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(54) **Title**: NEW 3-(1H-PYRAZOL-4-YL)-1H-PYRROLO[2,3-c]PYRIDINE DERIVATIVES AS NIK INHIBITORS

(57) **Abstract**: The present invention relates to pharmaceutical agents useful for therapy and/or prophylaxis in a mammal, and in particular to inhibitors of NF-κB-inducing kinase (NIK -also known as MAP3K14) useful for treating diseases such as cancer, inflammatory disorders, metabolic disordersand autoimmune disorders. The invention is also directed to pharmaceutical compositions comprising such compounds, to processes to prepare such compounds and compositions, 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.

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NEW 3-(1*H*-PYRAZOL-4-YL)-1*H*-PYRROLO[2,3-*c*]PYRIDINE DERIVATIVES AS NIK INHIBITORS

FIELD OF THE INVENTION

The present invention relates to pharmaceutical agents useful for therapy and/or prophylaxis in a mammal, and in particular to inhibitors of NF-κB-inducing kinase (NIK - also known as MAP3K14) useful for treating diseases such as cancer, inflammatory disorders, metabolic disorders including obesity and diabetes, and autoimmune disorders. The invention is also directed to pharmaceutical compositions comprising such compounds, to processes to prepare such compounds and compositions, 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

The present invention relates to pharmaceutical agents useful for therapy and/or prophylaxis in a mammal, and in particular to inhibitors of NF-κB-inducing kinase (NIK - also known as MAP3K14) useful for treating diseases such as cancer and inflammatory disorders. Nuclear factor-kappa B (NF-κB) is a transcription factor regulating the expression of various genes involved in the immune response, cell proliferation, apoptosis, and carcinogenesis. NF-κB 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-κB pathway activation. There are two NF-κB signaling pathways, