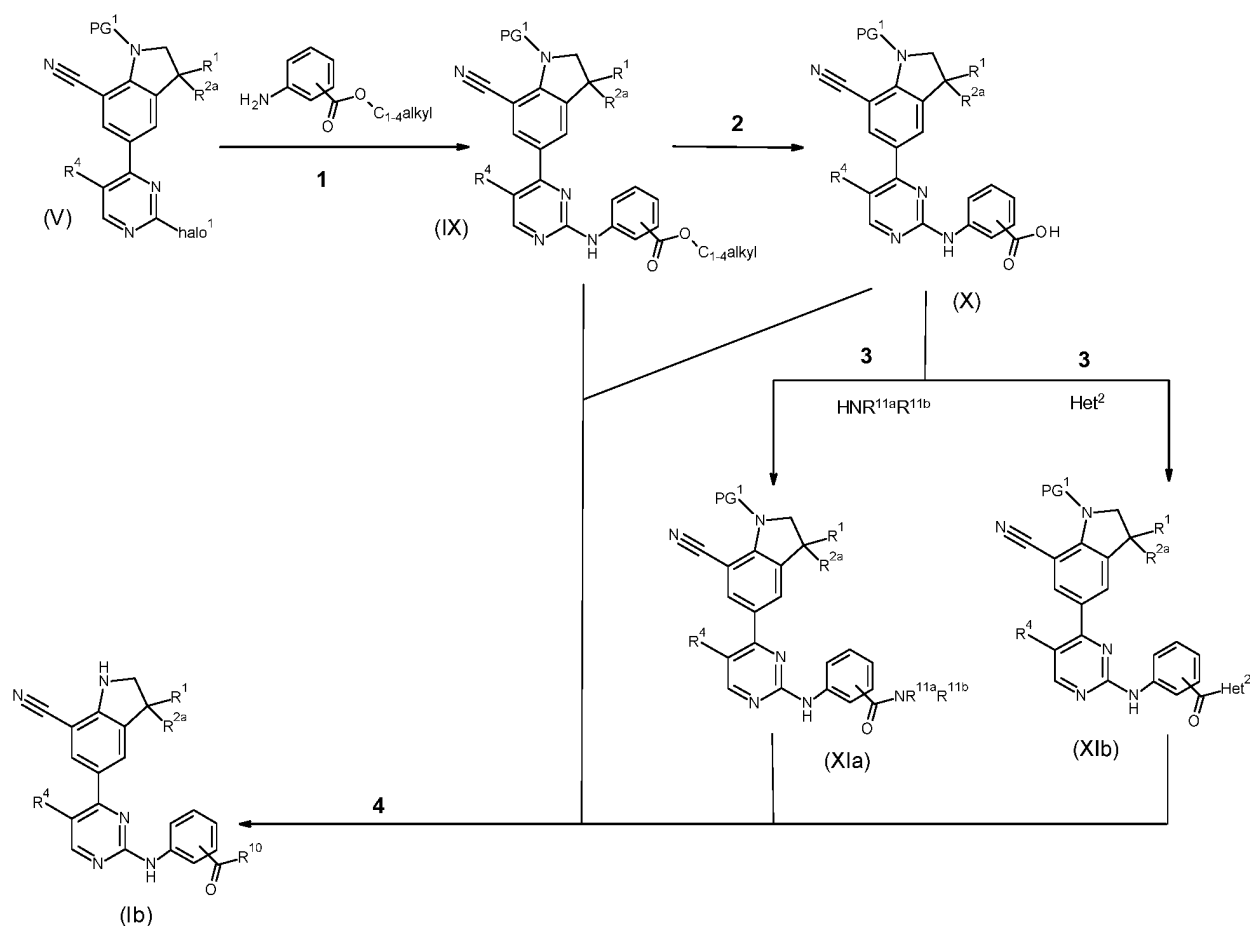
or alternatively at a suitable temperature such as for example 95 °C, in the presence of a suitable acid such as for example *p*-toluenesulfonic acid and a suitable solvent such as for example 1,4-dioxane;

6: at a suitable temperature such as for example 0 °C or room temperature or reflux, in 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 2

[0178] In general, compounds of Formula (I) wherein R² is R^{2a} being C₁₋₆alkyl, R³ is phenyl 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 (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 Scheme 2 are defined according to the scope of the present invention.

[0179] In Scheme 2, 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 (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 tetrahydrofuran and water;

3: at a suitable temperature such as for example room temperature, in presence of a suitable coupling reagent such

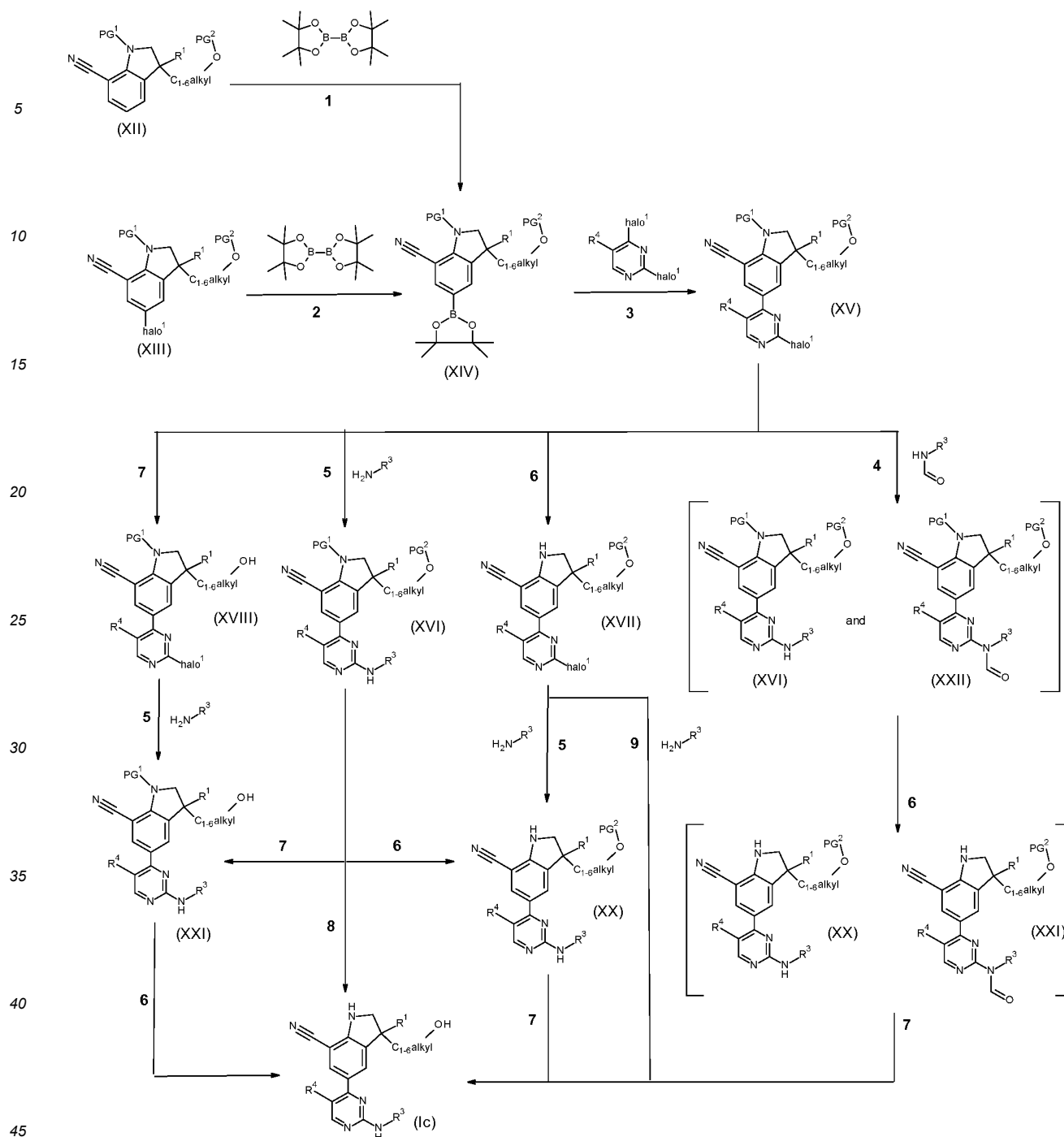
as for example 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), a suitable base such as for example *N,N*-diisopropylethylamine, and a suitable solvent such as for example dimethylformamide;

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.

Scheme 3

[0180] In general, compounds of Formula (I) wherein R² is R^{2b} being C₁₋₆alkyl substituted with one OH, 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 (Ic), can be prepared according to 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.

[0181] 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) $[(Ir(OCH_3)(C_8H_{12}))_2]$, 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), 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 $(Pd(PPh_3)_4)$, a suitable base such as for example sodium carbonate, and a suitable solvent such as for example 1,4-dioxane;

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 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;

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;

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;

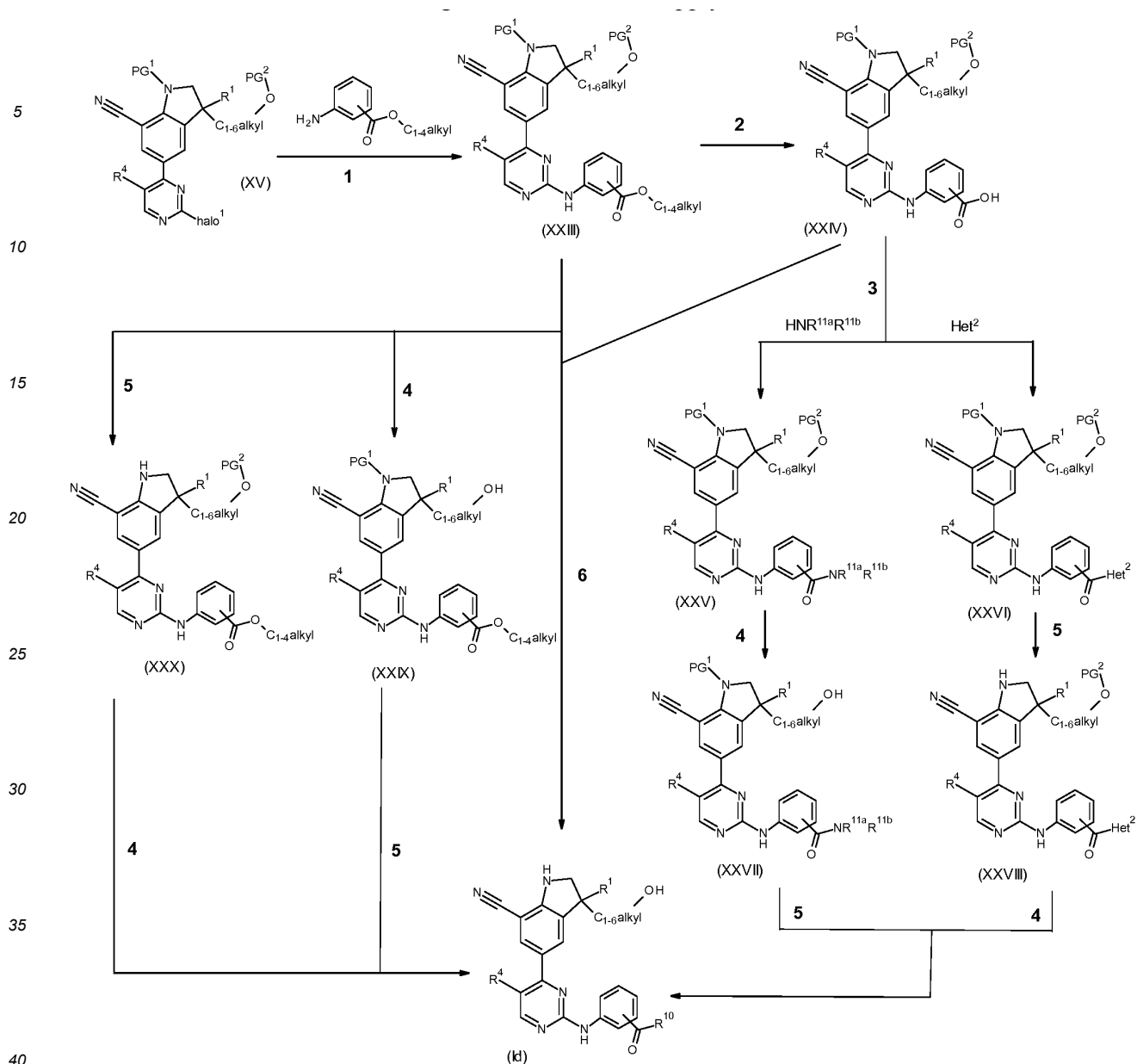
8: at a suitable temperature such as for example reflux, in presence of a suitable acid such as for example aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane, and a suitable time such as for example 6 hours;

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.

Scheme 4

[0182] In general, compounds of Formula (I) wherein R^2 is R^{2b} being C_{1-6} alkyl substituted with one OH, R^3 is phenyl substituted with $-\text{C}(=\text{O})-\text{R}^{10}$ and optionally substituted with other substituents according to the scope of the present invention, 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 (Id), can be prepared according to the following reaction Scheme 4. In Scheme 4 halo¹ is defined as Cl, Br or I; PG^1 represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl) and PG^2 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.

[0183] 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 (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 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 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

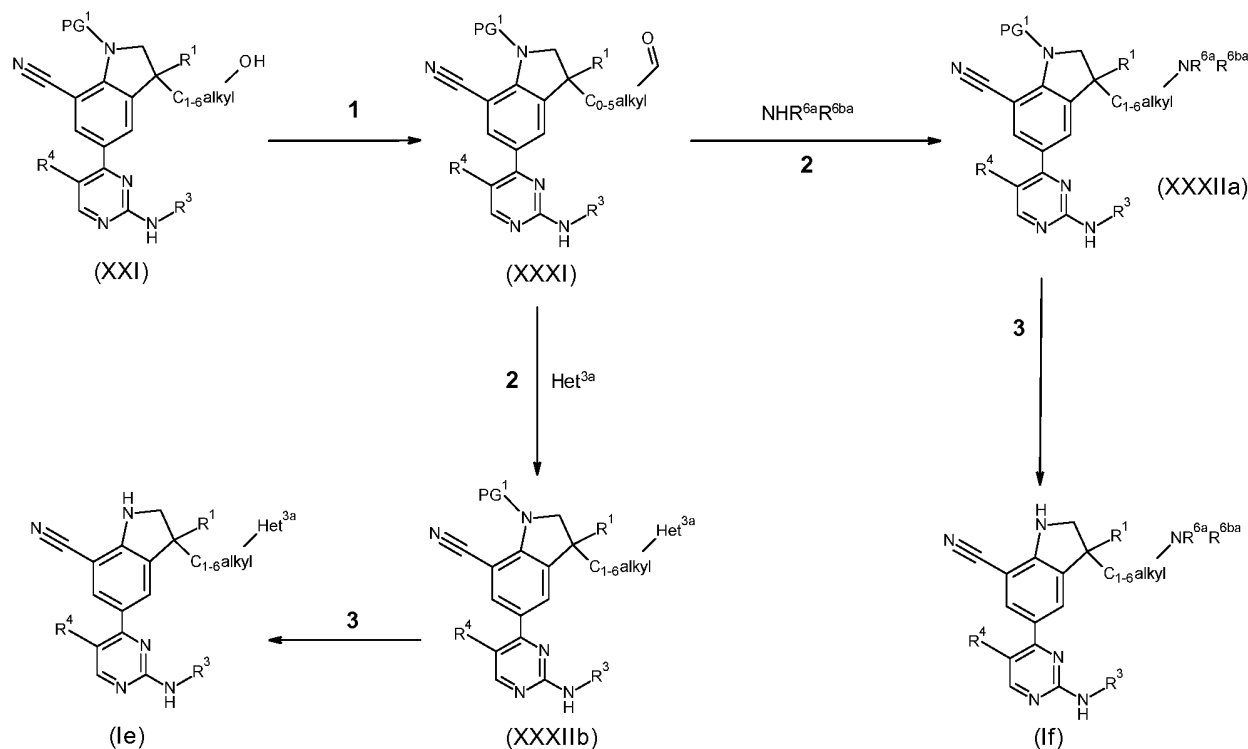
example 3 hours.

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

[0184] 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, 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 (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.

[0185] In Scheme 5, the following reaction conditions apply:



1: at a suitable temperature such as for example $-78^\circ C$, 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;

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;

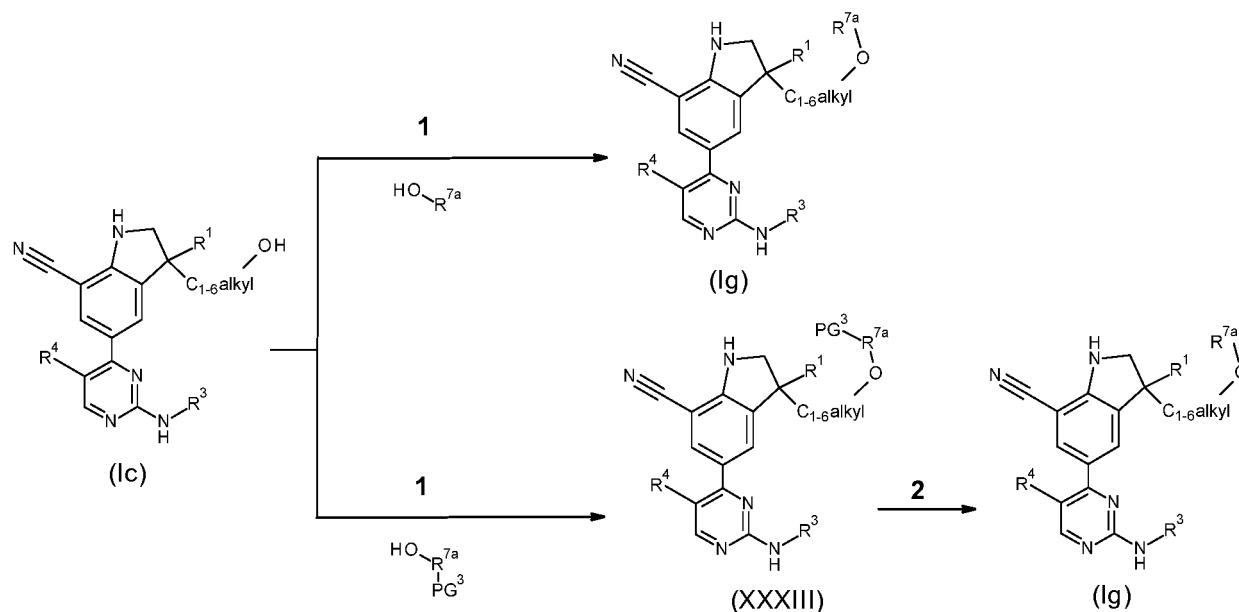
3: at a suitable temperature such as for example $0^\circ C$ or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane or alternatively in the presence of silica in a suitable solvent such as for example toluene at a suitable temperature such as for example $125^\circ C$, and a suitable time such as for example 3 hours.

Scheme 6

[0186] 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 , 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 (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*-(butoxycarbonyl), a

tert-butyl or a benzyl. All other variables in Scheme 6 are defined according to the scope of the present invention.

[0187] In Scheme 6, the following reaction conditions apply:



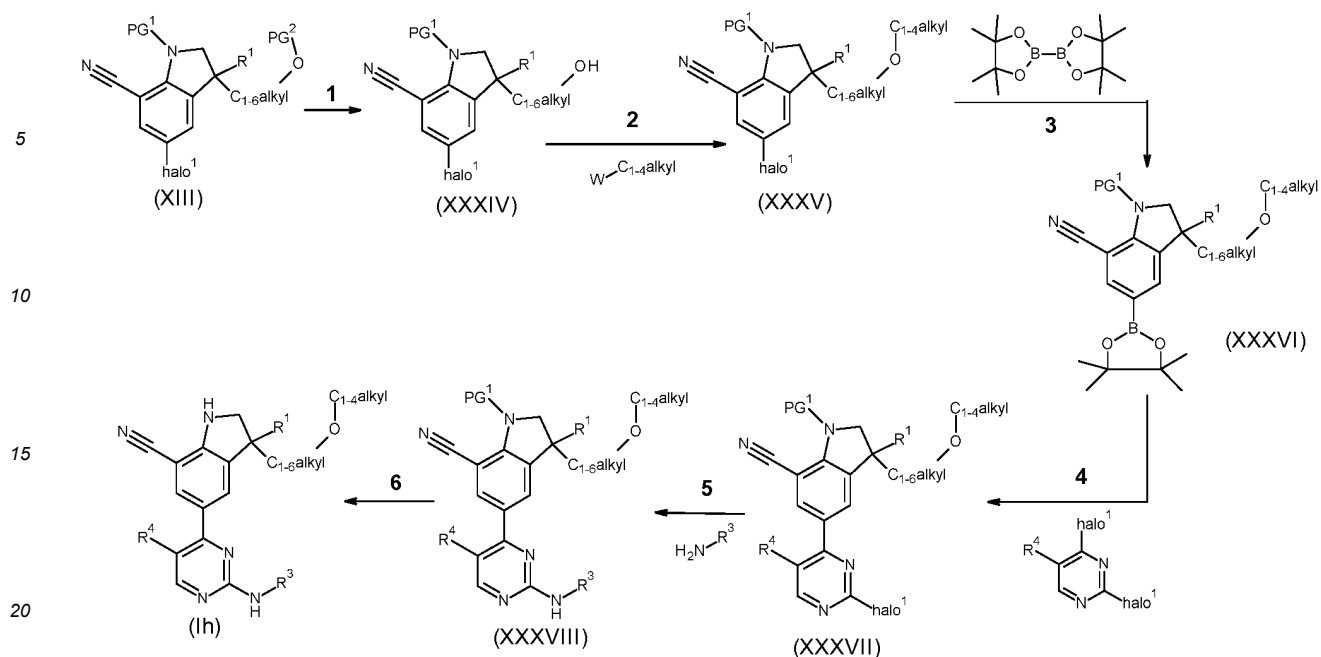
1: at a suitable temperature such as for example room temperature, in the presence of a suitable coupling reagent such as for example 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), in the presence of a suitable base as for example *N,N*-diisopropylethylamine, 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

[0188] In general, compounds of Formula (I) wherein R^2 is $\text{C}_{1-6}\text{alkyl}$ substituted with one OR^{7b} , R^{7b} being $\text{C}_{1-4}\text{alkyl}$, 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 (Ih), can be prepared according to the following reaction Scheme 7. In Scheme 7 halo¹ is defined as Cl, Br or I; PG^1 represents a suitable protecting group, such as for example *tert*-(butoxycarbonyl) and PG^2 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.

[0189] 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;

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 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;

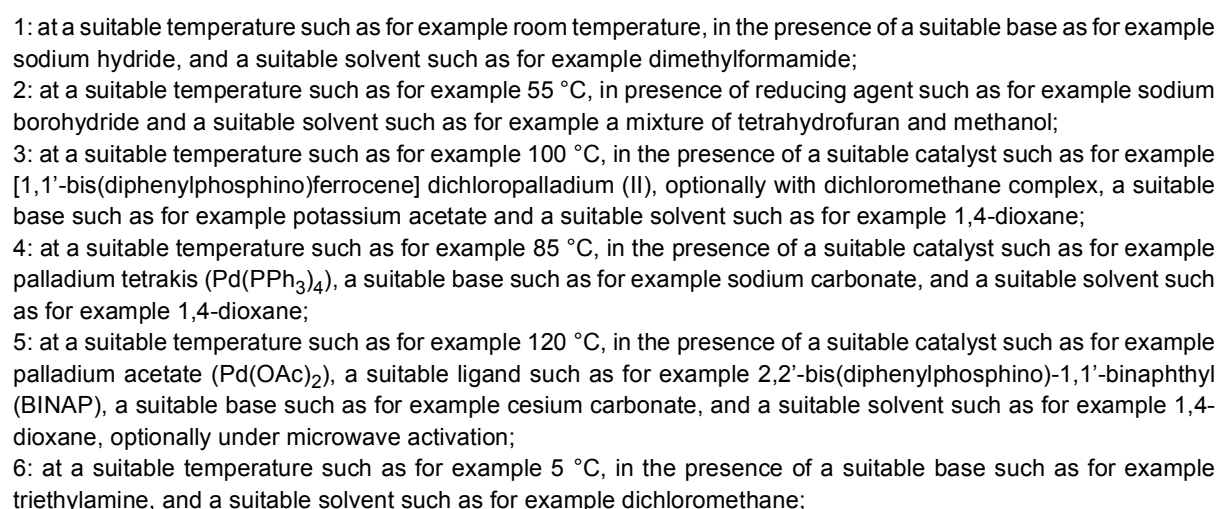
5: at a suitable temperature such as for example 100 °C, in the presence of a suitable catalyst such as for example palladium acetate (Pd(OAc)₂), a suitable ligand such as for example 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), a suitable base such as for example cesium carbonate, and a suitable 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.

Scheme 8

[0190] 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}, 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 (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.

[0191] In Scheme 8, the following reaction conditions apply:

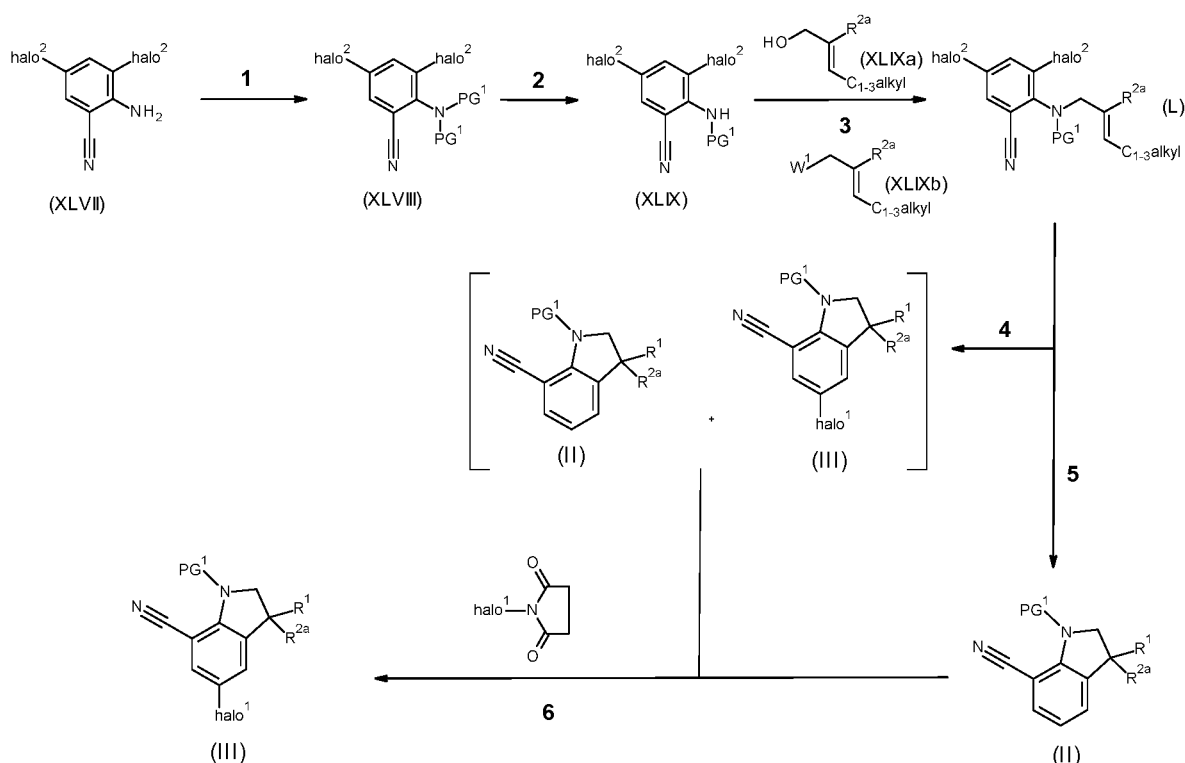


7: at a suitable temperature such as for example 80 °C, and a suitable solvent such as for example acetonitrile;
 8: at a suitable temperature such as for example 0 °C or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with 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

[0192] 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 according to the scope of the present invention.

[0193] In Scheme 9, the following reaction conditions apply:



1: at a suitable temperature such as for example 45 °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 dichloromethane;

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;

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 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]

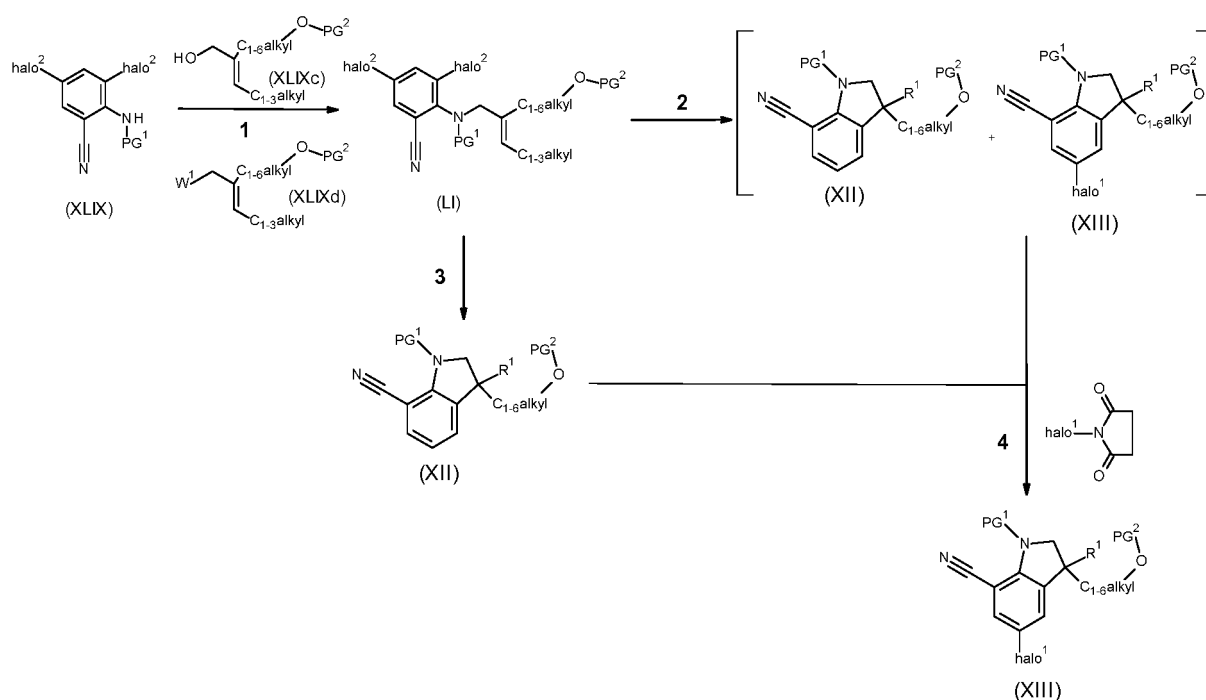
palladium, (II) chloride optionally with dichloromethane complex, and a suitable solvent such as for example dimethylformamide;

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.

Scheme 10

[0194] 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 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. All other variables in Scheme 10 are defined according to the scope of the present invention.

[0195] 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;

In case of (XLIXd), 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;

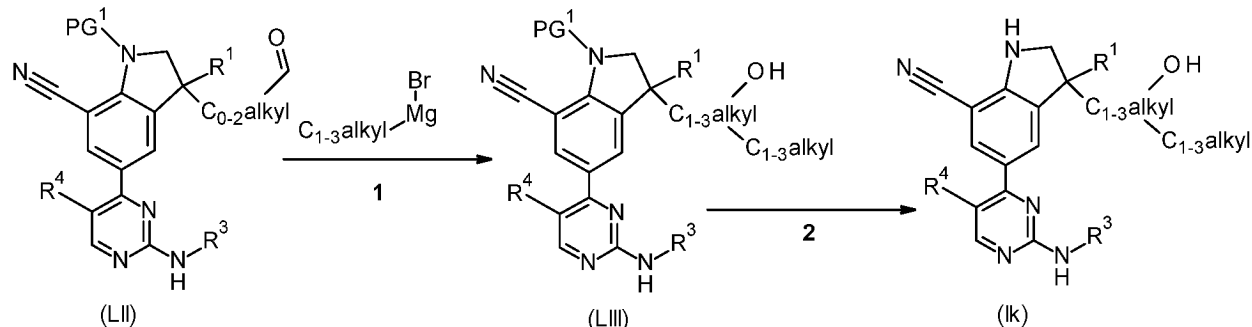
3: at a suitable temperature such as for example 60 °C, in the presence of sodium acetate, sodium formate dehydrate and tetraethylammonium chloride, a suitable catalyst such as for example [1,1'-bis(diphenylphosphino) ferrocene] palladium, (II) chloride optionally with dichloromethane complex, and a suitable solvent such as for example dimethylformamide;

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

[0196] In general, compounds of Formula (I) wherein R^2 is as shown in the scheme 11, 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 (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 according to the scope of the present invention.

[0197] In Scheme 11, the following reaction conditions apply:



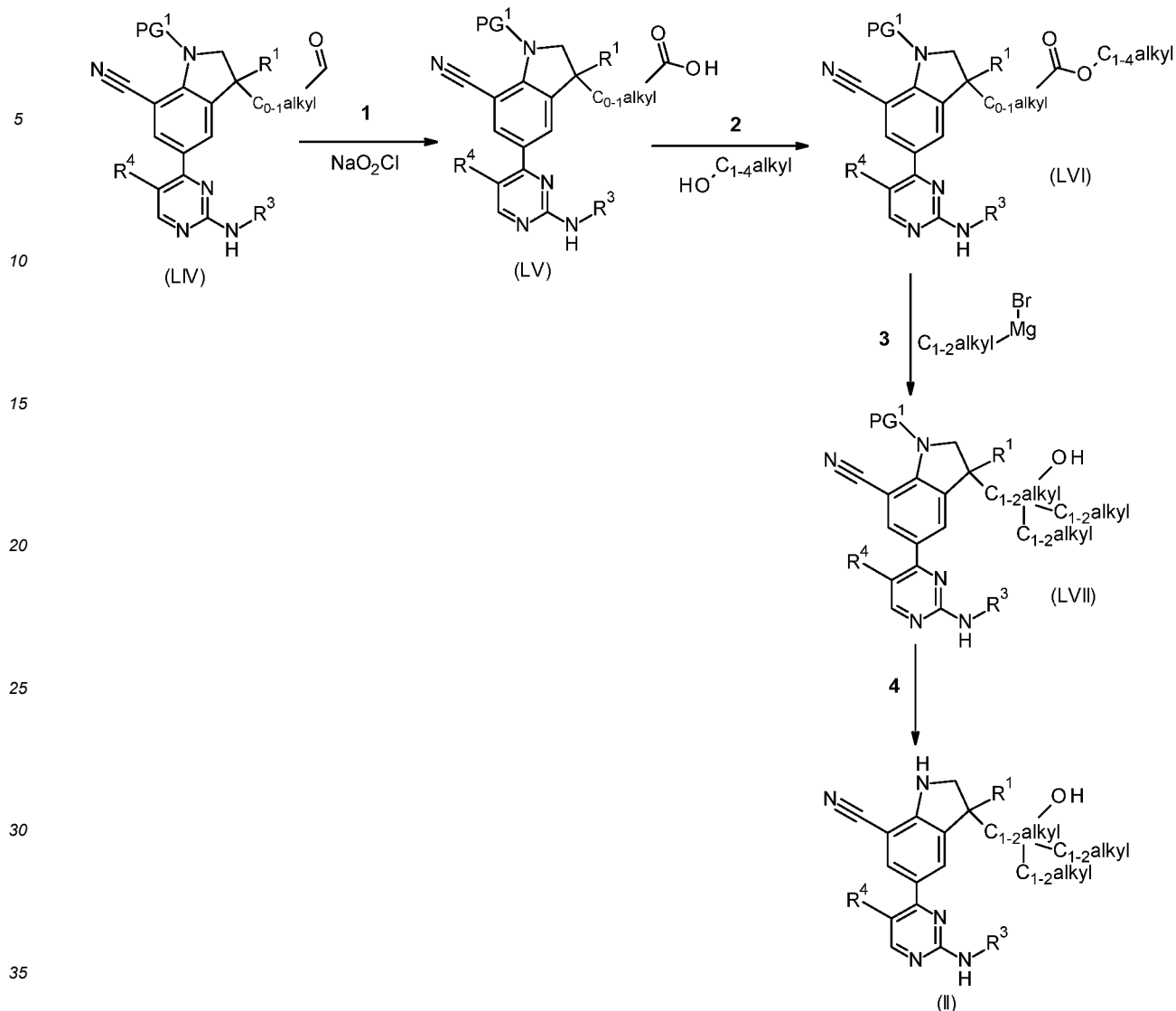
1: at a suitable temperature such as for example at room temperature, and a suitable solvent such as for example tetrahydrofuran;

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 example toluene at a suitable temperature such as for example 125°C and a suitable time such as for example 3 hours.

Scheme 12

[0198] In general, compounds of Formula (I) wherein R^2 is as shown in the scheme 12, 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 (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.

[0199] In Scheme 12, the following reaction 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;

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;

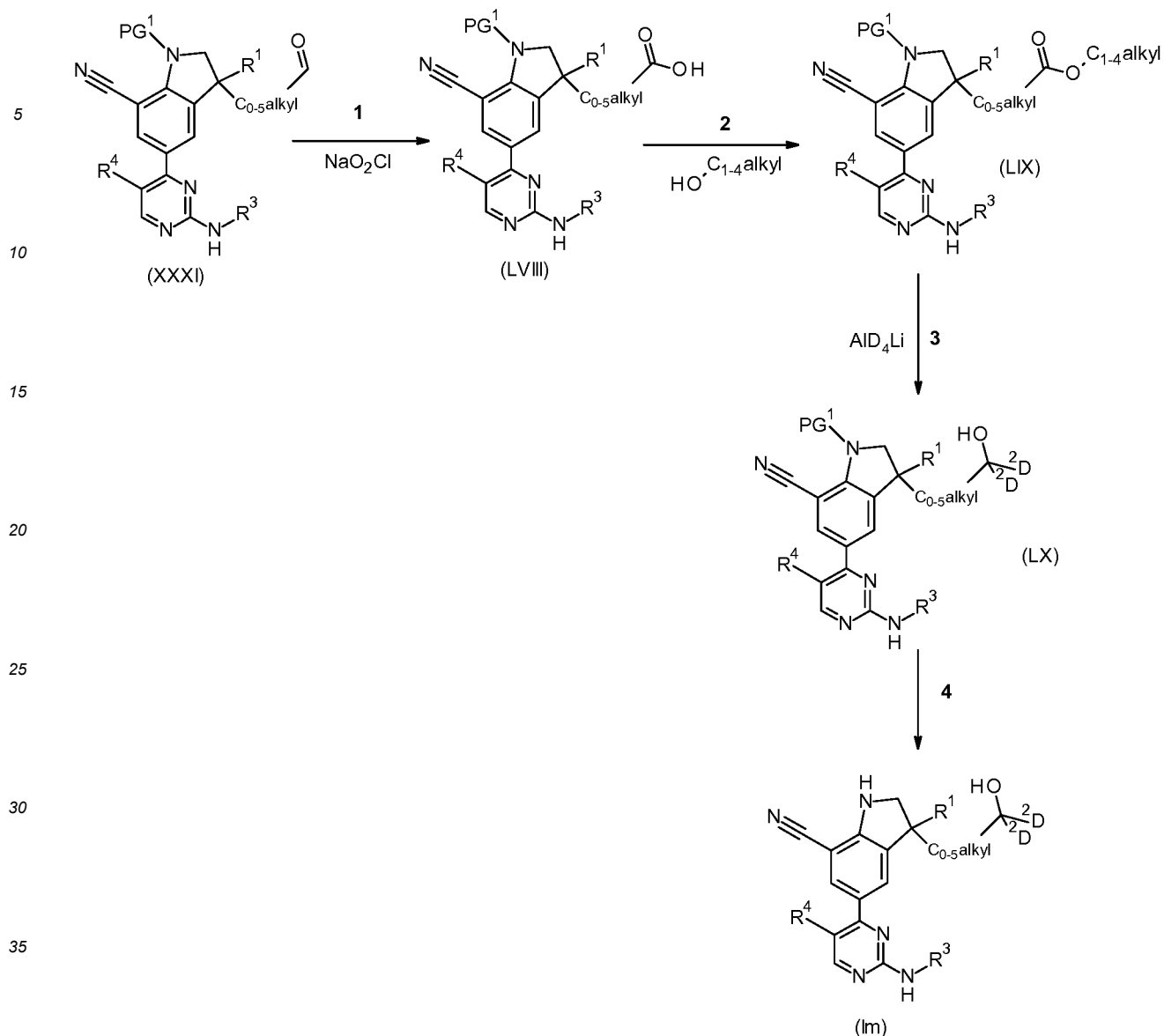
3: at a suitable temperature such as for example at room temperature, and a suitable solvent such as for example tetrahydrofuran;

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 example toluene at a suitable temperature such as for example 125°C and a suitable time such as for example 3 hours.

Scheme 13

[0200] In general, compounds of Formula (I) wherein R² is as shown in the scheme 13, 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 (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.

[0201] In Scheme 13, the following reaction 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;

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 aluminium deuteride);

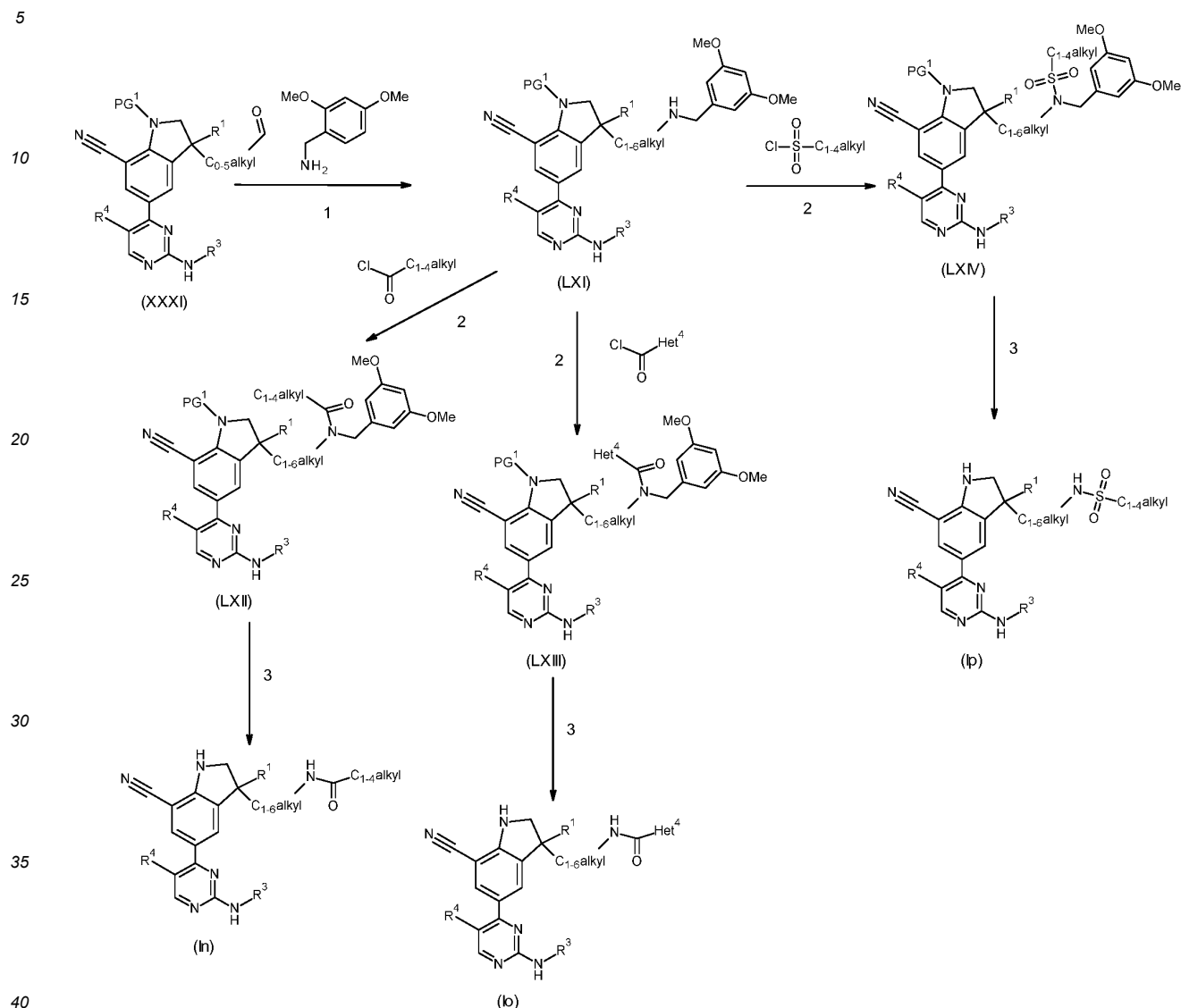
4: at a suitable temperature such as for example 0 °C or room temperature or reflux, in presence of a suitable acid such as for example trifluoroacetic acid or aqueous hydrochloric acid with a suitable solvent such as for example dichloromethane, methanol, ethyl acetate or 1,4-dioxane or alternatively 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.

Scheme 14

[0202] 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, 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 (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.

[0203] 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;

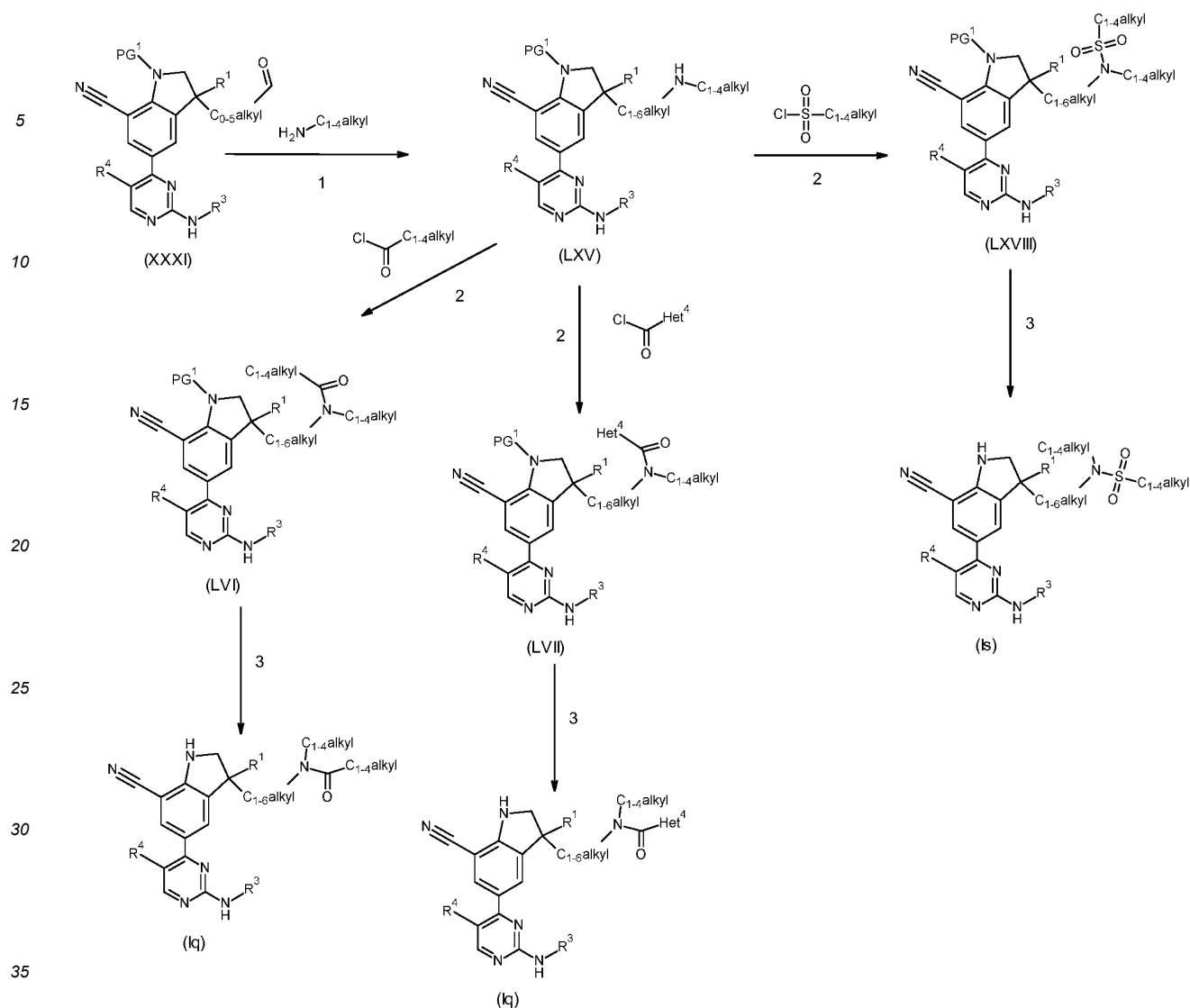
2: at a suitable temperature such as for example at room temperature, in the presence of a suitable base such as for example triethylamine, in a suitable solvent such as for example tetrahydrofuran;

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.

Scheme 15

[0204] 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)-Het⁴; -S(=O)₂-C₁₋₄alkyl, 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 (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*-(butoxycarbonyl). All other variables in Scheme 15 are defined according to the scope of the present invention.

[0205] 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;

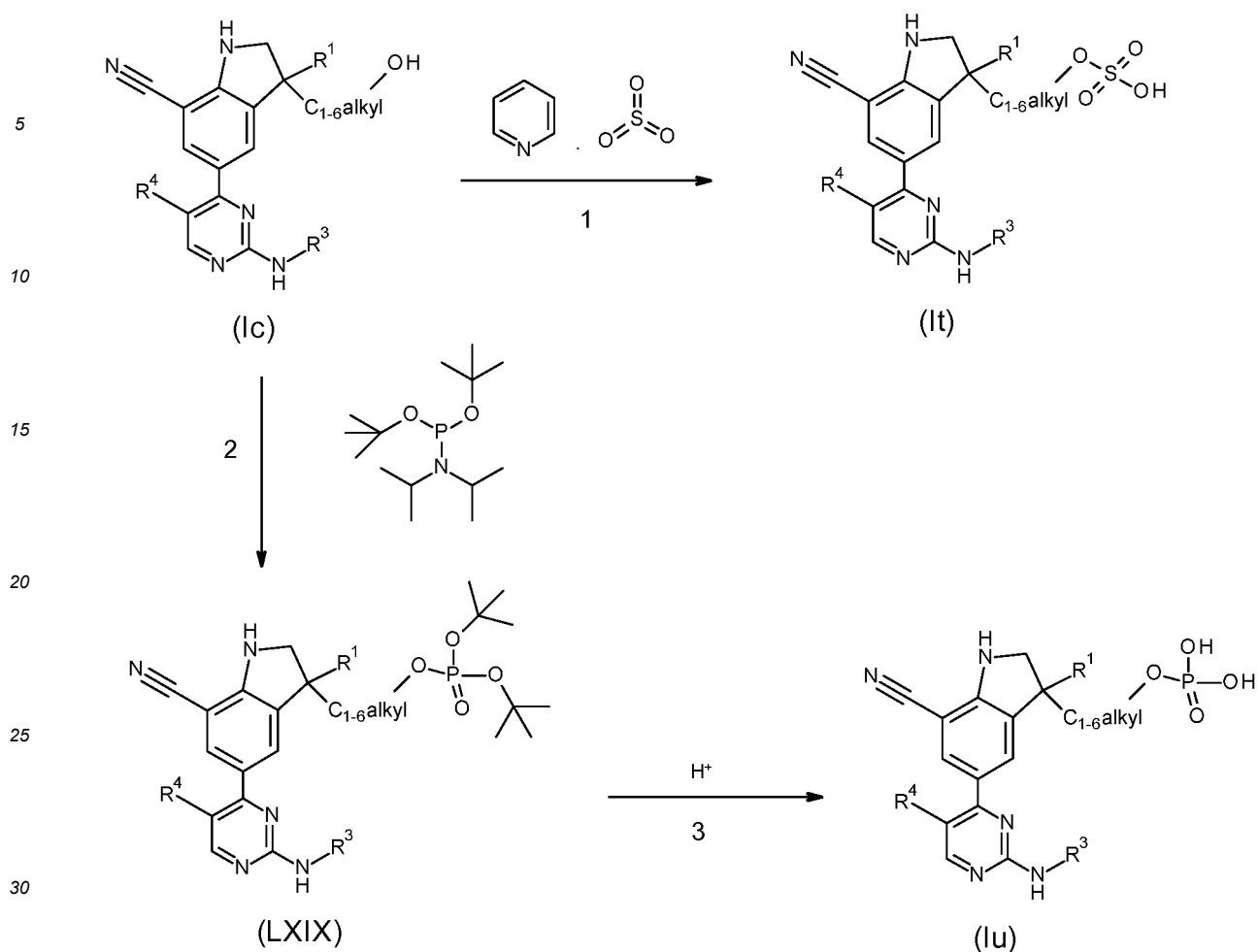
2: at a suitable temperature such as for example at room temperature, in the presence of a suitable base such as for example triethylamine, in a suitable solvent such as for example tetrahydrofuran;

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.

Scheme 16

[0206] In general, compounds of Formula (I) wherein R^2 is $\text{C}_{1-6}\text{alkyl}$ substituted with one OR^{7d} , R^{7d} being $-\text{S}(=\text{O})_2-\text{OH}$ or $-\text{P}(=\text{O})(\text{OH})_2$, 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 (It) and Formula (Iu), can be prepared according to the following reaction Scheme 16. All other variables in Scheme 16 are defined according to the scope of the present invention.

[0207] 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 hydroxide;

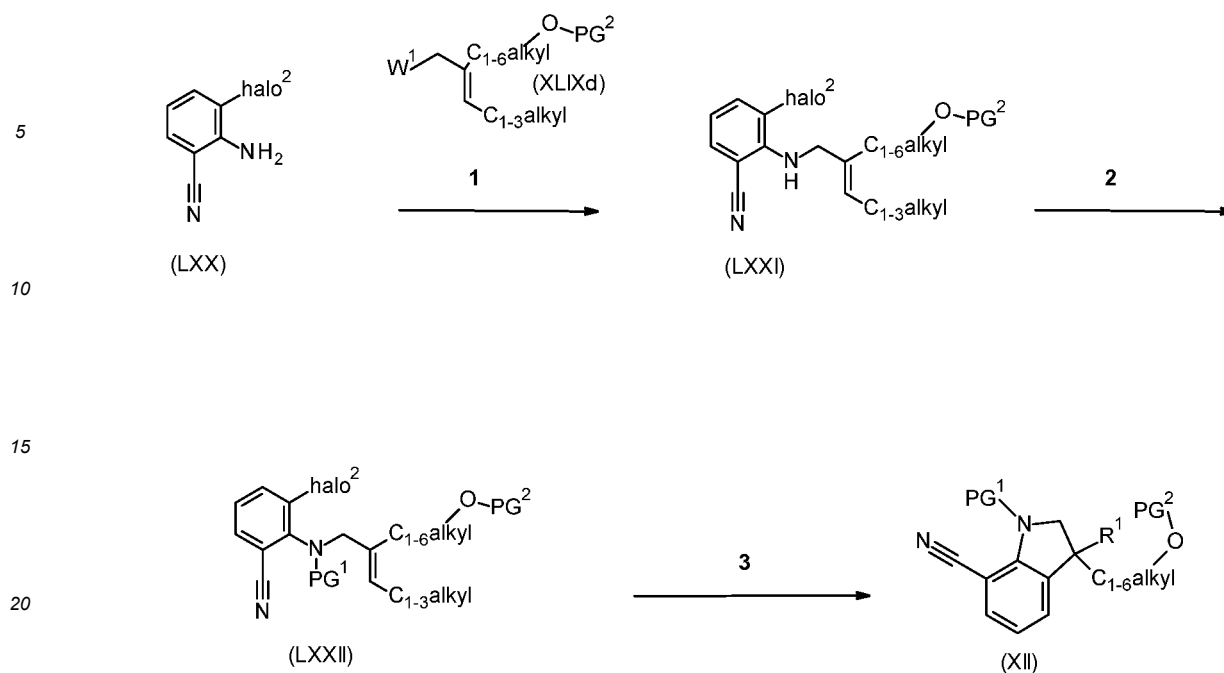
2: in the presence of a suitable reagent such as for example tetrazole, in the presence of a suitable oxidizing agent such as for example meta-chloroperoxybenzoic acid, in a suitable solvent such as for example acetonitrile;

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.

Scheme 17

[0208] In general, intermediates of Formula (XII) wherein all the variables are as defined according to the scope of the present invention can be prepared according to the following reaction Scheme 17.

[0209] 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;

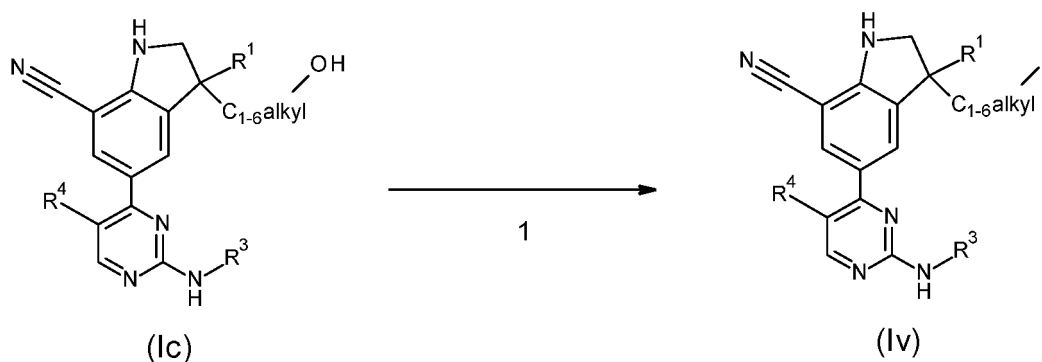
2: at a suitable temperature ranged between 65 and 70 °C, in the presence of a suitable reagent such as for example di-*tert*-butyl dicarbonate, in the presence of a suitable catalyst such as for example 4-dimethylaminopyridine (DMAP), and a suitable solvent such as for example tetrahydrofuran;

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.

Scheme 18

[0210] In general, compounds of Formula (I) wherein R² is C₁₋₆alkyl substituted with one R⁵, R⁵ being a 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 according to the following reaction Scheme 18. All other variables in Scheme 18 are defined according to the scope of the present invention.

[0211] In Scheme 18, the following reaction conditions apply:

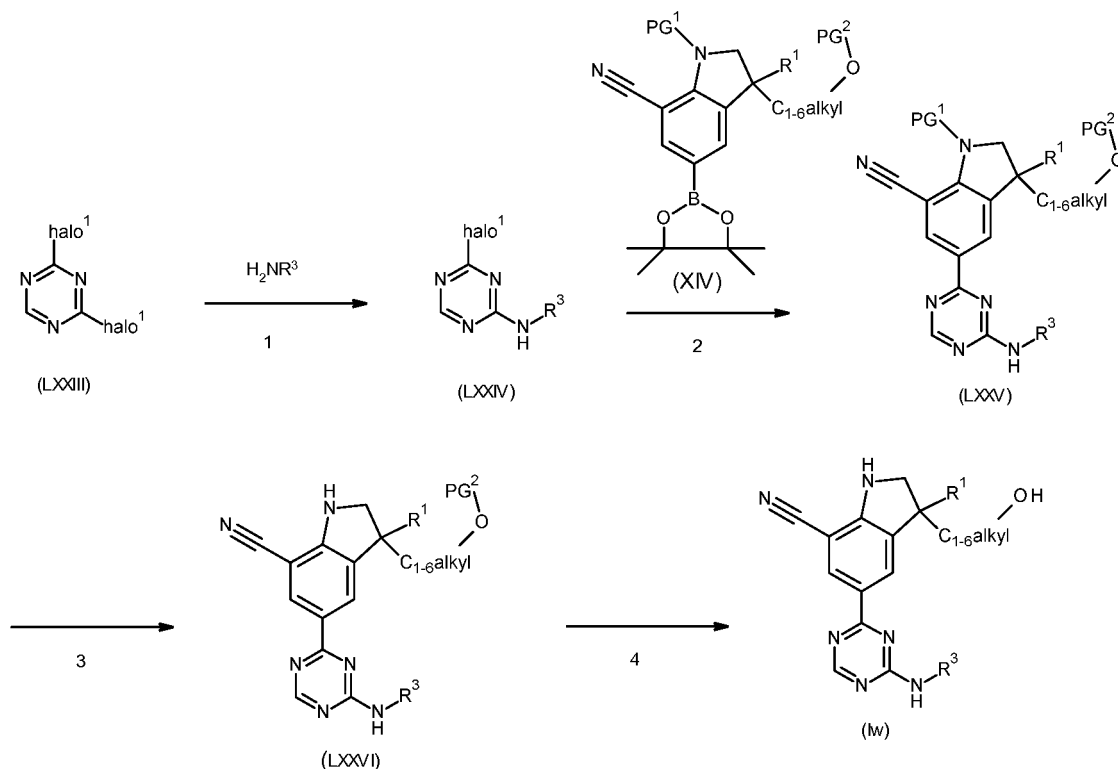


1: in the presence of a suitable fluorinating reagent such as for example diethylaminosulfur trifluoride, a suitable solvent such as for example dichloromethane, at a suitable temperature such as for example room temperature.

Scheme 19

[0212] 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 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.

[0213] In Scheme 19, the following reaction conditions apply:



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;

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 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;

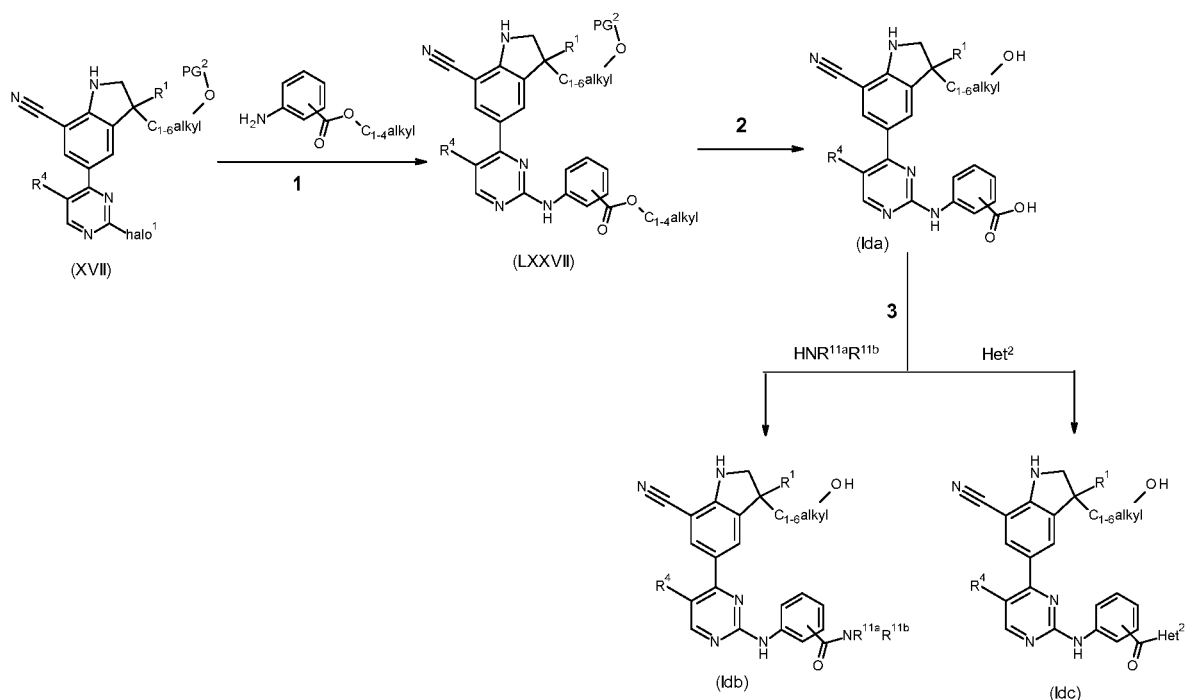
4: at a suitable temperature such as for example room temperature, in presence of a suitable desilylating agent such as for example *tetra-n*-butylammonium fluoride and a suitable solvent such as for example 2-methyltetrahydrofuran or tetrahydrofuran.

Scheme 20

[0214] In general, compounds of Formula (I) wherein R² is R^{2b} being C₁₋₆alkyl substituted with one OH, R³ is phenyl 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.

[0215] 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;

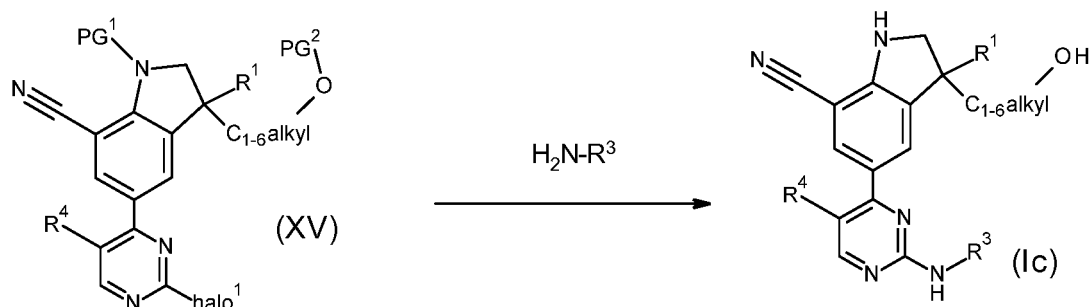
2: at a suitable temperature such as for example 60 °C, in presence of a suitable base such as for example lithium hydroxide, and a suitable solvent such as for example a mixture of tetrahydrofuran and water;

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 or dichloromethane.

Scheme 21

[0216] In general, compounds of Formula (I) wherein R² is R^{2b} being C₁₋₆alkyl substituted with one OH, 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 (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.

[0217] 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.

[0218] 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, formylation and coupling procedures.

[0219] 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 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.

[0220] 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-fluorenylmethylenecarbonyl (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

[0221] 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.

[0222] 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; keratocanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

[0223] 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 NF κ B signalling pathway (eg in NIK (MAP3K14), TRAF3, TRAF2, BIRC2 or BIRC3 genes).

[0224] 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.

[0225] 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.

[0226] 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.

[0227] 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.

[0228] 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.

[0229] 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.

[0230] 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.

[0231] 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.

[0232] 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.

[0233] It is disclosed 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.

[0234] 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 alia*, depending on the type of disease, the concentration of the compound in the therapeutic formulation, and the condition of the patient. 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.

[0235] Those of skill in the treatment of such diseases could determine the effective therapeutic daily amount from the test results presented hereinafter. An effective therapeutic daily amount would be from about 0.005 mg/kg to 50 mg/kg, in particular 0.01 mg/kg to 50 mg/kg body weight, more in particular from 0.01 mg/kg to 25 mg/kg body weight, preferably from about 0.01 mg/kg to about 15 mg/kg, more preferably from about 0.01 mg/kg to about 10 mg/kg, even more preferably from about 0.01 mg/kg to about 1 mg/kg, most preferably from about 0.05 mg/kg to about 1 mg/kg body weight. 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 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 administration. As described herein below, suitable pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

[0236] 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 pharmaceutically acceptable addition salt, or a solvate thereof, and a pharmaceutically acceptable carrier or diluent.

[0237] 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.

[0238] 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.

[0239] 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.

[0240] 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.

[0241] 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.

[0242] 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.

[0243] 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:

- 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;

- topoisomerase II inhibitors such as anti-tumour epipodophyllotoxins or podophyllotoxin derivatives for example etoposide, etoposide phosphate or teniposide;
- anti-tumour vinca alkaloids for example vinblastine, vincristine or vinorelbine;
- anti-tumour nucleoside derivatives for example 5-fluorouracil, leucovorin, gemcitabine, gemcitabine hcl, capecitabine, cladribine, fludarabine, nelarabine;
- alkylating agents such as nitrogen mustard or nitrosourea for example cyclophosphamide, chlorambucil, carmustine, thiotepa, mephalan (melphalan), lomustine, altretamine, busulfan, dacarbazine, estramustine, ifosfamide optionally in combination with mesna, pipobroman, procarbazine, streptozocin, temozolomide, uracil;
- anti-tumour anthracycline derivatives for example daunorubicin, doxorubicin optionally in combination with dexrazoxane, doxil, idarubicin, mitoxantrone, epirubicin, epirubicin hcl, valrubicin;
- molecules that target the IGF-1 receptor for example picropodophilin;
- tetracarcin derivatives for example tetrocarcin A;
- glucocorticoids for example prednisone;
- antibodies for example trastuzumab (HER2 antibody), rituximab (CD20 antibody), gemtuzumab, gemtuzumab ozogamicin, cetuximab, pertuzumab, bevacizumab, alemtuzumab, eculizumab, ibritumomab tiuxetan, nofetumomab, panitumumab, tositumomab, CNTO 328;
- estrogen receptor antagonists or selective estrogen receptor modulators or inhibitors of estrogen synthesis for example tamoxifen, fulvestrant, toremifene, droloxifene, faslodex, raloxifene or letrozole;
- aromatase inhibitors such as exemestane, anastrozole, letrozole, testolactone and vorozole;
- differentiating agents such as retinoids, vitamin D or retinoic acid and retinoic acid metabolism blocking agents (RAMBA) for example accutane;
- DNA methyl transferase inhibitors for example azacytidine or decitabine;
- antifolates for example premetrexed disodium;
- antibiotics for example antinomycin D, bleomycin, mitomycin C, dactinomycin, carminomycin, daunomycin, levamisole, plicamycin, mithramycin;
- antimetabolites for example clofarabine, aminopterin, cytosine arabinoside or methotrexate, 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;
- kinase inhibitors (e.g. EGFR (epithelial growth factor receptor) inhibitors, MTKI (multi target kinase inhibitors), mTOR inhibitors) for example flavoperidol, imatinib mesylate, erlotinib, gefitinib, dasatinib, lapatinib, lapatinib ditosylate, sorafenib, sunitinib, sunitinib maleate, temsirolimus;
- farnesyltransferase inhibitors for example tipifarnib;
- histone deacetylase (HDAC) inhibitors for example sodium butyrate, suberoylanilide hydroxamic acid (SAHA), depsipeptide (FR 901228), NVP-LAQ824, R306465, quisinostat, trichostatin A, vorinostat;
- Inhibitors of the ubiquitin-proteasome pathway for example PS-341, Velcade (MLN-341) or bortezomib;
- Yondelis;
- Telomerase inhibitors for example telomestatin;
- Matrix metalloproteinase inhibitors for example batimastat, marimastat, prinostat or metastat;
- Recombinant interleukins for example aldesleukin, denileukin diftiox, interferon alfa 2a, interferon alfa 2b, peginterferon alfa 2b;
- MAPK inhibitors;
- Retinoids for example alitretinoin, bexarotene, tretinoin;
- Arsenic trioxide;
- Asparaginase;
- Steroids for example dromostanolone propionate, megestrol acetate, nandrolone (decanoate, phenpropionate), dexamethasone;
- Gonadotropin releasing hormone agonists or antagonists for example abarelix, goserelin acetate, histrelin acetate, leuprolide acetate;
- Thalidomide, lenalidomide;
- Mercaptopurine, mitotane, pamidronate, pegademase, pegaspargase, rasburicase;
- BH3 mimetics for example ABT-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; oprelvekin; zoledronate, zoledronic acid; fentanyl; bisphosphonate; palifermin;
- a steroidal cytochrome P450 17alpha-hydroxylase-17,20-lyase inhibitor (CYP17), e.g. abiraterone, abiraterone ac-

etate.

[0244] The one or more other medicinal agents and the compound according to the present invention may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two or more compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular other medicinal agent and compound of the present invention being administered, their route of administration, the particular tumour being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

[0245] The weight ratio of the compound according to the present invention and the one or more other anticancer agent(s) when given as a combination may be determined by the person skilled in the art. Said ratio and the exact dosage and frequency of administration depends on the particular compound according to the invention and the other anticancer agent(s) used, the particular condition being treated, the severity of the condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. A particular weight ratio for the present compound of Formula (I) and another anticancer agent may range from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

[0246] 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.

[0247] 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.

[0248] 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.

[0249] 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.

[0250] 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.

[0251] 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.

[0252] The alkylating agents such as nitrogen mustard or nitrosourea is advantageously administered in a dosage of 100 to 500 mg per square meter (mg/m²) of body surface area, for example 120 to 200 mg/m², particularly for cyclophosphamide in a dosage of about 100 to 500 mg/m², for chlorambucil in a dosage of about 0.1 to 0.2 mg/kg, for carmustine in a dosage of about 150 to 200 mg/m², and for lomustine in a dosage of about 100 to 150 mg/m² per course of treatment.

[0253] 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.

[0254] 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 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 about 25 mg once a day.

[0255] 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 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.

[0256] The following examples further illustrate the present invention.

Examples

[0257] Several methods for preparing the compounds of this invention are illustrated in the following examples. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.

[0258] Hereinafter, the terms : 'ACN' means acetonitrile, 'AcOH' means acetic acid, 'AcCl' means acetyl chloride, 'Ar' means argon, 'BINAP' means 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 'BOC' or 'Boc' means tert-butyloxycarbonyl, 'Boc₂O' means di-tert-butyl dicarbonate, 'celite®' means diatomaceous earth, 'DCM' means dichloromethane, 'DIEA' or 'DIPEA' means diisopropylethylamine, 'DiPE' means diisopropylether, 'h' means hours(s), 'min' means minute(s), 'DMAP' means dimethylaminopyridine, 'DMF' means dimethylformamide, 'Et₂O' means diethylether, 'EtOAc' or 'AcOEt' means ethyl acetate, 'HPLC' means High-performance Liquid Chromatography, 'IPrNH₂' means isopropylamine, 'iPrOH' means isopropyl alcohol, 'KHMDs' means potassium bis(trimethylsilyl)amide, 'HATU' means 1-[bis(dimethylamino)methylene]-1H-[1,2,3]triazolo[4,5-b]pyridin-1-ium 3-oxide hexafluorophosphate, 'LC/MS' means Liquid Chromatography/Mass Spectrometry, 'LiHMDS' means Lithium bis(trimethylsilyl)amide, 'Me' means methyl, 'Me-THF' means 2-methyltetrahydrofuran, 'MeOH' means methanol, 'NBS' means N-bromosuccinimide, 'NCS' means N-chlorosuccinimide, 'NMR' means Nuclear Magnetic Resonance, 'Pd/C 10%' means palladium on carbon loading 10%, 'Pd(OAc)₂' means palladium (II) acetate, 'Pd(PPh₃)₂Cl₂' means bis(triphenylphosphine)palladium(II) chloride 'Pd(PPh₃)₄' means tetrakis(triphenylphosphine)palladium (0), 'Pd(dppf)Cl₂' or 'PdCl₂dppf' means [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), 'Pd(t-Bu₃P)₂' means bis(tri-tert-butyl-phosphine) palladium (0), 'rt' means room temperature, 'SFC' means supercritical fluid chromatography, 'ee' means enantiomeric excess, 'TBAF' means tetrabutylammonium fluoride, 'tBDMS', 'tBDMS' or 'SMDBT' means tertbutyldimethylsilyl, 'TEA' or 'Et₃N' means triethylamine, 'TFA' means trifluoroacetic acid, 'THF' means tetrahydrofuran, 'CV' means column volumes, 'Quant.' means quantitative, 'o/n' means overnight, '@' means at, 'eq.' or 'equiv.' means equivalent(s), 'Psi' means Pounds per Square Inch (pressure), 'M.P.', 'MP' or 'm.p.' means melting point, 'OR' means optical rotation, 'DSC' means Differential Scanning Calorimetry.

[0259] When a stereocenter is indicated with 'RS' this means that a racemic mixture was obtained. Compounds like compound 39 and compound 124 which have two stereocenters indicated with 'RS' were obtained as a mixture of diastereoisomers.

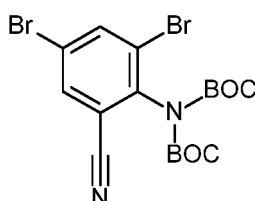
[0260] It is well known to one skilled in the art that protecting groups such as TBDMS can routinely be removed with TBAF in a variety of solvents such as for example THF. Similarly, conditions for removal of BOC protecting groups are well known to one skilled in the art, commonly including for example 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 MgSO₄, 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

Example A1

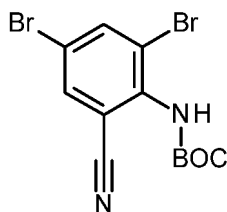
[0261] Preparation of intermediate 1:



[0262] 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), Boc₂O (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 NaHCO₃ (2 x 1 L) and brine (2 x 1 L), dried over MgSO₄, filtered and concentrated under vacuum to give 323 g of intermediate 1 (56% yield, yellow solid, 86% purity evaluated by LC/MS).

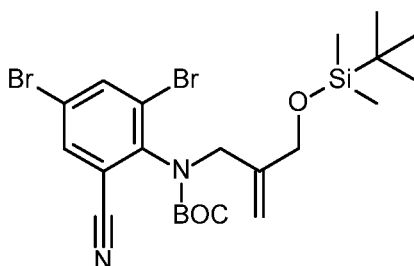
The product was used in the next step without any further purification.

[0263] Preparation of intermediate 2:



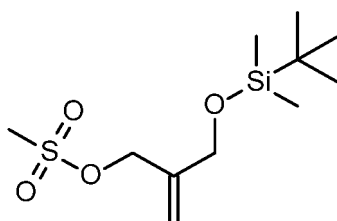
[0264] A mixture of intermediate 1 (620.00 g, 1.30 mol) and K_2CO_3 (539.02 g, 3.90 mol) in MeOH (6 L) was stirred at 65 °C for 3 h. The reaction mixture was cooled to 25 °C filtered and concentrated under vacuum. Then, the residue was dissolved in EtOAc (4 L) and the organic layer was washed with brine (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.

[0265] Preparation of intermediate 3:



[0266] 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 N_2 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 $MgSO_4$, 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 (SiO_2 , 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).

[0267] Preparation of intermediate 3a:



[0268] Triethylamine (196.3 mL; 1.408 mol) was added to a solution of 2-(((*tert*-butyldimethyl-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 $NaHCO_3$ (100 ml) and extracted with DCM (500ml*2). The organic layer was dried over $MgSO_4$, 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.

Alternative preparation of intermediate 3a:

[0269] A solution of 1,3-Hydroxy-2-methylenepropene (100 g) in dry THF (200 mL) was added dropwise at 0 °C to a

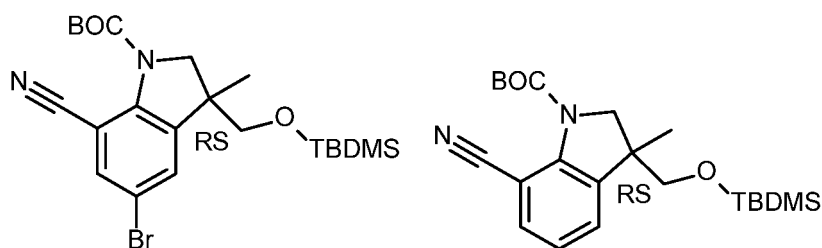
suspension of sodium hydride (0.95 eq.) in dry THF (600 mL). After 30 min a solution of *tert*-butyldimethylsilylchloride (0.95 eq.) in dry THF (200 mL) was added dropwise to the mixture. After approximately 18 hours at 0-5 °C the reaction was complete by GC and water (500 mL) was added slowly keeping 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).

Alternative preparation of intermediate 3:

[0270] 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.

Preparation of intermediate 4 and intermediate 4':

[0271]

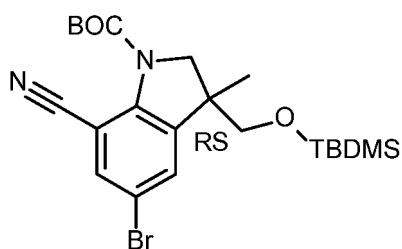


Intermediate 4

Intermediate 4'

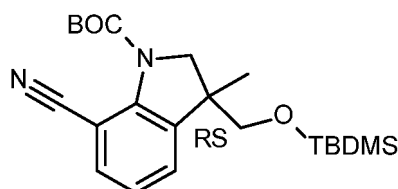
[0272] A suspension of intermediate 3 (120.00 g, 214.14 mmol), sodium acetate (45.67 g, 556.76 mmol), sodium formate (37.86 g, 556.76 mmol), Pd(OAc)₂ (4.81 g, 21.41 mmol) and tetraethylammonium chloride (44.35 g, 267.67 mmol) in DMF (1.26 L) was degassed under vacuum, purged with Ar three times, and 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 5 and 5'. 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' containing 38% of intermediate 4 (evaluated by LC/MS).

[0273] Alternative preparation of intermediate 4:



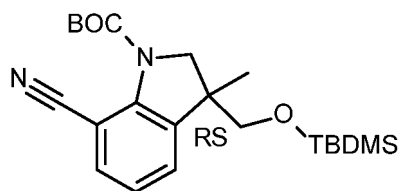
[0274] To a mixture of intermediates 4 and 4' in CH₃CN (1.60 L), 1-bromopyrrolidine-2,5-dione (212.20 g, 1.19 mol) was added and stirred at 40 °C for 16 h. The solvent was removed by evaporation under reduced pressure. The residue was dissolved in ethyl acetate (2 L), washed successively with NaHCO₃ (2 x 1L) and brine (2 x 1L), 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 110.00 g of intermediate 4 (56% yield, yellow oil, 97% purity evaluated by LC/MS).

[0275] Alternative preparation A of intermediate 4':



[0276] 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), *tetra-N*-butylammonium chloride (164.60 g, 592.20 mmol) was added 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).

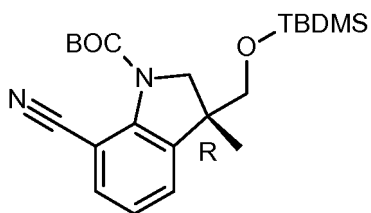
[0277] Alternative preparation B of intermediate 4':



[0278] Intermediate 550 (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

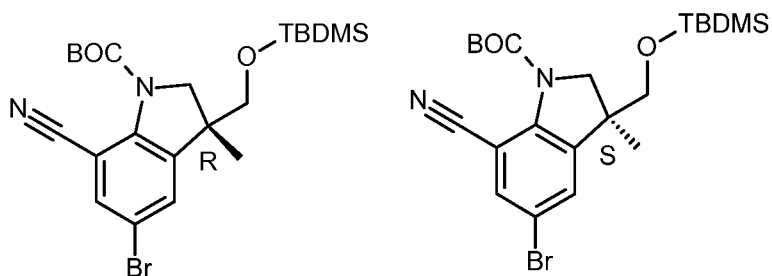
[0279]



Intermediate 4'R

[0280] Intermediates 4'R was obtained from a chiral chromatography separation of intermediate 4' (column CHIRAL-PAK IC 5cm *25 cm; mobile phase: hexane/EtOH:80/20; Flow rate: 60.0mL/min; Wavelength: UV 254 nm; Temperature: 35°C).

Preparation of intermediate 4R and intermediate 4S:

[0281]

Intermediate 4R

intermediate 4S

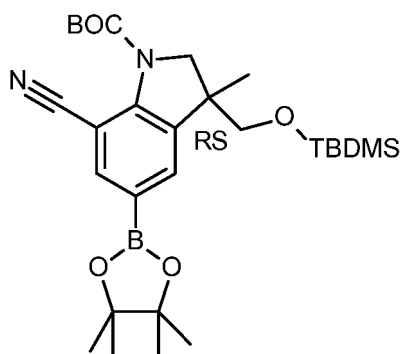
[0282] Intermediate 4 (500 g) was purified via Normal Phase Chiral separation (Stationary phase: Daicel Chiralpak IC 2000 gram 10 microhm, mobile phase: heptane/EtOH, Isocratic 80% heptane, 20% EtOH). The fractions containing the products were mixed and concentrated to afford 266 g of intermediate 4R (53% yield, ee> 98 %) and 225 g of intermediate 4S (45% yield, ee > 98 %).

[0283] Alternatively, intermediate 4 (10 g) was purified by chiral SFC (Stationary phase: CHIRALPAK IC 5 μ m 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%) .

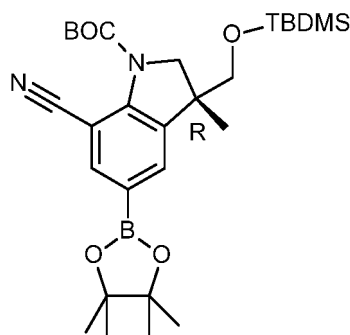
Example A2

[0284] Preparation of intermediate 5:



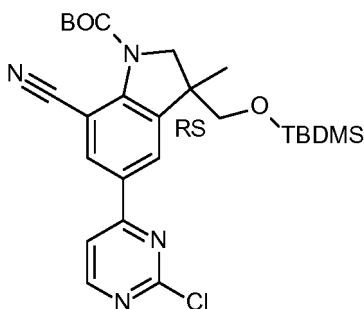
[0285] To a solution of intermediate 4 (127.00 g, 234.70 mmol) in 1,4-dioxane (1.2 L), bis(pinacolato)diboron (74.50 g, 293.40 mmol) and potassium acetate (69.11 g, 704.24 mmol) were added. Then, [1,1'-bis(diphenylphosphino) ferrocene] palladium, (II) chloride (8.59 g, 11.74 mmol) was added and stirred 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, 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.

[0286] Preparation of intermediate 5R:



[0287] 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), 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.

[0288] Preparation of intermediate 6:



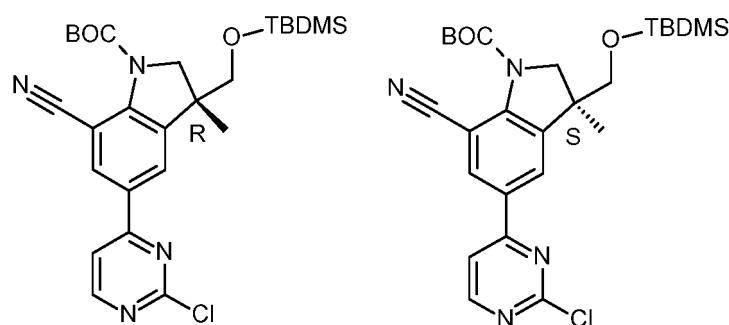
[0289] A solution of intermediate 5 (160.00 g, 302.70 mmol) in 1,4-dioxane (1.2 L) was treated with a solution of

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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 the mixture was 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).

Preparation of intermediate 6R and intermediate 6S:

[0290]



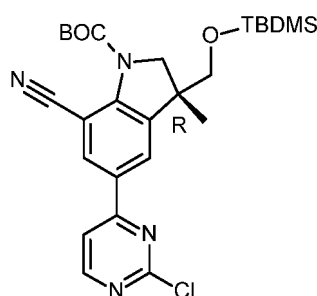
intermediate 6R

intermediate 6S

[0291] 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 containing small impurities (48% yield) and 25.1 g of intermediate 6S (48% yield).

[0292] Several combined batches of Intermediate 6R (50.10 g in total) were 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.

[0293] Alternative preparation of intermediate 6R:

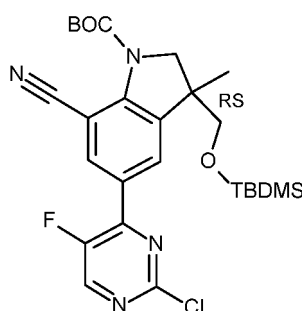


[0294] A solution of intermediate 5R (25.00 g, 41.90 mmol) in 1,4-dioxane (1.2 L) was treated with a solution of NaHCO₃ (10.50 g, 125.72 mmol) in water (80 mL). Then, 2,4-dichloropyrimidine (9.36 g, 62.86 mmol) and Pd(PPh₃)₄ (2.42 g, 2.09 mmol) were added under N₂. The reaction mixture was stirred at 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).

Alternative preparation of intermediate 6R:

[0295] 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.

[0296] Preparation of intermediate 6a:



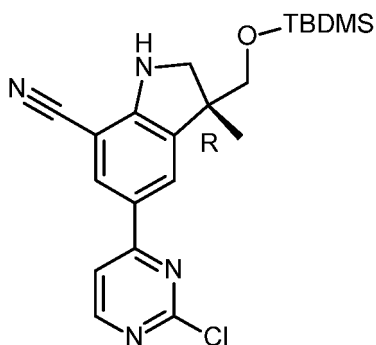
[0297] To a solution of intermediate 5 (3.89 g, 4.92 mmol), 5-fluoro-2,4-dichloropyrimidine (1.07 g, 6.40 mmol) and Cs₂CO₃ (4.81 g, 14.80 mmol) in 1,4-dioxane (25 mL) and distilled water (2.5 mL), Pd(PPh₃)₄ (0.28 g, 0.25 mmol) was added and the reaction mixture was heated overnight at 95 °C. The mixture was poured into ice and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent was evaporated. The residue was purified by column chromatography on silica gel (240 g, 15-40 μm, mobile phase: heptane/EtOAc, gradient from 1:0 to 0:1). The pure fractions were mixed and the solvent was evaporated to give 1.92 g of intermediate 6a (73% yield).

[0298] The intermediates in the Table below were prepared by using an analogous starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 6aR	From intermediate 5R and 5-fluoro-2,4-dichloropyrimidine	1820	83

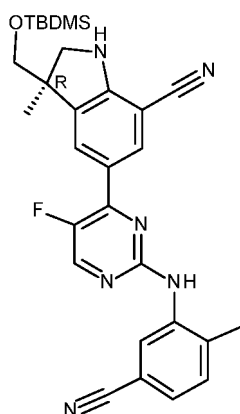
Example A3

[0299] Preparation of intermediate 7R:



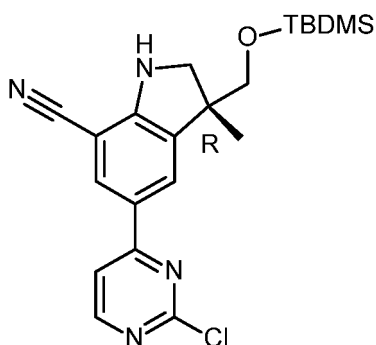
[0300] In a three neck round bottom flask, SiO_2 (35-70 μm) (200 g) was added to a solution of intermediate 6R (45.00 g, 87.36 mmol) in toluene (640 mL) at rt. The reaction mixture was reflux (bath temperature 125 $^\circ\text{C}$) for 6 h under mechanical agitation. Then, SiO_2 (35-70 μm) was filtered off, washed successively with THF and EtOAc, and the filtrate was evaporated to dryness to give 37.2 g of crude intermediate 7R which was directly engaged in the next steps.

[0301] Preparation of intermediate 392:



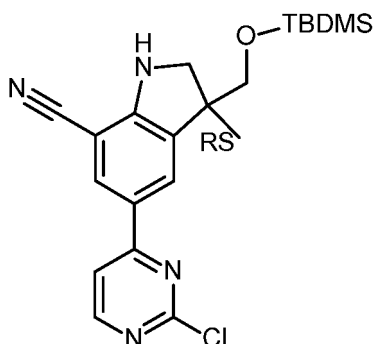
[0302] Intermediate 392 was prepared by using an analogous reaction protocol as the procedure described above to get intermediate 7R, but starting from intermediate 391 (310 mg; 98%).

[0303] Alternative preparation of intermediate 7R:



[0304] TFA (135 mL, 1.76 mol) was added dropwise at -10 $^\circ\text{C}$ (over 50 min) to a solution of intermediate 6R (20.00 g, 38.82 mmol) in DCM (550 mL). The reaction mixture was stirred below 0 $^\circ\text{C}$ for 15 min more, then poured in a mixture of crushed ice and a saturated aqueous solution of K_2CO_3 . After extraction with DCM (twice), the organic layers were combined, washed with an aqueous solution of K_2CO_3 , dried over MgSO_4 and evaporated to dryness. The residue (17.40 g) was purified by chromatography on silica gel (irregular SiOH , 80 g, mobile phase: $\text{NH}_4\text{OH}/\text{MeOH}/\text{DCM}$, gradient from 0% NH_4OH , 0% MeOH, 100% DCM to 0.2% NH_4OH , 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).

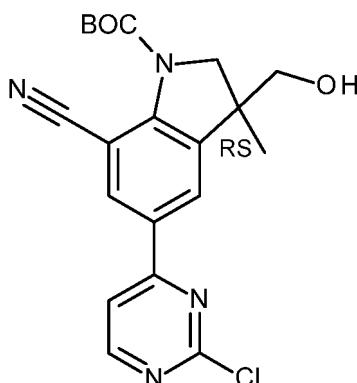
[0305] Preparation of intermediate 7:



[0306] 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 stirred at 0-5 °C for 1 h, then 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 a 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).

Example A4

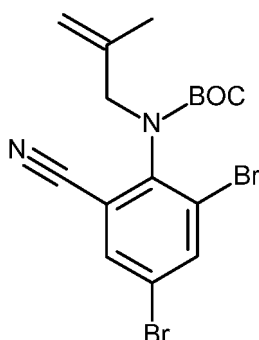
[0307] Preparation of intermediate 150:



[0308] A solution of intermediate 6 (500.00 mg, 0.97 mmol) in THF (5.71 mL, 70.21 mmol) 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 then brine, dried over MgSO₄ and evaporated in vacuo. The residue (483 mg) was purified by column 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 150 (92% yield).

Example A5

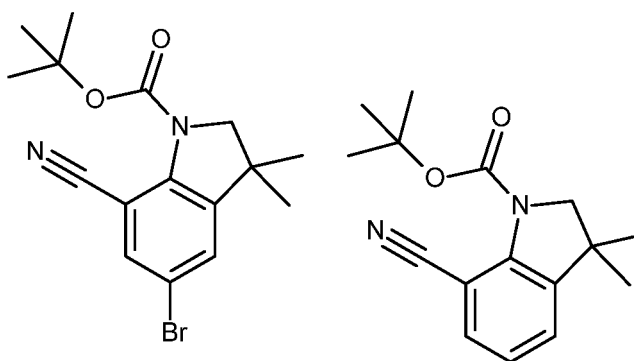
[0309] Preparation of intermediate 271:



[0310] 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 271 (94% yield).

Preparation of intermediate 272 and intermediate 272':

[0311]

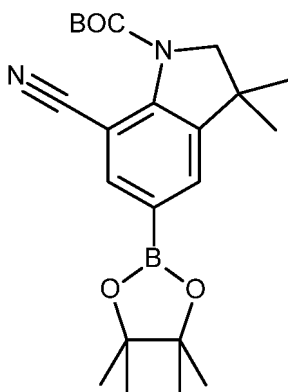


intermediate 272

intermediate 272'

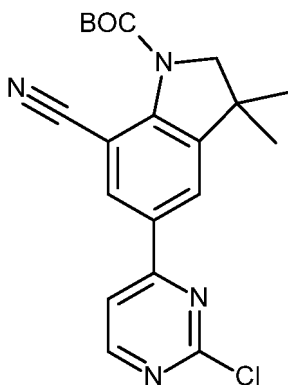
[0312] A mixture of intermediate 271 (10.80 g, 25.11 mmol), sodium acetate (5.35 g, 65.28 mmol), sodium formate (4.44 g, 65.28 mmol) and tetraethylammonium chloride (5.20 g, 31.38 mmol) in DMF (100 mL) was de-gassed by sonication for 10 min under a stream of Ar. Pd(OAc)₂ (563.00 mg, 2.51 mmol) was added 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, filtered and evaporated to dryness. The residue (8.3 g, mixture of intermediates 272 and 272') 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 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 272 (45% yield).

[0313] Preparation of intermediate 273:



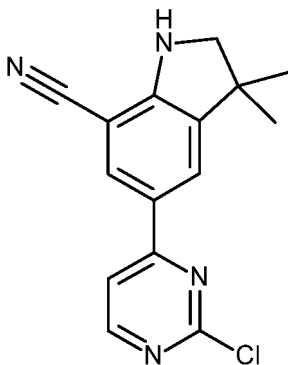
[0314] [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (243.00 mg, 0.30 mmol) was added to a solution of intermediate 272 (2.09 g, 5.95 mmol), bis(pinacolato)diboron (1.90 g, 7.44 mmol) and potassium acetate (1.75 g, 17.85 mmol) in 1,4-dioxane (45 mL) and the 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 273 (78% yield).

[0315] Preparation of intermediate 274:



[0316] A degassed suspension of intermediate 273 (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 274 (86% yield, 85% purity based on LC/MS).

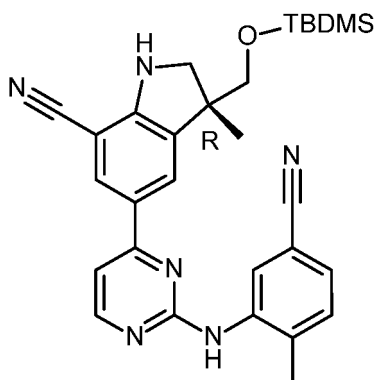
[0317] Preparation of intermediate 361:



[0318] TFA (6 mL) was added dropwise at 5 °C to a solution of intermediate 274 (3.00 g, 7.79 mmol) in DCM (60 mL) and the reaction mixture was stirred at 5 °C for 1 h. The reaction mixture was diluted with DCM and poured onto a mixture of ice and 10% aqueous K₂CO₃. The insoluble material was filtered, washed with water then Et₂O and dried to give 1.93 g of intermediate 361 (87% yield). M.P. = 207 °C (K).

Example A6

[0319] Preparation of intermediate 8R:

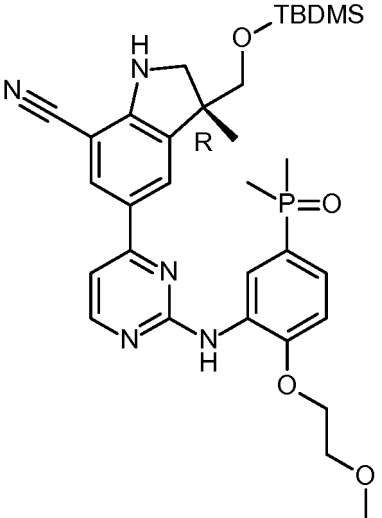
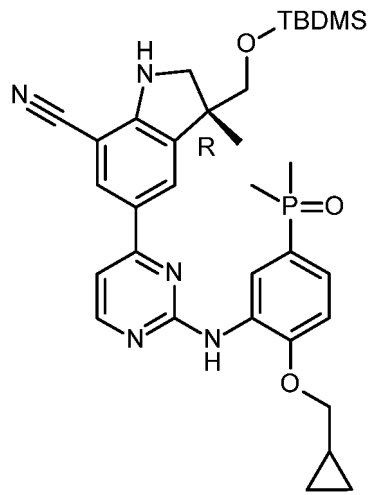
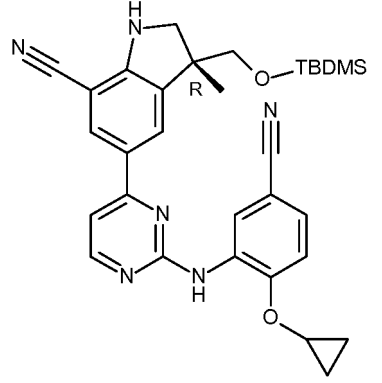


[0320] Method A: In a sealed vessel, a solution of intermediate 7R (14.75 g, 35.54 mmol) in 1,4-dioxane (285 mL) was purged with N₂. 3-amino-4-methylbenzonitrile (7 g, 53.312 mmol) and Cs₂CO₃ (23.16 g, 71.083 mmol) were successively added and the suspension was degassed after each addition. Then, Pd(OAc)₂ (798.00 mg, 3.55 mmol) and BINAP (2.21 g, 3.55 mmol) were added. The reaction mixture was degassed with N₂ and stirred at 120 °C (pre-heated bath) for 3 h. The reaction mixture was cooled to rt, poured onto ice-water and extracted with EtOAc. The organic layer was decanted, washed with brine, dried over MgSO₄, filtered over a pad of Celite® and concentrated to vacuum. The residue (30 g) was purified by column chromatography on silica gel (irregular SiOH, 400 g, mobile phase: DCM/EtOAc, gradient from 100:0 to 85:15 (12 x 200 mL)). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 14.3 g of intermediate 8R (79% yield contaminated by 7% of 3-amino-4-methylbenzonitrile as evaluated by ¹HNMR). This solid was suspended in Et₂O/CH₃CN and the mixture was sonicated at rt for 15 min. The precipitate was filtered, washed with CH₃CN and dried to give 8.6 g of intermediate 8R (47% yield). The filtrate was evaporated and the residue was purified by column chromatography on silica gel (irregular SiOH, 80 g, mobile phase: DCM/EtOAc, gradient from 100:0 to 90:10). The fractions containing the product were collected and evaporated to dryness. The resulting solid was suspended in Et₂O/CH₃CN and the mixture was sonicated at rt for 15 min. The precipitate was filtered, washed with CH₃CN and dried to give additional 2.6 g of intermediate 8R (14% yield). The global yield of this reaction was 62% (11.2 g).

Method B:

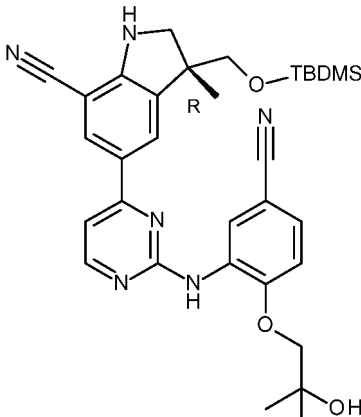
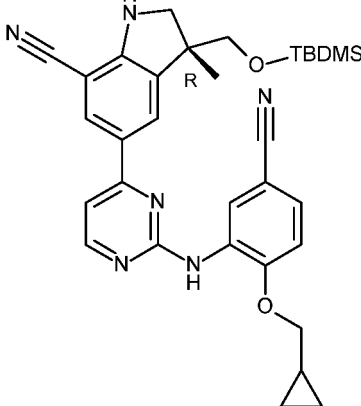
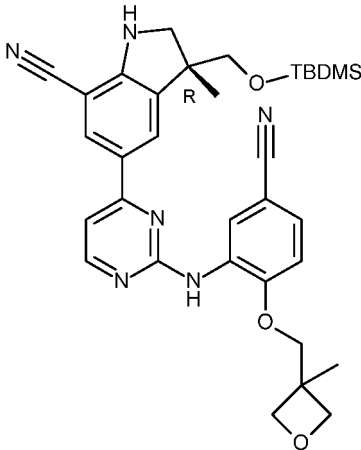
[0321] SiO₂ 35-70 μm (25 g) was added to a solution of intermediate 9R (6.10 g, 10.00 mmol) in toluene (75 mL) at rt. The reaction mixture was refluxed (bath temperature 125°C) for 6 h under vigorous agitation. Then, SiO₂ 35-70 μm was filtered off, washed successively with THF and EtOAc and the filtrate was evaporated to dryness. The residue was taken up with Et₂O and the precipitate was filtered and dried to give 4.34 g of intermediate 8R (85% yield).

[0322] The intermediates in the Table below were prepared by using an analogous method as described in Method A starting from the respective starting materials. The most relevant minor deviations from the initial method are indicated in the column 'Method'.

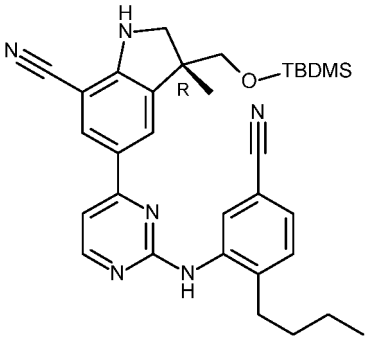
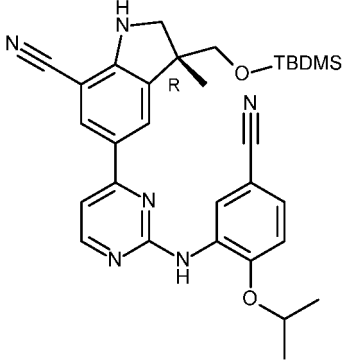
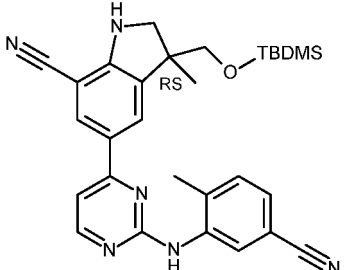
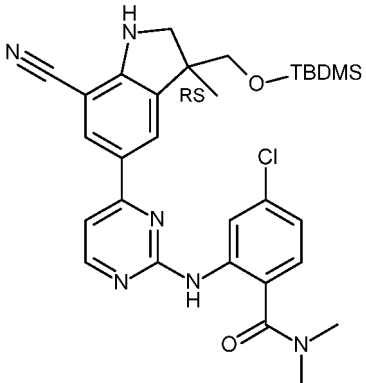
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 20	 From intermediate 7R and intermediate 24	247 (82% of purity based on LC/MS)	33	A
Intermediate 21	 From intermediate 7R and intermediate 27	325	44	A
Intermediate 42	 From intermediate 7R and intermediate 41	618 <i>orange oil</i>	32	A

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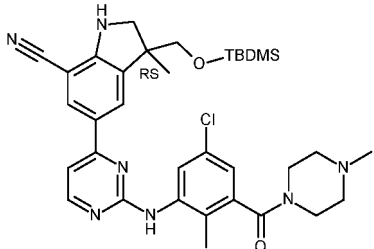
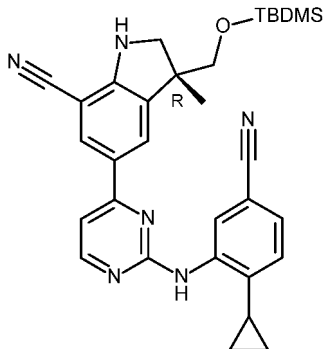
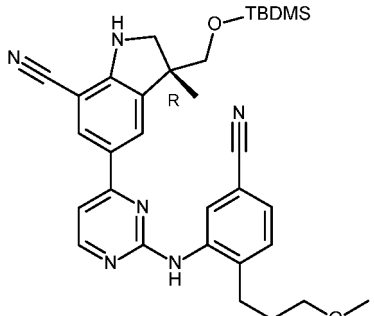
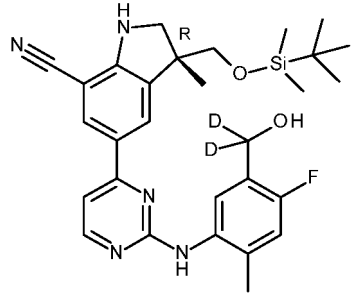
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 49	 From intermediate 7R and intermediate 48	292 (96% of purity based on LC/MS)	30	A
Intermediate 52	 From intermediate 7R and intermediate 51	843 (80% of purity based on LC/MS) <i>orange oil</i>	93	A
Intermediate 55	 From intermediate 7R and intermediate 54	1293 (94% of purity based on LC/MS) <i>yellow powder</i>	Quant.	A

(continued)

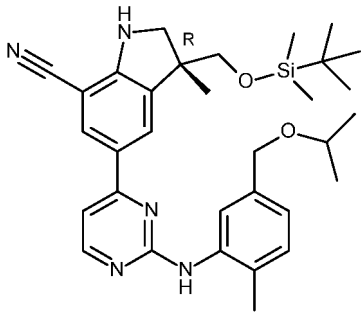
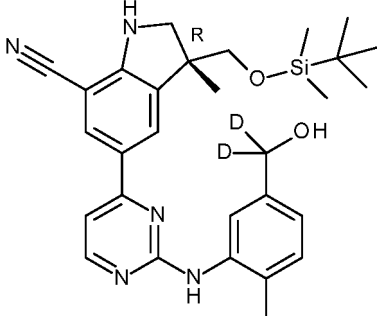
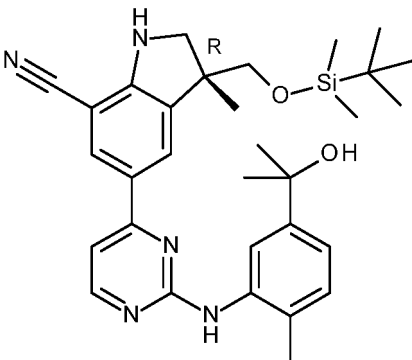
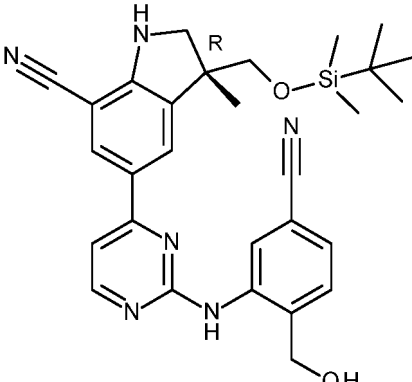
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 57	 From intermediate 7R and intermediate 56	344 (98% of purity based on LC/MS)	63	A
Intermediate 60	 From intermediate 7 R and intermediate 59	1010 (73% of purity based on LC/MS) <i>orange solid</i>	-	A
Intermediate 104	 From intermediate 7 and 3-amino-4-methylbenzonitrile	261 <i>yellow solid</i>	47	A with T = 95 °C
Intermediate 195	 From intermediate 7 and 2-amino-4-chloro-N,N-dimethylbenzamide	275 (94% of purity based on LC/MS)	66	A with T = 90 °C

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 199	 From intermediate 7 and intermediate 198	270 (80% of purity based on LC/MS)	74	A with T = 90 °C
Intermediate 246	 From intermediate 7R and intermediate 245	423	65	A
Intermediate 256	 From intermediate 7R and intermediate 255	1190 (94% of purity based on LC/MS)	87	A
Intermediate 394	 From intermediate 7R and intermediate 393	3100	55	A

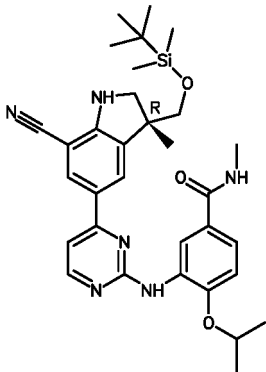
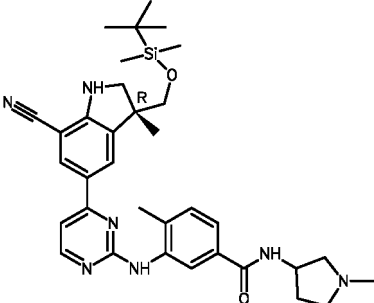
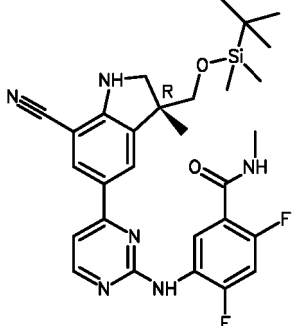
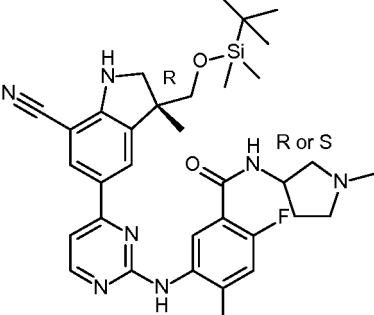
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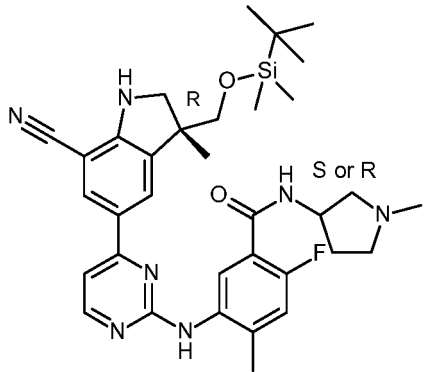
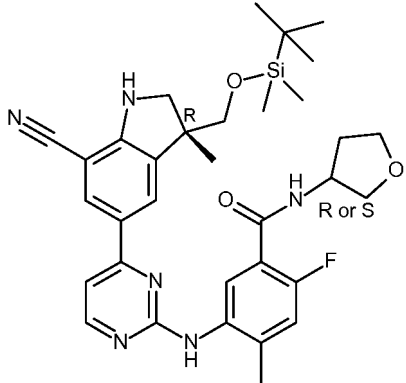
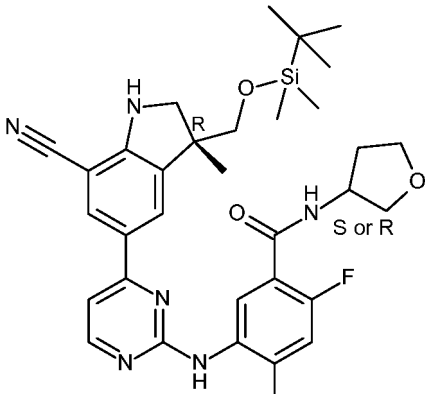
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 398	 From intermediate 7R and intermediate 397	220	52	A With T = 80°C
Intermediate 404	 From intermediate 7R and intermediate 403	167	31	A With T = 80°C
Intermediate 407	 From intermediate 7R and intermediate 406	190	26%	A With T = 80°C
Intermediate 412	 From intermediate 7R and 3-amino-4-(hydroxymethyl)benzonitrile	185	36	A

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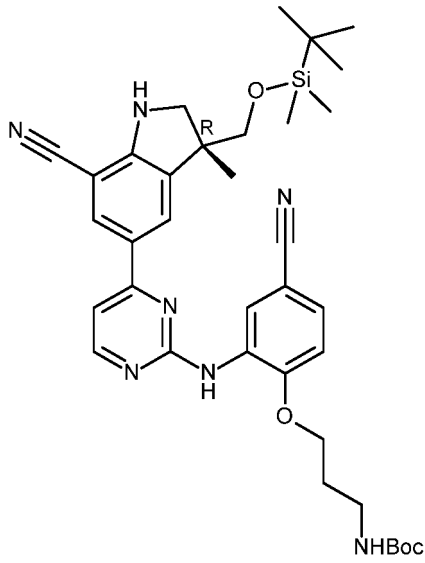
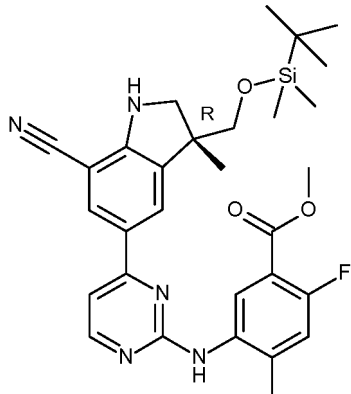
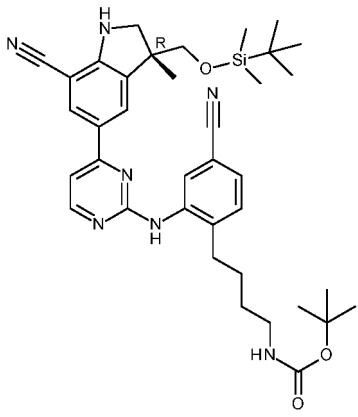
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 440	 from 3-amino-4-isopropoxy-N-methylbenzamide and intermediate 7R	597)	89	A
Intermediate 442	 From intermediate 441 and intermediate 7R	366 (81% of purity based on LC/MS)	52	A
Intermediate 444	 From intermediate 443 and intermediate 7R	423 (100% of purity based on LC/MS)	80	A
Intermediate 448	 From intermediate 447 and intermediate 7R	180	30	A

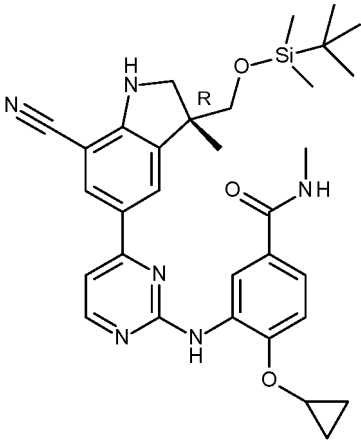
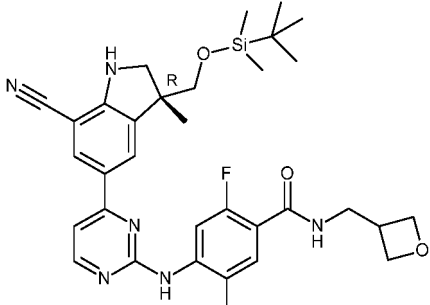
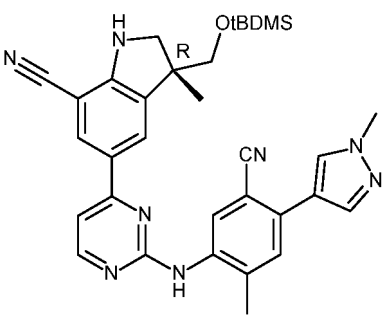
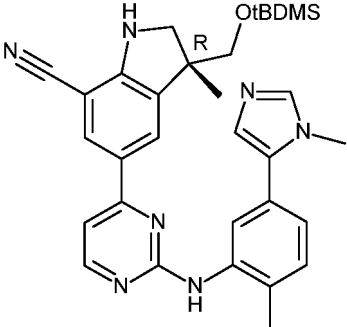
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 449	 From intermediate 447 and intermediate 7R	377 (100% of purity based on LC/MS)	54	A
Intermediate 453	 From intermediate 452 and intermediate 7R	124	19	A
Intermediate 454	 From intermediate 452 and intermediate 7R.	315	47	A

(continued)

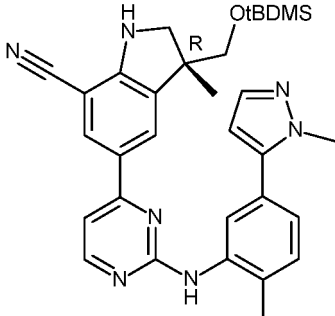
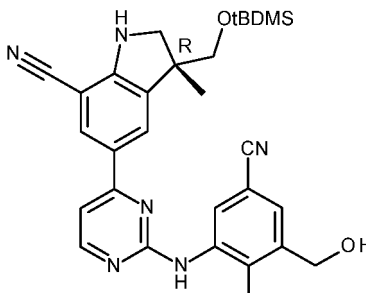
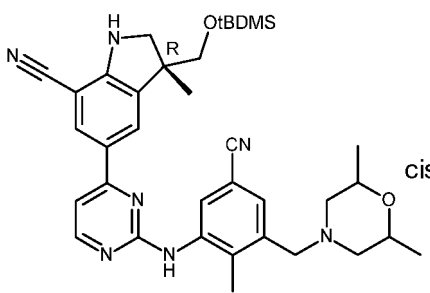
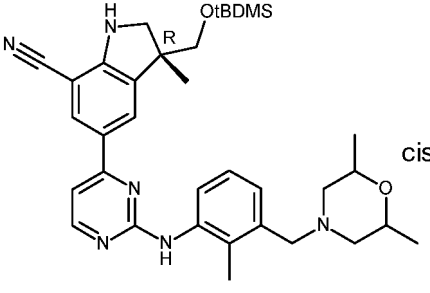
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 482	 From intermediate 481 and intermediate 7R .	690 (66% of purity based on LC/MS)	86	A
Intermediate 483	 From intermediate 7R and methyl 5-amino-2-fluoro-4-methylbenzoate	570 (79% of purity based on LC/MS)	84	A
Intermediate 486	 From intermediate 7R and intermediate 485	572 (83% of purity based on LC/MS)	74	A

(continued)

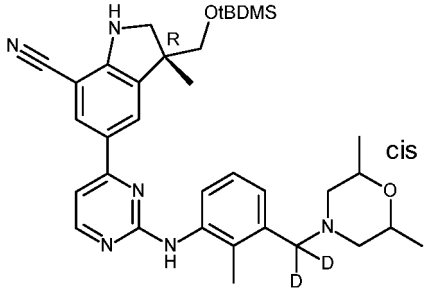
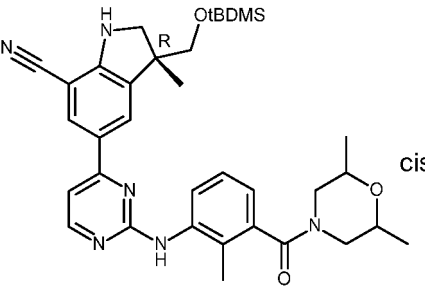
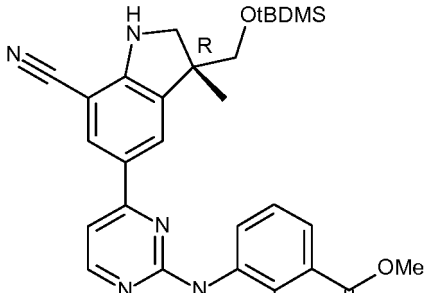
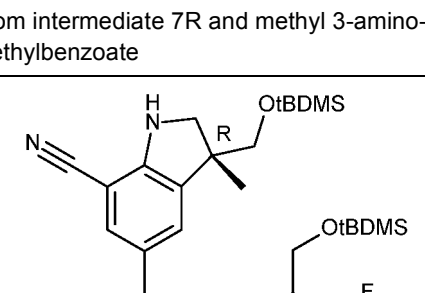
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 491	 From intermediate 490	147	26	A
Intermediate 496	 From intermediate 7R and intermediate 495	165	19	A
Intermediate 502	 From intermediate 7R and intermediate 499	568	80%	A (3h30@120°C)
Intermediate 503	 From intermediate 7R and intermediate 500	88	29% Purity 82% (LCMS)	A (3h30@120°C)

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(continued)

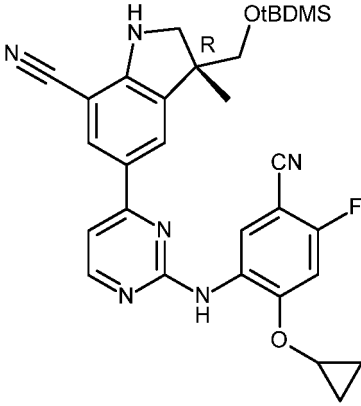
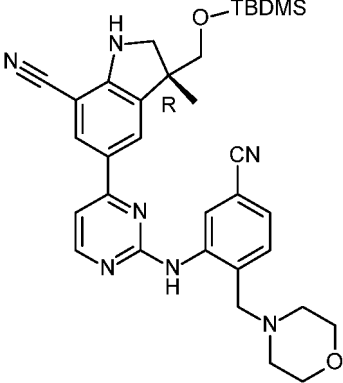
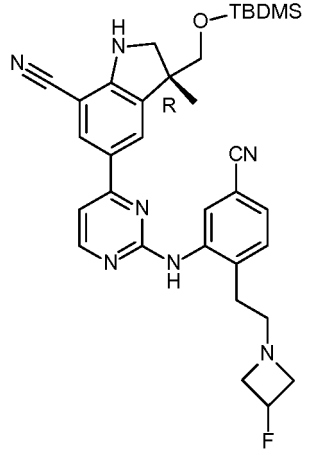
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 504	 From intermediate 7R and intermediate 500B	442	65%	A (3h30@120°C)
Intermediate 511	 From intermediate 7R and intermediate 510	233	49%	A (3h@120°C)
Intermediate 514	 From intermediate 7R and intermediate 513	591	77% Purity 54% (LCMS)	A (5h@120°C)
Intermediate 518	 From intermediate 7R and <i>rel</i>-3-[<i>cis</i>-2,6-dimethyl-4-morpholinyl] methyl]-2-methyl-benzenamine	142	86% Purity 70% (LCMS)	A (4h@120°C)

(continued)

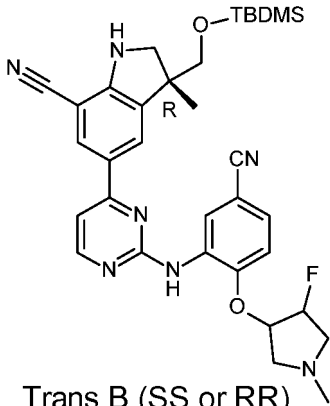
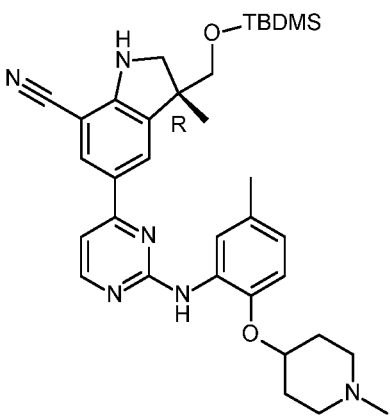
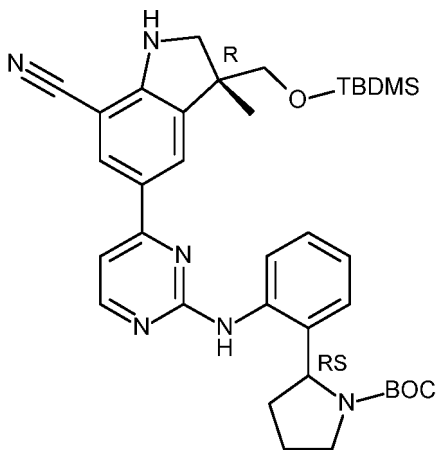
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 520	 From intermediate 7R and intermediate 519	221	61%	A (4h@120°C)
Intermediate 521	 From intermediate 7R and intermediate 521b	282	54%	A (4h@120°C)
Intermediate 522	 From intermediate 7R and methyl 3-amino-2-methylbenzoate	1050	53%	A (3h@120°C)
Intermediate 528	 From intermediate 7R and intermediate 527	306	43%	A (4h@120°C)

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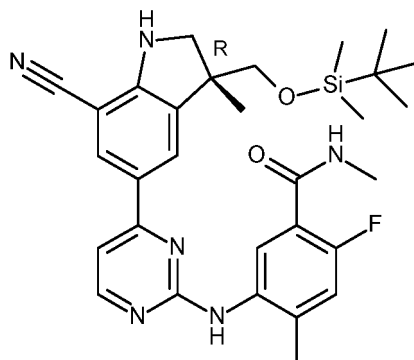
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 531	 From intermediate 7R and intermediate 530	527	77%	A (4h@120°C)
Intermediate 581	 From intermediate 7R and intermediate 580	215 Pale brown oil	65	A
Intermediate 600	 From intermediate 7R and intermediate 599	500	Quant.	A

(continued)

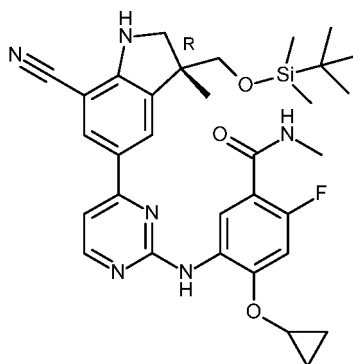
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 619	 Trans B (SS or RR) From intermediate 7R and intermediate 617	226	88	A
Intermediate 622	 From intermediate 7R and intermediate 621	70 Yellow solid	23	A
Intermediate 637	 From intermediate 7R and intermediate 636	571	64	A

[0323] Preparation of intermediate 423:

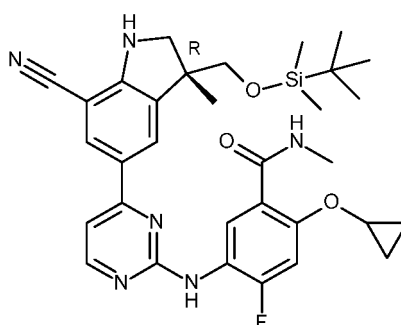


[0324] A mixture of intermediate 422 (8.68 g, 47.6 mmol), intermediate 7R (13.18 g, 31.8 mmol) and Cs_2CO_3 (20.7 g, 63.5 mmol) in 1,4-dioxane (260 mL) was purged with N_2 . $\text{Pd}(\text{OAc})_2$ (713 mg, 3.18 mmol) and BINAP (1.98 g, 3.18 mmol) were then added. The round bottom flask was sealed and the reaction mixture was purged with N_2 and was stirred at 120 °C for 3 hours. The resulting mixture was poured onto water and DCM. Then, filtered over celite®, decanted and the organic layer was separated, dried over MgSO_4 , filtered and evaporated. The residue (22.5 g) was purified by column chromatography over silica gel (Irregular SiOH , 40 μm , 120 g, mobile phase: heptane/EtOAc/MeOH: 60/35/5). The pure fractions were combined and the solvent was evaporated to give 10.66 g (60%) of intermediate 423 as a pale orange foam.

[0325] Preparation of intermediate 430



and intermediate 431

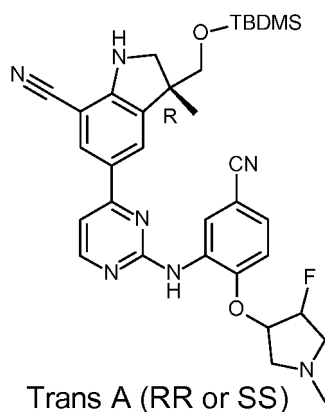


[0326] In a sealed tube, a mixture of intermediate 7R (936 mg; 2.25 mmol) in 1,4-dioxane (25 mL) was purged with N_2 . A mixture of intermediates 428 and 429 (758 mg; 3.38 mmol) and cesium carbonate (1.47 g; 4.51 mmol) were successively added and the suspension was degassed after each addition. Then, $\text{Pd}(\text{OAc})_2$ (51 mg; 0.226 mmol) and BINAP (140 mg; 0.226 mmol) were added. The flask was sealed, the reaction mixture was degassed with N_2 and stirred at 120°C (pre-heated bath) for 4 hours.

[0327] The reaction mixture was cooled to room temperature, poured onto water and extracted with DCM. The organic layer was decanted, dried over MgSO_4 , filtered over celite® and evaporated to dryness. The residue was 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 451 mg (33%) of intermediate

430 (33%) and 530 mg (39%) of intermediate 431.

[0328] Preparation of intermediate 618:

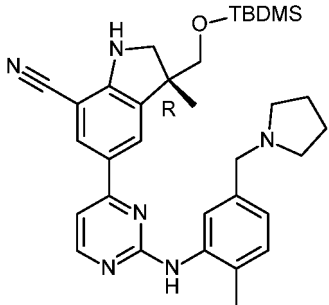
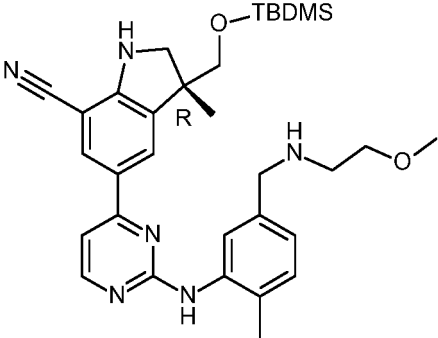
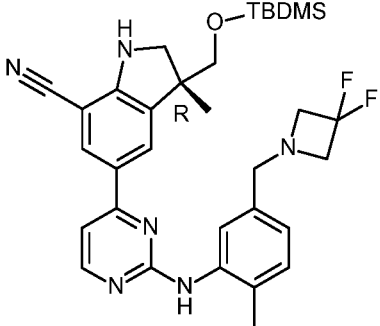


[0329] In a sealed vessel, a mixture of intermediate 7R (184 mg; 0.443 mmol) in dioxane (11 mL) was purged with N₂. Intermediate 616 (156 mg; 0.663 mmol) and cesium carbonate (289 mg; 0.886 mmol) were successively added and the suspension was degassed after each addition. Then Pd(OAc)₂ (10 mg; 0.044 mmol) and BINAP (27 mg; 0.044 mmol) were added. The reaction mixture was degassed with N₂ and stirred at 120°C (pre-heated bath) for 4 hours. The reaction mixture was cooled to room temperature, poured onto water and extracted with EtOAc. The organic layer was decanted, washed with water then brine, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 50g; mobile phase: gradient 0% MeOH, 100% DCM to 5% MeOH, 95% DCM). The fractions containing the product were collected and evaporated to dryness yielding 234 mg (86% yield, 87% purity evaluated by LCMS) of intermediate 618.

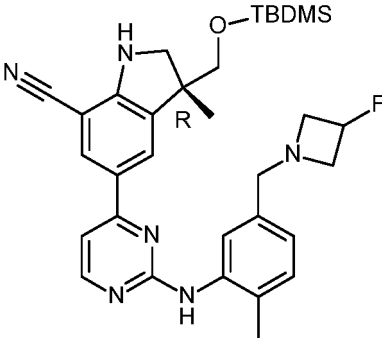
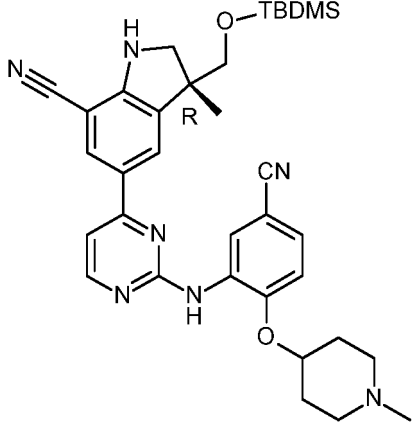
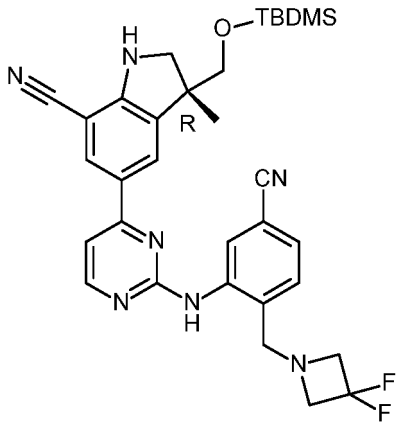
[0330] The intermediates in the Table below were prepared by using an analogous method as described in Method B starting from the respective starting materials. The most relevant minor deviations from the referenced method are indicated in the column 'Method'.

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 552	From intermediate 551	197 yellow oil	78	B

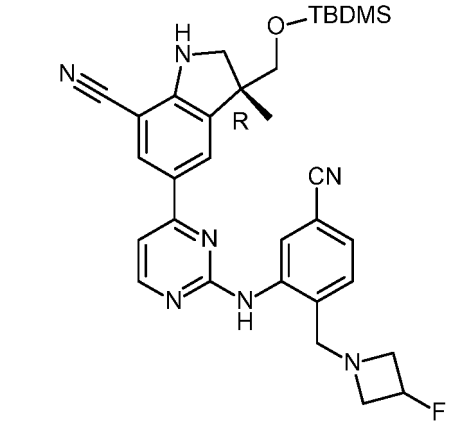
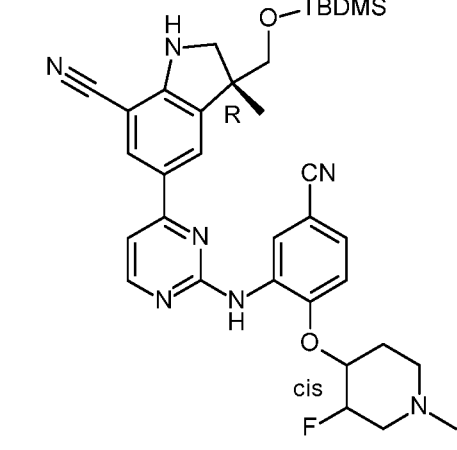
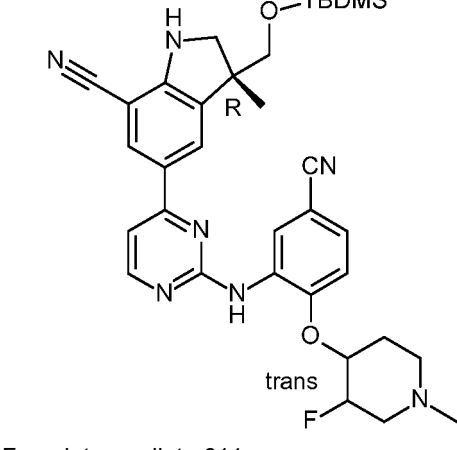
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 556	 From a mixture of intermediate 555 and intermediate 556	50 orange oil	60	B
Intermediate 558	 From a mixture of intermediates 557 and intermediate 558	390 yellow oil	94	B
Intermediate 561	 From a mixture of intermediates 560 and intermediate 561	419 yellow oil	quant.	B

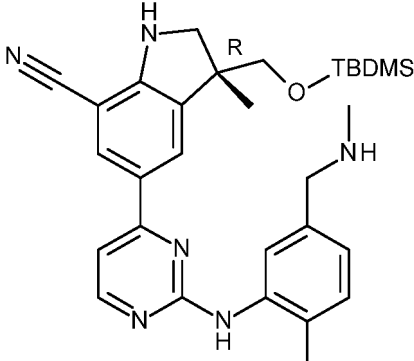
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 563	 From a mixture of intermediate 562 and intermediate 563	117 yellow oil	48	B
Intermediate 577	 From intermediate 576	363 Grey solid	69	B
Intermediate 593	 From intermediate 592	240	93	B

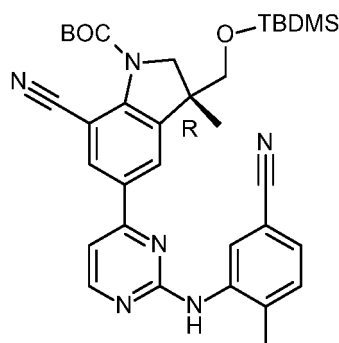
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 597	 From intermediate 596	170	100	B
Intermediate 606	 From intermediate 605	260 (75% purity evaluated by LCMS)	97	B
Intermediate 612	 From intermediate 611	90	87	B

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 641	 From intermediate 640	106	63	B

Example A7

[0331] Preparation of intermediate 9R:

Method C:

[0332] In a Sealed vessel, a mixture of 6R (5.15 g, 10.00 mmol) in 1,4-dioxane (80 mL) was purged with N₂. 3-amino-4-methylbenzonitrile (2.00 g, 15.00 mmol) and Cs₂CO₃ (6.51 g, 20.00 mmol) were successively added and the suspension was degassed after each addition. Then Pd(OAc)₂ (224.45 mg, 1.00 mmol) and BINAP (622.53 mg, 1.00 mmol) were added. The reaction mixture was degassed with N₂ and stirred at 120 °C (pre-heated bath) for 3 h. The reaction mixture was cooled to rt, poured onto ice-water and extracted with EtOAc. The organic layer was decanted, washed with brine, dried over MgSO₄, filtered over a pad of celite® and evaporated to dryness. The residue was purified by column chromatography on silica gel (irregular SiOH, 120 g, mobile phase: heptane/EtOAc, gradient from 85:15 to 70:30). The pure fractions were collected and evaporated to dryness to give 4.17 g of intermediate 9R (68% yield).

Method D:

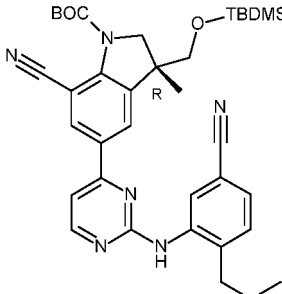
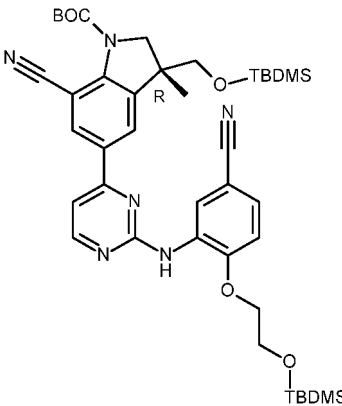
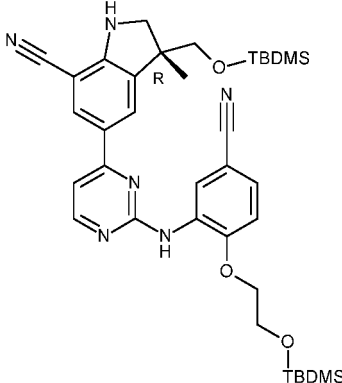
[0333] NaH (60% dispersion in mineral oil) (0.90 g, 22.49 mmol) was added portionwise to a stirred solution of *N*-(5-cyano-2-methylphenyl)-formamide (2.40 g, 15.00 mmol) in DMF (100 mL) under a N₂ atmosphere at rt and stirred for 30 min. Then, intermediate 6R (5.15 g, 1.00 mmol) was added and the reaction mixture was stirred at rt for 18 h. The resulting crude product was poured into water and extracted with EtOAc. The organic layer was decanted, washed successively with water and brine, dried over MgSO₄, filtered and concentrated to dryness to give 7.8 g of crude intermediate 9R which was used without any further purification in the next step.

[0334] The intermediates in the Table below were prepared by using an analogous method as described in Method C starting from the respective starting materials. The most relevant minor deviations from the referenced method are

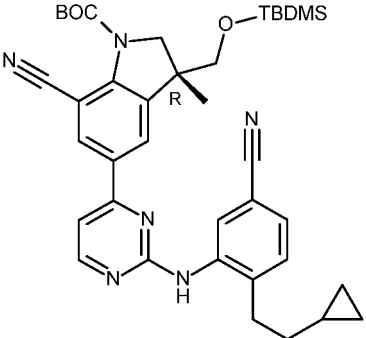
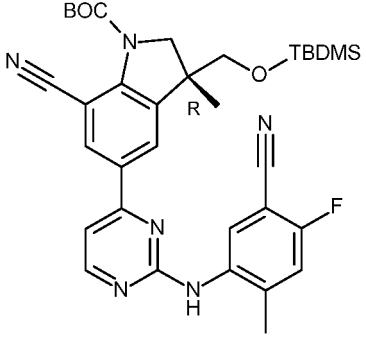
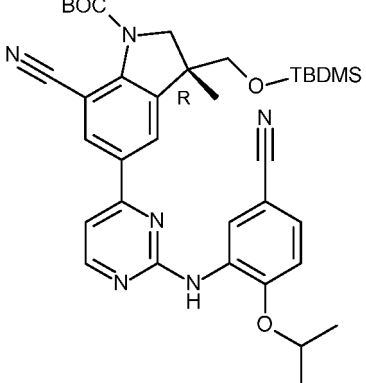
indicated in the column 'Method'.

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Mixture of Intermediate 11 / Intermediate 12	from intermediate 6R and a mixture of intermediates 16 and 17	1210 mixture of intermediate 11 and intermediate 12 (74:14 based on LC/MS)	-	C
Intermediate 18	from intermediate 6R and 3-amino-N,N-dimethyl benzamide	477 off-white foam	76	C

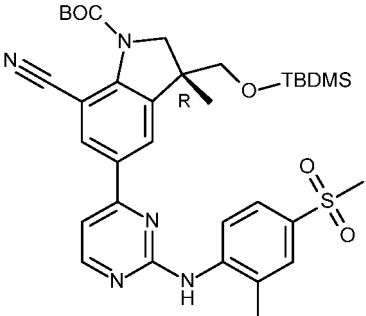
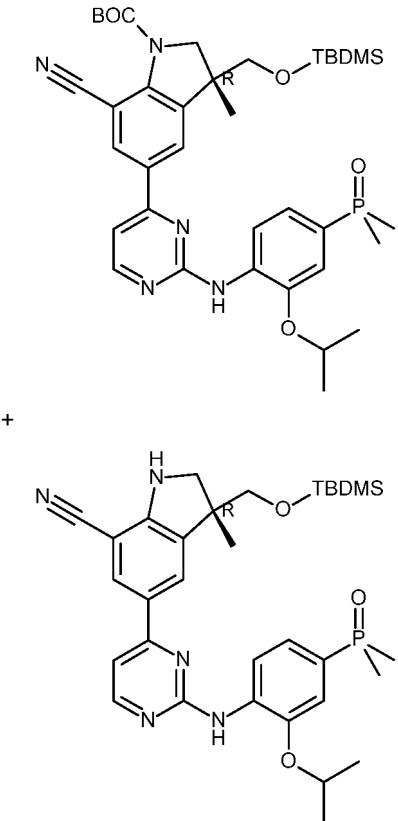
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 29	 from intermediate 6R and intermediate 28	337 (92% of purity based on LC/MS)	41	C
Intermediate 33 and Intermediate 34	  From intermediate 6R and intermediate 32	387 (intermediate 33) (89% of purity based on LC/MS) <i>orange oil</i> 474 (intermediate 34) (93% of purity based on LC/MS) <i>orange oil</i>	32 39	C

(continued)

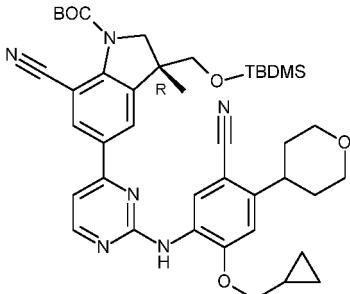
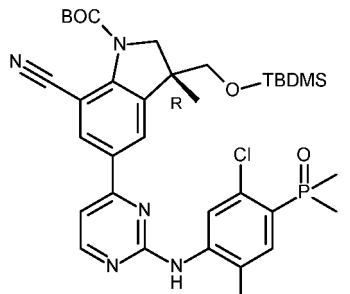
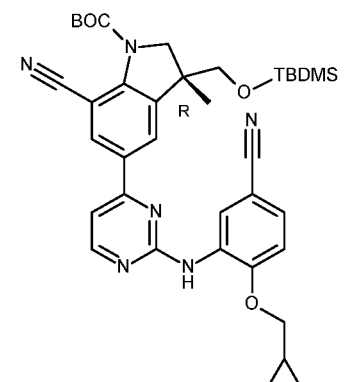
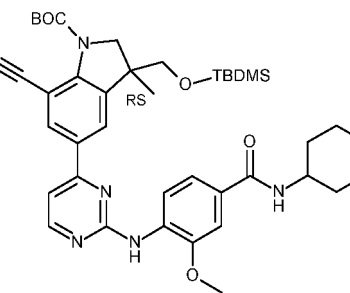
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 38	 From intermediate 6R and intermediate 37	778	60	C
Intermediate 45	 From intermediate 6R and intermediate 44	1090 (93% of purity based on LC/MS) <i>beige solid</i>	89	C
Intermediate 61	 From intermediate 6R and intermediate 59	525 (93% of purity based on LC/MS) <i>Light yellow powder</i>	83	C

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 63	 From intermediate 6R and methyl-4-(methylsulfonyl) aniline	536	36 (46 % purity based on LC/MS)	C
Mixture of Intermediate 68/ Intermediate 69	 From intermediate 6R and intermediate 67	1210 (mixture of intermediates 68/69: 98.7/1.3) <i>pale yellow foam</i>	93	C with T = 80 °C

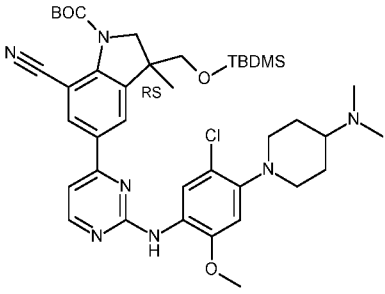
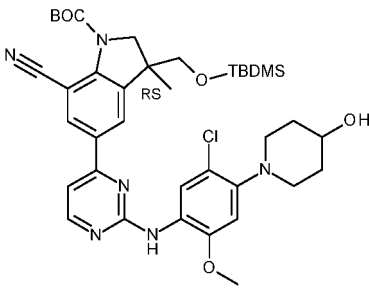
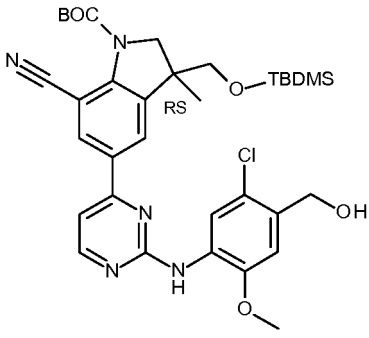
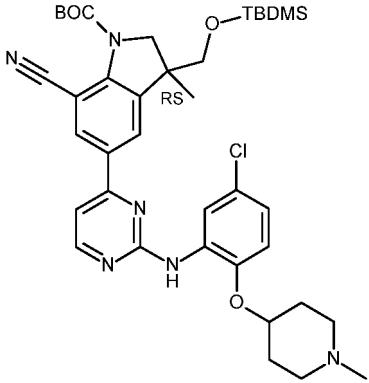
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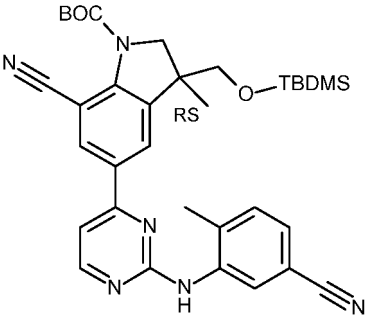
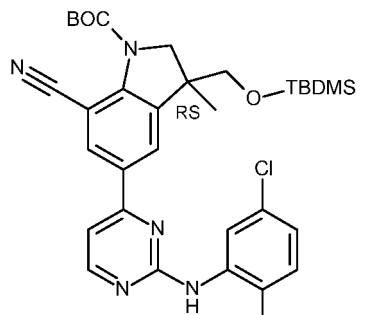
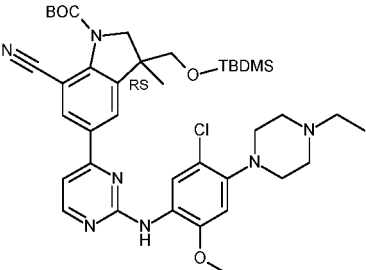
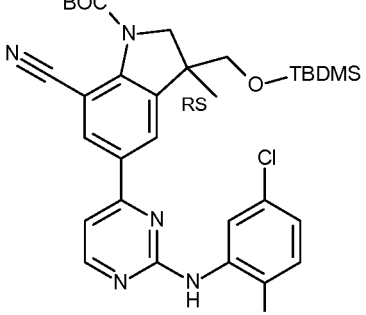
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 74	 From intermediate 6R and intermediate 73	2420 (73% of purity based on LC/MS) <i>brown foam</i>		C with T = 90 °C
Intermediate 77	 From intermediate 6R and intermediate 76	2500 (81% of purity based on LC/MS) <i>brown solid</i>		C
Intermediate 79	 From intermediate 6R and intermediate 51	919 (96% of purity based on LC/MS) <i>orange powder</i>	86	C
Intermediate 85	 From intermediate 6 and intermediate 84	292 <i>orange oil</i>	-	C with T = 85 °C

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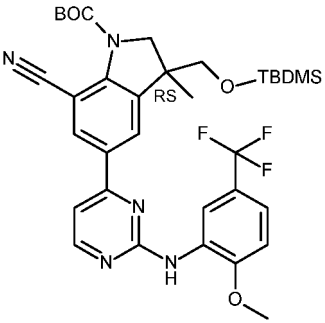
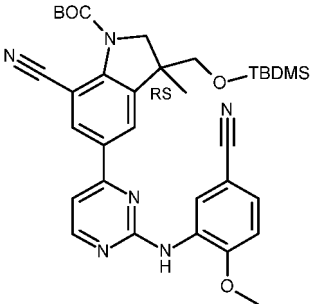
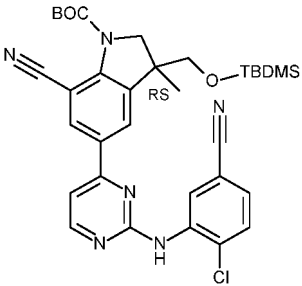
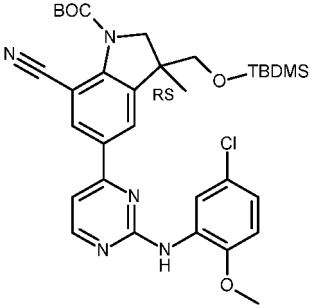
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 89	 From intermediate 6 and intermediate 88	247 <i>dark black foam</i>	-	C with T = 95 °C
Intermediate 93	 From intermediate 6 and intermediate 92	698	68 (based on a purity of 70% by LC/MS)	C with T = 95 °C
Intermediate 96	 From intermediate 6 and intermediate 95	387 <i>orange sticky oil</i>	-	C
Intermediate 100	 From intermediate 6 and intermediate 99	360	-	C with T = 85 °C

(continued)

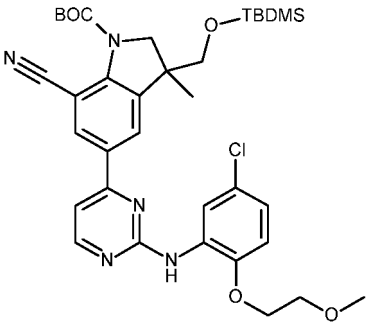
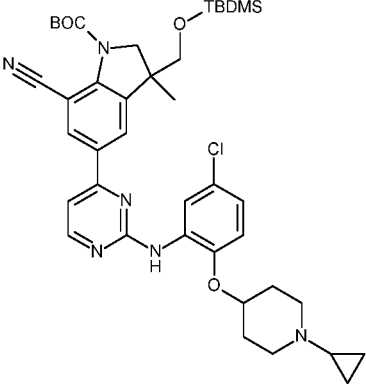
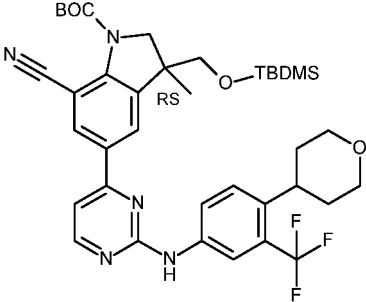
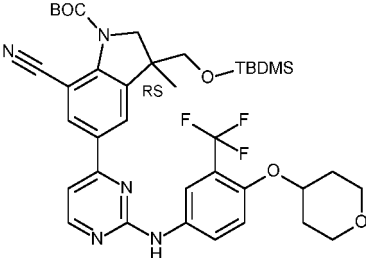
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 102	 From intermediate 6 and 3-amino-4-methylbenzonitrile	356 <i>brown solid</i>	-	C with T = 95 °C
Intermediate 105	 From intermediate 6 and 5-chloro- 2-methylaniline	540 <i>brown solid</i>	-	C with T = 95 °C
Intermediate 110	 From intermediate 6 and intermediate 109	249 (62% of purity based on LC/MS) <i>dark black foam</i>	98	C with T = 95 °C
Intermediate 112	 From intermediate 6 and 2,5-dichloroaniline	530 (80% of purity based on LC/MS)	Quant.	C with T = 95 °C

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 114	 From intermediate 6 and 2-methoxy-5-(trifluoromethyl)aniline	390 (55% of purity based on LC/MS) <i>brown solid</i>	-	C with T = 95 °C
Intermediate 116	 From intermediate 6 and 3-amino-4-methoxybenzonitrile	365 <i>brown oil</i>	-	C with T = 95 °C
Intermediate 118	 From intermediate 6 and 3-amino-4-chlorobenzonitrile	504 (70% of purity based on NMR) <i>white solid</i>	82	C with T = 95 °C
Intermediate 120	 From intermediate 6 and 5-chloro-2-methoxyaniline	960 (64% of purity based on LC/MS) <i>brown solid</i>	Quant.	C with T = 95 °C

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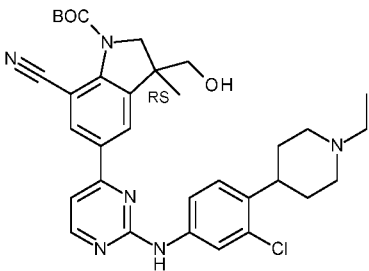
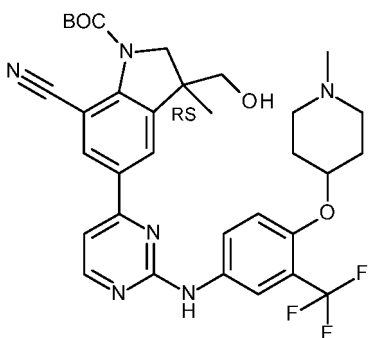
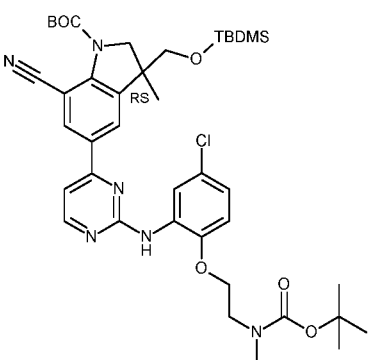
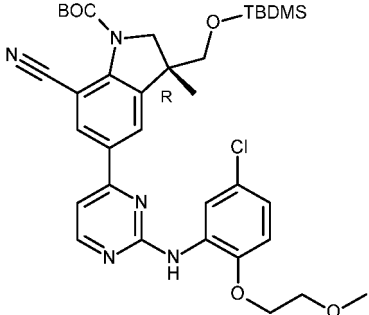
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 124	 From intermediate 6 and intermediate 123	308 (86% of purity based on LC/MS)	47	C with T = 95 °C
Intermediate 128	 From intermediate 6 and intermediate 127	530 (68% of purity based on LC/MS)	85	C with T = 95 °C
Intermediate 131	 From intermediate 6 and intermediate 130	530 M.P. (K) = 136 °C	75	C with T = 95 °C
Intermediate 135	 From intermediate 6 and intermediate 134	268 M.P. (K) = 133 °C	37	C with T = 95 °C

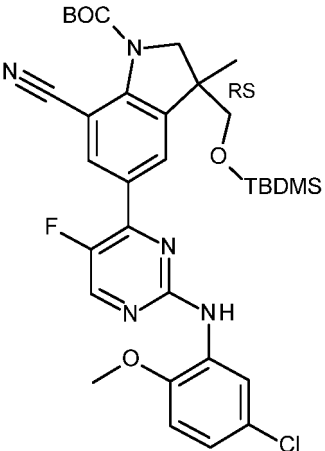
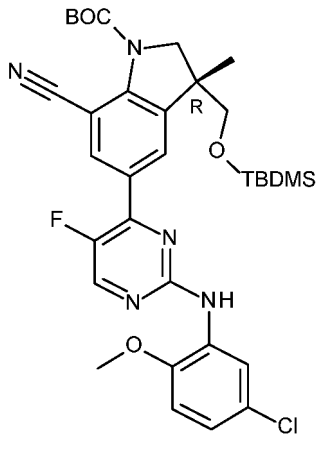
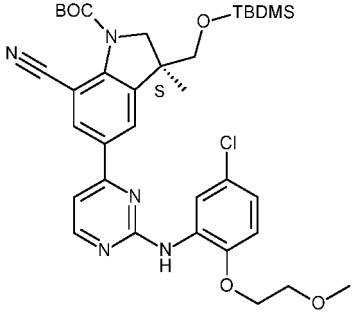
(continued)

113

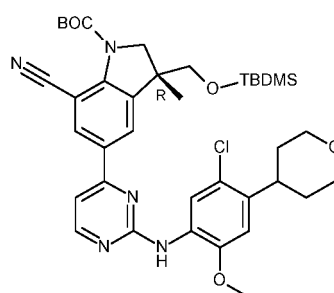
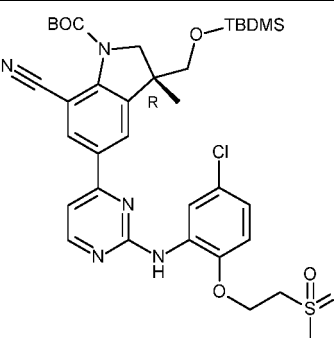
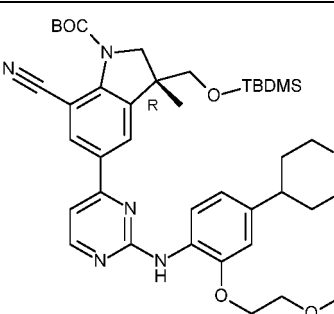
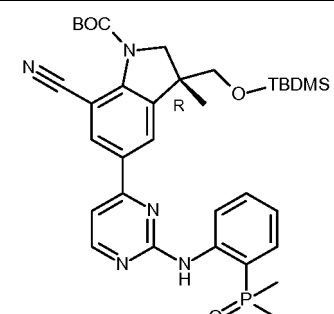
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 151	 From intermediate 150 and intermediate 149	139	38 (based on 74 % of purity by LC/MS)	C with T = 95 °C
Intermediate 157	 From intermediate 150 and intermediate 156	119 (98% of purity based on LC/MS)	25	C with T = 95 °C
Intermediate 161	 From intermediate 6 and intermediate 160	205 (95% of purity based on LC/MS) <i>white powder</i>	34	C
Intermediate 164	 From intermediate 6R and intermediate 123	269 (71% of purity based on LC/MS)	41	C with T = 95 °C

(continued)

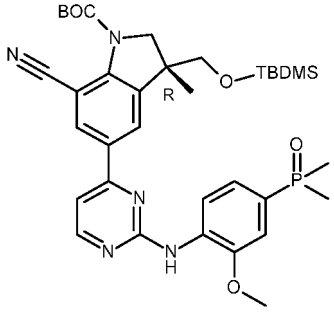
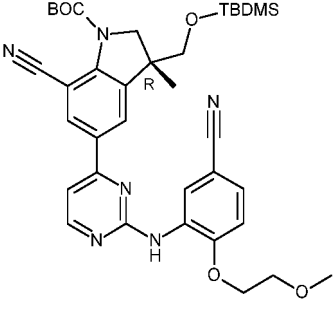
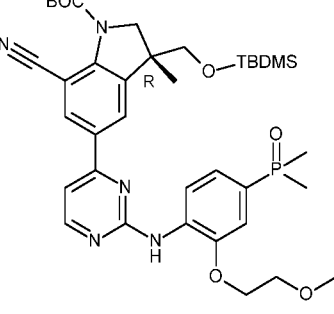
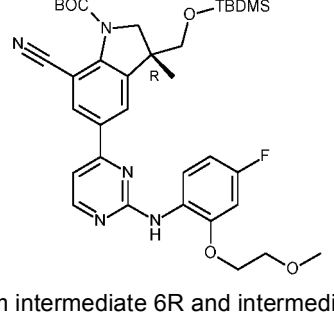
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 169	 From intermediate 6a and 5-chloro-2-methoxyaniline	411 (97% of purity based on LC/MS)	96	C
Intermediate 171	 From intermediate 6aR and 5-chloro-2-methoxyaniline	418 (91% of purity based on LC/MS)	97	C
Intermediate 196	 From intermediate 6S and intermediate 123	269	41	C with T = 95 °C

(continued)

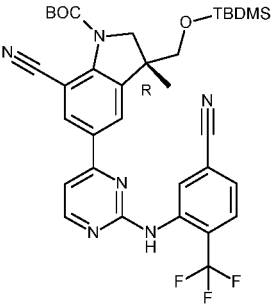
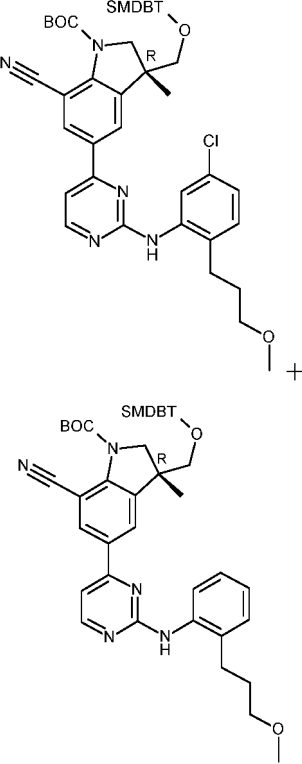
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 203	 From intermediate 6R and intermediate 202	582 (59% of purity based on LC/MS) <i>yellow solid</i>	quant.	C with T = 95 °C
Intermediate 205	 From intermediate 6R and 5-chloro-2-[2-methylsulfonyl] ethoxy]-benzamine	190	27	C
Intermediate 210	 From intermediate 6R and intermediate 209	620 <i>black foam</i>	Quant.	C with T = 95 °C
Intermediate 212	 From intermediate 6R and 2-(aminophenyl)dimethylphosphine oxide	740 (59% of purity based on LC/MS) <i>brown foam</i>	99	C with T = 95 °C

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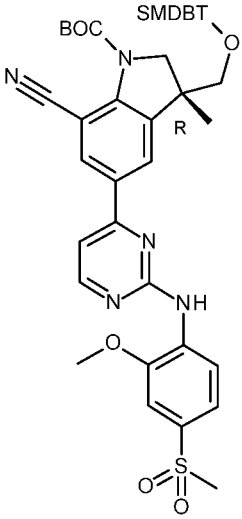
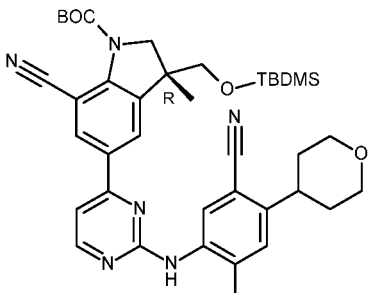
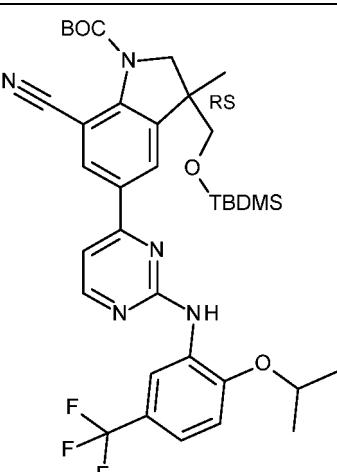
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 222	 From intermediate 6R and intermediate 221	760 (66% purity evaluated by LC/MS) <i>black foam</i>	Quant.	C with T = 95 °C
Intermediate 228	 From intermediate 6R and intermediate 227	400 (97% purity evaluated by LC/MS)	61	C
Intermediate 232	 From intermediate 6R and intermediate 231	630 (85% purity evaluated by LC/MS) <i>black foam</i>	quant.	C with T = 90 °C
Intermediate 240	 From intermediate 6R and intermediate 239	494 (93% purity evaluated by NMR)	77	C

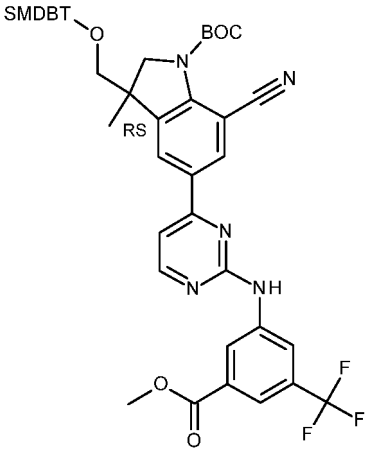
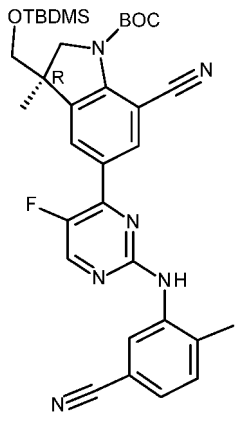
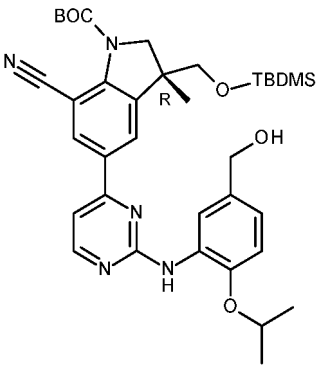
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 242	 From intermediate 6R and 3-amino-4-(trifluoromethyl)benzonitrile	613	95	C
Mixture of intermediate 247/intermediate 247'	 From intermediate 6R and intermediate 377/378	381 intermediate 247 (87% purity based on LC/MS)	48	C
		Intermediate 247' (11% purity based on LC/MS)		

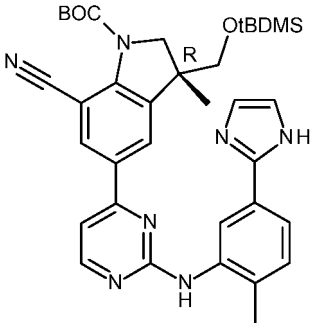
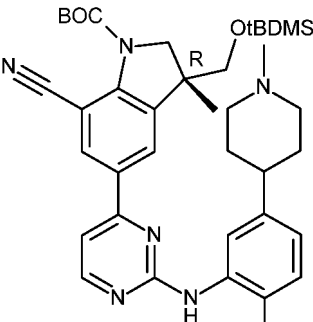
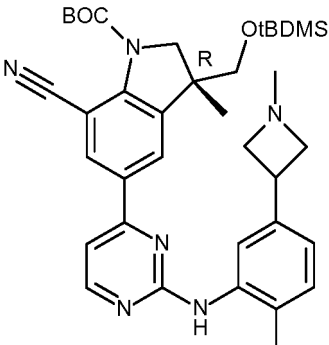
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 252	 From intermediate 6R and intermediate 251	397	60	C
Intermediate 261	 From intermediate 6R and intermediate 260	553 (84% purity evaluated by LC/MS) <i>orange powder</i>	82	C
Intermediate 265	 From intermediate 6 and 2-isopropoxy-5-(trifluoromethyl)aniline	502 (57% purity evaluated by LC/MS)	44	C

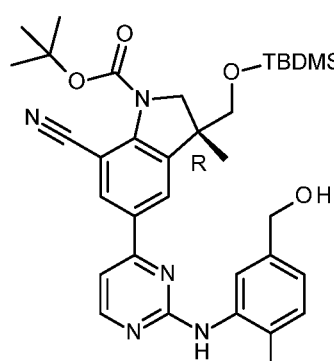
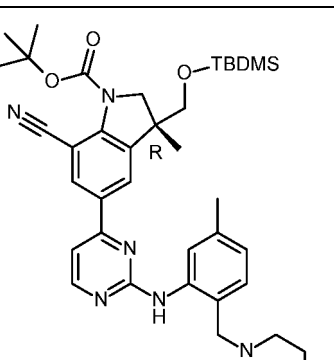
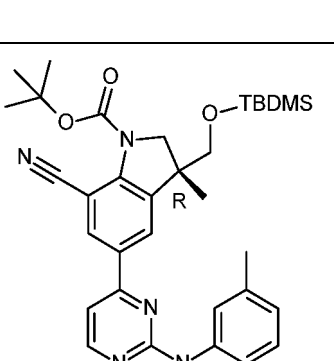
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 269	 From intermediate 6 and intermediate 268	372 (78% purity evaluated by LC/MS)	55	C with T = 90 °C
Intermediate 391	 From intermediate 6aR and 3-amino-4-methylbenzonitrile	375	90	C
Intermediate 417	 From intermediate 6R and intermediate 416	340	45	C With T = 80°C

(continued)

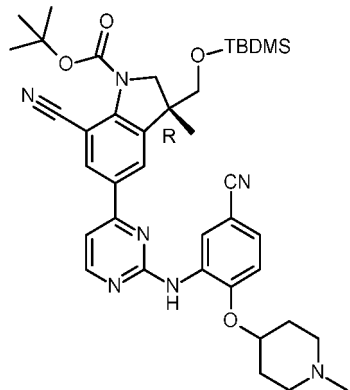
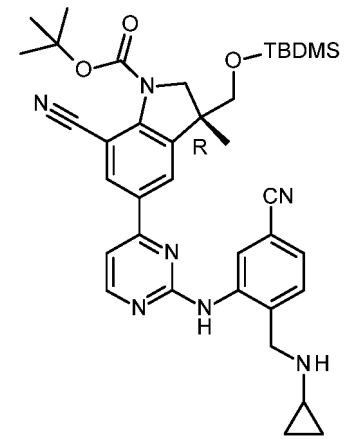
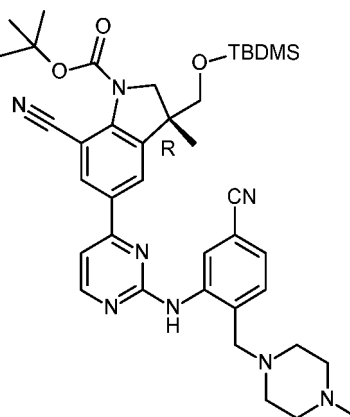
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 505	 From intermediate 6R and intermediate 501	360	57% Purity 84% (LCMS)	C (o/n@95°C)
Intermediate 508	 From intermediate 6R and 2-methyl-5-(1-methyl-4-piperidinyl)-benzenamine	100	17%	C (o/n@80°C)
Intermediate 537	 From intermediate 6R and intermediate 536	488	16% Purity 49% (LCMS)	C (3h@95°C)

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 551	 From intermediate 6R and 3-amino-4-methylbenzyl alcohol	4690 yellow foam	78	C
Intermediate 568	 From intermediate 6R and intermediate 567	540	80	C
Intermediate 572	 From intermediate 6R and intermediate 571	850	98	C

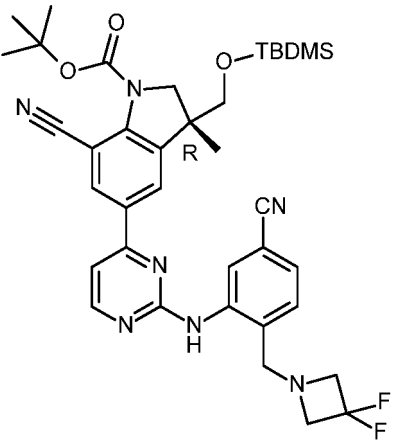
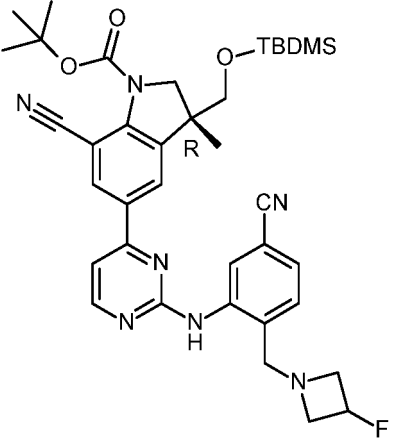
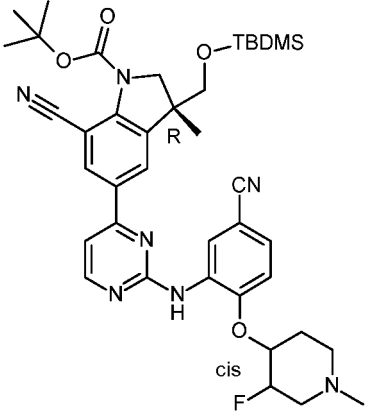
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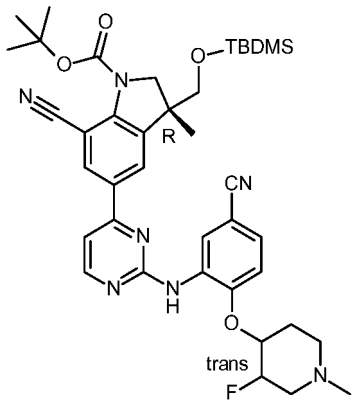
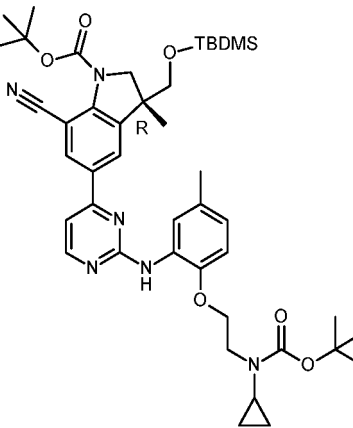
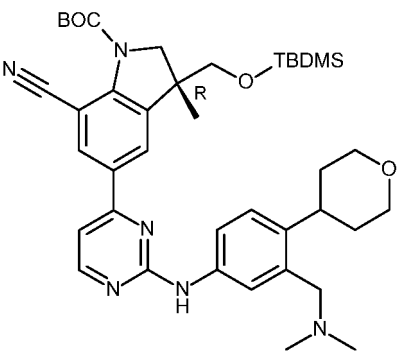
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 576	 From intermediate 6R and intermediate 575	633 Pale brown oil	82	C
Intermediate 584	 From intermediate 6R and intermediate 583	180	56	C
Intermediate 588	 From intermediate 6R and intermediate 587	315 (85% purity evaluated by LCMS)	77	C

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(continued)

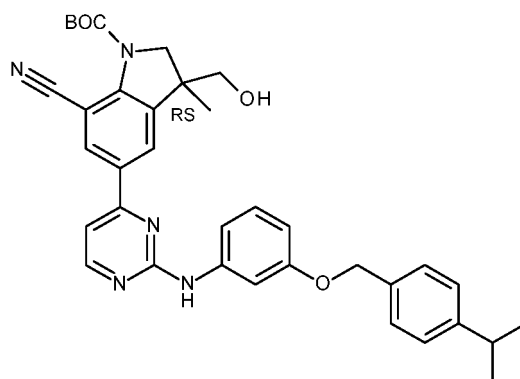
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 592	 From intermediate 6R and intermediate 591	300	74	C At 100°C for 1 hour
Intermediate 596	 From intermediate 6R and intermediate 595	240	53	C At 100°C for 1 hour
Intermediate 605	 From intermediate 6R and intermediate 604	310 (85% purity evaluated by LCMS)	73	C

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 611	 From intermediate 6R and intermediate 610	121 (55% purity evaluated by LCMS)	70	C At 100°C for 1 hour
Intermediate 627	 From intermediate 6R and intermediate 626	505	59	C
Intermediate 633	 from intermediate 6R and intermediate 632	552	80	C @ 85°C overnight

Example A8

[0335] Preparation of intermediate 154:



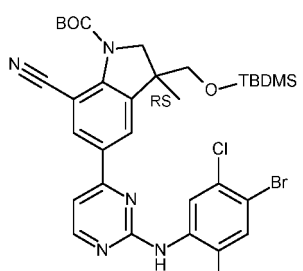
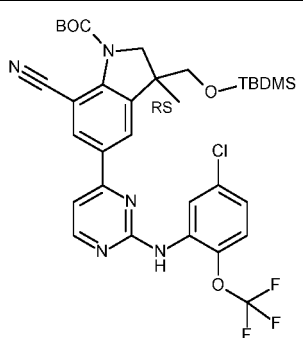
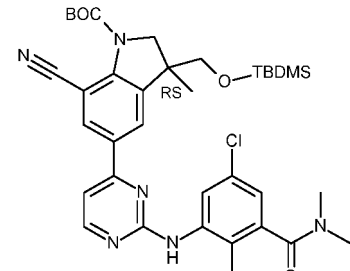
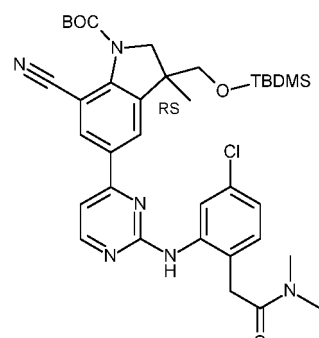
[0336] A mixture of intermediate 150 (300.00 mg, 0.75 mmol), intermediate 153 (198.67 mg, 0.82 mmol) and Cs_2CO_3 (609.59 mg, 1.87 mmol) in 1,4-dioxane (12.77 mL) was purged with N_2 . A catalytic amount of $\text{Pd}(\text{OAc})_2$ (13.44 mg, 59.87 μmol) and BINAP (37.28 mg, 59.87 μmol) were then added in the sealed tube. The reaction mixture was purged with N_2 and was stirred at 120 °C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The resulting mixture was poured out onto water and DCM. Then, filtered over celite®, decanted and the organic layer was separated, dried over MgSO_4 , filtered and evaporated. The residue (948 mg) was purified by column chromatography on silica gel (Irregular SiOH , 40 μm , 40 g, mobile phase: heptane/EtOAc/MeOH/ NH_4OH , gradient from 50% heptane, 50% EtOAc to 40% Heptane, 10% MeOH, 50% EtOAc, 1% NH_4OH). The pure fractions were combined and the solvent was evaporated to give 300 mg of intermediate 154 (66% yield).

[0337] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 154 starting from the respective starting materials.

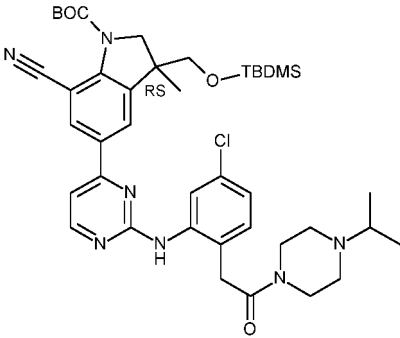
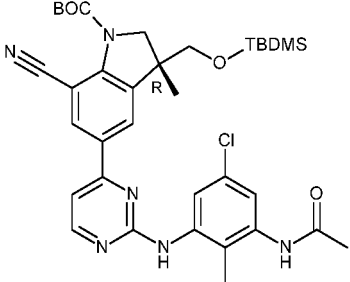
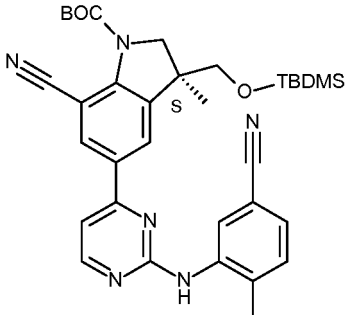
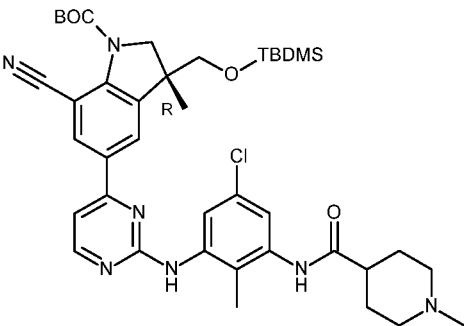
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 173	From intermediate 6 and 2-amino-4-chloro benzotrifluoride	418	64
Intermediate 179	CIS From intermediate 6 and intermediate 178	499	66

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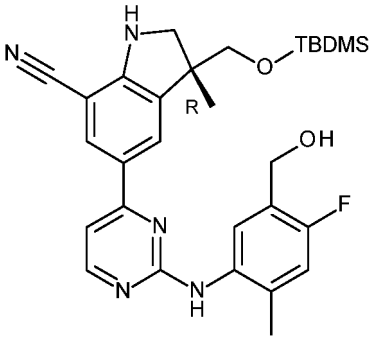
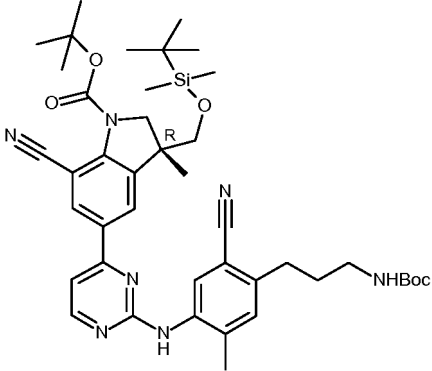
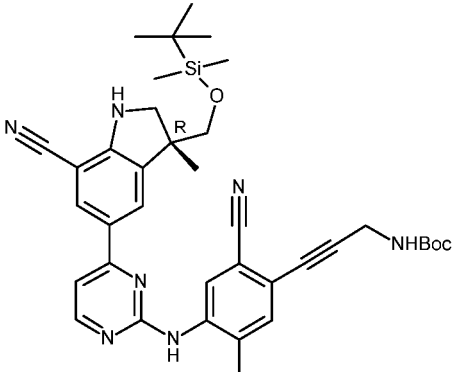
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 181	 From intermediate 6 and 4-bromo-5-chloro-2-methylaniline	180	27
intermediate 183	 From intermediate 6 and 5-chloro-2-(trifluoromethoxy)aniline	600	76
intermediate 187	 From intermediate 6 and intermediate 186	600 (69% of purity based on LC/MS)	89
Intermediate 190	 From intermediate 6 and intermediate 189	600	89

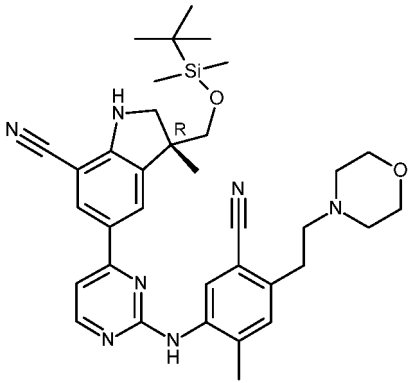
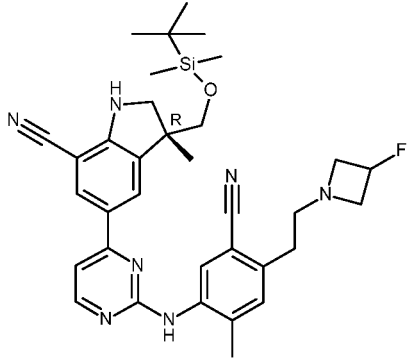
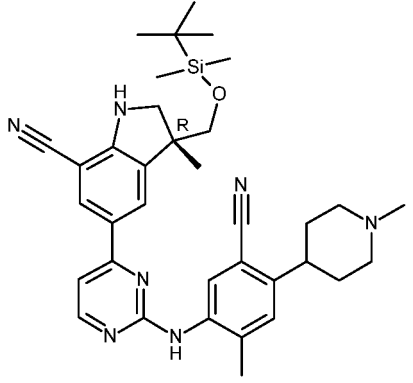
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 193	 From intermediate 6 and intermediate 192	300	40
Intermediate 218	 From intermediate 6R and intermediate 217	387	59
Intermediate 224	 From intermediate 6S and 3-amino-4-methylbenzonitrile	329 (82% purity evaluated by LC/MS) <i>yellow powder</i>	55
Intermediate 236	 From intermediate 6R and intermediate 235	207 (92% purity evaluated by LC/MS)	35

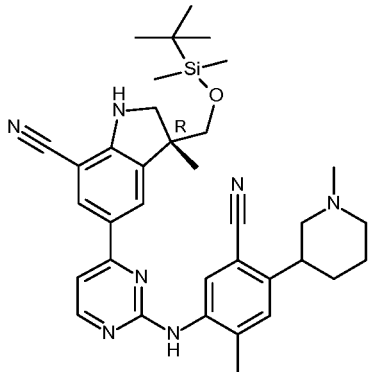
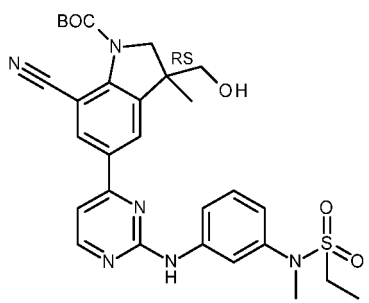
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 411	 From intermediate 7R and intermediate 410	610	95
Intermediate 458	 From intermediate 6R and intermediate 457	604	97
Intermediate 463	 From intermediate 7R and intermediate 462	629	78

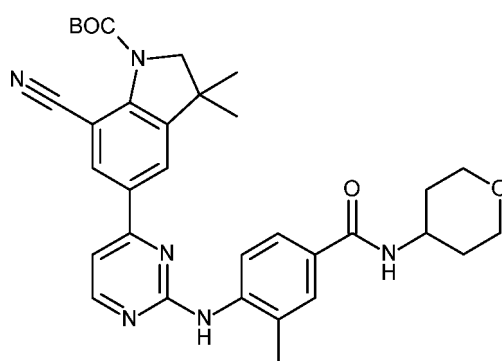
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 468	 From intermediate 7R and intermediate 467	396	100
Intermediate 471	 From intermediate 7R and intermediate 470	261 (68% of purity based on LC/MS)	68
Intermediate 474	 From intermediate 473 and intermediate 7R.	137	52

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 479	 From intermediate 478 and intermediate 7R.	377	54
Intermediate 644	 From intermediate 150 and intermediate 643	298 (85% of purity based on LC/MS)	45

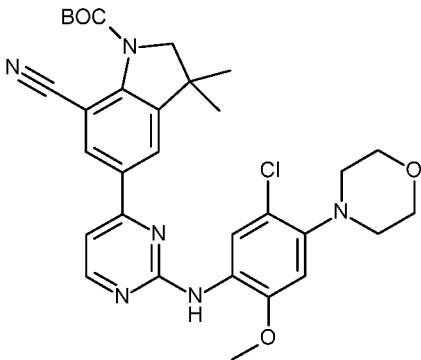
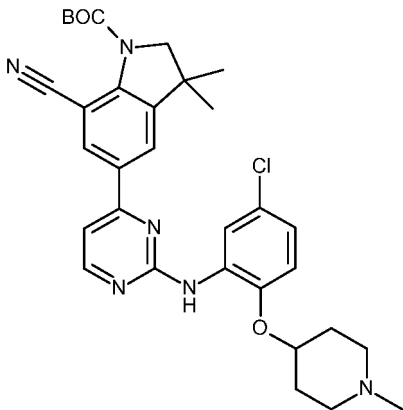
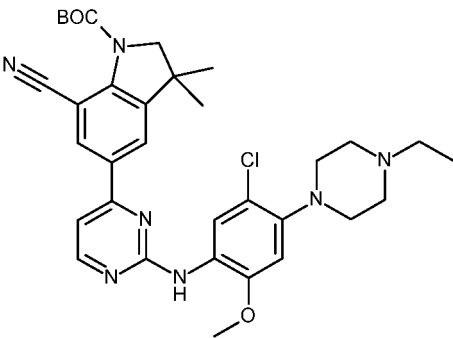
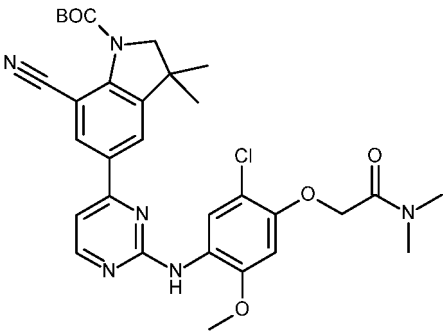
Example A9

[0338] Preparation of intermediate 277:

[0339] To a solution of intermediate 274 (0.10 g, 0.24 mmol), intermediate 276 (56.70 mg, 0.24 mmol), BINAP (14.90 mg, 0.024 mmol), Cs_2CO_3 (237.00 mg, 0.73 mmol) in 1,4-dioxane (3 mL) was added $\text{Pd}(\text{OAc})_2$ (5.39 mg, 0.024 mmol) and the reaction mixture was heated for 30 min at 95 °C. The reaction mixture was diluted with EtOAc, washed with water and brine. The organic layer was dried over Na_2SO_4 , and concentrated in vacuo to give 227 mg of intermediate 277 (65% purity based on LC/MS, yellow oil) and used as it is in the next step.

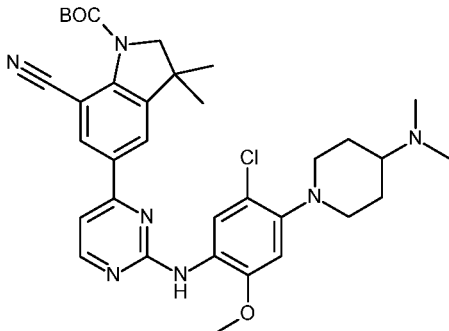
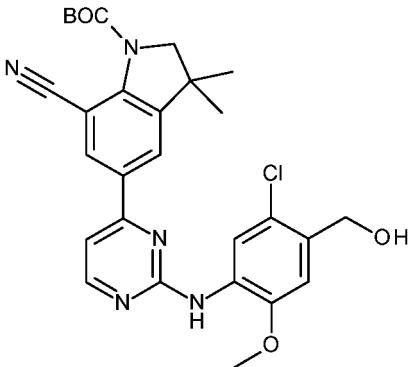
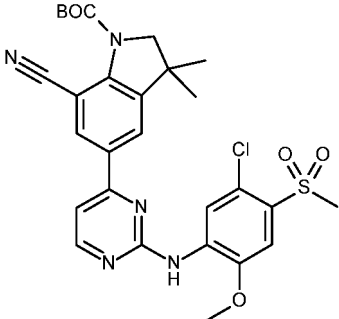
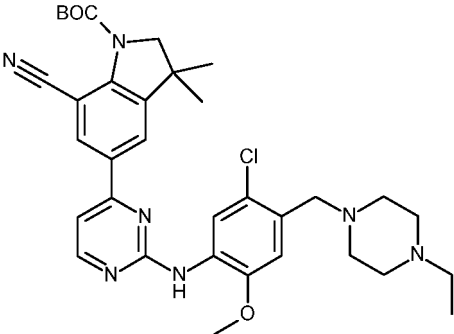
[0340] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 277 starting from the respective starting materials.

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Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 280	 From intermediate 274 and intermediate 279	124 (69% based on LC/MS)	-
Intermediate 281	 From intermediate 274 and intermediate 99	153 (90% based on LC/MS) <i>brown oil</i>	-
Intermediate 282	 From intermediate 274 and intermediate 109	124 (95% based on LC/MS) <i>brown oil</i>	Quant.
Intermediate 286	 From intermediate 274 and intermediate 285	157 (90% based on LC/MS) <i>brown oil</i>	Quant.

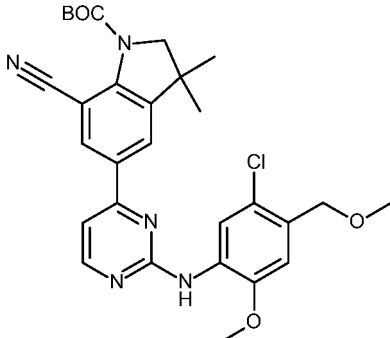
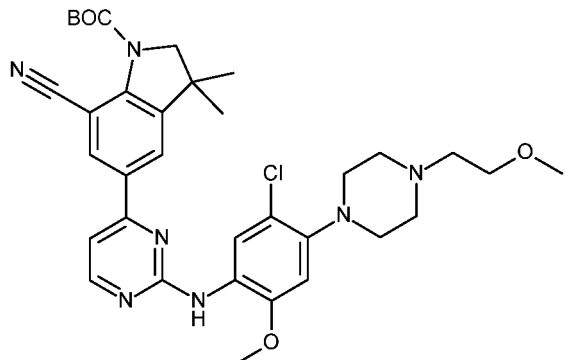
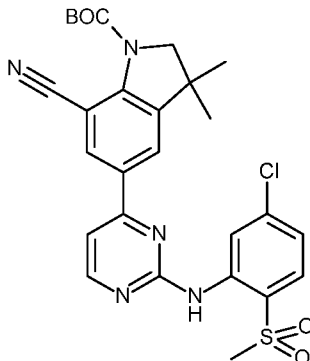
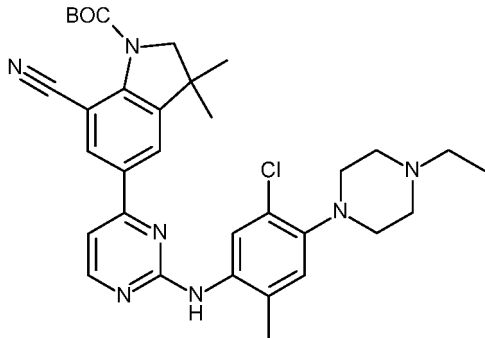
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(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 287	 From intermediate 274 and intermediate 88	126 (90% based on LC/MS) <i>brown oil</i>	Quant.
Intermediate 288	 From intermediate 274 and intermediate 95	107 (89% based on LC/MS) <i>brown oil</i>	Quant.
Intermediate 292	 From intermediate 274 and intermediate 291	152 (87% based on LC/MS) <i>brown oil</i>	Quant.
Intermediate 298	 From intermediate 274 and intermediate 297	101 (87% based on LC/MS) <i>brown oil</i>	Quant.

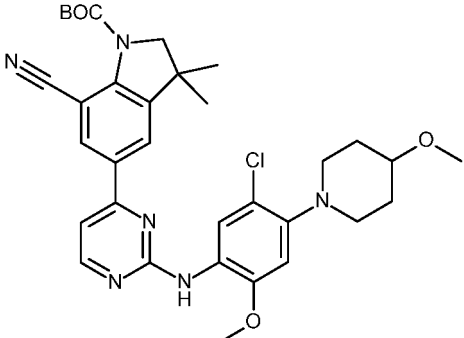
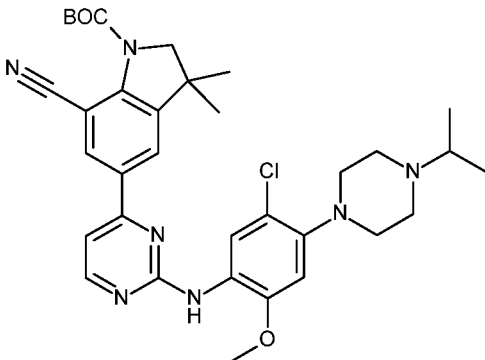
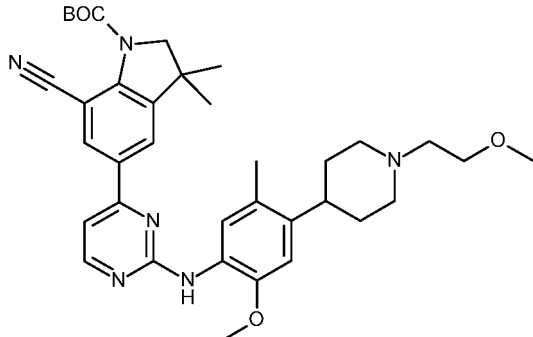
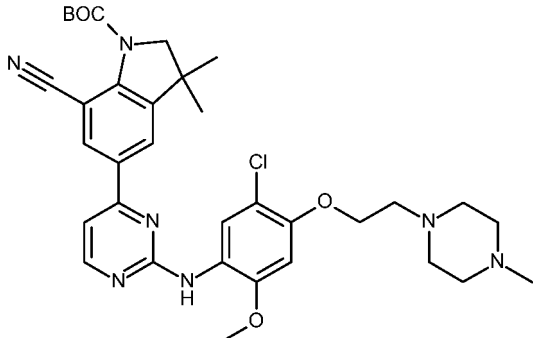
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(continued)

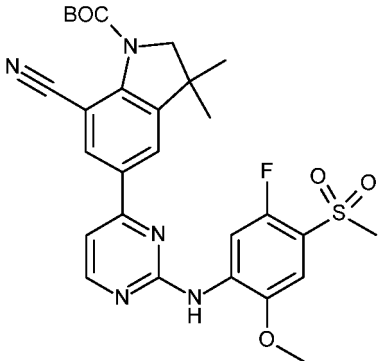
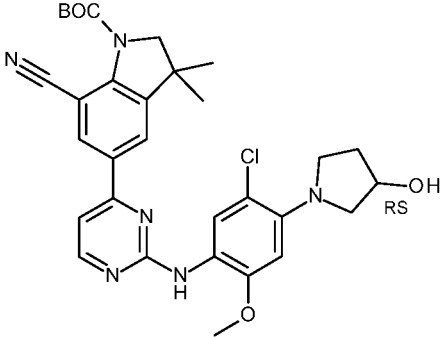
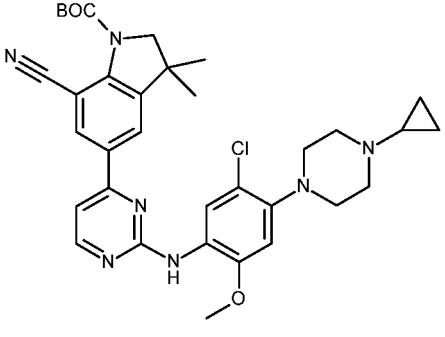
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 301	 From intermediate 274 and intermediate 300	199 (36% based on LC/MS) <i>brown solid</i>	-
Intermediate 304	 From intermediate 274 and intermediate 303	84 (93% based on LC/MS) <i>brown oil</i>	Quant.
Intermediate 306	 From intermediate 274 and intermediate 305	143 (20% based on LC/MS) <i>brown solid</i>	-
Intermediate 309	 From intermediate 274 and intermediate 308	152 (47% based on LC/MS)	-

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(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 312	 From intermediate 274 and intermediate 311	111 (85% based on LC/MS)	Quant.
Intermediate 315	 From intermediate 274 and intermediate 314	114 <i>brown oil</i> (87% based on LC/MS)	Quant.
Intermediate 320	 From intermediate 274 and intermediate 319	113 <i>brown oil</i> (51% based on LC/MS)	Quant.
Intermediate 323	 From intermediate 274 and intermediate 322	159 <i>brown solid</i> (45% based on LC/MS)	-

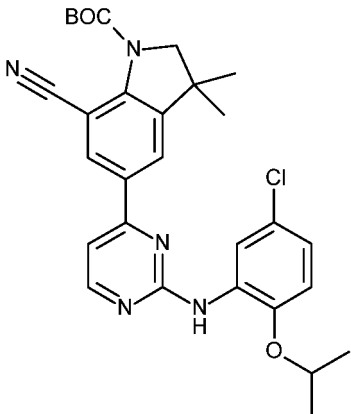
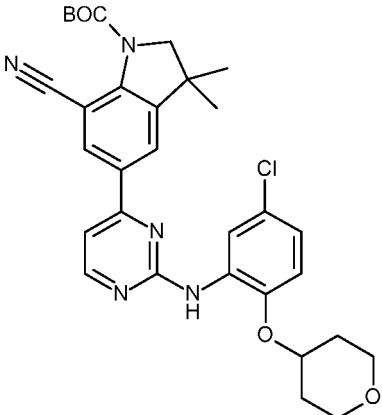
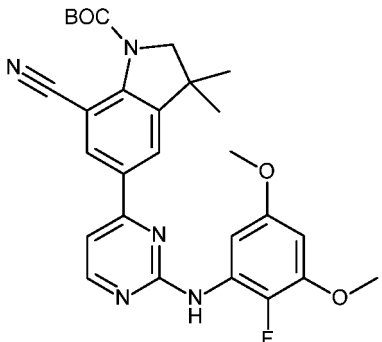
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 327	 From intermediate 274 and intermediate 326	153 <i>brown solid</i> (63% based on LC/MS)	-
Intermediate 330	 From intermediate 274 and intermediate 329	106 <i>brown solid</i> (84% based on LC/MS)	Quant.
Intermediate 333	 From intermediate 274 and intermediate 332	81 <i>brown oil</i> (90% based on LC/MS)	Quant.

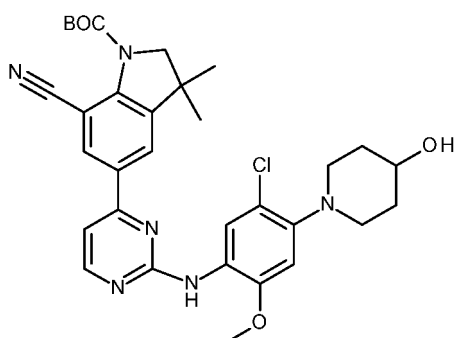
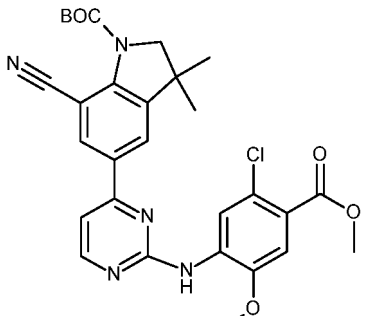
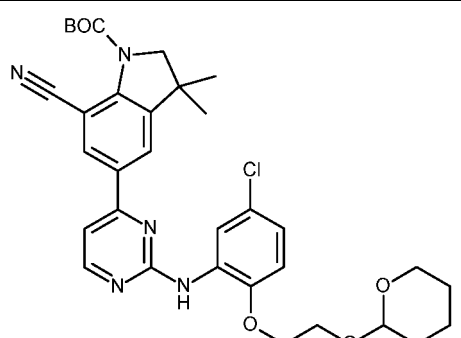
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 337	From intermediate 274 and intermediate 127	210 (80% based on LC/MS)	75
Intermediate 338	From intermediate 274 and intermediate 123	194	78
Intermediate 339	From intermediate 274 and intermediate 142	182 (90% based on LC/MS)	70

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 342	 From intermediate 274 and intermediate 341	61 (66% based on LC/MS)	25
Intermediate 345	 From intermediate 274 and intermediate 344	505 (80% based on LC/MS)	59
Intermediate 346	 From intermediate 274 and 2-fluoro-3,5-dimethoxyaniline	273 (91% based on LC/MS)	81

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 347	 From intermediate 274 and intermediate 92	559 (61% based on LC/MS)	62
Intermediate 352	 From intermediate 274 and intermediate 351	1306	84
Intermediate 353	 From intermediate 274 and intermediate 145	81 <i>yellow powder</i> (86% based on LC/MS)	22

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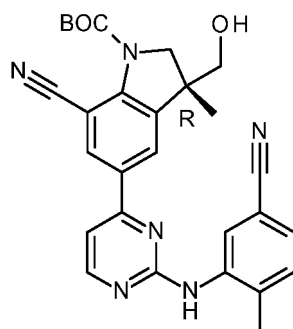


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Method E

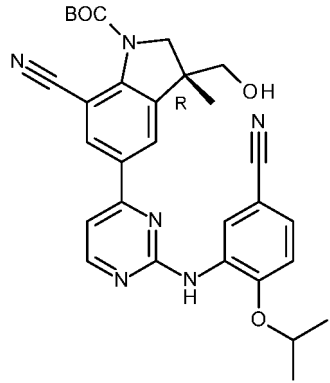
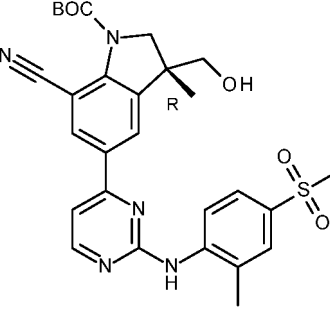
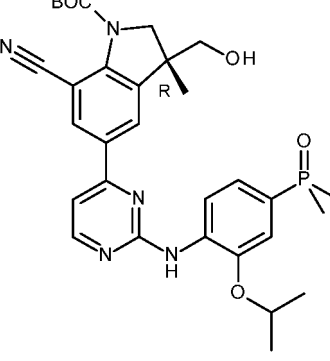
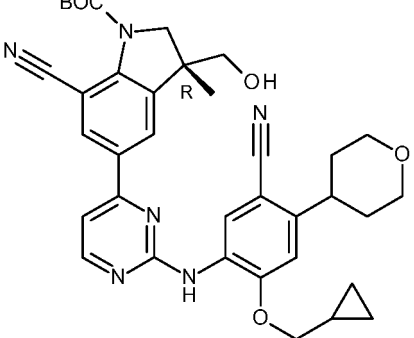
[0344] A mixture of intermediate 9R (5.30 g, 8.68 mmol) and TBAF (1M in THF, 17.3 mL, 17.35 mmol) in Me-THF (90 mL) was stirred at rt for 3 h. The reaction mixture was poured onto a 10% aqueous solution of K_2CO_3 , diluted with EtOAc and then with a saturated solution of NaCl (to help the decantation). The organic layer was decanted, washed again with 10% aqueous solution of K_2CO_3 (+ 100 mL of a saturated solution of NaCl), then with a saturated solution of NaCl. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was taken up with CH_3CN and the precipitate was filtered and dried to give 2.72 g of intermediate 10R (63% yield).

[0345] The intermediates in the Table below were prepared by using an analogous method as described in Method E starting from the respective starting materials. The most relevant minor deviations from the referenced method are indicated in the column 'Method'.

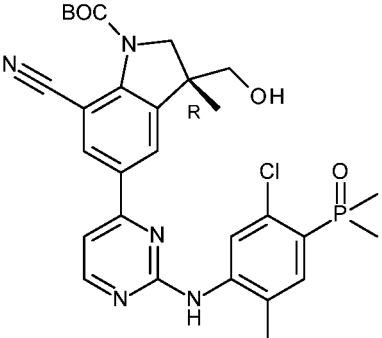
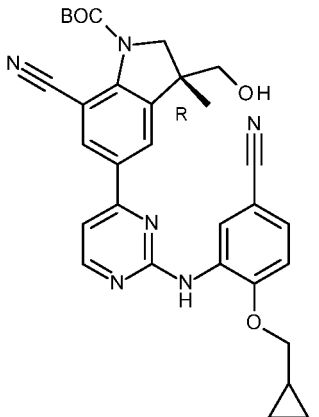
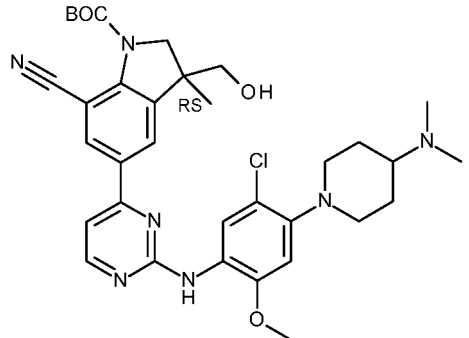
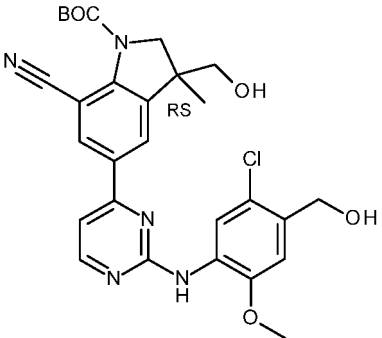
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 30	From intermediate 29	270 (95% of purity based on LC/MS)	98	E
Intermediate 35	From intermediate 33	560 (97% purity evaluated by LC/MS) <i>yellow powder</i>	84	E

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(continued)

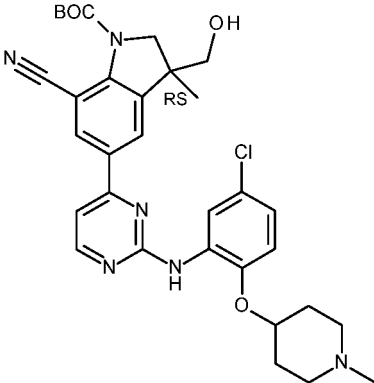
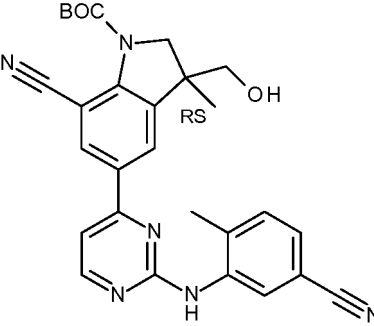
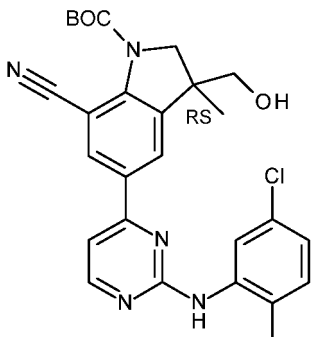
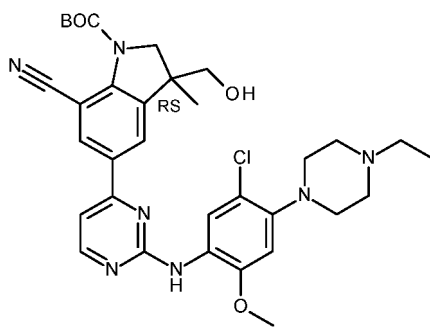
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 62	 From intermediate 61	373 (90% purity evaluated by LC/MS) <i>yellow powder</i>	93	E
Intermediate 64	 From intermediate 63	267	Quant.	E with 1.4 equiv. of TBAF
Intermediate 70	 From Intermediate 68	893 <i>off-white foam</i>	97	E with 1 equiv. of TBAF
Intermediate 75	 From Intermediate 74	887	60	E with 1.7 equiv. of TBAF

(continued)

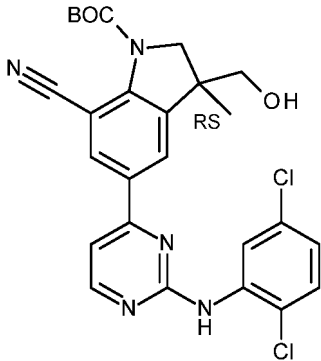
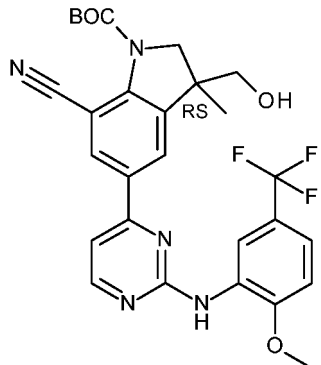
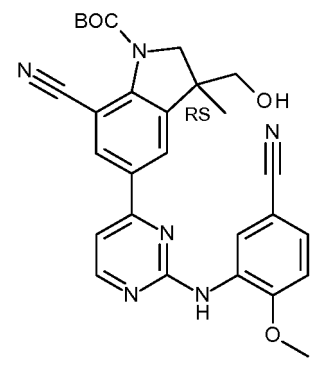
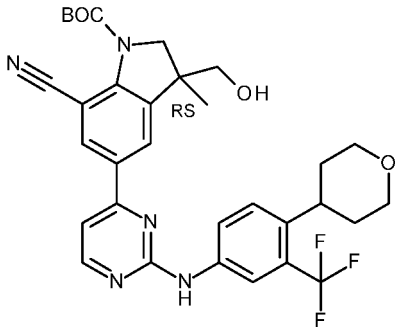
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 78	 From Intermediate 77	952 (90% purity evaluated by LC/MS) <i>white foam</i>	56	E with 1 equiv. of TBAF
Intermediate 80	 From Intermediate 79	653 <i>yellow powder</i>	86	E
Intermediate 90	 From intermediate 89	182 <i>brown oil</i>	-	E with THF as solvent and 1 equiv of TBAF
Intermediate 97	 From intermediate 96	272 <i>orange solid</i>	-	E with THF as solvent and 1 equiv of TBAF

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(continued)

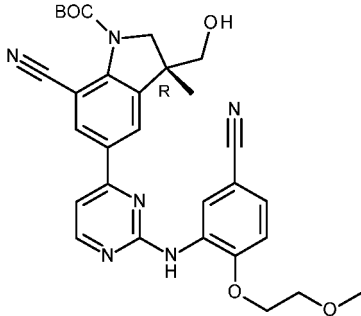
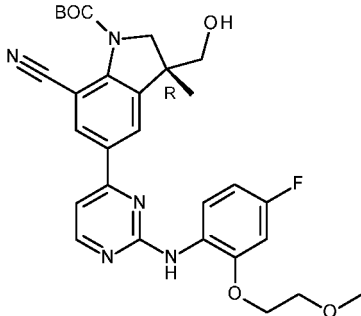
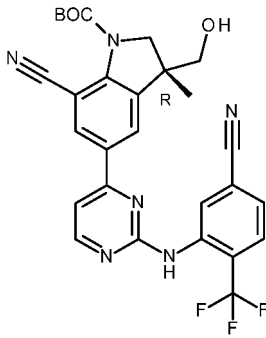
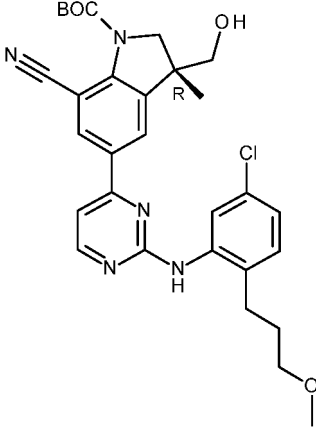
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 101	 From intermediate 100	302 <i>yellow oil</i>	-	E with THF as solvent and 1 equiv of TBAF
Intermediate 103	 From intermediate 102	289	-	E with THF as solvent and 1.1 equiv of TBAF
Intermediate 106	 From intermediate 105	390 <i>yellow solid</i>	-	E with THF as solvent and 1.1 equiv of TBAF
Intermediate 111	 From intermediate 110	246 (68% purity evaluated by LC/MS) <i>dark oil</i>	Quant.	E with THF as solvent and 1 equiv of TBAF

(continued)

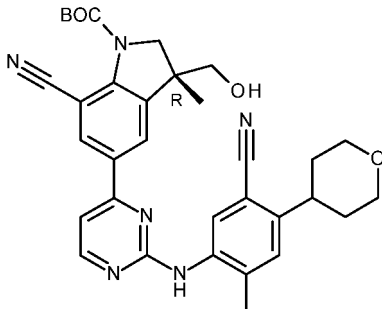
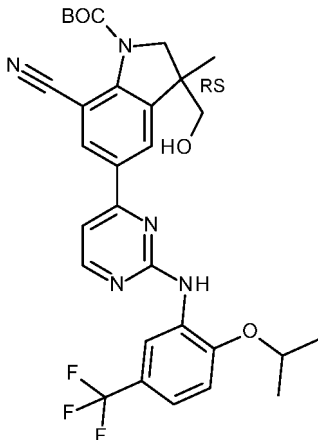
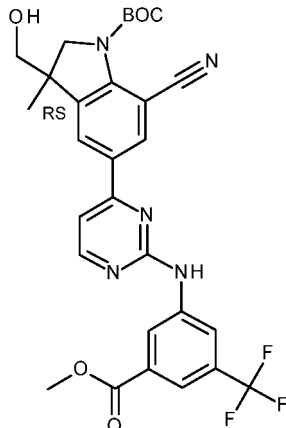
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 113	 From intermediate 112	424 <i>yellow solid</i>	-	E with THF as solvent and 1.1 equiv of TBAF
Intermediate 115	 From intermediate 114	323 (77% purity evaluated by LC/MS)	Quant.	E with THF as solvent and 1.1 equiv of TBAF
Intermediate 117	 From intermediate 116	298 <i>yellow solid</i>	Quant.	E with THF as solvent and 1.2 equiv of TBAF
Intermediate 132	 From intermediate 131	289 M.P. (K) = 203 °C	59	E with THF as solvent and 1.2 equiv of TBAF

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(continued)

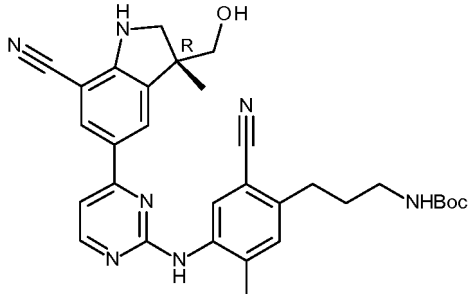
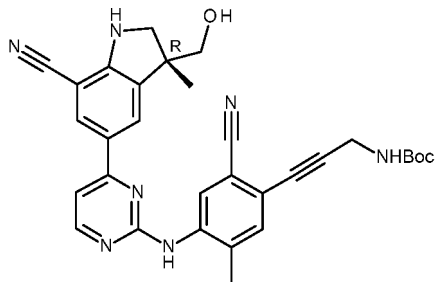
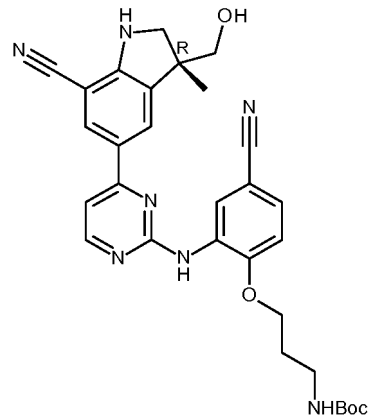
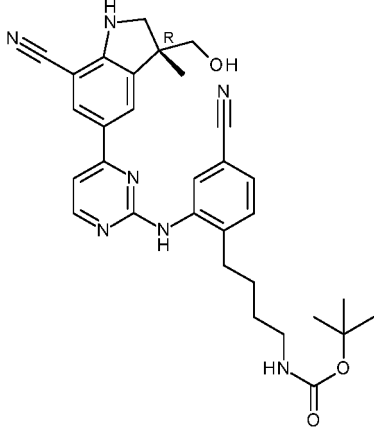
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 229	 From intermediate 228	3350	-	E and 1.2 equiv of TBAF
Intermediate 241	 From intermediate 240	406	99	E
Intermediate 243	 From intermediate 242	313	73	E
Intermediate 248	 From intermediate 247	227	82	E with 1.2 equiv. of TBAF

(continued)

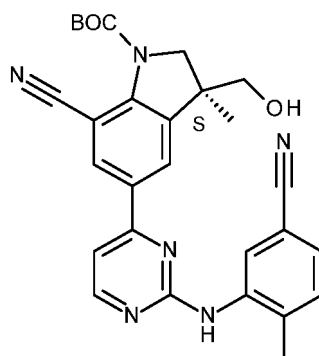
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 262	 From intermediate 261	373 <i>yellow powder</i>	81	E
Intermediate 266	 From intermediate 265	234	56	E
Intermediate 270	 From intermediate 269	230	46	E with THF and 1.9 equiv of TBAF

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(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 461	 From intermediate 459	84	48	E with 1.1 equiv of TBAF
Intermediate 464	 From intermediate 463	263	49	E with 1.1 equiv of TBAF
Intermediate 482bis	 From intermediate 482	63	17	with 0.5 equiv of TBAF
Intermediate 487	 From intermediate 486	460	100	

Example A12

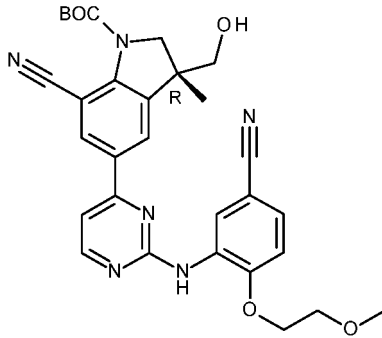
[0346] Preparation of intermediate 225:

[0347] TBAF (on silica gel 1.5 mmol/g) (1.08 g, 1.62 mmol) was added to a solution of intermediate 224 (329.00 mg, 0.54 mmol) in Me-THF (13.5 mL) and the reaction mixture was stirred at rt for 18 h. The following day, the reaction was checked and it was finished. The reaction mixture was diluted with EtOAc, twice with water and NaCl. The layers were separated and the organic layer was dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The residue (300 mg) was gathered with another batch (400 mg) for purification. Both crudes were purified by column chromatography on silica gel (irregular SiOH, 40 g, mobile phase DCM/MeOH, gradient from 100:0 to 96:4). The pure fractions were collected and evaporated to dryness to give 632 mg of intermediate 225 (light pink powder).

[0348] The intermediates in the Table below were prepared by using an analogous method starting as the one used for the preparation of intermediate 225 from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Mass (mg)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 39	From intermediate 38	310 (94% purity evaluated by LC/MS) Procedure with 4 equiv. of TBAF	48
Intermediate 206	From intermediate 205	91 Procedure with 6 equiv. of TBAF	58

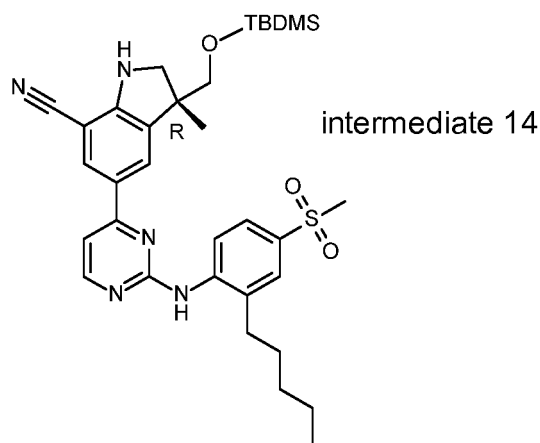
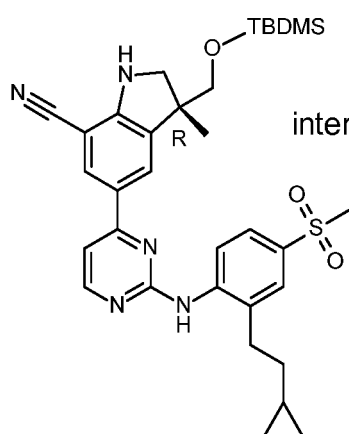
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 229	 From intermediate 228	227	68

Example A13

Preparation of intermediate 13 and intermediate 14:

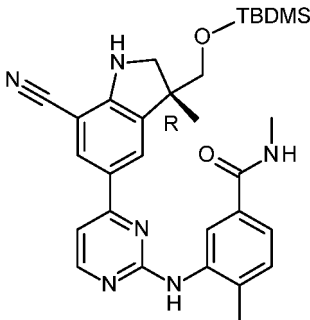
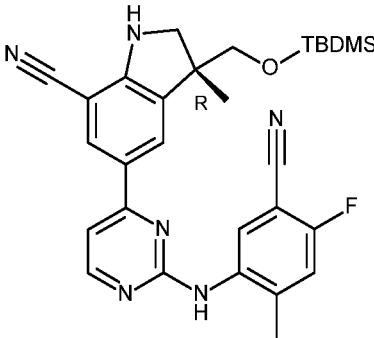
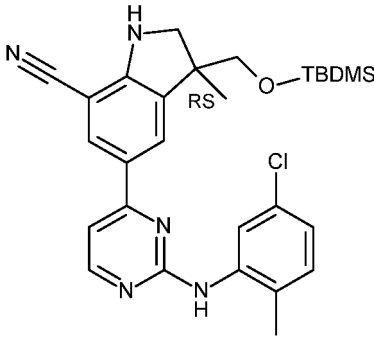
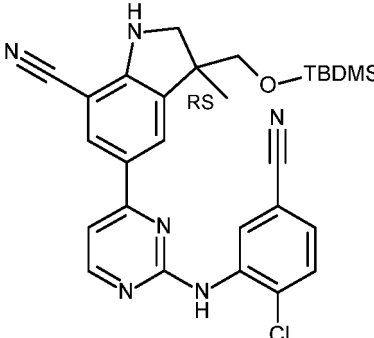
Method F

[0349]

[0350] To a solution of intermediate 11 and intermediate 12 (85/15) (1.11 g, 1.55 mmol) in DCM (35 mL), TFA (3.50 mL, 45.70 mmol) was added and stirred at rt for 30 min. The mixture was diluted with DCM and poured into an aqueous solution of NaHCO₃. The organic and aqueous layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were dried over MgSO₄, filtered and evaporated under vacuum. The residue (960 mg) was purified by column chromatography on silica gel (irregular SiOH, 15-40 μm, 50 g, dry loading on celite®, mobile phase: heptane/EtOAc/MeOH, gradient from 85% heptane, 15% EtOAc/MeOH (9:1) to 60% heptane, 40% EtOAc/MeOH (9:1)). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 695 mg of a mixture of intermediate 13 and intermediate 14 (85/15) (73% yield).

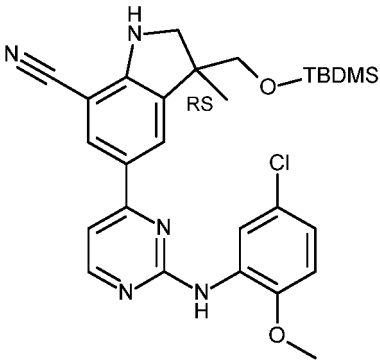
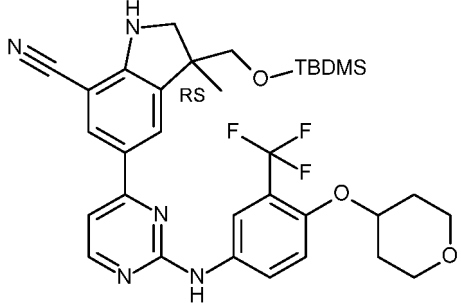
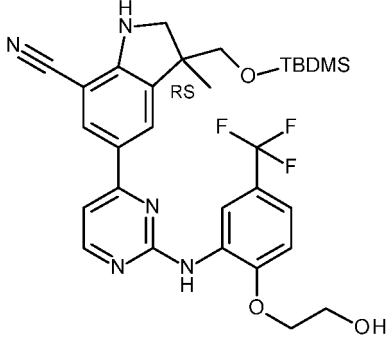
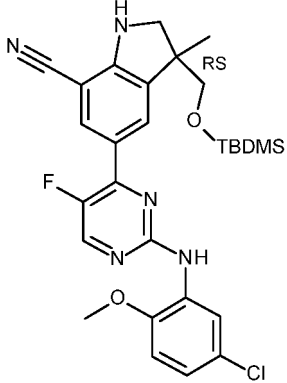
[0351] The intermediates in the Table below were prepared by using an analogous method as described in Method F starting from the respective starting materials. The most relevant minor deviations from the referenced method are indicated in the column 'Method'.

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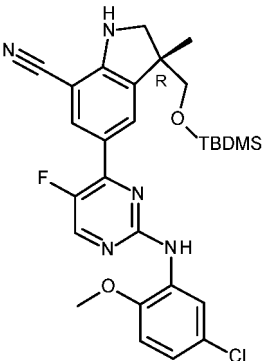
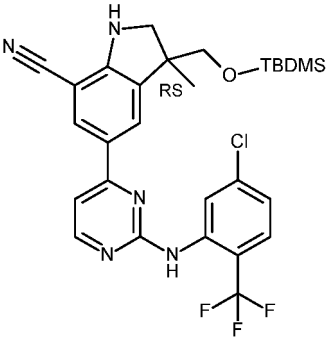
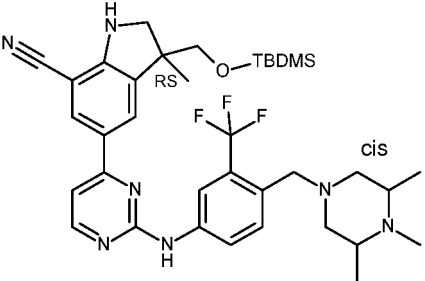
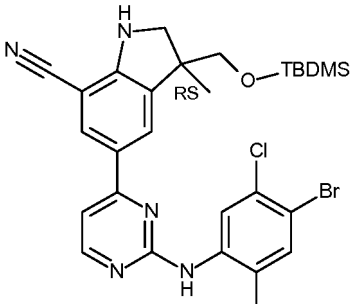
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 19	 From intermediate 18	403 <i>orange foam</i>	-	F
Intermediate 46	 From intermediate 45	500 (67% purity evaluated by LC/MS) <i>pale yellow solid</i>	67	F with DCM/TFA (6:1, v/v)
Intermediate 107	 From intermediate 105	363 <i>white solid</i>	51	F with DCM/TFA (5:1, v/v)
Intermediate 119	 From intermediate 118	251 (83% purity evaluated by LC/MS) <i>yellow solid</i>	63	F with DCM/TFA (7:1, v/v)

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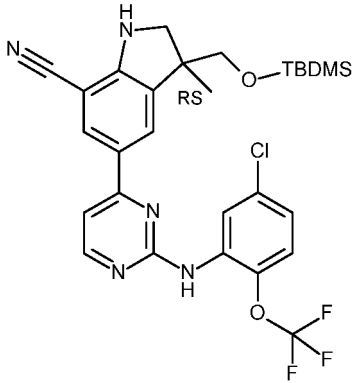
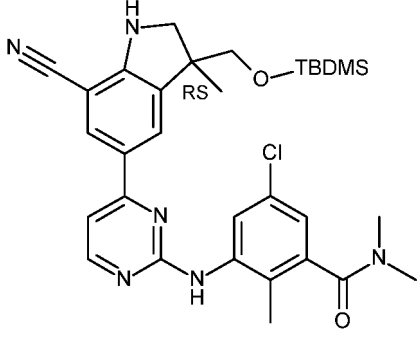
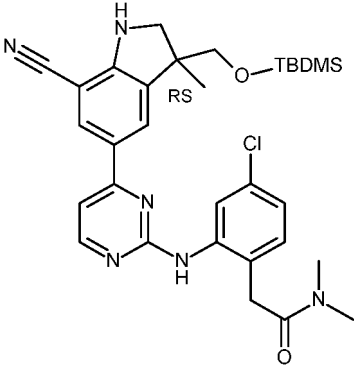
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 121	 From intermediate 120	176 (34% purity evaluated by LC/MS) <i>white foam</i>	34	F with DCM/TFA (4:1, v/v)
Intermediate 136	 From intermediate 135	97 M.P. (K) = 224 °C	66	F with DCM/TFA (4:1, v/v)
Intermediate 140	 From intermediate 139	195	74	F with DCM/TFA (4:1, v/v)
Intermediate 170	 From intermediate 169	145 (96% purity evaluated by LC/MS)	42	F with T = 5 °C with DCM/TFA (9:1, v/v)

(continued)

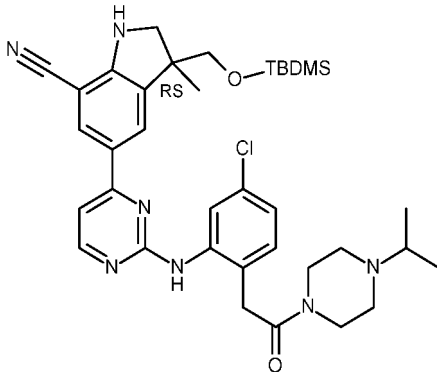
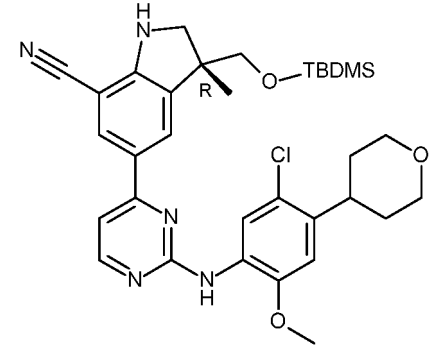
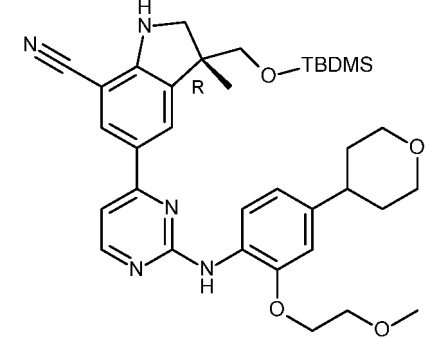
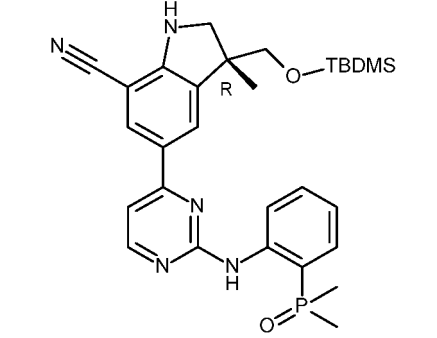
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 172	 From intermediate 171	133	38	F with T = 5 °C with DCM/TFA (9:1, v/v)
Intermediate 174	 From intermediate 173	207	58	F with T = 5 °C with DCM/TFA (4:1, v/v)
Intermediate 180	 CIS From intermediate 179	231	-	F with T=0-5 °C with DCM/TFA (4:1, v/v)
Intermediate 182	 From intermediate 181	104 (70% purity evaluated by LC/MS)	67	F with T=0-5 °C with DCM/TFA (4:1, v/v)

(continued)

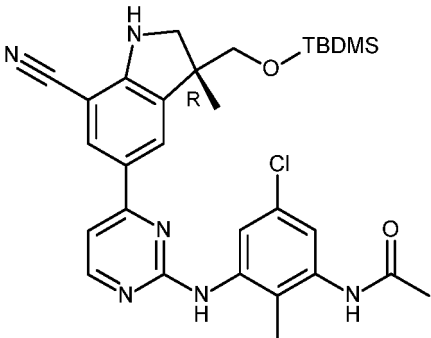
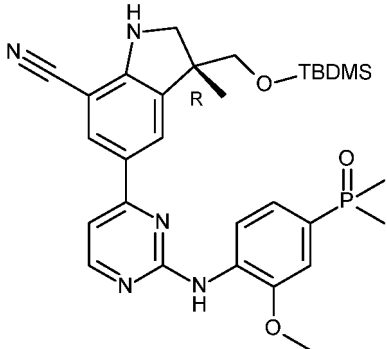
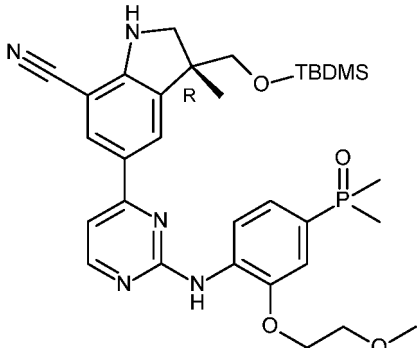
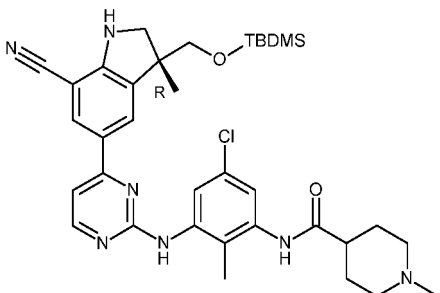
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 184	 From intermediate 183	337	77	F with T =0- 5 °C with DCM/TFA (4:1, v/v)
Intermediate 188	 From intermediate 187	213	60	F with T =0- 5 °C with DCM/TFA (4:1, v/v)
Intermediate 191	 From intermediate 190	384 (65% purity evaluated by LC/MS)	49	F with T =0- 5 °C with DCM/TFA (4:1, v/v)

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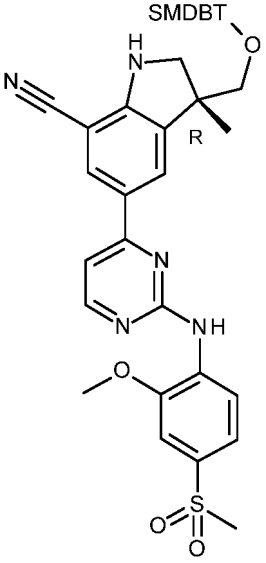
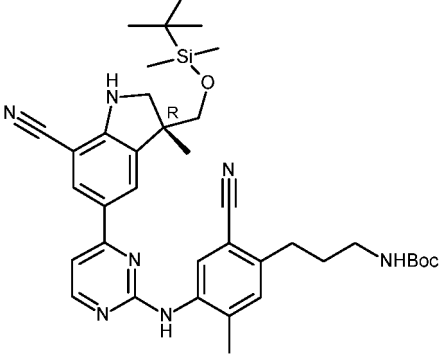
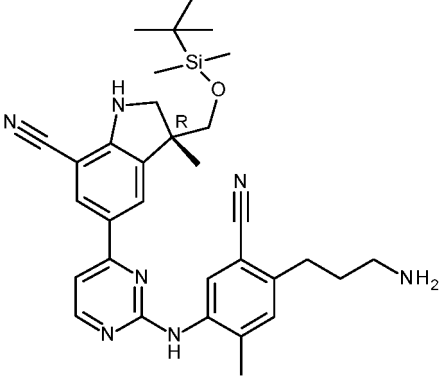
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 194	 From intermediate 193	252 (97% purity evaluated by LC/MS)	96	F with T=0-5 °C with DCM/TFA (4:1, v/v)
Intermediate 204	 From intermediate 203	168 <i>white solid</i>	57	F with DCM/TFA (6:1, v/v)
Intermediate 211	 From intermediate 210	207 <i>white foam</i>	48	F with DCM/TFA (7:1, v/v)
Intermediate 213	 From intermediate 212	240 <i>orange solid</i>	65	F with DCM/TFA (4:1, v/v)

(continued)

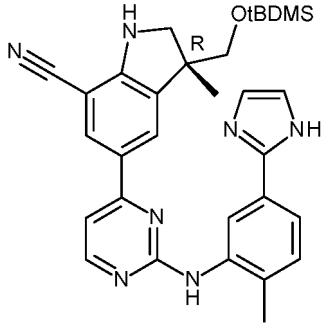
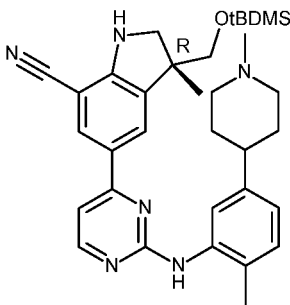
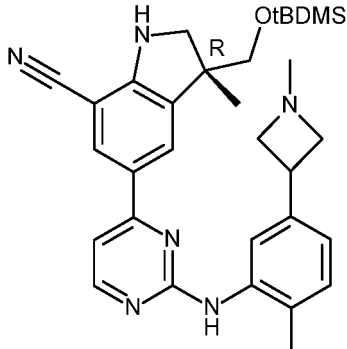
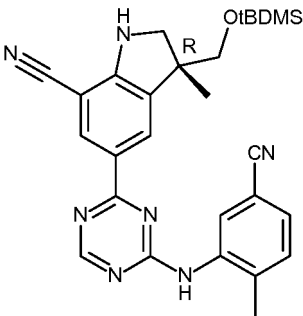
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 219	 From intermediate 218	179	54	F with T = 0 °C with DCM/TFA (6:1, v/v)
Intermediate 223	 From intermediate 222	324	76	F with DCM/TFA (4:1, v/v)
Intermediate 233	 From intermediate 232	349 <i>yellow solid</i>	76	F with DCM/TFA (7:1, v/v)
Intermediate 237	 From intermediate 236	132 (81% purity evaluated by LC/MS)	73	F with T = 0 °C with DCM/TFA (6:1, v/v)

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 253	 From intermediate 252	221	65	F with DCM/TFA (17:1, v/v)
Intermediate 459	 From intermediate 458	213	44	F With T = 5°C with DCM/TFA (7:1, v/v)
Intermediate 460	 From intermediate 458	91	22	F With T = 5°C with DCM/TFA (7:1, v/v)

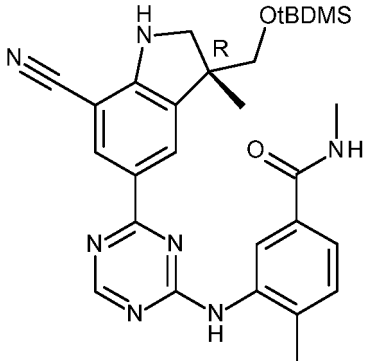
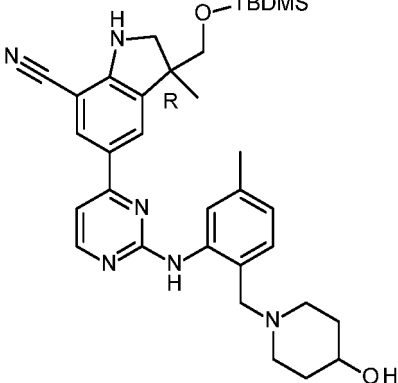
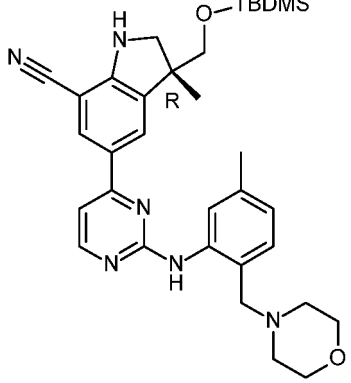
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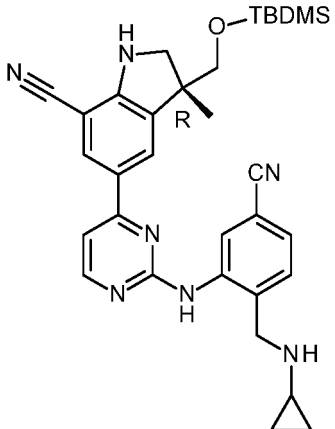
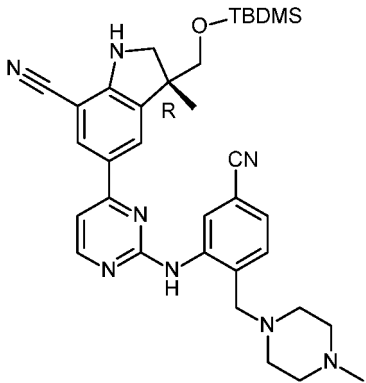
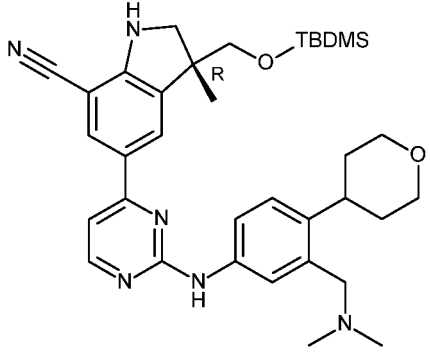
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 506	 From intermediate 505	370	Quant. Purity 69% (LCMS)	F with DCM/TFA (4:1, v/v)
Intermediate 509	 From intermediate 508	85	83% Purity 81% (LCMS)	F with DCM/TFA (4:1, v/v)
Intermediate 538	 From intermediate 537	355	89%	F with DCM/TFA (5:1, v/v)
Intermediate 545	 From intermediate 544	1100	94% Purity 43% (LC/MS)	F with DCM/TFA (9:1, v/v)

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(continued)

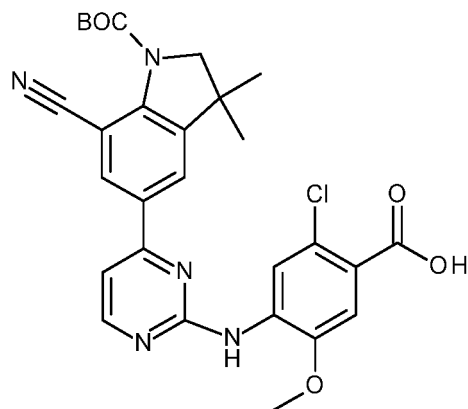
Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 548	 From intermediate 547	473	77% Purity 77% (LCMS)	F with DCM/TFA (8:1, v/v)
Intermediate 569	 From intermediate 658	260	56	F with T = 0°C and DCM/TFA (4:1, v/v)
Intermediate 573	 From intermediate 572	210	58	F with T = 0°C and DCM/TFA (4:1, v/v)

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)	Method
Intermediate 585	 From intermediate 584	98	89	F with T = 0°C and DCM/TFA (5:1, v/v)
Intermediate 589	 From intermediate 588	270	100	F with T = 0°C and DCM/TFA (4:1, v/v)
Intermediate 634	 From intermediate 633	166 61% purity based on LC/MS	-	F with DCM/TFA (18:1, v/v) during 15 hours

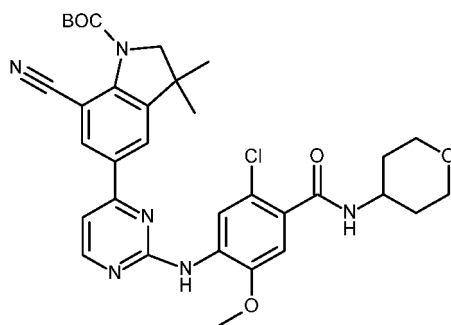
Example A14

[0352] Preparation of intermediate 354:



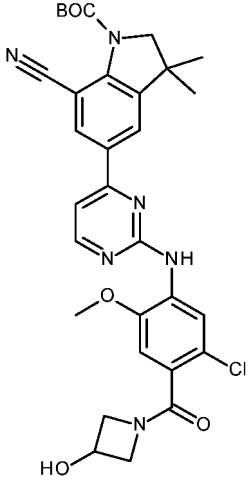
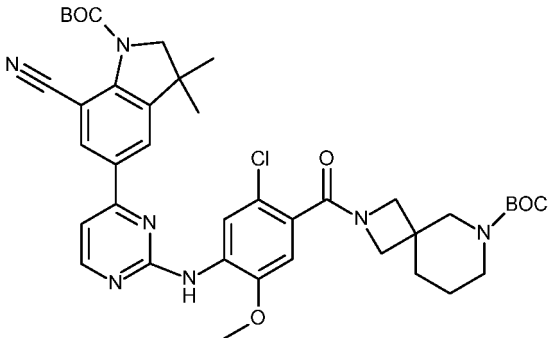
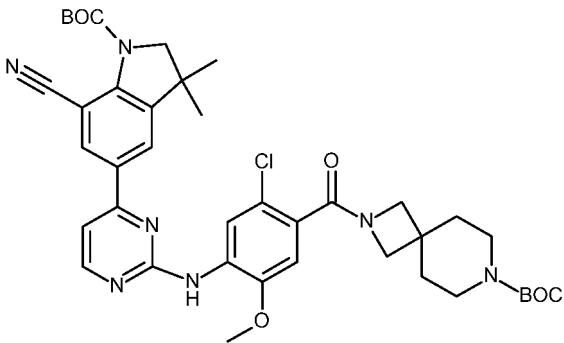
[0353] In a round bottom flask, intermediate 352 (0.10 g, 0.18 mmol) was diluted in a mixture of THF (1 mL) and water (1 mL). Then, LiOH (37.90 mg, 0.89 mmol) was added and the reaction mixture was stirred at 70 °C for 5 h 30 min. The reaction mixture was diluted with DCM and acidified with aqueous HCl 1M. The organic layer was separated quickly (to avoid any boc cleavage), dried over MgSO₄ and concentrated to afford 98 mg of intermediate 354 (quant. yield). Intermediate 354 was directly engaged in the next step without any further purification.

[0354] Preparation of intermediate 355:

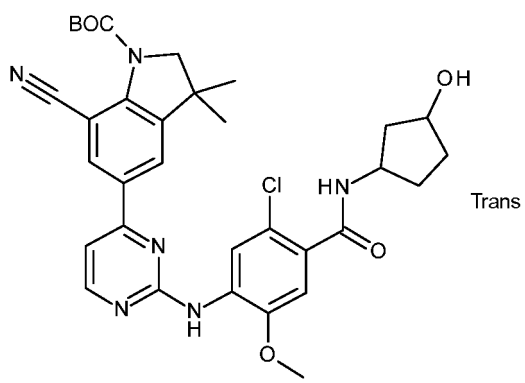
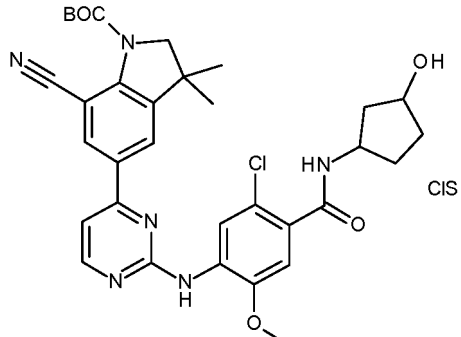
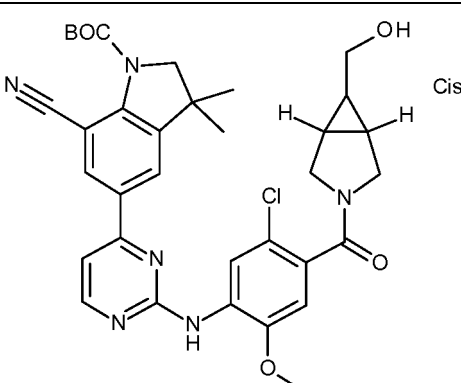


[0355] In a round bottom flask, intermediate 354 (98.00 mg, 0.18 mmol) and 4-aminotetrahydropyran (18.60 mg, 0.18 mmol) were diluted in DMF (2.5 mL) at rt. Then, HATU (135.00 mg, 0.36 mmol) and DIEA (92.10 μL, 0.53 mmol) were added and the reaction mixture was stirred at rt for 12 h. Then, the reaction mixture was partitioned between water and EtOAc, and the organic layer was washed with water, brine, dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (Irregular SiO₂, 24 g, mobile phase: DCM/MeOH, gradient from 100:0 to 95:5). The fraction containing the product were mixed and concentrated to afford 80 mg of intermediate 355 (71% yield).

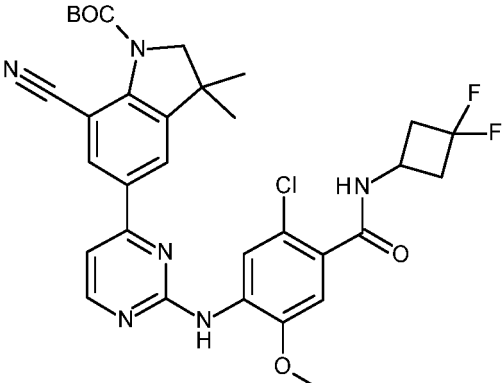
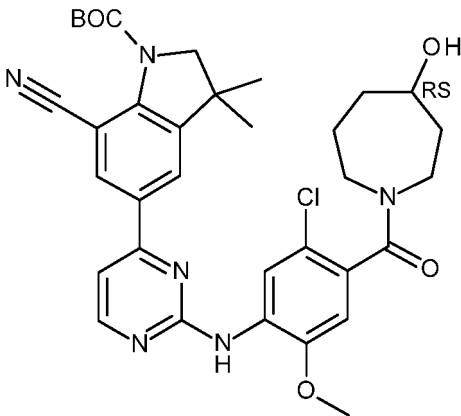
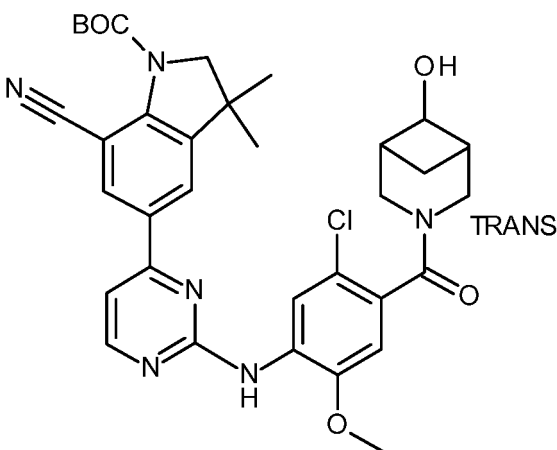
[0356] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 355 starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 357	 From intermediate 354 and 3-hydroxyazetidine hydrochloride	160 (70% purity based on LC/MS)	68
Intermediate 364	 From intermediate 354 and 6-Boc-2,6-diazaspiro[3.5]nonane oxalate	126	65
Intermediate 365	 From intermediate 354 and <i>tert</i>-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate hydrochloride	90	46

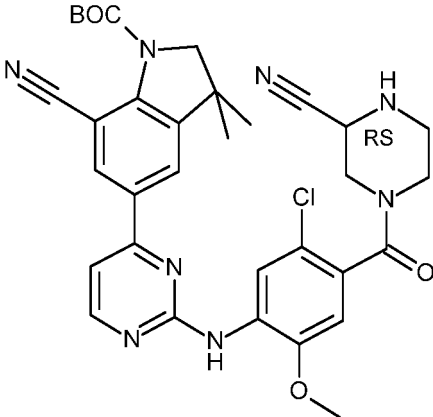
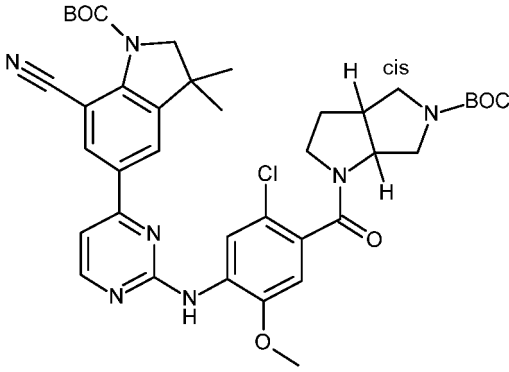
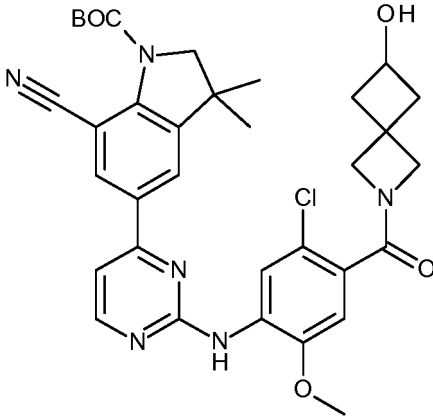
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 366	 TRANS From intermediate 354 and (1S,3S)-3-aminocyclopentanol	120 (90% purity based on LC/MS) <i>white solid</i>	62
Intermediate 367	 CIS From intermediate 354 and cis-3-aminocyclopentanol	140 (89% purity based on LC/MS) <i>yellow oil</i>	86
Intermediate 368	 CIS From intermediate 354 and 3-azabicyclo[3.1.0]hexane-6-methanol	150 (86% purity based on LC/MS) <i>yellow solid</i>	86

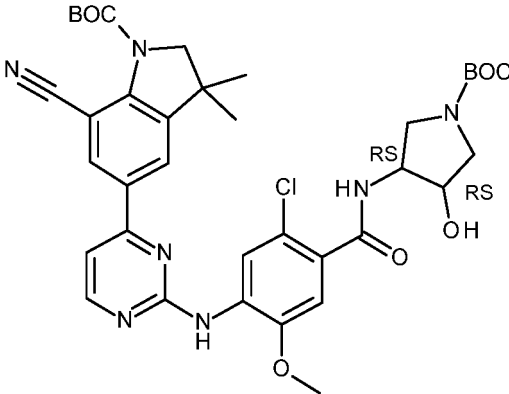
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 369	 From intermediate 354 and 3,3-difluorocyclobutanamine hydrochloride	110 (97% purity based on LC/MS)	61
Intermediate 370	 From intermediate 354 and 4-Hydroxyhexamethylenimine	160 (94% purity based on LC/MS)	92
Intermediate 371	 TRANS From intermediate 354 and 3-Azabicyclo[3.1.1]heptan-6-ol hydrochloride	150 (86% purity based on LC/MS)	79

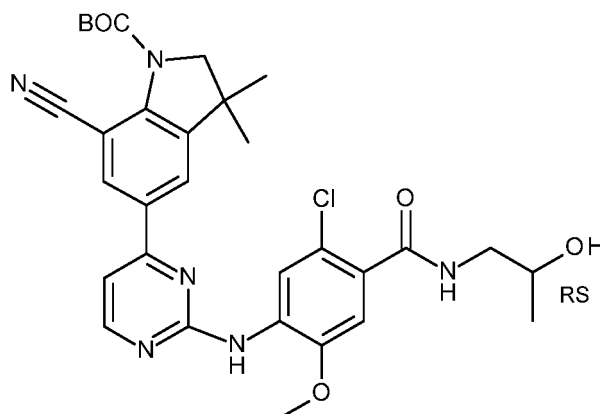
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 372	 From intermediate 354 and 2-cyanopiperazine	170 (43% purity based on LC/MS)	39
Intermediate 373	 CIS From intermediate 354 and cis pyrrolo[3,4-<i>b</i>] pyrrole-5(1<i>H</i>)-carboxylic acid, hexahydro-, 1,1-dimethylethyl ester	130 (86% purity based on LC/MS)	68
Intermediate 374	 From intermediate 354 and 2-azaspiro[3.3]heptan-6-ol	200 (38% purity based on LC/MS)	46

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 375 (mixture of 4 unseparated diastereoisomers)	 From intermediate 354 and trans-3-amino-1-boc-4-hydroxypyrrolidine	120 (96% purity based on LC/MS) <i>yellow oil</i>	58

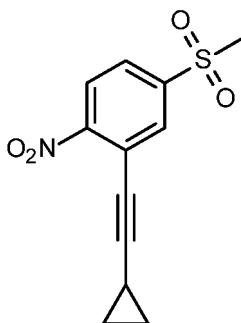
Example A15

[0357] Preparation of intermediate 363:

[0358] In a round bottom flask, intermediate 354 (0.10 g, 0.17 mmol) and amino-2-propanol (14.60 μ L, 0.19 mmol) were mixed in DMF (2.33 mL). Then, EDC-HCl (53.1 mg, 0.34 mmol) and DIEA (147.00 μ L, 0.85 mmol) were added and the reaction mixture was stirred for 3 h. As the conversion was very low, HATU (0.13 g, 0.34 mmol) and DIEA (2 equiv.) were added and the reaction mixture was stirred for 48 h. The reaction mixture was partitioned between water and EtOAc. The organic layer was washed one with water, then with brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by column chromatography on silica gel (irregular SiOH , 40 g, mobile phase DCM/MeOH, gradient from 100:0 to 96:4). The fractions containing the product were mixed and concentrated to afford 81 mg of intermediate 363 (78% yield).

Example A16

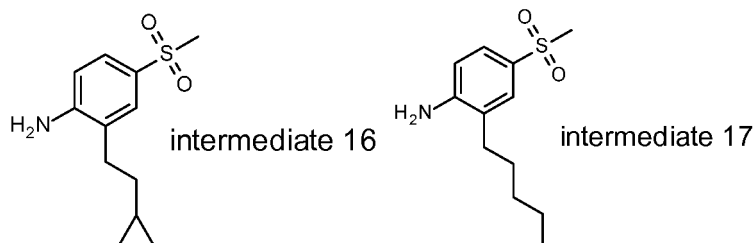
[0359] Preparation of intermediate 15:



[0360] In a Schlenk reactor, a mixture of 2-bromo-4-(methylsulfonyl)aniline (2.00 g, 8.00 mmol), ethynylcyclopropane (1.06 g, 16.00 mmol) and TEA (5.56 mL, 40.00 mmol) in dry DMF (40 mL) was purged with N₂. Then, Pd(PPh₃)₂Cl₂ (281.00 mg, 0.40 mmol) and CuI (152.00 mg, 0.80 mmol) were added. The mixture was purged with N₂ and stirred at 100 °C for 2 h. Then, additional ethynylcyclopropane (1.06 g, 16.00 mmol), Pd(PPh₃)₂Cl₂ (281 mg, 0.4 mmol) and CuI (152.00 mg, 0.80 mmol) were added. The mixture was purged with N₂ and stirred at 100 °C for 1 h. Then, additional ethynylcyclopropane (1.06 g, 16.00 mmol), Pd(PPh₃)₂Cl₂ (281 mg, 0.4 mmol) and CuI (152.00 mg, 0.80 mmol) were added. The mixture was purged with N₂ and stirred at 100 °C for 1 h. The resulting mixture was cooled down to rt and evaporated under vacuum. The residue (7 g) was purified by column chromatography on silica gel (irregular SiOH, 15-40 μm, 220 g, dry loading on celite®, mobile phase: DCM/EtOAc, gradient from 100:0 to 98:2). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 1.59 g of intermediate 15 (84% yield, containing 21% 2-bromo-4-(methylsulfonyl)aniline according to ¹H NMR, orange solid).

Preparation of intermediate 16 and intermediate 17:

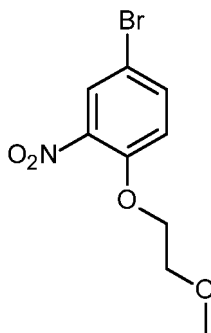
[0361]



[0362] In a sealed tube, a solution of intermediate 15 (930.00 mg, 3.95 mmol), ammonium formate (15.00 g, 237.14 mmol) and Pd/C (10 wt. %) (2.50 g, 2.37 mmol) in a mixture of iPrOH (32 mL) and Me-THF (16 mL) were added and stirred at 70 °C for 30 min. The crude product was filtered through a pad of celite® and the cake was washed with EtOAc and iPrOH. The filtrate was evaporated under vacuum and the residual oil was taken-up in DCM and washed with water. The organic layer was dried over MgSO₄, filtered off and concentrated under vacuum. The residue (880 mg) was purified by column chromatography on silica gel (irregular SiOH, 15-40 μm, 50 g, dry loading on celite®, mobile phase: heptane/EtOAc/MeOH, gradient from 85% heptane, 13.5% EtOAc and 1.5% MeOH to 30% heptane, 63% EtOAc and 7% MeOH). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 552 mg of a mixture of intermediate 16 and intermediate 17 (58% yield, pale yellow oil, 85/15 evaluating by ¹H NMR).

Example A17

[0363] Preparation of intermediate 22:



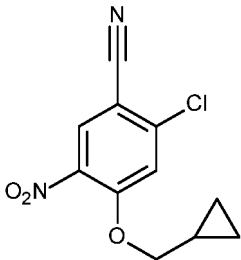
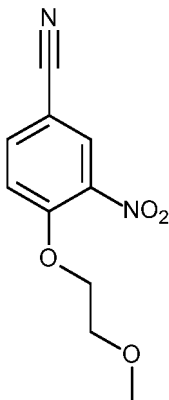
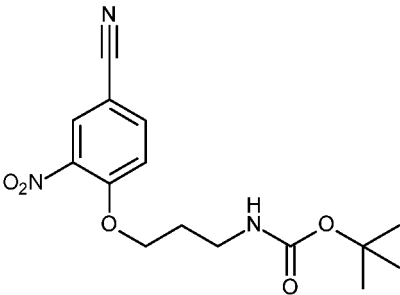
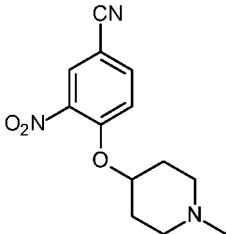
[0364] To a solution of 2-methoxyethanol (721.00 μ L, 9.09 mmol) in THF (24 mL), LiHMDS (1.5 M in toluene, 6.06 mL, 9.09 mmol) was added dropwise at 5 °C. After 30 min, 4-Fluoro-3-nitrobromobenzene (1.11 mL, 9.09 mmol) was quickly added and the reaction mixture was allowed to warm to rt and stirred overnight. The reaction mixture was quenched with water and diluted with EtOAc. The organic layer was decanted, washed with brine, dried over MgSO_4 , filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (SiO_2 , 120 g, 15-40 μ m, mobile phase: heptane/EtOAc, gradient from 100:0 to 0:100). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 1.923 g of intermediate 22 (77% yield).

[0365] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 22 starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Mass (g)'.

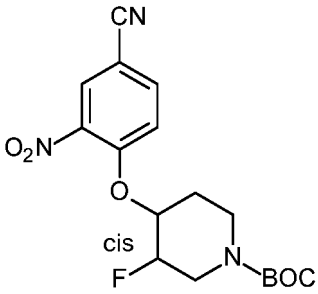
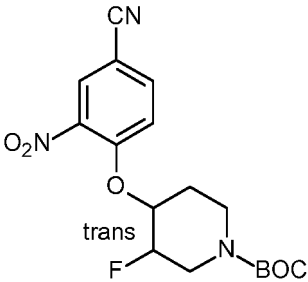
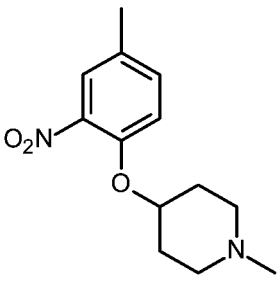
Intermediate number	Structure	Mass (g)	Yield (%)
Intermediate 25	From 4-fluoro-3-nitrobromo benzene	2.02	82
Intermediate 50	From 4-fluoro-3-nitro benzonitrile	3.90	99

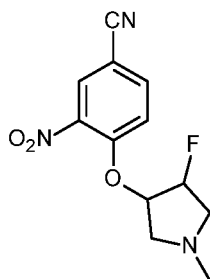
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(continued)

Intermediate number	Structure	Mass (g)	Yield (%)
Intermediate 71	 From 2-chloro-4-fluoro-5-nitrobenzonitrile	2.35 <i>brown solid</i> Procedure with Me-THF	93
Intermediate 226	 From 4-fluoro-3-nitrobenzonitrile	1.28 Procedure with Me-THF	96
Intermediate 480	 From 3-(tert-butoxycarbonylamino)-1-propanol and 4-chloro-3-nitrobenzonitrile	10.67 Procedure with LiHMDS 1N in THF	40
Intermediate 574	 From 4-fluoro-3-nitrobenzonitrile and 4-hydroxy-1-methylpiperidine	0.425 Procedure with Me-THF	54

(continued)

Intermediate number	Structure	Mass (g)	Yield (%)
Intermediate 601	 From 4-fluoro-3-nitrobenzonitrile and cis-1-boc-3-fluoro-4-hydroxypiperidine	0.420 Procedure with LiHMDS (1M in THF) in Me-THF.	92
Intermediate 607	 From 4-fluoro-3-nitrobenzonitrile and trans-1-boc-3-fluoro-4-hydroxypiperidine	0.200 Procedure with LiHMDS (1M in THF) in Me-THF	73
Intermediate 620	 From 4-fluoro-3-nitrotoluene and 4-hydroxy-1-methylpiperidine	0.273 Procedure in Me-THF	34

[0366] Preparation of intermediate 614 and intermediate 615

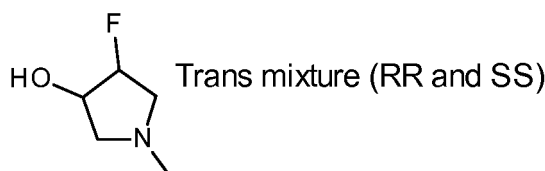
intermediate 614: Trans A (RR or SS)

intermediate 615: Trans B (SS or RR)

[0367] A solution of LiHMDS 1.5M in THF (5.6 mL; 8.42 mmol) was added dropwise at 5°C to a solution of intermediate 614a (590 mg; 4.95 mmol) in Me-THF (18.4 mL). After 30 min, 4-fluoro-3-nitrobenzonitrile (823 mg; 4.95 mmol) was

quickly added and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was poured onto iced water, a 10% aqueous solution of K_2CO_3 and extracted with EtOAc. The organic layer was decanted, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue (1.16 g; yellow solid) was purified by chromatography over silica gel (SiO_2 , 40 g, eluent: from 98% DCM, 2% MeOH, 0.2% NH_4OH to 95% DCM, 5% MeOH, 0.5% NH_4OH). The fractions containing the products were collected and the solvent was evaporated to give 486 mg of yellow solid racemic trans product (37%). The racemic trans product was purified by chiral SFC (Chiralpak AD-H 5 μm 250*30 mm, mobile phase: 95.7% CO_2 , 4.3% MeOH (0.3% $iPrNH_2$)). The pure fractions were collected and the solvent was evaporated to give 177 mg (13%) of intermediate 614 (Trans A; RR or SS; eluted first) and 174 mg (13%) of intermediate 615 (Trans B; SS or RR; eluted second).

[0368] Preparation of intermediate 614a:

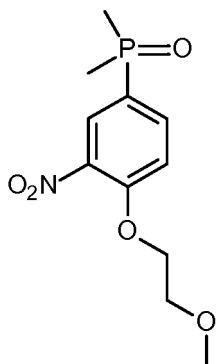


[0369] Formaldehyde (10.6 mL; 141.3 mmol) was added to a mixture of trans-4-fluoro-3-hydroxypyrrolidine hydrochloride (1 g; 7.06 mmol) and acetic acid (809 μL ; 14.13 mmol) in methanol (55 mL) at rt. The reaction mixture was stirred at rt for 30min, then sodium triacetoxyborohydride (3.74 g; 17.66 mmol) was added and the reaction mixture was stirred at rt for 3h. The mixture was basified with a saturated aqueous $NaHCO_3$ solution at 5°C.

[0370] The mixture was diluted with diethylether and washed with saturated aqueous $NaHCO_3$ solution. Then, the aqueous layer was extracted with diethylether (3 times) but intermediate 614a was still in aqueous layer. Then, the aqueous layer was extracted with EtOAc (3 times) but intermediate 614a was still in aqueous layer. Then, the aqueous layer was extracted with DCM (3 times). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent was evaporated at room temperature to give 1.09 g of intermediate 614a as a colourless volatile oil used without any further purification in the next step.

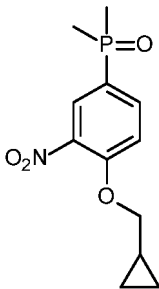
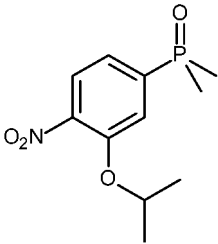
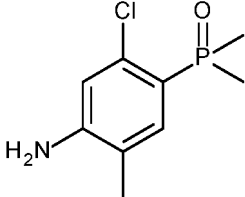
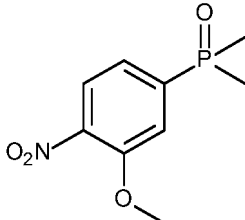
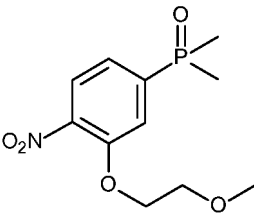
Example A18

[0371] Preparation of intermediate 23:

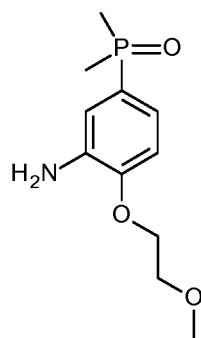


[0372] In a sealed tube, a solution of intermediate 22 (500.00 mg, 1.81 mmol), dimethylphosphine oxide (167.00 mg, 1.99 mmol) and K_3PO_4 (423.00 mg, 1.99 mmol) in dry DMF (7.5 mL) was purged with N_2 . Then, $Pd(OAc)_2$ (40.70 mg, 0.18 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (105 mg, 0.18 mmol) were added. The mixture was purged with N_2 and stirred at 130 °C for 3 h. The reaction was performed twice on the same quantity of intermediate 22. The 2 batches were combined. The resulting mixture was filtered on a pad of celite® and the cake was washed with EtOAc. The filtrate was evaporated under vacuum to give a brown oil. The residue was purified by column chromatography on silica gel (irregular $SiOH$, 15-40 μm , 80 g, dry loading on celite®, mobile phase: DCM/MeOH, gradient from 99.5:0.5 to 95:5). The desired fractions were collected and the solvent was concentrated to dryness under vacuum to give 0.895 g of intermediate 23 (90% yield, orange oil).

[0373] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 23 starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Mass'.

Intermediate number	Structure	Mass	Yield (%)
Intermediate 26	 From intermediate 25	569 mg	58
Intermediate 66	 From intermediate 65	765 mg <i>orange gum</i>	74
Intermediate 76	 From 4-bromo-5-chloro-2-methylaniline	1 g <i>white solid</i> Procedure with reaction temperature = 150 °C	51
Intermediate 220	 From 4-bromo-2-methoxy-1-nitrobenzene	334 mg <i>brown solid</i> Procedure with reaction temperature = 150 °C	68
Intermediate 230	 From intermediate 207	552 mg <i>red solid</i> Procedure with reaction temperature = 150 °C	83

[0374] Preparation of intermediate 24:

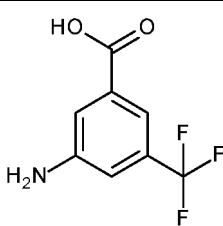


[0375] To a solution of intermediate 23 (877.00 mg, 3.21 mmol) in MeOH (23 mL), Raney nickel (19.00 mg, 0.32 mmol) was added under N₂. The mixture was stirred at rt under 1.5 bar of H₂ for 3 h. The mixture was filtered on a pad of Celite® and the cake was washed with EtOH. The filtrate was evaporated under vacuum to give 726 mg of intermediate 24 (93% yield).

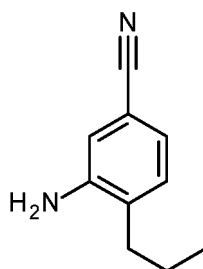
[0376] The intermediates in the Table below were prepared by using an analogous starting as the one used for the preparation of intermediate 24 from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Mass'.

Intermediate number	Structure	Mass	Yield (%)
Intermediate 27	From intermediate 26	490 mg	97
Intermediate 134	From intermediate 133	1.37 g Procedure with 3 bars pressure of H ₂	94
Intermediate 156	From intermediate 155	2.1 g Procedure with 3 bars pressure of H ₂	97

(continued)

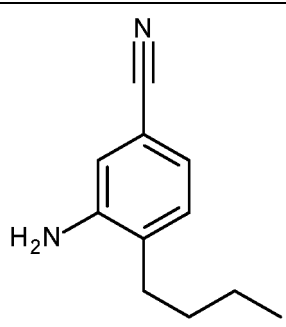
Intermediate number	Structure	Mass	Yield (%)
Intermediate 268	 From intermediate 267	16.7 g Procedure with 3 bars pressure of H ₂	100

Example A19

[0377] Preparation of intermediate 28:

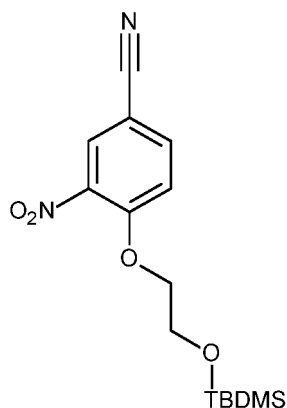
[0378] To a solution of 3-amino-4-iodobenzonitrile (0.50 g, 2.05 mmol) in THF (10 mL), a premixed degassed solution of Pd(*t*-Bu₃P)₂ (105 mg, 0.20 mmol) in a solution of n-propylzinc bromide in THF (0.5 M, 8.20 mL, 0.41 mmol) was added and stirred at rt for 2 h. The reaction mixture was poured onto a 10% aqueous solution of K₂CO₃ and EtOAc was added. The crude product was filtered through a pad of celite® and the organic layer was decanted, washed with water, dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (irregular SiOH, 24 g, mobile phase: heptane/EtOAc: gradient from 90% heptane, 10% EtOAc to 70% heptane, 30% EtOAc). The pure fractions were collected and evaporated to dryness to give 250 mg of intermediate 28 (76% yield).

[0379] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 28 starting from the respective starting materials.

Intermediate number	Structure	Mass	Yield (%)
Intermediate 56	 From 3-amino-4-iodobenzonitrile	212 mg	59

Example A20

[0380] Preparation of intermediate 31:

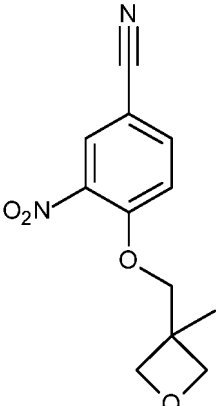
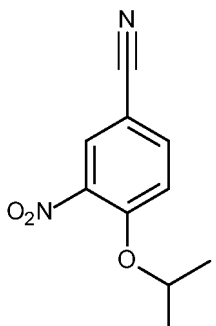
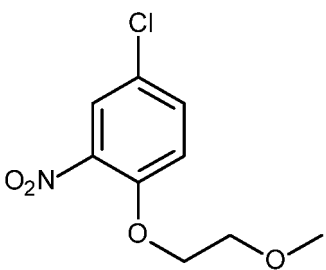
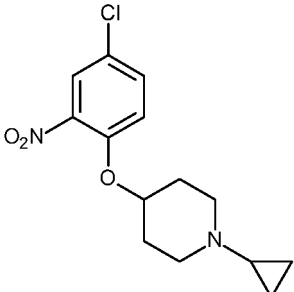


[0381] 4-fluoro-3-nitrobenzonitrile (1.00 g, 6.02 mmol) and 2-(*tert*-butyldimethylsiloxy)ethanol (1.32 mL, 6.62 mmol) were dissolved in distilled THF (7 mL) (to give a 0.1 - 0.2 M solution) under Ar and cooled to 0 °C. KHMDS (6.62 mL, 6.62 mmol) dissolved in distilled THF (5.3 mL) (to give 0.5 M solution) was added dropwise, resulting in a color change from colorless to dark. This solution was stirred from 0 °C to rt over 3 h and the reaction mixture was then diluted with DCM and washed once with saturated aqueous NH₄Cl. The aqueous layer was back-extracted once with DCM. The organic layers were combined, dried over MgSO₄, concentrated. The residue (1.5 g, black oil) was purified by column chromatography on silica gel (irregular SiOH, 80 g, mobile phase: heptane/EtOAc, gradient from 100% heptane, 0% EtOAc to 70% heptane, 30% EtOAc). The desired fractions were collected and evaporated to dryness to give 0.30 g of intermediate 31 (15% yield, orange powder). However, apurified again by column chromatography on silica gel (irregular SiOH, 80g, deposit solid, mobile phase: heptane/EtOAc, gradient from 100:0 to 70:30). The desired fractions were collected and evaporated to dryness to give 0.659 g of intermediate 31 (34% yield, orange powder) with a global yield of 49%.

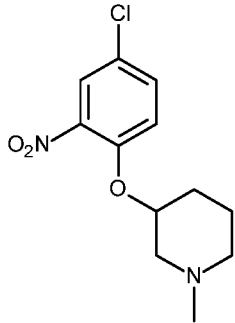
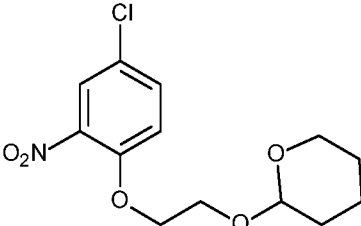
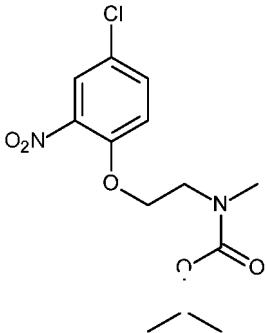
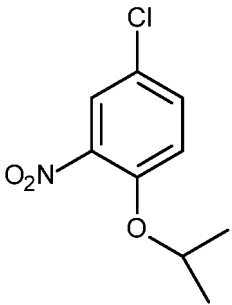
[0382] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 31 starting from the respective starting materials.

Intermediate number	Structure	Mass (g)	Yield (%)
Intermediate 40	From 4-fluoro-3-nitrobenzonitrile	1.354 <i>yellow powder</i>	44
Intermediate 47	From 4-fluoro-3-nitrobenzonitrile	1.636 <i>yellow powder</i>	76

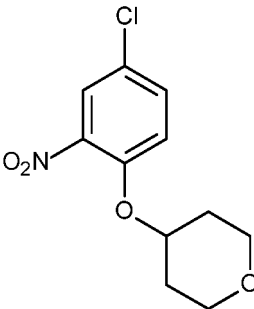
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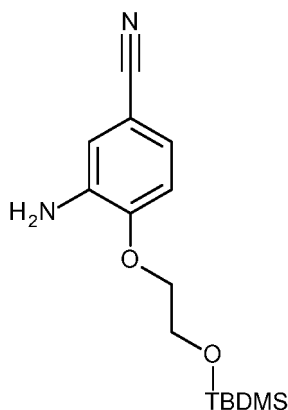
Intermediate number	Structure	Mass (g)	Yield (%)
Intermediate 53	 From 4-fluoro-3-nitrobenzonitrile	0.922	62
Intermediate 58	 From 4-fluoro-3-nitrobenzonitrile	0.305	34
Intermediate 122	 From 5-chloro-2-fluoro-nitrobenzonitrile	0.514	78
Intermediate 126	 From 5-chloro-2-fluoro-nitrobenzonitrile	0.515	61%

(continued)

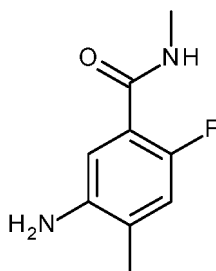
Intermediate number	Structure	Mass (g)	Yield (%)
Intermediate 141	 From 5-chloro-2-fluoro-nitrobenzonitrile	0.578	75
Intermediate 144	 From 5-chloro-2-fluoro-nitrobenzonitrile	1.159	64
Intermediate 159	 From 5-chloro-2-fluoro-nitrobenzonitrile	0.999	51
Intermediate 340	 From 5-chloro-2-fluoronitrobenzene	0.545	89

(continued)

Intermediate number	Structure	Mass (g)	Yield (%)
Intermediate 343	 From 5-chloro-2-fluoronitro benzene	0.653	89
		<i>colorless oil</i>	

[0383] Preparation of intermediate 32:

[0384] Iron powder (0.83 g, 14.87 mmol) was added to a solution of intermediate 31 (0.96 g, 2.97 mmol), NH_4Cl (0.64 g; 11.90 mmol) in EtOH (8.34 mL) and distilled water (4.19 mL). The reaction mixture was stirred at 75 °C for 3 h. The reaction mixture was filtered over a pad of celite® and washed with DCM. A saturated solution of NaHCO_3 was added and the mixture was extracted with DCM. The organic layer was dried over MgSO_4 , filtered and evaporated to dryness to give 701 mg of intermediate 32 (81% yield, brown oil).

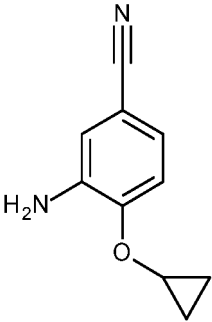
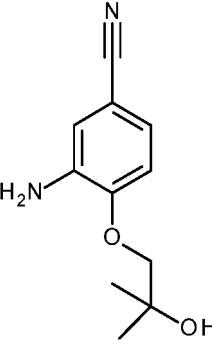
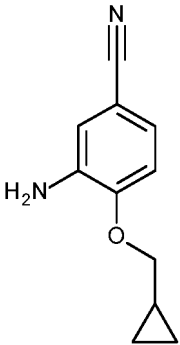
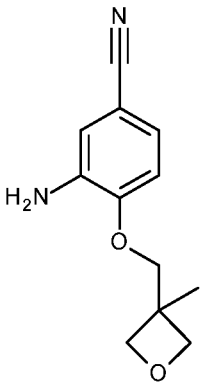
[0385] Preparation of intermediate 422:

[0386] A mixture of intermediate 421 (10.47 g; 49.35 mmol), iron powder (13.78 g; 246.72 mmol) and ammonium chloride (10.56 g; 197.38 mmol) in EtOH (350 mL) and water (118 mL) was heated at 80°C for 1hour. The reaction mixture was cooled down to room temperature, diluted with DCM, filtered over celite® and basified with a 10% aqueous solution of K_2CO_3 . The organic layer was decanted, dried over MgSO_4 , filtered and the solvent was evaporated to give 8.68 g (97%) of intermediate 422 as an orange solid which was used without any further purification in the next step.

[0387] The intermediates in the Table below were prepared by using an analogous method starting from the respective

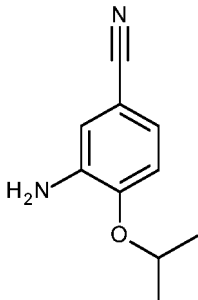
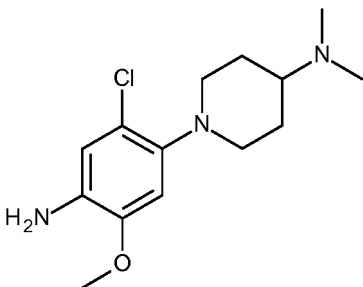
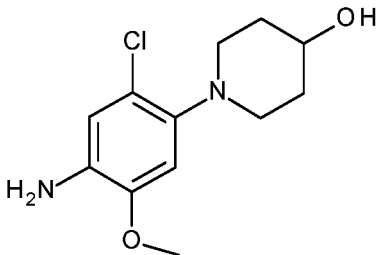
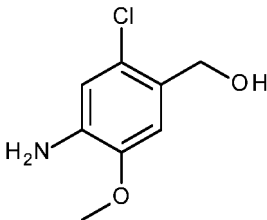
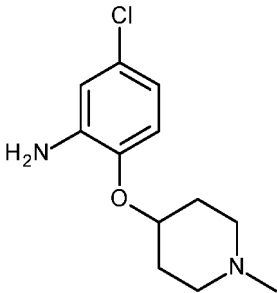
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starting materials as the one used for the preparation of intermediate 32. The most relevant minor deviations to the reference method are indicated as additional information in the column 'Mass (mg)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 41	 From intermediate 40	981 (90% purity evaluated by NMR) <i>white powder</i>	84
Intermediate 48	 From intermediate 47	938 <i>yellow powder</i>	66
Intermediate 51	 From intermediate 50	2440 (95% purity evaluated by LC/MS)	65
Intermediate 54	 From intermediate 53	738 <i>orange powder</i>	91

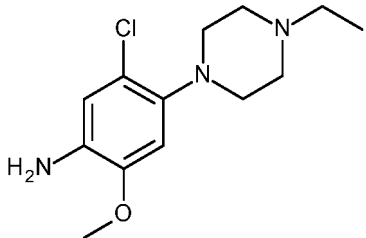
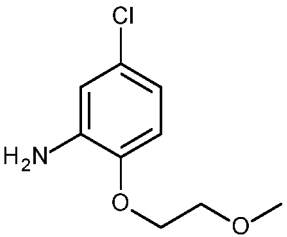
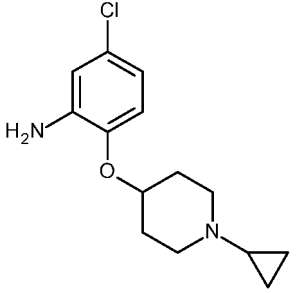
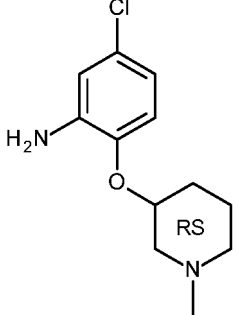
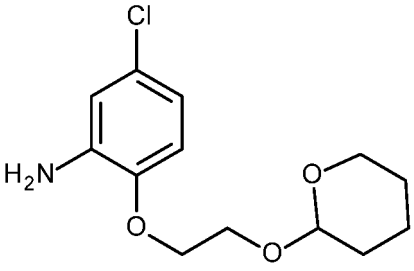
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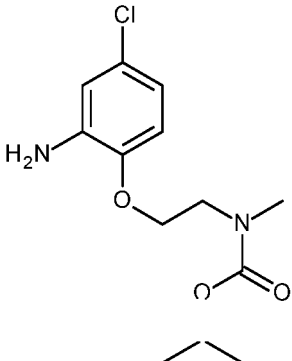
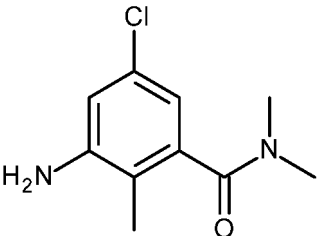
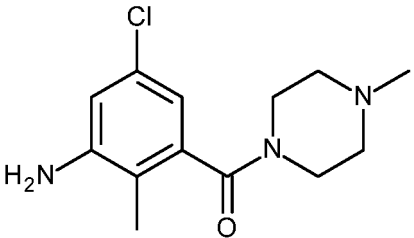
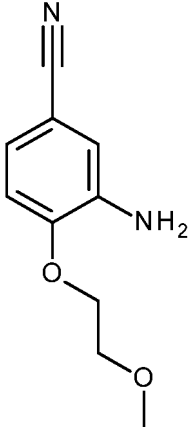
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 59	 From intermediate 58	650 <i>brown oil</i> Procedure with reaction temperature = 85 °C	95
Intermediate 88	 From intermediate 87	414 <i>dark red solid</i>	86
Intermediate 92	 From intermediate 91	997	68
Intermediate 95	 From intermediate 94	351 <i>pale yellow solid</i>	89
Intermediate 99	 From intermediate 98	1280 <i>off-white solid</i>	85

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(continued)

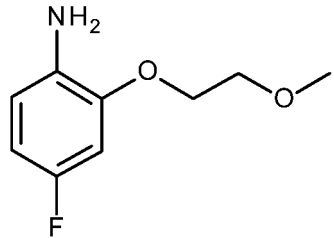
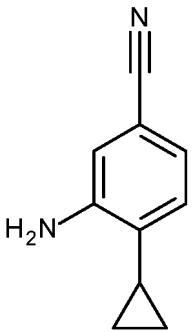
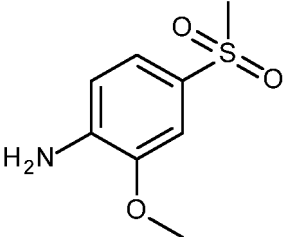
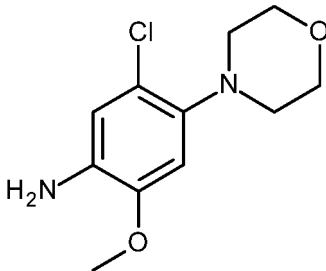
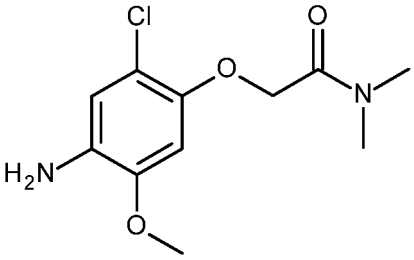
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 109	 From intermediate 108	436 <i>dark red solid</i>	95
Intermediate 123	 From intermediate 122	580 <i>yellow oil</i>	-
Intermediate 127	 From intermediate 126	512 Procedure with reaction temperature = 85 °C <i>yellow oil</i>	-
Intermediate 142	 From intermediate 141	429 Procedure with reaction temperature = 85 °C <i>orange powder</i>	85
Intermediate 145	 From intermediate 144	650 Procedure with reaction temperature = 85 °C <i>yellow oil</i>	62

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 160	 From intermediate 159	771 Procedure with reaction temperature = 85 °C <i>yellow oil</i>	85
Intermediate 186	 From intermediate 185	315 (92% purity evaluated by LC/MS)	-
Intermediate 198	 From intermediate 197	380 (96% purity evaluated by LC/MS)	95
Intermediate 227	 From intermediate 226	1.08 Procedure with reaction temperature = 100°C	97

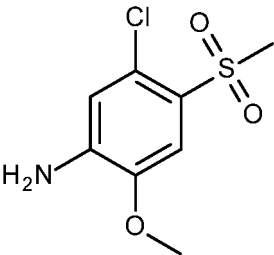
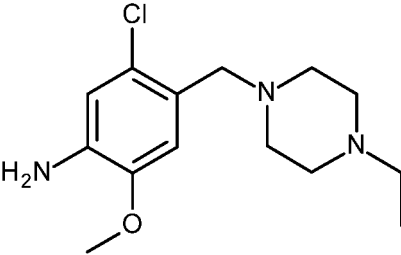
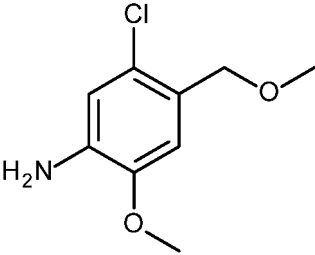
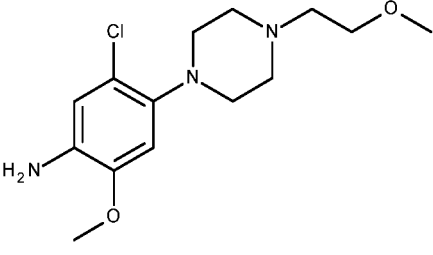
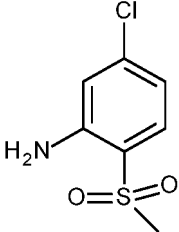
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(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 239	 From intermediate 238	255	85
Intermediate 245	 From intermediate 244	264	57
Intermediate 251	 From intermediate 250	1360	96
Intermediate 279	 From intermediate 278	625 (83% based on LC/MS)	-
Intermediate 285	 From intermediate 284	158 <i>light brown solid</i>	28

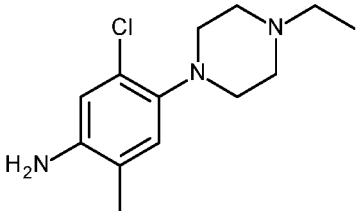
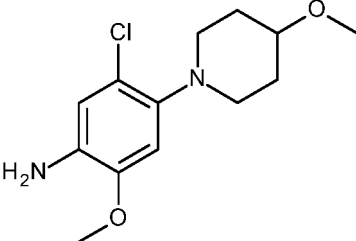
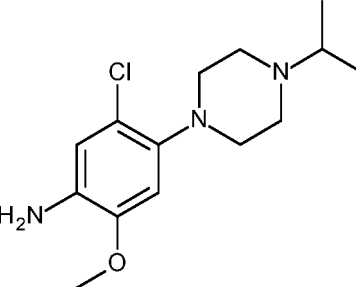
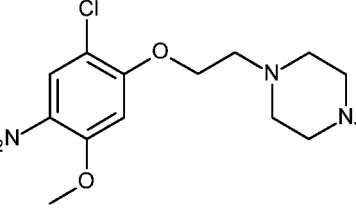
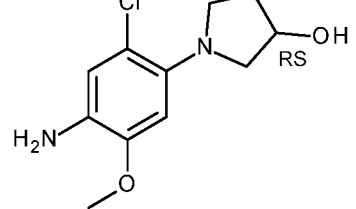
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(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 291	 From intermediate 290	492 <i>light brown solid</i>	64
Intermediate 297	 From intermediate 296	313 <i>pale yellow foam</i>	82
Intermediate 300	 From intermediate 299	221 <i>orange-brown syrup</i>	96
Intermediate 303	 From intermediate 302	257 (58% purity evaluated by LC/MS) <i>brown oil</i>	97
Intermediate 305	 From 4-chloro-1-methanesulfonyl-2-nitrobenzene	450 (83% purity based on LC/MS) <i>brown syrup</i>	-

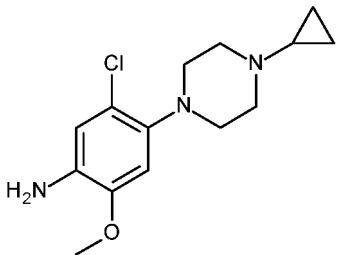
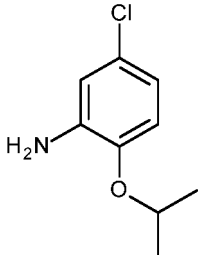
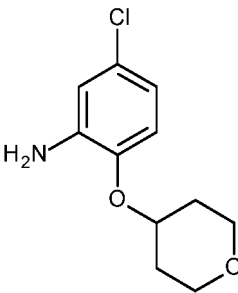
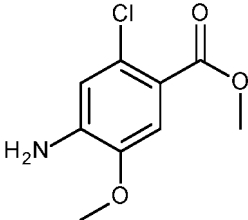
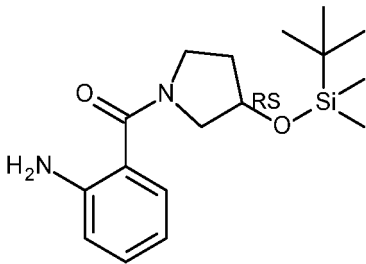
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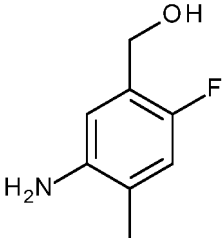
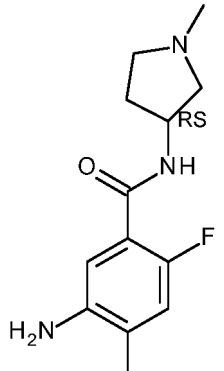
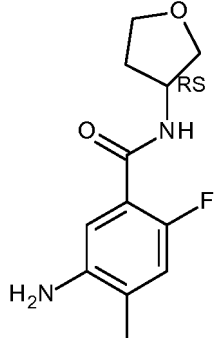
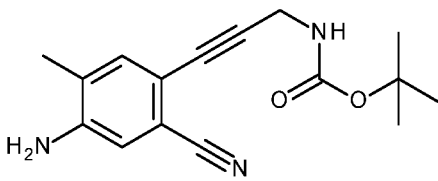
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 308	 From intermediate 307	371 (40% purity based on LC/MS) <i>brown solid</i>	84
Intermediate 311	 From intermediate 310	246 <i>brown oil</i>	94
Intermediate 314	 From intermediate 313	255 <i>brown oil</i>	98
Intermediate 322	 From intermediate 321	143 (17% purity based on LC/MS) <i>brown oil</i>	92
Intermediate 329	 From intermediate 328	217 <i>brown oil</i>	93

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(continued)

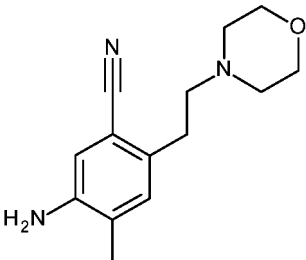
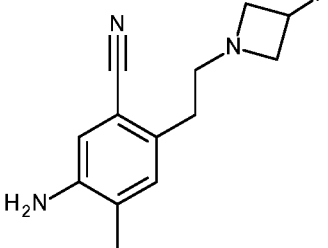
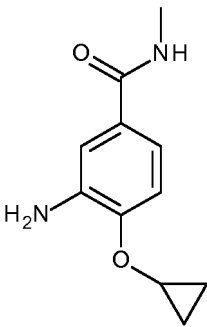
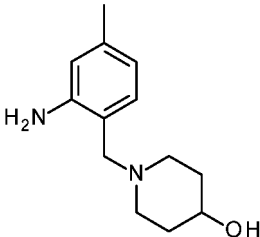
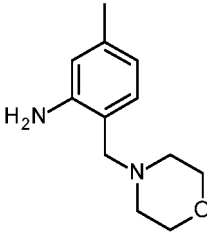
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 332	 From intermediate 331	221 (90% purity based on LC/MS) <i>brown oil</i>	80
Intermediate 341	 From intermediate 340	370 <i>yellow oil</i>	79
Intermediate 344	 From intermediate 343	679	-
Intermediate 351	 From intermediate 350	750	Quant.
Intermediate 360	 From intermediate 359	720	87

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 410	 From intermediate 409	980	100
Intermediate 447	 From intermediate 446	481	84
Intermediate 452	 From intermediate 451	447	100
Intermediate 462	 From intermediate 456	522	87

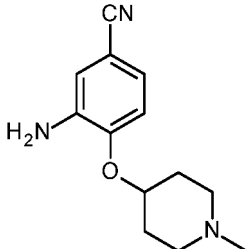
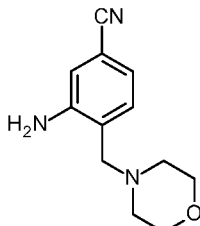
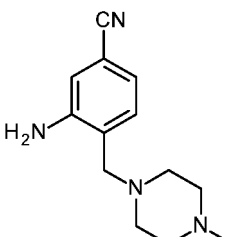
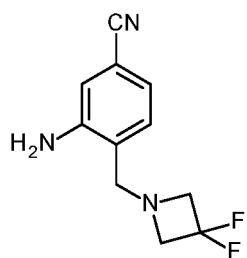
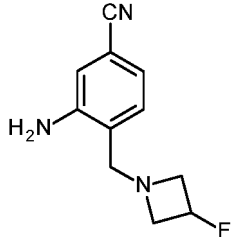
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(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 467	 From intermediate 466	260	99
Intermediate 470	 From intermediate 469	202 (74% of purity based on LC/MS)	92
Intermediate 490	 From intermediate 489	298	96
Intermediate 567	 From intermediate 566	320	73
Intermediate 571	 From intermediate 570	390	89

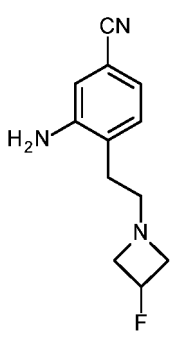
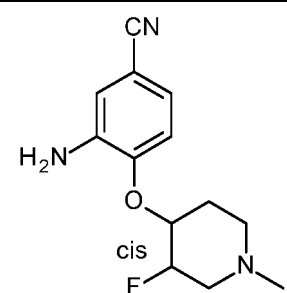
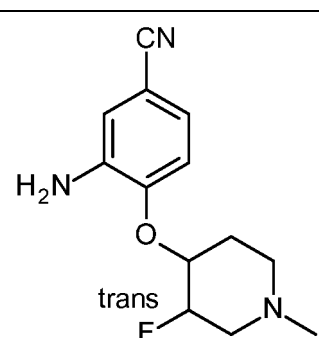
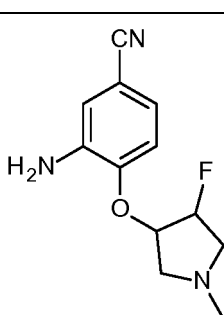
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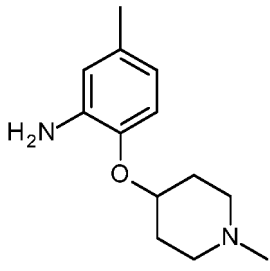
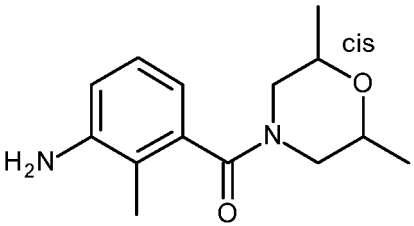
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 575	 From intermediate 574	376	100
Intermediate 580	 From intermediate 579	180 Yellow oil	93
Intermediate 587	 From intermediate 586	200	90
Intermediate 591	 From intermediate 590	150	43
Intermediate 595	 From intermediate 594	140	94

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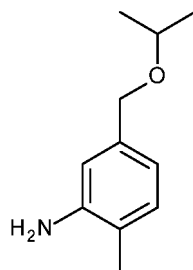
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 599	 From intermediate 598	375	99
Intermediate 604	 From intermediate 603	160	72
Intermediate 610	 From intermediate 609	64	72
Intermediate 617	 From intermediate 615	148	96

(continued)

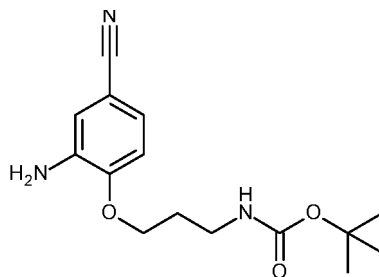
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 621	 From intermediate 620	173	73
Intermediate 521b	 From intermediate 521a	836	quantitative

[0388] Preparation of intermediate 397:



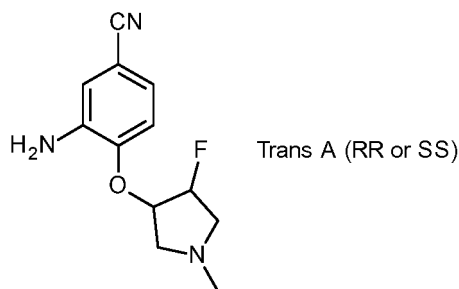
[0389] Intermediate 396 (2.1g; 10 mmol) was dissolved in THF (40 mL), Methanol (20 mL) and water (20 mL). Iron (2.8g; 50.18 mmol) and NH_4Cl (2.68g; 50.18 mmol) were added. The mixture was refluxed for 2 hours. The mixture was extracted with ethyl acetate (50 mL*2). The organic phase was washed by water (20 mL), brine (20 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give 1.75g (97%) of intermediate 397 as a brown oil.

[0390] Preparation of intermediate 481:



[0391] Intermediate 481 was prepared following an analogous method as the one used for the preparation of intermediate 397, starting from intermediate 480 (5.5g; 99%).

[0392] Preparation of intermediate 616:



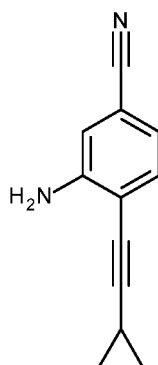
[0393] A mixture of intermediate 614 (177 mg; 0.667 mmol), iron powder (186 mg; 3.337 mmol) and ammonium chloride (143 mg; 2.67 mmol) in ethanol (6 mL) and water (1 mL) was heated at 70°C for 1 hour. The reaction mixture was cooled down to room temperature, diluted with DCM, filtered over Celite® and basified with a 10% aqueous solution of K₂CO₃. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness yielding 156 mg (99%) of intermediate 616.

15

Example A21

[0394] Preparation of intermediate 36:

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[0395] In a sealed tube, a solution of 3-amino-4-iodobenzonitrile (1.70 g, 6.97 mmol), cyclopropylacetylene (1.50 mL, 17.42 mmol) and TEA (3.00 mL, 20.90 mmol) in DMF (50 mL) was degassed (N₂ bubbling). Pd(PPh₃)₂Cl₂ (244.00 mg; 0.35 mmol) and CuI (267.00 mg; 1.39 mmol) were added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was poured onto water and extracted with Et₂O/EtOAc. The organic layer was decanted, washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (irregular SiOH, 40 g, mobile phase: heptane/EtOAc, gradient from 80% heptane, 20% EtOAc to 60% heptane, 40% EtOAc). The pure fractions were collected and evaporated to dryness to give 1.13 g of intermediate 36 (89% yield).

35

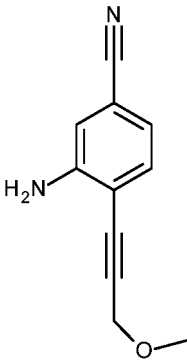
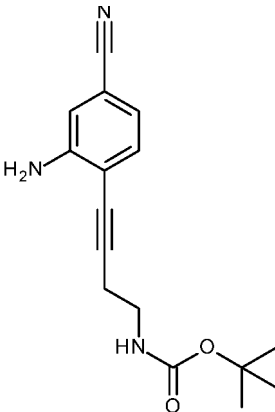
40

[0396] The intermediate in the Table below was prepared by using an analogous method as the one used for the preparation of intermediate 36 starting from the respective starting materials.

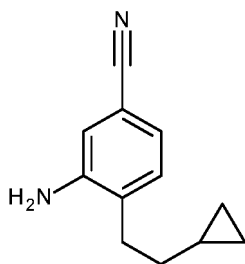
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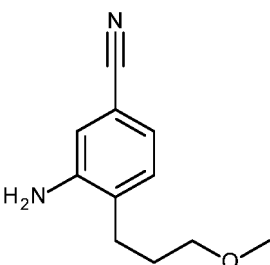
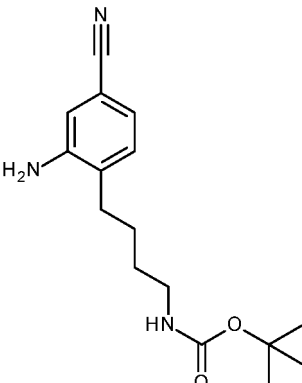
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 254	 From 3-amino-4-iodobenzonitrile	745	99
Intermediate 484	 From 3-amino-4-iodobenzonitrile and tert-butyl but-3-yn-1-ylcarbamate	7600	81

[0397] Preparation of intermediate 37:

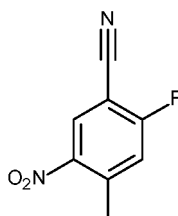


[0398] A suspension of activated charcoal (one spoon) and intermediate 36 (1.10 g, 6.04 mmol) in MeOH (30 mL) was stirred at room temperature all over the week end. The solids were removed by filtration over celite® and the filtrate was evaporated to dryness. The residue was dissolved in MeOH (30 mL) and Pd/C (10 wt. %, 220 mg) was added. The suspension was hydrogenated under Atm pressure of H₂ at rt for 3 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was purified by column chromatography on silica gel (irregular SiOH, 40g, mobile phase: heptane/EtOAc, gradient from 90% heptane, 10% EtOAc to 70% heptane, 30% EtOAc). The pure fractions were collected and evaporated to dryness to give 509 mg of intermediate 37 (45% yield).

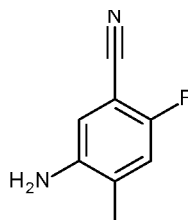
[0399] The intermediate in the Table below was prepared by using an analogous method as the one used for the preparation of intermediate 37 starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 255	 From intermediate 254	577	91
Intermediate 485	 From intermediate 484	6300	81

Example A22

[0400] Preparation of intermediate 43:

[0401] A solution of 2-fluoro-4-methylbenzonitrile (5.50 g, 40.70 mmol) in H_2SO_4 (45 mL) was cooled down at 0 °C. KNO_3 (8.23 g, 81.40 mmol) was then added portionwise. After stirring at 0 °C for 2 h, the reaction mixture was poured into a stirred solution of NaHCO_3 (103.00 g, 1.22 mol) in 1 L of ice water. The heterogeneous mixture was filtered on a glass frit. The precipitate was washed twice with water and collected. The solid was dried in vacuo at 50 °C for 12 h to give 6.68 g of intermediate 43 (91% yield, white solid).

[0402] Preparation of intermediate 44:

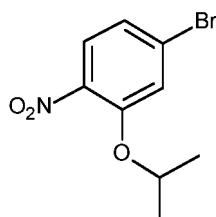
[0403] A solution of intermediate 43 (2.00 g, 11.10 mmol) in Me-THF (20 mL) and EtOH (20 mL) was hydrogenated

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at rt under 1 bar of H₂ in presence of a catalytic amount of Pd/C (10 wt. %, 591.00 mg, 0.55 mmol) for 2 h. The reaction mixture was filtered through a pad of celite® and the filtrate was evaporated under vacuum. The residue was solubilized in Me-THF (20 mL) and EtOH (20 mL) was hydrogenated at rt under 1 bar of H₂ in presence of a catalytic amount of Pd/C (10 wt. %, 591.00 mg, 0.55 mmol) for 2 h. The reaction mixture was filtered through a pad of celite® and the filtrate was evaporated under vacuum to give a black solid. The residue was purified by column chromatography on silica gel (irregular SiOH, 15-40 μm, 80 g, liquid loading, mobile phase: heptane/EtOAc, gradient: from heptane 80%, EtOAc 20% to heptane 60%, EtOAc 40%). The desired fraction were collected and evaporated to dryness to give 610 mg of intermediate 44 (37% yield, pale yellow solid).

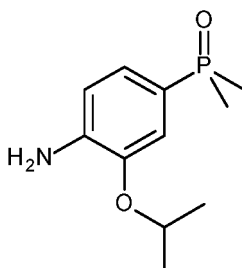
Example A23

[0404] Preparation of intermediate 65:



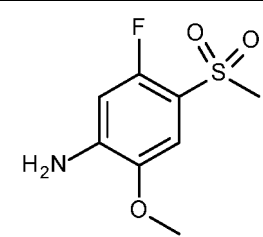
[0405] A mixture of 4-bromo-2-fluoro-1-nitrobenzene (3.00 g, 13.60 mmol) and CS₂CO₃ (13.50 g, 41.40 mmol) in iPrOH (30 mL) was stirred and refluxed for 2 h. The mixture was cooled down to rt and filtered on a pad of celite®. The cake was washed with iPrOH and the filtrate was evaporated in vacuo. The residue was taken-up in EtOAc and water. The layers were separated and the aqueous organic layer was washed with water, dried over MgSO₄, filtered off and evaporated in vacuo to give an orange liquid. The residue (3.6 g) was purified by column chromatography on silica gel (irregular SiOH, 15-40 μm, 120 g, dry loading on celite®, mobile phase: heptane/DCM, gradient: from 80% heptane, 20%DCM to 50% heptane, 50% DCM). The desired fraction were collected and evaporated to dryness to give 3.12 g of intermediate 65 (88% yield, yellow liquid (which crystalized on standing)).

[0406] Preparation of intermediate 67:

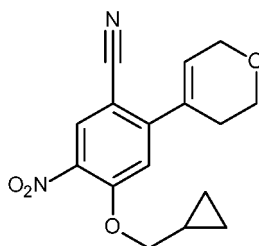


[0407] Pd/C (10 wt. %, 310.00 mg, 0.29 mmol) was added to a solution of intermediate 66 (750.00 mg, 2.92 mmol) in EtOH (30 ml) under N₂. The mixture was stirred at rt under H₂ atmosphere (P atm) for 3 h. The mixture was filtered on a pad of celite® and the cake was washed with EtOH. The filtrate was evaporated in vacuo to give 630 mg of intermediate 67 (89% yield, dark green oil).

[0408] The intermediate in the Table below was prepared by using an analogous method as the one used for the preparation of intermediate 67 starting from the respective starting materials.

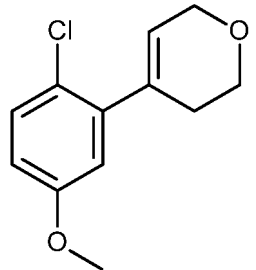
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 326	 From intermediate 325	533 (94% purity based on LC/MS)	96

Example A24

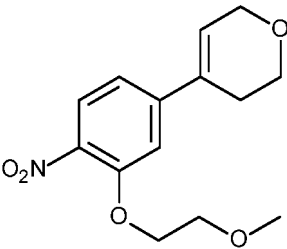
[0409] Preparation of intermediate 72:

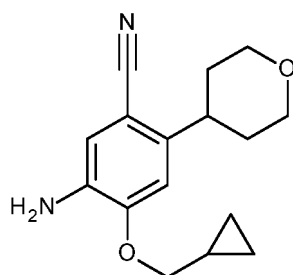
[0410] A mixture of intermediate 71 (2.35 g, 9.30 mmol), 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (3.00 g, 14.30 mmol) and K_2CO_3 (1.64 g, 11.80 mmol) in a mixture of 1,4-dioxane (80 mL) and distilled water (15 mL) was purged with N_2 . 1,1-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (630.00 mg, 0.97 mmol) was added and the mixture was purged with N_2 and stirred at 90 °C for 18 h. The mixture was partitioned between with EtOAc/water. The organic layer was washed with brine, dried over $MgSO_4$, evaporated and purified by column chromatography on silica gel (irregular SiOH 15-40 μm , 120 g, liquid injection (DCM), mobile phase: DCM/MeOH, gradient from 100:0 to 95:05 in 10 CV) to give 1.86 g of intermediate 72 (66% yield, brown solid).

[0411] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 72 starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Mass (mg)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 200	 From 4-chloro-3-iodoanisole	660 (70% purity evaluated by LC/MS) <i>light brown oil</i> reaction temperature = 60°C	86

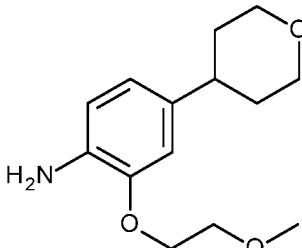
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 208	 From intermediate 207	1130 <i>pale brown solid</i> reaction temperature = 60°C	99

[0412] Preparation of intermediate 73:

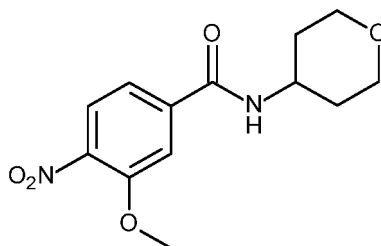
[0413] A mixture of intermediate 72 (0.80 g, 2.66 mmol) and Pd/C (10 wt. %, 140.00 mg, 0.13 mmol) in MeOH (25 mL) was stirred at rt under an atmosphere of H₂ for 2 h 15 min. The mixture was filtered over a pad of celite® and rinsed with MeOH to give 525 mg of intermediate 73 (72% yield, white solid). Then, the celite® was rinsed again with a mixture of DCM/MeOH (80:20) to give 200 mg of a mixture of intermediates 72 and 73.

[0414] The intermediate in the Table below was prepared by using an analogous method as the one used for the preparation of intermediate 73 starting from the respective starting materials.

Intermediate number	Structure	Mass	Yield (%)
Intermediate 209	 From intermediate 208	1 g <i>pale brown oil</i>	98

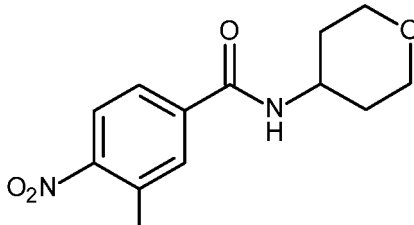
Example A25

[0415] Preparation of intermediate 83:

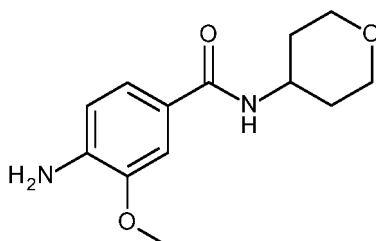


[0416] To a solution of 3-methoxy-4-nitrobenzoic acid (0.50 g, 2.54 mmol), HATU (1.25 g, 3.30 mmol) and DIEA (1.32 mL, 7.61 mmol) in DCM (10mL), 4-aminotetrahydropyran (0.26 g, 2.54 mmol) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with DCM, washed with water, dried over Na_2SO_4 and concentrated in vacuo. The residue was triturated in a minimum amount of DCM, the solid formed was recovered by filtration and dried in vacuo to give intermediate 83 (72% yield, pale yellow solid).

[0417] The intermediate in the Table below was prepared by using an analogous method as the one used for the preparation of intermediate 83 starting from the respective starting materials.

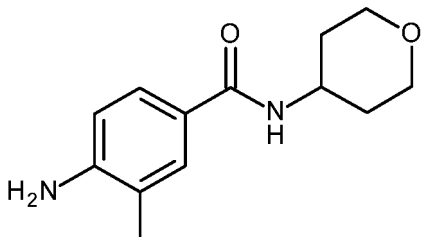
Intermediate number	Structure	Mass	Yield (%)
Intermediate 275	 From 3-methyl-4-nitrobenzoic acid	2.12 g <i>yellow solid</i>	81

[0418] Preparation of intermediate 84:

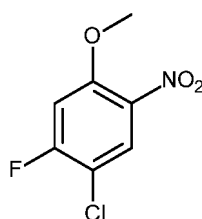


[0419] A suspension of intermediate 83 (0.51 g, 1.84 mmol), Pd/C (10 wt. %, 0.26 g) and ammonium formate (1.16 g, 18.37 mmol) in EtOH (50 mL) was stirred for 2 h at 80 °C. The reaction mixture was filtered through a pad of celite® and the solution was concentrated in vacuo. The residue was loaded onto an Isolute® SCX-2 cartridge (cation exchange chromatography) which was washed with MeOH and then the product was eluted with 2M ammonia in MeOH. The 2M ammonia in MeOH solution was concentrated in vacuo to give intermediate 84 (96% yield, white solid).

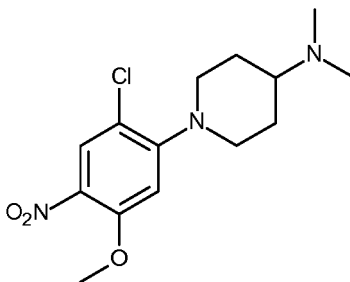
[0420] The intermediate in the Table below was prepared by using an analogous method as the one used for the preparation of intermediate 84 starting from the respective starting materials.

Intermediate number	Structure	Mass	Yield (%)
Intermediate 276	 From intermediate 275	1.97 g <i>off-white solid</i>	-

Example A26

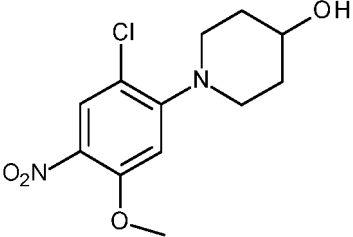
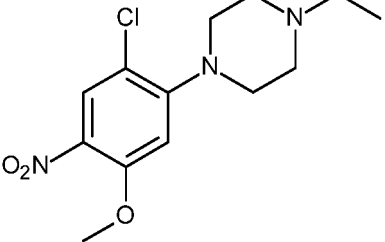
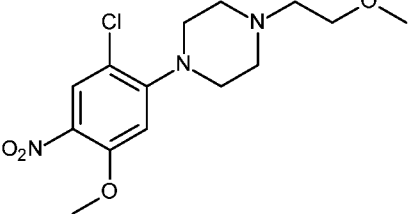
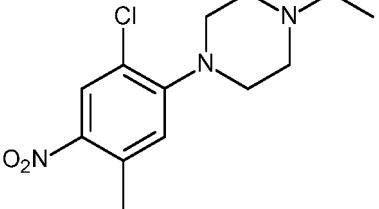
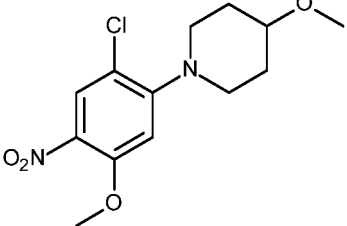
[0421] Preparation of intermediate 86:

[0422] To a solution of 4-chloro-5-fluoro-2-nitrophenol (10.00 g, 52.21 mmol) in dry DMF (50 mL), K_2CO_3 was added (11.00, 79.60 mmol), followed by iodomethane (4.00 mL, 64.25 mmol) and the resulting suspension was stirred at rt for 2.5 days. The resulting dark orange suspension was concentrated in vacuo to remove the DMF solvent, and the residue partitioned between EtOAc (300 mL) and 1N HCl (100 mL). The resulting was separated and the organic layer washed successively with 1M NaOH (100 mL), water (100 mL) and brine (100 mL), dried over Na_2SO_4 , filtered and evaporated to give 10.34 g of intermediate 86 (96% yield, dark orange solid).

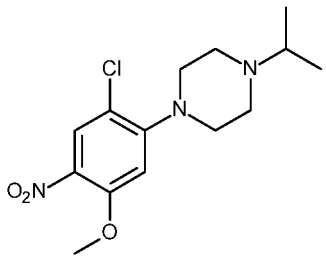
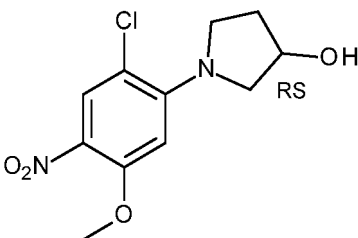
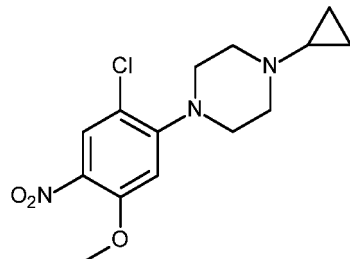
[0423] Preparation of intermediate 87:

[0424] A suspension of intermediate 86 (0.35 g, 1.70 mmol), 4-(dimethylamino)piperidine (0.41 g, 1.87 mmol) and $CsCO_3$ (1.10 g, 3.41 mmol) in DMF (4 mL) was heated to 80 °C for 15 min. The reaction mixture was partitioned between EtOAc and a saturated solution of $NaHCO_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the 553 mg of intermediate 87 (quant. yield, yellow oil).

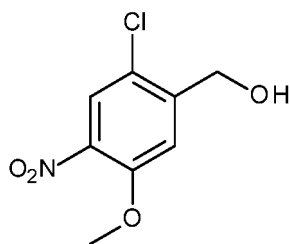
[0425] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 87 starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 91	 From intermediate 86	1630	78
Intermediate 108	 From intermediate 86	510 <i>yellow oil</i>	Quant.
Intermediate 302	 From intermediate 86	294 <i>yellow oil</i>	92
Intermediate 307	 From 4-chloro-5-fluoro-2-nitrotoluene	507 (46% purity evaluated by LC/MS) <i>orange-brown solid</i>	97
Intermediate 310	 From intermediate 86	292 (46% purity evaluated by LC/MS) <i>yellow oil</i>	Quant.

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 313	 From intermediate 86	290 (52% purity evaluated by LC/MS) <i>yellow oil</i>	95
Intermediate 328	 From intermediate 86	262 (47% purity evaluated by LC/MS) <i>orange solid</i>	99
Intermediate 331	 From intermediate 86	302 <i>yellow oil</i>	Quant.

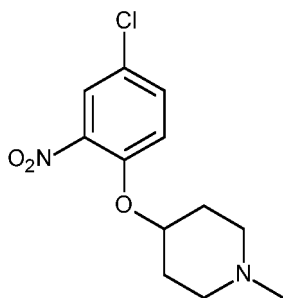
Example A27

[0426] Preparation of intermediate 94:

[0427] A suspension of 3-methoxy-4-nitrobenzoic acid (0.50 g, 2.73 mmol) and NCS (0.41 g, 3.00 mmol) in CH₃CN (5 mL) was heated to 80 °C for 2 h. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel (Si-PPC, 40 g, mobile phase cyclohexane/EtOAc, gradient from 100:0 to 20:80). The desired fraction were collected and evaporated to dryness to give 460 mg of intermediate 94 (77% yield, yellow solid).

Example A28

[0428] Preparation of intermediate 98:

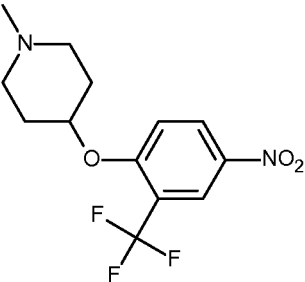


[0429] NaH (60% disp. in mineral oil) (0.41 g, 10.19 mmol) was added to a solution of N-methyl-4-piperidinol (1.08 g, 9.34 mmol) in DMF (9 mL) at 0 °C and the mixture was warmed to rt for 15 min. 5-chloro-2-fluoronitrobenzene (1.49 g, 8.49 mmol) was added and the mixture was stirred at rt for a further 2 h. The reaction mixture was partitioned between EtOAc and a saturated solution of NaHCO₃. The organic layer was washed with brine, and dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Si-PPC, 40 g, mobile phase: DCM/2 M ammonia in MeOH, gradient from 100:0 to 90:10). The desired fraction were collected and evaporated to dryness to give 1.69 g of intermediate 94 (74% yield, yellow oil).

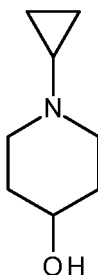
[0430] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 98 starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Structure'.

Intermediate number	Structure	Mass	Yield (%)
Intermediate 133	From 2-fluoro-5-nitrobenzotrifluoride	1.63 g	57
Intermediate 137	From 4-fluoro-3-nitrobenzotrifluoride	451 mg	47

(continued)

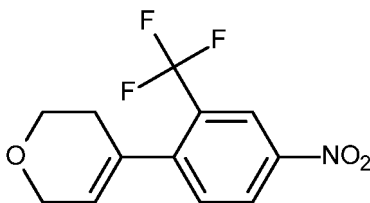
Intermediate number	Structure	Mass	Yield (%)
Intermediate 155	 From 2-fluoro-5-nitrobenzotrifluoride The reaction mixture was stirred at 100°C overnight after addition of all reagents	2.4 g	81

Example A29

[0431] Preparation of intermediate 125:

[0432] Sodium borohydride (0.54 g, 14.36 mmol) was added portion-wise to a solution of N-cyclopropyl-4-piperidinone (1.00 g, 7.18 mmol) in a mixture of DCM (33 mL) and MeOH (3.3 mL) at 0 °C under Ar. The mixture was stirred for 1 h and allowing to warm to rt. The pale yellow mixture was poured into 1M NaOH (20 mL). The layers were separated and the aqueous layer extracted with DCM (2 x 20 mL). The combined organic layers were passed through a phase separator and solvent evaporated under reduced pressure to obtain 1.25 g of intermediate 125 (yellow oil). The residue was used without further purification for the next step.

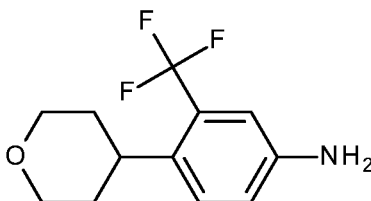
Example A30

[0433] Preparation of intermediate 129:

[0434] A solution of 2-bromo-5-nitrobenzotrifluoride (1.00 g, 3.704 mmol) and 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (1.01 g, 4.82 mmol) in a mixture of 1,4-dioxane (15.28 mL) and distilled water (2.59 mL) was treated with K₂CO₃ (2.36 g, 11.11 mmol) and purged with N₂. Dichloro [1,1-bis(diphenylphosphino)ferrocene]palladium II, DCM adduct (303.20 mg, 370.36 μmol) was then added and the reaction mixture was purged again with N₂ and stirred at 120 °C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 10 minutes [fixed hold time]. Then, water was added. The aqueous layer was extracted twice with DCM, dried over MgSO₄, filtered and evaporated. The residue was purified by column chromatography on silica gel (Irregular SiOH, 40 μm, mobile

phase DCM, 100% DCM). The pure fractions were combined and the solvent was evaporated to give 900 mg of intermediate 129.

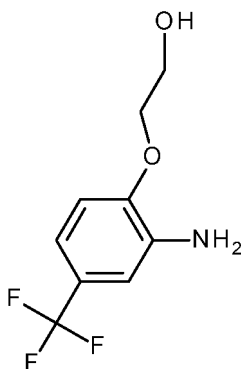
[0435] Preparation of intermediate 130:



[0436] A solution of intermediate 129 (690.00 mg, 2.53 mmol) in MeOH (10.23 mL) was hydrogenated at 60 °C with Pd/C (10 wt. %, 71.64 mg, 67.30 μ mol) as a catalyst under 8 bars pressure for 24 h. The catalyst was filtered off on a pad of Celite® and the filtrate was evaporated to give 609 mg of intermediate 130.

Example A31

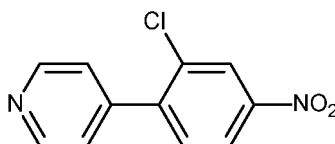
[0437] Preparation of intermediate 138:



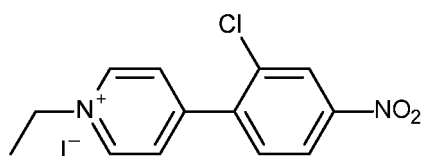
[0438] A mixture of intermediate 137 (0.67 g, 2.65 mmol) was hydrogenated at rt in EtOAc (15.50 mL) and MeOH (15.60 mL) with Pd/C (10 wt. %, 0.12 g, 0.11 mmol) as a catalyst in a Parr® pressure vessel reactor under 4 bars of H₂. After 4 h, the catalyst was filtered off on a pad of Celite®. The solvent was evaporated until dryness to give 535 mg of intermediate 138 (91% yield). This product was used without further purification for the next step.

Example A32

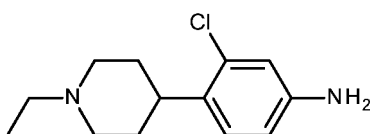
[0439] Preparation of intermediate 147:



[0440] To a solution of 1-bromo-2-chloro-4-nitrobenzene (1.00 g, 4.42 mmol) and pyridine-4-boronic acid, pinacol ester (1.10 g, 5.36 mmol), K₃PO₄ (2.70 g, 12.72 mmol), dichloro [1,1'-bis(diphenylphosphino)ferrocene] palladium II, DCM adduct (0.350 g, 0.43 mmol) in a mixture of 1,4-dioxane (15.00 mL) and distilled water (2.50 mL) was purged again with N₂. The reaction mixture was stirred at 110 °C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 10 min [fixed hold time]. This procedure was made with three batches of 1 g of 1-bromo-2-chloro-4-nitrobenzene. The three reactions were combined and water was added. The aqueous layer was extracted twice with DCM, dried over MgSO₄, filtered and evaporated to give. The residue (4.40 g) was purified by column chromatography on silica gel (Irregular SiOH, 40 μ m, mobile phase: heptane/EtOAc, gradient from 60:40 to 50:50). The pure fractions were combined and the solvent was evaporated to afford 1.97 g of intermediate 147 (66% yield) used as it for the next step.

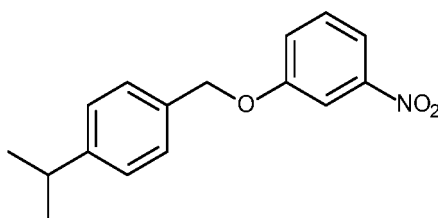
[0441] Preparation of intermediate 148:

[0442] Iodoethane (2.80 mL, 35.01 mmol) was added to a mixture of intermediate 147 (1.95 g, 8.31 mmol) in toluene (20 mL). This reaction was stirred in a sealed tube at reflux (115 °C) for 7 h. This reaction was cooled down to rt. Iodoethane (1.50 mL, 18.75 mmol) was added again and the mixture was stirred for further 5 h at reflux (120 °C). The solvent was concentrated to dryness to give 2.89 g of intermediate 148 (89% yield) used as it for the next step.

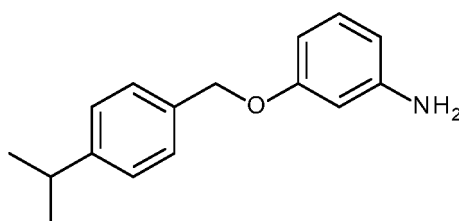
[0443] Preparation of intermediate 149:

[0444] A mixture of intermediate 148 (1.00 g, 2.56 mmol) was hydrogenated at rt in EtOH (35 mL) with platinum (IV) oxide (300 mg, 1.30 mmol) as a catalyst at 3 bars. After overnight, the catalyst was filtered off on a pad of Celite® and the solvent was concentrated until dryness. This residue was purified by column chromatography on silica gel (Irregular SiOH, 40 µm, 40 g, mobile phase: NH₄OH/DCM/MeOH, gradient form: 0.5% NH₄OH, 95% DCM, 5% MeOH to 1% NH₄OH, 90% DCM, 10% MeOH). The pure fractions were collected and the solvent was concentrated until dryness to give 0.690 g of intermediate 149 (98% yield, purity = 84% determined by LC/MS) used as it for the next step.

Example A33

[0445] Preparation of intermediate 152:

[0446] A mixture of 4-isopropylbenzyl bromide (4.18 g, 19.61 mmol), 3-nitrophenol (3.00 g, 21.57 mmol), K₂CO₃ (4.06 g, 29.41 mmol) in DMF was heated at 100 °C. After completion, water and EtOAc were added. The organic layer was washed with water, decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue was recrystallized with DiPE to give 2.87 g of intermediate 152 (54% yield). M. P. = 88 °C (K).

[0447] Preparation of intermediate 153:

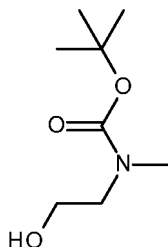
[0448] To a solution of intermediate 152 (2.80 g, 10.32 mmol) in a mixture of 1,4 dioxane (20 mL) and water (5 mL), Iron powder (5.80 g, 103.20 mmol) and iron(II) sulfate heptahydrate (6.30 g, 41.28 mmol) were added. The resulting solution was heated to reflux for overnight. The reaction mixture was filtered off on a pad of Celite® and washed with

EP 3 405 196 B1

DCM. The organic layer was washed with water and K_2CO_3 , dried over $MgSO_4$, filtered and evaporated to give 2.35 g of intermediate 153 (94% yield).

Example A34

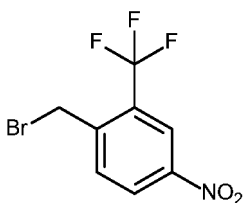
[0449] Preparation of intermediate 158:



[0450] TEA (3.52 mL, 25.00 mmol) was added to a solution of Boc_2O (3.00 g, 13.77 mmol) and 2-(methylamino)ethanol (1.00 mL, 12.52 mmol) in DCM (80 ml) and stirred at rt overnight. The mixture was washed with brine, dried on $MgSO_4$, filtrated and concentrated to afford 2.40 g of intermediate 158 (colorless oil).

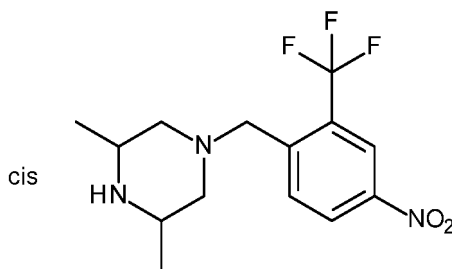
Example A36

[0451] Preparation of intermediate 175:



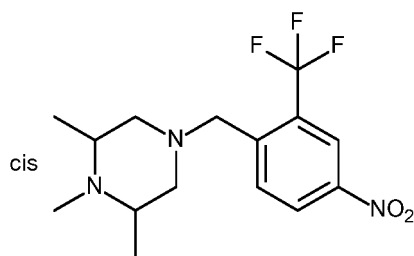
[0452] To a suspension of 2-methyl-5-nitrobenzotrifluoride (14.00 g, 68.25 mmol) in AcOH (58.60 mL, 1.02 mol), NBS (12.75 g, 71.66 mmol) and benzoyl peroxide (1.65 g, 6.83 mmol) was added. The reaction mixture was heated at reflux overnight (120 °C). Upon cooling, the solvent was removed in vacuo, EtOAc and aqueous $NaHCO_3$ were added, and the layers were separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 18 g of intermediate 175 (93% yield). It was used for the next step without further purification.

[0453] Preparation of intermediate 176 (CIS):



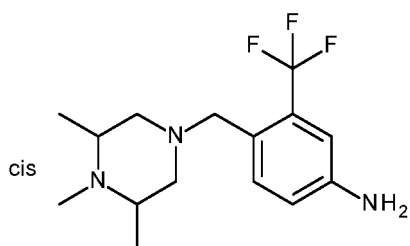
[0454] Cis-2,6-dimethylpiperazine (1.00 g, 8.49 mmol) were added to a stirred solution of intermediate 175 (3.62 g, 12.74 mmol) and TEA (4.72 mL, 33.98 mmol) in DCM (10.88 mL) at rt for 48 h. The reaction mixture was washed with a solution of 10 % K_2CO_3 . The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel (irregular $SiOH$, 15-40 μm , 80 g, mobile phase: DCM/MeOH/ NH_4OH , gradient from DCM: 100% to DCM: 98%, MeOH: 2%, NH_4OH : 0.1%) to give 1.82 g of intermediate 176 (68% yield).

[0455] Preparation of intermediate 177 (CIS):



[0456] Sodium cyanoborohydride (403.89 mg, 6.43 mmol) was added to a stirred a solution of intermediate 176 (1.70 g, 5.36 mmol) and formaldehyde (37 wt. % in water) (481.96 μ L, 6.43 mmol) in a mixture of MeOH (6.39 mL, 157.64 mmol) and AcOH (756.69 μ L, 13.22 mmol) at rt under N_2 and stirred at rt for 2 h. Then, the reaction mixture was poured out onto water, made basic with K_2CO_3 powder, extracted with DCM, dried over $MgSO_4$, filtered and evaporated to give intermediate 177 (96% yield). It was used for the next step without purification.

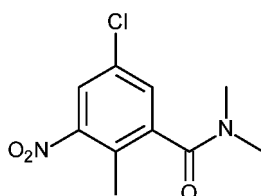
[0457] Preparation of intermediate 178: (CIS)



[0458] Intermediate 177 (500.00 mg, 1.51 mmol) in MeOH (12.41 mL) was hydrogenated with $RaNi$ (329.95 mg, 5.62 mmol) as a catalyst at rt under 3 bars pressure for 12 h. The catalyst was filtered off on a pad of Celite® and the filtrate was evaporated to give 489 mg of intermediate 178.

Example A37

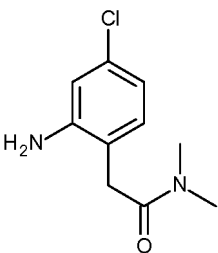
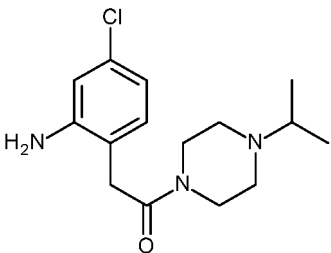
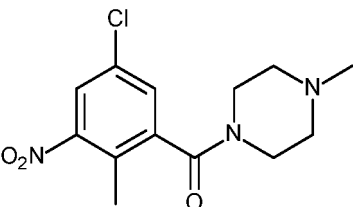
[0459] Preparation of intermediate 185:



[0460] Under N_2 at rt, a solution of dimethylamine in THF (2.0 M, 1.18 mL, 2.37 mmol) was added to a solution of 5-chloro-2-methyl-3-nitrobenzoic acid (340.00 mg, 1.58 mmol), HBTU (598.09 mg, 1.58 mmol) and DIPEA (679.42 μ L, 3.94 mmol) in DMF (9.77 mL, 126.16 mmol). The solution was stirred at rt for 6 h. The solution was poured out into cooled water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue (2.07 g) was purified by colonne chromatography on silica gel (SiO_2 , 40 g, mobile phase: DCM/MeOH/ NH_4OH , gradient from 100% DCM to 97% DCM, 3% MeOH, 0.3% NH_4OH). The pure fractions were collected and the solvent was evaporated until dryness to give 315 mg of intermediate 185 (82% yield).

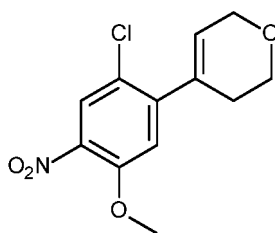
[0461] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 185 starting from the respective starting materials.

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Intermediate number	Structure	Mass	Yield (%)
Intermediate 189	 From (2-amino-4-chlorophenyl) acetic acid	530 mg	66
Intermediate 192	 From (2-amino-4-chlorophenyl) acetic acid	950 mg	85
Intermediate 197	 5-chloro-2-methyl-3-nitrobenzoic acid	444 mg	80

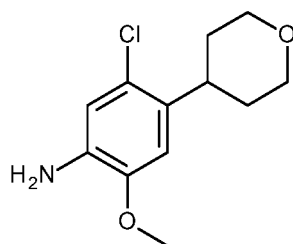
Example A38

[0462] Preparation of intermediate 201:



[0463] A mixture of intermediate 200 (68.00 mg, 0.21 mmol) and sodium nitrate (18.00 mg; 0.21 mmol) in TFA (0.70 mL) was stirred at rt for 6 h. The mixture was poured in a mixture of ice and aqueous NaHCO₃, extracted with EtOAc, washed with brine, dried over MgSO₄ and evaporated. The residue (60 g, black oil) was purified by column chromatography on silica gel (irregular SiOH, 15-40 μm, 12 g, liquid injection (DCM), mobile phase: DCM/MeOH, gradient from: 100:0 to 95:05 in 10 CV) to give 40 mg of a residue as a light yellow oil 2 containing intermediate 201 (66% purity). Further purification by achiral SFC (Stationary phase: CYANO 6 μm 150 x 21.2mm, mobile phase: 95% CO₂, 5% MeOH) was achieved to give 17 mg of intermediate 201 (30% yield, white solid).

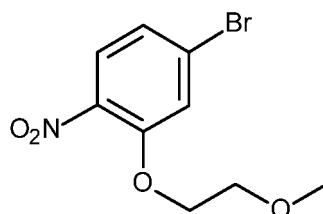
[0464] Preparation of intermediate 202:



[0465] A mixture of intermediate 201 (650.00 mg, 2.41 mmol) and platinum (IV) oxide (130.00 mg, 0.57 mmol) in a mixture of MeOH (20 mL) and THF (5 mL) was stirred at rt under an atmosphere of H₂ for 20 min (purged with H₂, 3 times (total time reaction: 1h)). The mixture was filtered over a pad of celite®. The organic layer was evaporated and purified by column chromatography on silica gel (irregular SiOH, 15-40 μm, 80 g, liquid injection (DCM), mobile phase: heptane/EtOAc, gradient from 100:0 to 0:100 in 10 CV). The pure fractions were collected and the solvent was evaporated until dryness to give 174 mg of intermediate 202 (30% yield, white solid).

Example A39

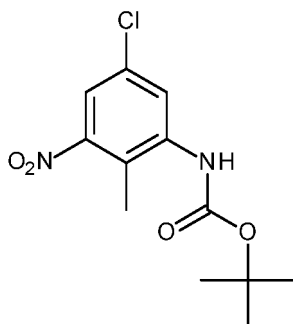
[0466] Preparation of intermediate 207:



[0467] NaH (60% dispersion in mineral oil) (182.00 mg, 4.55 mmol) was added slowly at 0 °C to 2-methoxyethanol (0.36 mL, 4.55 mmol) in THF (20 mL). The mixture was stirred under N₂ at 0 °C for 30 min. 4-bromo-2-fluoronitrobenzene (1.00 g, 4.55 mmol) was added and the mixture was stirred and heated slowly to rt for 5 h. The mixture was neutralized with HCl 1N (pH = 7) then extracted with a mixture of EtOAc/NaHCO₃. The organic layer was washed with brine, dried over MgSO₄, evaporated and purified by column chromatography on silica gel (irregular SiOH, 15-40 μm, 80 g, liquid injection (DCM), mobile phase; heptane/EtOAc, gradient from 100:0 to 50:50 in 10 CV) to give 1.13 g of intermediate 207 (90% yield, white solid).

Example A40

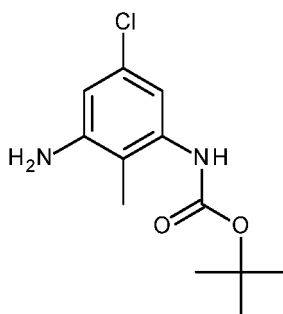
[0468] Preparation of intermediate 214:



[0469] 5-chloro-2-methyl-3-nitrobenzoic acid (3.00 g, 13.91 mmol), diphenylphosphoryl azide (4.49 mL, 20.87 mmol) and TEA (2.71 mL, 19.48 mmol) in a mixture of Me-THF (3.75 mL, 37.44 mmol) and 2-methyl-2-propanol (3.91 mL, 41.74 mmol) were refluxed at 3 h. The mixture was poured into NH₄Cl and the organic layer was extracted twice with EtOAc, dried over MgSO₄ and the solvent was evaporated until dryness. The residue (5.08 g) was taken up into EtOAc and a precipitate was appeared and was filtered (impurities). The filtrate was evaporated until dryness. The residue (4.77 g) was taken up in CH₃CN, and a precipitate was appeared and was filtered. The filtrate was evaporated until

dryness and purified by column chromatography on silica gel (Irregular SiOH and Si 60 15-40 μ m, 40 μ m, 80 g, solid deposit, mobile phase: Heptane/EtOAc, 80:20). The pure fractions were combined and the solvent was evaporated to give 3.42 g of intermediate 214 (86% yield).

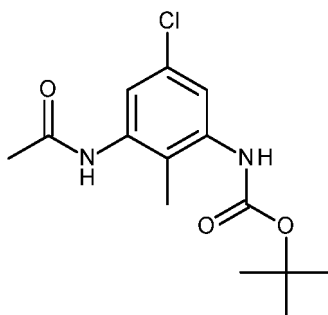
[0470] Preparation of intermediate 215:



[0471] To a stirred solution of intermediate 214 (200.00 mg, 0.70 mmol) in AcOH (8 mL), iron (389.56 mg, 6.98 mmol) was added and stirred at 70 °C for 2 h. The crude mixture was diluted with EtOAc, filtered over celite®, and the cake was washed with EtOAc. Water was added to the filtrate then K₂CO₃ powder until basic pH. The organic layer was washed with brine, dried over MgSO₄, filtered and evaporated. The residue (180 mg) was purified by column chromatography on silica gel (Irregular SiOH, 40 μ m, 24 g, mobile phase: heptane/EtOAc, 60:40).

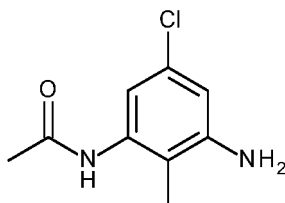
[0472] The pure fractions were combined and the solvent was evaporated to give 95 mg of intermediate 215 (53% yield).

[0473] Preparation of intermediate 216:



[0474] Intermediate 215 (1.00 g, 3.89 mmol), acetyl chloride (0.35 mL, 4.87 mmol) and TEA (3.25 mL, 23.37 mmol) in DCM (50 mL) were added at 0 °C stirred at rt overnight. The mixture was poured into NH₄Cl and the organic layer was extracted with DCM, washed with NaCl, and dried. The precipitate was filtered to give 483 mg of intermediate 216 (42% yield). The filtrate was evaporated until dryness and the residue (750 mg) was purified by column chromatography on silica gel (Irregular SiOH, 40 g, mobile phase: DCM/MeOH, gradient from 100:0 to 98:2). The pure fractions were combined and the solvent was evaporated to give 236 mg of intermediate 216 (20% yield). The two batches was gathered to give 719 mg of intermediate 216 (62% yield).

[0475] Preparation of intermediate 217:

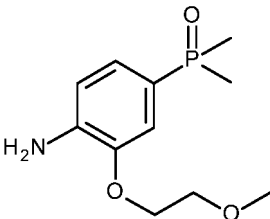


[0476] At 0 °C, a solution of HCl 4M in dioxane (2.76 mL, 11.04 mmol) was added to a stirred solution of intermediate 216 (660.00 mg, 2.21 mmol) in CH₃CN (49.5 mL). The mixture was stirred at 0 °C for 30 min and at rt for 1 h. The mixture was poured into cooled water and basified with NH₄OH. The organic layer was extracted twice with EtOAc, washed with brine, dried over MgSO₄, filtered and evaporated until dryness. The residue was taken up in DCM, washed with brine,

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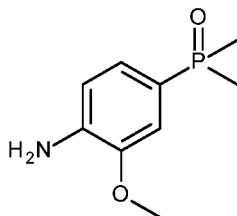
evaporated and purified by column chromatography on silica gel (Irregular SiOH, 24 g, solid deposit, mobile phase: heptane/MeOH/EtOAc/NH₄OH, 60:38:2:0.1). The pure fraction were combined and the solvent was evaporated to give 210 mg of intermediate 217 (48% yield).

[0477] The intermediate in the Table below was prepared by using an analogous method as the one used for the preparation of intermediate 217 starting from the respective starting materials.

Intermediate number	Structure	Mass	Yield (%)
Intermediate 235	 From intermediate 234	251 mg	Quant.

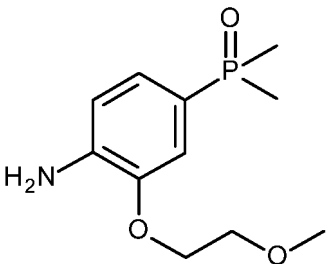
Example A41

[0478] Preparation of intermediate 221:



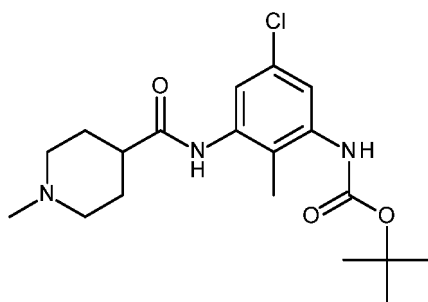
[0479] A mixture of intermediate 220 (334.00 mg, 1.46 mmol), zinc (953.00 mg, 14.60 mmol) and AcOH (0.83 mL, 14.60 mmol) in MeOH (8 mL) was stirred at rt for 2 h. The mixture was filtered on a pad of celite® then an extraction was performed with EtOAc and HCl 1N. The aqueous layer was basified with NaOH 1N and extracted with EtOAc (10 times). The organic layers were washed with brine, dried with MgSO₄ and evaporated to give 226 mg of intermediate 221 (78% yield, brown oil).

[0480] The intermediate in the Table below was prepared by using an analogous method starting from the respective starting materials.

Intermediate number	Structure	Mass	Yield (%)
Intermediate 231	 From intermediate 230	496 mg <i>pale brown oil</i>	97

Example A42

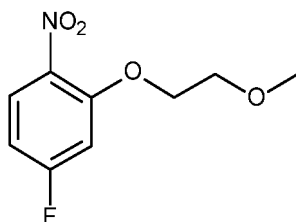
[0481] Preparation of intermediate 234:



[0482] A solution of HATU (2.02 g, 5.32 mmol), DIPEA (1.85 mL, 10.63 mmol) and ethyl 1-methyl-4-piperidine carboxylate, HCl salt (827.80 mg, 4.61 mmol) in Me-THF (9.10 mL, 90.86 mmol) were stirred at 70 °C for 2 h. Then, intermediate 215 (910.00 mg, 3.54 mmol) was added and the mixture was stirred at 70 °C overnight. The mixture was poured out onto water and the organic layer was extracted twice with DCM, dried over MgSO_4 , filtered and evaporated until dryness. The residue (776 mg) was taken up in MeOH and DCM, triturated and filtered. The precipitate was dried until dryness to give 315 mg of intermediate 234 (23% yield).

Example A43

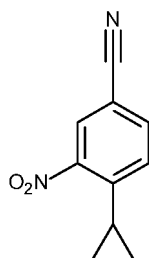
[0483] Preparation of intermediate 238:



[0484] DIAD (3.00 mL, 15.28 mmol) was added dropwise at 5 °C to a mixture of 5-fluoro-2-nitrophenol (1.60 g, 10.18 mmol), 2-methoxyethanol (807.00 μL , 10.18 mmol) and PPh_3 (1.4 mmol/g on polystyrene) (10.90 g, 15.28 mmol) in THF (30 mL). The mixture was stirred at rt for 2 h. Water was added and the reaction mixture was extracted with DCM. The organic layer was decanted, dried over MgSO_4 , filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (irregular SiOH , 40 g, mobile phase: heptane/EtOAc, gradient from 80:20 to 60:40). The fractions were collected and evaporated to dryness to give 954 mg of intermediate 238 (43% yield).

Example A44

[0485] Preparation of intermediate 244:

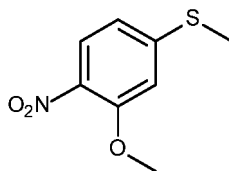


[0486] Di(1-adamantyl)-N-butylphosphine (157.00 mg, 0.44 mmol) and $\text{Pd}(\text{OAc})_2$ (98.00 mg, 0.44 mmol) were added to a degassed N_2 solution of 4-chloro-3-nitrobenzonitrile (800.00 mg, 4.38 mmol), potassiumcyclopropyltrifluoroborate (972.00 mg, 6.57 mmol) and CsCO_3 (2.85 g, 8.76 mmol) in a mixture of 1,4-dioxane (18 mL) and distilled water (4 mL). The reaction mixture was stirred and heated at 100 °C for 18 h. Then, it was cooled to rt, diluted with DCM and poured onto water. The organic layer was decanted, dried over MgSO_4 , filtered over celite® and evaporated to dryness. The residue was purified by column chromatography on silica gel (irregular SiOH , 24 g, mobile phase: DCM/MeOH, gradient

from 100:0 to 98:2). The pure fractions were collected and evaporated to dryness to give 546 mg of intermediate 244 (66% yield).

Example A45

[0487] Preparation of intermediate 249:

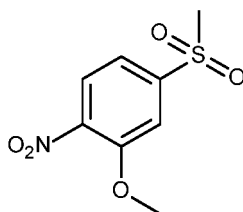


[0488] To a solution of 4-fluoro-2-methoxy-1-nitrobenzene (2.00 g, 11.70 mmol) in MeOH (38 mL), a solution of sodium thiomethoxide (1.50 g, 21.00 mmol) was added dropwise in distilled water (6.5 ml) and MeOH (38 mL) and the resulting mixture was stirred at reflux under N₂ overnight. The mixture was cooled to rt and concentrated in vacuo. The residue was triturated in a mixture of DCM and MeOH (1:1) and the solid was filtered off. The filtrate was purified by column chromatography on silica gel (15-40 μm, 240 g, mobile phase: heptane/EtOAc, gradient from 100:0 to 50:50). The pure fractions were mixed and the solvent was evaporated to give 2.11 g of intermediate 249 (91% yield).

[0489] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 249 starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Mass (mg)'.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 289	From intermediate 86	1194 (Procedure with EtOH and distilled water) <i>yellow solid</i>	Quant.
Intermediate 324	From 3,4-difluoro-6-nitroanisole	195 (Procedure with EtOH and distilled water)	8

[0490] Preparation of intermediate 250:

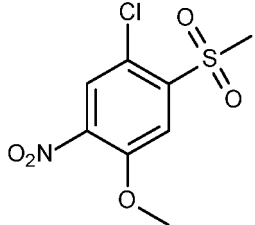
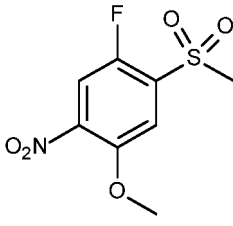


[0491] A solution of intermediate 249 (2.11 g, 10.60 mmol) in DCM (106 ml) under an Ar atmosphere was treated with mCPBA (5.49 g, 31.80 mmol) and stirred at rt for 24 h. The mixture was filtered off. The filtrate was concentrated and purified by column chromatography on silica gel (SiO₂, dry loading, mobile phase: heptane/EtOAc, gradient from 1:0 to

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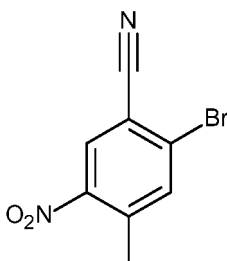
0:1). The pure fractions were combined and concentrated to dryness to afford 1.65 g of intermediate 250 (67% yield, pale yellow crystalline solid).

[0492] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 250 starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 290	 From intermediate 289	864 <i>pale yellow crystalline solid</i>	65
Intermediate 325	 From intermediate 324	629 <i>white solid</i>	62

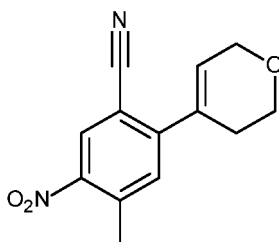
Example A46

[0493] Preparation of intermediate 257:



[0494] To a solution of 2-bromo-4-methylbenzonitrile (2.00 g, 10.20 mmol) in H₂SO₄ (7 mL) at 0 °C, a solution of KNO₃ in H₂SO₄ (5 mL) was added (1.03 g, 10.20 mmol). After stirring at 0 °C for 1.5 h, the reaction mixture was poured into 500 mL of ice water. The precipitate was collected by filtration and washed with copious amounts of water. The precipitate was dried to provide 2.01 g of intermediate 257 (82% yield, white powder).

[0495] Preparation of intermediate 258:

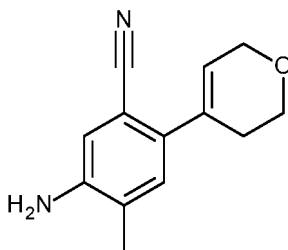


[0496] In a sealed tube, a solution of intermediate 257 (1.00 g, 4.15 mmol), 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (1.05 g, 4.98 mmol) and K₃PO₄ (1.76 g, 8.30 mmol) in a mixture of 1,4-dioxane (29 mL) and distilled water (3.86 mL) was degassed under N₂. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichlo-

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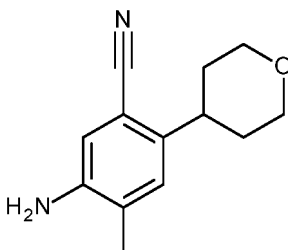
romethane (340.00 mg, 0.41 mmol) was added and the reaction mixture was degassed again under N₂ and heated at 80 °C for 5 h. The reaction mixture was cooled to rt, poured onto water and extracted with DCM. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue (2g, black oil) was purified by column chromatography on silica gel (irregular SiOH, 80 g, mobile phase: heptane/EtOAc, gradient from 100:0 to 75:25). The pure fractions were collected and evaporated to dryness to give 0.787 g of intermediate 258 (78% yield, white powder).

[0497] Preparation of intermediate 259:



[0498] A mixture of intermediate 258 (0.79 g, 3.22 mmol) and Pd/C (10 wt. %, 72.00 mg, 0.067 mmol) in EtOAc (10 mL) was stirred at rt under an atmosphere of H₂ overnight. The mixture was filtered over a pad of celite® and evaporated to dryness to give intermediate 259 (white solid). This residue was used as such in the next reaction step.

[0499] Preparation of intermediate 260:



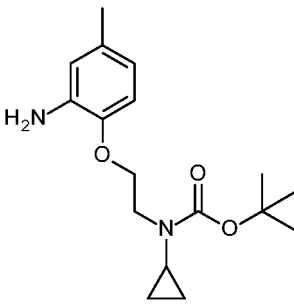
[0500] A mixture of intermediate 259 (0.70 g, 3.27 mmol) and Pd/C (10 wt. %, 174.00 mg, 0.16 mmol) in EtOH (11.5 mL) was stirred at rt under an atmosphere of H₂ overnight. The mixture was filtered over a pad of celite®. The organic layer was evaporated to give 512 mg of intermediate 260 (72% yield, 90% purity based on LC/MS, white solid).

[0501] The intermediates in the Table below were prepared by using an analogous method as the one used for the preparation of intermediate 259 starting from the respective starting materials. The most relevant minor deviations from the original procedure are indicated in the column "Mass"

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 583	From intermediate 582	225	93

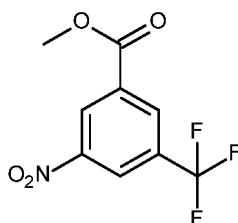
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(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 626	 From intermediate 625	500 Procedure with EtOAc as solvent	78

Example A47

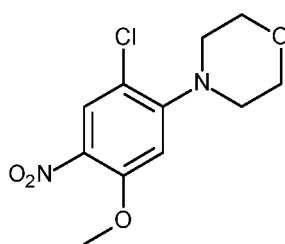
[0502] Preparation of intermediate 267:



[0503] AcCl (19.5 mL) was added dropwise to a solution of 3-nitro-5-(trifluoromethyl)benzoic acid (19.50 g, 83.00 mmol) in MeOH (195 mL) at rt and stirred 18 h. The resulting mixture was concentrated under vacuum, washed with a solution of 10% of K₂CO₃, extracted twice with DCM, dried over MgSO₄, filtrated and concentrated under vacuum to give 19 g of intermediate 267 (92% yield).

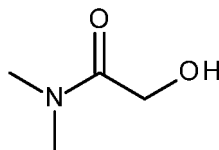
Example A48

[0504] Preparation of intermediate 278:

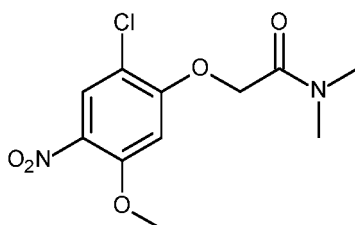


[0505] A mixture of 1-bromo-2-chloro-5-methoxy-4-nitrobenzene (1.00 g, 3.75 mmol), morpholine (395.00 μ L, 4.12 mmol), K₂CO₃ (1.04 g, 7.51 mmol) in DMF (10 mL) was stirred and heated at 80 °C for 18 h. Further morpholine (35.00 μ L, 0.40 mmol) was added and the reaction mixture was stirred and heated at 80 °C for a further 23 h. The reaction mixture was added to ice/water and stirred to give a yellow precipitate. It was filtered off, washed with water and EtO₂, dried over MgSO₄ and concentrated in vacuo to give a yellow solid. The filtrate was further extracted with EtOAc (twice) and the combined organics were washed successively with water, and saturated brine, dried over anhydrous Na₂SO₄. Solvent was removed in vacuo to give a brown solid (100 mg) which was combined with the precipitate and purified by column chromatography on silica gel (80 g silica cartridge, mobile phase: cyclohexane/EtOAc containing 0-40% EtOAc) to give 703 mg of intermediate 278 (69% yield, yellow solid).

Example A49

[0506] Preparation of intermediate 283:

[0507] Ethyl glycolate (0.91 mL, 9.61 mmol) was dissolved in dimethylamine (40% in water) (10 mL) and the resulting mixture was stirred at rt for 18 h. The reaction was evaporated under reduced pressure. The residue was taken up in EtOH and evaporated under reduced pressure (twice) to give a colorless oil. The residue (950 mg) was purified by column chromatography on silica gel (SiO₂, 25 g, mobile phase DCM/MeOH, gradient from 100:0 to 95:5). The fractions containing the product were combined and evaporated under reduced pressure to give 576 mg of intermediate 283 (58 % yield, colorless oil).

[0508] Preparation of intermediate 284:

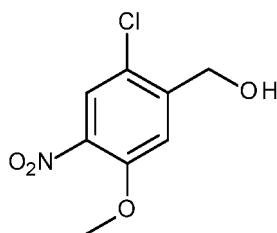
[0509] To a solution of intermediate 283 (376.00 mg, 3.65 mmol) in THF (20 mL), NaH (60% dispersed in mineral oil) (145.92 mg, 3.65 mmol) was added portionwise and the resulting mixture was stirred at rt under N₂ for 30 min. Intermediate 86 (0.50 g, 2.43 mmol) was added and the resulting mixture was stirred for 1 h. The reaction was quenched with 1M aqueous NH₄Cl and extracted with thrice with EtOAc. The organic layer were separated, combined, dried over Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (SiO₂, 40 g, mobile phase: DCM/MeOH, gradient from 100:0 to 95:5). The fractions containing the product were combined and evaporated under reduced pressure to give 619 mg of intermediate 284 (88% yield, off-white solid).

[0510] The intermediate in the Table below was prepared by using an analogous method as the one used for the preparation of intermediate 284 starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 321	From intermediate 86 and 1-(2-hydroxyethyl)-4-methyl piperazine	344 (43% purity based on LC/MS) <i>yellow solid</i>	72

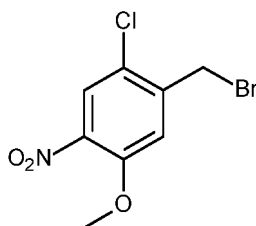
Example A50

[0511] Preparation of intermediate 294:



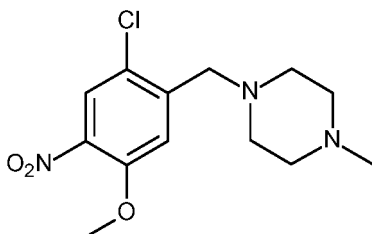
[0512] A suspension of 3-methoxy-4-nitro-phenyl-methanol (1.00 g, 5.46 mmol) and NCS (1.14 g, 8.54 mmol) in CH₃CN (10 mL) was heated to 80 °C for 2 h. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel (SiO₂, mobile phase: cyclohexane/EtOAc, gradient from 1:0 to 1:1). The desired fractions were collected to afford the 1.093 g of intermediate 294 (89% yield, yellow solid).

[0513] Preparation of intermediate 295:



[0514] A stirred mixture of intermediate 294 (0.60 g, 2.76 mmol), CBr₄ (1.19 g, 3.59 mmol), PPh₃ (0.94 g, 3.59 mmol) and THF (5.5 ml) under N₂ atmosphere at 0 °C was warmed to rt and stirred for 30 min. The mixture was diluted with water and extracted with DCM. The organic phase was dried over MgSO₄, filtered and the filtrate concentrated in vacuo. The residue was purified by column chromatography on silica gel (SiO₂, mobile phase: cyclohexane/EtOAc, gradient from 1:0 to 0:1). The desired fractions were collected to afford 714 mg of intermediate 295 (95% yield, off-white solid).

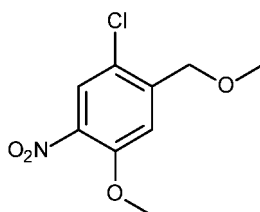
[0515] Preparation of intermediate 296:



[0516] A stirred mixture of intermediate 295 (0.41 g, 1.45 mmol), 1-ethylpiperazine (0.41 ml, 3.20 mmol), K₂CO₃ (0.44 g, 3.20 mmol) and DMF (6 ml) was heated at 80 °C for 30 min. The mixture was cooled to rt and partitioned between water and EtOAc. The organic phase was dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. The residue was purified by column chromatography on silica gel (SiO₂, mobile phase: pentane and EtOAc (1:1 to 0:1) followed by DCM and MeOH (1:0 to 9:1)). The desired fractions were collected to afford 421 mg of intermediate 296 (92% yield, yellow oil).

Example A51

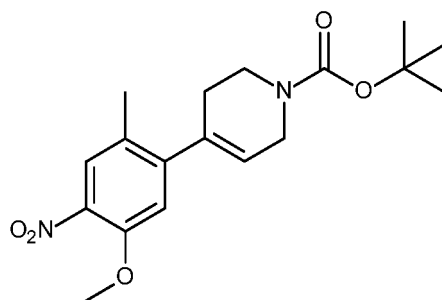
[0517] Preparation of intermediate 299:



[0518] To a stirred suspension of intermediate 294 (100.00 mg, 0.46 mmol) and CS_2CO_3 (0.450 g, 1.38 mmol) in a mixture of THF (0.5 mL) and DMF (0.5 mL) under an Ar atmosphere, was added iodomethane (286 μL , 4.60 mmol). The reaction mixture was stirred at rt for 18 h. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with saturated brine, dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by column chromatography on silica gel (SiO_2 , 12 g silica cartridge, mobile phase: cyclohexane/EtOAc, gradient from 100:0 to 70:30). The desired fractions were collected to give 39 mg of intermediate 299 (36% yield, very pale yellow solid).

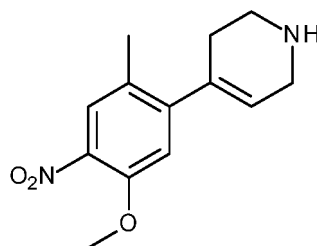
Example A52

[0519] Preparation of intermediate 316:



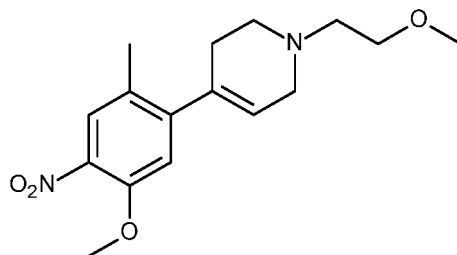
[0520] A solution of 5-bromo-4-methyl-2-nitroanisole (60.00 mg, 0.24 mmol) and N-Boc 1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (202.00 mg, 0.65 mmol) in 1,4-dioxane (5 mL) was degassed by bubbling Ar through the stirred solution in a 10 mL screw-top reaction vial for 10 min. Freshly prepared 2M aqueous sodium carbonate (0.50 mL, 1.0 mmol), degassed by bubbling N_2 through the stirred solution for 15 min, was added, followed by the catalyst [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (20.00 mg, 0.027 mmol). The reaction vial was sealed under Ar and the mixture heated to 100 °C (block temperature) for 16 h. The mixture was cooled to rt and diluted with EtOAc (50 mL) and water (25 mL). The aqueous layer was separated and further extracted with EtOAc (25 mL). The combined organic layers were washed with water (25 mL), brine (10 mL), dried over Na_2SO_4 , filtered through a plug of celite® and evaporated to give a red gum. This residue was purified by column chromatography on silica gel (SiO_2 , 4 g, 50 μm cartridge, mobile phase: cyclohexane/EtOAc, 1CV 100% cyclohexane, then linear gradient from 1:0 to 0:1). The desired fractions were combined and evaporated to give 94 mg of intermediate 316 (quant. yield, red glass).

[0521] Preparation of intermediate 317:



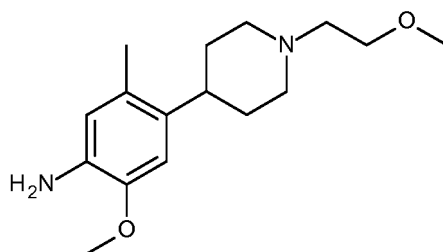
[0522] A solution of intermediate 316 (850.00 mg, 2.40 mmol) and TFA (1.90 mL, 24.80 mmol) in DCM (20 mL) was stirred at rt for 6 h. The reaction mixture was directly purified by cation exchange chromatography (50 g Isolute SCX-2 cartridge, mobile phase: DCM/MeOH, gradient from 1:0 (200 mL), 1:1 (100 mL) to 0:1 (50 mL). The receiver flask was exchanged and the product released from the cartridge with a solution of 2M ammonia in MeOH (150 mL). The resulting red product solution was evaporated to dryness to give 566 mg of intermediate 317 (93% yield, red coloured glass).

[0523] Preparation of intermediate 318:



[0524] A solution of intermediate 317 (566.00 mg, 2.28 mmol), 2-bromo-1-methoxyethane (520.00 μ L, 2.77 mmol) and DIEA (1.20 mL, 7.01 mmol) in DMF (20 mL) was stirred at rt for 18 h. The reaction was not complete, also 260 μ L (2.77 mmol) of 2-bromo-1-methoxyethane was added portionwise again and stirring continued for a further 7h. Then the mixture was stood at rt over the weekend. The reaction mixture was then diluted with DCM (20 mL) and directly purified by cation exchange chromatography (50 g Isolute SCX-2 cartridge, mobile phase: DCM/MeOH, gradient from 1:0 (100 mL), 1:1 (100 mL) to 0:1 (50 mL). The receiver flask was exchanged and the cartridge eluted with a solution of 2M ammonia in MeOH to release the product as a red solution. The solvents were evaporated and the crude product purified by column chromatography on silica gel (SiO₂, 12 g, 15 μ m SiO₂ cartridge, mobile phase: DCM/MeOH, gradient from 100:0 to 95:5). Relevant fractions were combined and evaporated to give 461 mg of intermediate 318 (66% yield, pale yellow gum).

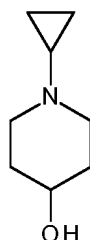
[0525] Preparation of intermediate 319:



[0526] A suspension of intermediate 318 (461.00 mg, 1.51 mmol), and Pd/C (10 wt. %, 100 mg) in DCM (15 mL) and MeOH (5 mL) was stirred at rt under an H₂ atmosphere for 1 h. The reaction mixture was filtered through a pad of celite® and concentrated in vacuo. The residue was re-suspended in DCM (15 mL) and MeOH (5 mL) with Pd/C (10 wt. %, (100 mg) and stirred under an H₂ atmosphere for a further 72 h. The reaction mixture was filtered through a pad of celite® and concentrated in vacuo to give 420 mg of intermediate 319 (quant. yield, yellow oil).

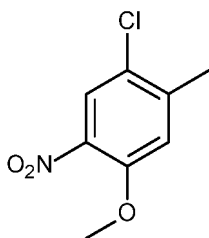
Example A53

[0527] Preparation of intermediate 334:

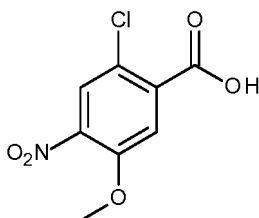


[0528] NaBH₄ (0.54 g, 14.36 mmol) was added portionwise to a solution of N-cyclopropyl-4-piperidine (1.00 g, 7.18 mmol) in a mixture of DCM (33 mL) and MeOH (3.3 mL) at 0 °C under Ar. The mixture was stirred for 1 h and allowing to warm to rt. The, the pale yellow mixture was poured into 1M NaOH (20 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 20 mL). The combined organic layers were passed through a phase separator and solvent evaporated under reduced pressure to obtain 1.25 g of intermediate 334 (yellow oil). The residue was used as it for the next step.

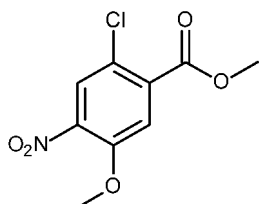
Example A54

[0529] Preparation of intermediate 348:

[0530] NaH (60% dispersed in mineral oil) (1.28 g, 31.99 mmol) was added portionwise to a solution of 4-chloro-3-methyl-6-nitrophenol (5.00 g, 26.66 mmol) in DMF (60 mL) at 0 °C and the mixture was stirred for 15 min at this temperature. Iodomethane (1.83 mL, 29.33 mmol) was added and the mixture was warmed to rt and stirred for 24 h. The reaction mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Si-PPC, 80 g, mobile phase: cyclohexane/EtOAc, gradient from 1:0 to 4:1). The desired fraction were collected and concentrated under vacuum to give 4.09 g of intermediate 348 (76% yield, pale yellow solid).

[0531] Preparation of intermediate 349:

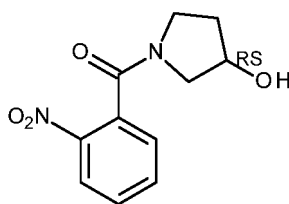
[0532] A suspension of intermediate 348 (4.00 g, 19.80 mmol) and KMnO₄ (6.27 g, 39.70 mmol) in distilled water (400 mL) was heated at reflux for 24 h. A second portion of KMnO₄ (6.27 g, 39.70 mmol) was added and heating was continued for a further 24 h. Then, the reaction mixture was cooled down to 0 °C and acidified to pH 2 with conc. HCl. The aqueous layer was extracted several times with EtOAc. The organic layer was dried over MgSO₄ and concentrated under vacuum. The residue was taken up with DCM and the precipitate was filtered to afford 1.81 g of intermediate 349 (23 % yield based on a purity of 60% evaluated by ¹H NMR). Intermediate 349 was directly engaged in the next step without any further purification.

[0533] Preparation of intermediate 350:

[0534] Intermediate 349 (1.81 g, 4.69 mmol) was dissolved in MeOH (90 mL). Then, conc. H₂SO₄ (1.81 mL) was added and the resulting mixture was heated under reflux for 18 h. Then, the reaction mixture was cooled down to rt, mixed with another batch (from 498 mg of intermediate 349) and partitioned between water and EtOAc. The organic layer was separated, dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (irregular SiO₂, 80 g, mobile phase: heptane/EtOAc, 80:20). The fractions containing the products were mixed and the solvent was concentrated to afford 830 mg of intermediate 350 (77% yield).

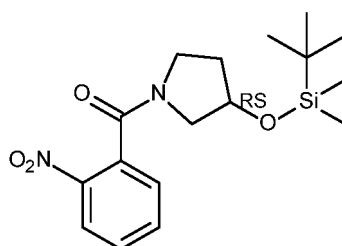
Example A55

[0535] Preparation of intermediate 358:



[0536] A mixture of 2-nitrobenzoic acid (1.00 g, 5.98 mmol), 3-pyrrolidinol (727.00 μ L, 8.97 mmol), HATU (3.40 g, 8.97 mmol) and TEA (2.50 mL, 17.95 mmol) in a mixture of DCM/THF (40 mL, 1:1, v/v) was stirred at rt for 2 h. The reaction mixture was diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3 . The organic layer was decanted, dried over $MgSO_4$, filtered and evaporated to dryness. The residue (2.6 g) was purified by column chromatography on silica gel (irregular $SiOH$, 24 g, mobile phase: $NH_4OH/MeOH/DCM$, gradient from 0% NH_4OH , 0% $MeOH$, 100% DCM to 1% NH_4OH , 10% $MeOH$, 90% DCM). The pure fractions were collected and evaporated to dryness to give 2 g of intermediate 358 used as it is for the next step.

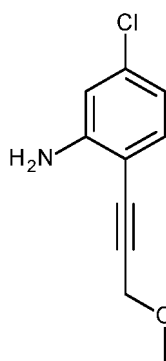
[0537] Preparation of intermediate 359:



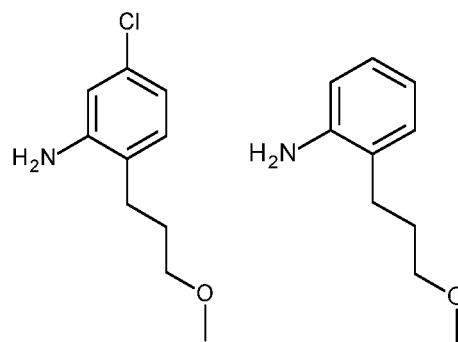
[0538] A solution of TBDMS-Cl (1.08 g, 7.18 mmol) in DCM (5 mL) was added to a mixture of intermediate 358 (1.41 g, 5.98 mmol) and imidazole (1.22 g, 17.95 mmol) in Me-THF (25 mL) and the reaction mixture was stirred overnight at rt. The reaction mixture was diluted with DCM and poured onto water. The organic layer was decanted, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (irregular $SiOH$, 40 g, mobile phase: $DCM/MeOH$, gradient from 100:0 to 97:3). The pure fractions were collected and evaporated to dryness to give 921 mg of intermediate 359 (44% yield). Intermediate 359 was used as it is for the next step.

Example A56

[0539] Preparation of intermediate 376:



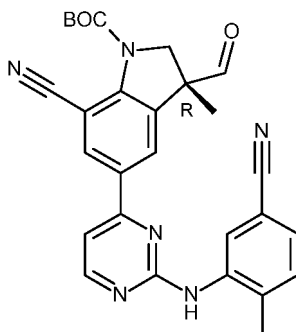
[0540] In a round bottom flask, 5-chloro-2-iodoaniline (2.00 g, 7.89 mmol), methyl propargyl ether (1.00 mL, 11.84 mmol) and TEA (1.92 mL, 13.41 mmol) were diluted in DMF. The mixture was degassed (N_2 bubbling) and $Pd(PPh_3)_2Cl_2$ (0.28 g, 0.39 mmol) and CuI (0.30 g, 1.58 mmol) were added. The reaction mixture was stirred at rt for 4 h. The reaction mixture was apportioned between water and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified by column chromatography on silica gel (irregular SiO_2 , 40 g, mobile phase: heptane/EtOAc, gradient from 90:10 to 80:20). The product fractions were concentrated to afford 1.013 g of intermediate 376 (70% yield, orange liquid which solidify upon standing).

Preparation of intermediate 377 and intermediate 378:**[0541]**

intermediate 377 intermediate 378

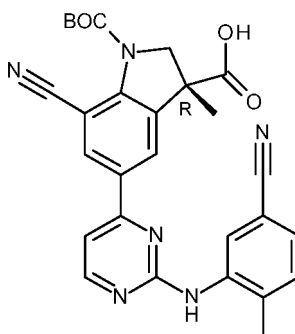
[0542] In a round bottom flask, intermediate 376 (1.01g, 5.58 mmol) was diluted in MeOH (50.8 mL). Then the solution was degassed with N₂ and Pd/C (10 wt. %, 0.50 g, 4.74 mmol) was added. The reaction mixture was then hydrogenated at 1 bar for 4 h. The reaction mixture was filtered over a pad of celite® and the filtrate was concentrated. Then, the residue was diluted in MeOH (50 mL) and degassed with N₂. Pd/C (10 wt. %, 0.50 g, 4.74 mmol) was added and the reaction mixture was then hydrogenated at 1 bar for 4 h. The reaction mixture was filtered over a pad of celite® and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (irregular SiOH, 80 g, mobile phase: heptane/EtOAc, gradient from 95:5 to 80:20). The fractions containing the product were mixed and concentrated to afford 336 mg of a mixture of intermediates 377 and 378 (21% yield, purity 70:30 based on NMR).

Example A57

[0543] Preparation of intermediate 380:

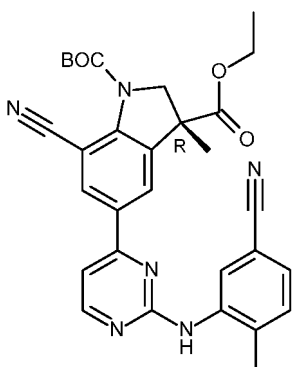
[0544] DCM (30 mL) was cooled to -78 °C and oxalyl chloride (4.53 mL, 9.06 mmol) was added followed by dodecylmethyl sulfoxide (2.11 g, 9.06 mmol). After 30 min, a suspension of intermediate 10R (3.00 g, 6.04 mmol) in DCM (30 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C, then DIPEA (5.21 mL, 30.21 mmol) was added. The stirring was continued for 3 h at -78 °C and the reaction mixture was allowed to warm to rt and stirred for overnight. A diluted solution of NH₄Cl was added and the aqueous layer was extracted twice with DCM. The combined layers were dried over MgSO₄, filtered and evaporated to dryness. The residue was crystallized from Et₂O and the precipitate was filtered, washed with DiPE and dried to give 2.62 g of intermediate 380 (87% yield).

[0545] Preparation of intermediate 381:



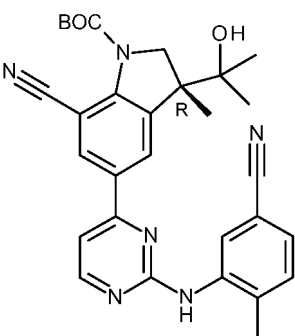
[0546] Intermediate 380 (600.00 mg, 1.21 mmol) was dissolved in a mixture of tert-butyl alcohol (44 mL) and 2-methyl-2-butene (22 mL). Then, distilled water (44 mL) was added, followed by sodium dihydrogenophosphate (2.18 g, 18.20 mmol) and NaO_2Cl (2.19 g, 24.26 mmol). The suspension was stirred vigorously at rt overnight. The mixture was poured into NH_4Cl and extracted with EtOAc. The organic layer was dried over MgSO_4 , filtered and the solvent was evaporated to give 619 mg of intermediate 381 (100% yield).

[0547] Preparation of intermediate 382:



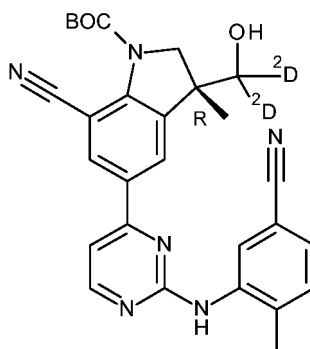
[0548] A mixture of EtOH (0.28 mL, 4.85 mmol), intermediate 381 (0.62 g, 1.21 mmol), HATU (0.51 mg, 1.33 mmol), DIPEA (0.52 mL, 3.03 mmol) and DMAP (14.80 mg, 0.12 mmol) in DMF (14.4 mL) was stirred at rt for 24 h. The solution was poured onto water and extracted with EtOAc. The organic layer was washed successively with water and brine, dried over MgSO_4 , filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (15-40 μm , 40 g, mobile phase: DCM/MeOH, gradient from 100:0 to 98:2). The pure fractions were combined and evaporated to dryness to give 239 mg of intermediate 382 (37% yield, 98% purity based on LC/MS).

[0549] Preparation of intermediate 383:



[0550] In a round bottom flask, intermediate 382 (0.18 g, 0.34 mmol) was diluted in THF (33 mL). Then, the solution was cooled to 0 °C and methylmagnesium bromide (0.42 mL, 1.36 mmol) was added dropwise. The solution was stirred allowing the temperature to raise rt. Additional methylmagnesium bromide (0.42 mL, 1.36 mmol) was added at rt and the reaction mixture was stirred for an additional 2 h. The mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO_4 , filtered and the solvent was

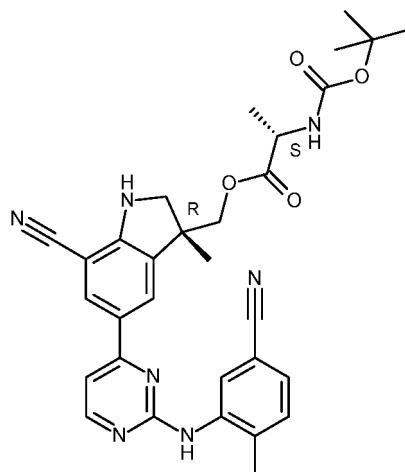
[0551] Preparation of intermediate 384:



Example A59

CNc1ccc(C#N)cc1Nc2ncnc3c2c4c(c5ccccc5C#N)C[C@H](C4)COC(=O)CNC(=O)OC(C)(C)C

[0555] Preparation of intermediate 386:



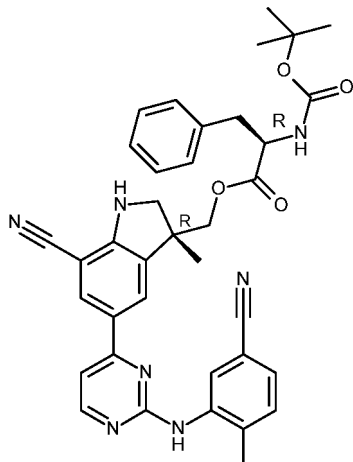
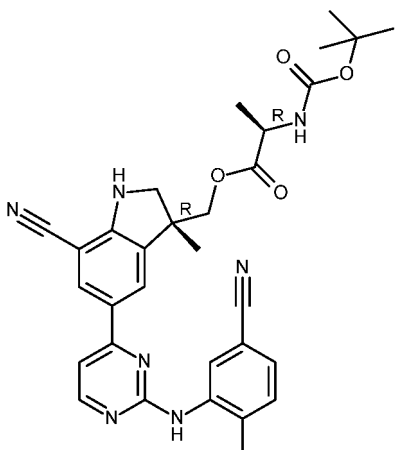
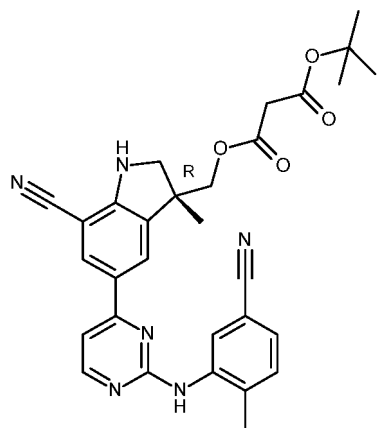
[0556] A mixture of compound 1 (2.1 g; 5.30 mmol), Boc-L-Alanine (2.5 g; 13.24 mmol), HATU (5 g; 13.24 mmol), DIPEA (4.5 mL; 26.48 mmol) and DMAP (35 mg; 0.29 mmol) in DMF (63 mL) was stirred at room temperature for 18 hours. The solution was poured onto water and extracted with EtOAc. The organic layer was washed with H₂O, then brine, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 150g; mobile phase: 65% Heptane, 5% MeOH (+10% NH₄OH), 35% AcOEt). The pure fractions were collected and evaporated to dryness yielding 2.73g (91%) of intermediate 386.

[0557] The intermediates in the Table below were prepared by using an analogous method as reported for the preparation of intermediates 385 and 386, starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 387	From compound 1 and Boc-L-Valine	438	58

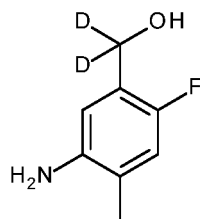
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(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 388	 From compound 1 and Boc-D-Phenylalanine	800	98
Intermediate 389	 From compound 1 and Boc-D-Alanine	288	Quantitative
Intermediate 390	 From compound 1 and 3-tert-butoxypropanoic acid	364	54

Example A60

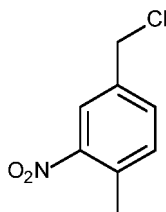
[0558] Preparation of intermediate 393:



[0559] Lithium aluminium deuteride (263 mg; 6.27 mmol) was added portionwise at 5°C to a solution of methyl-5-amino-2-fluoro-4-methylbenzoate (383 mg; 2.09 mmol) in THF (20 mL) and the reaction mixture was stirred at room temperature for 5h. The reaction mixture was quenched carefully by adding EtOAc and poured onto ice water. Then, more EtOAc was added and the organic layer was decanted, washed with brine, dried over MgSO₄, filtered and the solvent was evaporated to give 337 mg (quant.) of a brown solid which was used without without purification in the next step.

Example A61

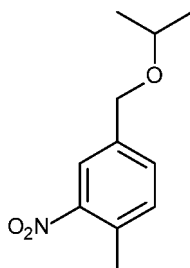
[0560] Preparation of intermediate 395:



[0561] A mixture of 4-Methyl-3-nitrobenzyl alcohol (2.5g; 14.95 mmol) and thionyl chloride (10 mL) in DCM (40 mL) was stirred at 80°C overnight. The mixture was evaporated in vacuum.

[0562] The crude compound (3g) was purified by silica gel column chromatography (eluent: Petrol ether/ Ethyl acetate: 10/1). The fractions containing the product were evaporated in vacuum to give 2.7g (97%) of intermediate 395 as a yellow solid.

[0563] Preparation of intermediate 396:

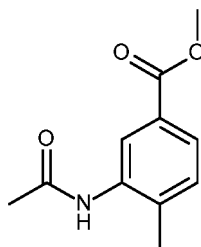


[0564] A mixture of intermediate 395 (2.7g; 14.55 mmol) and sodium isopropoxide (8.63g; 105.14 mmol) in isopropanol was stirred at 100°C overnight. Water (100 mL) was added, and the aqueous layer was extracted with ethyl acetate (150 mL*2). The organic layer was washed by brine (100 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum.

[0565] The crude compound (3g) was purified by column chromatography over silica gel (eluent: Petrol ether/ Ethyl acetate: 10/1). The fractions containing the product were evaporated in vacuum to give 2.1g (69%) of intermediate 396 as clear oil.

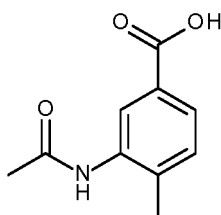
Example A62

[0566] Preparation of intermediate 399:



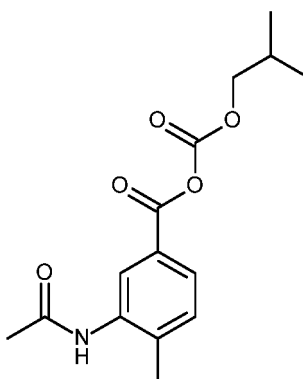
[0567] To a solution of Methyl 3-amino-4-methylbenzoate (5g; 30.27 mmol) and triethylamine (4.59g; 45.4 mmol) in DCM (50 mL) was added dropwise acetyl chloride (3.09g; 39.35 mmol) at 0°C. The reaction mixture was stirred at room temperature overnight. An aqueous saturated solution of NaHCO₃ (100 mL) was added. The mixture was filtered and the filter cake was washed by water (30 mL*2) and petroleum ether (30 mL*2). The cake was dried in vacuum to give 5.6g (88%) of intermediate 399 as a white solid.

[0568] Preparation of intermediate 400:



[0569] To a solution of intermediate 399 (3.4g; 16.24 mmol) in a 1/2 mixture of THF/water (30 mL) was added sodium hydroxide (3.25g; 81.2 mmol) at room temperature. The mixture was stirred at room temperature for 24 hours and poured into a mixture of water (30mL) and ethyl acetate (30mL). The aqueous layer was separated and acidified by HCl (12M) until pH=2. The precipitated solid was filtered and dried to afford 2.7g (86%) of intermediate 400 as white solid.

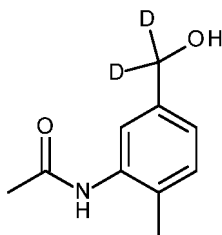
[0570] Preparation of intermediate 401:



[0571] To a solution of intermediate 400 (2.7g; 13.97 mmol) in THF (20 mL) was added dropwise isobutyl chloroformate (2.3g; 16.8 mmol) at 0°C. Then, DIPEA (5.42g; 41.93 mmol) was added at 0°C. and the mixture was stirred at 0°C for 2 hours.

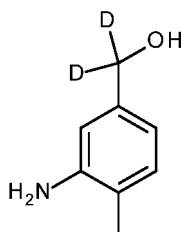
[0572] The mixture was diluted with ethyl acetate (30mL) and the organic layer was washed with water (15mL*3). The organic layer was dried (MgSO₄), filtered and concentrated to afford 3.87g (94%) of intermediate 401 as a light yellow solid.

[0573] Preparation of intermediate 402:



[0574] To a solution of intermediate 401 (2g; 6.82 mmol) in deuterated methanol (50 mL) was added, slowly at 0°C, sodium borodeuteride (1.43g; 34.1 mmol). The mixture was stirred at room temperature for 30 min. The mixture was concentrated and the residue was purified by column chromatography on silica gel (eluent: petrol/ethyl acetate: from 100:0 to 0:100. The fractions containing the product were collected and the solvent was evaporated to afford 988 mg (80%) of intermediate 402 as a white solid.

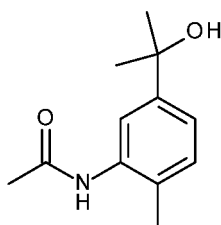
[0575] Preparation of intermediate 403:



[0576] The mixture of intermediate 402 (980 mg; 5.41 mmol) and sodium hydroxide (18.2g; 324.45 mmol) in a 4/1 mixture of methanol/water (20 mL) was stirred at 90°C for 48 hours. The mixture was concentrated, diluted with water (20mL) and extracted with ethyl acetate (15mL*3). The organic layer was dried (MgSO₄), filtered and concentrated to afford 650 mg (86%) of intermediate 403 as a light yellow solid.

Example A63

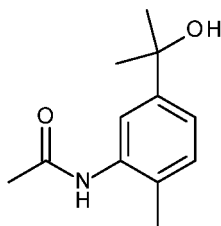
[0577] Preparation of intermediate 405:



[0578] To a solution of intermediate 399 (1g; 4.82 mmol) in THF (30 mL) was added, dropwise at -78°C under N₂, methylmagnesium bromide (3M in Et₂O; 8.04 mL; 24.13 mmol). The reaction mixture was stirred at room temperature overnight. A saturated solution of NH₄Cl (60 mL) was added and, the reaction mixture was extracted with ethyl acetate (50 mL*3). The organic layer was washed by brine (50 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum to give the crude compound.

[0579] The crude compound (0.9g) was purified by column chromatography over silica gel (eluent: Petroleum ether/Ethyl acetate: 1/3). The fractions containing the product were evaporated in vacuum to give 700mg (70%) of intermediate 405 as white solid.

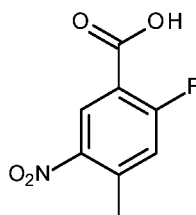
[0580] Preparation of intermediate 406:



[0581] Intermediate 406 was prepared following a similar procedure than the one used for the preparation of intermediate 403, starting from intermediate 405 (490 mg; 89%; yellow solid).

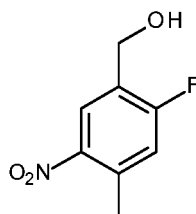
Example A64

[0582] Preparation of intermediate 408:



[0583] To a solution of 2-fluoro-4-methylbenzoic acid (1 g; 6.5 mmol) in sulfuric acid (15 mL) was added, dropwise over 3 minutes at 0°C, a mixture of freshly prepared C (0.415 mL) and B (0.44 mL; 10.5 mmol). The mixture was stirred at 0°C for 3 hrs and added cautiously to 66 ml of ice/ice water. The resulting mixture was stirred for 1 hour. The obtained precipitate was filtered and dried under vacuum at 50°C to give 1.26g (98%) of intermediate 408 as a white solid.

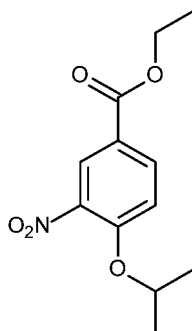
[0584] Preparation of intermediate 409:



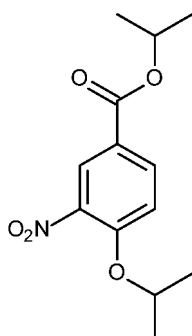
[0585] Intermediate 408 (1.26 g; 6.32 mmol) was dissolved in THF (15.7 mL). Borane-THF complex (1M; 19 mL; 19 mmol) was added dropwise at 0°C. The mixture was stirred overnight at 50°C. The mixture was quenched with 60 mL of a saturated aqueous NaHCO₃ and extracted with ethyl acetate (80 mL *3). The organic layer was washed with brine (100 mL), dried over MgSO₄ and filtered. The solvent was removed under vacuum to give 1.17g (100%) of intermediate 409 as yellow solid.

Example A65

[0586] Preparation of intermediate 413



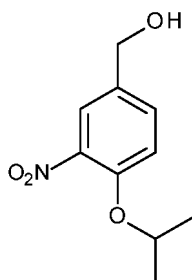
and intermediate 414



Sodium bis(trimethylsilyl)amide (28.15 mL; 28.15 mmol) was added dropwise to a solution of isopropanol (2.15 mL; 28.15 mmol) and THF (150 mL) at 0 °C and the reaction was stirred for 10 minutes. The resulting solution was added to a solution of ethyl-4-fluoro-3-nitrobenzoate (4g; 18.76 mmol) in THF (50 mL) at 0 °C and the reaction mixture stirred overnight. Water (80 mL) was added and the mixture was extracted with ethyl acetate (100 mL*3), dried over sodium sulfate, filtered and evaporated to give a yellow solid.

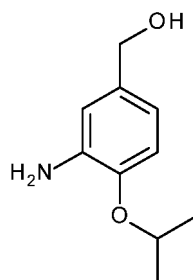
[0587] The residue was purified by flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 60/40). The fractions containing the product were collected and the solvent was concentrated to dryness under vacuum to give 3.2g of an undetermined mixture of intermediates 413 and 414 as yellow solid.

[0588] Preparation of intermediate 415:



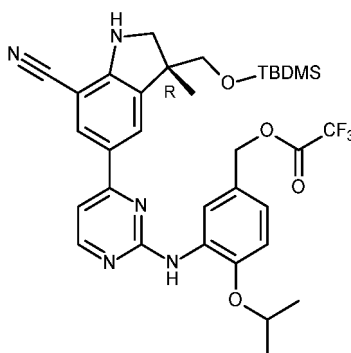
[0589] Lithium aluminium hydride (0.7g; 18.44 mmol) was added to a solution of intermediates 413 and 414 (3.2g) in THF (60 mL) at 0°C. The mixture was stirred overnight at rt. At 0°C, water (0.49 ml) was added followed by a 10% aqueous solution NaOH (0.49 ml) and additional water (1.47 ml). The mixture was dried over MgSO₄, filtered and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 60/40). The fractions containing the product were collected and the solvent was concentrated to dryness under vacuum to give 420 mg (32%) of intermediate 415 as a yellow oil.

[0590] Preparation of intermediate 416



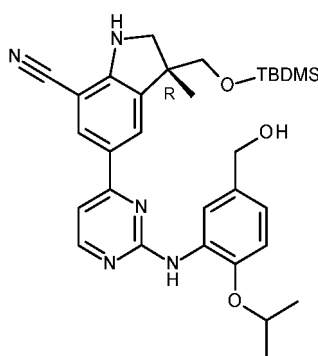
[0591] A mixture of intermediate 415 (500mg; 2.37 mmol) in methanol (10 mL) was hydrogenated at rt (15 Psi) with platinum on activated charcoal as a catalyst. After uptake of H₂ (3 equiv), the mixture was stirred overnight at rt. The catalyst was filtered off and the filtrate was evaporated to give 400 mg (93%) of intermediate 416 as a brown oil.

[0592] Preparation of intermediate 418:



[0593] To a solution of intermediate 417 (340mg; 0.41mmol) in DCM was added trifluoroacetic acid (0.8 mL; 10.45 mmol). The mixture was stirred for 2h at rt, then poured onto water (15 mL) and the pH was adjusted to 10 with a saturated aqueous Na₂CO₃. The mixture was extracted with DCM (30 mL*3), dried over MgSO₄, filtered and evaporated to give 420mg (59%) of intermediate 418 as yellow solid.

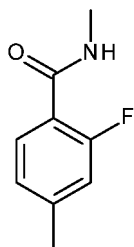
[0594] Preparation of intermediate 419:



[0595] A mixture of intermediate 418 (400 mg; 0.36 mmol) and potassium carbonate (178.5 mg; 1.29 mmol) in methanol (5 mL) was stirred for 30 mn at 80°C. The suspension was filtered through a pad of Celite which was washed with EtOAc (10 mL*3). The combined filtrates were concentrated to dryness to give 320 mg (95%) of intermediate 419 as a yellow oil.

Example A66

[0596] Preparation of intermediate 420:

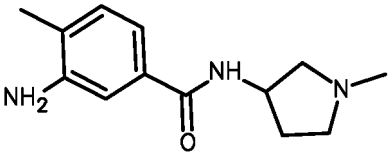
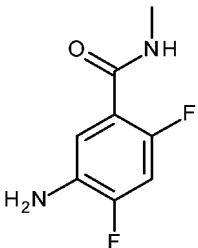
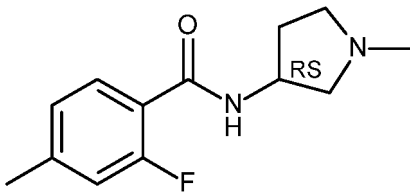
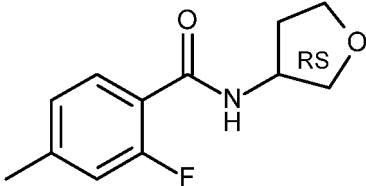
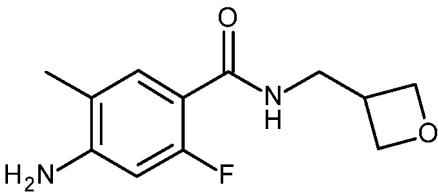


[0597] This reaction was made twice on 5 g of 2-fluoro-4-methylbenzoic acid. A mixture of 2-fluoro-4-methylbenzoic acid (5 g; 32.4 mmol), HATU (13.6 g; 35.7 mmol), and DIPEA (12.3 mL; 71.4 mmol) was stirred in DCM (129 mL) for 30 min and methylamine (17.8 mL g; 35.7 mmol) was added. The mixture was stirred at rt for 5h. The mixture was evaporated. The residue was purified by chromatography over silica gel (15-40 μ m, 120 g, eluent: heptane/EtOAc: 80/20 to 10/90). The pure fractions were mixed and the solvent was evaporated to give 9.07 g (84%) of intermediate 420.

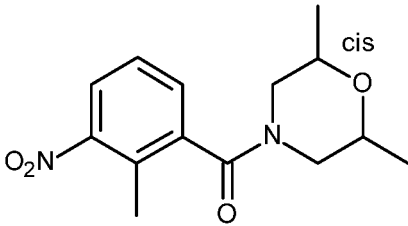
[0598] The intermediates in the Table below were prepared by using an analogous method as reported for the preparation of intermediates 420, starting from the respective starting materials. The most relevant minor deviations from the existing procedure are indicated in the column "Mass"

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 432	from 3-amino-4-methylbenzoic acid and 1-(2-aminoethyl) pyrrolidine	288	36
Intermediate 434	From 3-amino-4-methylbenzoic acid and 2-(4-morpholino) ethylamine	126	12
Intermediate 436	From 3-amino-4-methylbenzoic acid and dimethylamine	700	100
Intermediate 438	From 3-amino-4-methylbenzoic acid and 2-(4-morpholino) ethylamine.	1530	100

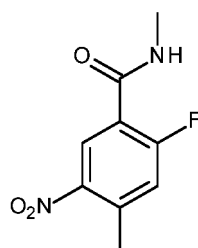
(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 441	 From 3-amino-4-methylbenzoic acid and 1-methylpyrrolidin-3-amine	441 Procedure with 2.5 eq. of COMU instead of 1.1 eq. of HATU	53
Intermediate 443	 From 2-fluoro-4-methylbenzoic acid and methylamine	356	66
Intermediate 445	 From 2-fluoro-4-methylbenzoic acid and 1-methylpyrrolidin-3-amine	773	100
Intermediate 450	 From 2-fluoro-4-methylbenzoic acid and 3-aminotetrahydrofuran hydrochloride	554	77
Intermediate 495	 From oxetan-3-ylmethanamine and intermediate 494	900	76

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 521a	 From 2-methyl-3-nitrobenzoic acid and cis-2,6-dimethylmorpholine	1500	98

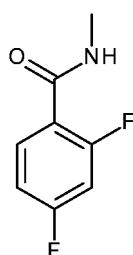
[0599] Preparation of intermediate 421:



[0600] A mixture of fuming nitric acid (3.3 mL; 79.28 mmol) in sulfuric acid (4 mL) was added dropwise at 5°C over 3 minutes (ice bath) to a solution of intermediate 420 (9 g; 53.83 mmol) in sulfuric acid (120 mL) [no exothermicity]. The reaction mixture was stirred at 5°C for 3 hours and quenched precautionously with ice/ice-water (500 mL) at 0-5°C. The mixture was vigorously stirred for 1h. The precipitate was filtered, washed with ice-water (3 x 300 mL) and dried. The obtained solid was solubilized with DCM and the organic layer was dried over MgSO₄, filtered and the solvent was evaporated to give 10.47 g (92%) of intermediate 421 as a white solid.

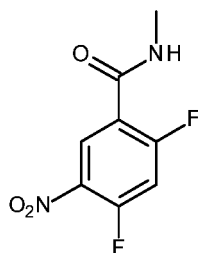
Example A67

[0601] Preparation of intermediate 424:



[0602] A mixture of 2,4-difluorobenzoic acid (2 g; 12.65 mmol), HATU (5.3 g; 13.915 mmol), and DIPEA (4.8 mL; 27.83 mmol) in DCM (50 mL) was stirred for 30 min and 2N methylamine in THF (7 mL; 13.915 mmol) was added. The reaction mixture was stirred at room temperature for 18 hours, poured onto water and extracted with DCM. The organic layer was decanted, filtered through chromabond® and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 40g; gradient: 20% EtOAc, 80% heptane to 40% EtOAc, 60% heptane). The pure fractions were collected and evaporated to dryness yielding 1.68 g (77%) of intermediate 424.

[0603] Preparation of intermediate 425:

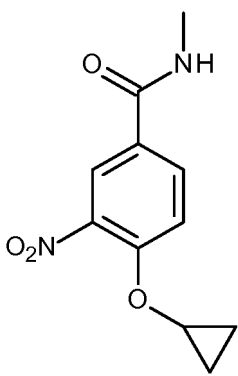


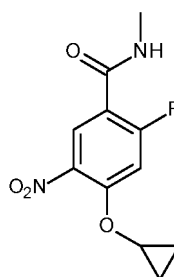
[0604] A mixture of fuming nitric acid (0.6 mL; 14.456 mmol) in concentrated sulphuric acid (1 mL) was added dropwise at 5°C to a solution of intermediate 424 (1.68 g; 9.816 mmol) in concentrated sulphuric acid (21 mL). The reaction mixture was stirred at 5°C for 4 hours and poured onto ice water. The suspension was stirred at room temperature for 30 min and the precipitate was filtered, washed with water and dried yielding 1.38 g (65%) of intermediate 425.

[0605] The intermediates in the Table below were prepared by using an analogous method as reported for the preparation of intermediates 425, starting from the respective starting materials.

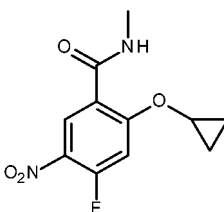
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 446	From intermediate 445	638	70
Intermediate 451	From intermediate 450	426	65

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 489	 From intermediate 488	354	53

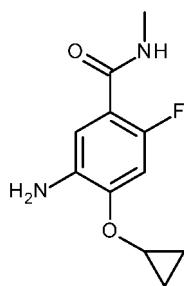
[0606] Preparation of intermediate 426

and intermediate 427

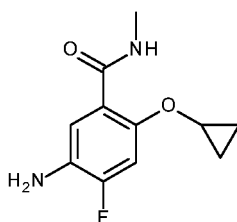


A mixture of intermediate 425 (1.15 g; 5.32 mmol), cyclopropanol (337 μ L; 5.32 mmol) and cesium carbonate (3.5 g; 10.64 mmol) in 1,4-dioxane (15 mL) was heated at 80°C for 1 hour. The reaction mixture was cooled to room temperature, and diluted with DCM. The organic layer was washed with water, filtered through chromabond® and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 50g; mobile phase: gradient from 20% EtOAc, 80% heptane to 40% EtOAc, 60% heptane). The fractions containing the products were collected and evaporated to dryness yielding 860 mg (63%) of a mixture of intermediates 426 and 427 directly used in the next step without any further purification.

[0607] Preparation of intermediate 428



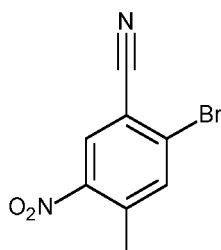
and intermediate 429



A mixture of intermediate 426 and 427 (860 mg; 3.38 mmol), iron powder (945 mg; 16.91 mmol) and ammonium chloride (724 mg; 13.53 mmol) in ethanol (22 mL) and water (5.6 mL) was heated at 70°C for 1 hour. The reaction mixture was cooled down to room temperature, diluted with DCM, filtered over Celite® and basified with a 10% aqueous solution of K₂CO₃. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness yielding 791 mg of a mixture of intermediates 428 and 429 directly engaged in the next step.

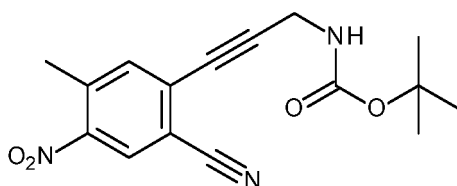
Example A68

[0608] Preparation of intermediate 455:



[0609] To a solution of 2-bromo-4-methylbenzonitrile (4.0 g; 20.40 mmol) in sulfuric acid (6 mL) at 0°C was added potassium nitrate (2.063 g; 20.40 mmol) in sulfuric acid (18 mL). After stirring at 0°C for 1.5 hour, the reaction mixture was poured into 500 mL of ice water. The precipitate was collected by filtration and washed with copious amounts of water. The precipitate was dried to give 4.5 g (91%) of intermediate 455.

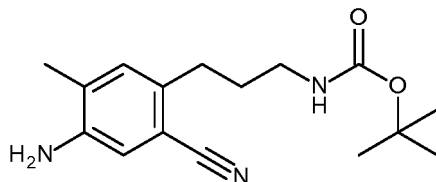
[0610] Preparation of intermediate 456:



[0611] A mixture of intermediate 455 (500 mg; 2.07 mmol), *N*-*tert*-butyl-3-oxoprop-1-yn-1-ylamine (483 mg; 3.11 mmol), tri-*tert*-butylphosphine (0.0287 mL; 0.122 mmol), diisopropylamine (0.33 mL; 2.41 mmol), copper (I) iodide (4.7 mg; 0.024 mmol) and dichlorobis(triphenylphosphine)palladium (57 mg; 0.081 mmol) in 1,4-dioxane (8.8 mL) was purged with N₂ three

times and was heated at 45°C for 1 h. The mixture was poured into ice and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent was evaporated. The residue was purified by chromatography over silica gel (80 g; 15-40 μm, eluent: heptane/EtOAc: 100/0 to 0/100). The pure fractions were mixed and the solvent was evaporated to give 0.594 g (91%) of intermediate 456.

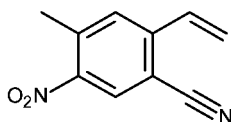
[0612] Preparation of intermediate 457:



[0613] A mixture of intermediate 456 (555 mg; 1.76 mmol) and Pd (10%) on activated charcoal (187 mg) in EtOAc (11 mL) was hydrogenated at rt under 1 bar of H₂ overnight. The mixture was filtered over celite and the filtrate was evaporated until dryness to give 0.352 g (69%) of intermediate 457.

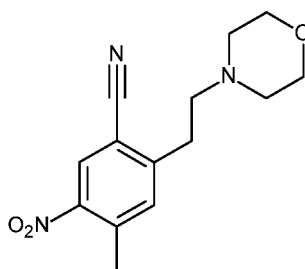
Example A69

[0614] Preparation of intermediate 465:



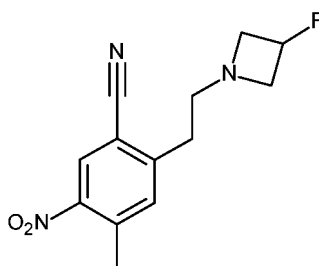
[0615] A mixture of intermediate 455 (0.5 g; 2.074 mmol), 2-vinyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.528 mL; 3.11 mmol) and tetrakis(triphenylphosphine)palladium(0) (120 mg; 0.104 mmol) in 2N Na₂CO₃ (1.82 mL; 3.63 mmol) and 1,4-dioxane (5.2 mL) was degassed and then heated at 100°C overnight. The mixture was poured into ice and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent was evaporated. The residue was purified by chromatography over silica gel (80 g, 15-40 μm, eluent: heptane/EtOAc: 100/0 to 0/100). The pure fractions were mixed and the solvent was evaporated to give 0.181 g (46%) of intermediate 465.

[0616] Preparation of intermediate 466:



[0617] A mixture of intermediate 465 (250 mg; 1.33 mmol) and morpholine (821 mg; 6.64 mmol) in MeOH (4.7 mL) was stirred at 60°C for 1 h in a sealed tube. The mixture was poured into ice and extracted with DCM. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent was evaporated. The residue was purified by chromatography over silica gel (15-40 μm, 24 g, eluent: DCM/MeOH: 100/0 to 95/5). the pure fractions were mixed and the solvent was evaporated to give 0.329 g (90%) of intermediate 466.

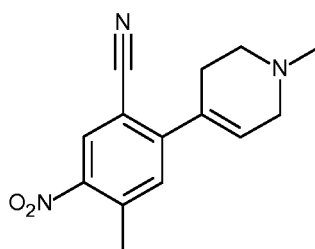
[0618] Preparation of intermediate 469:



[0619] Intermediate 469 was prepared using an analogous method as the one used for the preparation of intermediate 466, starting from intermediate 465 and 3-fluoroazetidine hydrochloride (247 mg; 67%).

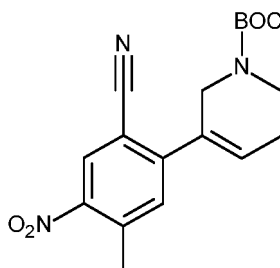
Example A70

[0620] Preparation of intermediate 472:



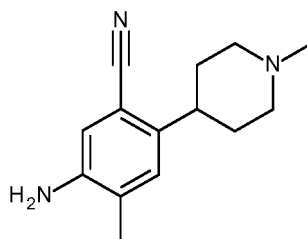
[0621] A mixture of intermediate 455 (500 mg; 2.07 mmol), 1-methyl-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (509 mg; 2.28 mmol) and potassium phosphate (881 mg; 41.5 mmol) in 1,4-dioxane (7 mL) and water (4 mL) was degassed with N_2 . 1,1'-Bis (diphenylphosphino) ferrocene- palladium(ii) dichloride dichloromethane (17 mg; 0.0207 mmol) was added and the reaction mixture was heated at 120°C for 15 min using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W. The mixture was poured onto water and extracted with DCM. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular $SiOH$, 80 g; mobile phase: DCM/MeOH: 100/0 to 95/5). The fractions containing the product were collected and evaporated to dryness to give 0.515 g (96%) of intermediate 472.

[0622] Preparation of intermediate 475:



[0623] Intermediate 475 was synthesized by using the same method than the one used for the preparation of intermediate 472 starting from intermediate 455 and tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.45g; 93%).

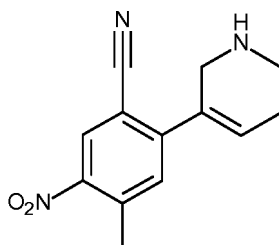
[0624] Preparation of intermediate 473:



[0625] A solution of intermediate 472 (0.478 mg; 1.86 mmol) in MeOH (21.9 mL) was hydrogenated under 2 bars of H₂ at rt in presence of 10% palladium on activated charcoal (54.8 mg) overnight. The mixture was filtered off over celite and the filtrate was evaporated. The residue was purified by chromatography over silica gel (40 g, 15-40 μm, eluent: DCM/MeOH: 100/0 to 90/10). The fractions containing the product were mixed and the solvent was evaporated to give 0.155 g (36%) of intermediate 473.

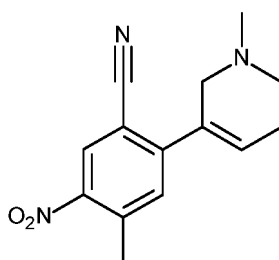
Example A71

[0626] Preparation of intermediate 476:



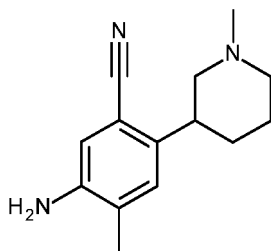
[0627] TFA (4.4 mL; 58 mmol) was added to a solution of intermediate 475 (1.45 g; 4.22 mmol) in DCM (22 ml) and the mixture stirred for 30 mins, then poured into ice, basified with K₂CO₃ and extracted with DCM. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent was evaporated yielding 0.89g (87%) of intermediate 476.

[0628] Preparation of intermediate 477:



[0629] Formaldehyde (0.54 mL; 7.24 mmol) was added to a solution of intermediate 476 (0.873 g; 3.59 mmol) and sodium acetate (0.295 g; 3.6 mmol) in MeOH (30 ml) and DCM (15 ml) and the mixture stirred at room temperature for 5 minutes. Sodium triacetoxyborohydride (1.53 g; 7.19 mmol) was then added and the mixture was stirred for 1h. The mixture was poured into ice, basified with K₂CO₃ and extracted with DCM. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent was evaporated. The residue was purified by chromatography over silica gel (15-40 μm, 80 g, eluent: DCM/MeOH: 100/0 to 90/10). The pure fractions were mixed and the solvent was evaporated to give 1.15 g (99%) of intermediate 477.

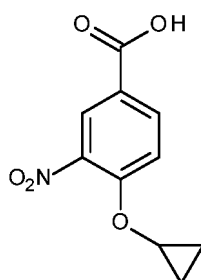
[0630] Preparation of intermediate 478:



[0631] Intermediate 478 was synthesized by using an analogous method than the one used for the preparation of intermediate 473 starting from intermediate 477 (1.04g; 84% of purity based on LC/MS).

Example A72:

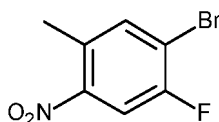
[0632] Preparation of intermediate 488:



[0633] A mixture of intermediate 40 (575 mg; 2.816 mmol) in concentrated HCl (11 mL) was heated at 100°C for 5 hours. The reaction mixture was cooled to room temperature, poured onto iced water and extracted with Et₂O. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness yielding 632 mg of intermediate 488.

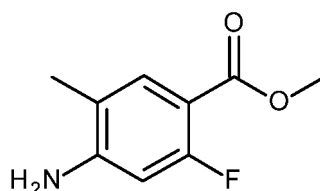
Example A73:

[0634] Preparation of intermediate 492:



[0635] A solution of potassium nitrate (2.46g; 0.024 mol) in concentrated sulfuric acid (36 ml) was added dropwise at a temperature below 5°C to a solution of 3-bromo-4-fluorotoluene (2.52 mL; 0.02 mol) in concentrated sulfuric acid (4 ml). The mixture was stirred at 5°C for 2 hours, then, poured onto ice water. The obtained precipitate was filtered and dried yielding 3.94g (84%) of intermediate 492.

[0636] Preparation of intermediate 493:

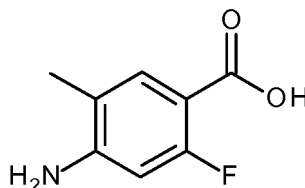


[0637] Into an autoclave (300 mL) purged with N₂ was added intermediate 492 (2.93 g; 12.5 mmol) in MeOH (117 mL). Triethylamine (3.58 mL; 25 mmol) was added then 1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.615 g; 0.751 mmol). The autoclave was purged and the mixture was stirred overnight under 30 bars of carbon monoxide at 90°C. The mixture was evaporated. The residue was purified by chromatography over silica gel (15-40

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μm , 90 g, eluent: heptane/EtOAc: 100/0 to 0/100). The pure fractions were mixed and the solvent was evaporated to give 1.22 g (28%) of intermediate 493.

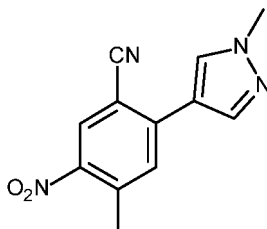
[0638] Preparation of intermediate 494:



[0639] A solution of lithium hydroxide (0.9 g; 21.4 mmol) in water (4.4 mL) was added to a solution of intermediate 494 (0.982 g; 5.36 mmol) in THF (47 mL). The reaction mixture was refluxed overnight. The mixture was poured into ice, acidified with aqueous 3N HCl and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO_4 , filtered and the solvent was evaporated yielding 907 mg of intermediate 494 directly engaged in the next step.

Example A74:

[0640] Preparation of intermediate 497:

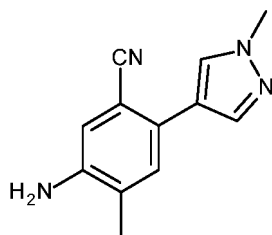


[0641] In a sealed tube, a solution of 2-bromo-4-methyl-5-nitro-benzonitrile (1.0 g; 4.15 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.29 g; 6.22 mmol) and K_3PO_4 (2.64 g; 12.44 mmol) in 1,4-dioxane (30.8 mL) and distilled water (9.7 mL) was purged with N_2 . PdCl_2dppf (340 mg; 415 μmol) was added, the reaction mixture was purged again with N_2 and heated at 80 °C for 18h. The reaction mixture was poured into an aqueous solution of K_2CO_3 and extracted with EtOAc. The organic layer was dried over MgSO_4 , filtered and evaporated until dryness. The residue was purified by chromatography over silica gel (irregular SiOH , 40g; mobile phase: gradient from 0% EtOAc, 100% heptane to 40% EtOAc, 60% heptane). The fractions were collected and evaporated to dryness yielding 800 mg (80%) of intermediate 497.

[0642] The compounds in the table below were prepared using analogous method as described for intermediate 497 starting from the respective starting materials.

Intermediate number	Structure	Quantity	Yield
Intermediate 498	From 5-bromo-1-methyl-1H-imidazole and 4,4,5,5-tetramethyl-2-(4-methyl-3-nitrophenyl)-1,3,2-Dioxaborolane	170 mg	52%

[0643] Intermediate 499:



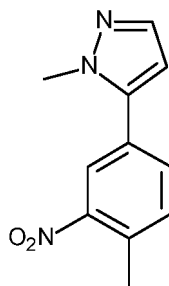
[0644] A mixture of intermediate 497 (800 mg; 3.30 mmol) and Pd/C (10% wt; 176 mg) in MeOH (8.3 mL) was stirred at room temperature under 1 atm. of H₂ overnight. The reaction mixture was filtered over celite® and the filtrate was evaporated to dryness yielding 700 mg of intermediate 499.

[0645] The compounds in the table below were prepared using analogous method as described for the preparation of intermediate 499, starting from the respective starting materials.

Intermediate number	Structure	Quantity	Yield
Intermediate 500	From intermediate 498	147 mg	100%
Intermediate 500B	From intermediate 500A	700 mg	93%
Intermediate 501	From 2-(4-methyl-3-nitrophenyl)-1H-imidazole	1.4 g	87%

Example A75:

[0646] Intermediate 500A:

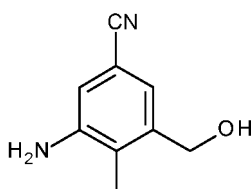


[0647] A mixture of 2-nitro-4-bromo toluene (1g; 4.629 mmol), 1-Methyl-1*H*-pyrazole-5-boronic acid (874 mg; 6.94 mmol), K_2CO_3 (1.024 g; 7.406 mmol), $PdCl_2dppf$ (339 mg; 0.463 mmol) in DMF (19 mL) was stirred at 85 °C for 18 h. The reaction mixture was evaporated. The residue was dissolved with EtOAc. The organic layer was washed with water then brine, dried over $MgSO_4$, filtered and evaporated to dryness.

[0648] The residue was purified by chromatography over silica gel (mobile phase: gradient from 0% EtOAc, 100% heptane to 30% EtOAc, 70% heptane). The fractions were collected and evaporated to dryness yielding 870 mg (87%) of intermediate 500A.

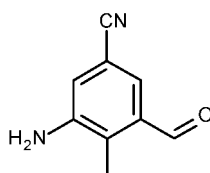
Example A76

[0649] Intermediate 510:



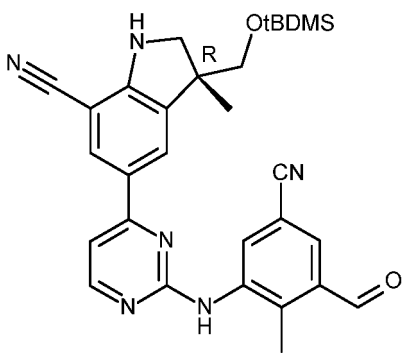
[0650] A solution of lithium aluminium hydride 1M in THF (1.5 mL; 1.56 mmol) was added drop wise at 0°C to a solution of 3-amino-5-cyano-2-methyl-benzoic acid methyl ester (297 mg; 1.56 mmol) in THF (10 mL) and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was poured onto iced water and extracted with EtOAc. The organic layer was decanted, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness yielding 216 mg (85%) of intermediate 510.

[0651] Intermediate 512:

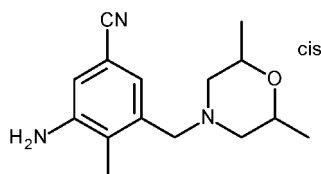


[0652] A mixture of intermediate 510 (341 mg; 2.10 mmol) and manganese dioxide (913 mg; 10.51 mmol) in 1,4-dioxane (20 mL) was heated at 100°C for 6 hours. The reaction mixture was cooled to room temperature, diluted with DCM, filtered through a pad of celite® and evaporated to dryness yielding 300 mg (89%) of intermediate 512 which was directly engaged in the next step.

[0653] The compounds in the table below were prepared using analogous method as described for the preparation of intermediate 512 starting from the respective starting materials. The most relevant minor deviations from the original method are indicated in the column "Quantity"

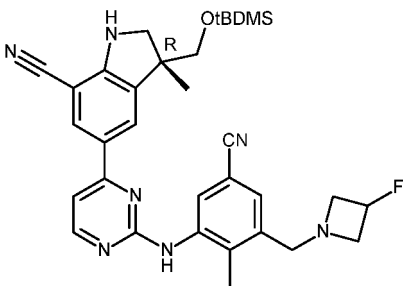
Intermediate number	Structure	Quantity	Yield
Intermediate 515	 From intermediate 511	120 mg Procedure modification: 18h@100°C	42%

[0654] Preparation of intermediate 513:

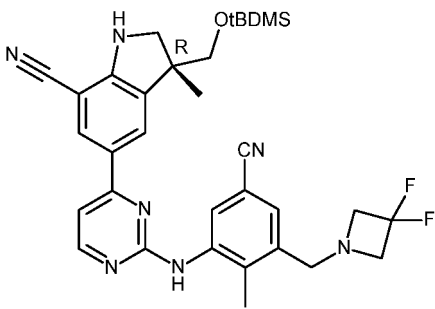


[0655] A mixture of intermediate 512 (551 mg; 3.44 mmol), cis-2,6-dimethylmorpholine (847 μ L; 6.88 mmol) and AcOH (387 μ L; 6.76 mmol) in DCM (20 mL) was stirred at room temperature for 1 hour. Then sodium triacetoxyborohydride (1.45 g; 6.88 mmol) was added. The reaction mixture was stirred at room temperature over the weekend. The reaction mixture was poured onto a 10% aqueous solution of K_2CO_3 and extracted with DCM. The organic layer was decanted, filtered through chromabond® and evaporated to dryness. The residue was purified by chromatography (irregular SiOH, 24g; mobile phase: gradient from 20% EtOAc, 80% heptane to 40% EtOAc, 60% heptane). The pure fractions were collected and evaporated to dryness yielding 632 mg (52%, purity 73% based on LC/MS) of intermediate 513 which was directly engaged in the next step.

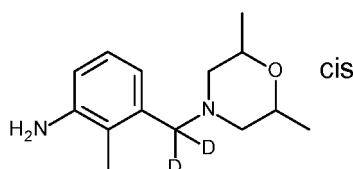
[0656] The compounds in the table below were prepared using analogous method as described for the preparation of intermediate 513, starting from the respective starting materials.

Intermediate number	Structure	Quantity	Yield
Intermediate 516	 From intermediate 515 and 3-fluoroazetidine hydrochloride	100 mg	55%

(continued)

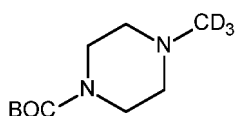
Intermediate number	Structure	Quantity	Yield
Intermediate 517	 From intermediate 515 and 3,3-difluoroazetidine	106 mg Purity 81% (LCMS)	31%

Example A77

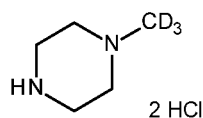
[0657] Preparation of intermediate 519:

[0658] Lithium aluminium deuteride (203 mg; 4.832 mmol) was added portion wise at 5°C to a solution of intermediate 521b (400 mg; 1.61 mmol) in THF (16 mL) and the reaction mixture was stirred at room temperature for 3 days. The reaction mixture was quenched carefully by adding EtOAc and poured onto ice water and more EtOAc was added. The organic layer was decanted, washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 12g; mobile phase: gradient from 0% MeOH, 100% DCM to 5% MeOH, 95% DCM). The pure fractions were collected and evaporated to dryness yielding 286 mg (75%) of intermediate 519.

Example A78

[0659] Preparation of intermediate 523:

[0660] A mixture of 1-Boc-piperazine (5 g; 26.845 mmol), iodomethane-D₃ (1.7 mL; 26.845 mmol) and potassium carbonate (11 g; 80.54 mmol) in ACN (200 mL) was heated to 85°C for 18 h. The suspension was filtered and the insoluble material was washed with EtOAc. The combined filtrates were evaporated to dryness. The residue was taken up with DCM and the insoluble material was filtered. The filtrate was concentrated and purified by chromatography over silica gel (irregular SiOH, 40g; mobile phase: gradient from 5% MeOH, 95% DCM to 10% MeOH, 90% DCM). The pure fractions were collected and evaporated to dryness yielding 3.25 g (59%) of intermediate 523.

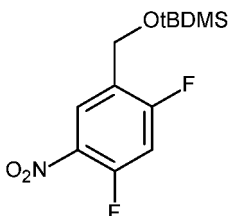
[0661] Preparation of intermediate 524:

[0662] A solution of HCl 4N in 1,4-dioxane (11 mL; 44.27 mmol) was added to a solution of intermediate 523 (3 g;

14.757 mmol) in ACN (70 mL) and the reaction mixture was stirred for 18 hours. The precipitate was filtered, washed with ACN, then Et₂O and dried yielding 2.54 g (98%) of intermediate 524.

Example A79

[0663] Preparation of intermediate 525:

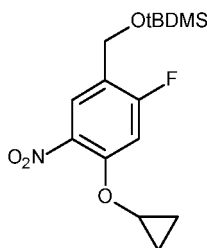


[0664] A solution of chloro *tert*-butyldimethyl silane (391 mg; 2.59 mmol) in DCM (1.7 mL) was added drop wise at 5°C to a solution of 2,4-difluoro-5-nitro-benzenemethanol (490 mg; 2.59 mmol) and Et₃N (720 µL; 5.18 mmol) in DCM (3 mL) and the reaction mixture was stirred at room temperature overnight.

[0665] Alternatively, the same reaction was performed using the same conditions starting from 2,4-difluoro-5-nitro-benzenemethanol (500 mg; 2.644 mmol) and trifluoromethanesulfonic acid *tert*-butyldimethylsilyl ester (0.607 mL; 2.64 mmol). The two reaction mixtures were combined for the work-up:

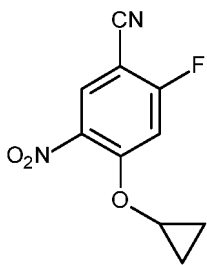
DCM was added and the suspension was poured onto a saturated aqueous solution of NH₄Cl. The organic layer was decanted, washed with water then with a 10% aqueous solution of K₂CO₃, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 40 g; mobile phase: gradient from 10% EtOAc, 90% heptane to 30% EtOAc, 70% heptane). The pure fractions were collected and evaporated to dryness yielding 858 mg of intermediate 525 (quantitative).

[0666] Preparation of intermediate 526:

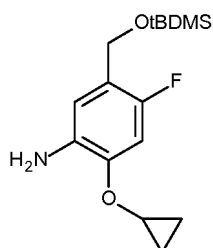


[0667] A mixture of intermediate 525 (858 mg; 2.83 mmol), cyclopropanol (717 µL; 11.3 mmol) and cesium carbonate (1.84 g; 5.66 mmol) in 1,4-dioxane (9.5 mL) was heated at 100°C for 2h. The reaction mixture was heated at 100°C overnight, cooled to room temperature and diluted with DCM. Water was added and the reaction mixture was extracted with DCM (three times). The combined organic layers were washed with water, 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 10% EtOAc, 90% heptane to 20% EtOAc, 80% heptane). The pure fractions were collected and evaporated to dryness yielding 581 mg (60%) of intermediate 526.

[0668] The intermediate in the table below was prepared using analogous method as described for the preparation of intermediate 526 starting from the respective starting material. The most relevant minor deviation from the original procedure is indicated in the column "yield"

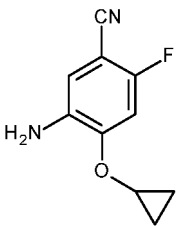
Intermediate number	Structure	Quantity	Yield
Intermediate 529	 From 2,4-difluoro-5-nitrobenzonitrile	790 mg	65% Procedure modification: 1h@80°C

[0669] Preparation of intermediate 527:



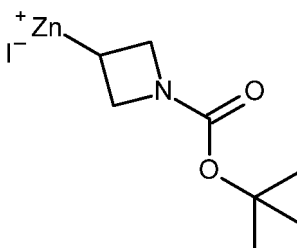
[0670] A mixture of intermediate 526 (527 mg; 1.543 mmol), iron powder (431 mg; 7.717 mmol) and NH_4Cl (330 mg; 6.174 mmol) in EtOH (10 mL) and distilled water (2.5 mL) was heated at 70°C for 1 hour. The reaction mixture was cooled down to room temperature, diluted with DCM, filtered over celite® and basified with a 10% aqueous solution of K_2CO_3 . The organic layer was decanted, dried over MgSO_4 , filtered and evaporated to dryness yielding 485 mg (quantitative) of intermediate 527 directly engaged in the next step without any further purification.

[0671] The intermediate in the table below was prepared using analogous method as described for the preparation of intermediate 527 starting from the respective starting material.

Intermediate number	Structure	Quantity	Yield
Intermediate 530	 From intermediate 529	670 mg	98%

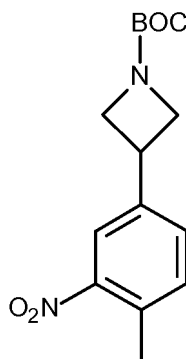
Example A80

[0672] Preparation of intermediate 532:



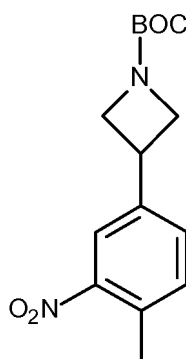
[0673] In a dried flask, zinc (4.05g; 62 mmol) was suspended in dried dimethylacetamide (200 mL) under N₂. The suspension was warmed to 65°C, and then dibromoethane (0.45g; 2.39mmol) and chlorotrimethylsilane (0.207g; 1.91mmol) were added, and then stirred at 65°C for 0.5 hour. 1-*tert*-Butoxycarbonyl-3-iodoazetidine (13.5g; 47.68mmol) in dimethylacetamide (100 mL) was added dropwise at 65°C and the reaction mixture was stirred at room temperature for 1 hour. The crude product was directly used without work-up and purification for the next reaction step.

[0674] Preparation of intermediate 533:



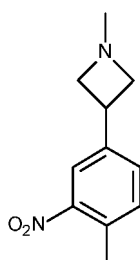
[0675] A mixture of 4-bromo-1-methyl-2-nitrobenzene (6.06g; 28.08 mmol), intermediate 532 (16.62g; 47.68 mmol), Pd(dppf)Cl₂.DCM (703mg; 0.86 mmol) and copper (I) iodide (323.7mg; 1.7mmol) in dimethylacetamide (300 mL) was stirred at 90°C overnight under N₂. Water (900 mL) was added and the reaction mixture was extracted with ethyl acetate (600 mL*2). The organic layers were combined, washed with water, brine, dried over Na₂SO₄, filtered, and evaporated in vacuum. The crude intermediate (8g) was purified by column chromatography over silica gel (eluent: Petrol ether/Ethyl acetate=3/1). The fractions containing the product were mixed and evaporated in vacuum to give 5g of intermediate 533 (61%) as a yellow oil.

[0676] Preparation of intermediate 534:



[0677] A solution of intermediate 533 (5g; 17.1mmol) and HCl 4M in dioxane (50 mL; 200 mmol) in dioxane (20mL) was stirred at room temperature overnight. The mixture was evaporated in vacuum to give 3.91g of crude intermediate 534 which was directly engaged in the next reaction step without any further purification.

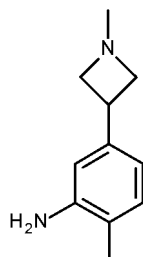
[0678] Preparation of intermediate 535:



[0679] A mixture of intermediate 534 (3.9 g; 17.10 mmol), paraformaldehyde (3 g; 102.62 mmol) and sodium acetate

(1.4 g; 17.10 mmol) in MeOH (150 mL) was stirred at room temperature for 2 hours. Sodium triacetoxyborohydride (21.7 g; 102.62 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was slowly basified with a saturated aqueous solution of NaHCO₃ (400 mL) and extracted with DCM (2 X 300 mL). The organic layer was washed by brine, dried over Na₂SO₄, filtered, and evaporated to dryness. The residue was purified by chromatography over silica gel (mobile phase: petrol ether/ EtOAc (1/2)). The desired fractions were evaporated to dryness yielding 1.58g (45%) of intermediate 535.

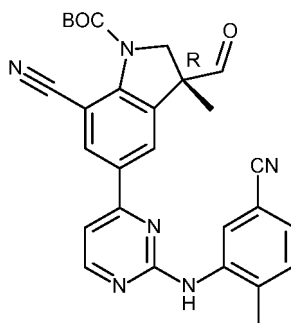
[0680] Preparation of intermediate 536:



[0681] Intermediate 535 (1.58g; 7.66 mmol) was dissolved in THF (20 mL), MeOH (10 mL) and distilled water (10 mL). Iron powder (2.1g; 38.35 mmol) and NH₄Cl (2g; 38.30 mmol) were added. The reaction mixture was refluxed overnight, filtered through celite® and the filter cake was washed with 80 mL of a mixture EtOAc/MeOH (8/1). The filtrate was evaporated to dryness. The residue was purified by chromatography over silica gel (mobile phase: EtOAc/ MeOH (5/1)). The desired fractions were evaporated to dryness yielding 880 mg (65%) of intermediate 536.

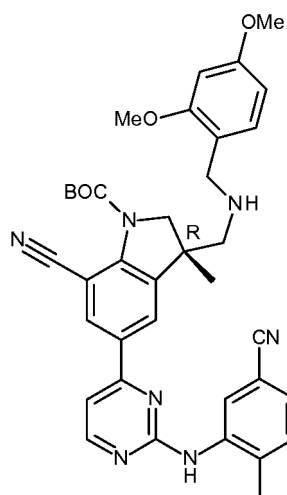
Example A81

[0682] Alternative preparation of intermediate 380:



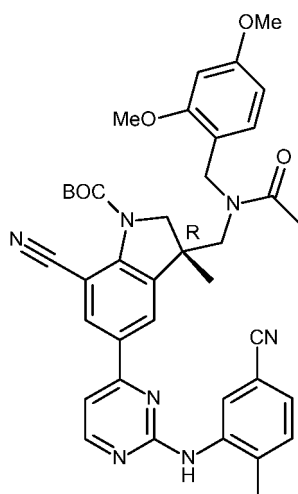
[0683] DCM (5 mL) was cooled to -78°C and oxalyl chloride (3 mL; 6.04 mmol) was added followed by DMSO (865 µL; 12.1 mmol). After 30 min, a suspension of intermediate 10R (2 g; 4.03 mmol) in DCM (15 mL) was added drop wise. The reaction mixture was stirred for 30 min at -78°C, then DIPEA (4.1 mL; 24.17 mmol) was added. The stirring was continued for 3 hours at -78°C and the reaction mixture was allowed to warm to room temperature and stirred for 30 min. A diluted aqueous solution of NH₄Cl was added and the aqueous layer was extracted with DCM (twice). The combined layers were dried over MgSO₄, filtered and evaporated to dryness. The residue was crystallized from Et₂O and the precipitate was filtered, washed with DiPE and dried yielding 2 g of intermediate 380.

[0684] Preparation of intermediate 540:



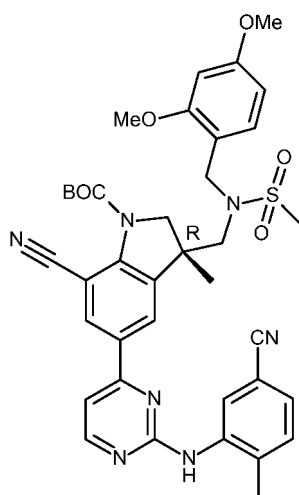
[0685] A solution of intermediate 380 (2 g; 4.044 mmol), 2,4-dimethoxybenzylamine (3.6 mL; 24.26 mmol) and AcOH (1.4 mL; 24.26 mmol) in DCE (100 mL) was stirred for 3 hours and $\text{NaBH}(\text{OAc})_3$ (8.5 g; 40.44 mmol) was added. The reaction mixture was stirred at room temperature overnight. A saturated aqueous solution of NaHCO_3 was added and the aqueous layer was extracted with DCM. The organic layer was dried over MgSO_4 , filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH , 80g; mobile phase: gradient from 40% EtOAc, 60% heptane to 2% MeOH, 60% EtOAc, 40% heptane). The fractions containing the product were collected and evaporated to dryness yielding 1 g (38%) of intermediate 540 and 855 mg of intermediate 380.

[0686] Preparation of intermediate 541:



[0687] A mixture of intermediate 540 (500 mg; 0.77 mmol), acetyl chloride (66 μL ; 0.93 mmol) and Et_3N (215 μL ; 1.55 mmol) in THF (10 mL) was stirred at room temperature for 18 hours. 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 was purified by chromatography over silica gel (irregular SiOH , 24g; mobile phase: gradient from 0% MeOH, 100% DCM to 6% MeOH, 94% DCM). The fractions containing the product were collected and evaporated to dryness yielding 540 mg (quantitative) of intermediate 541.

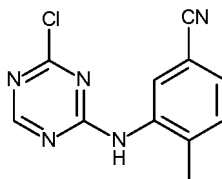
[0688] Preparation of intermediate 542:



[0689] A mixture of intermediate 540 (415 mg; 0.64 mmol), methanesulfonyl chloride (74 μ L; 0.96 mmol) and Et_3N (223 μ L; 1.61 mmol) in THF (8 mL) was stirred at room temperature for 18 hours. 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 was purified by chromatography over silica gel (irregular SiOH , 40g; mobile phase: 0.1% NH_4OH , 99.5% DCM, 0.5% MeOH). The fractions containing the product were collected and evaporated to dryness yielding 318 mg (68%) of intermediate 542.

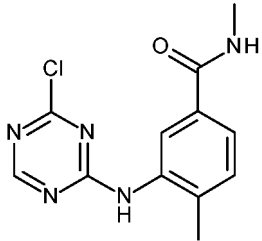
Example A82

[0690] Preparation of intermediate 543:

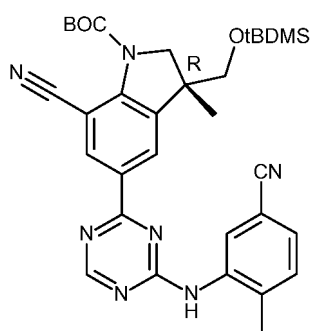


[0691] DIPEA (1 mL; 5.8 mmol) was added to a solution of 3-amino-4-methylbenzonitrile (661 mg; 5 mmol) and 2,4-dichloro-1,3,5-triazine (750 mg; 5 mmol) in ACN (30 mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed by evaporation and the residue was partitioned between water and EtOAc. The organic layer was decanted, washed with water, then brine, dried over MgSO_4 , filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH ; mobile phase: gradient from 0% EtOAc, 100% petroleum ether to 50% EtOAc, 50% petroleum ether). The fractions containing the product were collected and evaporated to dryness yielding 700 mg (57%) of intermediate 543.

[0692] The intermediate in the table below was prepared using analogous method as described for the preparation of intermediate 243, starting from the respective starting materials. The most relevant minor deviation from the original method is indicated in the column "Quantity"

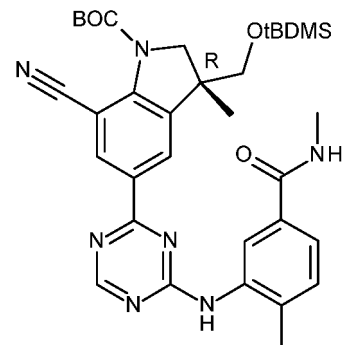
Intermediate number	Structure	Quantity	Yield
Intermediate 546	 From 3-amino-N,4-dimethylbenzamide and 2,4-dichloro-1,3,5-triazine	740 mg Procedure with acetone as solvent in place of ACN	40%

[0693] Preparation of intermediate 544:



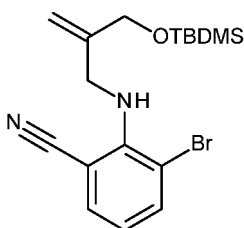
[0694] A solution of intermediate 5R (1.58 g; 3 mmol), intermediate 243 (663 mg; 2.7 mmol) and aqueous 2M NaHCO₃ (6 mL; 12 mmol) in 1,4-dioxane (24 mL) was purged with N₂. PdCl₂dppf (219 mg; 0.3 mmol) was added, the reaction mixture was purged again with N₂ and heated at 80°C for 10h. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and evaporated until dryness. The residue was purified by chromatography over silica gel (irregular SiOH; mobile phase: gradient from 0% EtOAc, 100% petroleum ether to 50% EtOAc, 50% petroleum ether). The fractions were collected and evaporated to dryness yielding 600 mg (32%) of intermediate 544.

[0695] The intermediate in the table below was prepared using analogous method as described for the preparation of intermediate 544, starting from the respective starting materials.

Intermediate number	Structure	Quantity	Yield
Intermediate 547	 From intermediate 5R and intermediate 546	560 mg	46%

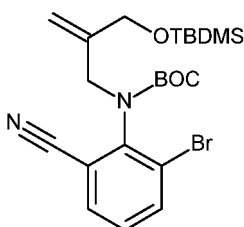
Example A83

[0696] Preparation of intermediate 549:



[0697] 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 High Performance Liquid Chromatography (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 63.3g of intermediate 549.

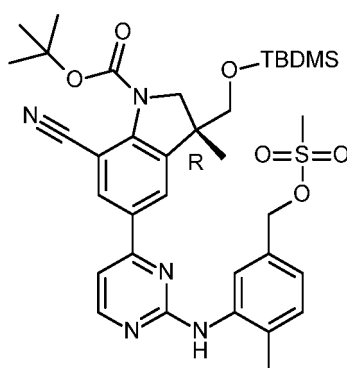
[0698] Preparation of intermediate 550:



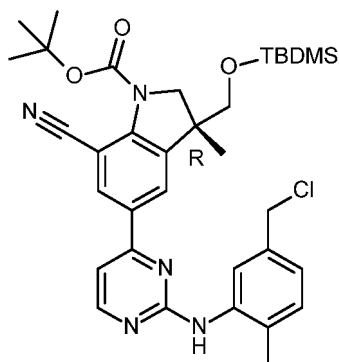
[0699] To a solution of intermediate 549 (50.0 g) in dry THF (500 mL) was added dimethylaminopyridine (0.5 eq.) and the temperature was adjusted to 65-70 °C. Di-*tert*-butyldicarbonate (2.2 eq.) was then added and the mixture was stirred for 2 hours monitoring the conversion by HPLC. Water (350 mL) was 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 550 .

Example A84

[0700] Preparation of intermediate 553

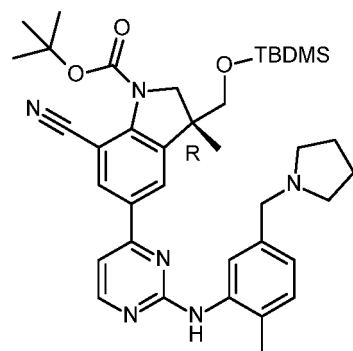


and intermediate 554

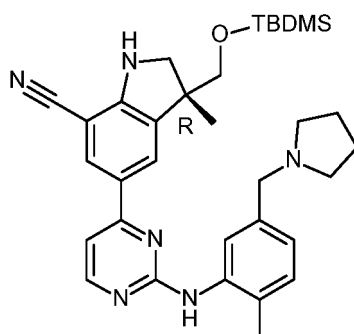


[0701] Methanesulfonyl chloride (377 μL ; 4.87 mmol) was added dropwise to a solution of intermediate 8 (1.5 g; 2.44 mmol) and Et_3N (848 μL ; 6.09 mmol) in DCM (24 mL) at 5°C under N_2 flow. The reaction mixture was stirred at 5°C for 1 h, and then 2 h at room temperature. The reaction mixture was poured out into ice water and DCM was added. The organic layer was filtered through CHROMABOND® and the solvent was evaporated (30°C) to give 1.86 g of orange foam intermediate 553 and intermediate 554. The crude product was used without further purification in the next reaction step.

[0702] Preparation of intermediate 555

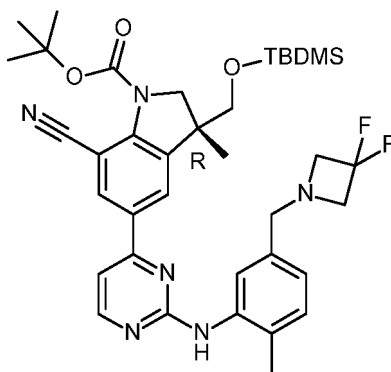


and intermediate 556

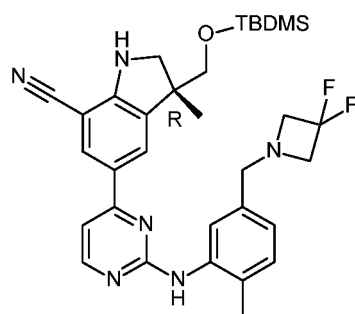


[0703] In a sealed tube, a mixture of intermediate 553 and intermediate 554 (269 mg; 0.39 mmol), pyrrolidine (0.32 mL; 3.88 mmol) in ACN (2 mL) was heated at 140°C using one single mode microwave (Anton Parr®) with a power output ranging from 0 to 400 W for 1 h. The mixture was poured into water and EtOAc. The organic layer was washed with water, brine, dried over MgSO_4 , filtered and evaporated to dryness. The residue (160 mg, yellow oil) was purified by chromatography over silica gel (irregular bare silica 40 g, mobile phase: 0.4% NH_4OH , 96% DCM, 4% MeOH). The fractions containing the products were collected and the solvent was evaporated to give 59 mg of intermediate 555 (23%) and 39 mg of mixture of intermediate 555 and intermediate 556. The two fractions were combined for the next reaction step.

[0704] Preparation of intermediate 560

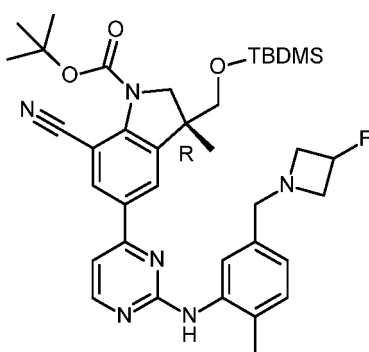


and intermediate 561

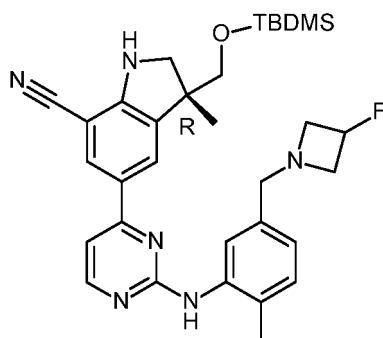


[0705] In a sealed tube, a mixture of intermediate 553 and intermediate 554 (850 mg; 1.23 mmol), 3,3-difluoroazetidine hydrochloride (476 mg; 3.68 mmol) and DIPEA (844 μ L; 4.9 mmol) in ACN (10 mL) was heated at 140°C using one single mode microwave (Anton Parr) with a power output ranging from 0 to 400 W for 1h fixed hold time. The mixture was poured into water and EtOAc. The organic layer was washed with brine, dried over MgSO_4 , filtered and evaporated to dryness. The residue (1.05 g; orange oil) was purified by chromatography over silica gel (irregular bare silica 40 g; mobile phase: 99% DCM, 1% MeOH). The fractions containing the products were collected and the solvent was evaporated to give 555 mg of mixture of intermediate 560 and intermediate 561.

[0706] Preparation of intermediate 562

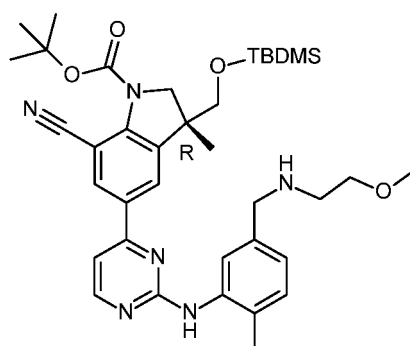


and intermediate 563

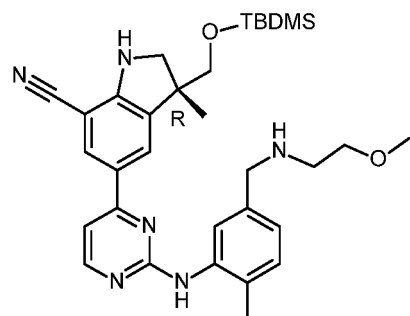


[0707] Intermediate 562 and intermediate 563 were prepared according to an analogous procedure as described for the synthesis of a mixture of intermediate 560 and intermediate 561, using a mixture of intermediate 553 and intermediate 554 and 3-fluoroazetidine hydrochloride as starting materials (289 mg; yellow oil mixture of intermediate 562 and intermediate 563).

[0708] Preparation of intermediate 557

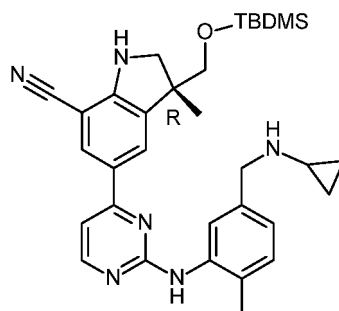


and intermediate 558

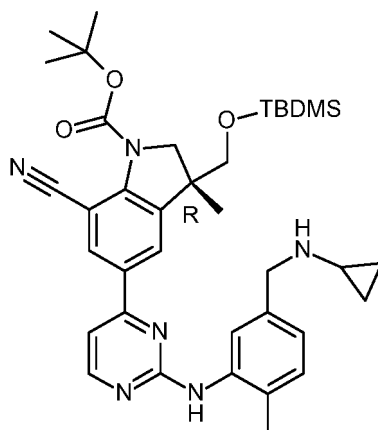


[0709] Intermediate 557 and intermediate 558 were prepared according to an analogous procedure as described for the synthesis of a mixture of intermediate 555 and intermediate 556, using a mixture of intermediate 553 and intermediate 554 and 2-methoxyethylamine as starting materials (485 mg).

[0710] Preparation of intermediate 559



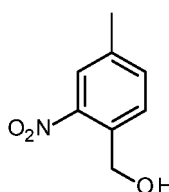
and intermediate 559bis



[0711] Intermediate 559 (145 mg; 10%) and intermediate 559bis (168 mg; 10%) was prepared according to an analogous procedure as described for the synthesis of a mixture of intermediate 555 and intermediate 556, using a mixture of intermediate 553 and intermediate 554 and cyclopropylamine as starting materials. The time of the reaction was reduced to 5 min due to overpressure.

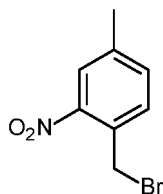
Example A85

[0712] Preparation of intermediate 564:



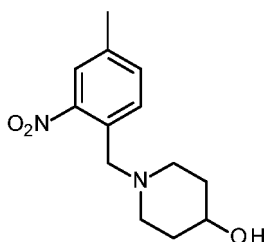
[0713] Borane dimethyl sulfide complex (9.9 mL; 19.87 mmol) was added dropwise to a solution of 4-methyl-2-nitrobenzoic acid (3 g; 16.56 mmol) in THF (18 mL) and the mixture was stirred at 80°C overnight. The mixture was cooled down to rt and a 3M aqueous solution of HCl was added dropwise into the reaction system until effervescence was no longer observed. The mixture was extracted with EtOAc. The organic layer was washed with a saturated aqueous solution of Na₂CO₃ and brine, dried over MgSO₄, filtered and removed under reduced pressure to give 2.46 g (89%) of intermediate 24.

[0714] Preparation of intermediate 565:



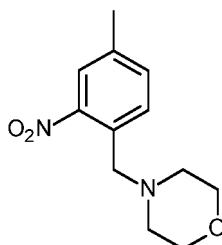
[0715] Phosphorus tribromide was added to a solution of intermediate 564 (2.46 g; 14.70 mmol) in diethylether (150 mL). The reaction was stirred at rt overnight. Then, a saturated aqueous solution of NaHCO_3 was added dropwise to the reaction mixture until neutral pH was obtained. The mixture was extracted with diethyl ether and the organic layer was washed with brine. The resulting organic layer was dried over MgSO_4 , filtered and concentrated in vacuo to give 2.39 g (71%) of intermediate 566.

[0716] Preparation of intermediate 567:



[0717] A mixture of intermediate 566 (1.17 g; 5.09 mmol), 4-hydroxypiperidine (1.03 g; 10.17 mmol) and Et_3N (2.13 mL; 15.26 mmol) in ACN (25 mL) was stirred at reflux 1 h and then, stirred at rt overnight. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was removed under reduced pressure to yield 1g (78%) of intermediate 567 that was used in the next reaction step without further purification.

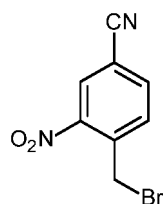
[0718] Preparation of intermediate 570:



[0719] Tetrahydro-1,4-oxazine (574 μL ; 6.52 mmol) was added to intermediate 565 (500 mg; 2.17 mmol) in ACN (10 mL) and the solution was heated at 80°C for 1 h. The mixture was diluted with EtOAc and washed with aqueous NaHCO_3 and brine. The organic layer was dried over MgSO_4 , filtered and removed under reduced pressure to give 500 mg (97%) of intermediate 570.

Example A86

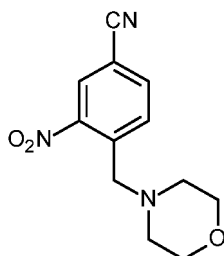
[0720] Preparation of intermediate 578:



[0721] A mixture of 3-nitro-p-tolunitrile (1.2 g; 7.40 mmol), *N*-bromosuccinimide (2.6 g; 14.80 mmol) and benzoyl peroxide (182 mg; 0.75 mmol) in acetic acid (15 mL) in a sealed tube was heated at 140°C using one single mode

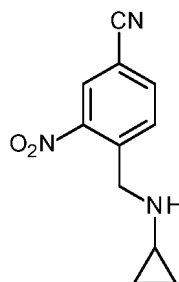
microwave (Biotage Initiator EXP 60®) with a power output ranging from 0 to 400 W for 40 min. The mixture was poured into ice-water, K_2CO_3 solid and EtOAc were added. The mixture was extracted with EtOAc (3x). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was taken up with toluene and the solvent was evaporated to give 1.47 g of brown oil of a mixture of intermediate 578 and 3-nitro-p-tolunitrile which was used in the next reaction step without any further purification.

[0722] Preparation of intermediate 579:



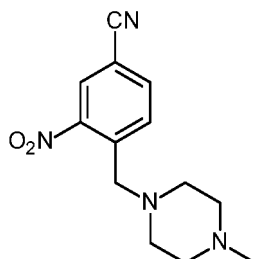
[0723] Et_3N (1.71 mL; 12.20 mmol) was added to a solution of a mixture intermediate 578 and 3-nitro-p-tolunitrile (1.47 g; 6.10 mmol) and morpholine (0.8 mL; 9.15 mmol) in DCM (20 mL). The reaction was stirred at rt overnight. Water and DCM were added. The mixture was extracted with DCM (3X). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated to dryness. The residue (3.07 g) was taken up with DCM and the mixture was filtered off. The cake was washed with DCM (twice) and the filtrate was evaporated to dryness. The residue (1.33 g; brown oil) was purified by chromatography over silica gel (SiO_2 ; 40 g, eluent: from 90% heptane, 10% EtOAc to 80% heptane, 20% EtOAc). The fractions containing the product were collected and the solvent was evaporated to give 226 mg (15%) intermediate 579 as a yellow oil.

[0724] Preparation of intermediate 582:



[0725] Cyclopropylamine (367 μ L; 5.29 mmol) was added to a mixture of intermediate 578 (500 mg; 1.76 mmol) in ACN (6 mL). The reaction mixture was stirred at room temperature for 1 h. The crude was diluted with EtOAc and washed with $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and removed under reduced pressure to give a crude that was purified by flash chromatography eluting with DCM-MeOH to give 350 mg (91%) of intermediate 582.

[0726] Preparation of intermediate 586:

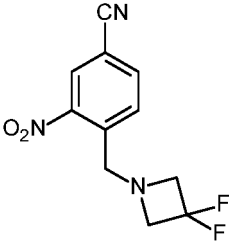
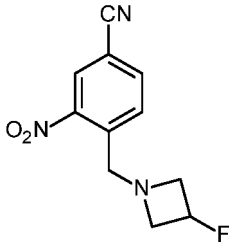


[0727] Intermediate 578 (400 mg; 1.66 mmol) was added to a mixture of *N*-methylpiperazine (502 μ L; 3.32 mmol) and Et_3N (694 μ L; 4.98 mmol) in ACN (5 mL). The reaction mixture stirred at room temperature overnight. The solvent was removed and the crude was dissolved in EtOAc and quenched with water. The organic layer was dried, filtered and concentrated. The crude was purified by flash chromatography use heptane and DCM. The pure fractions were collected

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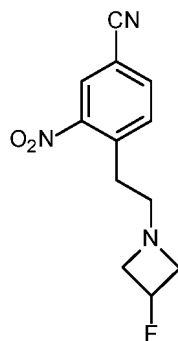
and the solvent was evaporated to give 250 mg (58%) of intermediate 586.

[0728] The compounds in the Table below were prepared by using an analogous method as the one used for the preparation of, starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 590	 From intermediate 578 and 3,3-difluoroazetidine hydrochloride	320	61
Intermediate 594	 From intermediate 578 and 3-fluoroazetidine hydrochloride	125 (92% purity evaluated by LCMS)	64

Example A87

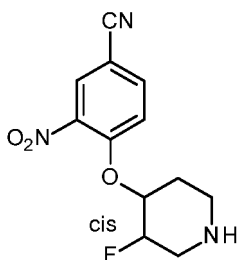
[0729] Preparation of intermediate 598:



[0730] In a sealed tube, a mixture of 4-ethenyl-3-nitro-benzonitrile (353 mg; 2.03 mmol), 3-fluoroazetidine hydrochloride (678 mg; 6.08 mmol) and Et₃N (1.1 mL; 8.11 mmol) in MeOH (9 mL) was refluxed for 1 h. The reaction mixture was poured onto water and extracted with DCM. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue (519 mg) was purified by chromatography over silica gel (irregular SiOH, 24 g; mobile phase: gradient from 0.2% NH₄OH, 2% MeOH, 98% DCM to 0.5% NH₄OH, 5% MeOH, 95% DCM). The fractions containing the product were collected and evaporated to give 431 mg (85%) of intermediate 598.

Example A88

[0731] Preparation of intermediate 602:

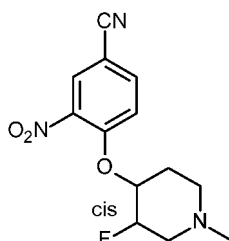


[0732] In a round bottom flask containing intermediate 601 (440 mg; 1.20 mmol) and 1,4-dioxane (7 mL) was added 4M solution of HCl in dioxane (7.5 mL; 30.11 mmol) and the reaction mixture was stirring to room temperature overnight. The crude was concentrated and was quenched with a saturated solution of NaHCO_3 and extracted with DCM. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to give 300 mg of intermediate 602 (94%).

[0733] The compound in the table below was prepared by using an analogous method as the one used for the preparation of intermediate 602, starting from the respective starting materials.

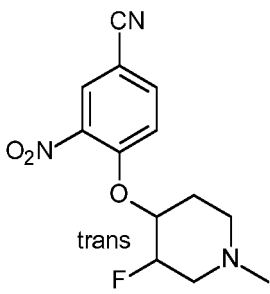
Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 608	From intermediate 607	130	90

[0734] Preparation of intermediate 603:

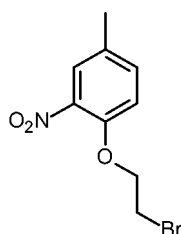


[0735] To a solution of intermediate 602 (300 mg; 1.13 mmol) in MeOH (mL) was added formaldehyde (184 μL ; 2.26 mmol) and then formic acid (427 μL ; 0.01 mmol). The reaction mixture was stirred at room temperature 1 h. Then, sodium triacetoxyborohydride (300 mg; 1.41 mmol) was added and the stirring was continued for 1 h. Then, the reaction mixture was carefully quenched by addition of saturated solution of NaHCO_3 and extracted with EtOAc. The organic layer was evaporated to dryness and loaded into a silica gel column (ethyl acetate 100%). The pure fractions were collected and the solvent was evaporated to give 250 mg (79%) of intermediate 603.

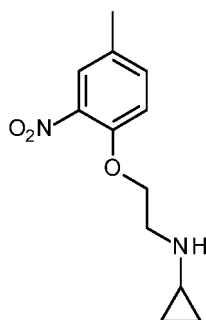
[0736] The compound in the table below was prepared by using an analogous method as the one used for the preparation of intermediate 603 starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Intermediate 609	 From intermediate 608	99	72

Example A89

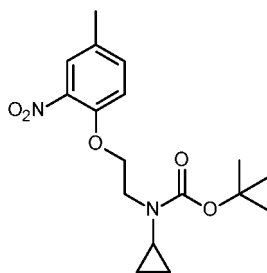
[0737] Preparation of intermediate 623:

[0738] 4-Methyl-2-nitrophenol (1 g; 6.53 mmol) was dissolved in ACN (50 mL), producing a clear, bright yellow solution. K_2CO_3 (4.5 g; 32.65 mmol) was added, and the reaction was stirred until the color darkened to a deep red. 1,2-dibromoethane (2.8 mL; 32.65 mmol) was added and the reaction was refluxed 80°C overnight. The reaction mixture was filtered and the filtrate was evaporated. The crude (yellow oil) was purified on a silica gel column, eluting with 5% EtOAc/heptane to give 1.37 g (80%) of intermediate 623.

[0739] Preparation of intermediate 624:

[0740] Intermediate 624 was prepared following a similar protocol than the one used for the preparation of intermediate 570 starting from intermediate 623 and cyclopropylamine (600mg; 48%).

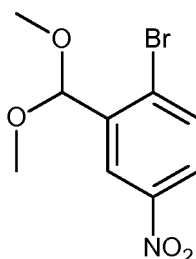
[0741] Preparation of intermediate 625:



[0742] A solution of intermediate 624 (550 mg; 2.33 mmol) in DCM (10 mL) at 0°C was added Boc₂O (559 mg; 2.56 mmol). The mixture was stirred at rt for 2h. The crude was diluted with DCM and washed with water, dried over MgSO₄ and removed under reduced pressure to give a crude that was purified by flash chromatography eluting with DCM-MeOH. The fractions containing the product were collected and the solvent was evaporated to give 704 mg (90%) of intermediate 625.

Example A90

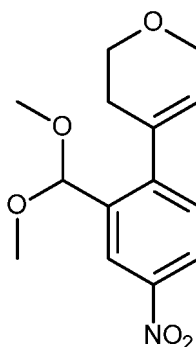
[0743] Preparation of intermediate 628:



[0744] In a round bottom flask, 2-bromo-5-nitrobenzaldehyde (29.17g , 0.127 mol), trimethyl orthoformate (21mL, 0.192 mol), p-toluenesulfonic acid monohydrate (2.4g , 12.6 mmol) were mixed in MeOH (600mL). Then, the reaction mixture was refluxed for 8 hours. The reaction was cooled down and the solvent was removed. The residue was taken up with water, K₂CO₃ and DCM. The organic layer was separated, dried over MgSO₄, filtered and evaporated until dryness to give 34g (97%) of intermediate 628.

Preparation of intermediate 629:

[0745]

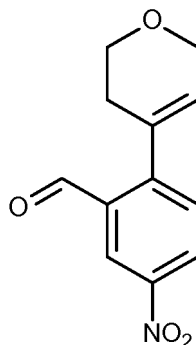


[0746] A mixture of intermediate 628 (15g ; 54.33mmol), 1,2,3,6-Tetrahydropyran-4-boronic acid pinacol ester (13.8g ; 65.7mmol), potassium phosphate (34.8g; 0.164mol), PdCl₂dppf.DCM (4.5g ; 5.5mmol) in dioxane (210mL) and water (60mL) was degassed with N₂ in a sealed tube and heated at 80°C for 16 hours. The mixture was poured into a mixture of water and K₂CO₃ and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and evaporated until dryness. The residue (25.5g) was purified by silica gel chromatography (330g of SiOH 35-40μm, gradient from 90%

EP 3 405 196 B1

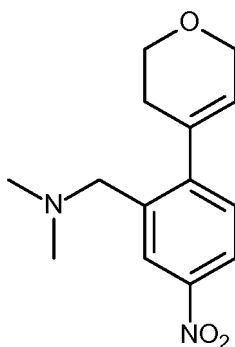
heptane 10% EtOAc to 60% heptane 40% EtOAc). The fractions were collected and evaporated until dryness to give 12.21 g (80%) of intermediate 629.

[0747] Preparation of intermediate 630:



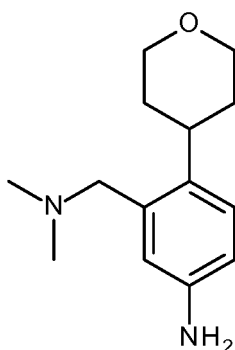
[0748] HCl (3M in water; 58.28 mL; 0.175 mol) was added to a solution of intermediate 630 (12.21g ; 43.72 mmol) in 1,4-dioxane (233mL) at room temperature. The mixture was stirred for 2 hours. Water then EtOAc was added. The organic layer was separated, dried over MgSO_4 , filtered and evaporated until dryness to afford 8.97g (88%) of intermediate 630.

[0749] Preparation of intermediate 631:



[0750] A solution of intermediate 630 (8.97g ; 38.5mmol), dimethylamine (9.7mL ; 76.6mmol) in ACN (240mL) was stirred for 30min. Then, sodium triacetoxyborohydride (16.3g ; 76.9mmol) was added and stirred at room temperature for 15 hours. Water was added and the reaction mixture was basified with K_2CO_3 and extracted with EtOAc. The organic layer was dried over MgSO_4 , filtered and evaporated until dryness. A purification of the residue (8.24g) was performed by silica gel chromatography (Stationary phase: irregular SiOH 15-40 μm 120g, Mobile phase: gradient from DCM 100% to DCM 95%, MeOH 5%, 0.1% NH_4OH). The desired fractions were collected and solvent evaporated until dryness to give 2.15g of intermediate 631 and 4.22g of an impure fraction which was purified by silica gel chromatography (Stationary phase: irregular SiOH 15-40 μm 80g, Mobile phase: gradient from DCM 100% to DCM 95%, MeOH 5%, 0.1% NH_4OH). The desired fractions were collected and solvent evaporated until dryness to give additional 2.65g of intermediate 631. Global yield: 47%

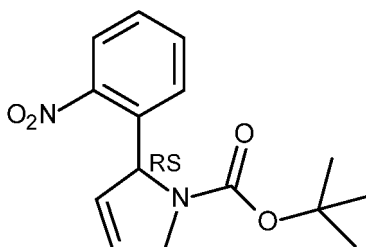
[0751] Preparation of intermediate 632:



[0752] A mixture of intermediate 632 (2.15 g; 8.2 mmol), Pd/C 10% (0.43g) in MeOH (50mL) was hydrogenated with 3 bars of H₂ at room temperature for 15 hours. The mixture was filtered through a celite® pad and the filtrate was evaporated until dryness to give 1.76g (92%) of intermediate 632.

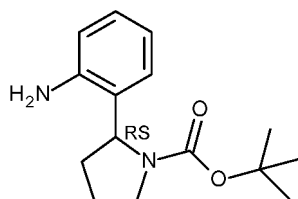
Example A91

[0753] Preparation of intermediate 635:



[0754] In a sealed glassware, a mixture of 1-bromo-2-nitrobenzene (800 mg; 3.96 mmol), *N*-Boc-2,3-dihydro-1H-pyrrole (938 mg; 5.54 mmol) and potassium carboante (1.6 g; 11.88 mmol) in DMF dry (30 mL) was bubbled with nitrogen (10 minutes). Then, triphenylphosphine (207 mg; 0.792 mmol) and Pd(OAc)₂ (89 mg; 0.396 mmol) were added. The reaction mixture was heated to 100°C overnight, cooled to room temperature, poured onto water and extracted with EtOAc. The mixture was filtered through a pad of celite® and the organic layer was decanted, washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 40g; mobile phase: gradient from 20% EtOAc, 80% heptane to 40% EtOAc, 60% heptane). The fractions containing the product were collected and evaporated to dryness yielding 482 mg (42%) of intermediate 635.

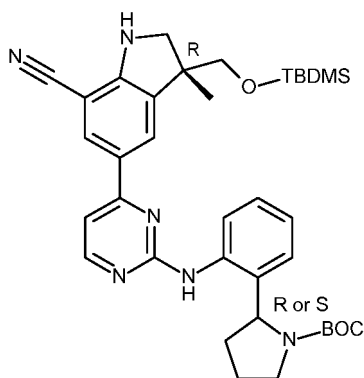
[0755] Preparation of intermediate 636:



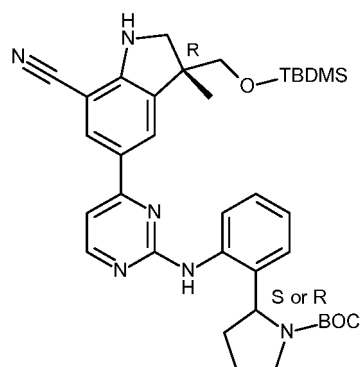
[0756] A mixture of intermediate 635 (482 mg; 1.66 mmol) and Adam's catalyst (Platinum(IV) oxide) (75 mg; 0.332 mmol) in EtOH (40 mL) were hydrogenated under 2 bars of H₂ for 2h. The catalyst was removed by filtration over celite® and the filtrate was evaporated to dryness yielding 437 mg of intermediate 636.

Example A92

[0757] Preparation of intermediate 638



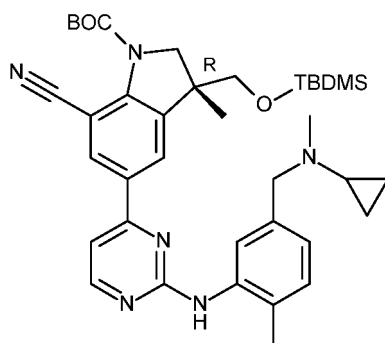
and intermediate 639



[0758] Intermediates 638 and 639 were obtained via a SFC separation performed on intermediate 637 (CHIRALPAK AD-H 5 μ m 250x20mm; mobile phase: 80% CO₂, 20% iPrOH). The pure fractions were collected and evaporated to dryness yielding 169mg of intermediate 638 and 177mg of intermediate 639

Example A93

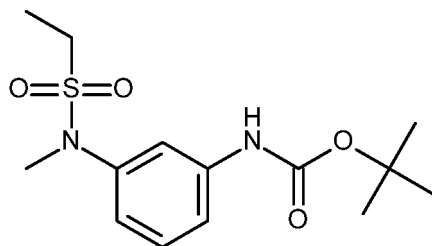
[0759] Preparation of intermediate 640:



[0760] Sodium triacetoxyborohydride (133 mg; 0.63 mmol) was added to a mixture of intermediate 559bis (164 mg; 0.25 mmol), formaldehyde (375 μ L; 5.01 mmol), acetic acid (28.7 μ L; 0.50 mmol) in MeOH (2 mL) at rt. The reaction mixture was stirred at rt under N₂ overnight. The mixture was basified with a saturated aqueous solution of NaHCO₃ and the solvent was evaporated. The mixture was diluted with EtOAc and washed with a saturated aqueous solution of NaHCO₃. The aqueous layer was extracted with EtOAc (2x). The organics layers were combined and washed with water, brine, dried over MgSO₄, filtered and the solvent was evaporated.

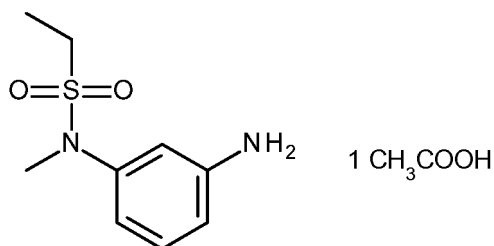
[0761] The residue (209 mg) was purified by chromatography over silica gel (SiO₂, 4 g; eluent: from 99% DCM, 1% MeOH, 0.1% NH₄OH to 99% DCM, 1% MeOH, 0.1% NH₄OH). The fractions containing the product were collected and the solvent was evaporated to afford 106 mg (63%) of intermediate 640 as a yellow oil.

Example A94

[0762] Preparation of intermediate 642:

[0763] Ethanesulfonyl chloride (1.28 mL; 13.5 mmol) was added into a solution of *tert*-butyl-(3-(methylamino)phenyl)carbamate (2 g, 9 mmol), triethylamine (3.79 mL, 26.99 mmol) in ACN (100 mL) at room temperature. The solution was stirred at room temperature for 4h00. Water was added and the reaction mixture was extracted with DCM. The organic layer was separated and dried over MgSO_4 , filtered and the solvent was evaporated.

[0764] The residue (3.2g) was purified by silica gel chromatography (Irregular SiOH , 40 μm , 80g, Mobile phase: gradient from 90%: DCM, 10% Heptane to 97% DCM, 3% MeOH, 0.3% NH_4OH). The fractions were combined and the solvent was evaporated to give 2.55g of an impure fraction which was repurified by silica gel chromatography (Irregular SiOH , 40 μm , 80g, Mobile phase: gradient from 70%: DCM, 30% Heptane to 97% DCM, 3% MeOH, 0.3% NH_4OH). The fractions were combined and the solvent was evaporated to give 1.24g (39%, 88% of purity based on LC/MS) of intermediate 642 (39% pure at 88%).

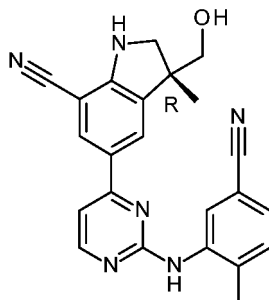
[0765] Preparation of intermediate 643:

[0766] A solution of intermediate 642 (1.24 g, 3.47 mmol) in TFA (2.66 mL, 34.71 mmol) and DCM (22.1 mL) was stirred at rt for 12h. The solvent was evaporated.

[0767] The residue was purified by silica gel chromatography (irregular SiOH , 15-40 μm , 40g, mobile phase: from DCM: 100% to DCM: 97%, MeOH: 3%, NH_4OH : 0.3%) to give 1.17g of intermediate 643.

B. Preparation of the final compounds

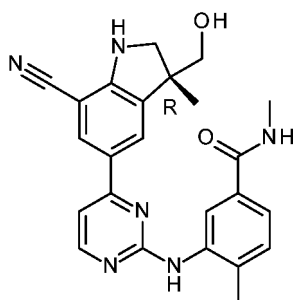
Example B1

[0768] Preparation of compound 1:

[0769] A mixture of intermediate 8R (36.00 g, 71.08 mmol) and TBAF (1M in THF, 142.15 mL, 142.15 mmol) in Me-THF (0.7 L) was stirred at rt for 3 h 30 min. The reaction mixture was poured onto a 10% aqueous solution of K_2CO_3

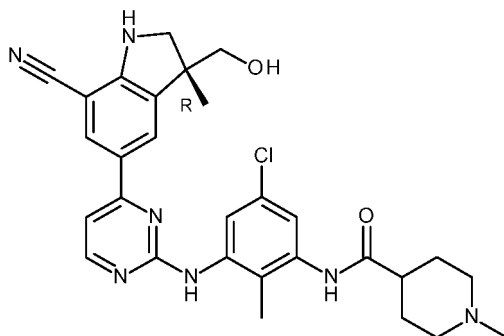
(700 mL), diluted with EtOAc (700 mL). Then, 100 mL of a saturated solution of NaCl was added (to help the decantation). The organic layer was decanted, washed again with 300 mL of a 10% aqueous solution of K_2CO_3 (+ 100 mL of a saturated solution of NaCl), then with a saturated solution of NaCl (200 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was taken up 3 times with 300 mL of EtOH and evaporated to dryness. The residue was taken up with CH_3CN and stirred at 50 °C. Then, the precipitate was filtered and dried (50 °C under vacuum for 5 h) to give 27 g of compound 1 (96% yield). Then, different batches of compound 1 coming from different reactions (batch 1: 36.8 g, batch 2: 27 g, batch 3: 5.7 g, batch 4: 7.45 g and batch 5: 6.7 g) were mixed together in CH_3N (250 mL) and the suspension was stirred for 15 min. The precipitate was filtered and dried at 50 °C overnight to give 81.1 g of compound 1 (97.1% yield). M.P.: 222 °C (DSC).

[0770] Preparation of compound 4:



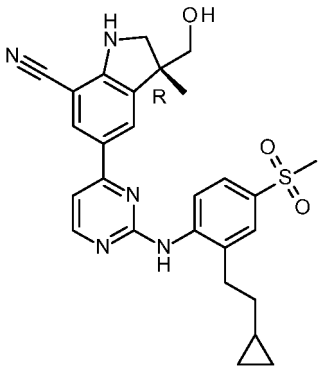
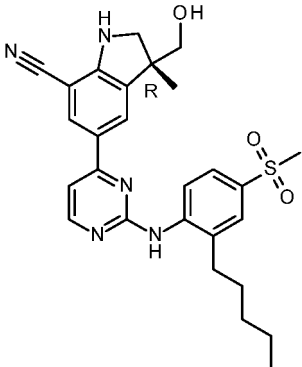
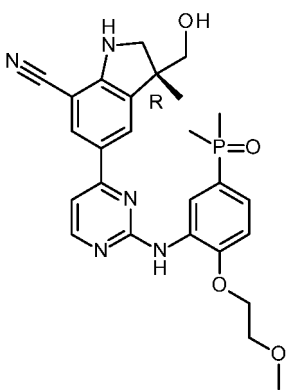
[0771] A solution of intermediate 19 (403.00 mg, 0.74 mmol) in Me-THF (8.9 mL) was treated with TBAF (1M in THF) (0.82 mL, 0.82 mmol) and stirred at rt for 17 h. Celite® was added and the crude mixture was evaporated in vacuo to give a dry load which was purified by column chromatography on silica gel (irregular SiOH 15-40 μ m, 40 g, mobile phase: DCM/(MeOH containing 5% aq. NH_3), gradient from 98:2 to 85:15). The fractions containing the product were combined and evaporated to dryness to give a solid. This solid was recrystallized from EtOH. After cooling down to rt, the mixture was filtered on a glass frit. The solid was washed with Et_2O , collected and dried in vacuo to afford 191 mg of compound 4 (60% yield over 2 steps, pale yellow solid). M.P. = 193 °C (DSC).

[0772] Preparation of compound 68:

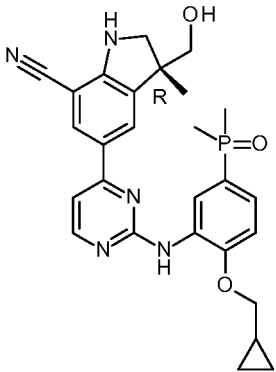
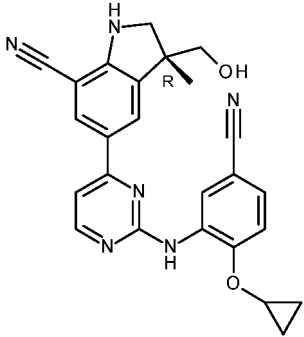
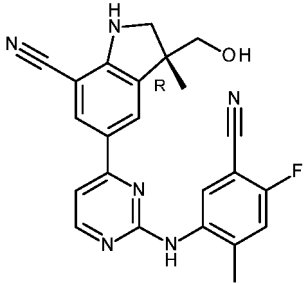
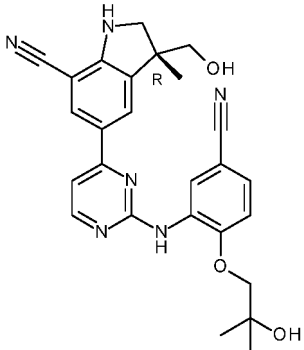


[0773] A mixture of intermediate 237 (132.00 mg, 0.20 mmol) and TBAF (1M in THF) (0.30 mL, 1 M, 0.30 mmol) in Me-THF (1.60 mL) was stirred at rt for 24 h. The mixture was poured out onto water and the organic layer was extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated until dryness (batch 1, 52 mg). The aqueous phase was extracted again with DCM and MeOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness (batch 2, 770 mg). An insoluble product in the aqueous layer was filtered over celite®. The celite was washed successively with DCM and MeOH. This organic layer was dried over $MgSO_4$, filtered and evaporated to dryness (batch 3, 300 mg). The batches were combined and purified by column chromatography on silica gel (Irregular SiOH, solid deposit, mobile phase: DCM/MeOH, gradient from 100:0 to 90:10). The pure fractions were collected and the solvent was evaporated. The residue (84 mg) was taken up in EtOH, triturated, filtered and dried to give 31 mg of compound 68 (28% yield).

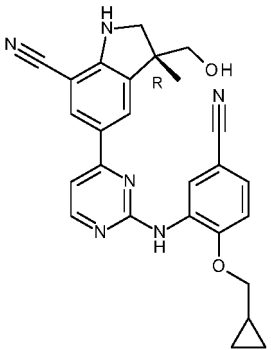
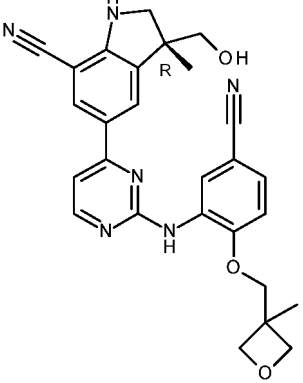
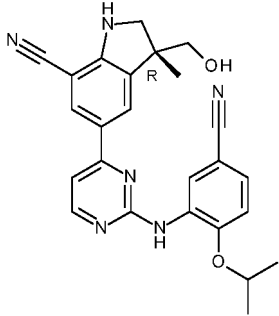
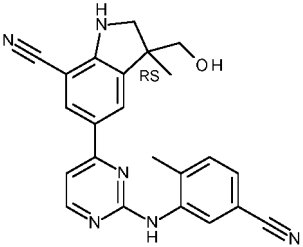
[0774] The compounds in the Table below were prepared by using an analogous method as the one reported for the preparation of compound 1, starting from the respective starting materials. The most relevant minor deviations to the reference method are indicated as additional information in the column 'Mass (mg)'.

Compound number	Structure	Mass (mg)	Yield (%)
Compound 2	 From a mixture of intermediate 13 and intermediate 14	310 <i>pale yellow foam</i> Procedure with 1 equiv of TBAF	55
Compound 3	 From a mixture of intermediate 13 and intermediate 14	52 <i>yellow fluffy solid</i> Procedure with 1 equiv of TBAF	9
Compound 5	 From intermediate 20	79 Procedure with 1 equiv of TBAF	39

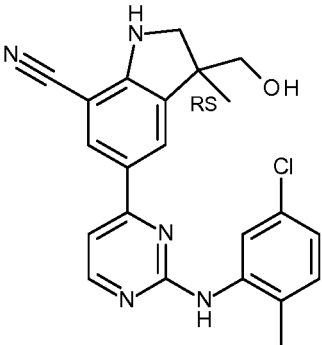
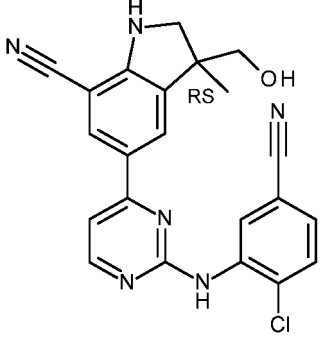
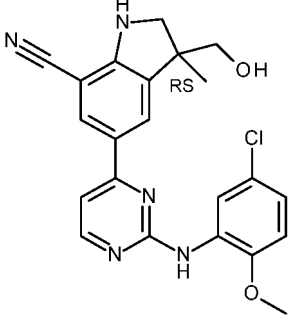
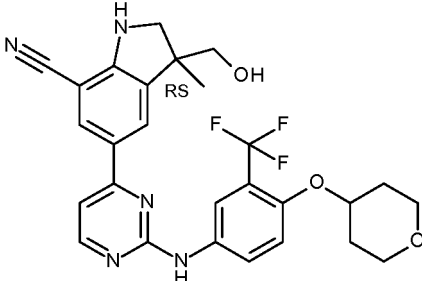
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 6	 From intermediate 21	173 Procedure with 1 equiv of TBAF	65
Compound 10	 From intermediate 42	37 white powder	8
Compound 11	 From intermediate 46	228 off-white solid Procedure with 1 equiv of TBAF	87
Compound 12	 From intermediate 49	120 yellow powder	41

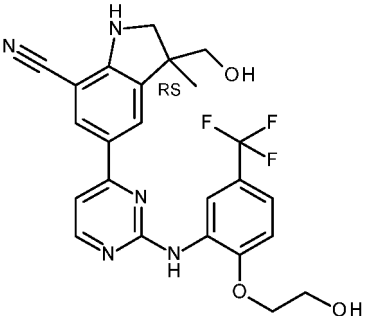
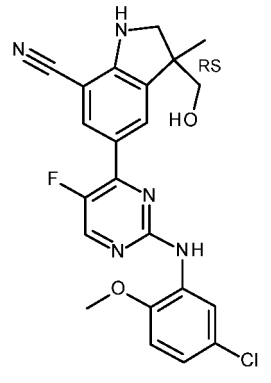
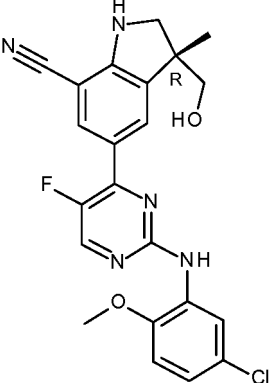
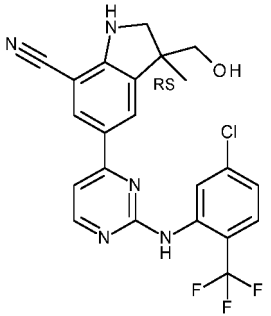
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Compound number	Structure	Mass (mg)	Yield (%)
Compound 13	 From intermediate 52	319 <i>white powder</i>	47
Compound 14	 From intermediate 55	538 <i>yellow powder</i>	51
Compound 16	 From intermediate 60	426 <i>yellow powder</i>	53
Compound 26	 From intermediate 104	121 <i>yellow solid</i> Procedure with 1 equiv of TBAF	60

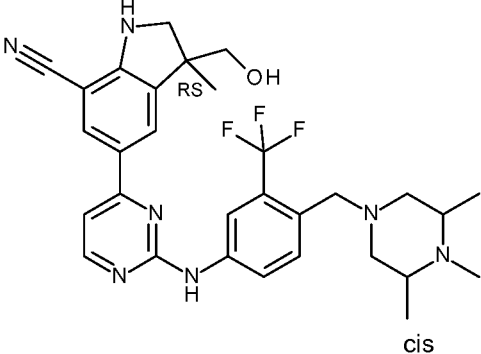
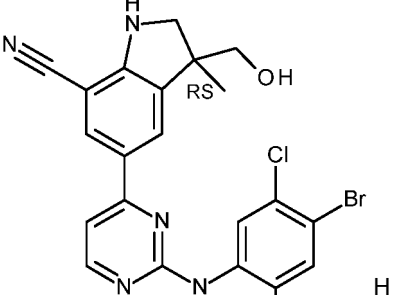
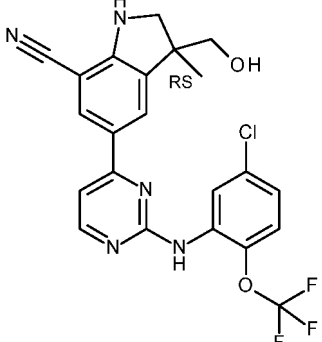
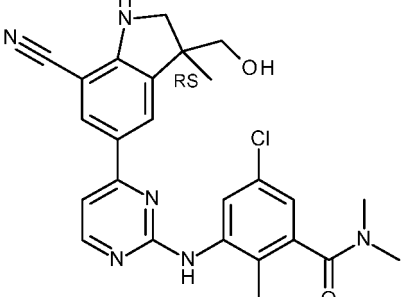
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Compound number	Structure	Mass (mg)	Yield (%)
Compound 27	 From intermediate 107	276 <i>white solid</i> Procedure with 1 equiv of TBAF	97
Compound 32	 From intermediate 119	68 <i>white solid</i> Procedure with 1 equiv of TBAF	35
Compound 33	 From intermediate 121	49 <i>yellow solid</i> Procedure with 1 equiv of TBAF	35
Compound 37	 From intermediate 136	44 Procedure with 1 equiv of TBAF	59

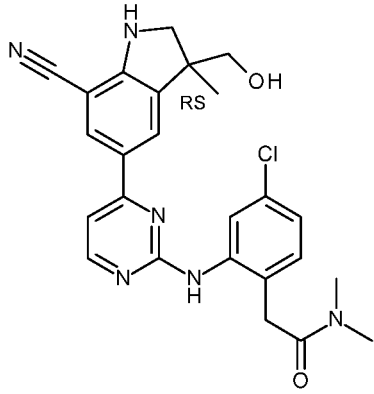
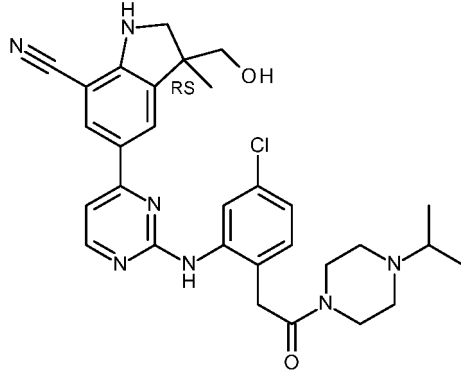
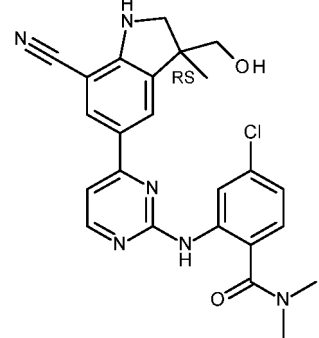
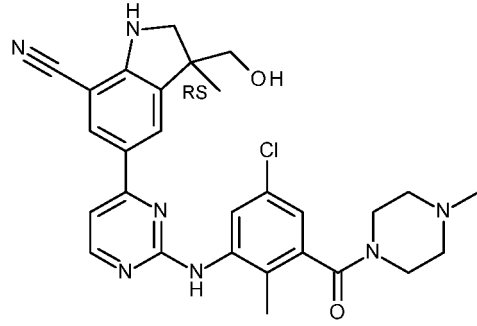
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Compound number	Structure	Mass (mg)	Yield (%)
Compound 38	 From intermediate 140	102 Procedure with 1 equiv of TBAF	65
Compound 47	 From intermediate 170	70 Procedure with 1 equiv of TBAF	61
Compound 48	 From intermediate 172	62 Procedure with 1 equiv of TBAF	59
Compound 49	 From intermediate 174	69 Procedure with 1 equiv of TBAF	42

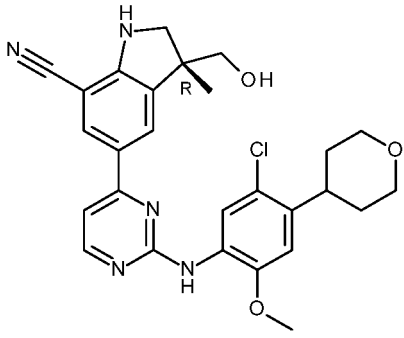
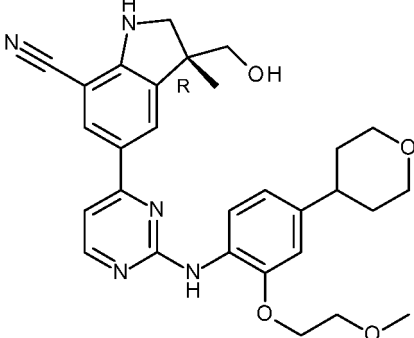
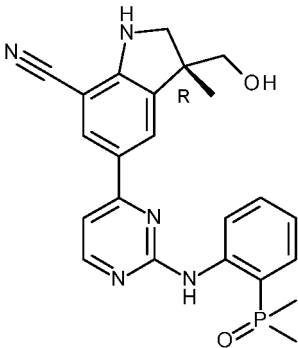
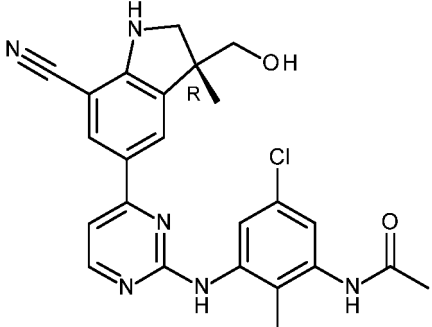
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Compound number	Structure	Mass (mg)	Yield (%)
Compound 50	 CIS From intermediate 180	94 Procedure with 1 equiv of TBAF	49
Compound 51	 From intermediate 182	47 Procedure with 1 equiv of TBAF	80
Compound 52	 From intermediate 184	209 Procedure with 1.1 equiv of TBAF	78
Compound 53	 From intermediate 188	63 Procedure with 1 equiv of TBAF	37

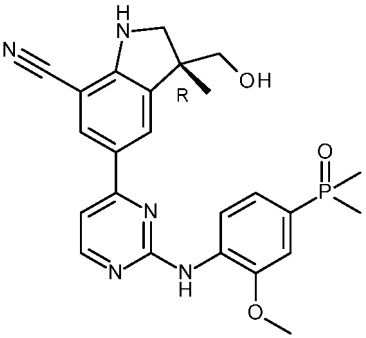
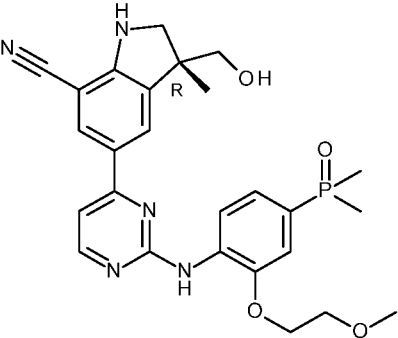
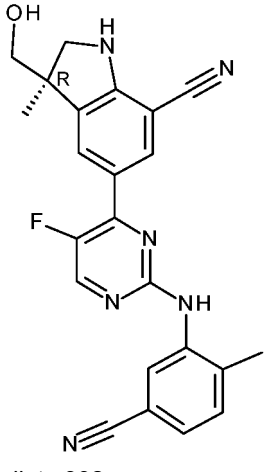
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 54	 From intermediate 191	81 Procedure with 1 equiv of TBAF	40
Compound 55	 From intermediate 194	103 Procedure with 1 equiv of TBAF	49
Compound 56	 From intermediate 195	68 Procedure with 1 equiv of TBAF	31
Compound 58	 From intermediate 199	121 Procedure with 1 equiv of TBAF	54

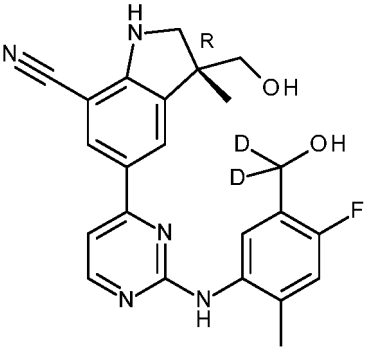
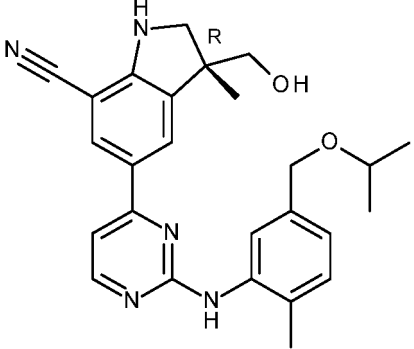
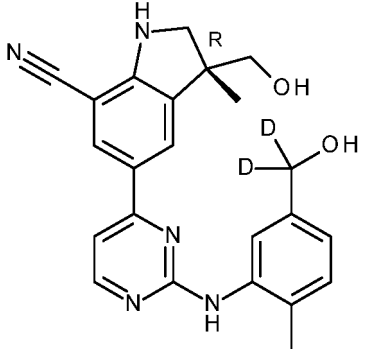
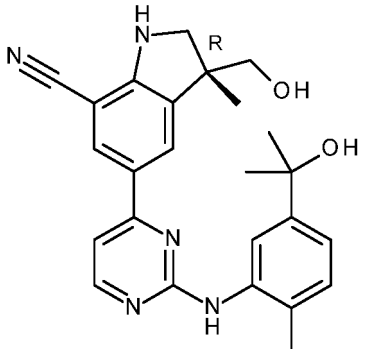
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Compound number	Structure	Mass (mg)	Yield (%)
Compound 59	 From intermediate 204	115 Procedure with 1.3 equiv of TBAF	84
Compound 61	 From intermediate 211	164 <i>off-white solid</i> Procedure with 1.5 equiv of TBAF	97
Compound 62	 From intermediate 213	175 <i>yellow solid</i> Procedure with 1.6 equiv of TBAF	92
Compound 63	 From intermediate 219	70 Procedure with 1.5 equiv of TBAF	49

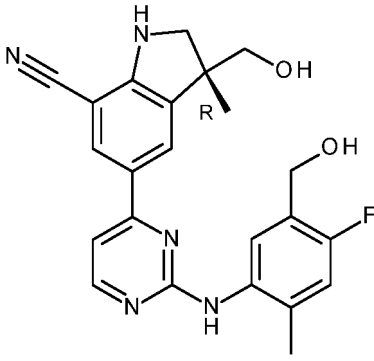
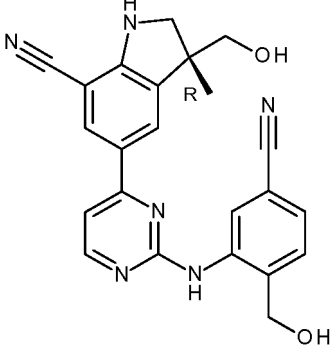
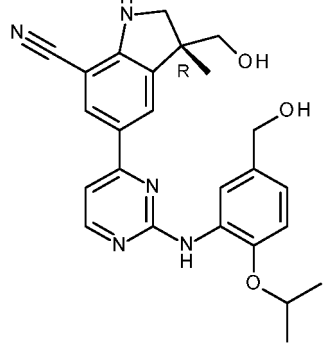
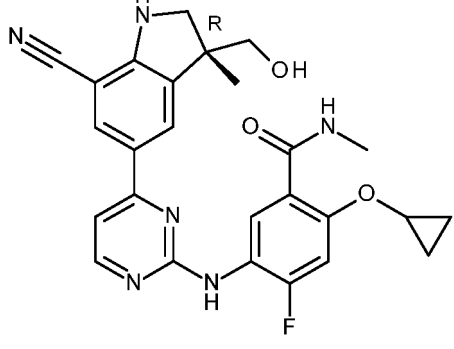
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 64	 From intermediate 223	105 <i>white solid</i> Procedure with 1.8 equiv of TBAF	40
Compound 67	 From intermediate 233	184 <i>white solid</i> Procedure with 1.8 equiv of TBAF	65
Compound 147	 From intermediate 392	310 <i>White morphous solid</i> Procedure with 4 equiv of TBAF and THF as solvent	98

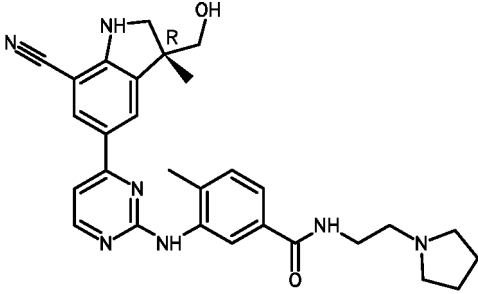
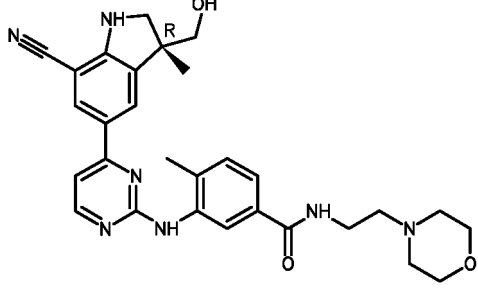
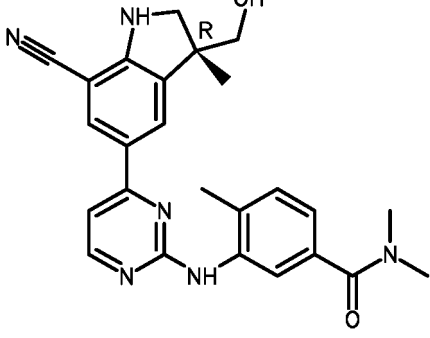
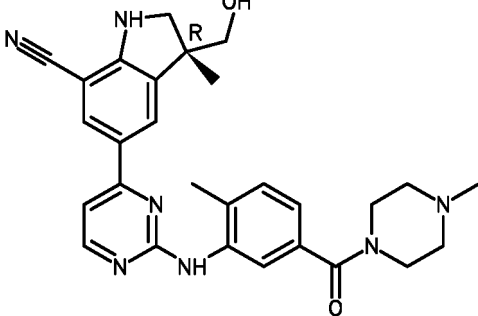
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 148	 From intermediate 394	1987	81
Compound 149	 From intermediate 398	45 Procedure with 1.2 equiv of TBAF and THF as solvent	25
Compound 150	 From intermediate 404	108 Procedure with 1.2 equiv of TBAF and THF as solvent	80
Compound 151	 From intermediate 407	24 Procedure with 1.2 equiv of TBAF and THF as solvent	32

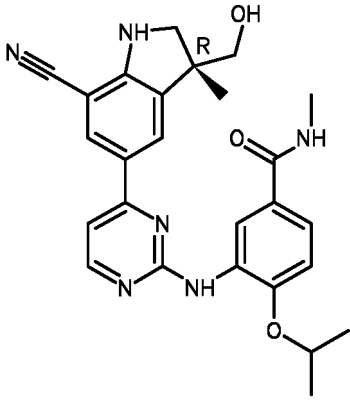
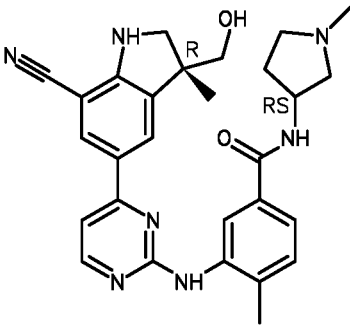
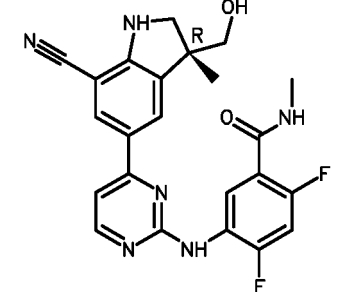
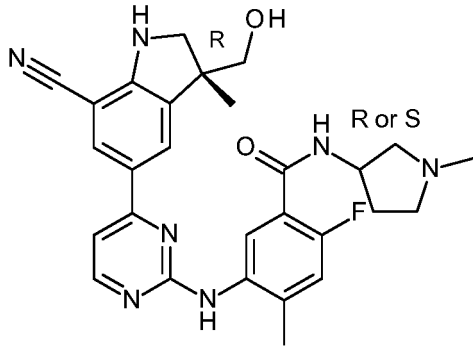
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 152	 From intermediate 411	234 Procedure with 1.1 equiv of TBAF	49
Compound 153	 From intermediate 412	74	51
Compound 154	 From intermediate 419	45 Procedure with 1.2 equiv of TBAF and THF as solvent	26
Compound 157	 From intermediate 431	371	86

(continued)

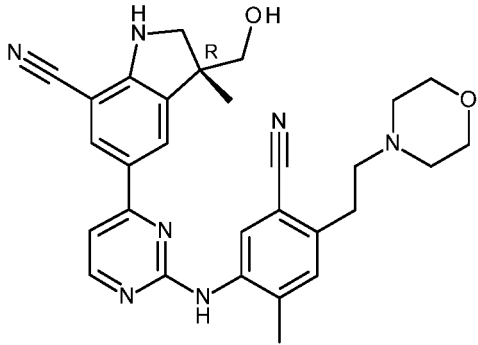
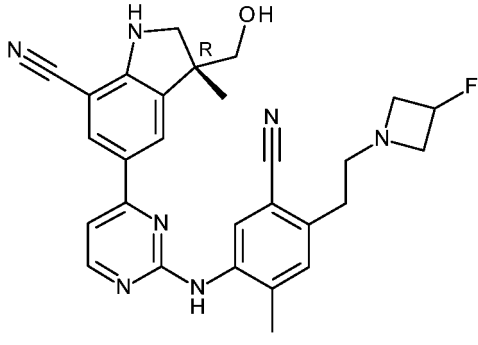
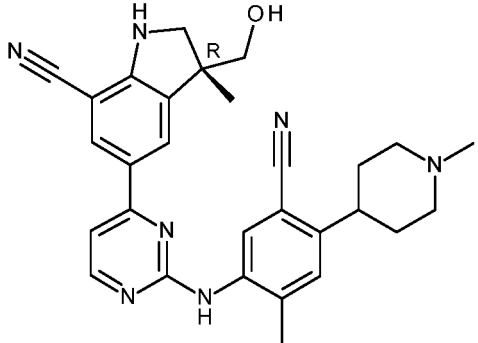
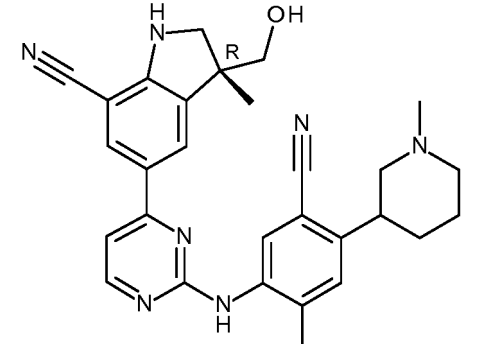
Compound number	Structure	Mass (mg)	Yield (%)
Compound 158	 From intermediate 433	14 Procedure with 1.1 equiv of TBAF	27
Compound 159	 From intermediate 435	75 Procedure with 1.1 equiv of TBAF	50
Compound 160	 From intermediate 437	205 Procedure with 1.1 equiv of TBAF	73
Compound 161	 From intermediate 439	236 Procedure with 1.1 equiv of TBAF	66

(continued)

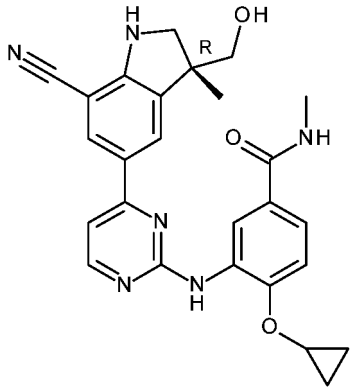
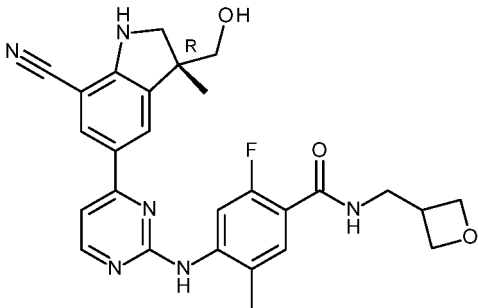
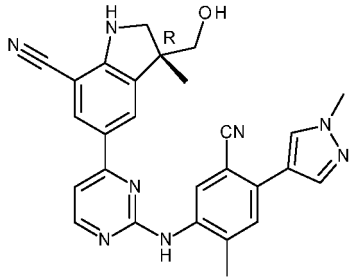
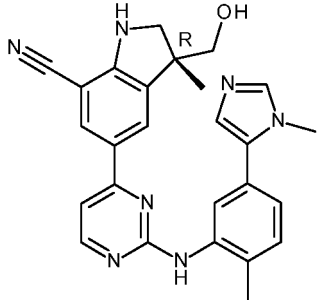
Compound number	Structure	Mass (mg)	Yield (%)
Compound 162	 From intermediate 440	302	63
Compound 163	 From intermediate 442	148	50
Compound 165	 From intermediate 444	233	69
Compound 166	 From intermediate 448	100	68

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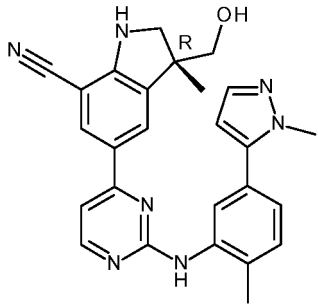
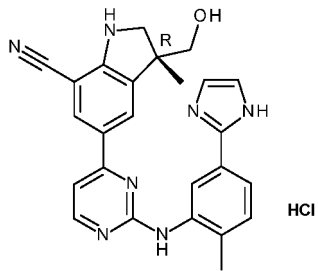
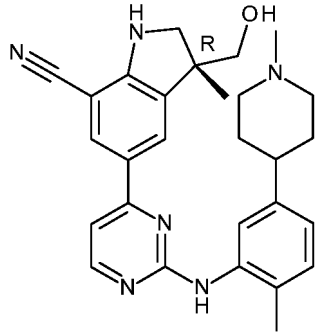
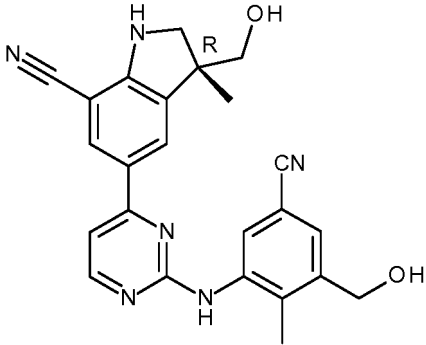
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 173	 From intermediate 468	143 Procedure with 1.1 equiv of TBAF	44
Compound 174	 From intermediate 471	90 Procedure with 1.1 equiv of TBAF	42
Compound 175	 From intermediate 474	51 Procedure with 1.1 equiv of TBAF	46
Compound 177	 From intermediate 479	180 Procedure with 1.1 equiv of TBAF	61

(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 186	 From intermediate 491	87	74
Compound 187	 From intermediate 496	89	66
Compound 188	 From intermediate 502	177	39
Compound 189	 From intermediate 503	29	41

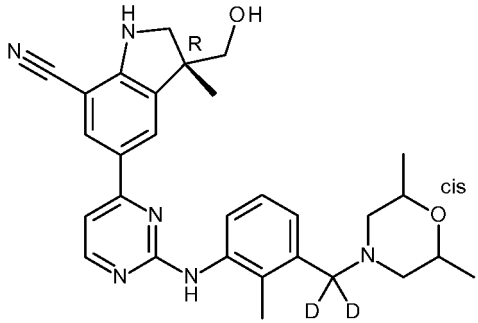
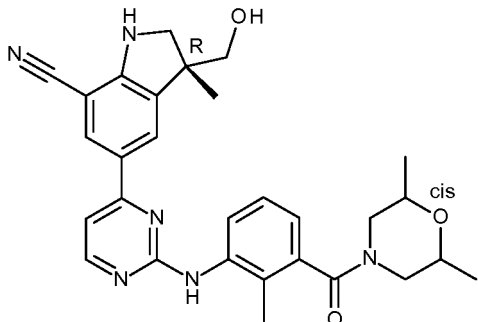
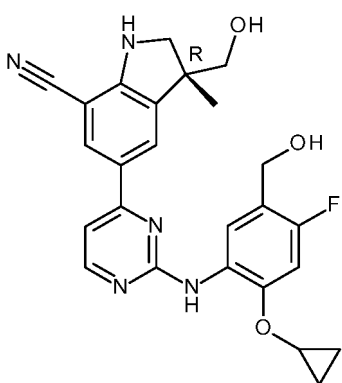
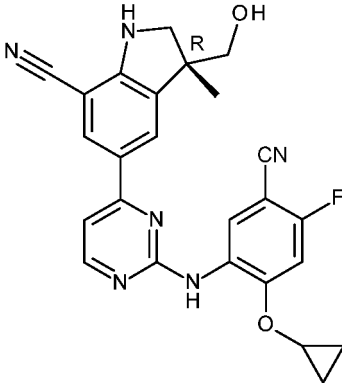
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 190	 From intermediate 504	300	85
Compound 191	 From intermediate 506	152 Procedure with 1 equiv. of TBAF and THF as solvent	68
Compound 192	 From intermediate 509	25 Procedure with 1 equiv. of TBAF and THF as solvent	37
Compound 193	 From intermediate 511	52	28

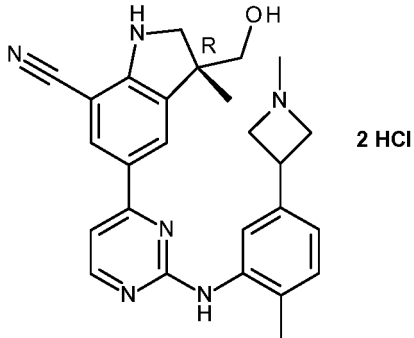
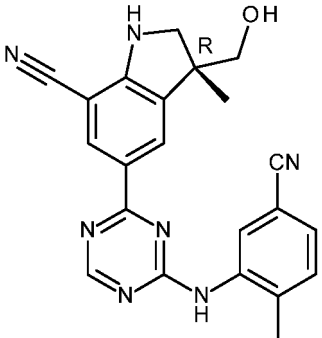
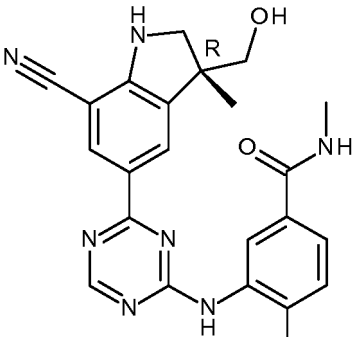
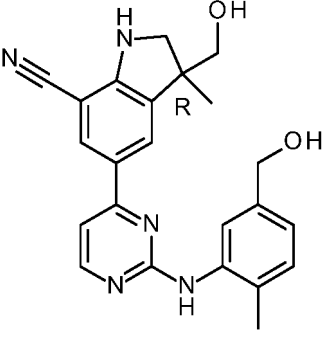
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 194	From intermediate 514	163	33
Compound 195	From intermediate 516	62	76
Compound 196	From intermediate 517	45	52
Compound 197	From intermediate 518	51	43

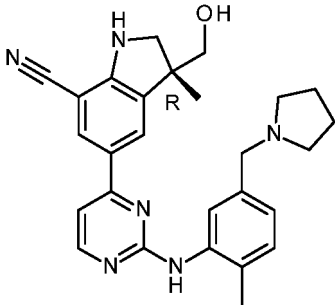
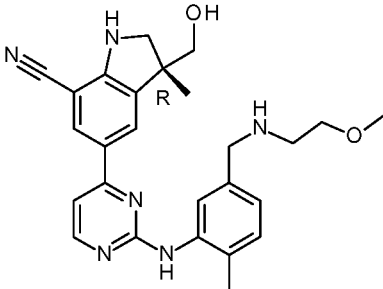
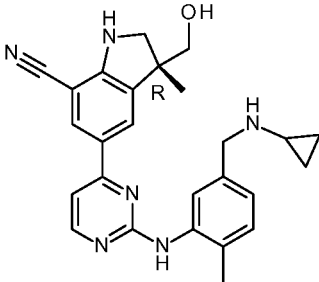
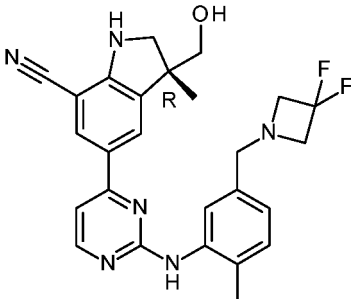
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 198	 From intermediate 520	127	71
Compound 199	 From intermediate 521	65	28
Compound 208	 From intermediate 528	168 Procedure with 5 equiv. of TBAF	86
Compound 209	 From intermediate 531	267	63

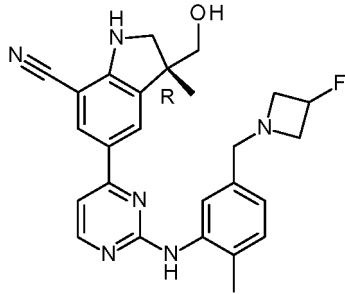
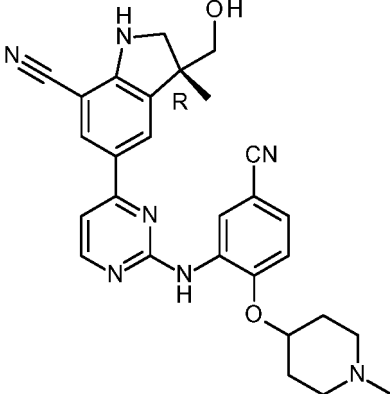
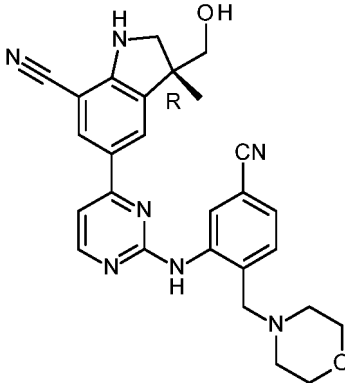
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 210	 From intermediate 538	57 Procedure with 3 equiv. of TBAF and THF as solvent	38
Compound 213	 From intermediate 545	170 Procedure with 4 equiv. of TBAF and THF as solvent	45
Compound 214	 From intermediate 548	150 Procedure with THF as solvent	51
Compound 215	 From intermediate 552	129 Off-white solid	48

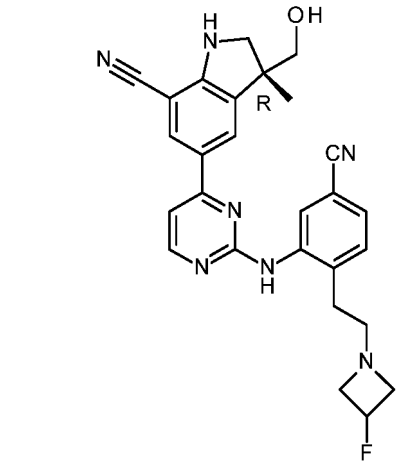
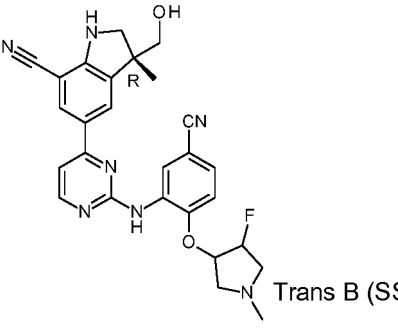
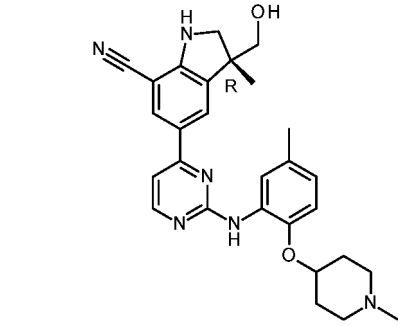
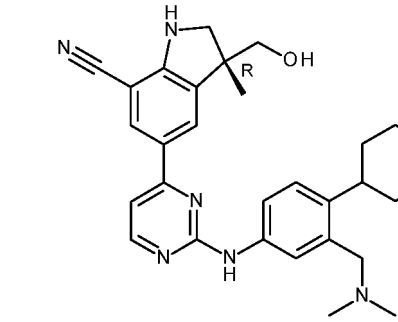
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 216	 From intermediate 556	34 Yellow foam	85
Compound 217	 From intermediate 558	236 White solid	76
Compound 218	 From intermediate 559	25 Yellow solid	22
Compound 219	 From intermediate 561	262 Pale yellow solid	78

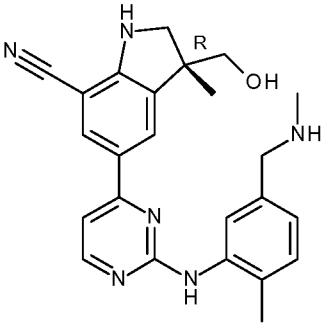
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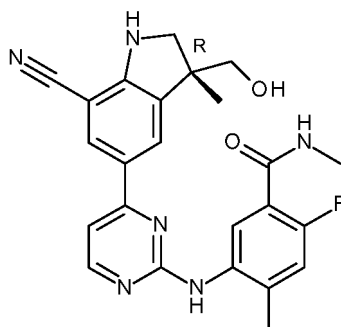
Compound number	Structure	Mass (mg)	Yield (%)
Compound 220	 From intermediate 563	38 Off-white solid	44
Compound 223	 From intermediate 577	243 Pale yellow solid Procedure with 3 equiv. of TBAF	82
Compound 224	 From intermediate 581	129 Orange solid	74

(continued)

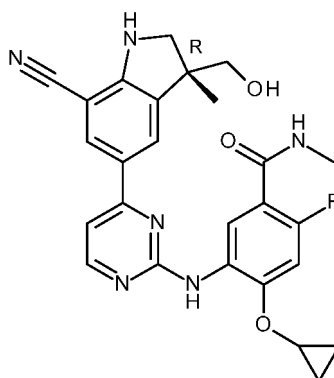
Compound number	Structure	Mass (mg)	Yield (%)
Compound 229	 From intermediate 600	270	67
Compound 233	 Trans B (SS or RR) From intermediate 619	123	78
Compound 234	 From intermediate 622	38 Off-white solid Procedure with 3 equiv. of TBAF	67
Compound 236	 From intermediate 634	147	-

(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 239	 From intermediate 641	8	21

[0775] Preparation of compound 155:

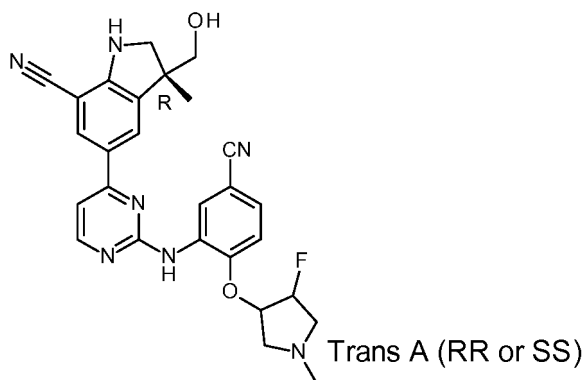
[0776] A solution of intermediate 423 (10.66 g, 19 mmol) in Me-THF (210 mL) was treated with TBAF (1M in THF) (38 mL, 38 mmol) and stirred at rt for 3 h. The reaction mixture was poured onto a 10% aqueous solution of K_2CO_3 and concentrated. DCM/MeOH (9/1) was added and the mixture was washed with 10% aqueous K_2CO_3 (3 x 400 mL), water (2 x 200 mL) and with brine (2 x 400 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was dissolved under reflux in CH_3CN (800 mL + 200 mL). The solution was allowed to cool to room temperature overnight. Then, the precipitate was filtered and dried to give 6.37 g of compound 155 (75%) as an off-white solid. M.P.: 218°C (DSC).

[0777] Preparation of compound 156:

[0778] TBAF (1M in THF) (1.5 mL; 1.5 mmol) was added dropwise to a solution of intermediate 430 (451 mg; 0.748 mmol) in Me-THF (15 mL) and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture

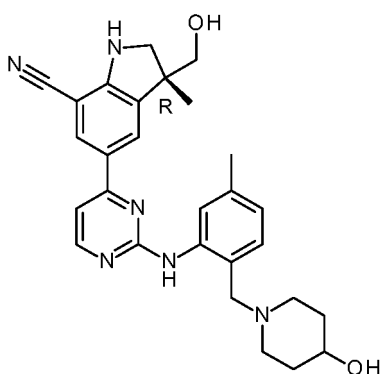
was poured onto a 10% aqueous solution of K_2CO_3 and extracted with EtOAc. The organic layer was washed with 10% aqueous K_2CO_3 (2 X 30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The residue was crystallized from ACN. The precipitate was filtered, washed with Et_2O and dried yielding 295 mg (81%) of compound 156. M.P.: 206°C (DSC)

[0779] Preparation of compound 232:



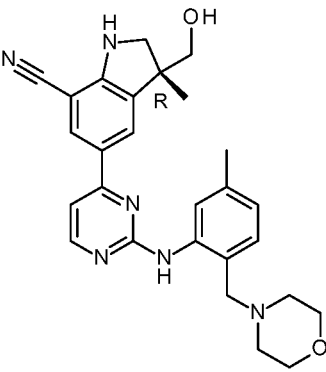
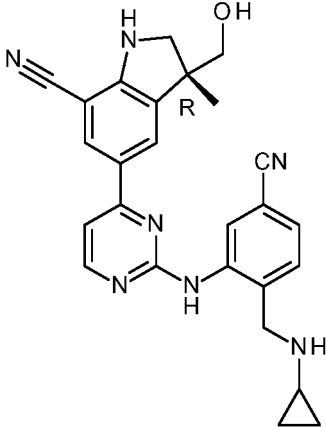
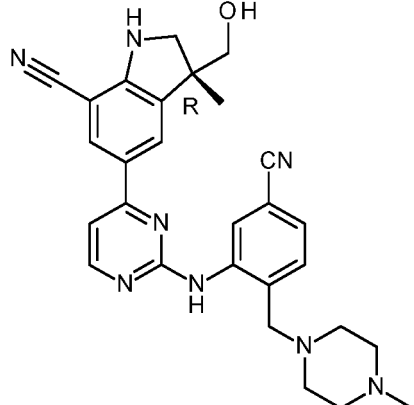
[0780] TBAF (1M in THF; 0.65 mL; 0.65 mmol) was added dropwise to a solution of intermediate 618 (234 mg; 0.328 mmol) in Me-THF (10 mL) and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was poured onto a 10% aqueous solution of K_2CO_3 and extracted with EtOAc. The organic layer was washed with 10% aqueous K_2CO_3 (2 x 30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The residue was crystallized from ACN and the precipitate was filtered, washed with Et_2O and dried yielding 133 mg of an intermediate compound which was suspended in MeOH at 50°C and stirred for 30 min. The precipitate was filtered and dried yielding 77 mg (47%) of compound 232. M.P.: 167°C (DSC)

[0781] Preparation of compound 221:



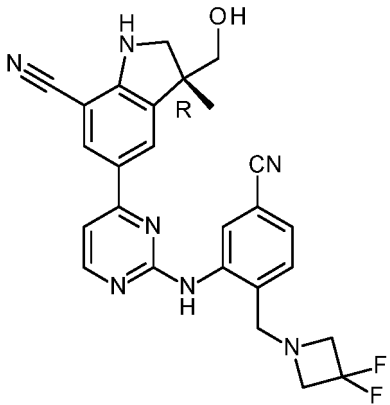
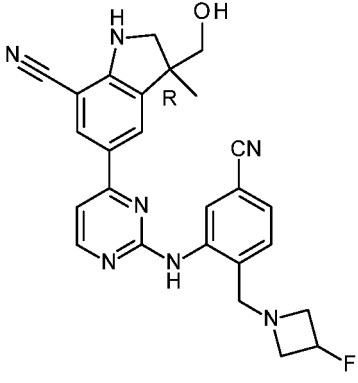
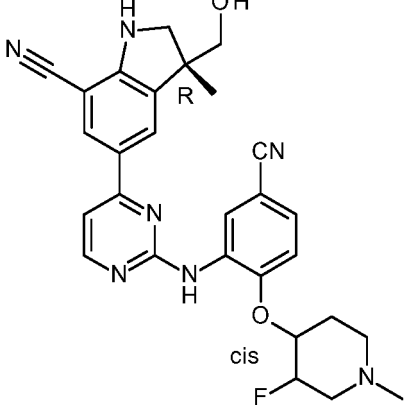
[0782] Tetrabutylammonium fluoride trihydrate (164.4 mg; 0.52 mmol) was added to a mixture of intermediate 569 (260 mg; 0.43 mmol) in Me-THF (2 mL) and stirred overnight. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with DCM. The organic layer was dried, filtered and concentrated under reduced pressure. The crude was purified with silica gel chromatography heptane and ethyl acetate as eluent starting with heptane and increasing the proportion of EtOAc. The fractions containing the product were mixed and concentrated affording 170mg (81%) of compound 221. MP = 181°C (MP50).

[0783] The compounds in the Table below were prepared by using an analogous method as the one reported for the preparation of compound 221, starting from the respective starting materials. The most relevant minor deviations to the reference method are indicated as additional information in the column 'Mass (mg)'.

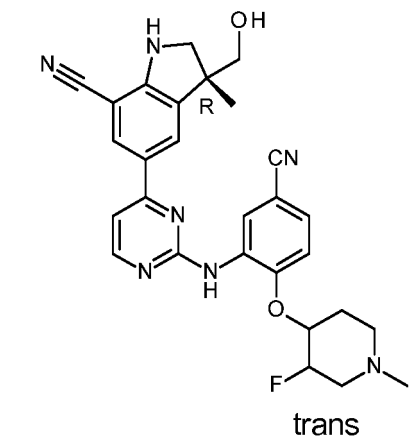
Compound number	Structure	Mass (mg)	Yield (%)
Compound 222	 From intermediate 573	110	65
Compound 225	 From intermediate 585	42	55
Compound 226	 From intermediate 589	120	31

EP 3 405 196 B1

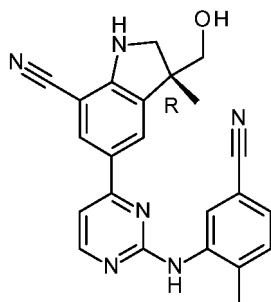
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 227	 From intermediate 593	140	72
Compound 228	 From intermediate 597	110	83
Compound 230	 From intermediate 606	130	61

(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 231	 From intermediate 612	38	52

Example B2

[0784] Alternative preparation A of compound 1:

[0785] To a solution of intermediate 7R (231 g, 0.556 mol) in 1,4-dioxane (2.3 L), *p*-toluenesulfonic acid monohydrate (179 g, 0.95 mol) and 3-amino-4-methylbenzonitrile (110 g, 0.83 mol) were added, purged three times with N₂ and stirred at 95 °C for 12 h. Then, the reaction mixture was cooled down to 20 °C, and a solution of NaHCO₃ was added to neutralize the mixture. The precipitated solid formed was filtrated and combined with another precipitate coming from a reaction performed on 179 g of intermediate 7R. The resulting solid was dissolved in Me-THF (5 L), washed with water three times (3 x 5 L). A silanethiol resin [from Shanghai Meryer CO.,LTD] (60 g) was added to the mixture and reflux for 1.5 h. Then, the resulting mixture was filtered through a pad of celite® and concentrated under vacuum. The residue was suspended in EtOH (5L) overnight, filtered and dissolved in THF (3L). Methyl *tert*-butylether (6 L) was added to THF and the solid was precipitated, filtered and dried to afford 243g of compound 1.

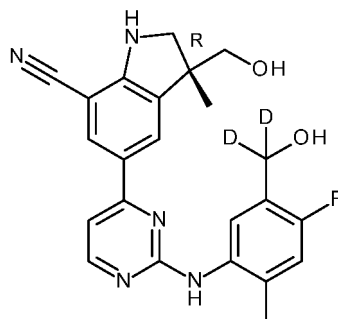
Alternative preparation B of compound 1:

[0786] A solution of intermediate 6R (10.0 g) and *p*-toluenesulfonic acid (3.0 eq) in dioxane (100 mL) was azeotropically dried until the content of water was <0.1% (determined by KF titration). 3-Amino-4-methylbenzonitrile (1.3 eq.) was then added and the mixture was azeotropically dried until the content of water was <0.3% (determined by KF titration) and the volume was approximately 50 mL. The mixture was then heated to 90 °C for 24 hours monitoring the conversion by HPLC. After complete conversion, the mixture was cooled to room temperature and water (50 mL) was added. After 1 hour of stirring, the layers were separated. The organic layer was concentrated to approximately 50 mL and methyl *tert*-butylether (100 mL) was added over 2 hours at 50 °C. The mixture was cooled to 10 °C over 4 hours, and then filtered affording after drying 5g (purity 98% evaluated by HPLC) of compound 1.

Recrystallization of compound 1:

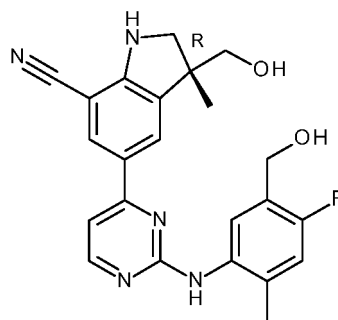
[0787] To a solution of compound 1 (270 g) in THF (1350 mL) at room temperature, methyl *tert*-butylether (2160 mL) was slowly added. The mixture was filtered and the product was dried under vacuum at 50 °C, to obtain 210 g (99.4% of purity evaluated by HPLC) of compound 1 as a yellow solid.

[0788] Alternative preparation of compound 148:



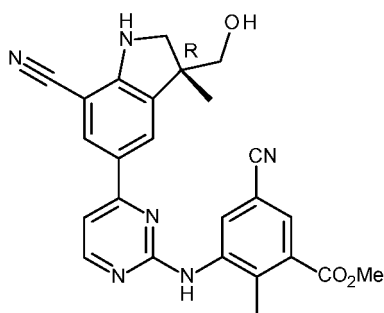
[0789] Compound 148 was also prepared following a similar procedure than the alternative preparation A of compound 1 starting from intermediate 7R and intermediate 393 (151 mg; 24%)

[0790] Alternative preparation of compound 152:



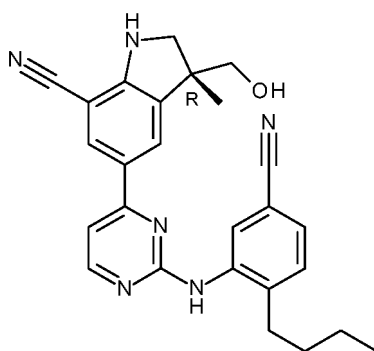
[0791] Compound 152 was also prepared following a similar procedure than the alternative preparation A of compound 1 starting from intermediate 7R and intermediate 410.

[0792] Preparation of compound 200:

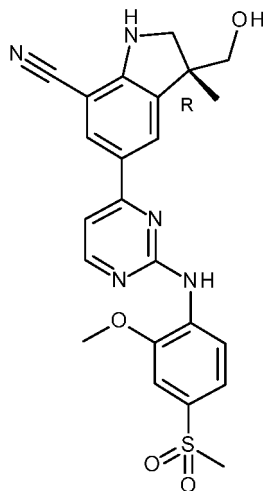


[0793] A mixture of intermediate 7R (415 mg; 1 mmol), 3-amino-5-cyano-2-methyl-benzoic acid methyl ester (285 mg; 1.5 mmol) and *p*-toluenesulfonic acid monohydrate (323 mg; 1.7 mmol) in 1,4-dioxane (5 mL) was heated at 95°C overnight. The reaction mixture was poured onto a 10% aqueous solution of K₂CO₃ and extracted with a mixture of DCM/MeOH. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue was taken up with ACN and the precipitate was filtered and dried yielding 216 mg (47%) of compound 200. M.P.: 260°C (Kofler)

Example B3

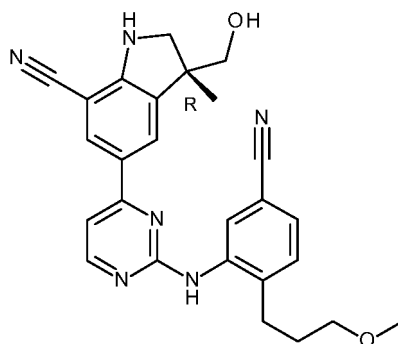
[0794] Preparation of compound 15:

[0795] TBAF (1.5 mmol/g on silica) (1.60 g, 2.46 mmol) was added at rt to a solution of intermediate 57 (340.00 mg, 0.61 mmol) in Me-THF (15 mL) and the reaction mixture was stirred at rt for 18 h. The reaction was not complete. Also, a solution of TBAF (1M in THF) (1.00 mL, 1.00 mmol) was added and the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with EtOAc, filtered through paper and poured onto a 10% aqueous solution of K_2CO_3 . The organic layer was decanted, washed with water, then brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (irregular SiOH, 40 g, mobile phase $NH_4OH/MeOH/EtOAc/heptane$, 0.5% NH_4OH , 10% MeOH, 50% EtOAc, 40% heptane). The pure fractions were collected and evaporated to dryness. The residue was taken up with Et_2O and the precipitate was filtered and dried to give 134 mg of compound 15 (50% yield). M.P. (gum) = 110 °C (K).

[0796] Preparation of compound 73:

[0797] In a round bottom flask, intermediate 253 (221.00 mg, 0.38 mmol) was diluted in Me-THF (10.3 mL). Then, the solution was cooled to 0 °C and TBAF (on silica gel 1.5mmol/g, 1.52 mL, 2.29 mmol) was added. The reaction mixture was stirred for 3 h allowing the temperature to reach rt and then partitioned between a saturated solution of $NaHCO_3$ and DCM. The layers were separated. The aqueous layer was extracted again with DCM. The organic layers were mixed, dried over $MgSO_4$, filtered and concentrated. The residue (225 mg) was purified by column chromatography on silica gel (irregular SiOH, 40 g, mobile phase: $NH_4OH/DCM/MeOH$, gradient from 0.2% NH_4OH , 2% MeOH, 98% DCM to 1 % NH_4OH , 10% MeOH, 90% DCM). The pure fractions were collected, evaporated to dryness. The residue (79 mg, 44%) was crystallized from Et_2O . The precipitate was filtered and dried to give 54 mg of compound 73 (30% yield). M.P. = 201 °C (DSC).

[0798] Preparation of compound 74:



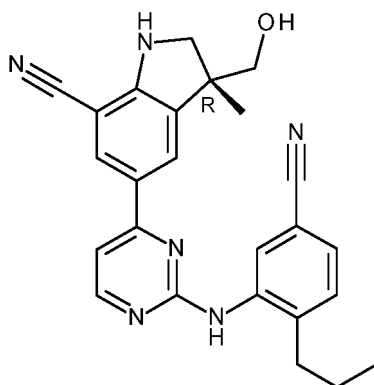
[0799] TBAF (on silica gel 1.5 mmol/g) (3.70 g, 5.57 mmol) was added to a solution of intermediate 256 (1.20 g, 1.39 mmol) in Me-THF (35 mL) and the reaction mixture was stirred at rt for 18 h. TBAF (1M in THF) (2.80 mL, 2.78 mmol) was added and the reaction mixture was stirred at rt for 2 additional hours. The reaction mixture was diluted with DCM, filtered through paper and poured onto a 10% aqueous solution of K_2CO_3 . The organic layer was decanted, washed with water, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (irregular SiOH, 40 g, mobile phase DCM/MeOH/ NH_4OH , gradient from 0.3% NH_4OH , 3% MeOH, 97% DCM to 1% NH_4OH , 10% MeOH, 90% DCM). The fractions containing the product were collected and evaporated to dryness and the residue was purified a second time by column chromatography on silica gel (irregular SiOH, 40 g, mobile phase DCM/MeOH/ NH_4OH with 0.5% NH_4OH , 5% MeOH, 95% DCM). The pure fractions were collected and evaporated to dryness. The residue (520 mg, 54%) was crystallized from CH_3CN/Et_2O and the precipitate was filtered and dried to give 443 mg of compound 74 (46% yield). M.P. = 124 °C (K).

[0800] 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 'Mass (mg)'.

Compound number	Structure	Mass (mg)	Yield (%)
Compound 71	From intermediate 246	160 Procedure with 3 equiv. of TBAF (1.5 mmol/g on silica)	48

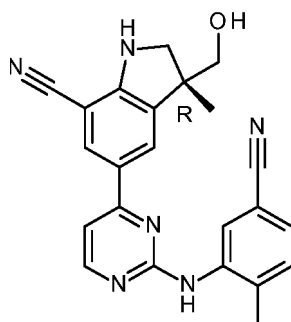
Example B4

[0801] Preparation of compound 7 :



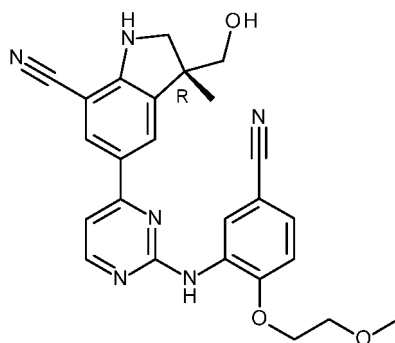
[0802] TFA (1.50 mL, 19.60 mmol) was added dropwise to a solution of intermediate 30 (270.00 mg, 0.51 mmol) in DCM (stab. with amylene 10 mL) at 5 °C and the reaction mixture was stirred for 1 h at this temperature. The reaction mixture was quenched with a 10% aqueous solution of K_2CO_3 and extracted with DCM. The organic layer was decanted, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was crystallized from CH_3CN and the precipitate was filtered and dried to give 165 mg of compound 7 (75% yield). M.P.: 215 °C (DSC).

[0803] Alternative preparation of compound 1:



[0804] TFA (3.93 mL, 51.35 mmol) was added at 5 °C to a solution of intermediate 10R (1.16 g, 2.33 mmol) in DCM (25.4 mL). The reaction mixture was stirred for 30 min. The reaction mixture was diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3 , dried over $MgSO_4$, filtered and evaporated to dryness. The residue (1200 mg, yellow solid) was purified by column chromatography on silica gel (irregular $SiOH$, deposit solid, 30 g, mobile phase: $NH_4OH/DCM/MeOH$, gradient from 100% DCM to 95% DCM 5% $MeOH$, 0.5% NH_4OH). The fractions containing the products were collected and evaporated to dryness to give three batches (batch 1: 167 mg, batch 2: 568 mg and batch 3: 253 mg as yellow powder). The batches 2 and 3 were gathered and purified via chiral SFC (Stationary phase: CHIRALPAK IC 5 μm 250 x 30 mm, mobile phase: 60% CO_2 , 36% $EtOH$, 4% DCM). The fractions containing the product were combined and evaporated to dryness. The residue (388 mg) was combined with two other batches of compound 1 (517 mg and 200 mg) and taken up with CH_3CN to provide 1.165 g of compound 1 (light yellow powder).

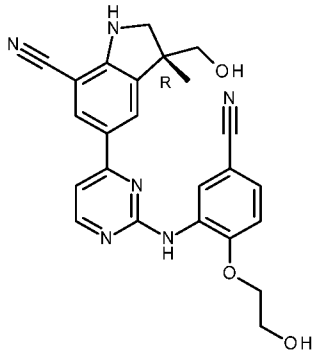
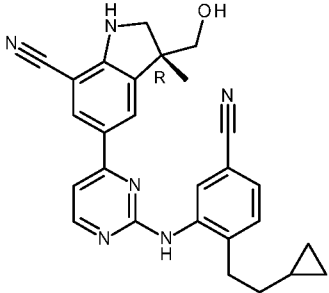
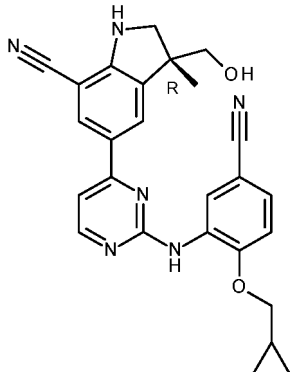
[0805] Preparation of compound 66:



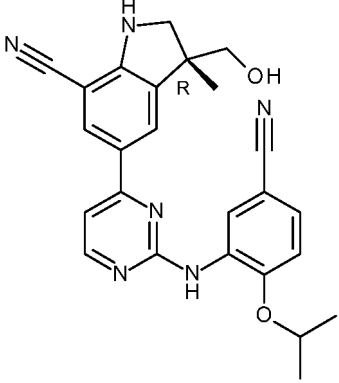
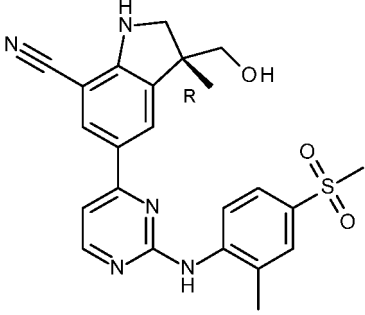
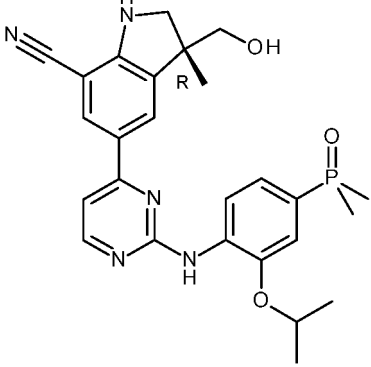
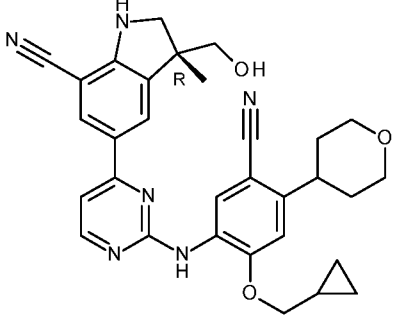
[0806] TFA (0.47 mL, 6.12 mmol) was added at 5 °C to a solution of intermediate 229 (227.00 mg, 0.41 mmol) in DCM

(10 mL, stabilized with amylene). The reaction mixture was stirred at 0 °C for 1 h, diluted with DCM and poured onto a 10% aqueous solution of K₂CO₃. The organic layer was decanted, washed with water, dried over MgSO₄, filtered and evaporated to dryness. The residue was suspended in EtOH and the mixture was heated at 50 °C for 2 h. The precipitate was filtered and dried to give 114 mg of compound 66 (61% yield). M.P. = 165 °C (K).

[0807] The compounds in the Table below were prepared by using an analogous method as the ones reported for the preparation of compounds 7, 1 or 66 starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Mass (mg)'.

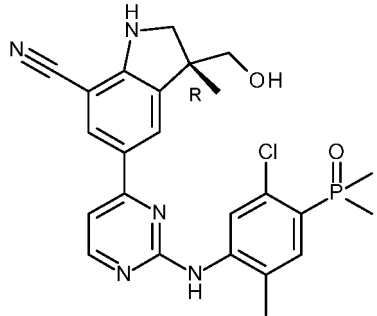
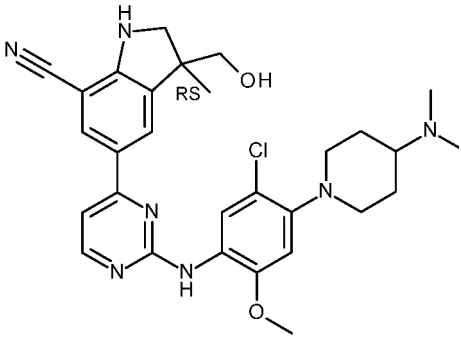
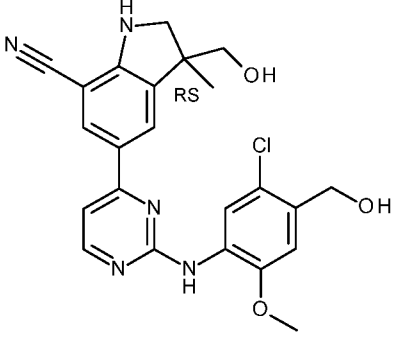
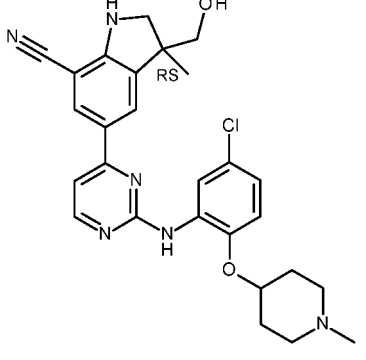
Compound number	Structure	Mass (mg)	Yield (%)
Compound 8	 From intermediate 35	32 <i>yellow powder</i> Procedure with DCM/TFA (10:1, v/v)	7
Compound 9	 From intermediate 39	160	63
Compound 13	 From intermediate 80	188 <i>yellow powder</i>	35

(continued)

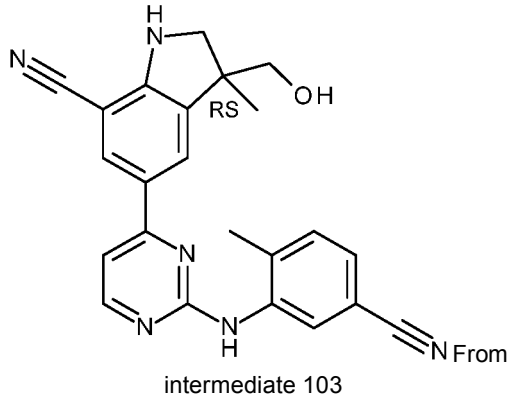
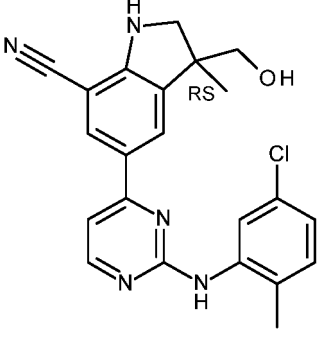
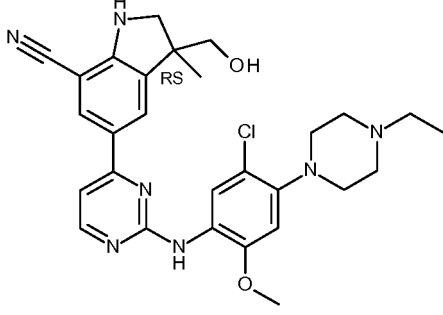
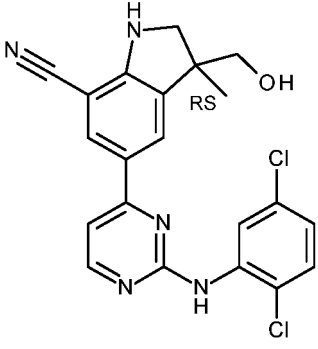
Compound number	Structure	Mass (mg)	Yield (%)
Compound 16	 From intermediate 62	79 <i>light yellow powder</i>	24
Compound 17	 From intermediate 64	57 Procedure with DCM/TFA (5:1, v/v)	27
Compound 18	 From intermediate 70	583 <i>off-white solid</i> Procedure with DCM/TFA (10:1, v/v)	79
Compound 19	 From intermediate 75	339 <i>white solid</i> Procedure with DCM/TFA (10:1, v/v)	45

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(continued)

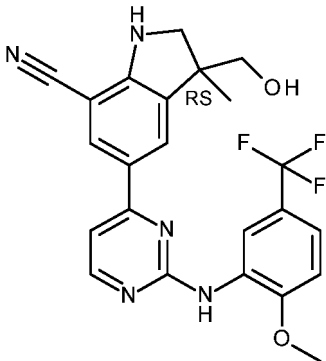
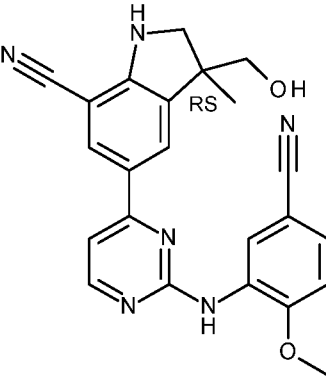
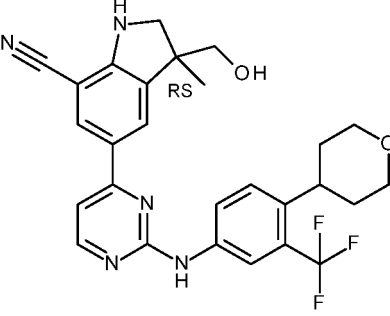
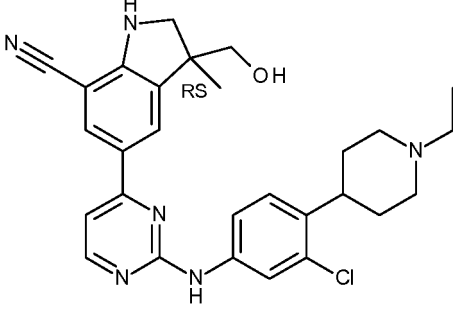
Compound number	Structure	Mass (mg)	Yield (%)
Compound 20	 From intermediate 78	440 <i>white solid</i> Procedure with DCM/TFA (10:1, v/v)	58
Compound 22	 From intermediate 90	30 (98% purity based on LC/MS) <i>off-white solid</i> with DCM/TF A (1:1, v/v)	20
Compound 24	 From intermediate 97	17 <i>off-white solid</i> Procedure with DCM/TFA (1:1, v/v)	9
Compound 25	 From intermediate 101	139 <i>pale yellow solid</i> Procedure with DCM/TFA (1:1, v/v)	55

(continued)

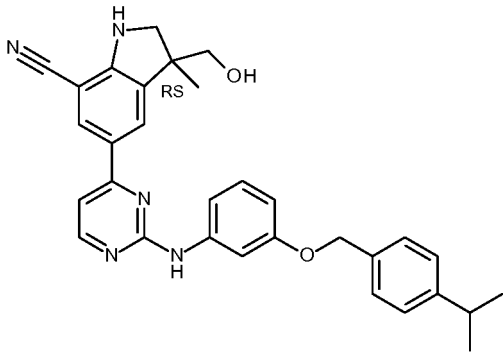
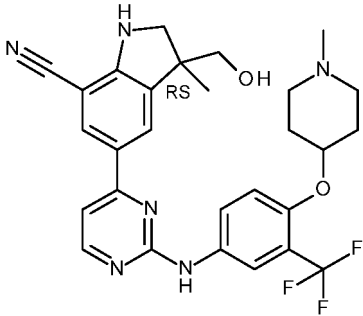
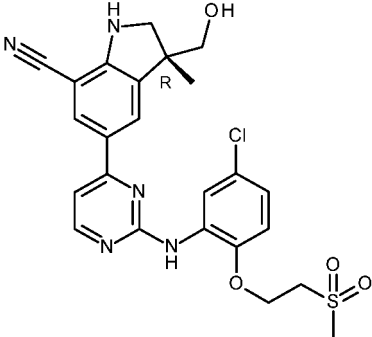
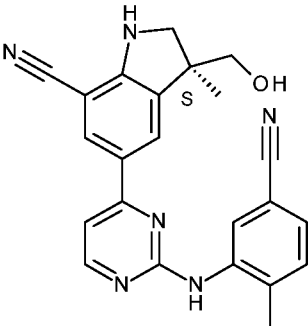
Compound number	Structure	Mass (mg)	Yield (%)
Compound 26	 intermediate 103	52 <i>white solid</i> Procedure with DCM/TFA (5:2, v/v)	23
Compound 27	 From intermediate 106	38 <i>white solid</i> Procedure with DCM/TFA (5:2, v/v)	16
Compound 28	 intermediate 111 From	32 <i>off-white solid</i> Procedure with DCM/TFA (1:1, v/v)	23
Compound 29	 From intermediate 113	60 <i>white solid</i> Procedure with DCM/TFA (5:2, v/v)	24

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(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 30	 From intermediate 115	116 <i>beige solid</i> Procedure with DCM/TFA (5:2,v/v)	44
Compound 31	 From intermediate 117	40 <i>orange solid</i> Procedure with DCM/TFA(5:2, v/v)	17
Compound 36	 From intermediate 132	71 Procedure with DCM/TFA (4: 1,v/v)	29
Compound 41	 From intermediate 151	30 Procedure with DCM/TFA (4: 1,v/v)	36

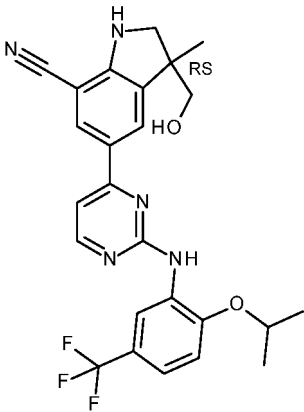
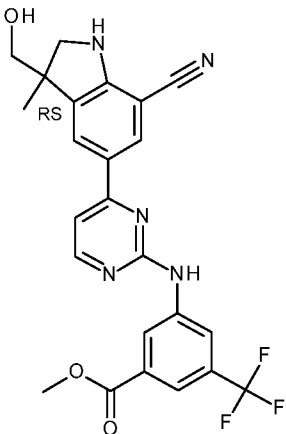
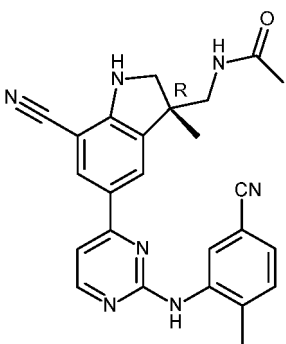
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 42	 From intermediate 154	55 Procedure with DCM/TFA (4:1, v/v)	22
Compound 43	 From intermediate 157	35 Procedure with DCM/TFA (4:1, v/v)	35
Compound 60	 From intermediate 206	15 Procedure with DCM/TFA (12:1, v/v)	20
Compound 65	 From intermediate 225	142 <i>yellow powder</i> Procedure with DCM/TFA (6:1, v/v)	28

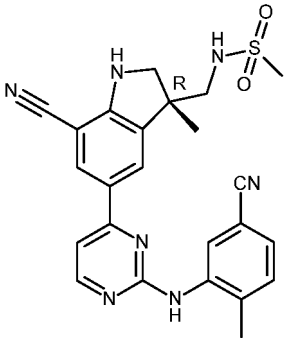
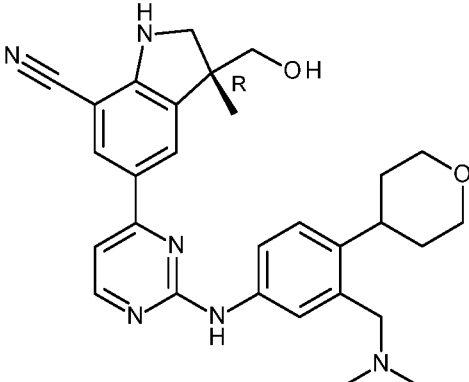
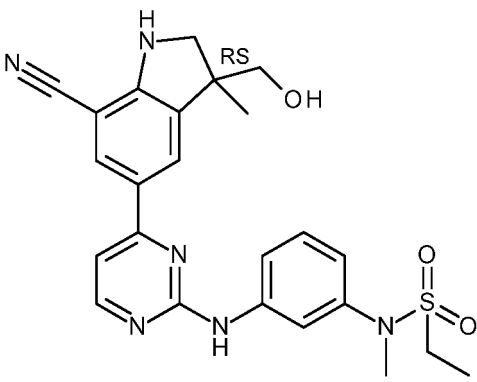
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 69	From intermediate 241	75 Procedure with DCM/TFA (6:1, v/v)	24
Compound 70	From intermediate 243	117 Procedure with DCM/TFA (8:1, v/v)	46
Compound 72	From intermediate 248	95 Procedure with DCM/TFA (15:1, v/v)	51
Compound 75	From intermediate 262	118 <i>white powder</i> Procedure with DCM/TFA (6:1, v/v)	38

(continued)

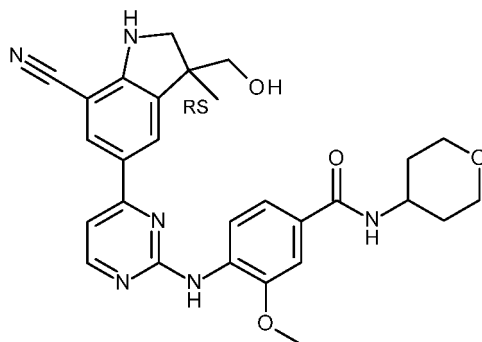
Compound number	Structure	Mass (mg)	Yield (%)
Compound 76	 From intermediate 266	65 Procedure with DCM/TFA (4:1, v/v)	34
Compound 77	 From intermediate 270	65 Procedure with DCM/TFA (5:1, v/v)	34
Compound 211	 From intermediate 541	113 Procedure with DCM/TFA (7.5:1, v/v) at room temperature	33%

(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 212	 From intermediate 542	88 Procedure with DCM/TFA (7.5:1,v/v) at room temperature	43%
Compound 236	 From intermediate 633	198 with DCM/TFA(18:1,v/v) during 15 hours)	51
Compound 240	 Form intermediate 644	85 with DCM/TFA(4:1,v/v)	40

Example B5

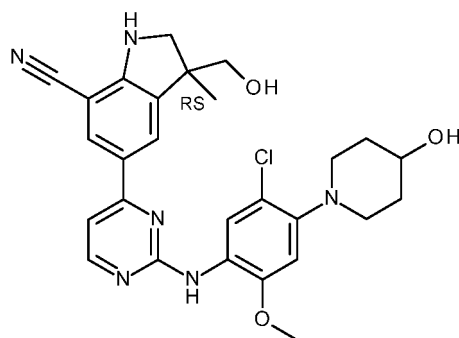
[0808] Preparation of compound 21:



[0809] To a solution of intermediate 85 (0.28 g, 0.29 mmol) in DCM (3 mL), TFA (3 mL) was added and the reaction mixture was stirred at rt for 2 h. The solution was concentrated in vacuo and neat TFA (3 mL) was added, the reaction mixture was stirred for a further 4 h. The reaction mixture was stirred for a further 1 h and the solution was concentrated in vacuo. The residue was treated with K_2CO_3 (0.24 g, 1.75 mmol) in DMF (2 mL) for 2 h at 50 °C. The reaction mixture was partitioned between EtOAc and water, and the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by mass triggered auto purification system.

Example B6

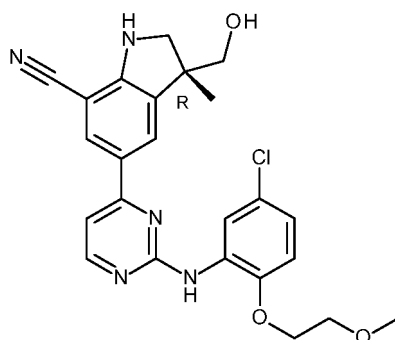
[0810] Preparation of compound 23:



[0811] HCl (3M in H_2O) (2.18 mL, 6.55 mmol) was added to a solution of intermediate 93 (698.00 mg, 0.65 mmol) in MeOH (10 mL) and the reaction mixture was stirred 6 h at reflux. The reaction mixture was cooled down to rt, diluted with DCM and carefully neutralized with a saturated solution of $NaHCO_3$. Then, few mL of MeOH were added to solubilize the precipitate. The reaction mixture was separated and the aqueous layer was extracted with DCM/MeOH (9/1). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue (620 mg) was taken up with DCM/MeOH (9/1). The precipitate was filtered and taken up again with 15 mL DCM/MeOH (9/1). The resulting slurry suspension was stirred 30 min at rt. The precipitate was filtered, washed with Et_2O and dried. The resulting residue (226 mg) was purified by column chromatography on silica (irregular SiOH, solid deposit, 40 g, mobile phase: DCM/MeOH, gradient from 98:2 to 94:6). The fractions containing the product were concentrated to give two batches of compound 23: batch A (131 mg, 38% yield) and batch B (23 mg, 6% yield). The batch A, containing some solvents, was solubilized in DCM/MeOH, concentrated and taken up with CH_3CN . The precipitate was filtered to afford after drying a batch C of compound 23 (112 mg) but still containing some solvent. Finally, the batch C was dissolved in DCM/EtOH, concentrated and taken up with CH_3CN . The precipitate was filtered and dried to afford additional 93 mg of compound 23 (27% yield). M.P.: > 260°C (K).

[0812] The global yield was 33%.

[0813] Preparation of compound 45:



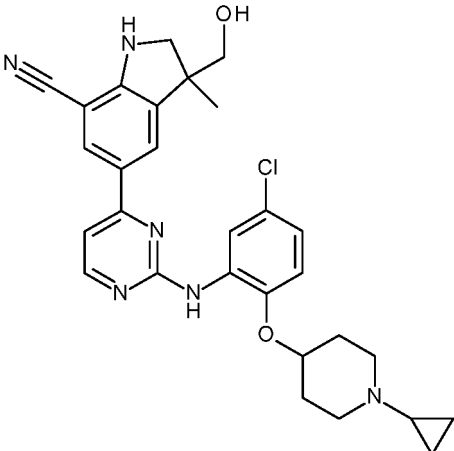
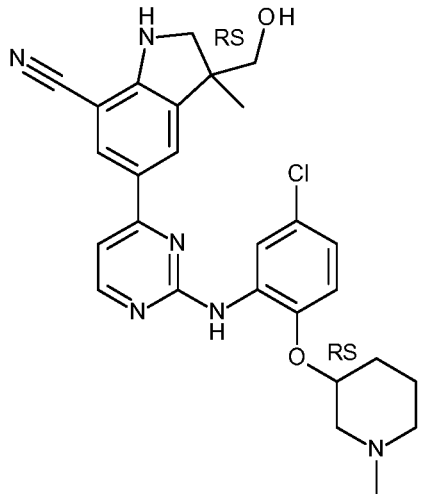
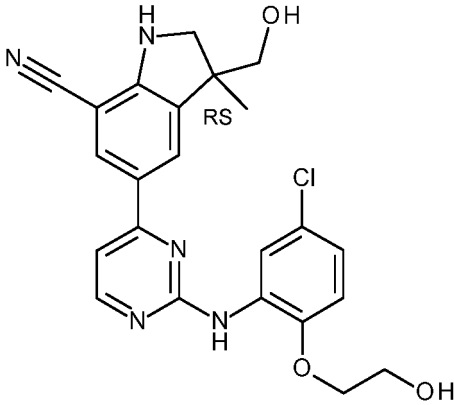
[0814] HCl (3M in H₂O) (1.32 mL, 3.95 mmol) was added to a solution of intermediate 164 (269.00 mg, 0.40 mmol) in MeOH (6.0 mL) and the reaction mixture was stirred 10 h at reflux. The reaction mixture was cooled to rt, poured onto a 10% aqueous solution of K₂CO₃ and extracted with DCM. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness to provide an orange powder. The residue (220 mg) was purified by column chromatography on silica gel (Irregular SiOH, 25 g, solid deposit, mobile phase NH₄OH/DCM/MeOH, gradient from 0% NH₄OH, 0% MeOH, 100% DCM to 1% NH₄OH, 10% MeOH, 90% DCM). The fractions containing the product were collected and evaporated to dryness to give 69 mg of a yellow solid. This solid was taken up in Et₂O to provide 62 mg of compound 45 (34% yield, white powder).

M.P. = 169 °C (K).

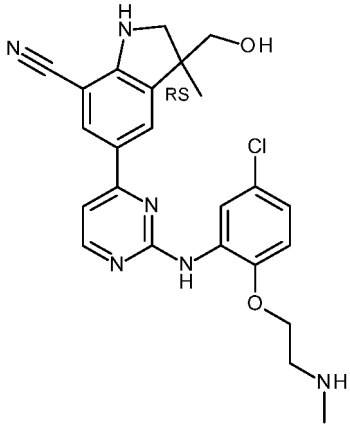
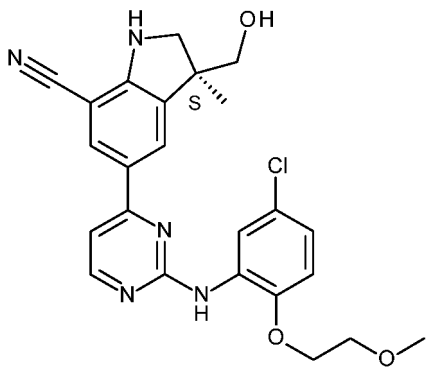
[0815] The compounds in the Table below were prepared by using an analogous method as the ones reported for the preparation of compounds 23 or 45, starting from the respective starting materials.

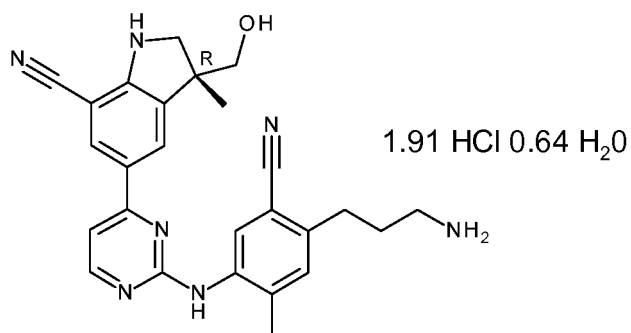
Compound number	Structure	Mass (mg)	Yield (%)
Compound 23	From intermediate 93	93	27
Compound 34	From intermediate 124	96 <i>white powder</i>	47

(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 35	 From intermediate 128	105 <i>white powder</i>	28
Compound 39 (mixture of 4 unseparated diastereoisomers)	 From intermediate 143	77 <i>white powder</i>	61
Compound 40	 From intermediate 146	83 <i>yellow powder</i>	37

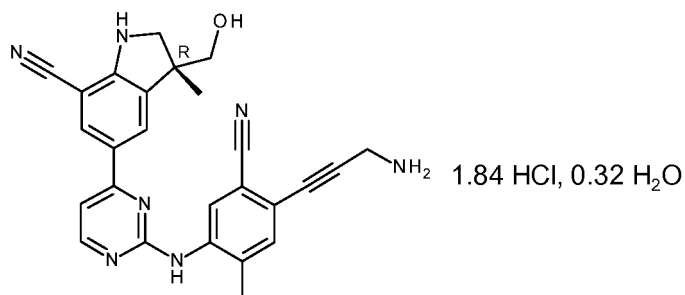
(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 44	 From intermediate 161	37 white powder	31
Compound 57	 From intermediate 196	39	21

[0816] Preparation of compound 170:

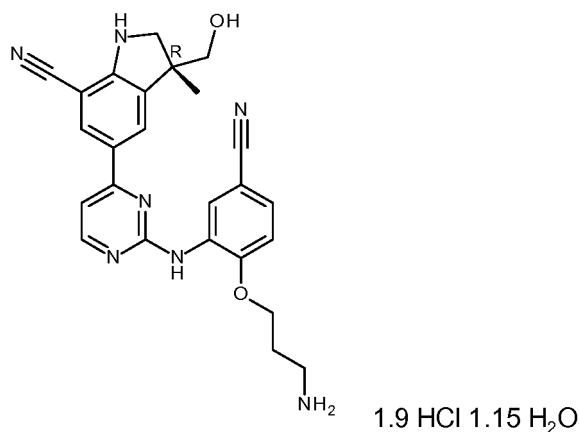
[0817] 4 N HCl in 1,4-dioxane (0.19 mL; 0.759 mmol) was added at room temperature to a solution of intermediate 461 (84 mg; 0.152 mmol) in acetonitrile (2.4 mL) and the reaction mixture was stirred for 3 hours. The precipitate was filtered, washed with acetonitrile and dried at 50°C under vacuo to give 0.068 g (82%) of compound 170. MP = 207°C (kofler).

[0818] Preparation of compound 171:



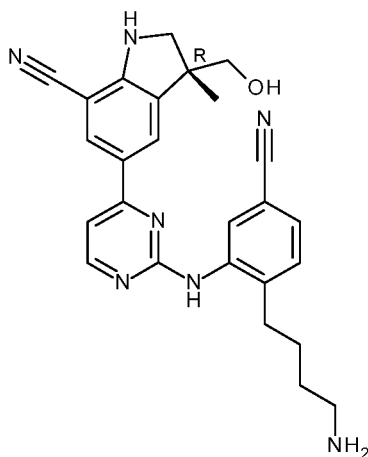
[0819] Compound 171 was synthesized by using an analogous method than the one used for the preparation of compound 170, starting from intermediate 464 (235 mg; 99%; MP = 249°C, kofler).

[0820] Preparation of compound 180:



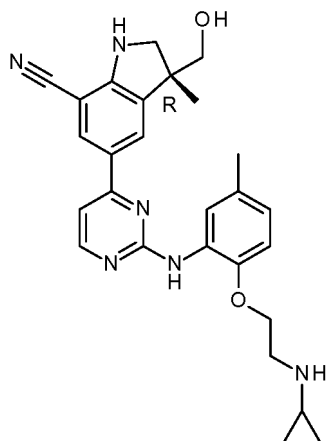
[0821] Compound 180 was synthesized by using an analogous method than the one used for the preparation of compound 170, starting from intermediate 482bis (162 mg; 81%; MP = gum at 194°C, kofler).

[0822] Preparation of compound 184:



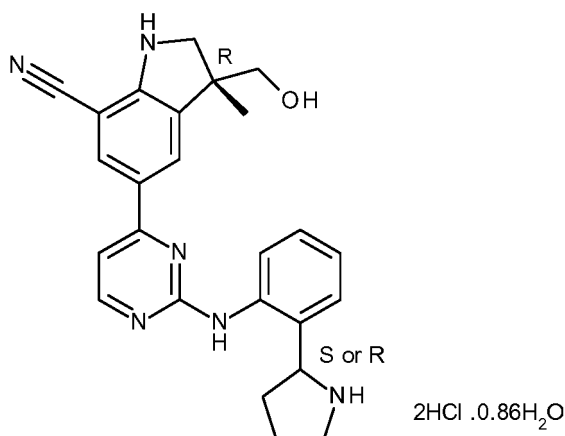
[0823] Compound 184 was synthesized by using an analogous method (using HCl 3N in cyclopentylmethyl ether) than the one used for the preparation of compound 170, starting from intermediate 487 (223 mg; 60%; MP = gum at 134°C, kofler).

[0824] Preparation of compound 235:



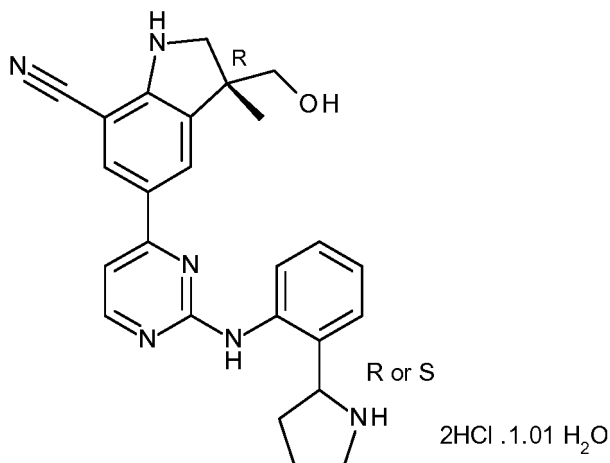
[0825] In a round bottom flask containing intermediate 627 (500 mg; 0.64 mmol) and 1,4-dioxane (20 mL) was added HCl 4M/dioxane (3.5 mL; 14.01 mmol) and the reaction mixture was stirred at room temperature overnight. The crude was concentrated and was quenched with a saturated solution of NaHCO_3 and extracted with DCM (2x50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to give a crude that was purified by flash chromatography eluting with DCM (75%):MeOH (25%). The fractions containing the product were collected and the solvent was evaporated to give 95 mg (32%) of compound 235.

[0826] Preparation of compound 237:



[0827] Compound 237 was synthesized by using an analogous method (using DCM as solvent) than the one used for the preparation of compound 235 starting from intermediate 639 (123mg; 86%).

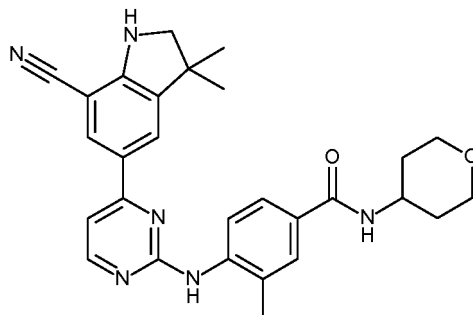
[0828] Preparation of compound 238:



[0829] Compound 238 was synthesized by using an analogous method (using DCM as solvent) than the one used for the preparation of compound 235 starting from intermediate 638 (116mg; 88%).

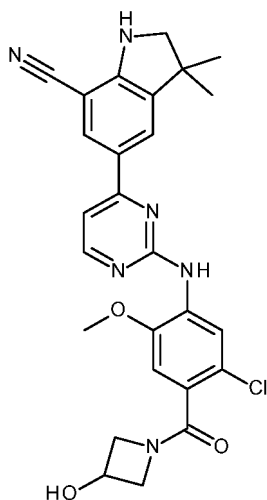
Example B7

[0830] Preparation of compound 78:



[0831] To a solution of intermediate 277 (227.00 mg, 0.242 mmol) in DCM (3mL), TFA (3 mL) was added and stirred at rt for 2 h. The solution was concentrated in vacuo to give an orange oil. The residue was purified by reverse phase semi-preparative HPLC (C18 column, Mobile phase: H₂O + 0.1% HCO₂H/CH₃CN, gradient 30% to 80% in CH₃CN). The desired fractions were combined and freeze-dried to give 32 mg of compound 78 (26%, yellow solid).

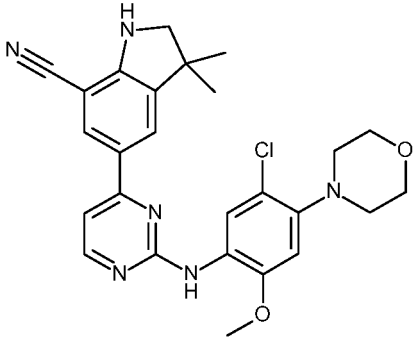
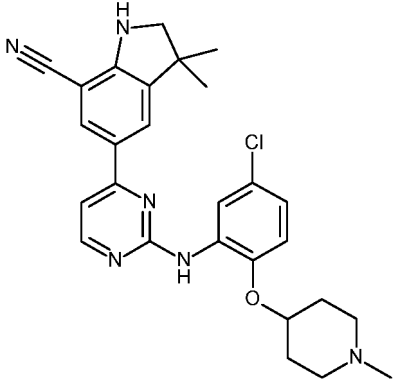
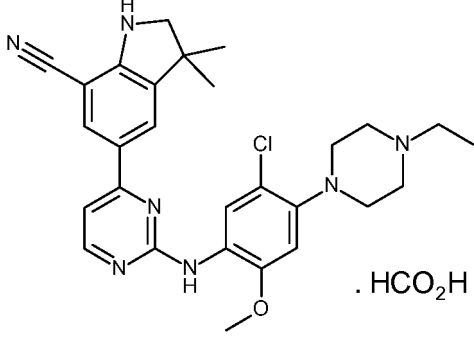
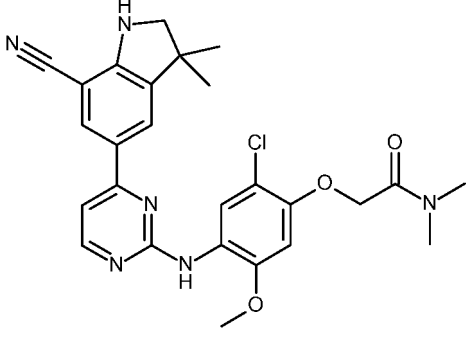
[0832] Preparation of compound 110:



[0833] Intermediate 357 (500 mg, 0.83 mmol) was stirred in DCM (37.5 mL). To this solution, TFA (12.5 ml) was added at 0 °C and stirred at rt for 1 h. To the resulting reaction mixture, NaHCO₃ was added until pH = 8. Some solids precipitated and were filtered to give the crude product. The residue was purified by preparative high-performance liquid chromatography (Waters Xbridge Prep OBD C18 100 x 19 mm x 5 μm, mobile phase: CH₃CN/H₂O (10mM NH₄HCO₃) from 30% to 60% of CH₃CN in 12 min, then 100% of CH₃CN in 2 min, flow rate = 25 mL/min). The pure fractions were collected and the solvent was evaporated under vacuum. The aqueous layer was lyophilized to give 102 mg of compound 110 (24% yield, white solid).

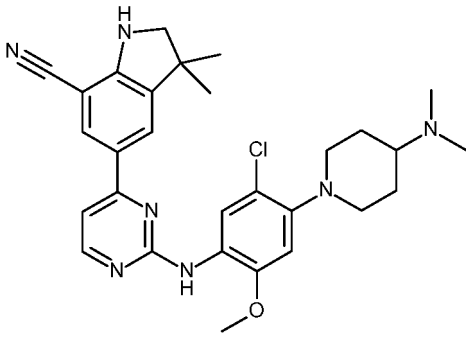
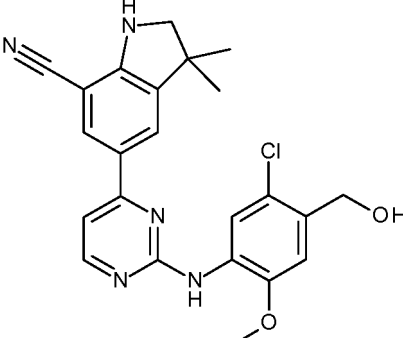
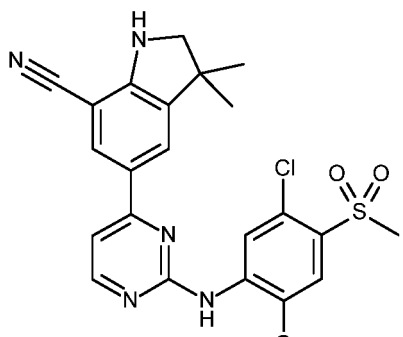
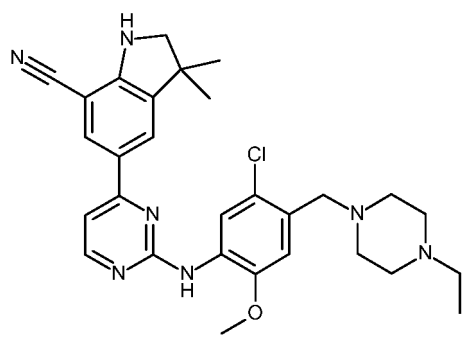
[0834] The compounds in the Table below were prepared by using an analogous method as the ones reported for the synthesis of compounds 78 or 110 starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Mass (mg)'.

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Compound number	Structure	Mass (mg)	Yield (%)
Compound 79	 From intermediate 280	15 Procedure with DCM/TFA (5:2, v/v) <i>white solid</i>	15
Compound 80	 From intermediate 281	65 <i>off-white solid</i> Procedure with DCM/TFA (2:1, v/v)	51
Compound 81	 From intermediate 282	57 <i>off-white solid</i> Procedure with DCM/TFA (2:1, v/v) . HCO ₂ H	50
Compound 82	 From intermediate 286	40 <i>off-white solid</i>	30

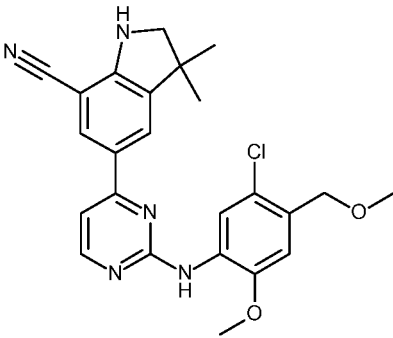
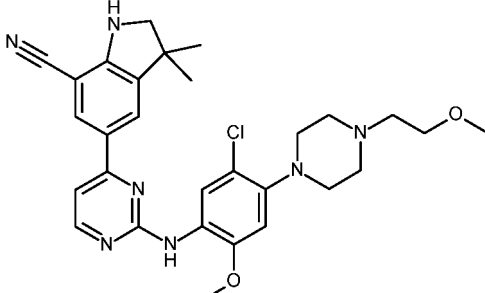
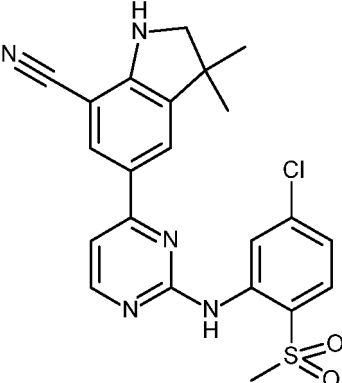
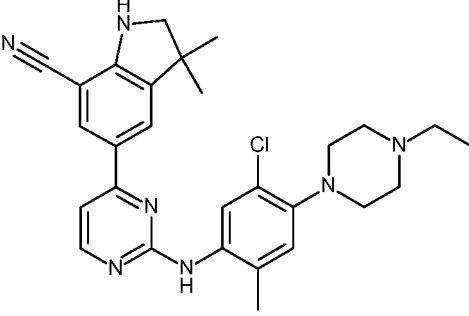
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(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 83	 From intermediate 287	12 Procedure with DCM/TFA (2:1, v/v) <i>off-white solid</i>	12
Compound 84	 From intermediate 288	31 Procedure with DCM/TFA (2:1, v/v) <i>white solid</i>	36
Compound 85	 From intermediate 282	35 <i>off-white solid</i>	28
Compound 87	 From intermediate 298	33 <i>off-white solid</i>	39

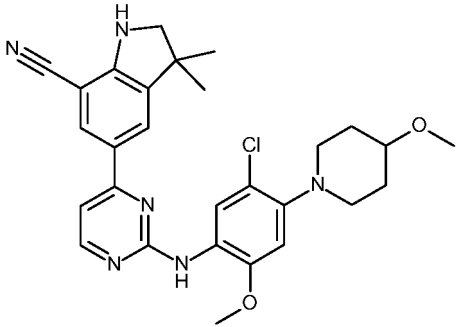
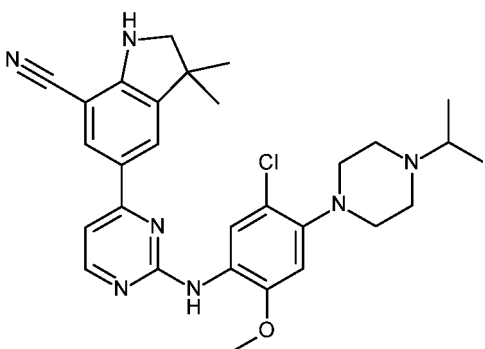
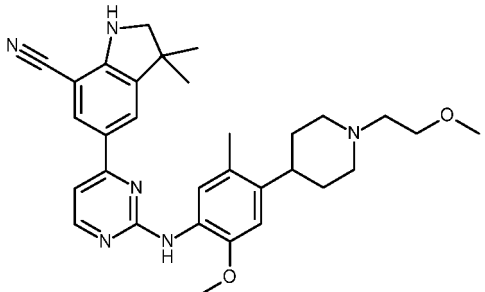
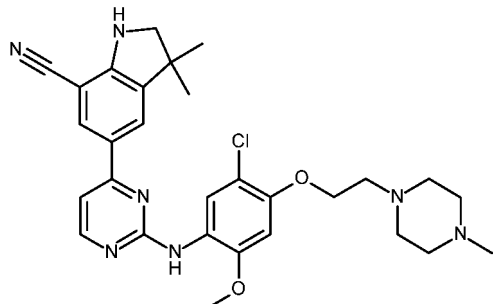
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(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 88	 From intermediate 301	8 Procedure with DCM/TF A (2:1, v/v)	10
Compound 89	 From intermediate 304	38	53
Compound 90	 From intermediate 306	9.2 off-white solid	11
Compound 91	 From intermediate 310	22 Procedure with DCM/TF A (2:1, v/v)	24

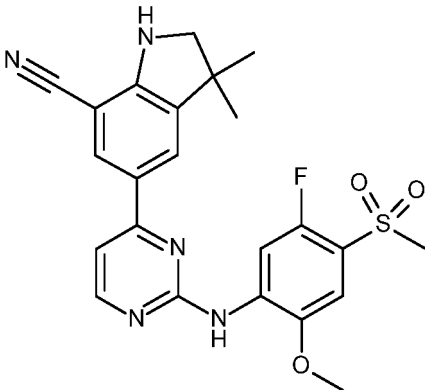
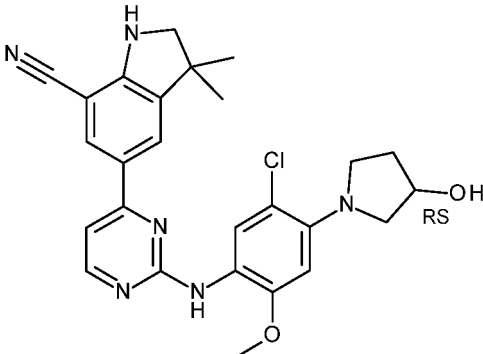
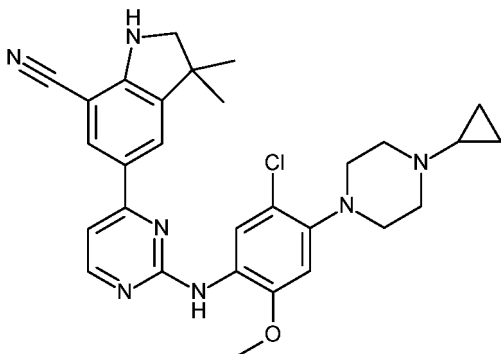
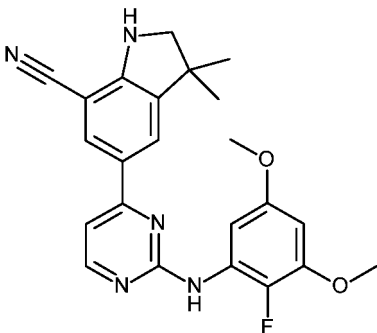
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(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 92	 From intermediate 312	51 <i>pale yellow solid</i>	54
Compound 93	 From intermediate 315	56 <i>pale yellow solid</i>	58
Compound 94	 From intermediate 320	26 <i>pale yellow solid</i>	27
Compound 95	 From intermediate 323	5 <i>yellow solid</i> Procedure with DCM/TF A (2:1, v/v)	5

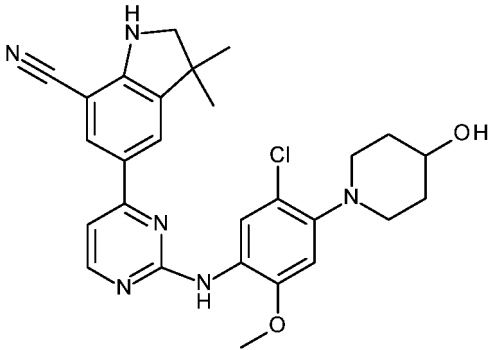
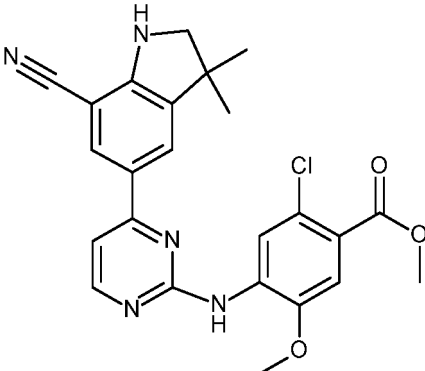
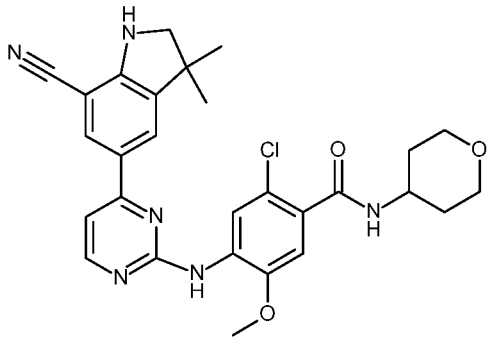
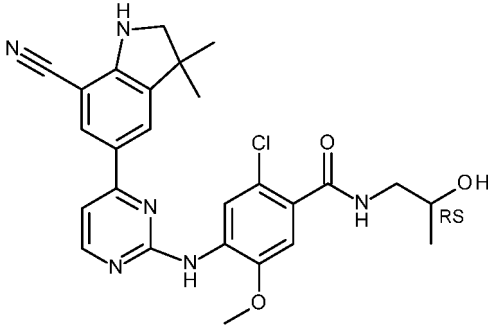
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(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 96	 From intermediate 327	27 <i>tan solid</i> Procedure with DCM/TF A (2:1, v/v)	32
Compound 97	 From intermediate 330	42 <i>pale yellow solid</i>	47
Compound 98	 From intermediate 333	38 <i>pale yellow solid</i>	55
Compound 104	 From intermediate 346	63 Procedure with DCM/TF A (10:3, v/v)	29

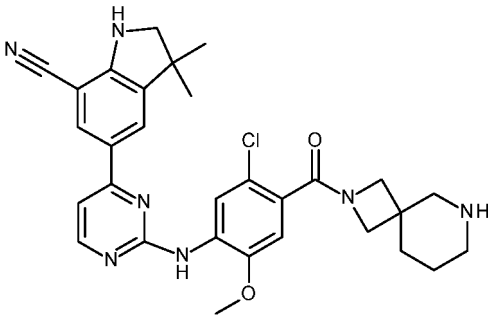
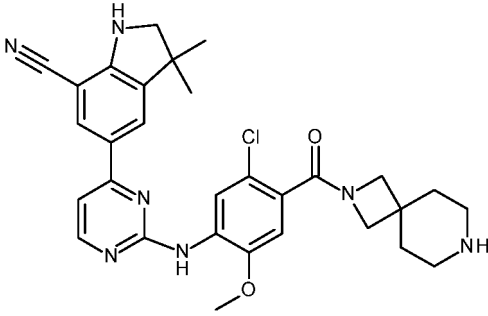
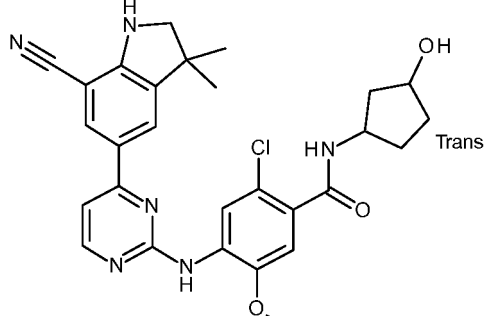
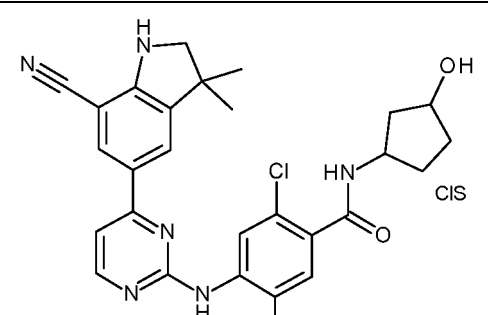
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(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 105	 From intermediate 347	113 Procedure with DCM/TF A (9:1, v/v)	24
Compound 106	 From intermediate 352	27 Procedure with DCM/TF A (10:1, v/v)	33
Compound 108	 From intermediate 355	10 Procedure with DCM/TF A (10:1, v/v)	15
Compound 112	 From intermediate 363	16 Procedure with DCM/TF A (10:1, v/v)	23

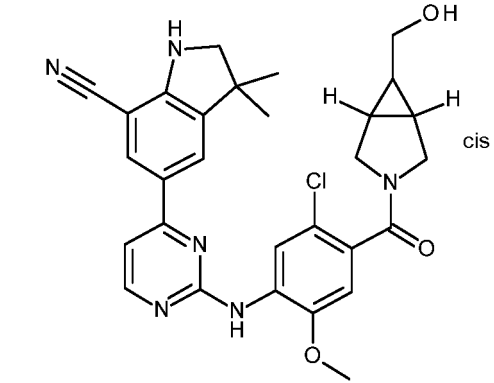
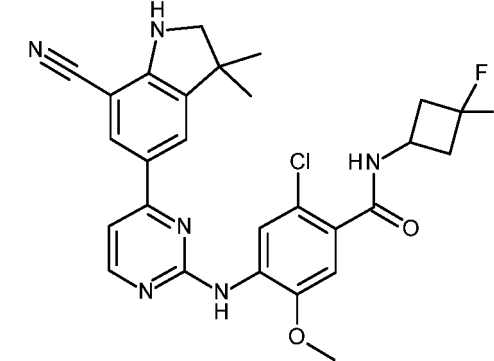
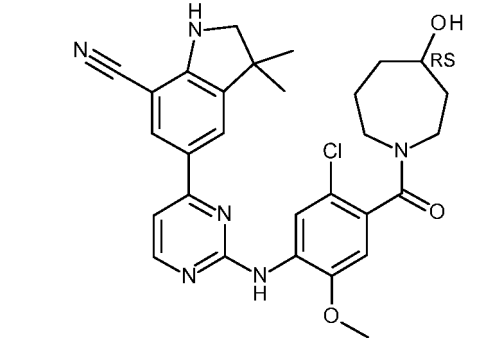
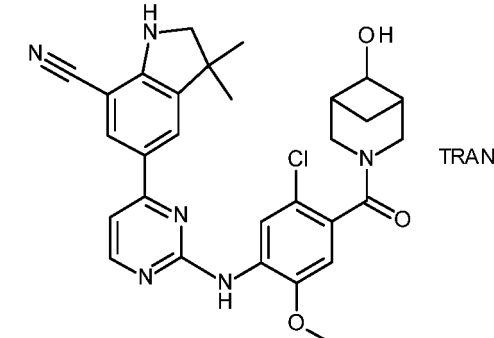
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(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 113	 From intermediate 364	16 Procedure with DCM/TF A (5:1, v/v)	17
Compound 114	 From intermediate 365	10 Procedure with DCM/TF A (11:1, v/v)	15
Compound 115	 TRANS; From intermediate 366	36.5 Procedure with DCM/TF A (5:1, v/v) <i>white solid</i>	40
Compound 116	 CIS; From intermediate 367	6.8 Procedure with DCM/TF A (3:1, v/v) <i>yellow solid</i>	6

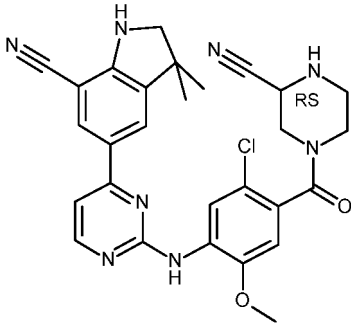
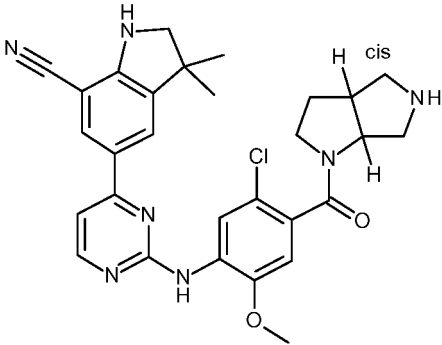
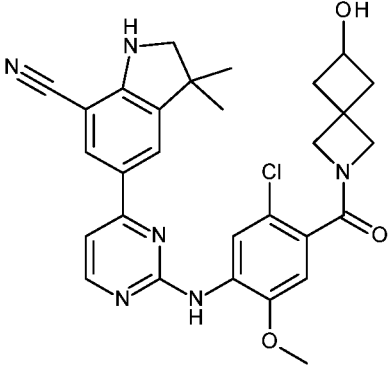
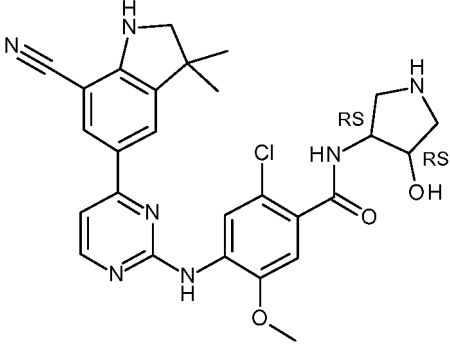
EP 3 405 196 B1

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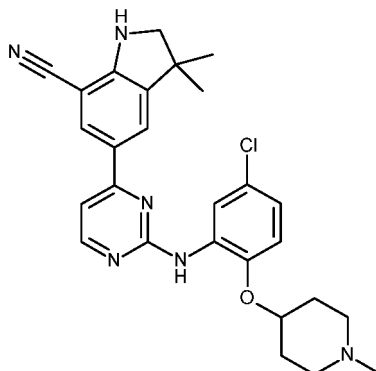
Compound number	Structure	Mass (mg)	Yield (%)
Compound 117	 CIS; From intermediate 368	45 <i>white solid</i>	53
Compound 118	 From intermediate 369	42 <i>white solid</i> Procedure with DCM/TF A (3:1, v/v)	45
Compound 119	 From intermediate 370	60 <i>white solid</i>	44
Compound 120	 TRANS From intermediate 371	50 <i>white solid</i>	85

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(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 121	 From intermediate 372	20	39
Compound 122	 CIS; From intermediate 373	56 white solid	58
Compound 123	 From intermediate 374	16 white solid	19
Compound 124 (mixture of 4 unseparated diastereoisomers)	 From intermediate 375	40 white solid	54

Example B8

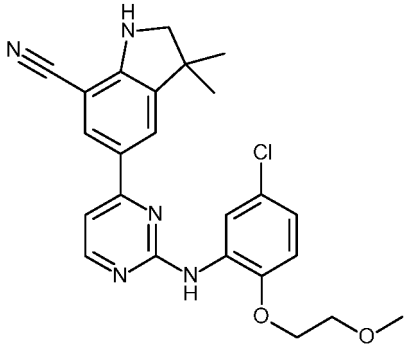
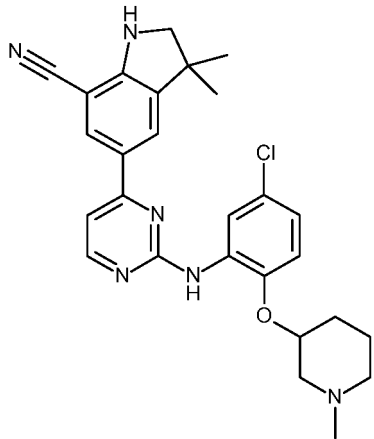
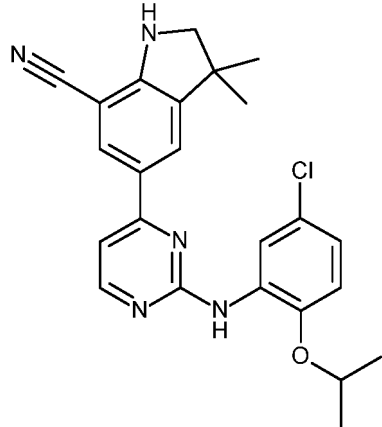
[0835] Preparation of compound 80:

[0836] HCl (3M in H₂O) (1.72 mL, 5.16 mmol) was added to a solution of intermediate 281 (304.00 mg, 0.52 mmol) in EtOAc (19.3 mL) and the reaction mixture was stirred 2 h at rt. The reaction was checked by LC/MS after 2 h but no conversion was observed. Also, the reaction was heated at 45 °C overnight. In order to speed the conversion, the temperature was elevated until 65°C for one more day. After completion of the reaction, the resulting mixture was cooled to rt, 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 (183 mg, yellow oil) was purified by column chromatography on silica gel (irregular SiOH, 24 g, mobile phase: NH₄OH/MeOH/DCM, gradient from 0% NH₄OH, 0% MeOH, 100% DCM to 1.5% NH₄OH, 15% MeOH, 85% DCM). The fractions containing the product were evaporated. The residue (103 mg, yellow oil) was purified by reverse phase semi-preparative HPLC (Stationary phase: X-Bridge-C18, 5 μm 30 x 150 mm, mobile phase: gradient from 40% NH₄HCO₃ 0.5%, 60% MeOH to 0% NH₄HCO₃ 0.5%, 100% MeOH). The fractions containing the product were concentrated to give a colorless oil. The residue (60 mg) was precipitated with Et₂O to give 54 mg of compound 78 (21% yield, white powder). M. P = 192 °C (K).

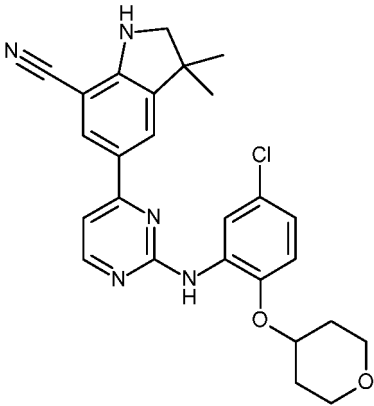
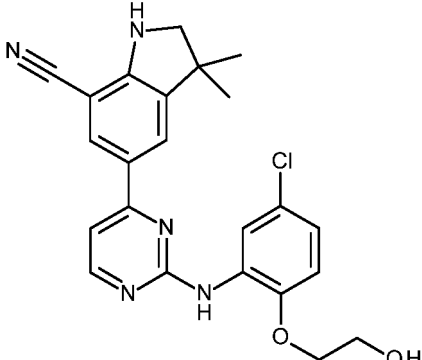
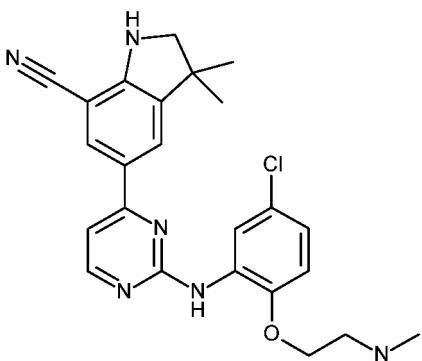
[0837] The compounds in the Table below were prepared by using an analogous method as the one reported for the preparation of compound 80 starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Mass (mg)'.

Compound number	Structure	Mass (mg)	Yield (%)
compound 99	From intermediate 337	63 <i>white powder</i> Procedure with MeOH as solvent	36

(continued)

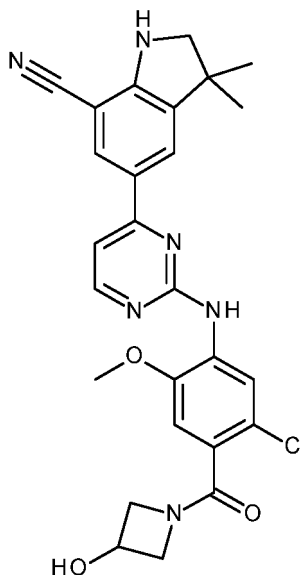
Compound number	Structure	Mass (mg)	Yield (%)
Compound 100	 From intermediate 338	18 <i>white powder</i> Procedure with MeOH as solvent	11
Compound 101	 From intermediate 339	40 <i>white powder</i> Procedure with MeOH as solvent	26
Compound 102	 From intermediate 342	80 (100% purity based on LC/MS) Procedure with EtOAc as solvent <i>white powder</i> 22 Procedure with MeOH as solvent (100% purity based on LC/MS) <i>white powder</i>	23 44

(continued)

Compound number	Structure	Mass (mg)	Yield (%)
Compound 103	 From intermediate 345	83 <i>yellow powder</i>	20
Compound 107	 From intermediate 353	15 <i>white powder</i> Procedure with MeOH as solvent	26
Compound 109	 From intermediate 356	48 <i>yellow powder</i> Procedure with MeOH as solvent	63

Example B9

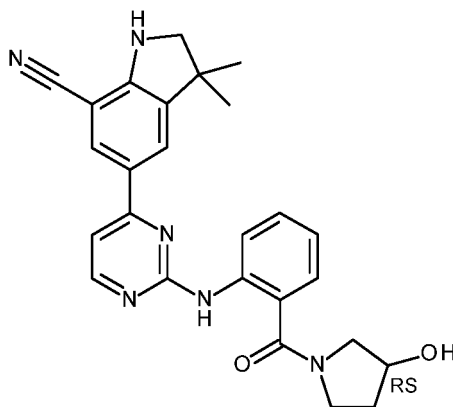
[0838] Preparation of compound 110:



[0839] A mixture of intermediate 357 (160.00 mg, 0.26 mmol) in HCl/Dioxane (4M) was stirred at rt for 3 h. The mixture was evaporated under vacuo and purified by high-performance liquid chromatography (Column: Waters Xbridge Prep OBD C18 150 x 30, 5 μ m, mobile phase: water (0.05 % ammonia hydroxide v/v)/CH₃CN, gradient from 33% to 63% of CH₃CN in 10 min, then 100% of CH₃CN in 3 min with a flow rate of 25 mL/min). The desired fractions were collected, and the solvent was concentrated in vacuum to give 38 mg of compound 110 (28% yield).

Example B10

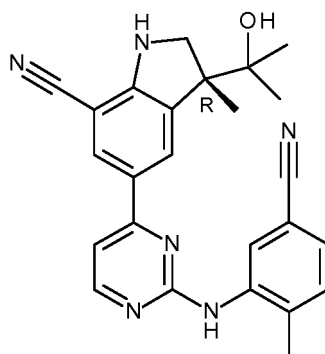
[0840] Preparation of compound 111:



[0841] TBAF (1M in THF) (0.59 mL, 0.59 mmol) was added to a solution of intermediate 362 (168.00 mg, 0.29 mmol) in Me-THF (5 mL) and the reaction mixture was stirred at rt for 4 h. The reaction mixture was diluted with EtOAc and poured onto a 10% aqueous solution of K₂CO₃. The organic layer was decanted, washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The residue was crystallized from CH₃CN/DiPE and the precipitate was filtered and dried to give 102 mg of compound 111 (76% yield). M.P. = 219°C (K).

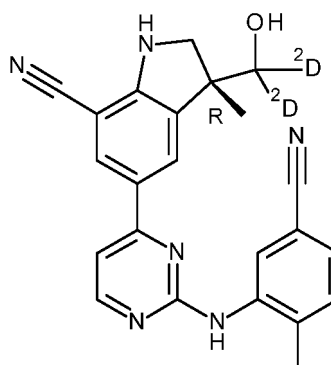
Example B11

[0842] Preparation of compound 135:



[0843] TFA (0.88 mL, 11.50 mmol) was added dropwise to a solution of intermediate 383 (178.00 mg, 0.34 mmol) in DCM (stabilized with amylene) (6 mL) at 5 °C and the reaction mixture was stirred for 30 min at this temperature. The reaction mixture was quenched with 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 was purified by column chromatography on silica gel (irregular $SiOH$, 24 g, mobile phase: DCM/MeOH, gradient from 97:3 to 95:5). The pure fractions were collected and evaporated to dryness. The residue (98 mg) was purified by chromatography over silica gel by achiral SFC (Stationary phase: 2-ethylpyridine 6 μm 150 x 21.2 mm, mobile phase: 75% CO_2 , 25% MeOH (0.3% $iPrNH_2$)). The pure fractions were mixed and the solvent was evaporated. The residue (52 mg) was crystallized from Et_2O , filtered and dried to give 25 mg of compound 135 (17% yield).

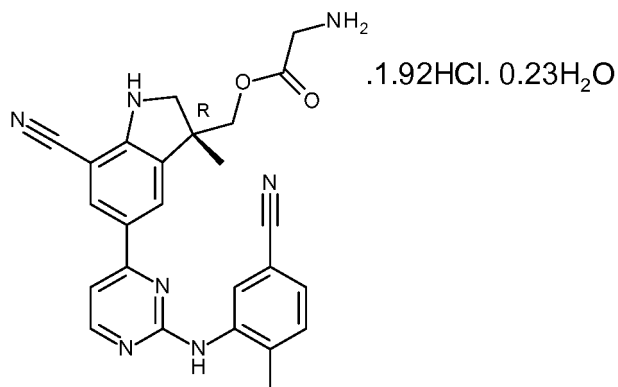
[0844] Preparation of compound 136:



[0845] TFA (0.77 mL, 10.02 mmol) was added dropwise to a solution of intermediate 384 (147.00 mg, 0.29 mmol) in DCM (stabilized with amylene) (5 mL) at 5 °C and the reaction mixture was stirred for 1 h at this temperature. The reaction mixture was quenched with 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 was purified by column chromatography on silica gel (irregular $SiOH$, 24 g, mobile phase: DCM/MeOH, gradient from 97:3 to 95:5). The pure fractions were collected and evaporated to dryness. The residue (44 mg) was purified by reverse phase (stationary phase: YMC-actus Triart-C18, 10 μm , 30 x 150 mm, mobile phase: gradient from 60% NH_4HCO_3 0.2%, 40% MeOH to 0% NH_4HCO_3 0.2%, 100% MeOH). The mixture was taken up by CH_3CN , filtered and dried to give 24 mg of compound 136 (20% yield).

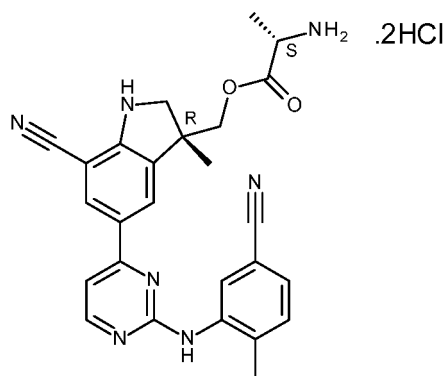
Example B12

[0846] Preparation of compound 137:



[0847] HCl (4M in dioxane) (8 mL; 32.24 mmol) was added at room temperature to a solution of intermediate 385 (3.57 g; 6.45 mmol) in ACN (95 mL) and the reaction mixture was stirred for 3 hours. The suspension was sonicated for 15 min and, then, the precipitate was filtered, washed with ACN and dried at 50°C under vacuo yielding 2.92g (86%) of compound 137, M.P.: 290°C (DSC).

[0848] Preparation of compound 138:



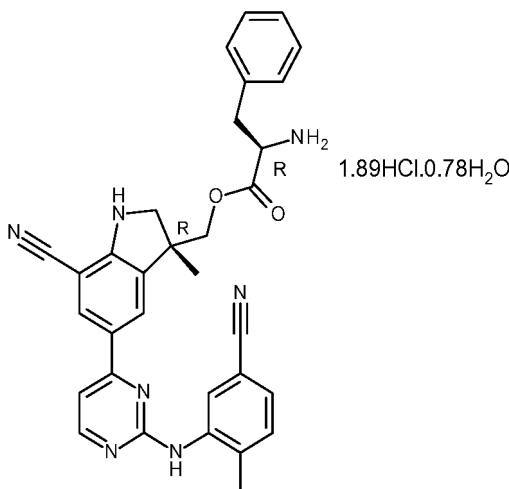
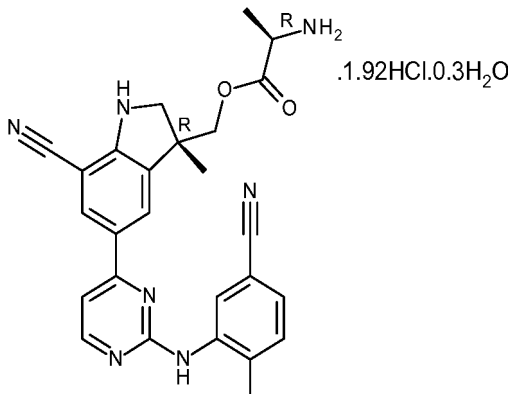
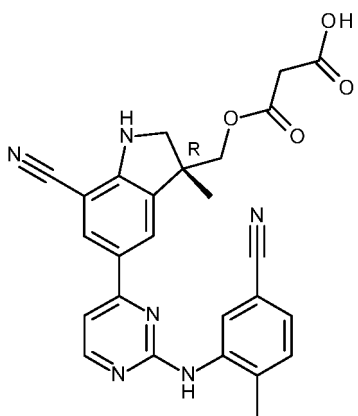
[0849] HCl (4M in dioxane) (35.2 mL; 140.93 mmol) was added at room temperature to a solution of intermediate 386 (16 g; 28.19 mmol) in ACN (400 mL) and the reaction mixture was stirred for 3 hours. Then, the suspension was sonicated for 30 minutes. The precipitate was filtered, washed with ACN and dried yielding 14.21g (93%) of compound 138.

[0850] The compounds in the Table below were prepared by using an analogous method as reported for the preparation compounds 137 and 138, starting from the respective starting materials.

Intermediate number	Structure	Mass (mg)	Yield (%)
Compound 139	Chemical structure of compound 139, shown as a salt with 1.92 HCl and 1.17 H₂O. From intermediate 387	230	54

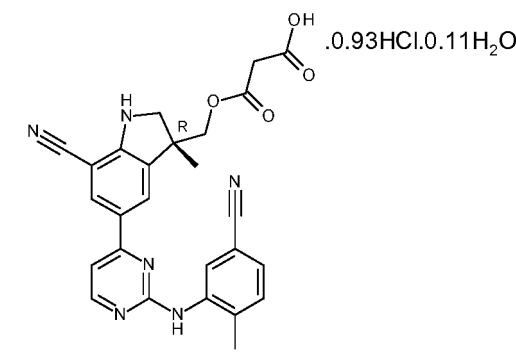
EP 3 405 196 B1

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Compound 140	 From intermediate 388	563	72
Compound 141	 From intermediate 389	241	88
Compound 142a	 From intermediate 390	80	24

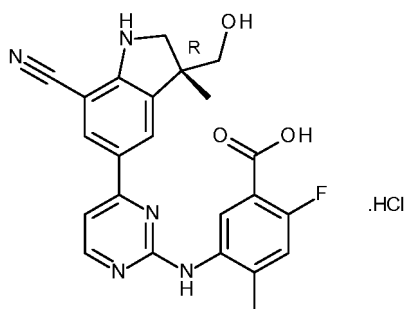
EP 3 405 196 B1

(continued)

Intermediate number	Structure	Mass (mg)	Yield (%)
Compound 142b	 From intermediate 390	200	47

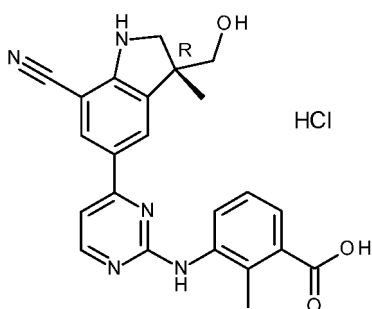
Example B13

[0851] Preparation of compound 182:



[0852] A solution of lithium hydroxide (213 mg; 5.074 mmol) in water (5 mL) was added to a solution of intermediate 483 (570 mg; 1.015 mmol) in THF (25 mL) and the reaction mixture was stirred for 18 hours. A solution of lithium hydroxide (213 mg; 5.074 mmol) in water (2 mL) was added again and the reaction mixture was stirred at room temperature for 24 hours more. The reaction mixture was heated at 60°C for 4 hours. The reaction mixture was acidified with 3N aqueous HCl, diluted with ACN and concentrated. The residue was crystallized from water. The precipitate was filtered and dried to give 402 mg (84%) of compound 182.

[0853] Preparation of compound 202:

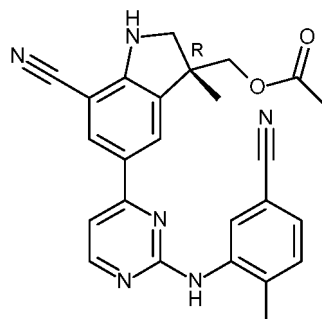


[0854] Compound 202 was prepared following an analogous method than the one used for the preparation of compound 182 starting from intermediate 522 (491 mg; 84%).

C. Conversion of the final compounds

Example C1

[0855] Preparation of compound 125:

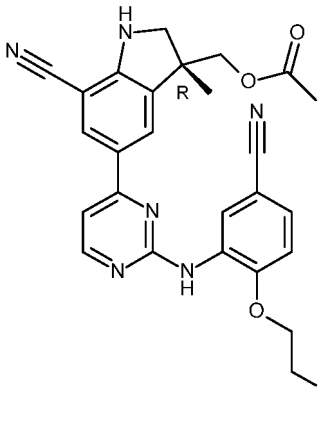
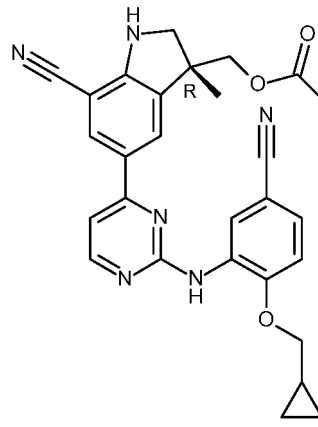


[0856] DIPEA (2.16 mL, 12.51 mmol) was added dropwise at 5 °C to a mixture of compound 1 (992.00 mg, 2.50 mmol), acetic acid (0.28 mL, 5.00 mmol) and HATU (3.80 g, 10.01 mmol) in a mixture of THF (4.07 mL) and DMF (3.88 mL). The mixture was stirred at rt overnight. Then, water was added and the reaction mixture was extracted with DCM. The organic layer was decanted, dried over MgSO₄, filtered and evaporated to dryness. The residue (2 g, yellow oil) was purified by column chromatography on silica gel (irregular SiOH, 120 g, mobile phase: DCM/MeOH, gradient from 100:0 to 98:2). The fractions containing the product were collected and evaporated to dryness to give 566 mg of a first batch of compound 125 (58% purity based on LC/MS, yellow oil). The others fractions were collected and evaporated to dryness to give a second batch of compound 125 (800 mg, yellow oil). This batch was purified again by column chromatography on silica gel (irregular SiOH, 40 g, mobile phase: DCM, 100%). The fractions containing the products were gathered and evaporated. The residue (563 mg, yellow powder) was taken up with CH₃CN to provide 393 mg of compound 125 (36% yield, yellow powder). M.P = 213 °C (K).

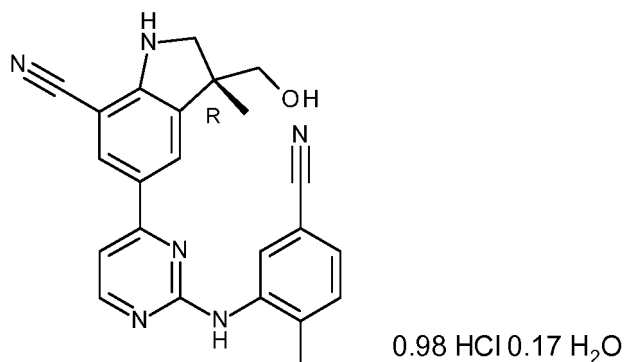
[0857] The compounds in the Table below were prepared by using an analogous method as the one reported for the compound 125 starting from the respective starting materials. The most relevant minor deviations to the referenced method are indicated as additional information in the column 'Mass (mg)'.

Compound number	Structure	Mass (mg)	Yield (%)
Compound 126	From compound 1	30 <i>white powder</i>	6

(continued)

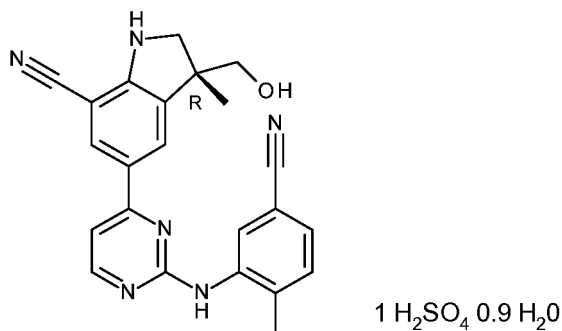
Compound number	Structure	Mass (mg)	Yield (%)
Compound 127	 From compound 66	55 white powder	18
Compound 128	 From compound 13	40 white powder	32

Example C2

[0858] Preparation of compound 129:

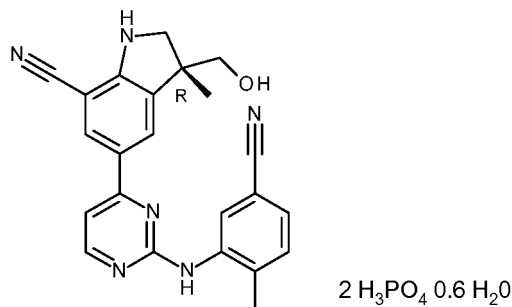
[0859] HCl (4M in dioxane) (126.00 μ L, 0.50 mmol) was added dropwise at 5 °C to a suspension of compound 1 (200.00 mg, 0.50 mmol) in CH₃CN (20 mL). The reaction mixture was allowed to warm to rt and stirred overnight. The precipitate was filtered, washed with CH₃CN and dried at 50 °C under vacuum all over the week end to give 204 mg of compound 129 (93% yield). M.P. = 190 °C (K).

Example C3

[0860] Preparation of compound 130:

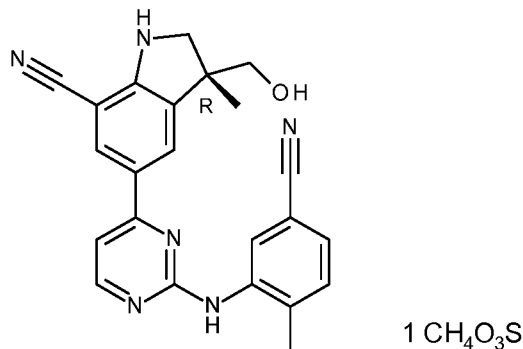
[0861] Aqueous H₂SO₄ (3M) (168.00 μL, 0.50 mmol) was added dropwise at 5 °C to a suspension of compound 1 (200.00 mg, 0.50 mmol) in CH₃CN (20 mL). The reaction mixture was allowed to warm to rt and stirred overnight. The precipitate was filtered, washed with CH₃CN and dried at 50 °C under vacuum all over the week end to give 214 mg of compound 130 (83% yield). M.P. = 264 °C (K).

Example C4

[0862] Preparation of compound 131:

[0863] Phosphoric acid (3M) (168.00 μL, 0.50 mmol) was added dropwise at 5 °C to a suspension of compound 1 (200.00 mg, 0.50 mmol) in CH₃CN (20 mL). The reaction mixture was allowed to warm to rt and stirred overnight. The precipitate was filtered, washed with CH₃CN and dried at 50 °C under vacuum all over the week end to give 228 mg of compound 131 (75% yield). M.P. = 174 °C (K).

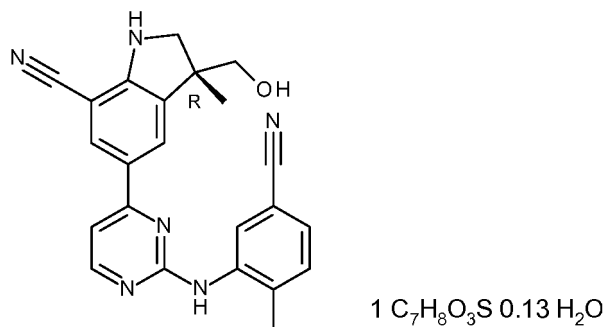
Example C5

[0864] Preparation of compound 132:

[0865] Methanesulfonic acid (33.00 μL , 0.50 mmol) was added dropwise to a suspension of compound 1 (200.00 mg, 0.50 mmol) in CH_3CN (20 mL). The reaction mixture was stirred overnight. The precipitate was filtered, washed with Et_2O and dried at 50 °C under vacuum to give 115 mg of compound 132 (46% yield). M.P. = 234 °C (K).

Example C6

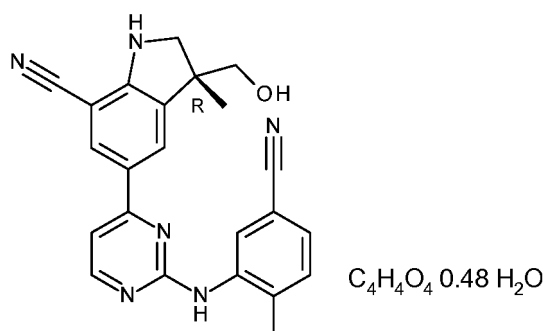
[0866] Preparation of compound 133:



[0867] A solution of p-toluenesulfonic acid, monohydrate (96.00 mg, 0.50 mmol) in water (0.5 mL) was added dropwise to a suspension of compound 1 (200.00 mg, 0.50 mmol) in CH_3CN (20 mL). The reaction mixture was stirred overnight. The precipitate was filtered, washed with Et_2O and dried at 50 °C under vacuum to give 229 mg of compound 133 (79% yield). M.P. = 262 °C (K).

Example C7

[0868] Preparation of compound 134:



[0869] A solution of maleic acid (58.56 mg, 0.50 mmol) in CH_3CN (0.50 mL) and water (0.50 mL) was added dropwise to a suspension of compound 1 (200.00 mg, 0.50 mmol) in CH_3CN (20 mL). The reaction mixture was allowed to warm to rt and stirred overnight. The precipitate was filtered, washed with Et_2O and dried at 50 °C under vacuum to give 169 mg of compound 134 (65% yield). M.P. = 190 °C (K).

Example C8

[0870] Preparation of compound 143:



20 **[0872]** Fraction A was taken up with toluene, then EtOH and the solvent was evaporated to dryness. The precipitate was taken up with ACN, filtered and dried yielding 233 mg of Fraction B (97%).

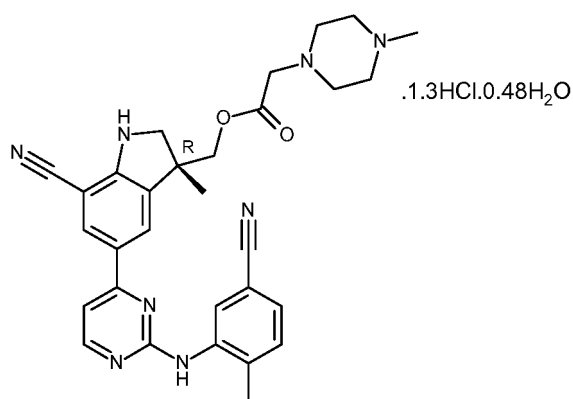
[0874] Preparation of compound 144:



45 **[0876]** Fraction A was washed with water then acetone and dried yielding 127 mg (51%) of compound 144.

50

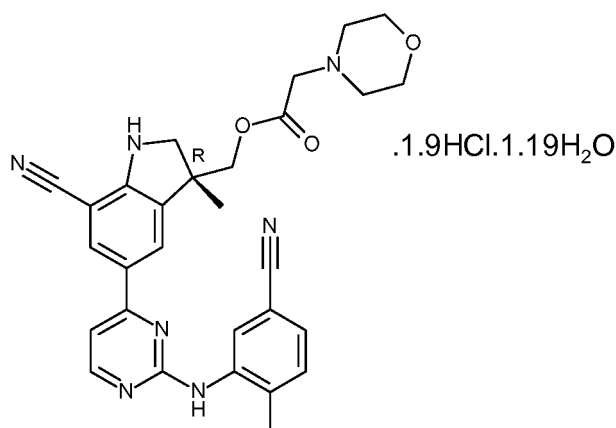
55



[0878] A mixture of compound 1 (250 mg; 0.63 mmol), 4-methyl-1-piperazineacetic acid (249 mg; 1.58 mmol), HATU (599 mg; 1.58 mmol), DIPEA (543 μ L; 3.15 mmol) and

[0879] DMAP (4 mg; 0.034 mmol) in DMF (7.5 mL) was stirred at room temperature for 18 hours. The solution was poured onto water and extracted with EtOAc. The organic layer was washed with H₂O, then brine, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 24g; mobile phase: 0.2% NH₄OH, 2% MeOH, 98% DCM to 0.5% NH₄OH, 5% MeOH, 95% DCM). The pure fractions were collected and evaporated to dryness yielding 395 mg of an intermediate fraction which was dissolved in ACN (15 mL). The solution was cooled to 5°C and HCl (4M indioxane) (473 μ L; 1.89 mmol) was added. The suspension was stirred for 3 hours and the precipitate was filtered and dried yielding 203 mg (54%) compound 145, M.P.: gum at 216°C (Kofler).

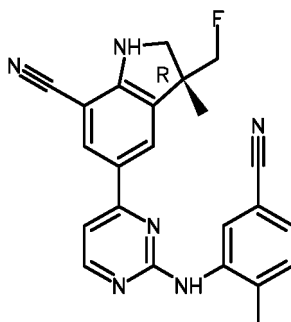
[0880] Preparation of compound 146:



[0881] Compound 146 was prepared following a similar procedure than the one used for the preparation of compound 145 starting from compound 1 and 4-methyl-1-morpholine acetic acid. 86 mg (22%) of compound 146 were obtained, gum at 186°C (Kofler).

Example C10

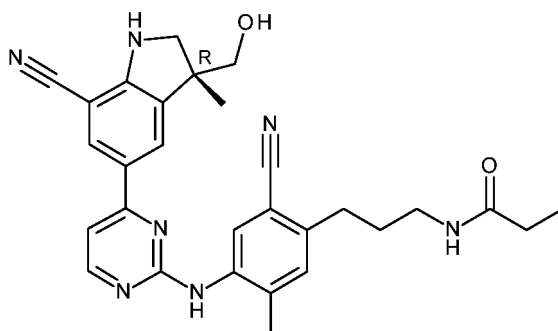
[0882] Preparation of compound 164:



[0883] Diethylaminosulfur trifluoride (0.247 mL; 2.02 mmol) was added to a solution of compound 1 (200 mg; 0.504 mmol) in THF (7 mL) at -78°C. After 2 hours, diethylaminosulfur trifluoride (0.247 mL; 2.02 mmol) was added again and the mixture was stirred at rt for 20 hours. The mixture was poured into ice. The obtained precipitate was filtered off. The mother layer was basified by potassium carbonate and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent was evaporated. The residue was purified by chromatography over silica gel (50g, 15-40 μm, solid deposit, eluent: DCM/MeOH: 100/0 to 95/5). The pure fractions were mixed and the solvent was evaporated. The resulting residue (0.05g) was purified via achiral SFC (stationary phase: diethylaminopropyl 5μm150x21.2mm, mobile phase: 85% CO₂, 15% MeOH). The pure fractions were mixed and the solvent was evaporated to give 0.02 g (10%) of compound 164. M.P.=194°C (Kofler).

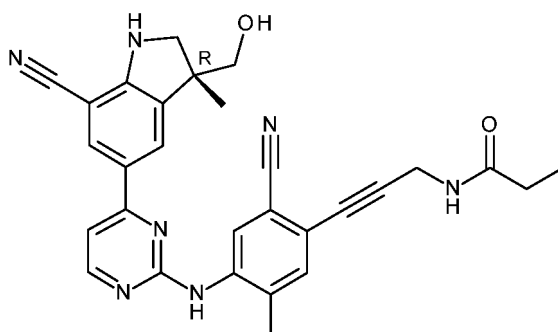
Example C11

[0884] Preparation of compound 172:



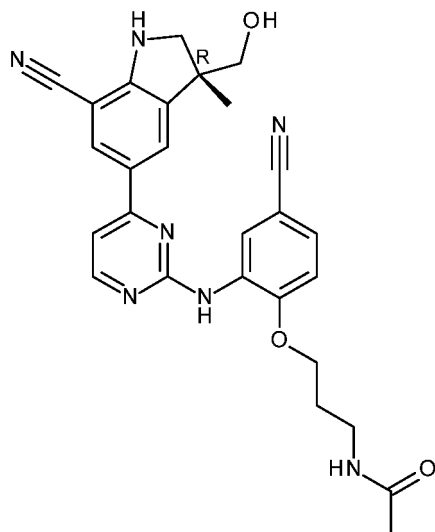
[0885] A mixture of compound 170 (39 mg; 0.086 mmol), propanoic acid (0.095 mL; 0.0946 mmol), HATU (36 mg; 0.0946 mmol) and DIPEA (0.0445 mL; 0.258 mmol) in DCM (0.8 mL) was stirred at room temperature for 18 hours. The solution was poured onto water and extracted with DCM. The organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 4 g; mobile phase: DCM/MeOH: 100/0 to 95/5). The pure fractions were collected and evaporated to dryness to give 20 mg (46%) of compound 172. MP = 193°C (Kofler).

[0886] Preparation of compound 176:



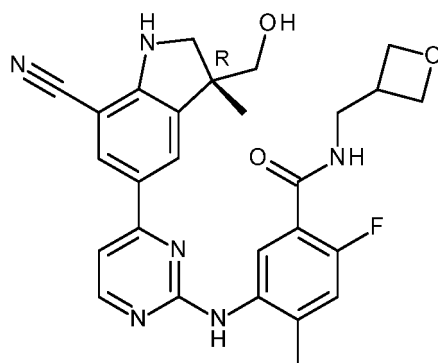
[0887] Compound 176 was synthesized by using an analogous method than the one used for the preparation of compound 172 above, starting from compound 171 (21 mg; 20%).

[0888] Preparation of compound 181:



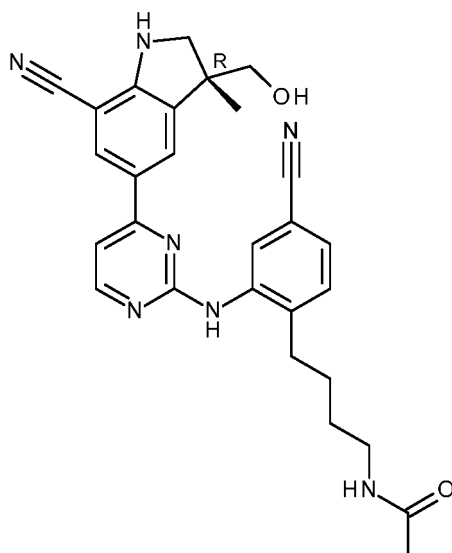
[0889] Compound 181 was synthesized by using an analogous method as the one used for the preparation of compound 172, starting from compound 180 (4 mg; 18%).

[0890] Preparation of compound 183:



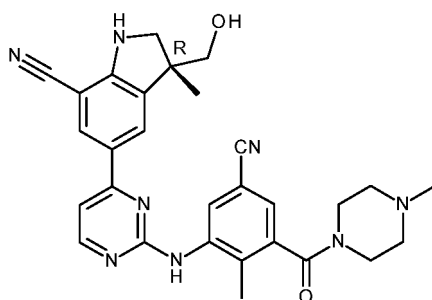
[0891] Compound 183 was synthesized by using an analogous method (solvent: DCM/THF/DMF: 50/50/5) as the one used for the preparation of compound 172, starting from compound 182 (280 mg; 65%; MP = 209°C; DSC).

[0892] Preparation of compound 185:



[0893] Compound 184 was synthesized by using an analogous method (solvent: DCM/THF) than the one used for the preparation of compound 172, starting from compound 184 (35 mg; 45%; MP = gum at 156°C; Kofler).

[0894] Preparation of compound 203:



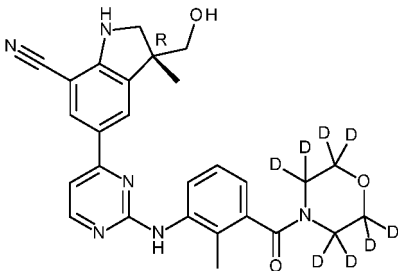
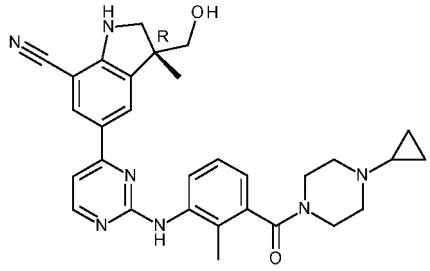
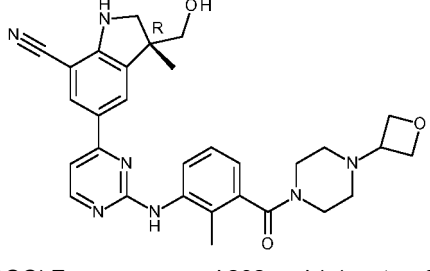
[0895] A mixture of compound 201 (260 mg; 0.38 mmol), 1-methylpiperazine (63 μ L; 0.57 mmol), HATU (159 mg; 0.42 mmol) and DIEA (265 μ L; 1.52 mmol) in DCM (10 mL) was stirred at room temperature for 18 hours. Water was added and the reaction mixture was extracted with DCM. The organic layer was filtered through chromabond® and evaporated to dryness. The residue was purified (180 mg) by chromatography over silica gel (irregular SiOH, 10g; mobile phase: gradient from 0.3% NH_4OH , 3% MeOH, 97% DCM to 1.5% NH_4OH , 15% MeOH, 85% DCM). The pure fractions were collected and evaporated to dryness. The residue was taken up with ACN and the precipitate was filtered and dried yielding 72 mg (36%) of compound 203. M.P.: 294°C (DSC).

[0896] The compounds in the table below were prepared using an analogous method as described for the preparation of compound 203, starting from the respective starting materials.

Compound number	Structure	Quantity	Yield
Compound 204		78 mg	40%
	From compound 201 and intermediate 524		

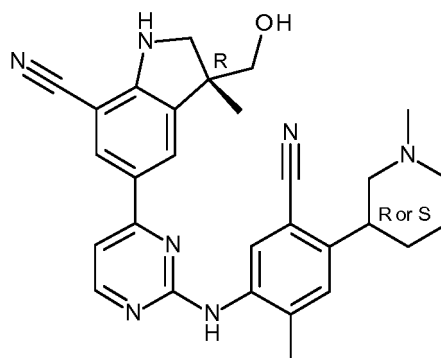
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(continued)

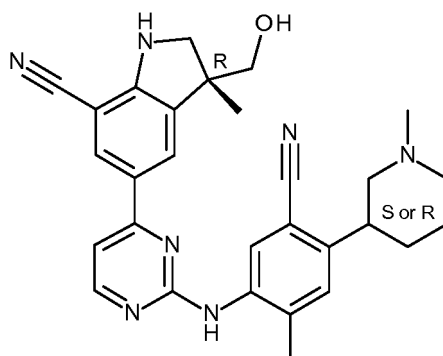
Compound number	Structure	Quantity	Yield
Compound 205	 From compound 202 and morpholine-d8	331 mg	38%
Compound 206	 From compound 202 and 1-cyclopropylpiperazine	205 mg	71%
Compound 207	 M.P.: 268°C (DSC) From compound 202 and 1-(oxetan-3-yl)piperazine	200 mg	67%

Example C12

[0897] Preparation of compound 178



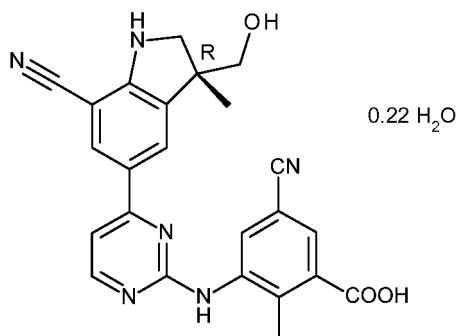
and compound 179



[0898] Compound 178 and compound 179 were obtained from an achiral SFC purification (stationary phase: Chiralpak IC 5 μ m 250x20mm, mobile phase: 50% CO₂, 50% EtOH (0.3% iPrNH₂)). The fractions containing the products were mixed and the solvent was evaporated to afford respectively 47 mg of compound 178 and 43 mg of compound 179.

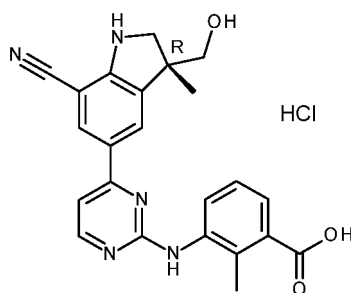
Example C13

[0899] Preparation of compound 201:



[0900] A solution of LiOH.H₂O (77 mg; 1.83 mmol) in distilled water (2 mL) was added to a solution of compound 8 (166 mg; 0.365 mmol) in THF (10 mL) and the reaction mixture was stirred for 18 hours. The reaction mixture was acidified with 6N aqueous HCl, diluted with ACN and concentrated. The residue was crystallized from water/ACN. The precipitate was filtered, washed with water and dried yielding 118 mg (72%) of compound 201. M.P.: 220°C (gum, Kofler).

[0901] Preparation of compound 202:



[0902] Compound 202 was prepared following an analogous method than the one used for the preparation of compound 501 starting from intermediate 522 (491 mg; 84%).

Analytical Part

LCMS (Liquid chromatography/Mass spectrometry)

[0903] 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).

[0904] 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 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	Run time
					Column T	
Method 1	Waters: Acquity UPLC [®] -DAD and Quattro Micro [™]	aters: BEH C18 (1.7 μ m, 2.1 x 100 mm)	A: 95% CH ₃ COONH ₄ 7 mM / 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 μ m, 2.1 x 100m m)	A: 95% CH ₃ COONH ₄ 7 mM / 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 μ m, 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	Waters: Acquity UPLC [®] H-Class - DAD and QDa	BEH [®] -C18 (1.7 μ m, 2.1 x 1000 mm)	A: 95% CH ₃ COONH ₄ 7 mM/5% CH ₃ CN, B: CH ₃ CN	95% A to 5% A in 1 min, held for 1.6 min, back to 95% A in 1.2 min, held for 0.5 min.	0.5	3.3
					40	
Method 5	Agilent 1200 equip with MSD 6110	XBridge ShieldRP18 (5 μ m, 2.1x50 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	10
					40	
Method 6	Waters: Micromass ZQ2000 - Waters Acquity UPLC system equipped with PDA detector	Acquity HST - C 18 (1.8 μ M, 2.1 x 100 mm)	A: 95% Water (with 0.1% CH ₃ COOH), B: CH ₃ CN (with 0.1% CH ₃ COOH)	95% A held 0.4 min, then from 95% A to 5% A 5.2 min, held for 0.8 min.	0.4	6.4
					40	
Method 7	Agilent 1100	ACE C18 column (3 μ M, 3.0 x 50 mm)	A: 95% Water (with 0.05% TFA), B: CH ₃ CN	95% A to 0% A 5.2 min	2.2	6.4
					50	

(continued)

Method code	Instrument	Column	Mobile phase	gradient	Flow	Run time
					Column T	
Method 8	Agilent 1200 equip with MSD 6110	Phenomene x Luna-C18, 50×2mm, 5µm	A: H ₂ O (0.1% TFA), B: CH ₃ CN (0.05% 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 50	10
Method 9	Agilent 1200 equip with MSD 6110	Phenomene x Luna-C18, 50×2mm, 5µm	A :H ₂ O (0.1% TFA), B:CH ₃ CN (0.05% TFA)	90% A held for 0.8 mn then 90% A to 20% A in 3.7 mn, held for 2mn, back to 90% A in 2 mn, held for 0.5 min.	0.8 50	10
Method 10	Agilent 1290 Infinity DAD LC/MS G6110A	Phenomene x Kinetex C18 (50 x 2.1 mm, 1.7 µm)	A: 0.1% HCOOH in H ₂ O B: CH ₃ CN	From 90% A to 10% A in 1.5 min, held for 0.4 min, to 90% A in 0.1 min.	1.5 60	2.0
Method 11	Agilent 1100series DAD LC/MS G1956A	YMC ODS-AQC18 (50 x 4.6 mm, 3.0 µm)	A: 0.1% HCOOH in H ₂ O B: CH ₃ CN	From 95% A to 5% A in 4.8 min, held for 1.0 min, to 90% A in 0.2 min.	2.6 35	6.0
Method 12	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: CH ₃ CN	From 95% A to 5% A in 4.8 min, held for 1.0 min, to 95% A in 0.2 min.	2.6 35	6.0

Melting points

[0905] For a number of compounds, melting points (MP) were determined with a DSC1 (Mettler-Toledo). Melting points were measured with a temperature gradient of 10 °C/minute. Maximum temperature was 350 °C. Values are peak values. Indicated in the table as DSC.

[0906] For a number of compounds, melting points were obtained with a Kofler hot bench (indicated with (K) in the analytical table), consisting of a heated plate with linear temperature gradient, a sliding pointer and a temperature scale in degrees Celsius.

[0907] For a number of compounds, melting points were obtained with an automatic Melting Point Apparatus WRS-2A (indicated with WRS-2A in the analytical table). Melting points were measured with a temperature gradient of 5 °C per minute starting from room temperature to a maximum value of 320 °C.

[0908] 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 second) to a maximum value of 300 °C.

Table: Co. No. means compound number; Retention time (R_t) in min; MP means melting point (°C); dec means decomposition; n.d. means not determined.

Co. No.	MP (°C)	MP Method	R _t	[M+H] ⁺	LCMS Method	Co. No.	MP (°C)	MP Method	R _t	[M+H] ⁺	LCMS Method
1	222	DSC	2.71	397	1	3	-	-	2.95	506	1
2	-	-	2.82	504	1	4	193	DSC	2.23	429	1

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Co. No.	MP (°C)	MP Method	Rt	[M+H] ⁺	LCMS Method
5	115 (gum)	K	2.17	508	1
6	148 (gum)	K	2.49	504	1
7	215	DSC	3.01	424	1
8	184	K	2.44	443	1
9	120 (gum)	K	3.17	541	1
10	215	K	3.01	439	1
11	215	DSC	2.74	415	1
12	159	K	2.64	471	1
13	194	K	3.13	453	1
14	162	K	2.76	483	1
15	110 (gum)	K	1.32	439	4
16	162 (gum)	K	3.10	441	1
17	148	K	2.44	450	1
18	263	DSC	2.41	492	1
19	284	DSC	3.21	537	1
20	-	-	2.25	482	1
21	-	-	3.74	515	6
22	-	-	3.16	548	6
23	>260	K	2.67	520	6
24	-	-	3.93	452	6
25	-	-	3.26	505	6
26	195	DSC	2.72	396	6
27	289	DSC	3.04	405	6
28	-	-	3.15	534	6
29	210	DSC	3.35	426	1
30	224	DSC	3.14	456	1
31	295	DSC	2.79	413	1
32	274	DSC	2.97	417	1
33	239	DSC	3.13	422	1
34	184	K	3.06	466	1
35	192	K (gum)	3.40	531	1
36	263	K	2.99	510	1
37	221	K	2.88	525	1
38	190	K	2.54	486	2
39	173	K (gum)	2.73	505	2
40	236	K	2.41	452	2
41	>260	K	2.40	503	1
42	183	K	3.49	506	1
43	237	K	2.43	539	1
44	168	K	2.39	465	1

Co. No.	MP (°C)	MP Method	Rt	[M+H] ⁺	LCMS Method
45	169	K	3.06	466	1
47	>250	K	3.28	440	1
48	>250	K	3.28	440	1
49	172	K	3.29	460	1
50	190	K	2.65	566	1
51	200	K	3.29	484	1
52	217	K	3.34	476	1
53	245	K	2.51	477	1
54	154	K	2.69	477	1
55	135	K (gum)	2.72	560	1
56	170	K	2.70	463	1
57	188	K	3.06	466	1
58	183	K	2.38	532	1
59	267	DSC	3.12	507	1
60	132	K (gum)	2.38	513	1
61	-	-	2.70	516	1
62	228	DSC	2.29	434	1
63	262	K	2.37	463	1
64	160	DSC	2.18	464	1
65	218	K	2.45	397	2
66	165	K	2.74	457	1
67	188	DSC	2.19	508	1
68	-	-	2.19	546	1
69	157	DSC	2.87	450	1
70	237	DSC	2.97	451	1
71	210	DSC	2.97	423	1
72	189	DSC	3.20	464	1
73	201	DSC	2.55	466	1
74	124	K	2.86	455	1
75	228	K	2.75	481	1
76	-	-	3.37	484	2
77	-	-	2.85	484	2
78	-	-	4.15	483	6
79	-	-	5.55	491	6
80	192	K	3.81	489	6
81	-	-	3.67	518	6
82	-	-	4.68	507	6
83	-	-	3.69	532	6
84	-	-	4.82	436	6
85	-	-	5.10	484	6
87	-	-	3.71	532	6
88	-	-	5.83	450	6
89	-	-	3.72	548	6
90	-	-	5.47	454	6
91	-	-	3.46	502	6

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	Co. No.	MP (°C)	MP Method	Rt	[M+H] ⁺	LCMS Method		Co. No.	MP (°C)	MP Method	Rt	[M+H] ⁺	LCMS Method
	92	-	-	5.91	519	6		137	290	DSC	2.60	454	1
5	93	-	-	3.77	532	6		138	-	-	2.67	468	1
	94	-	-	3.62	527	6		139	202	K (gum)	2.90	496	1
	95	-	-	3.50	548	6		140	180	K (gum)	3.01	544	1
	96	-	-	4.97	468	6		141	212	K (gum)	2.57	468	2
10	97	-	-	4.59	491	6		142 a	138	DSC	2.11	483	1
	98	-	-	3.77	530	6		142 b	214	DSC	2.18	483	1
	99	120	K (gum)	4.15	515	1		143	>270	K	2.18	477	1
	100	171	K	3.61	450	1		144	-	-	2.17	477	1
15	101	104	K (gum)	3.76	489	1		145	216 (gum)	K	2.61	573	1
	102	112	K (gum)	4.01	434	1		146	186 (gum)	K	2.85	524	1
	103	126	K (gum)	3.66	476	1		147	-	-	1.32	415	7
	104	176	K	3.12	420	2		148	231	DSC	2.43	422	1
20	105	>250	K	3.20	505	1		149	-	-	3.27	444	9
	106	208	K	3.56	464	1		150	-	-	3.67	404	8
	107	176	K	3.22	436	1		151	122	-	2.75	430	9
	108	>260	K	2.97	533	1		152	229	DSC	2.43	420	1
25	109	152	K	2.93	449	1		153	144 (gum)	K	2.38	413	1
	110	-	-	4.95	505	5		154	250	WRS-2A	3.02	446	9
	111	219	K	2.65	455	1		155	218	DSC	2.38	447	1
	112	>260	K	2.77	507	1		156	206	DSC	2.58	489	2
	113	178	K	2.62	558	1		157	235	DSC	2.5	489	2
30	114	206	K (gum)	2.54	558	1		158	-	-	2.16	512	1
	115	-	-	5.04	533	5		159	140 (gum)	K	2.23	528	1
	116	-	-	5.10	533	5		160	206	K	2.43	443	1
	117	-	-	5.01	545	5		161	245	DSC	2.28	498	1
35	118	-	-	5.65	539	5		162	143	DSC	2.63	473	1
	119	-	-	5.07	547	5		163	150	K	2.04	498	1
	120	-	-	5.19	545	5		164	194	K	2.95	399	2
	121	193	K	5.03	543	5		165	224	DSC	2.41	451	1
40	122	-	-	3.22	544	3		166	116	DSC	2.15	516	1
	123	287	K	3.62	545	3		167	239	DSC	2.15	516	1
	124	-	-	5.07	534	5		168	246	DSC	2.42	503	1
	125	213	K	2.98	439	1		169	256	DSC	2.41	503	1
45	126	200	K	3.25	467	1		170	207	K	2.11	454	1
	127	158	K	3.01	499	1		171	249	K	2.19	450	2
	128	156	K (gum)	3.37	495	1		172	193	K	2.49	510	1
	129	190	K	2.70	397	1		173	183	DSC	2.57	510	1
50	130	264	K	2.71	397	1		174	211	DSC	2.66	498	1
	131	174	K	2.71	397	1							
	132	234	K	2.70	397	1							
	133	262	K	2.71	397	1							
	134	190	K	2.71	397	1							
55	135	166	K (gum)	2.91	425	1							
	136	219	K	2.76	397	1							

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Co. No.	MP (°C)	MP Method	Rt	[M+H] ⁺	LCMS Method
175	226	K	2.24	494	1
176	-	-	2.56	506	1
177	222	DSC	2.38	494	1
178	230	K	2.27	494	2
179	188 (gum)	K	2.26	494	2
180	194 (gum)	K	2.16	456	1
181	-	-	2.44	498	1
182	-	-	0.82	434	4
183	209	DSC	2.33	503	1
184	134 (gum)	K	2.15	454	1
185	156 (gum)	K	2.41	496	1
186	172	DSC	2.44	472	2
187	240	DSC	2.37	503	1
188	190	K	2.56	477	1
189	239	K	2.43	452	1
190	128	K	2.63	452	1
191	122	WRS-2A	2.42	438	9
192	250	WRS-2A	2.47	469	9
193	188 (gum)	K	2.32	427	1
194	193	DSC	2.88	524	2
195	210	K	2.70	484	1
196	240	K	2.84	502	1
197	223	DSC	2.99	499	1
198	222	DSC	2.98	501	1
199	170 (gum)	K	2.53	513	1
200	260	K	2.75	455	1
201	220 (gum)	K	1.78	441	1
203	294	DSC	2.23	523	1
204	297	DSC	2.23	526	1
205	201	K	2.28	493	1
206	238	DSC	2.53	524	1
207	268	DSC	2.15	540	1
208	234	DSC	2.59	462	2
209	254	DSC	3.12	457	1
210	--	-	2.34	441	9
211	160 (gum)	K	2.65	438	1
212	168	K	2.78	474	1

Co. No.	MP (°C)	MP Method	Rt	[M+H] ⁺	LCMS Method
213	304	WRS-2A	4.66	398	8
214	252	K	4.08	430	8
215	225	DSC	2.38	402	1
216	108 (gum)	K	2.25	455	1
217	151	DSC	2.18	459	1
218	115 (gum)	K	2.49	441	1
219	181	DSC	2.86	477	1
220	140	K	2.65	459	1
221	181	MP50	2.17	485	11
222	-	-	0.59	471	10
223	129	DSC	2.38	496	1
224	238	K	2.98	482	1
225	181	MP50	2.17	452	11
226	298	MP50	2.36	495	11
227	223	MP50	3.64	488	11
228	170	MP50	2.26	470	11
229	207	DSC	2.83	484	1
230	-	-	2.45	514	11
231	-	-	2.45	514	11
232	167	DSC	2.61	500	2
233	162	DSC	2.76	500	1
234	192	DSC	2.41	485	2
235	133	MP50	2.36	471	12
236	249	K	2.39	499	1
237	-	-	2.12	427	1
238	-	-	2.12	427	1
239	116 (gum)	K	2.05	415	1
240	259	K	2.57	479	1

OR

[0909] 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).

[0910] Specific rotation (OR): $[\alpha]_{\lambda}^{\theta} = (100 * \alpha) / (c * l)$

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.

[0911] θ is the temperature (°C) and λ the wavelength of the light used.

[0912] Unless otherwise indicated, temperature is 20 °C, and the sodium D line is used (589 nanometer).

[0913] OR data: Solvent: DMF (unless otherwise indicated); temperature : 20 °C (unless otherwise indicated); wavelength : 589 nm (unless otherwise indicated); 'Conc.' means concentration of the sample in grams per 100 mL; 'OR' means optical rotation (specific rotation); 'Co. No.' means compound number

Co. No.	OR (°)	Conc.
1	+ 48.33	0.3
2	+ 21.17	0.227
3	+ 17.21	0.215
4	+ 8.89	0.225
7	+ 27.2	0.261
8	+ 21.43	0.28
9	+ 29.92	0.264
10	+ 50	0.25
11	+ 43.61	0.342
12	+ 57.28	0.183
13	+ 64.29	0.28
14	+ 49.12	0.34
15	+ 35.19	0.27
16	+ 68.64	0.22
17	+ 18.08	0.26
18	+ 9.51	0.284
19	+ 47.99	0.292
20	+ 29.2	0.25

Co. No.	OR (°)	Conc.
45	+ 32.5	0.2
48	+ 29.63	0.27
57	- 35.2	0.25
59	+ 28.51	0.245
60	+ 15.2	0.25
61	+ 13.2	0.25
62	+ 15.84	0.227
63	+5.49	0.255
64	+ 20.63	0.16
65	-43.85	0.26
66	+ 60.43	0.23
67	+ 16.5	0.273
68	+ 16.15	0.26
69	+ 17.31	0.26
70	+ 17.31	0.26
71	+ 36.36	0.253
72	+ 21.60	0.25
73	+ 19.33	0.3

Co. No.	OR (°)	Conc.
74	+ 34.75	0.259
75	+ 28.18	0.33
125	+ 70.57	0.35
126	+ 74.52	0.231
127	+ 73	0.2
128	+ 100	0.2
129	+ 63.33	0.21
130	+ 52.08	0.221
131	+ 30.81	0.214
132	+ 43.6	0.241
133	+ 43.86	0.207
134	+ 36.19	0.21
135	+ 23.08	0.26
137	+51.55	0.258
138	+54.55	0.275
139	+58.54	0.205
140	+35.65	0.292
141	+87.5	0.28

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	Co. No.	OR (°)	Conc.
5	142a	+38.04	0.276
	142b	+69.96	0.273
	143	+65.15	0.264
	144	-64.35	0.264
	145	+74.44	0.266
10	146	+17.45	0.275
	148	+9.44	0.339
	149	+13.21	0.106 (MeOH)
15	150	+11.67	0.3
	151	+8.33	0.3 (MeOH)
	152	+13.01	0.269
	153	+61.94	0.258
20	154	+8.08	0.099 (MeOH)
	155	+11.07	0.262
	156	+12.41	0.29
25	157	+9.16	0.251
	158	+12 (at 436 nm)	0.25
30	159	+8.45	0.296
	160	+10.17	0.295
	161	+10.77	0.26
	162	+9.23	0.26
35	164	+43.6	0.25
	165	+13.31	0.338
	166	+12	0.275
	167	+9.42	0.276
	168	+4.12	0.267
40	169	+20.56	0.248
	170	+54	0.25
	171	+54.8	0.25
	173	+29.62	0.26
45	174	+31.79	0.28
	175	+34.64	0.28
	176	+25.94	0.266
	178	+9.66	0.29
50	179	+57.14	0.28
	180	+17.49	0.263

Co. No.	OR (°)	Conc.
183	+12.5	0.256
184	+34.2	0.269
185	+31.52	0.257
186	+7.58	0.264
187	+21.43	0.266
188	+ 26.18	0.275
189	+ 21.14	0.175
190	+ 29.42	0.258
191	+ 40	0.105 (MeOH)
192	+28	0.1 (MeOH)
193	+34.58	0.24
194	+22.91	0.227
195	+21.05	0.285
196	+28.46	0.26
200	+31.37	0.271
201	+29.44	0.248
203	+27.89	0.251
204	+27.09	0.251
205	+10.04	0.259
206	+9.73	0.298
207	+10.76	0.288
208	+18.29	0.257
209	+47.92	0.288
211	+80.43	0.281
212	+58.7	0.23
213	+31.11	0.135 T=24°C
214	+14.29	0.238
215	+14.62	0.26
216	+10.07	0.278
217	+11.54	0.26
218	+12.69	0.26
219	+8.63	0.255
220	+10.94	0.256
221	+13.72	0.277
222	+18.39	0.261
223	+46.55	0.29
224	+44.17	0.24
225	+34.16	0.322

Co. No.	OR (°)	Conc.
226	+34.2	0.2 (MeOH)
227	+39.3	0.23 (MeOH)
228	+44.2	0.16 (MeOH)
229	+50.33	0.302
232	+40.15	0.269
233	+46.85	0.254
234	+15.75	0.254
235	+20.27	0.301
236	+ 12.4	0.258

SFC-MS Method:

55 General procedure for SFC-MS method

[0914] The SFC measurement was performed using an Analytical Supercritical fluid chromatography (SFC) system composed by a binary pump for delivering carbon dioxide (CO₂) and modifier, an autosampler, a column oven, a diode

array detector equipped with a high-pressure flow cell standing up to 400 bars. If configured with a Mass Spectrometer (MS) the flow from the column was brought to the (MS). It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.

Table: Analytical SFC-MS Methods (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes, Backpressure (BPR) in bars.

Method number	column	mobile phase	gradient	Flow ----- Col T	Run time ----- BPR
1	Daicel Chiralpak® AD-3 column (3 µm, 100 x 4.6 mm)	A:CO ₂ B: MeOH(0.3% iPrNH ₂)	35% B hold 6 min	3.5 ----- 35	6 ----- 103

Table: Analytical SFC-MS data - R_t means retention time (in minutes), method refers to the method used for (SFC) MS analysis of enantiomerically pure compounds.

Co. No.	R _t	Chiral purity UV Area%	Method number
232	2.59	100	1
233	2.20	98.79	1

NMR

[0915] 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 deuterium lock and equipped with reverse double-resonance (¹H, ¹³C, 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.

Compound 1: ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.92 (s, 1 H), 8.40 (d, *J* = 5.3 Hz, 1 H), 8.17 (d, *J* = 1.2 Hz, 1 H), 8.07 (d, *J* = 1.2 Hz, 1 H), 7.92 (d, *J* = 1.3 Hz, 1 H), 7.48 - 7.40 (m, 3 H), 7.36 (d, *J* = 5.4 Hz, 1 H), 4.98 (t, *J* = 5.4 Hz, 1 H), 3.69 (d, *J* = 9.8 Hz, 1 H), 3.44 (dd, *J* = 10.7 Hz, 5.3 Hz, 1 H), 3.34 - 3.39 (m, 1 H, partially obscured by solvent peak), 3.29 (d, *J* = 9.8 Hz, 1 H), 2.37 (s, 3 H), 1.27 (s, 3 H).

Compound 4: ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.80 (s, 1 H), 8.33 - 8.37 (m, 2 H), 8.20 (d, *J* = 0.9 Hz, 1 H), 8.04 (d, *J* = 1.6 Hz, 1 H), 7.91 (d, *J* = 1.6 Hz, 1 H), 7.52 (dd, *J* = 7.9 Hz, 1.9 Hz, 1 H), 7.36 (s, 1 H), 7.30 - 7.22 (m, 2 H), 4.95 (br s, 1 H), 3.70 (d, *J* = 9.1 Hz, 1 H), 3.42 (dd, *J* = 9.8 Hz, 1.8 Hz, 1 H), 3.34 - 3.39 (m, 1 H, partially obscured by solvent peak), 3.27 (d, *J* = 9.1 Hz, 1 H), 2.77 (d, *J* = 4.4 Hz, 3 H), 2.30 (s, 3 H), 1.24 (s, 3 H).

Compound 45: ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.62 (d, *J* = 2.5 Hz, 1 H), 8.49 (d, *J* = 5.4 Hz, 1 H), 8.13 (d, *J* = 1.6 Hz, 1 H), 8.12 (s, 1 H), 8.00 (d, *J* = 1.3 Hz, 1 H), 7.50 (s, 1 H), 7.46 (d, *J* = 5.4 Hz, 1 H), 7.12 (d, *J* = 8.5 Hz, 1 H), 7.01 (dd, *J* = 8.7 Hz, 2.7 Hz, 1 H), 5.01 (t, *J* = 5.4 Hz, 1 H), 4.24 - 4.20 (m, 2 H), 3.74 - 3.69 (m, 3 H), 3.46 (dd, *J* = 10.7 Hz, 5.3 Hz, 1 H), 3.42 - 3.34 (m, 4 H), 3.31 - 3.37 (m, 1H, partially obscured by solvent peak), 1.30 (s, 3 H).

Compound 66: ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.77 (d, *J* = 1.9 Hz, 1 H), 8.50 (d, *J* = 5.4 Hz, 1 H), 8.19 (s, 1 H), 8.11 (d, *J* = 1.9 Hz, 1 H), 7.97 (d, *J* = 1.6 Hz, 1 H), 7.51 - 7.45 (m, 3 H), 7.27 (d, *J* = 8.5 Hz, 1 H), 4.97 (t, *J* = 5.5 Hz, 1 H), 4.34 - 4.30 (m, 2 H), 3.77 - 3.74 (m, 2 H), 3.71 (d, *J* = 9.8 Hz, 1 H), 3.47 (dd, *J* = 10.7 Hz, 5.3 Hz, 1 H), 3.38 (dd, *J* = 10.7 Hz, 5.7 Hz, 1 H), 3.35 (s, 3H), 3.31 (d, *J* = 10.1 Hz, 1 H), 1.30 (s, 3 H).

Compound 68: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.39 (s, 1 H) 8.90 (s, 1 H) 8.36 (d, *J* = 5.0 Hz, 1 H) 8.07 (s, 1 H) 7.93 (s, 1 H) 7.62 (s, 1 H) 7.39 (s, 1 H) 7.32 (d, *J* = 5.4 Hz, 1 H) 7.22 (s, 1 H) 4.99 (br t, *J* = 5.2 Hz, 1 H) 3.69 (br d, *J* = 9.8 Hz, 1 H) 3.50 - 3.35 (m, 2 H, partially obscured by solvent peak) 3.29 (br d, *J* = 10.1 Hz, 1 H) 2.81 (br d, *J* = 11.0 Hz, 2 H) 2.31 - 2.40 (m, 1 H) 2.16 (s, 3 H) 2.07 (s, 3 H) 1.87 (br t, *J* = 11.2 Hz, 2 H) 1.78 (br d, *J* = 11.0 Hz, 2 H) 1.58 - 1.73 (m, 2 H) 1.27 (s, 3 H).

Compound 73: ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.67 (d, *J* = 8.5 Hz, 1 H), 8.51 (d, *J* = 5.4 Hz, 1 H), 8.33 (s, 1 H), 8.16 (d, *J* = 1.6 Hz, 1 H), 8.03 (d, *J* = 1.6 Hz, 1 H), 7.54 (dd, *J* = 8.5 Hz, 1.9 Hz, 1 H), 7.46 - 7.50 (m, 3 H), 5.04 (t, *J*

= 5.4 Hz, 1 H), 4.01 (s, 3 H), 3.68 (d, J = 9.5 Hz, 1 H), 3.47 (dd, J = 10.7 Hz, 5.3 Hz, 1 H), 3.40 (dd, J = 10.4 Hz, 5.3 Hz, 1 H), 3.29 - 3.33 (m, 1 H, partially obscured by solvent peak), 3.21 (s, 3 H), 1.30 (s, 3 H).

Compound 74: ^1H NMR (500 MHz, DMSO- d_6): δ 8.92 (s, 1 H), 8.38 (d, J = 5.0 Hz, 1 H), 8.16 (s, 1 H), 8.05 (d, J = 1.3 Hz, 1 H), 7.91 (s, 1 H), 7.51 (dd, J = 7.9 Hz, 1.3 Hz, 1 H), 7.38 - 7.45 (m, 2 H), 7.35 (d, J = 5.4 Hz, 1 H), 4.97 (t, J = 5.2 Hz, 1 H), 3.69 (d, J = 9.8 Hz, 1 H), 3.44 (dd, J = 10.4 Hz, 5.3 Hz, 1 H), 3.33 - 3.38 (m, 1 H, partially obscured by solvent peak), 3.27 - 3.31 (m, 3 H), 3.21 (s, 3 H), 2.79 (t, J = 7.6 Hz, 2 H), 1.78 (q, J = 6.9 Hz, 2 H), 1.27 (s, 3 H).

Compound 110: ^1H NMR (400 MHz, DMSO- d_6): δ 8.63 (s, 1 H), 8.50 (d, J = 5.5 Hz, 1 H), 8.19 (br. s., 1 H), 8.15 (d, J = 1.5 Hz, 1 H), 8.05 (d, J = 1.5 Hz, 1 H), 7.49 (m, 2 H), 7.06 (s, 1 H), 5.80 (br. s., 1 H), 4.52 (m, 1 H), 4.23 (m, 1 H), 4.10 (m, 1 H), 3.93 (s, 3 H), 3.76 (m, 2 H), 3.45 (s, 2 H), 1.33 (s, 6 H).

Compound 125:

^1H NMR (400 MHz, DMSO- d_6): δ 8.90 (s, 1 H), 8.42 (d, J = 5.0 Hz, 1 H), 8.18 (s, 1 H), 8.12 (d, J = 1.5 Hz, 1 H), 8.02 (s, 1 H), 7.51 (s, 1 H), 7.41 - 7.49 (m, 2 H), 7.38 (d, J = 5.6 Hz, 1 H), 4.00 - 4.14 (m, 2 H), 3.62 (d, J = 10.1 Hz, 1 H), 3.39 (d, J = 10.6 Hz, 1 H), 2.36 (s, 3 H), 1.94 (s, 3 H), 1.35 (s, 3 H).

Compound 138:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 9.47 (br s, 1H) 8.51 (br s, 2H) 8.47 (d, J =5.7 Hz, 1H) 8.22 (s, 1H) 8.20 (d, J =1.3 Hz, 1H) 8.08 (s, 1H) 7.57 - 8.03 (m, 1H) 7.46 - 7.56 (m, 3H) 5.20 - 7.15 (m, 1H) 4.35 (d, J =10.7 Hz, 1H) 4.14 (d, J =10.7 Hz, 1H) 3.95 - 4.09 (m, 1H) 3.73 (d, J =10.7 Hz, 1H) 3.47 (d, J =10.7 Hz, 1H) 2.39 (s, 3H) 1.40 (s, 3H) 1.25 (d, J =7.3 Hz, 3H)

Compound 137: ^1H NMR (400 MHz, DMSO- d_6) δ ppm 9.24 (br s, 1H) 8.45 (d, J =5.6 Hz, 1H) 8.36 (br s, 3H) 8.20 (s, 1H) 8.17 (d, J =1.5 Hz, 1H) 8.06 (d, J =1.5 Hz, 1H) 7.63 (br s, 1H) 7.48 - 7.53 (m, 1H) 7.42 - 7.48 (m, 2H) 6.34 (br s, 2H) 4.22 (s, 2H) 3.76 - 3.89 (m, 2H) 3.70 (d, J =10.6 Hz, 1H) 3.42 (d, J =10.6 Hz, 1H) 2.38 (s, 3H) 1.39 (s, 3H)

Compound 148:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 8.72 (s, 1H) 8.30 (br d, J =5.0 Hz, 1H) 8.03 (s, 1H) 7.91 (s, 1H) 7.57 (br d, J =7.3 Hz, 1H) 7.35 (s, 1H) 7.23 (br d, J =5.4 Hz, 1H) 7.02 (br d, J =10.7 Hz, 1H) 5.15 (s, 1H) 4.99 (br t, J =5.0 Hz, 1H) 3.67 (br d, J =9.8 Hz, 1H) 3.39 - 3.46 (m, 1H) 3.34 - 3.39 (m, 1H) 3.28 (br d, J =9.8 Hz, 1H) 2.21 (s, 3H) 1.26 (s, 3H)

Compound 155:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 8.86 (s, 1 H) 8.40 (d, J =5.4 Hz, 1H) 8.12 - 8.20 (m, 1H) 8.10 (d, J =1.6 Hz, 1H) 8.01 (br d, J =7.3 Hz, 1H) 7.97 (d, J =1.3 Hz, 1H) 7.43 (s, 1H) 7.34 (d, J =5.4 Hz, 1H) 7.23 (d, J =11.3 Hz, 1H) 5.01 (t, J =5.4 Hz, 1H) 3.75 (d, J =9.5 Hz, 1H) 3.46 - 3.53 (m, 1H) 3.41 (dd, J =10.7, 5.7 Hz, 1H) 3.34 (d, J =9.5 Hz, 1H) 2.85 (d, J =4.4 Hz, 3H) 2.34 (s, 3H) 1.31 (s, 3H)

Compound 156:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 8.53 (br d, J =7.9 Hz, 1H) 8.39 (d, J =5.4 Hz, 1H) 8.06 - 8.13 (m, 2H) 7.93 - 8.06 (m, 2H) 7.40 (s, 1H) 7.36 (d, J =5.0 Hz, 1H) 7.25 (d, J =12.3 Hz, 1H) 4.93 (t, J =5.4 Hz, 1H) 3.99 - 4.07 (m, 1H) 3.72 (br d, J =9.8 Hz, 1H) 3.47 - 3.53 (m, 1H) 3.40 (br dd, J =10.6, 5.5 Hz, 1H) 3.29 (br d, J =9.8 Hz, 1H) 2.81 (d, J =4.4 Hz, 3H) 1.29 (s, 3H) 0.67 - 0.91 (m, 4H)

Compound 232: ^1H NMR (500 MHz, DMSO- d_6) δ ppm 8.72 (s, 1H) 8.45 - 8.56 (m, 2H) 8.12 (s, 1H) 7.97 (s, 1H) 7.52 (br d, J =8.2 Hz, 1H) 7.43 - 7.48 (m, 2H) 7.22 (br d, J =8.5 Hz, 1H) 5.23 - 5.42 (m, 1H) 5.05 - 5.17 (m, 1H) 4.97 (br t, J =5.0 Hz, 1H) 3.71 (br d, J =9.8 Hz, 1H) 3.44 - 3.52 (m, 1H) 3.38 (br dd, J =10.6, 5.5 Hz, 1H) 3.28 - 3.33 (m, 2H, partially obscured by solvent peak) 3.25 (br dd, J =9.8, 6.6 Hz, 1H) 2.74 - 2.95 (m, 2H) 2.28 (s, 3H) 1.30 (s, 3H)

Pharmacological Part

Biological assay A

Inhibition of auto-phosphorylation of recombinant human NF-kappaB-inducing kinase (NIK/MAP3K14) activity (AlphaScreen®)

[0916] NIK/MAP3K14 auto-phosphorylation activity was measured using the AlphaScreen® (α screen) 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 Na_3VO_4 , 5 mM MgCl_2 , 0.01% Tween® 20. Assays were carried out in 384 well Alphasplates (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 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 IC_{50} 's were determined by fitting a sigmoidal curve to % inhibition of control versus Log_{10} compound concentration.

Biological assay B

Effect of compounds on P-IKK α levels in L363 (NIK translocated multiple myeloma) cells

[0917] 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 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 μ l 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 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. 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

[0918] ADS 125117, 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 determine the IC₅₀ a sigmoidal curve was fitted to the plot of % inhibition of control P-IKK α levels versus Log₁₀ compound concentration.

[0919] Note: Compounds 237 and 238 were tested at a maximum top concentration of 823 nM.

Biological assay C

Determination of antiproliferative activity on JJN-3 (NIK translocated) and KMS12-BM (NIK WT) multiple myeloma cells

[0920] 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 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. 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).

[0921] Within an experiment, the results for each treatment were the mean of 2 replicate wells. 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.

[0922] Data for the compounds of the invention in the above assays are provided in Table A (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 (IC ₅₀ (nM))	Inhibition of pIKK α _L-363 (IC ₅₀ (nM))	KMS-12 Proliferation inhibition (IC ₅₀ (nM))	JJN-3 Proliferation inhibition (IC ₅₀ (nM))
1	1.8	2.2	5188	85
2	4.3	4.8	>10000	58
3	10.2	15.1	>10000	115
4	4.2	20.9	>10000	759

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(continued)

5	Compound	Auto-phosphorylation inhibition of NIK (IC50 (nM))	Inhibition of pIKKα_L-363 (IC50 (nM))	KMS-12 Proliferation inhibition (IC50 (nM))	JJN-3 Proliferation inhibition (IC50 (nM))
	5	2511.9	>10000	n.d.	n.d.
	6	446.7	>10000	n.d.	n.d.
10	7	5.8	n.d.	2512	148
	8	1.3	32.4	>10000	87
	9	10.7	8.1	10233	162
15	10	7.4	11.5	1227	67
	11	1.8	6.0	>10000	617
	12	4.1	25.7	4898	138
	13	9.2	30.9	>10000	146
20	14	5.5	21.4	>10000	170
	15	11.0	~269.1	>10000	117
	16	15.5	15.5	550	258
25	17	1.1	6.8	479	56
	18	2.6	20.0	~8128	407
	19	27.5	38.9	>10000	1950
	20	1.7	11.5	~1585	63
30	21	2.5	4.5	891	51
	22	2.5	11.5	631	7
	23	7.1	12.0	>10000	71
35	24	4.5	6.0	2818	13
	25	3.6	33.9	589	12
	26	3.7	n.d.	>10000	255
	27	9.2	n.d.	>10000	106
40	28	n.d.	n.d.	n.d.	n.d.
	29	17.4	n.d.	>10000	166
	30	51.3	n.d.	>10000	>10000
45	31	5.3	n.d.	>10000	2344
	32	4.0	n.d.	>10000	170
	33	11.2	n.d.	>10000	85
	34	20.9	n.d.	>10000	316
50	35	37.2	n.d.	7079	129
	36	75.9	n.d.	6457	51
	37	37.2	n.d.	4169	17
55	38	30.9	n.d.	>10000	182
	39	7.4	n.d.	2344	87
	40	8.7	n.d.	>10000	155

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(continued)

5	Compound	Auto-phosphorylation inhibition of NIK (IC50 (nM))	Inhibition of pIKKα_L-363 (IC50 (nM))	KMS-12 Proliferation inhibition (IC50 (nM))	JJN-3 Proliferation inhibition (IC50 (nM))
	41	1.7	n.d.	110	13
	42	309.0	n.d.	>10000	4266
10	43	2.5	n.d.	251	9
	44	8.3	n.d.	>10000	219
	45	9.1	37.2	>10000	490
15	47	15.1	n.d.	>10000	776
	48	8.9	n.d.	>10000	447
	49	24.6	n.d.	>10000	1622
	50	3.0	n.d.	102	9
20	51	49.0	n.d.	>10000	363
	52	41.7	n.d.	>10000	676
	53	3.6	n.d.	1259	33
25	54	9.8	n.d.	>10000	275
	55	15.5	n.d.	>10000	282
	56	125.9	n.d.	>10000	1738
	57	50.1	n.d.	>10000	>10000
30	58	2.6	n.d.	6761	85
	59	23.4	n.d.	4074	129
	60	2754.2	n.d.	n.d.	n.d.
35	61	11.0	n.d.	>10000	186
	62	912.0	n.d.	n.d.	n.d.
	63	1.7	n.d.	~5012	7
	64	1.8	18.2	1230	~246
40	65	4.1	103.1	>10000	1102
	66	3.0	5.9	19	251
	67	4.3	n.d.	>10000	~1698
45	68	0.8	1.9	1479	16
	69	4.9	n.d.	>10000	1023
	70	3.9	n.d.	>10000	2188
50	71	7.2	n.d.	>10000	148
	72	11.0	n.d.	>10000	123
	73	2.2	1.4	>10000	68
	74	4.0	16.2	~1148	182
55	75	3.6	n.d.	~3311	105
	76	186.2	n.d.	>10000	2344
	77	46.8	n.d.	~2455	126

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(continued)

5	Compound	Auto-phosphorylation inhibition of NIK (IC50 (nM))	Inhibition of pIKKα_L-363 (IC50 (nM))	KMS-12 Proliferation inhibition (IC50 (nM))	JJN-3 Proliferation inhibition (IC50 (nM))
	78	2.7	7.9	2042	87
	79	47.9	75.9	~5129	91
10	80	15.2	208.9	1000	124
	81	n.d.	n.d.	n.d.	n.d.
	82	7.6	5.3	>10000	22
15	83	n.d.	n.d.	n.d.	n.d.
	84	19.1	12.9	~7586	251
	85	11.3	41.7	>10000	57
	87	7.1	93.3	1175	35
20	88	85.1	n.d.	>10000	178
	89	20.9	n.d.	>10000	~100
	90	218.8	n.d.	>10000	>10000
25	91	7.2	n.d.	>10000	~107
	92	138.0	n.d.	>10000	389
	93	11.5	n.d.	>10000	83
	94	9.8	n.d.	>10000	166
30	95	9.3	n.d.	>10000	129
	96	9.1	n.d.	>10000	~81
	97	45.7	n.d.	4365	59
35	98	128.8	n.d.	>10000	105
	99	218.8	n.d.	8318	380
	100	91.2	n.d.	>10000	1413
	101	49.0	n.d.	1349	447
40	102	403.3	n.d.	>10000	3548
	103	104.7	n.d.	>10000	3715
	104	12.0	n.d.	>10000	2138
45	105	28.5	22.9	~6607	118
	106	63.1	123.0	>10000	1622
	107	41.7	n.d.	>10000	1023
	108	11.0	3.8	>3981	39
50	109	53.7	n.d.	n.d.	676
	110	4.2	n.d.	>10000	193
	111	3548.1	n.d.	>10000	3467
55	112	4.3	n.d.	>10000	20
	113	2.6	n.d.	~407	28
	114	2.2	n.d.	490	19

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(continued)

5	Compound	Auto-phosphorylation inhibition of NIK (IC50 (nM))	Inhibition of pIKKα_L-363 (IC50 (nM))	KMS-12 Proliferation inhibition (IC50 (nM))	JJN-3 Proliferation inhibition (IC50 (nM))
	115	4.9	n.d.	>10000	166
	116	6.8	n.d.	>10000	162
10	117	4.7	n.d.	1549	19
	118	25.7	n.d.	>10000	933
	119	7.1	n.d.	1380	28
15	120	15.5	n.d.	>10000	25
	121	8.5	n.d.	120	12
	122	4.7	n.d.	~4467	35
	123	8.5	n.d.	1047	14
20	124	1.6	n.d.	437	525
	125	13.8	3.6	~6918	182
	126	112.2	~6.9	~8913	151
25	127	128.8	11.5	>10000	570
	128	251.2	20.9	>10000	407
	129	1.4	3.2	~7943	330
	130	1.5	2.2	9772	167
30	131	1.3	4.7	>10000	324
	132	1.3	2.2	5012	128
	133	0.7	3.0	4365	170
35	134	0.9	2.8	5495	91
	135	58.9	4365.2	n.d.	n.d.
	136	1.7	<0.66	>10000	269
	137	6.0	2.7	~10000	545
40	138	11.2	2.1	~4786	102
	139	56.2	26.9	~8913	302
	140	51.3	56.2	~9120	550
45	141	8.7	2.2	>10000	33
	142a	12.0	2.2	>10000	3631
	142b	17.0	~58.9	>10000	977
	143	6.5	12.3	>10000	200
50	144	5.8	~1174.9	>10000	~10000
	145	17.4	436.5	n.d.	n.d.
	146	19.9	5.2	>10000	78
55	147	3.9	1.2	>10000	302
	148	4.7	8.9	>10000	523
	149	10.0	102.3	n.d.	n.d.

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(continued)

5	Compound	Auto-phosphorylation inhibition of NIK (IC50 (nM))	Inhibition of pIKKα_L-363 (IC50 (nM))	KMS-12 Proliferation inhibition (IC50 (nM))	JJN-3 Proliferation inhibition (IC50 (nM))
	150	0.8	2.2	>10000	91
	151	22.4	426.6	n.d.	n.d.
10	152	2.3	7.8	>10000	272
	153	1.3	6.3	>10000	240
	154	1.4	6.6	>10000	141
15	155	3.5	7.7	>10000	467
	156	4.8	7.8	>10000	251
	157	4.9	12.9	~7586	178
	158	5.4	91.2	>10000	1230
20	159	5.5	20.4	>10000	4786
	160	11.2	64.6	>10000	4786
	161	20.4	407.4	n.d.	n.d.
25	162	5.5	19.5	>10000	288
	163	3.5	33.1	>10000	437
	164	26.9	288.4	n.d.	n.d.
	165	3.6	6.0	~5248	1122
30	166	8.9	18.6	>10000	955
	167	7.6	19.1	6166	562
	168	10.7	14.5	>10000	~1413
35	169	8.7	8.3	>10000	~1000
	170	1.0	2.3	~4677	81
	171	1.1	34.7	>10000	955
	172	4.8	2.4	>10000	65
40	173	1.8	1.3	>10000	29
	174	3.5	2.0	>10000	71
	175	1.8	2.8	~191	27
45	176	3.8	5.9	>10000	91
	177	3.2	1.2	~246	14
	178	2.0	2.6	~891	42
	179	2.2	1.4	1288	58
50	180	3.7	44.7	n.d.	n.d.
	181	5.1	7.8	>10000	195
	182	n.d.	n.d.	n.d.	n.d.
55	183	9.1	7.1	>10000	501
	184	2.8	19.1	>10000	178
	185	6.5	6.6	n.d.	n.d.

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(continued)

5	Compound	Auto-phosphorylation inhibition of NIK (IC50 (nM))	Inhibition of pIKKα_L-363 (IC50 (nM))	KMS-12 Proliferation inhibition (IC50 (nM))	JJN-3 Proliferation inhibition (IC50 (nM))
	186	4.6	n.d.	n.d.	n.d.
	187	3.2	n.d.	1097	39
10	188	2.6	5.4	>10000	54
	189	30.9	1621.8	n.d.	n.d.
	190	34.7	2630.3	n.d.	n.d.
15	191	13.8	4073.8	n.d.	n.d.
	192	72.4	2951.2	537	1175
	193	1.6	1.7	>10000	22
	194	3.6	1.4	479	17
20	195	6.2	1.9	~3715	30
	196	7.8	1.0	>10000	14
	197	6.0	4.8	~240	33
25	198	4.6	5.6	~550	63
	199	6.9	7.4	>10000	76
	200	1.7	~0.66	>10000	41
	201	2.8	~1202.3	n.d.	n.d.
30	202	n.d.	n.d.	n.d.	n.d.
	203	6.6	1.8	~5888	14
	204	6.2	1.5	~3981	14
35	205	6.0	11.2	>10000	162
	206	5.3	n.d.	~7244	71
	207	5.0	13.2	~9550	66
	208	6.5	10.7	>10000	389
40	209	14.5	14.8	>10000	132
	210	33.1	>10000	n.d.	n.d.
	211	16.2	3162.3	n.d.	n.d.
45	212	25.1	~4466.9	n.d.	n.d.
	213	4.2	5.0	>10000	1072
	214	6.9	n.d.	n.d.	n.d.
	215	1.5	2.9	>10000	199
50	216	49.0	144.5	n.d.	n.d.
	217	9.8	107.2	~7943	4266
	218	3.6	~1230.3	n.d.	n.d.
55	219	15.5	5495.4	n.d.	n.d.
	220	10.2	72.4	>10000	4571
	221	32.4	645.7	n.d.	n.d.

(continued)

Compound	Auto-phosphorylation inhibition of NIK (IC ₅₀ (nM))	Inhibition of pIKK α _L-363 (IC ₅₀ (nM))	KMS-12 Proliferation inhibition (IC ₅₀ (nM))	JJN-3 Proliferation inhibition (IC ₅₀ (nM))
222	31.6	302.0	n.d.	n.d.
223	1.6	3.1	~851	23
224	14.1	83.2	>10000	3236
225	20.0	19.5	>10000	195
226	4.3	33.1	>10000	74
227	7.9	32.4	~3162	96
228	5.4	19.5	>10000	120
229	7.6	22.4	>10000	251
230	6.3	7.7	>10000	46
231	7.8	12.3	>10000	89
232	5.5	11.5	>10000	282
233	4.6	21.4	>10000	741
234	3.5	5.9	~6607	20
235	3.9	60.3	2692	457
236	2.6	42.7	178	32
237	213.8	>831.8	n.d.	n.d.
238	955.0	>831.8	n.d.	n.d.
239	13.8	354.8	n.d.	n.d.
240	2.5	11.2	302	44

Prophetic composition examples

[0923] "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.

[0924] Typical examples of recipes for the formulation of the invention are as follows:

1. Tablets

[0925]

Active ingredient	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg
Talcum	10 mg
Magnesium stearate	5 mg
Potato starch	ad 200 mg

2. Suspension

[0926] 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*

[0927] 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*

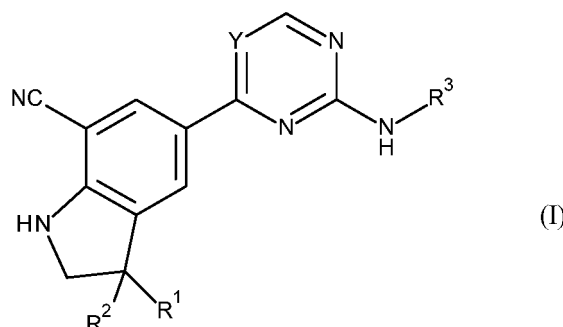
[0928]

Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

[0929] In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

Claims

1. A compound of Formula (I):



a tautomer or a stereoisomeric form thereof, wherein

R¹ represents C₁₋₄alkyl;

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

Y represents CR⁴ or N;

R⁴ represents hydrogen or halo;

R⁵ represents halo, 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 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;

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 phenyl optionally substituted with 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; R²¹; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het¹⁹; -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; C₂₋₆alkenyl substituted with one R¹³; C₂₋₆alkynyl; and C₂₋₆alkynyl substituted with one R¹³;

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;

R²¹ represents 3,6-dihydro-2H-pyran-4-yl or 1,2,3,6-tetrahydro-4-pyridinyl, wherein 1,2,3,6-tetrahydro-4-pyridinyl may optionally be substituted on the N-atom with C₁₋₄alkyl or 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, 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}, Het⁴, Het⁷ and Het⁸ 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}, Het⁴, Het⁷ and Het⁸ 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

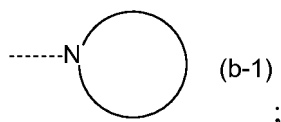
C₁₋₄alkyl substituted with one substituent selected from the group consisting of

-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 a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl and Het⁷; 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-Het⁸; 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;

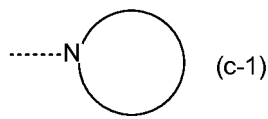
R¹³ represents -O-C₁₋₄alkyl, -C(=O)NR^{15a}R^{15b}, NR^{19a}R^{19b}, C₃₋₆cycloalkyl, Het^{1d}, or -C(=O)-Het^{1f};

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;

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 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^{15a}, R^{17a} and R^{19a} each independently represents hydrogen or C₁₋₄alkyl;

R^{14b}, R^{14d}, R^{15b}, R^{17b} and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl;

-C(=O)-C₁₋₄alkyl; C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and

-O-C₁₋₄alkyl; -C(=O)-C₁₋₄alkyl substituted with one substituent selected from the group consisting of halo, -OH and -O-C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl;

R^{20a} and R^{20b} 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;

or a pharmaceutically acceptable addition salt, or a solvate thereof.

2. The compound according to claim 1, wherein

Y represents CR⁴;

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

R³ represents phenyl optionally substituted with 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-

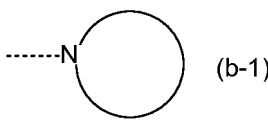
C₃₋₆cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; R²¹; -P(=O)-(C₁₋₄alkyl)₂; -NH-C(=O)-C₁₋₄alkyl; -NH-C(=O)-Het^{1g};

-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;

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}; C₁₋₄alkyl; C₁₋₄alkyl-Het⁵; C₁₋₄alkyl substituted with one, two or three substit-

uents 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; and

R^{14b}, R^{14d}, 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.

3. The compound according to claim 1, wherein

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

R^{6a} represents hydrogen;

R^{6b} represents -C(=O)-C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl;

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

R^{8a} represents hydrogen;

R^{8b} represents C₃₋₆cycloalkyl;

R³ represents phenyl optionally substituted with 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; -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; C₂₋₆alkenyl substituted with one R¹³; and C₂₋₆alkynyl substituted with one R¹³;

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; 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 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 -O-C₁₋₄alkyl; and

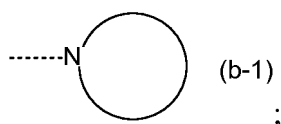
wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of OH, halo, C₁₋₄alkyl, -O-C₁₋₄alkyl, and -N(C₁₋₄alkyl)₂;

Het^{1b}, Het^{1e}, Het^{1g}, Het⁷ and Het⁸ 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}, Het⁷ and Het⁸ containing one or two heteroatoms each independently selected from O 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 and C₃₋₆cycloalkyl; 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, and halo;

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 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 N-atoms; wherein in case (b-1) contains one or two additional N-atoms, said one or two N-atoms may optionally be substituted with a substituent each independently selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl and Het⁷; and

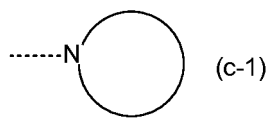
wherein (b-1) may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, cyano, C₁₋₄alkyl, and C₁₋₄alkyl-OH;

R^{11b} represents Het^{1e}; C₁₋₄alkyl; -C₁₋₄alkyl-Het⁵; -C₁₋₄alkyl-Het⁸, C₁₋₄alkyl substituted with one, two or three OH substituents; or C₃₋₆cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo and -OH;

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

Ar¹ represents phenyl;

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 and N;

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

R^{14b}, R^{14d}, R^{15b}, R^{17b} and R^{19b} each independently represents hydrogen; C₁₋₄alkyl; C₃₋₆cycloalkyl; -C(=O)-C₁₋₄alkyl; C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OH and -O-C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl.

4. The compound according to claim 1 or 2, wherein R⁵ represents -NR^{6a}R^{6b}, or -OR⁷;

R^{6a} represents hydrogen;

R^{6b} represents -C(=O)-C₁₋₄alkyl; or -S(=O)₂-C₁₋₄alkyl;

R⁷ represents hydrogen, -C(=O)-R⁹, -S(=O)₂-OH, or -(C=O)-CH(NH₂)-C₁₋₄alkyl-Ar¹;

R⁹ represents C₁₋₄alkyl, or C₁₋₄alkyl substituted with one substituent selected from the group consisting of -NH₂, -COOH, and Het⁶;

R³ represents phenyl optionally substituted with 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; -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}; C₁₋₄alkyl substituted with one, two or three halo atoms; C₁₋₄alkyl substituted with one, two or three -OH substituents; and C₁₋₄alkyl substituted with one R¹³;

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; 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 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 -O-C₁₋₄alkyl; and

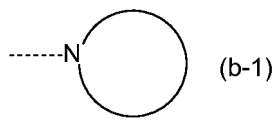
wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one, two or three ring C-atoms with one or two substituents each independently selected from the group consisting of -OH, halo, C₁₋₄alkyl, -O-C₁₋₄alkyl, and -N(C₁₋₄alkyl)₂;

Het^{1b}, Het^{1e}, and Het^{1g} 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} and Het^{1g} containing one or two heteroatoms each independently selected from O 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 and C₃₋₆cycloalkyl; 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 -OH substituents;

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



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(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl optionally containing one additional N-atom, or a N-linked 6- to 11-membered bicyclic saturated heterocyclyl, including fused, spiro and bridged cycles, optionally containing one or two additional N-atoms;

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 -OH, cyano, and C₁₋₄alkyl-OH;

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

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

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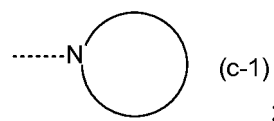
R¹² represents -OH, -O-C₁₋₄alkyl, -NR^{14a}R^{14b}, -C(=O)NR^{14c}R^{14d}, -S(=O)₂-C₁₋₄alkyl, C₃₋₆cycloalkyl, Ar², or Het^{1c};

Ar¹ represents phenyl;

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

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

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

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

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

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

C₃₋₆cycloalkyl; or C₁₋₄alkyl substituted with one -O-C₁₋₄alkyl.

5. The compound according to claim 1 or 2, wherein

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Y represents CR⁴;

R⁴ represents hydrogen;

R⁵ represents -OR⁷;

R⁷ represents hydrogen or -C(=O)-R⁹;

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R⁹ represents C₁₋₄alkyl;

R³ represents phenyl substituted with 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; -O-C₁₋₄alkyl-R¹²; -O-C₃₋₆cycloalkyl; -O-Het^{1b}; -NH-C(=O)-Het^{1g}; and C₁₋₄alkyl substituted with one R¹³;

R¹⁰ represents -NR^{11a}R^{11b} or Het²;

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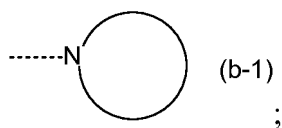
Het^{1g} represents a 4- to 7-membered monocyclic saturated heterocyclyl, attached to the remainder of the molecule of Formula (I) through any available ring carbon atom, said Het^{1g} containing one or two N-atoms; wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a C₁₋₄alkyl substituent;

Het^{1b} 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} containing one or two N-atoms; wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a C₁₋₄alkyl substituent; and wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted on one ring C-atom with one halo substituent;

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

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(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl wherein (b-1) may optionally be substituted on one C-atom with one -OH substituent;
R^{11b} represents C₁₋₄alkyl;
R¹³ represents -O-C₁₋₄alkyl;
R¹² represents -O-C₁₋₄alkyl; and
R^{11a} represents hydrogen.

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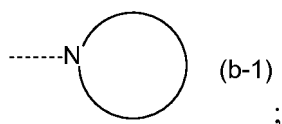
6. The compound according to claim 1 or 2, wherein

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R⁴ represents hydrogen;
R⁵ represents -OR⁷;
R⁷ represents hydrogen or -C(=O)-R⁹;
R⁹ represents C₁₋₄alkyl;
R³ represents phenyl substituted with 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; -O-C₁₋₄alkyl-R¹²; -NH-C(=O)-Het¹⁹; and C₁₋₄alkyl substituted with one R¹³;
R¹⁰ represents -NR^{11a}R^{11b} or Het²;
Het¹⁹ 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 Het¹⁹ containing one or two N-atoms; wherein said 4- to 7-membered monocyclic saturated heterocyclyl may optionally be substituted, where possible, on one or two ring N-atoms with a C₁₋₄alkyl substituent;
Het² represents a heterocyclyl of formula (b-1):

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(b-1) represents a N-linked 4- to 7-membered monocyclic saturated heterocyclyl wherein (b-1) may optionally be substituted on one C-atom with one -OH substituent;
R^{11b} represents C₁₋₄alkyl;
R¹³ represents -O-C₁₋₄alkyl;
R¹² represents -O-C₁₋₄alkyl; and
R^{11a} represents hydrogen.

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7. The compound according to claim 1 or 2, wherein

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R² represents C₁₋₆alkyl substituted with one R⁵;
R⁴ represents hydrogen;
R⁵ represents -OR⁷;
R⁷ represents hydrogen; and
R³ represents phenyl substituted with one, two or three substituents each independently selected from the group consisting of halo; cyano; and C₁₋₆alkyl.

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8. The compound according to any one of claims 1 to 6, wherein

R¹ represents methyl;
R² represents methyl or -CH₂-OH.

9. The compound according to any one of claims 1 to 4, wherein R^4 is hydrogen.

10. The compound according to any one of claims 1 to 6, wherein

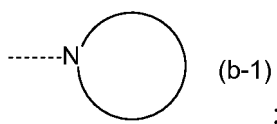
R^5 represents $-OR^7$; and
 R^7 represents hydrogen.

11. The compound according to claim 1 or 2, 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; 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, C_{1-4} alkyl, cyano, $-C(=O)-C_{1-4}$ alkyl, $-O-C_{1-4}$ alkyl, $-NH_2$, $-NH(C_{1-4}$ alkyl), and $-N(C_{1-4}$ alkyl)₂.

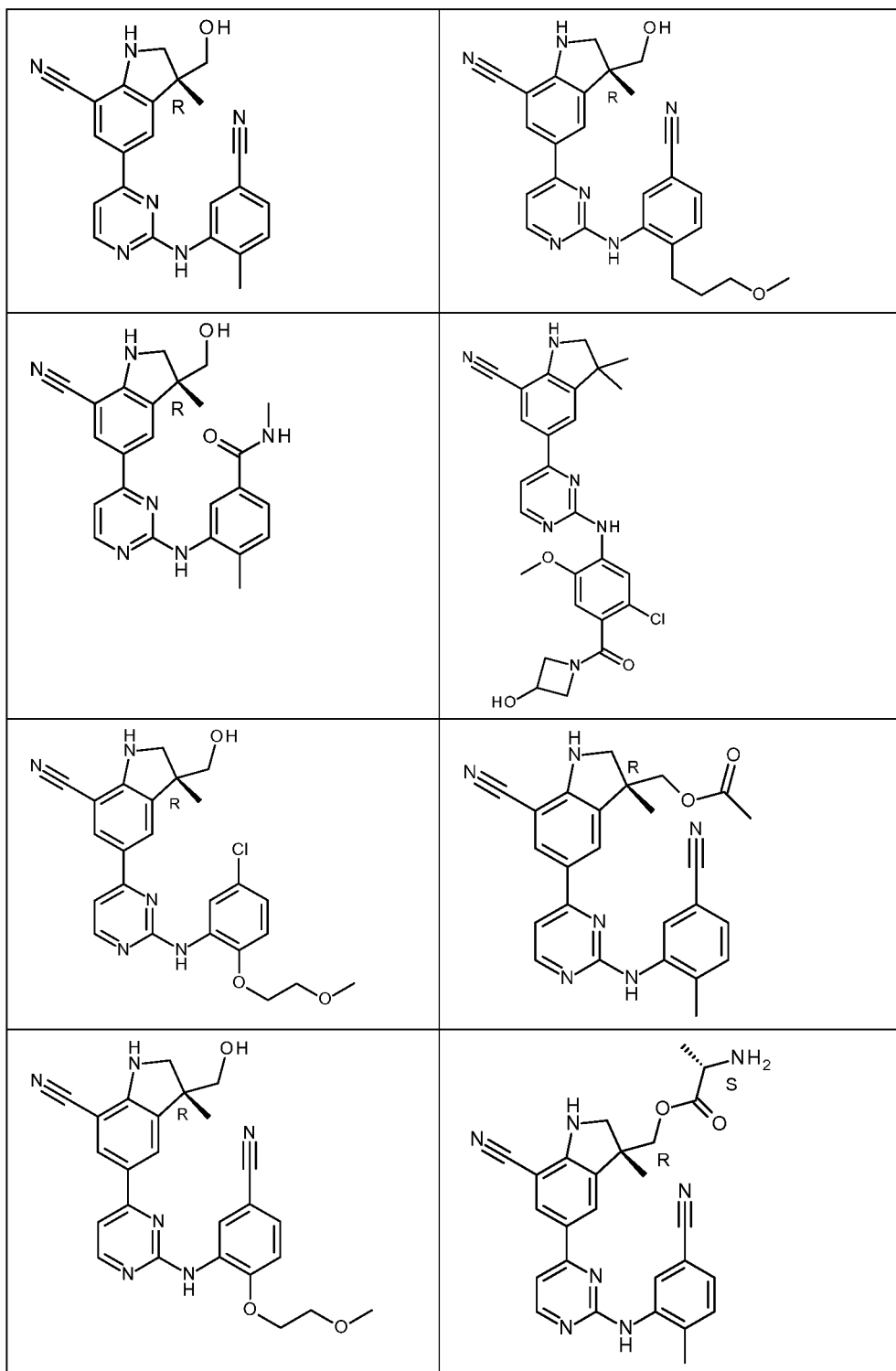
12. The compound according to claim 1 or 2, wherein

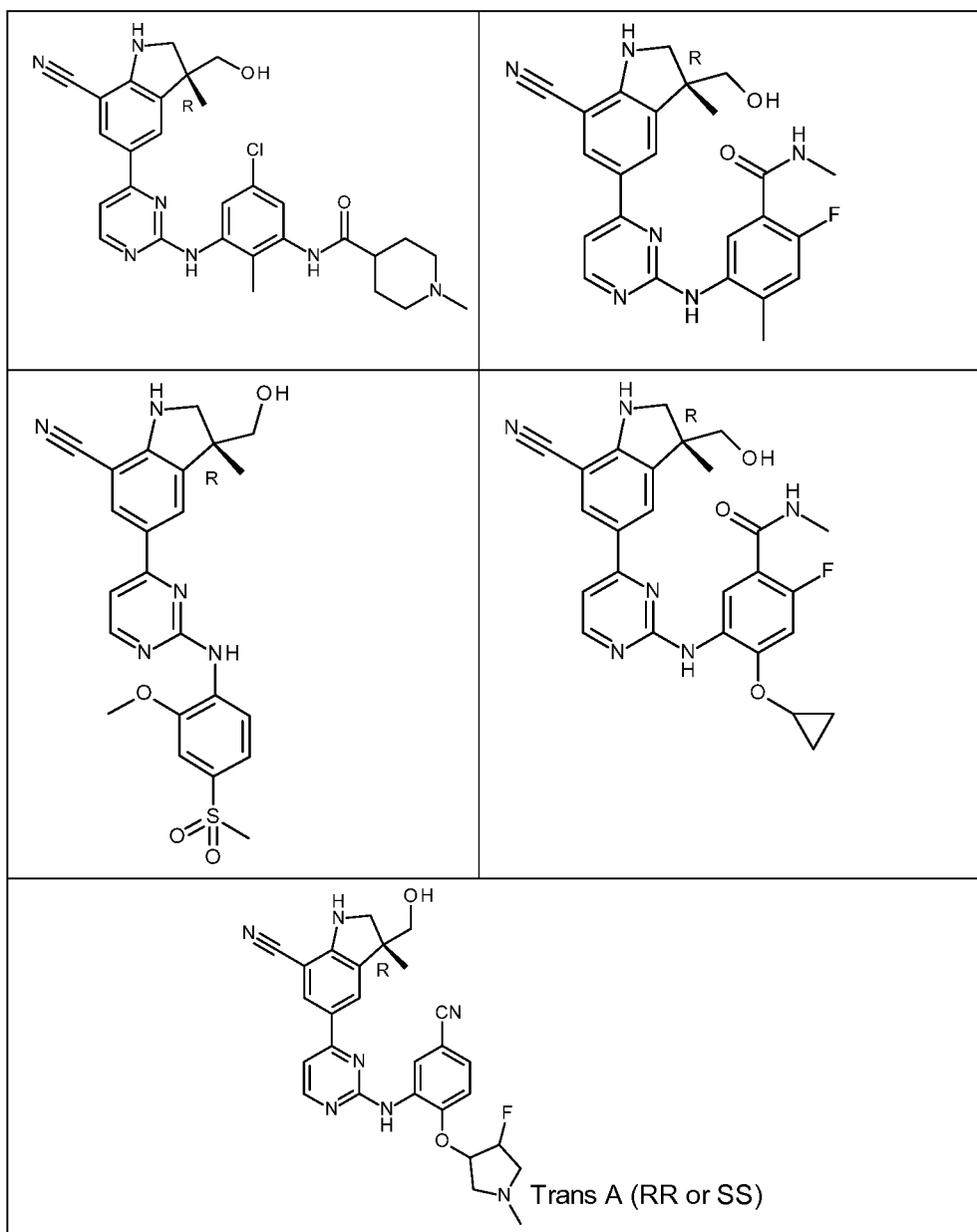
Het² represents a heterocyclyl of formula (b-1):



(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; wherein in case (b-1) contains one additional N-atom, said N-atom may optionally be substituted with C_{1-4} alkyl; 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, C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl)₂, and C_{1-4} alkyl- $-OH$.

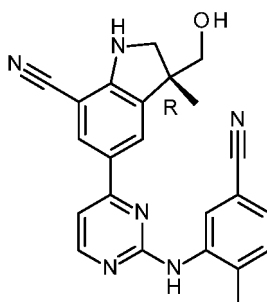
13. The compound according to claim 1, wherein the compound is selected from





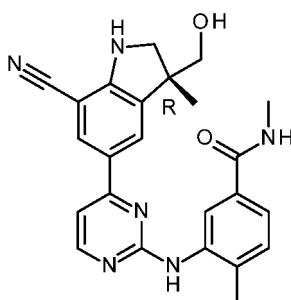
tautomers and stereoisomeric forms thereof,
and the pharmaceutically acceptable addition salts, and the solvates thereof.

14. The compound according to claim 1, wherein the compound is



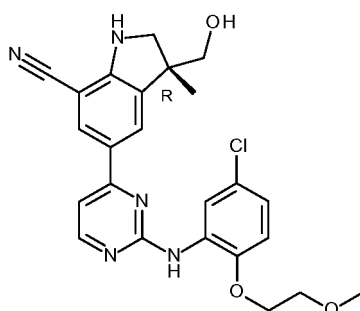
or a pharmaceutically acceptable addition salt or a solvate thereof.

15. The compound according to claim 1, wherein the compound is



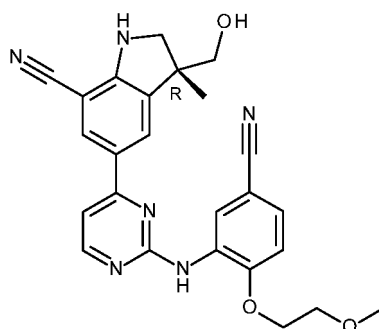
or a pharmaceutically acceptable addition salt or a solvate thereof.

16. The compound according to claim 1, wherein the compound is



or a pharmaceutically acceptable addition salt or a solvate thereof.

17. The compound according to claim 1, wherein the compound is



or a pharmaceutically acceptable addition salt or a solvate thereof.

18. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 17 and a pharmaceutically acceptable carrier or diluent.

19. A compound as claimed in any one of claims 1 to 17 for use as a medicament.

20. A compound as claimed in any one of claims 1 to 17 for use in the prevention or treatment of cancer.

21. The compound according to claim 20 for use in the prevention or treatment of B-cell malignancies.

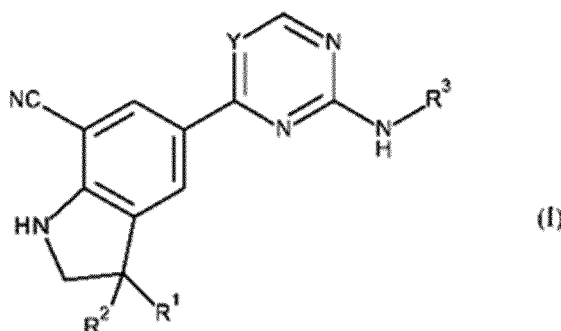
22. The compound according to claim 21 wherein the B-cell malignancy is selected from multiple myeloma, hodgkins lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma or chronic lymphocytic leukemia.

23. A pharmaceutical composition as claimed in claim 18 for use in the prevention or treatment of cancer.

24. A compound as defined in any one of claims 14-17 for use in the treatment of a haematological malignancy.

Patentansprüche

1. Verbindung der Formel (I):



ein Tautomer oder eine stereoisomere Form davon, wobei R¹ ein C₁₋₄-Alkyl repräsentiert;

R² ein C₁₋₆-Alkyl oder C₁₋₆-Alkyl, das mit einem R⁵ substituiert ist repräsentiert;

Y CR⁴ oder N repräsentiert;

R⁴ Wasserstoff oder Halogen repräsentiert;

R⁵ Halogen, Het^{3a}, -NR^{6a}R^{6b} oder -OR⁷ repräsentiert;

R^{6a} Wasserstoff oder C₁₋₄-Alkyl repräsentiert;

R^{6b} Wasserstoff, C₁₋₄-Alkyl; C₃₋₆-Cycloalkyl; -C(=O)-C₁₋₄-Alkyl; -C(=O)-Het⁴; -S(=O)₂-C₁₋₄-Alkyl, das mit einem Substituenten, ausgewählt aus der Gruppe bestehend aus -OH und -NR^{16a}R^{16b} substituiert ist; oder C₁₋₄-Alkyl, das mit einem Substituenten, ausgewählt aus der Gruppe bestehend aus -OH und -S(=O)₂-C₁₋₄-Alkyl substituiert ist, repräsentiert;

R⁷ Wasserstoff, C₁₋₄-Alkyl, C₁₋₄-Alkyl-NR^{8a}R^{8b}, -C(=O)-R⁹, -S(=O)₂-OH, -P(=O)₂-OH, -(C=O)-CH(NH₂)-C₁₋₄-Alkyl-Ar¹ oder -C₁₋₄-Alkyl-Het^{3b} repräsentiert;

R⁸ Wasserstoff oder C₁₋₄-Alkyl repräsentiert;

R^{8b} Wasserstoff, C₁₋₄-Alkyl oder C₃₋₆-Cycloalkyl repräsentiert;

R⁹ C₁₋₆-Alkyl oder C₁₋₆-Alkyl, das mit einem Substituenten, ausgewählt aus der Gruppe bestehend aus -NH₂, -COOH und Het⁶ substituiert ist repräsentiert;

R^{16a} und R^{16b} jeweils unabhängig Wasserstoff, C₁₋₄-Alkyl oder C₃₋₆-Cycloalkyl repräsentieren;

R³ Phenyl repräsentiert, das wahlweise mit einem, zwei oder drei Substituenten substituiert ist, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen; Cyano; C₁₋₆-Alkyl, -O-C₁₋₄-Alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄-Alkyl; -S(=O)(=N-R^{20a})C₁₋₄-Alkyl, -O-C₁₋₄-Alkyl, das mit einem, zwei oder drei Halogenatomen substituiert ist; -O-C₁₋₄-Alkyl-R¹², C₃₋₆-Cycloalkyl; -O-C₃₋₆-Cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; R²¹; -P(=O)-(C₁₋₄-Alkyl)₂; -NH-C(=O)-C₁₋₄-Alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄-Alkyl, das mit einem, zwei oder drei Halogenatomen substituiert ist; C₁₋₄-Alkyl, das mit einem, zwei oder drei -OH Substituenten substituiert ist; C₁₋₄-Alkyl, das mit einem R¹³ substituiert ist; C₁₋₄-Alkyl, das mit einem R¹⁸ substituiert ist; C₂₋₆-Alkenyl; C₂₋₆-Alkenyl, das mit einem R¹³ substituiert ist; C₂₋₆-Alkyl; und C₂₋₆-Alkyl, das mit einem R¹³ substituiert ist;

R¹⁰ -OH, -O-C₁₋₄-Alkyl, -NR^{11a}R^{11b} oder Het² repräsentiert;

R¹⁸ einen 5-gliedrigen aromatischen Ring repräsentiert, der ein, zwei oder drei N-Atome enthält; wobei der 5-gliedrige aromatische Ring wahlweise mit einem Substituenten substituiert sein kann, ausgewählt aus der Gruppe bestehend aus C₁₋₄-Alkyl und C₃₋₆-Cycloalkyl;

R²¹ 3,6-Dihydro-2H-pyran-4-yl oder 1,2,3,6-Tetrahydro-4-pyridinyl repräsentiert; wobei das 1,2,3,6-Tetrahydro-4-pyridinyl wahlweise an dem N-Atom mit C₁₋₄-Alkyl oder C₃₋₆-Cycloalkyl substituiert sein kann;

Het^{1a}, Het^{1c} und Het^{1d} jeweils unabhängig ein 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocycl, das ein oder zwei Heteroatome enthält, die jeweils unabhängig ausgewählt sind aus O, S, S(=O)_p und N; oder ein 6- bis 11-gliedriges, bicyclisches, gesättigtes Heterocycl, einschließlich kondensierte, Spiro- und verbrückte Ringe, das ein, zwei oder drei Heteroatome enthält, die jeweils unabhängig ausgewählt sind aus O, S, S(=O)_p und N, repräsentieren;

wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocycl oder das 6- bis 11-gliedrige, bicyclische,

gesättigte Heterocyclyl, wenn möglich, wahlweise an einem, zwei oder drei N-Ringatomen mit einem Substituenten substituiert sein kann, der jeweils unabhängig ausgewählt ist aus der Gruppe bestehend aus C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl und C₁₋₄-Alkyl, das mit einem Substituenten, ausgewählt aus der Gruppe bestehend aus -OH und -O-C₁₋₄-Alkyl substituiert ist; und

wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl oder das 6- bis 11-gliedrige, bicyclische, gesättigte Heterocyclyl wahlweise an einem, zwei oder drei C-Ringatomen mit einem oder zwei Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus -OH, Halogen, C₁₋₄-Alkyl, Cyano, -C(=O)-C₁₋₄-Alkyl, -O-C₁₋₄-Alkyl, -NH₂, -NH(C₁₋₄-Alkyl) und -N(C₁₋₄-Alkyl)₂;

Het^{1b}, Het^{1e}, Het^{1g}, Het⁴, Het⁷ und Het⁸ jeweils unabhängig ein 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentieren, das durch jedes verfügbaren C-Ringatom an den Rest des Moleküls der Formel (I) gebunden ist, wobei das Het^{1b}, Het^{1e}, Het^{1g}, Het⁴, Het⁷ und Het⁸ ein oder zwei Heteroatome enthält, jeweils unabhängig ausgewählt aus O, S, S(=O)_p und N;

wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl wahlweise, wenn möglich, an einem oder zwei N-Ringatomen mit einem Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl und C₁₋₄-Alkyl, das mit einem Substituenten substituiert ist, ausgewählt aus der Gruppe bestehend aus -OH und -O-C₁₋₄-Alkyl; und

wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl wahlweise an einem, zwei oder drei C-Ringatomen mit einem oder zwei Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus -OH, Halogen, C₁₋₄-Alkyl, Cyano, -C(=O)-C₁₋₄-Alkyl, -O-C₁₋₄-Alkyl, -NH₂, -NH(C₁₋₄-Alkyl) und -N(C₁₋₄-Alkyl)₂;

Het² ein Heterocyclyl der Formel (b-1) repräsentiert;



(b-1) ein N-gebundenes 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl, das wahlweise ein zusätzliches Heteroatom enthält, ausgewählt aus O, S, S(=O)_p und N, oder ein N-gebundenes 6- bis 11-gliedriges, bicyclisches, gesättigtes Heterocyclyl, einschließlich kondensierte, Spiro- oder verbrückte Ringe, das wahlweise ein oder zwei zusätzliche Heteroatome enthält, die jeweils unabhängig ausgewählt sind aus O, S, S(=O)_p und N, repräsentiert;

wobei in dem Fall, dass (b-1) ein oder zwei zusätzliche N-Atome enthält, das eine oder die zwei N-Atome wahlweise mit einem Substituenten substituiert sein kann/können, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl und Het⁷; und

wobei (b-1) wahlweise an ein, zwei oder drei C-Ringatomen mit einem oder zwei Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen, -OH, Cyano, C₁₋₄-Alkyl, -O-C₁₋₄-Alkyl, -NH₂, -NH(C₁₋₄-Alkyl), -N(C₁₋₄-Alkyl)₂ und C₁₋₄-Alkyl-OH;

R^{11b} Wasserstoff; Het^{1e}; C₁₋₄-Alkyl; -C₁₋₄-Alkyl-Het⁵; -C₁₋₄-Alkyl-Het⁸; C₁₋₄-Alkyl, das mit einem, zwei oder drei Substituenten substituiert ist, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen, -OH und -O-C₁₋₄-Alkyl; C₃₋₆-Cycloalkyl; oder C₃₋₆-Cycloalkyl, das mit einem, zwei oder drei Substituenten substituiert ist, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen, -OH und -O-C₁₋₄-Alkyl, repräsentiert;

R¹³ -O-C₁₋₄-Alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆-Cycloalkyl, Het^{1d} oder -C(=O)-Het^{1f} repräsentiert; R¹² -OH, -O-C₁₋₄-Alkyl, -NR^{14a}R^{14b}, -C(=O)NR^{14c}R^{14d}, -S(=O)₂-C₁₋₄-Alkyl, -S(=O)(=N-R^{20b})-C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl, Ar² oder Het^{1c} repräsentiert;

Ar¹ Phenyl repräsentiert, wahlweise substituiert mit einer Hydroxygruppe;

Ar² Phenyl repräsentiert, wahlweise substituiert mit einem C₁₋₄-Alkyl,

Het^{3a}, Het^{3b}, Het⁵, Het⁶ und Het^{1f} jeweils unabhängig ein Heterocyclyl der Formel (c-1) repräsentieren:



(c-1) ein N-gebundenes 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentiert, das

wahlweise ein zusätzliches Heteroatom enthält, ausgewählt aus O, S, S(=O)_p und N; wobei in dem Fall, das (c-1) ein zusätzliches N-Atom enthält, das zusätzliche N-Atom wahlweise mit C₁₋₄-Alkyl oder C₃₋₆-Cycloalkyl substituiert sein kann; und
 wobei (c-1) wahlweise an ein oder zwei C-Ringatomen mit einem oder zwei Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen, C₁₋₄-Alkyl und C₃₋₆-Cycloalkyl;

R^{11a}, R^{14a}, R^{14c}, R^{15a}, R^{17a} und R^{19a} jeweils unabhängig Wasserstoff oder C₁₋₄-Alkyl repräsentieren;
 R^{14b}, R^{14d}, R^{15b}, R^{17b} und R^{19b} jeweils unabhängig Wasserstoff; C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl; -C(=O)-C₁₋₄-Alkyl; C₁₋₄-Alkyl, das mit einem Substituenten, ausgewählt aus der Gruppe bestehend aus Halogen, -OH und -O-C₁₋₄-Alkyl substituiert ist; -C(=O)-C₁₋₄-Alkyl, das mit einem Substituenten, ausgewählt aus der Gruppe bestehend aus Halogen, -OH und -O-C₁₋₄-Alkyl substituiert ist; oder -S(=O)₂-C₁₋₄-Alkyl repräsentieren;
 R^{20a} und R^{20b} jeweils unabhängig Wasserstoff; C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl; oder C₁₋₄-Alkyl, das mit einem Substituenten substituiert ist, ausgewählt aus der Gruppe bestehend aus -OH und -O-C₁₋₄-Alkyl repräsentieren;
 p 1 oder 2 repräsentiert;
 oder ein pharmazeutisch akzeptables Additionssalz oder ein Solvat davon.

2. Verbindung nach Anspruch 1, wobei

Y CR⁴ repräsentiert;
 R⁵ Het^{3a}, -NR^{6a}R^{6b} oder -OR⁷ repräsentiert;
 R³ Phenyl repräsentiert, wahlweise substituiert mit einem, zwei oder drei Substituenten, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen; Cyano; C₁₋₆-Alkyl, -O-C₁₋₄-Alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄-Alkyl; -S(=O)(=N-R^{20a})-C₁₋₄-Alkyl, -O-C₁₋₄-Alkyl, das mit einem, zwei oder drei Halogenatomen substituiert ist; -O-C₁₋₄-Alkyl-R¹², C₃₋₆-Cycloalkyl; -O-C₃₋₆-Cycloalkyl; Het^{1a}; -O-Het^{1b}; R¹⁸; R²¹; -P(=O)-(C₁₋₄-Alkyl)₂; -NH-C(=O)-C₁₋₄-Alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄-Alkyl, das mit einem, zwei oder drei Halogenatomen substituiert ist; C₁₋₄-Alkyl, das mit einem, zwei oder drei -OH Substituenten substituiert ist; C₁₋₄-Alkyl, das mit einem R¹³ substituiert ist; C₁₋₄-Alkyl, das mit einem R¹⁸ substituiert ist; C₂₋₆-Alkenyl; und C₂₋₆-Alkenyl, das mit einem R¹³ substituiert ist;
 Het² ein Heterocycl der Formel (b-1) repräsentiert;



(b-1) ein N-gebundenes 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocycl, das wahlweise ein zusätzliches Heteroatom enthält, ausgewählt aus O, S, S(=O)_p und N, oder ein N-gebundenes 6- bis 11-gliedriges, bicyclisches, gesättigtes Heterocycl, einschließlich kondensierte, Spiro- oder verbrückte Ringe, das wahlweise ein oder zwei zusätzliche Heteroatome enthält, die jeweils unabhängig ausgewählt sind aus O, S, S(=O)_p und N, repräsentiert;
 wobei in dem Fall, dass (b-1) ein oder zwei zusätzliche N-Atome enthält, das eine oder die zwei N-Atome wahlweise mit einem C₁₋₄-Alkyl, substituiert sein kann/können; und
 wobei (b-1) wahlweise an ein, zwei oder drei C-Ringatomen mit einem oder zwei Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen, -OH, Cyano, C₁₋₄-Alkyl, -O-C₁₋₄-Alkyl, -NH₂, -NH(C₁₋₄-Alkyl), -N(C₁₋₄-Alkyl)₂ und C₁₋₄-Alkyl-OH;

R^{11b} Wasserstoff; Het^{1e}; C₁₋₄-Alkyl, -C₁₋₄-Alkyl-Het⁵, C₁₋₄-Alkyl, das mit einem, zwei oder drei Substituenten substituiert ist, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen, -OH und -O-C₁₋₄-Alkyl; C₃₋₆-Cycloalkyl; oder C₃₋₆-Cycloalkyl, das mit einem, zwei oder drei Substituenten substituiert ist, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen, -OH und -O-C₁₋₄-Alkyl, repräsentiert; und
 R^{14b}, R^{14d}, R^{15b}, R^{17b} und R^{19b} jeweils unabhängig Wasserstoff; C₁₋₄-Alkyl; C₃₋₆-Cycloalkyl; oder C₁₋₄-Alkyl, das mit einem Substituenten substituiert ist, ausgewählt aus der Gruppe bestehend aus Halogen, -OH und -O-C₁₋₄-Alkyl repräsentieren.

3. Verbindung nach Anspruch 1, wobei

R⁵ Halogen, -NR^{6a}R^{6b} oder -OR⁷ repräsentiert;

R^{6a} Wasserstoff repräsentiert;

R^{6b} -C(=O)-C₁₋₄-Alkyl; oder -S(=O)₂-C₁₋₄-Alkyl repräsentiert;

R⁷ Wasserstoff, C₁₋₄-Alkyl-NR^{8a}R^{8b}, -C(=O)-R⁹, -S(=O)₂-OH oder -(C=O)-CH(NH₂)-C₁₋₄-Alkyl-Ar¹ repräsentiert;

R^{8a} Wasserstoff repräsentiert;

R^{8b} C₃₋₆-Cycloalkyl repräsentiert;

R³ Phenyl repräsentiert, das wahlweise mit einem, zwei oder drei Substituenten substituiert ist, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen; Cyano; C₁₋₆-Alkyl; -O-C₁₋₄-Alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄-Alkyl; -O-C₁₋₄-Alkyl-R¹²; C₃₋₆-Cycloalkyl; -O-C₃₋₆-Cycloalkyl, Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄-Alkyl)₂; -NH-C(=O)-C₁₋₄-Alkyl; -NH-C(=O)-Het^{1g}; -NR^{17a}R^{17b}; C₁₋₄-Alkyl, das mit einem, zwei oder drei Halogenatomen substituiert ist; C₁₋₄-Alkyl, das mit einem, zwei oder drei -OH Substituenten substituiert ist; C₁₋₄-Alkyl, das mit einem R¹³ substituiert ist; C₂₋₆-Alkenyl, das mit einem R¹³ substituiert ist; C₂₋₆-Alkynyl, das mit einem R¹³ substituiert ist;

R¹⁸ einen 5-gliedrigen aromatischen Ring repräsentiert, der ein, zwei oder drei N-Atome enthält; wobei der 5-gliedrige aromatische Ring wahlweise mit einem Substituenten substituiert sein kann, ausgewählt aus der Gruppe bestehend aus C₁₋₄-Alkyl;

Het^{1a}, Het^{1c} und Het^{1d} jeweils unabhängig ein 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentieren, das ein oder zwei Heteroatome enthält, jeweils unabhängig ausgewählt aus O und N;

wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl wahlweise, wenn möglich, an einem oder zwei N-Ringatomen mit einem Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl und C₁₋₄-Alkyl, das mit einem -O-C₁₋₄-Alkyl substituiert ist; und wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl wahlweise an einem, zwei oder drei C-Ringatomen mit einem oder zwei Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus -OH, Halogen, C₁₋₄-Alkyl, -O-C₁₋₄-Alkyl und -N(C₁₋₄-Alkyl)₂;

Het^{1b}, Het^{1e}, Het^{1g}, Het⁷ und Het⁸ jeweils unabhängig ein 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentieren, das durch ein verfügbares Ringkohlenstoffatom an den Rest des Moleküls der Formel (I) gebunden ist, wobei das Het^{1b}, Het^{1e}, Het^{1g}, Het⁷ und Het⁸ ein oder zwei Heteroatome enthalten, jeweils unabhängig ausgewählt aus O und N;

wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl, wenn möglich, wahlweise an einem oder zwei N-Ringatomen mit einem Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus -C₁₋₄-Alkyl und C₃₋₆-Cycloalkyl; und

wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl wahlweise an einem, zwei oder drei C-Ringatomen mit einem oder zwei Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus -OH und Halogen;

Het² ein Heterocyclyl der Formel (b-1) repräsentiert;



(b-1) ein N-gebundenes 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl, das wahlweise ein zusätzliches Heteroatom enthält, ausgewählt aus O und N, oder ein N-gebundenes 6- bis 11-gliedriges, bicyclisches, gesättigtes Heterocyclyl, einschließlich kondensierte, Spiro- oder verbrückte Ringe, das wahlweise ein oder zwei zusätzliche N-Atome enthält, repräsentiert;

wobei in dem Fall, dass (b-1) ein oder zwei zusätzliche N-Atome enthält, das eine oder die zwei N-Atome wahlweise mit einem Substituenten substituiert sein kann/können, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl und Het⁷; und

wobei (b-1) wahlweise an ein, zwei oder drei C-Ringatomen mit einem oder zwei Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus -OH, Cyano, C₁₋₄-Alkyl und C₁₋₄-Alkyl-OH,

R^{11b} Het^{1e}; C₁₋₄-Alkyl; -C₁₋₄-Alkyl-Het⁵, -C₁₋₄-Alkyl-Het⁸, C₁₋₄-Alkyl, das mit einem, zwei oder drei -OH Substituenten substituiert ist; oder C₃₋₆-Cycloalkyl, das mit einem, zwei oder drei Substituenten substituiert ist, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen und -OH, repräsentiert;

R¹² -OH, -O-C₁₋₄-Alkyl, -NR^{14a}R^{14b}, -C(=O)NR^{14c}R^{14d}, -S(=O)₂-C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl, Ar² oder Het^{1c} re-

präsentiert;

Ar¹ Phenyl repräsentiert;

Het⁵, Het⁶ und Het^{1f} jeweils unabhängig ein Heterocyclyl der Formel (c-1) repräsentieren:

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(c-1) ein N-gebundenes 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentiert, das wahlweise ein zusätzliches Heteroatom enthält, ausgewählt aus O und N; wobei in dem Fall, dass (c-1) ein zusätzliches N-Atom enthält, das zusätzliche N-Atom wahlweise mit einem C₁₋₄-Alkyl substituiert sein kann; und R^{14b}, R^{14d}, R^{15b}, R^{17b} und R^{19b} jeweils unabhängig Wasserstoff, C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl; -C(=O)-C₁₋₄-Alkyl; C₁₋₄-Alkyl, das mit einem Substituenten substituiert ist, ausgewählt aus der Gruppe bestehend aus -OH und -O-C₁₋₄-Alkyl; oder -S(=O)₂-C₁₋₄-Alkyl repräsentieren.

4. Verbindung nach Anspruch 1 oder 2, wobei R⁵ -NR^{6a}R^{6b} oder -OR⁷ repräsentiert;

R^{6a} Wasserstoff repräsentiert;
 R^{6b} -C(=O)-C₁₋₄-Alkyl; oder -S(=O)₂-C₁₋₄-Alkyl repräsentiert;
 R⁷ Wasserstoff, -C(=O)-R⁹, -S(=O)₂-OH oder -(C=O)-CH(NH₂)-C₁₋₄-Alkyl-Ar¹ repräsentiert;
 R⁹ C₁₋₄-Alkyl oder C₁₋₄-Alkyl, das mit einem Substituenten substituiert ist, ausgewählt aus der Gruppe bestehend aus -NH₂, -COOH und Het⁶, repräsentiert;
 R³ Phenyl repräsentiert, das wahlweise mit einem, zwei oder drei Substituenten substituiert ist, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen; Cyano; C₁₋₆-Alkyl, -O-C₁₋₄-Alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄-Alkyl; -O-C₁₋₄-Alkyl-R¹²; C₃₋₆-Cycloalkyl; -O-C₃₋₆-Cycloalkyl, Het^{1a}; -O-Het^{1b}; R¹⁸; -P(=O)-(C₁₋₄-Alkyl)₂; -NH-C(=O)-C₁₋₄-Alkyl; -NH-C(=O)-Het^{1g}; C₁₋₄-Alkyl, das mit einem, zwei oder drei Halogenatomen substituiert ist; C₁₋₄-Alkyl, das mit einem, zwei oder drei -OH Substituenten substituiert ist; und C₁₋₄-Alkyl, das mit einem R¹³ substituiert ist;
 R¹⁰ -OH, -O-C₁₋₄-Alkyl, -NR^{11a}R^{11b} oder Het² repräsentiert;
 R¹⁸ einen 5-gliedrigen aromatischen Ring repräsentiert, der ein, zwei oder drei N-Atome enthält; wobei der 5-gliedrige aromatische Ring wahlweise mit einem Substituenten substituiert sein kann, ausgewählt aus der Gruppe bestehend aus C₁₋₄-Alkyl;
 Het^{1a}, Het^{1c} und Het^{1d} jeweils unabhängig ein 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentieren, das ein oder zwei Heteroatome enthält, jeweils unabhängig ausgewählt aus O und N; wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl wahlweise, wenn möglich, an einem oder zwei N-Ringatomen mit einem Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl und C₁₋₄-Alkyl, das mit einem -O-C₁₋₄-Alkyl substituiert ist; und wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl wahlweise an einem, zwei oder drei C-Ringatomen mit einem oder zwei Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend -OH, Halogen, C₁₋₄-Alkyl, -O-C₁₋₄-Alkyl und -N(C₁₋₄-Alkyl)₂;
 Het^{1b}, Het^{1e} und Het^{1g} jeweils unabhängig ein 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentieren, das durch ein verfügbares Ringkohlenstoffatom an den Rest des Moleküls der Formel (I) gebunden ist, wobei das Het^{1b}, Het^{1e} und Het^{1g} ein oder zwei Heteroatome enthalten, jeweils unabhängig ausgewählt aus O und N;
 wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl, wenn möglich, wahlweise an einem oder zwei N-Ringatomen mit einem Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus C₁₋₄-Alkyl und C₃₋₆-Cycloalkyl; und
 wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl wahlweise an einem, zwei oder drei C-Ringatomen mit einem oder zwei -OH Substituenten substituiert sein kann;
 Het² ein Heterocyclyl der Formel (b-1) repräsentiert;

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(b-1) ein N-gebundenes 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl, das wahlweise ein zusätzliches N-Atom enthält, oder ein N-gebundenes 6- bis 11-gliedriges, bicyclisches, gesättigtes Heterocyclyl, einschließlich kondensierte, Spiro- und verbrückte Ringe, das wahlweise ein oder zwei zusätzliche N-Atome enthält, repräsentiert;

wobei in dem Fall, dass (b-1) ein oder zwei zusätzliche N-Atome enthält, das eine oder die zwei N-Atome wahlweise mit einem C₁₋₄-Alkyl, substituiert sein kann/können; und

wobei (b-1) wahlweise an ein, zwei oder drei C-Ringatomen mit einem oder zwei Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus -OH, Cyano und C₁₋₄-Alkyl-OH;

R^{11b} Het^{1e}; C₁₋₄-Alkyl, -C₁₋₄-Alkyl-Het⁵; C₁₋₄-Alkyl, das mit einem, zwei oder drei -OH Substituenten substituiert ist; oder C₃₋₆-Cycloalkyl, das mit einem, zwei oder drei Substituenten substituiert ist, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen und -OH, repräsentiert;

R¹³ -O-C₁₋₄-Alkyl, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, C₃₋₆-Cycloalkyl, Het^{1d} oder -C(=O)-Het^{1f} repräsentiert;

R¹² -OH, -O-C₁₋₄-Alkyl, -NR^{14a}R^{14b}, -C(=O)NR^{14c}R^{14d}, -S(=O)₂-C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl, Ar² oder Het^{1c} repräsentiert;

Ar¹ Phenyl repräsentiert;

Ar² Phenyl repräsentiert, das wahlweise mit einem C₁₋₄-Alkyl substituiert ist;

Het⁵, Het⁶ und Het^{1f} jeweils unabhängig ein Heterocyclyl der Formel (c-1) repräsentieren:



(c-1) ein N-gebundenes 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentiert, das wahlweise ein zusätzliches Heteroatom enthält, ausgewählt aus O und N;

wobei in dem Fall, dass (c-1) ein zusätzliches N-Atom enthält, das zusätzliche N-Atom wahlweise mit einem C₁₋₄-Alkyl substituiert sein kann;

R^{11a}, R^{14a}, R^{14c}, R^{15a} und R^{19a} jeweils unabhängig Wasserstoff oder C₁₋₄-Alkyl repräsentieren;

R^{14b}, R^{14d}, R^{15b} und R^{19b} jeweils unabhängig Wasserstoff; C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl oder C₁₋₄-Alkyl, das mit einem -O-C₁₋₄-Alkyl substituiert ist, repräsentieren.

5. Verbindung nach Anspruch 1 oder 2, wobei

Y CR⁴ repräsentiert;

R⁴ Wasserstoff repräsentiert;

R⁵ -OR⁷ repräsentiert;

R⁷ Wasserstoff oder C(=O)-R⁹ repräsentiert;

R⁹ C₁₋₄-Alkyl repräsentiert;

R³ Phenyl repräsentiert, das mit einem, zwei oder drei Substituenten substituiert ist, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen; Cyano; C₁₋₆-Alkyl; -O-C₁₋₄-Alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄-Alkyl; -O-C₁₋₄-Alkyl-R¹²; -O-C₃₋₆-Cycloalkyl; -O-Het^{1b}; -NH-C(=O)-Het^{1g}; und C₁₋₄-Alkyl, das mit einem R¹³ substituiert ist;

R¹⁰ -NR^{11a}R^{11b} oder Het² repräsentiert;

Het^{1g} ein 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentiert, das durch ein verfügbares Ringkohlenstoffatom an den Rest des Moleküls der Formel (I) gebunden ist, wobei das Het^{1g} ein oder zwei N-Atome enthält;

wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl, wenn möglich, wahlweise an einem oder zwei N-Ringatomen mit einem C₁₋₄-Alkyl substituiert sein kann;

Het^{1b} ein 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentiert, das durch ein verfügbares Ringkohlenstoffatom an den Rest des Moleküls der Formel (I) gebunden ist, wobei das Het^{1b} ein oder zwei N-Atome enthält;

wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl, wenn möglich, wahlweise an einem oder zwei N-Ringatomen mit einem C₁₋₄-Alkyl Substituenten substituiert sein kann; und

wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl wahlweise an einem C-Ringatom mit einem Halogen-Substituenten substituiert sein kann;

Het² ein Heterocyclyl der Formel (b-1) repräsentiert;



(b-1) ein N-gebundenes 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentiert, wobei (b-1) wahlweise an einem C-Atom mit einem -OH Substituenten substituiert sein kann;

R^{11b} C₁₋₄-Alkyl repräsentiert;

R¹³ -O-C₁₋₄-Alkyl repräsentiert;

R¹² -O-C₁₋₄-Alkyl repräsentiert; und

R^{11a} Wasserstoff repräsentiert.

6. Verbindung nach Anspruch 1 oder 2, wobei

R⁴ Wasserstoff repräsentiert;

R⁵ -OR⁷ repräsentiert;

R⁷ Wasserstoff oder -C(=O)-R⁹ repräsentiert;

R⁹ C₁₋₄-Alkyl repräsentiert;

R³ Phenyl repräsentiert, das mit einem, zwei oder drei Substituenten substituiert ist, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen; Cyano; C₁₋₆-Alkyl; -O-C₁₋₄-Alkyl; -C(=O)-R¹⁰; -S(=O)₂-C₁₋₄-Alkyl; -O-C₁₋₄-Alkyl-R¹², -NH-C(=O)-Het¹⁹; und C₁₋₄-Alkyl, das mit einem R¹³ substituiert ist;

R¹⁰ -NR^{11a}R^{11b} oder Het² repräsentiert;

Het¹⁹ ein 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentiert, das durch ein verfügbares Ringkohlenstoffatom an den Rest des Moleküls der Formel (I) gebunden ist, wobei das Het¹⁹ ein oder zwei N-Atome enthält;

wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl, wenn möglich, wahlweise an einem oder zwei N-Ringatomen mit einem C₁₋₄-Alkyl Substituenten substituiert sein kann;

Het² ein Heterocyclyl der Formel (b-1) repräsentiert;



(b-1) ein N-gebundenes 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentiert, wobei (b-1) wahlweise an einem C-Atom mit einem -OH Substituenten substituiert sein kann;

R^{11b} C₁₋₄-Alkyl repräsentiert;

R¹³ -O-C₁₋₄-Alkyl repräsentiert;

R¹² -O-C₁₋₄-Alkyl repräsentiert; und

R^{11a} Wasserstoff repräsentiert.

7. Verbindung nach Anspruch 1 oder 2, wobei

R² C₁₋₆-Alkyl, das mit einem R⁵ substituiert ist repräsentiert;

R⁴ Wasserstoff repräsentiert;

R⁵ -OR⁷ repräsentiert;

R⁷ Wasserstoff repräsentiert; und

R³ Phenyl repräsentiert, das mit einem, zwei oder drei Substituenten substituiert ist, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen; Cyano; und C₁₋₆-Alkyl.

8. Verbindung nach einem der Ansprüche 1 bis 6, wobei

R¹ Methyl repräsentiert;

R² Methyl oder -CH₂-OH repräsentiert.

9. Verbindung nach einem der Ansprüche 1 bis 4, wobei

R⁴ Wasserstoff ist.

10. Verbindung nach einem der Ansprüche 1 bis 6, wobei

R⁵ -OR⁷ repräsentiert; und
R⁷ Wasserstoff repräsentiert.

11. Verbindung nach Anspruch 1 oder 2, wobei

Het^{1a}, Het^{1c} und Het^{1d} jeweils unabhängig ein 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentieren, das ein oder zwei Heteroatome enthält, jeweils unabhängig ausgewählt aus O, S, S(=O)_p und N; wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl, wenn möglich, wahlweise an ein oder zwei N-Ringatomen mit einem Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus C₁₋₄-Alkyl, C₃₋₆-Cycloalkyl und C₁₋₄-Alkyl, das mit einem Substituenten substituiert ist, ausgewählt aus der Gruppe bestehend aus -OH und -O-C₁₋₄-Alkyl; und wobei das 4- bis 7-gliedrige, monocyclische, gesättigte Heterocyclyl wahlweise an einem, zwei oder drei C-Ringatomen mit einem oder zwei Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus -OH, Halogen, C₁₋₄-Alkyl, Cyano, -C(=O)-C₁₋₄-Alkyl, -O-C₁₋₄-Alkyl, -NH₂, -NH(C₁₋₄-Alkyl) und -N(C₁₋₄-Alkyl)₂.

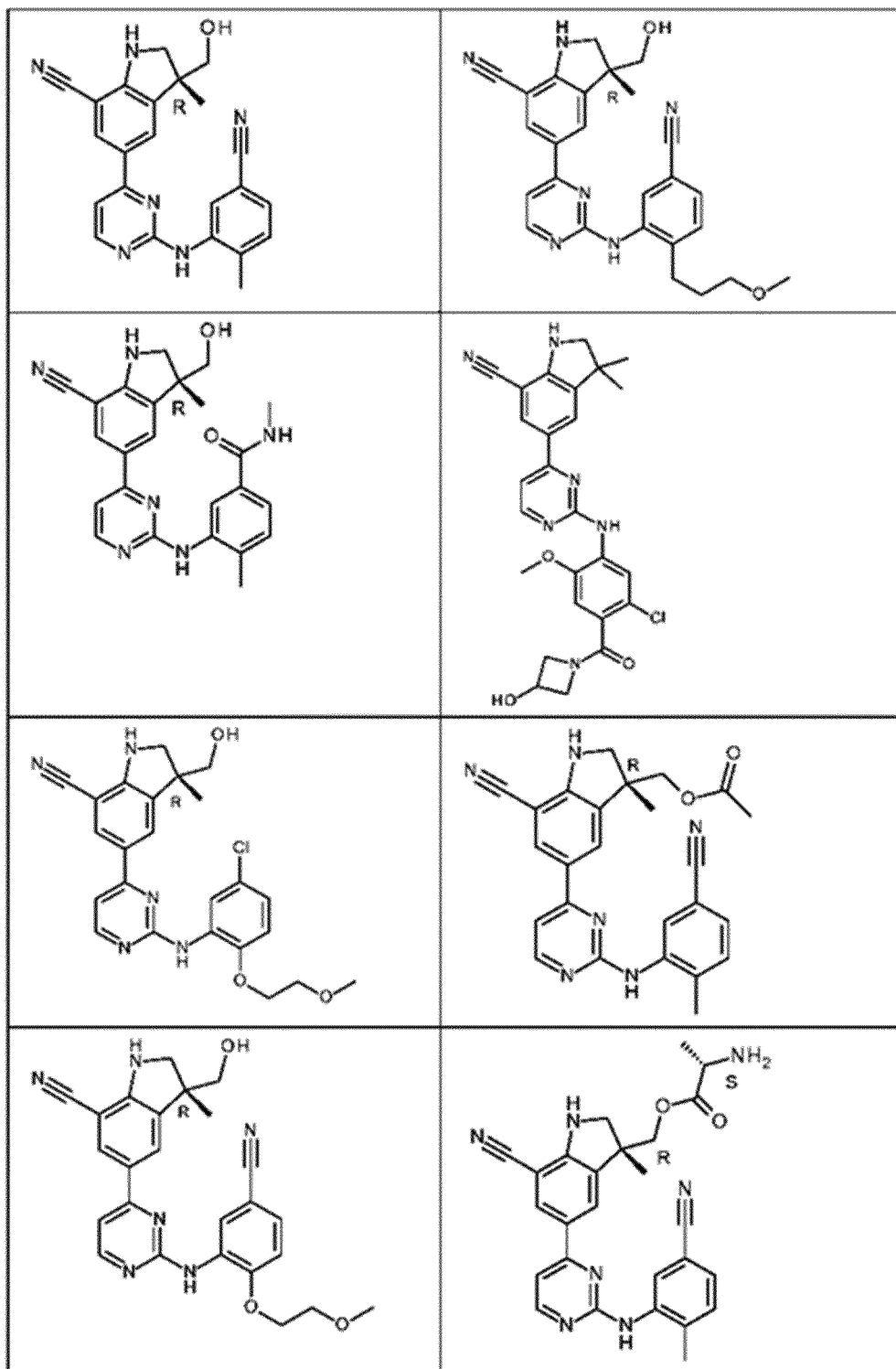
12. Verbindung nach Anspruch 1 oder 2, wobei

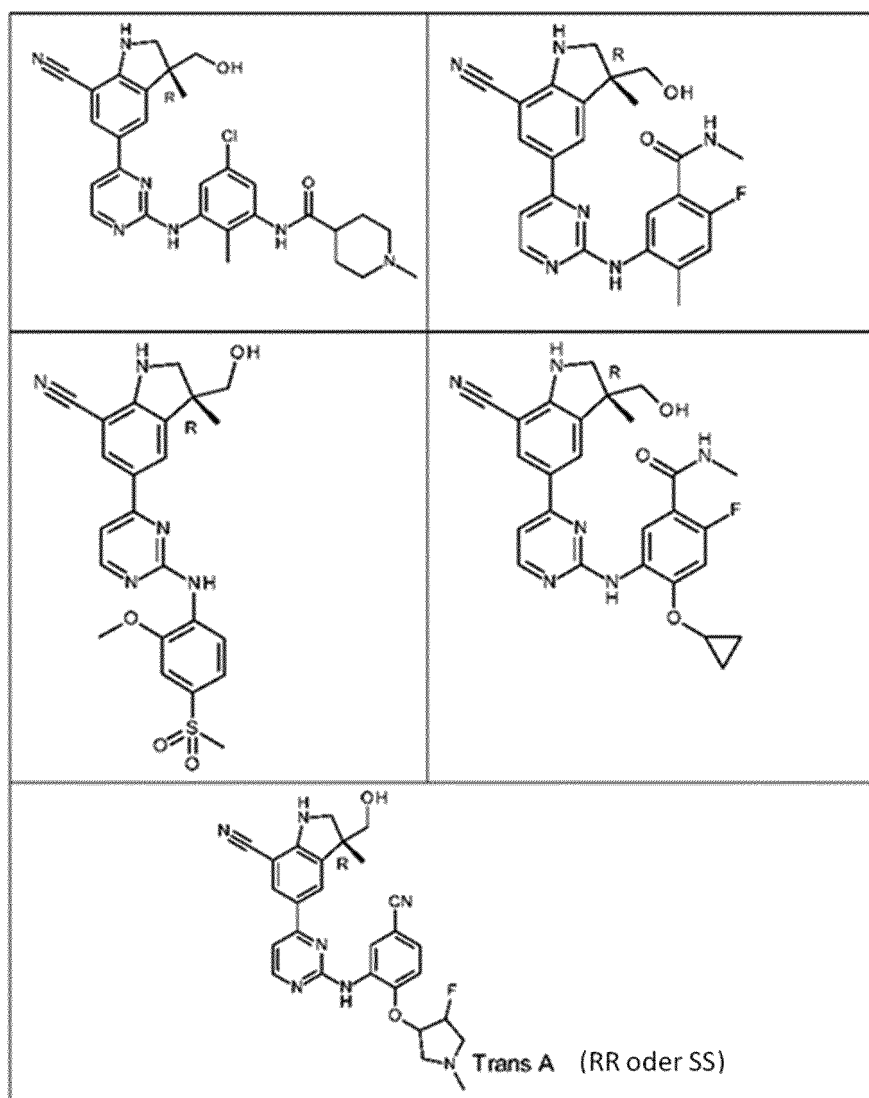
Het² ein Heterocyclyl der Formel (b-1) repräsentiert;



(b-1) ein N-gebundenes 4- bis 7-gliedriges, monocyclisches, gesättigtes Heterocyclyl repräsentiert, das wahlweise ein zusätzliches Heteroatom enthält, ausgewählt aus O, S, S(=O)_p und N; wobei in dem Fall, das (b-1) ein zusätzliches N-Atom enthält, das N-Atom wahlweise mit C₁₋₄-Alkyl substituiert sein kann; und wobei (b-1) wahlweise an ein, zwei oder drei C-Ringatomen mit einem oder zwei Substituenten substituiert sein kann, jeweils unabhängig ausgewählt aus der Gruppe bestehend aus Halogen, -OH, Cyano, C₁₋₄-Alkyl, -O-C₁₋₄-Alkyl, -NH₂, -NH(C₁₋₄-Alkyl), -N(C₁₋₄-Alkyl)₂ und C₁₋₄-Alkyl-OH.

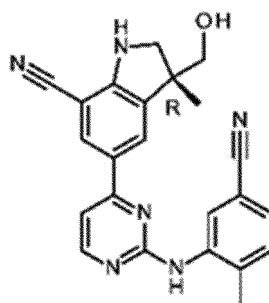
13. Verbindung nach Anspruch 1, wobei die Verbindung ausgewählt ist aus





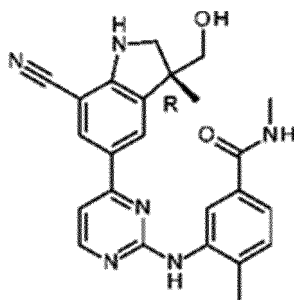
Tautomeren und stereoisomeren Formen davon,
und den pharmazeutisch akzeptablen Additionssalzen und den Solvaten davon.

14. Verbindung nach Anspruch 1, wobei die Verbindung



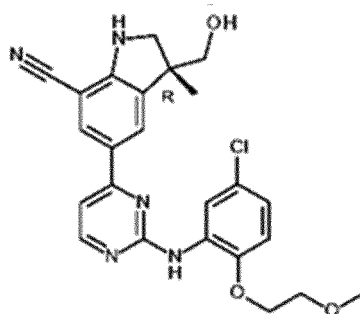
oder ein pharmazeutisch akzeptables Additionssalz oder ein Solvat davon ist.

15. Verbindung nach Anspruch 1, wobei die Verbindung



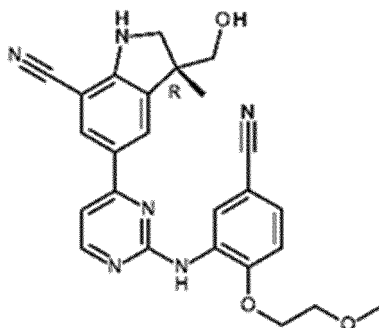
oder ein pharmazeutisch akzeptables Additionssalz oder ein Solvat davon ist.

16. Verbindung nach Anspruch 1, wobei die Verbindung



oder ein pharmazeutisch akzeptables Additionssalz oder ein Solvat davon ist.

17. Verbindung nach Anspruch 1, wobei die Verbindung



oder ein pharmazeutisch akzeptables Additionssalz oder ein Solvat davon ist.

18. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 17 und einen pharmazeutisch akzeptablen Trägerstoff oder Verdünner.

19. Verbindung nach einem der Ansprüche 1 bis 17 zur Verwendung als ein Arzneimittel.

20. Verbindung nach einem der Ansprüche 1 bis 17 zur Verwendung bei der Prävention oder Behandlung von Krebs.

21. Verbindung nach Anspruch 20 zur Verwendung bei der Prävention oder Behandlung von B-Zell-Malignomen.

22. Verbindung nach Anspruch 21, wobei das B-Zell-Malignom ausgewählt ist aus multiplem Myelom, Hodgkin-Lymphom, Mantelzellenlymphom, diffusem großzelligem B-Zelllymphom oder chronischer lymphatischer Leukämie.

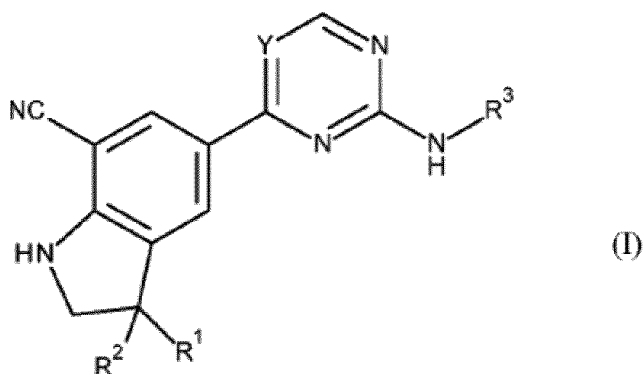
23. Pharmazeutische Zusammensetzung nach Anspruch 18 zur Verwendung bei der Prävention oder Behandlung von

Krebs.

24. Verbindung nach einem der Ansprüche 14 bis 17 zur Verwendung bei der Behandlung eines hämatologischen Malignoms.

Revendications

1. Composé de formule (I) :



un tautomère ou une forme stéréoisomère de celle-ci, dans laquelle

R₁ représente un groupe alkyle en C₁₋₄ ;

R₂ représente un groupe alkyle en C₁₋₆ ou un groupe alkyle en C₁₋₆ substitué par un R⁵ ;

Y représente CR⁴ ou N ;

R⁴ représente un atome d'hydrogène ou un atome d'halogène ;

R⁵ représente un atome d'halogène, Het^{3a}, -NR^{6a}R^{6b} ou -OR⁷ ;

R^{6a} représente un atome d'hydrogène ou un groupe alkyle en C₁₋₄ ;

R^{6b} représente un atome d'hydrogène ; un groupe alkyle en C₁₋₄ ; un groupe cycloalkyle en C₃₋₆ ; -C(=O)-alkyle en C₁₋₄ ; -C(=O)-Het⁴ ; -S(=O)₂-alkyle en C₁₋₄ ; -C(=O)-alkyle en C₁₋₄ substitué par un substituant sélectionné dans le groupe constitué par -OH et -NR^{16a}R^{16b} ; ou un groupe alkyle en C₁₋₄ substitué par un substituant sélectionné dans le groupe constitué par -OH et -S(=O)₂-alkyle en C₁₋₄ ; R⁷ représente un atome d'hydrogène, un groupe alkyle en C₁₋₄, -alkyle en C₁₋₄-NR^{8a}R^{8b}, -C(=O)-R⁹, -S(=O)₂-OH, -P(=O)₂-OH, -(C=O)-CH(NH₂)-alkyle en C₁₋₄-Ar¹ ou -alkyle en C₁₋₄-Het^{3b} ;

R^{8a} représente un atome d'hydrogène ou un groupe alkyle en C₁₋₄ ;

R^{8b} représente un atome d'hydrogène, un groupe alkyle en C₁₋₄ ou un groupe cycloalkyle en C₃₋₆ ;

R⁹ représente un groupe alkyle en C₁₋₆ ou un groupe alkyle en C₁₋₆ substitué par un substituant sélectionné dans le groupe constitué par -NH₂, -COOH et Het⁶ ;

R^{16a} et R^{16b} représentent chacun indépendamment un atome d'hydrogène, un groupe alkyle en C₁₋₄ ou un groupe cycloalkyle en C₃₋₆ ;

R³ représente un groupe phényle éventuellement substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène ; un groupe cyano ; un groupe alkyle en C₁₋₆ ; -O-alkyle en C₁₋₄ ; -C(=O)-R¹⁰ ; -S(=O)₂-alkyle en C₁₋₄ ; -S(=O)(=N-R^{20a})-alkyle en C₁₋₄ ; -O-alkyle en C₁₋₄ substitué par un, deux ou trois atomes d'halogène ; -O-alkyle en C₁₋₄-R¹² ; un groupe cycloalkyle en C₃₋₆ ; -O-cycloalkyle en C₃₋₆ ; Het^{1a} ; -O-Het^{1b} ; R¹⁸ ; R²¹ ; -P(=O)-(alkyle en C₁₋₄)₂ ; -NH-C(=O)-alkyle en C₁₋₄ ; -NH-C(=O)-Het^{1g} ; -NR^{17a}R^{17b} ; un groupe alkyle en C₁₋₄ substitué par un, deux ou trois atomes d'halogène ; un groupe alkyle en C₁₋₄ substitué par un, deux ou trois substituants-OH ; un groupe alkyle en C₁₋₄ substitué par un R¹³ ; un groupe alkyle en C₁₋₄ substitué par un R¹⁸ ; un groupe alcényle en C₂₋₆ ; un groupe alcényle en C₂₋₆ substitué par un R¹³ ; un groupe alcynyle en C₂₋₆ ; et un groupe alcynyle en C₂₋₆ substitué par un R¹³ ; R¹⁰ représente -OH, -O-alkyle en C₁₋₄, -NR^{11a}R^{11b} ou Het² ;

R¹⁸ représente un cycle aromatique à 5 chaînons contenant un, deux ou trois atomes N ; ledit cycle aromatique à 5 chaînons pouvant être éventuellement substitué par un substituant sélectionné dans le groupe constitué par un groupe alkyle en C₁₋₄ et un groupe cycloalkyle en C₃₋₆ ;

R²¹ représente un groupe 3,6-dihydro-2H-pyran-4-yle ou un groupe 1,2,3,6-tétrahydro-4-pyridinyle, le groupe

1,2,3,6-tétrahydro-4-pyridinyle pouvant éventuellement être substitué sur l'atome N par un groupe alkyle en C₁₋₄ ou un groupe cycloalkyle en C₃₋₆ ;

Het^{1a}, Het^{1c} et Het^{1d} représentent chacun indépendamment un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons contenant un ou deux hétéroatomes, chacun indépendamment sélectionné parmi O, S, S(=O)_p et N ; ou un groupe hétérocyclyle saturé bicyclique à 6 à 11 chaînons, notamment des cycles condensés, spiro et pontés, contenant un, deux ou trois hétéroatomes, chacun indépendamment sélectionné parmi O, S, S(=O)_p et N ;

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons ou ledit groupe hétérocyclyle saturé bicyclique à 6 à 11 chaînons pouvant être éventuellement substitué, le cas échéant, sur un, deux ou trois atomes N du cycle par un substituant indépendamment sélectionné dans le groupe constitué par un groupe alkyle en C₁₋₄, un groupe cycloalkyle en C₃₋₆ et un groupe alkyle en C₁₋₄ substitué par un substituant sélectionné dans le groupe constitué par -OH et -O-alkyle en C₁₋₄ ; et

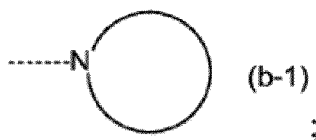
ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons ou ledit groupe hétérocyclyle saturé bicyclique à 6 à 11 chaînons pouvant être éventuellement substitué sur un, deux ou trois atomes C du cycle par un ou deux substituants, chacun indépendamment sélectionné dans le groupe constitué par -OH, un atome d'halogène, un groupe alkyle en C₁₋₄, un groupe cyano, -C(=O)-alkyle en C₁₋₄, -O-alkyle en C₁₋₄, -NH₂, -NH(alkyle en C₁₋₄) et -N(alkyle en C₁₋₄)₂ ;

Het^{1b}, Het^{1e}, Het^{1g}, Het⁴, Het⁷ et Het⁸ représentent chacun indépendamment un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons, attaché au reste de la molécule de formule (I) par le biais d'un quelconque atome de carbone du cycle disponible, lesdits Het^{1b}, Het^{1e}, Het^{1g}, Het⁴, Het⁷ et Het⁸ contenant un ou deux hétéroatomes, chacun indépendamment sélectionné parmi O, S, S(=O)_p et N ;

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué, le cas échéant, sur un ou deux atomes N du cycle par un substituant indépendamment sélectionné dans le groupe constitué par un groupe alkyle en C₁₋₄, un groupe cycloalkyle en C₃₋₆ et un groupe alkyle en C₁₋₄ substitué par un substituant sélectionné dans le groupe constitué par -OH et -O-alkyle en C₁₋₄ ; et

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué sur un, deux ou trois atomes C du cycle par un ou deux substituants, chacun indépendamment sélectionné dans le groupe constitué par -OH, un atome d'halogène, un groupe alkyle en C₁₋₄, un groupe cyano, -C(=O)-alkyle en C₁₋₄, -O-alkyle en C₁₋₄, -NH₂, -NH(alkyle en C₁₋₄) et -N(alkyle en C₁₋₄)₂ ;

Het² représente un groupe hétérocyclyle de formule (b-1) :



(b-1) représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons N-lié contenant éventuellement un hétéroatome supplémentaire sélectionné parmi O, S, S(=O)_p et N ou un groupe hétérocyclyle saturé bicyclique à 6 à 11 chaînons N-lié, notamment des cycles condensés, spiro et pontés, contenant éventuellement un ou deux hétéroatomes supplémentaires, chacun sélectionné parmi O, S, S(=O)_p et N ; dans le cas où (b-1) contient un ou deux atomes N supplémentaires, ledit ou lesdits deux atomes N pouvant être éventuellement substitués par un substituant sélectionné indépendamment dans le groupe constitué par un groupe alkyle en C₁₋₄, un groupe cycloalkyle en C₃₋₆ et Het⁷ ; et

(b-1) pouvant être éventuellement substitué sur un, deux ou trois atomes C du cycle par un ou deux substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène, -OH, un groupe cyano, un groupe alkyle en C₁₋₄, -O-alkyle en C₁₋₄, -NH₂, -NH(alkyle en C₁₋₄), -N(alkyle en C₁₋₄)₂ et un groupe alkyle en C₁₋₄-OH ;

R^{11b} représente un atome d'hydrogène ; Het^{1e} ; un groupe alkyle en C₁₋₄ ; -alkyle en C₁₋₄-Het⁵ ; -alkyle en C₁₋₄-Het⁸ ; un groupe alkyle en C₁₋₄ substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène, -OH et -O-alkyle en C₁₋₄ ; un groupe cycloalkyle en C₃₋₆ ; ou un groupe cycloalkyle en C₃₋₆ substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène, -OH et -O-alkyle en C₁₋₄ ;

R¹³ représente -O-alkyle en C₁₋₄, -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, un groupe cycloalkyle en C₃₋₆, Het^{1d} ou -C(=O)-Het^{1f} ;

R¹² représente -OH, -O-alkyle en C₁₋₄, -NR^{14a}R^{14b}, -C(=O)NR^{14c}R^{14d}, -S(=O)₂-alkyle en C₁₋₄, -S(=O)(=N-R^{20b})-alkyle en C₁₋₄, un groupe cycloalkyle en C₃₋₆, Ar² ou Het^{1c} ;

Ar¹ représente un groupe phényle éventuellement substitué par un groupe hydroxy ; Ar² représente un groupe phényle éventuellement substitué par un groupe alkyle en C₁₋₄ ;
 Het^{3a}, Het^{3b}, Het⁵, Het⁶ et Het^{1f} représentent chacun indépendamment un groupe hétérocyclyle de formule (c-1) :

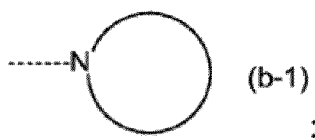


(c-1) représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons N-lié contenant éventuellement un hétéroatome supplémentaire sélectionné parmi O, S, S(=O)_p et N ;
 dans le cas où (c-1) contient un atome N supplémentaire, ledit atome N supplémentaire pouvant être éventuellement substitué par un groupe alkyle en C₁₋₄ ou un groupe cycloalkyle en C₃₋₆ ; et
 (c-1) pouvant être éventuellement substitué sur un ou deux atomes C du cycle par un ou deux substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène, un groupe alkyle en C₁₋₄ et un groupe cycloalkyle en C₃₋₆ ;

R^{11a}, R^{14a}, R^{14c}, R^{15a}, R^{17a} et R^{19a} représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁₋₄ ;
 R^{14b}, R^{14d}, R^{15b}, R^{17b} et R^{19b} représentent chacun indépendamment un atome d'hydrogène ; un groupe alkyle en C₁₋₄ ; un groupe cycloalkyle en C₃₋₆ ; -C(=O)-alkyle en C₁₋₄ ; un groupe alkyle en C₁₋₄ substitué par un substituant sélectionné dans le groupe constitué par un atome d'halogène, -OH et -O-alkyle en C₁₋₄ ; -C(=O)-alkyle en C₁₋₄ substitué par un substituant sélectionné dans le groupe constitué par un atome d'halogène, -OH et -O-alkyle en C₁₋₄ ; ou -S(=O)₂-alkyle en C₁₋₄ ;
 R^{20a} et R^{20b} représentent chacun indépendamment un atome d'hydrogène ; un groupe alkyle en C₁₋₄ ; un groupe cycloalkyle en C₃₋₆ ; ou un groupe alkyle en C₁₋₄ substitué par un substituant sélectionné dans le groupe constitué par -OH et -O-alkyle en C₁₋₄ ;
 p représente 1 ou 2 ;
 ou un sel d'addition pharmaceutiquement acceptable ou un solvate de celui-ci.

2. Composé selon la revendication 1, dans lequel

Y représente CR⁴ ;
 R⁵ représente Het^{3a}, -NR^{6a}R^{6b} ou -OR⁷ ;
 R³ représente un groupe phényle éventuellement substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène ; un groupe cyano ; un groupe alkyle en C₁₋₆ ; -O-alkyle en C₁₋₄ ; -C(=O)-R¹⁰ ; -S(=O)₂-alkyle en C₁₋₄ ; -S(=O)(=N-R^{20a})-alkyle en C₁₋₄ ; -O-alkyle en C₁₋₄ substitué par un, deux ou trois atomes d'halogène ; -O-alkyle en C₁₋₄-R¹² ; un groupe cycloalkyle en C₃₋₆ ; -O-cycloalkyle en C₃₋₆ ; Het^{1a} ; -O-Het^{1b} ; R¹⁸ ; R²¹ ; -P(=O)-(alkyle en C₁₋₄)₂ ; -NH-C(=O)-alkyle en C₁₋₄ ; -NH-C(=O)-Het^{1g} ; -NR^{17a}R^{17b} ; un groupe alkyle en C₁₋₄ substitué par un, deux ou trois atomes d'halogène ; un groupe alkyle en C₁₋₄ substitué par un, deux ou trois substituants-OH ; un groupe alkyle en C₁₋₄ substitué par un R¹³ ; un groupe alkyle en C₁₋₄ substitué par un R¹⁸ ; un groupe alcényle en C₂₋₆ ; et un groupe alcényle en C₂₋₆ substitué par un R¹³ ;
 Het² représente un groupe hétérocyclyle de formule (b-1) :



(b-1) représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons N-lié contenant éventuellement un hétéroatome supplémentaire sélectionné parmi O, S, S(=O)_p et N ou un groupe hétérocyclyle saturé bicyclique à 6 à 11 chaînons N-lié, notamment des cycles condensés, spiro et pontés, contenant éventuellement un ou deux hétéroatomes supplémentaires, chacun indépendamment sélectionné parmi O, S, S(=O)_p et N ;

dans le cas où (b-1) contient un ou deux atomes N supplémentaires, ledit ou lesdits deux atomes N pouvant être éventuellement substitués par un groupe alkyle en C₁₋₄ ; et

(b-1) pouvant être éventuellement substitué sur un, deux ou trois atomes C du cycle par un ou deux substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène, -OH, un groupe cyano, un groupe alkyle en C₁₋₄, -O-alkyle en C₁₋₄, -NH₂, -NH(alkyle en C₁₋₄), -N(alkyle en C₁₋₄)₂ et un groupe alkyle en C₁₋₄-OH ;

R^{11b} représente un atome d'hydrogène ; Het^{1e} ; un groupe alkyle en C₁₋₄ ; un groupe alkyle en C₁₋₄-Het⁵ ; un groupe alkyle en C₁₋₄ substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène, -OH et -O-alkyle en C₁₋₄ ; un groupe cycloalkyle en C₃₋₆ ; ou un groupe cycloalkyle en C₃₋₆ substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène, -OH et -O-alkyle en C₁₋₄ ; et

R^{14b}, R^{14d}, R^{15b}, R^{17b} et R^{19b} représentent chacun indépendamment un atome d'hydrogène ; un groupe alkyle en C₁₋₄ ; un groupe cycloalkyle en C₃₋₆ ; ou un groupe alkyle en C₁₋₄ substitué par un substituant sélectionné dans le groupe constitué par un atome d'halogène, -OH et -O-alkyle en C₁₋₄.

3. Composé selon la revendication 1, dans lequel

R⁵ représente un atome d'halogène, -NR^{6a}R^{6b} ou -OR⁷ ;

R^{6a} représente un atome d'hydrogène ;

R^{6b} représente -C(=O)-alkyle en C₁₋₄ ou -S(=O)₂-alkyle en C₁₋₄ ;

R⁷ représente un atome d'hydrogène, -alkyle en C₁₋₄-NR^{8a}R^{8b}, -C(=O)-R⁹, -S(=O)₂-OH ou -(C=O)-CH(NH₂)-alkyle en C₁₋₄-Ar¹ ;

R^{8a} représente un atome d'hydrogène ;

R^{8b} représente un groupe cycloalkyle en C₃₋₆ ;

R³ représente un groupe phényle éventuellement substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène ; un groupe cyano ; un groupe alkyle en C₁₋₆ ; -O-alkyle en C₁₋₄ ; -C(=O)-R¹⁰ ; -S(=O)₂-alkyle en C₁₋₄ ; -O-alkyle en C₁₋₄-R¹² ; un groupe cycloalkyle en C₃₋₆ ; -O-cycloalkyle en C₃₋₆ ; Het^{1a} ; -O-Het^{1b} ; R¹⁸ ; -P(=O)-(alkyle en C₁₋₄)₂ ; -NH-C(=O)-alkyle en C₁₋₄ ; -NH-C(=O)-Het^{1g} ; -NR^{17a}R^{17b} ; un groupe alkyle en C₁₋₄ substitué par un, deux ou trois atomes d'halogène ; un groupe alkyle en C₁₋₄ substitué par un, deux ou trois substituants -OH ; un groupe alkyle en C₁₋₄ substitué par un R¹³ ; un groupe alcényle en C₂₋₆ substitué par un R¹³ ; et un groupe alcynyle en C₂₋₆ substitué par un R¹³ ; R¹⁸ représente un cycle aromatique à 5 chaînons contenant un, deux ou trois atomes N ; ledit cycle aromatique à 5 chaînons pouvant être éventuellement substitué par un substituant sélectionné dans le groupe constitué par un groupe alkyle en C₁₋₄ ;

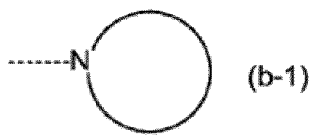
Het^{1a}, Het^{1c} et Het^{1d} représentent chacun indépendamment un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons contenant un ou deux hétéroatomes, chacun indépendamment sélectionné parmi O et N ; ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué, le cas échéant, sur un ou deux atomes N du cycle par un substituant indépendamment sélectionné dans le groupe constitué par un groupe alkyle en C₁₋₄, un groupe cycloalkyle en C₃₋₆ et un groupe alkyle en C₁₋₄ substitué par un substituant sélectionné dans le groupe constitué par un -O-alkyle en C₁₋₄ ; et

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué sur un, deux ou trois atomes C du cycle par un ou deux substituants, chacun indépendamment sélectionné dans le groupe constitué par -OH, un atome d'halogène, un groupe alkyle en C₁₋₄, -O-alkyle en C₁₋₄ et -N(alkyle en C₁₋₄)₂ ; Het^{1b}, Het^{1e}, Het^{1g}, Het⁷ et Het⁸ représentent chacun indépendamment un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons, attaché au reste de la molécule de formule (I) par le biais d'un quelconque atome de carbone du cycle disponible, lesdits Het^{1b}, Het^{1e}, Het^{1g}, Het⁷ et Het⁸ contenant un ou deux hétéroatomes, chacun indépendamment sélectionné parmi O et N ;

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué, le cas échéant, sur un ou deux atomes N du cycle par un substituant indépendamment sélectionné dans le groupe constitué par un groupe alkyle en C₁₋₄ et un groupe cycloalkyle en C₃₋₆ ; et

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué sur un, deux ou trois atomes C du cycle par un ou deux substituants, chacun indépendamment sélectionné dans le groupe constitué par -OH et un atome d'halogène ;

Het² représente un groupe hétérocyclyle de formule (b-1) :



(b-1) représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons N-lié contenant éventuellement un hétéroatome supplémentaire sélectionné parmi O et N, ou un groupe hétérocyclyle saturé bicyclique à 6 à 11 chaînons N-lié, notamment des cycles condensés, spiro et pontés, contenant éventuellement un ou deux atomes N supplémentaires ;

dans le cas où (b-1) contient un ou deux atomes N supplémentaires, ledit ou lesdits deux atomes N pouvant être éventuellement substitués par un substituant sélectionné indépendamment dans le groupe constitué par un groupe alkyle en C₁₋₄, un groupe cycloalkyle en C₃₋₆ et Het⁷ ; et

(b-1) pouvant être éventuellement substitué sur un, deux ou trois atomes C du cycle par un ou deux substituants, chacun indépendamment sélectionné dans le groupe constitué par -OH, un groupe cyano, un groupe alkyle en C₁₋₄ et un groupe alkyle en C₁₋₄-OH ;

R^{11b} représente Het^{1e} ; un groupe alkyle en C₁₋₄ ; -alkyle en C₁₋₄-Het⁵ ; -alkyle en C₁₋₄-Het⁸ ; un groupe alkyle en C₁₋₄ substitué par un, deux ou trois substituants OH ; ou un groupe cycloalkyle en C₃₋₆ substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène et -OH ;

R¹² représente -OH, -O-alkyle en C₁₋₄, -NR^{14a}R^{14b}, -C(=O)NR^{14c}R^{14d}, -S(=O)₂-alkyle en C₁₋₄, un groupe cycloalkyle en C₃₋₆, Ar² ou Het^{1c} ;

Ar¹ représente un groupe phényle ;

Het⁵, Het⁶ et Het^{1f} représentent chacun indépendamment un groupe hétérocyclyle de formule (c-1) :



(c-1) représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons N-lié contenant éventuellement un hétéroatome supplémentaire sélectionné parmi O et N ;

dans le cas où (c-1) contient un atome N supplémentaire, ledit atome N supplémentaire pouvant être éventuellement substitué par un groupe alkyle en C₁₋₄ ; et

R^{14b}, R^{14d}, R^{15b}, R^{17b} et R^{19b} représentent chacun indépendamment un atome d'hydrogène ; un groupe alkyle en C₁₋₄ ; un groupe cycloalkyle en C₃₋₆ ; -C(=O)-alkyle en C₁₋₄ ; un groupe alkyle en C₁₋₄ substitué par un substituant sélectionné dans le groupe constitué par -OH et -O-alkyle en C₁₋₄ ; ou -S(=O)₂-alkyle en C₁₋₄.

4. Composé selon la revendication 1 ou 2, dans lequel

R⁵ représente -NR^{6a}R^{6b} ou -OR⁷ ;

R^{6a} représente un atome d'hydrogène ;

R^{6b} représente -C(=O)-alkyle en C₁₋₄ ; ou -S(=O)₂-alkyle en C₁₋₄ ;

R⁷ représente un atome d'hydrogène, -C(=O)-R⁹, -S(=O)₂-OH ou -(C=O)-CH(NH₂)-alkyle en C₁₋₄-Ar¹ ;

R⁹ représente un groupe alkyle en C₁₋₄ ou un groupe alkyle en C₁₋₄ substitué par un substituant sélectionné dans le groupe constitué par -NH₂, -COOH et Het⁶ ;

R³ représente un groupe phényle éventuellement substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène ; un groupe cyano ; un groupe alkyle en C₁₋₆ ; -O-alkyle en C₁₋₄ ; -C(=O)-R¹⁰ ; -S(=O)₂-alkyle en C₁₋₄ ; -O-alkyle en C₁₋₄-R¹² ; un groupe cycloalkyle en C₃₋₆ ; -O-cycloalkyle en C₃₋₆ ; Het^{1a} ; -O-Het^{1b} ; R¹⁸ ; -P(=O)-(alkyle en C₁₋₄)₂ ; -NH-C(=O)-alkyle en C₁₋₄ ; -NH-C(=O)-Het^{1g} ; un groupe alkyle en C₁₋₄ substitué par un, deux ou trois atomes d'halogène ; un groupe alkyle en C₁₋₄ substitué par un, deux ou trois substituants -OH ; un groupe alkyle en C₁₋₄ substitué par un R¹³ ; R¹⁰ représente -OH, -O-alkyle en C₁₋₄, -NR^{11a}R^{11b} ou Het² ;

R¹⁸ représente un cycle aromatique à 5 chaînons contenant un, deux ou trois atomes N ; ledit cycle aromatique à 5 chaînons pouvant être éventuellement substitué par un substituant sélectionné dans le groupe constitué

par un groupe alkyle en C_{1-4} ;

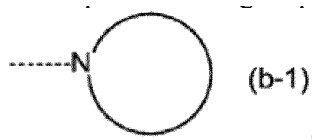
Het^{1a}, Het^{1c} et Het^{1d} représentent chacun indépendamment un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons contenant un ou deux hétéroatomes, chacun indépendamment sélectionné parmi O et N ; ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué, le cas échéant, sur un ou deux atomes N du cycle par un substituant indépendamment sélectionné dans le groupe constitué par un groupe alkyle en C_{1-4} , un groupe cycloalkyle en C_{3-6} et un groupe alkyle en C_{1-4} substitué par un -O-alkyle en C_{1-4} ; et

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué sur un, deux ou trois atomes C du cycle par un ou deux substituants, chacun indépendamment sélectionné dans le groupe constitué par -OH, un atome d'halogène, un groupe alkyle en C_{1-4} , -O-alkyle en C_{1-4} et -N(alkyle en C_{1-4})₂ ; Het^{1b}, Het^{1e} et Het^{1g} représentent chacun indépendamment un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons, attaché au reste de la molécule de formule (I) par le biais d'un quelconque atome de carbone du cycle disponible, lesdits Het^{1b}, Het^{1e} et Het^{1g} contenant un ou deux hétéroatomes, chacun indépendamment sélectionné parmi O et N ;

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué, le cas échéant, sur un ou deux atomes N du cycle par un substituant indépendamment sélectionné dans le groupe constitué par un groupe alkyle en C_{1-4} et un groupe cycloalkyle en C_{3-6} ; et

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué sur un, deux ou trois atomes C du cycle par un ou deux substituants -OH ;

Het² représente un groupe hétérocyclyle de formule (b-1) :



(b-1) représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons N-lié contenant éventuellement un hétéroatome supplémentaire sélectionné parmi O et N, ou un groupe hétérocyclyle saturé bicyclique à 6 à 11 chaînons N-lié, notamment des cycles condensés, spiro et pontés, contenant éventuellement un ou deux atomes N supplémentaires ;

dans le cas où (b-1) contient un ou deux atomes N supplémentaires, ledit ou lesdits deux atomes N pouvant être éventuellement substitués par un groupe alkyle en C_{1-4} ; et

(b-1) pouvant être éventuellement substitué sur un, deux ou trois atomes C du cycle par un ou deux substituants, chacun indépendamment sélectionné dans le groupe constitué par -OH, un groupe cyano et un groupe alkyle en C_{1-4} -OH ;

R^{11b} représente Het^{1e} ; un groupe alkyle en C_{1-4} ; un groupe alkyle en C_{1-4} -Het⁵ ; un groupe alkyle en C_{1-4} substitué par un, deux ou trois substituants OH ; ou un groupe cycloalkyle en C_{3-6} substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène et -OH ;

R¹³ représente -O-alkyle en C_{1-4} , -C(=O)NR^{15a}R^{15b}, -NR^{19a}R^{19b}, un groupe cycloalkyle en C_{3-6} , Het^{1d} ou -C(=O)-Het^{1f} ;

R¹² représente -OH, -O-alkyle en C_{1-4} , -NR^{14a}R^{14b}, -C(=O)NR^{14c}R^{14d}, -S(=O)₂-alkyle en C_{1-4} , un groupe cycloalkyle en C_{3-6} , Ar² ou Het^{1c} ;

Ar¹ représente un groupe phényle ;

Ar² représente un groupe phényle éventuellement substitué par un groupe alkyle en C_{1-4} ;

Het⁵, Het⁶ et Het^{1f} représentent chacun indépendamment un groupe hétérocyclyle de formule (c-1) :



(c-1) représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons N-lié contenant éventuellement un hétéroatome supplémentaire sélectionné parmi O et N ;

dans le cas où (c-1) contient un atome N supplémentaire, ledit atome N supplémentaire pouvant être

éventuellement substitué par un groupe alkyle en C_{1-4} ; R^{11a} , R^{14a} , R^{14c} , R^{15a} et R^{19a} représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C_{1-4} ;
 R^{14b} , R^{14d} , R^{15b} et R^{19b} représentent chacun indépendamment un atome d'hydrogène; un groupe alkyle en C_{1-4} ; un groupe cycloalkyle en C_{3-6} ; ou un groupe alkyle en C_{1-4} substitué par un -O-alkyle en C_{1-4} .

5. Composé selon la revendication 1 ou 2, dans lequel

Y représente CR^4 ;

R^4 représente un atome d'hydrogène ;

R^5 représente $-OR^7$;

R^7 représente un atome d'hydrogène ou $-C(=O)-R^9$;

R^9 représente un groupe alkyle en C_{1-4} ;

R^3 représente un groupe phényle substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène ; un groupe cyano ; un groupe alkyle en C_{1-6} ; -O-alkyle en C_{1-4} ; $-C(=O)-R^{10}$; $-S(=O)_2$ -alkyle en C_{1-4} ; -O-alkyle en $C_{1-4}-R^{12}$; -O-cycloalkyle en C_{3-6} ; -O-Het^{1a} ; -NH-C(=O)-Het^{1g} ; et un groupe alkyle en C_{1-4} substitué par R^{13} ;

R^{10} représente $-NR^{11a}R^{11b}$ ou Het² ;

Het^{1g} représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons, attaché au reste de la molécule de formule (I) par le biais d'un quelconque atome de carbone du cycle disponible, ledit Het^{1g} contenant un ou deux atomes N ;

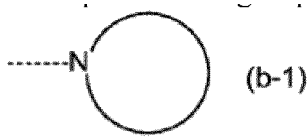
ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué, le cas échéant, sur un ou deux atomes N du cycle par un substituant alkyle en C_{1-4} ;

Het^{1b} représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons, attaché au reste de la molécule de formule (I) par le biais d'un quelconque atome de carbone du cycle disponible, ledit Het^{1b} contenant un ou deux atomes N ;

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué, le cas échéant, sur un ou deux atomes N du cycle par un substituant alkyle en C_{1-4} ; et

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué sur un atome C du cycle par substituant halogène ;

Het² représente un groupe hétérocyclyle de formule (b-1) :



(b-1) représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons N-lié

(b-1) pouvant être éventuellement substitué sur un atome C du cycle par un substituant -OH ;

R^{11b} représente un groupe alkyle en C_{1-4} :

R^{13} représente -O-alkyle en C_{1-4} ;

R^{12} représente -O-alkyle en C_{1-4} ; et

R^{11a} représente un atome d'hydrogène.

6. Composé selon la revendication 1 ou 2, dans lequel

R^4 représente un atome d'hydrogène ;

R^5 représente $-OR^7$;

R^7 représente un atome d'hydrogène ou $-C(=O)-R^9$;

R^9 représente un groupe alkyle en C_{1-4} ;

R^3 représente un groupe phényle substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène ; un groupe cyano ; un groupe alkyle en C_{1-6} ; -O-alkyle en C_{1-4} ; $-C(=O)-R^{10}$; $-S(=O)_2$ -alkyle en C_{1-4} ; -O-alkyle en $C_{1-4}-R^{12}$; -NH-C(=O)-Het^{1g} ; et un groupe alkyle en C_{1-4} substitué par un R^{13} ;

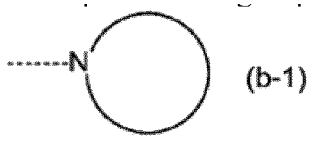
R^{10} représente $-NR^{11a}R^{11b}$ ou Het² ;

Het^{1g} représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons, attaché au reste de la molécule de formule (I) par le biais d'un quelconque atome de carbone du cycle disponible, ledit Het^{1g} contenant un ou

deux atomes N ;

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué, le cas échéant, sur un ou deux atomes N du cycle par un substituant alkyle en C₁₋₄ ;

Het² représente un groupe hétérocyclyle de formule (b-1) :



(b-1) représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons N-lié

(b-1) pouvant être éventuellement substitué sur un atome C du cycle par un substituant -OH ;

R^{11b} représente un groupe alkyle en C₁₋₄ :

R¹³ représente -O-alkyle en C₁₋₄ ;

R¹² représente -O-alkyle en C₁₋₄ ; et

R^{11a} représente un atome d'hydrogène.

7. Composé selon la revendication 1 ou 2, dans lequel

R² représente un groupe alkyle en C₁₋₆ substitué par un R⁵ ;

R⁴ représente un atome d'hydrogène ;

R⁵ représente -OR⁷ ;

R⁷ représente un atome d'hydrogène ; et

R³ représente un groupe phényle substitué par un, deux ou trois substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène ; un groupe cyano ; et un groupe alkyle en C₁₋₆.

8. Composé selon l'une quelconque des revendications 1 à 6, dans lequel

R¹ représente un groupe méthyle ;

R² représente un groupe méthyle ou -CH₂-OH.

9. Composé selon l'une quelconque des revendications 1 à 4, dans lequel R⁴ représente un atome d'hydrogène.

10. Composé selon l'une quelconque des revendications 1 à 6, dans lequel

R⁵ représente -OR⁷ ; et

R⁷ représente un atome d'hydrogène.

11. Composé selon la revendication 1 ou 2, dans lequel

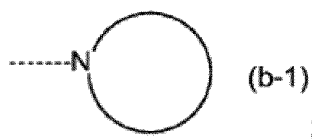
Het^{1a}, Het^{1c} et Het^{1d} représentent chacun indépendamment un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons contenant un ou deux hétéroatomes, chacun indépendamment sélectionné parmi O, S, S(=O)_p et N ;

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué, le cas échéant, sur un ou deux atomes N du cycle par un substituant indépendamment sélectionné dans le groupe constitué par un groupe alkyle en C₁₋₄, un groupe cycloalkyle en C₃₋₆ et un groupe alkyle en C₁₋₄ substitué par un substituant sélectionné dans le groupe constitué par -OH et -O-alkyle en C₁₋₄ ; et

ledit groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons pouvant être éventuellement substitué sur un, deux ou trois atomes C du cycle par un ou deux substituants, chacun indépendamment sélectionné dans le groupe constitué par -OH, un atome d'halogène, un groupe alkyle en C₁₋₄, un groupe cyano, -C(=O)-alkyle en C₁₋₄, -O-alkyle en C₁₋₄, -NH₂, -NH(alkyle en C₁₋₄) et -N(alkyle en C₁₋₄)₂.

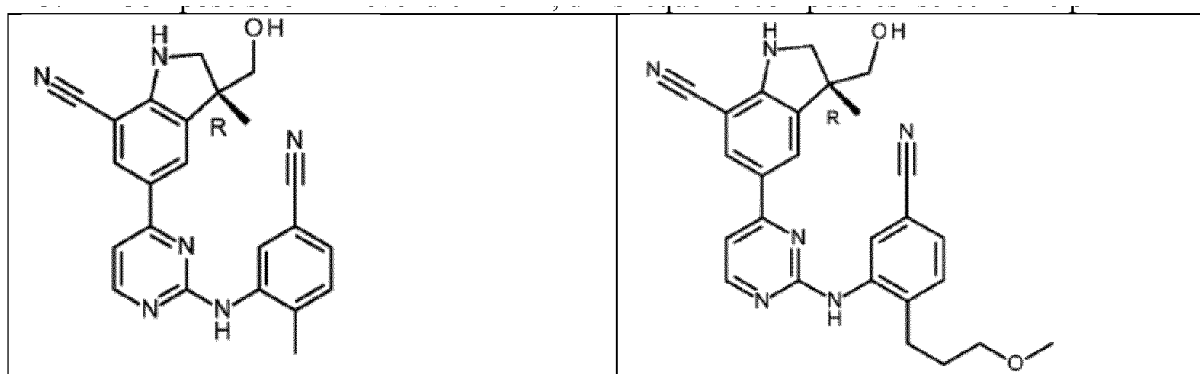
12. Composé selon la revendication 1 ou 2, dans lequel

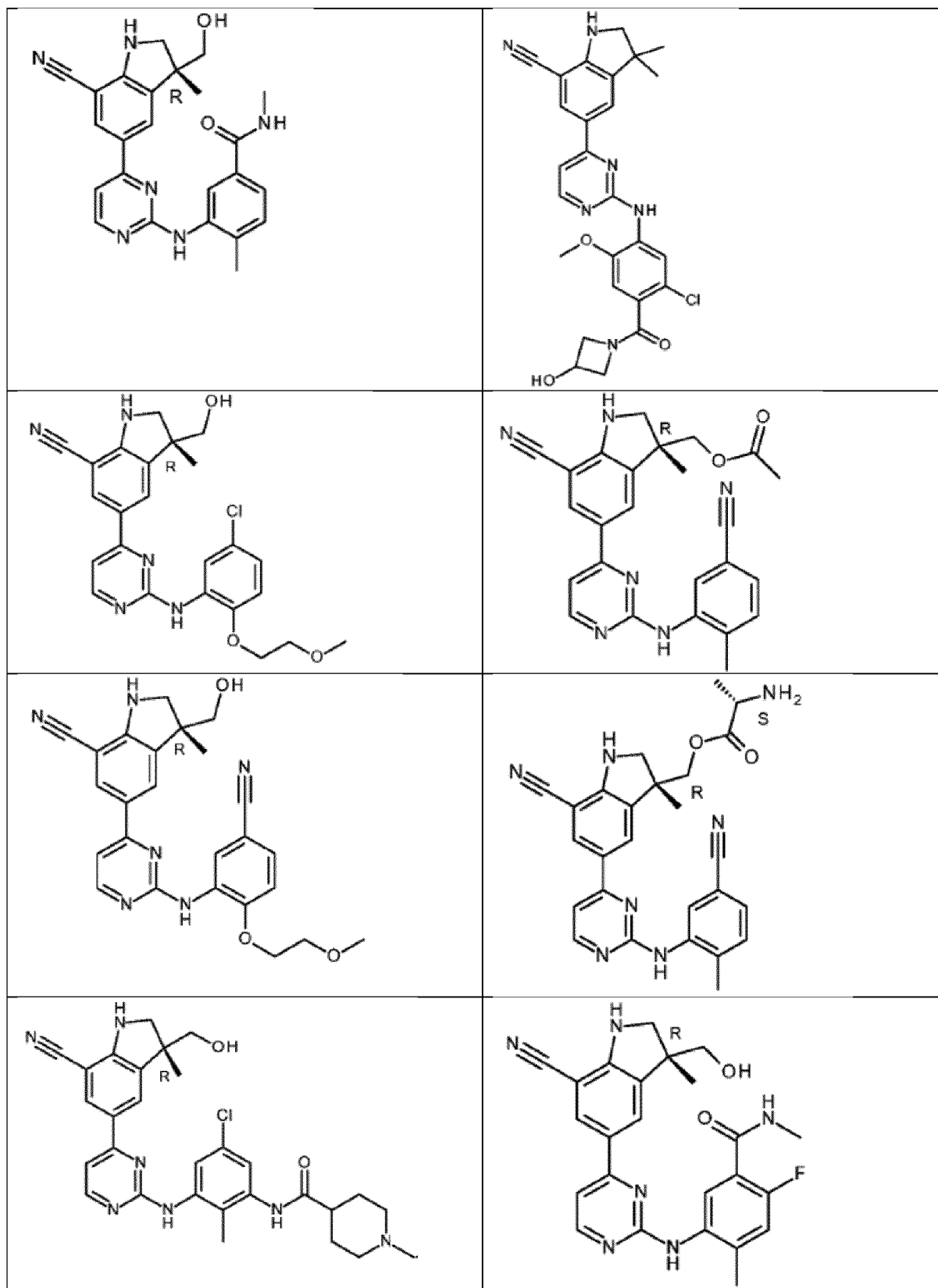
Het² représente un groupe hétérocyclyle de formule (b-1) :

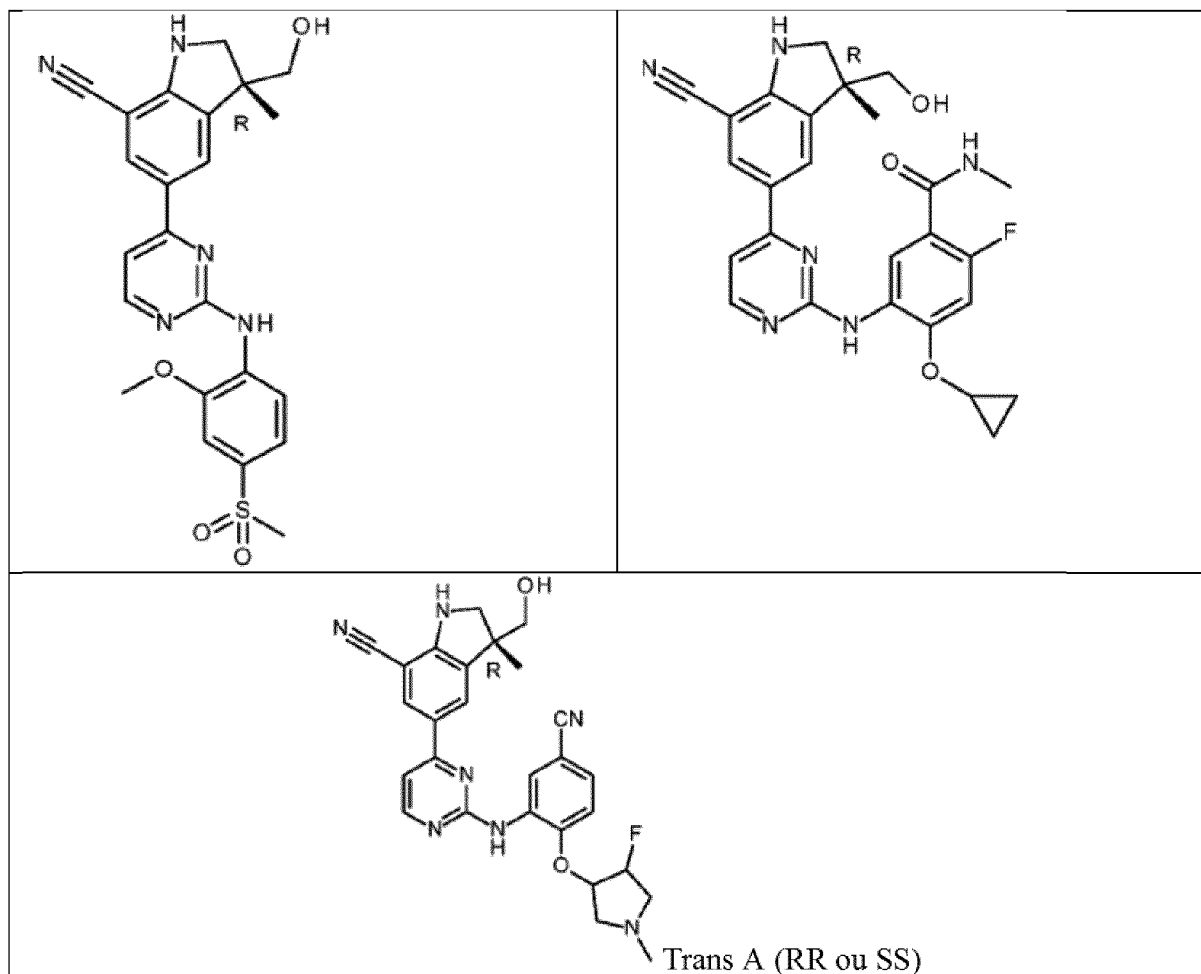


(b-1) représente un groupe hétérocyclyle saturé monocyclique à 4 à 7 chaînons N-lié contenant éventuellement un hétéroatome supplémentaire sélectionné parmi O, S, S(=O)_p et N ;
 dans le cas où (b-1) contient un atome N supplémentaire, ledit atome N pouvant être éventuellement substitué par un groupe alkyle en C₁₋₄ ; et
 (b-1) pouvant être éventuellement substitué sur un, deux ou trois atomes C du cycle par un ou deux substituants, chacun indépendamment sélectionné dans le groupe constitué par un atome d'halogène, -OH, un groupe cyano, un groupe alkyle en C₁₋₄, -O-alkyle en C₁₋₄, -NH₂, -NH(alkyle en C₁₋₄), -N(alkyle en C₁₋₄)₂ et un groupe alkyle en C₁₋₄-OH.

13. Composé selon la revendication 1, dans lequel le composé est sélectionné parmi

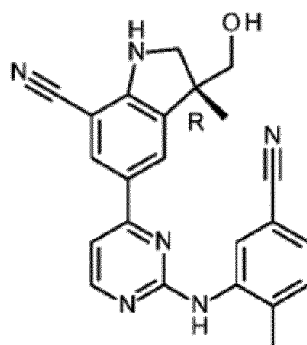






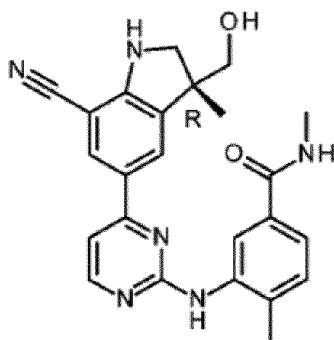
des tautomères et des formes stéréoisomères de ceux-ci,
et les sels d'addition pharmaceutiquement acceptables et les solvates de ceux-ci.

14. Composé selon la revendication 1, dans lequel le composé est



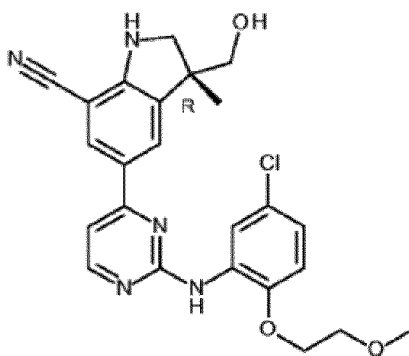
ou un sel d'addition pharmaceutiquement acceptable ou un solvate de celui-ci.

15. Composé selon la revendication 1, dans lequel le composé est



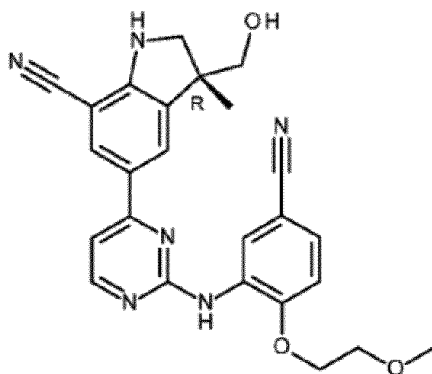
ou un sel d'addition pharmaceutiquement acceptable ou un solvate de celui-ci.

16. Composé selon la revendication 1, dans lequel le composé est



ou un sel d'addition pharmaceutiquement acceptable ou un solvate de celui-ci.

17. Composé selon la revendication 1, dans lequel le composé est



ou un sel d'addition pharmaceutiquement acceptable ou un solvate de celui-ci.

18. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 17 et un véhicule ou un diluant pharmaceutiquement acceptable.

19. Composé selon l'une quelconque des revendications 1 à 17 pour une utilisation en tant que médicament.

20. Composé selon l'une quelconque des revendications 1 à 17 pour une utilisation dans la prévention ou le traitement d'un cancer.

21. Composé selon la revendication 20 pour une utilisation dans la prévention ou le traitement de malignités des cellules B.

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22. Composé selon la revendication 21 dans lequel la malignité des cellules B est sélectionnée parmi un myélome multiple, un lymphome de Hodgkin, un lymphome à cellules du manteau, un lymphome diffus à grandes cellules B ou une leucémie lymphoïde chronique.

5 **23.** Composition pharmaceutique selon la revendication 18 pour une utilisation dans la prévention ou le traitement d'un cancer.

24. Composé tel que défini dans l'une quelconque des revendications 14 à 17 pour une utilisation dans le traitement
10 d'une malignité hématologique.

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REFERENCES CITED IN THE DESCRIPTION

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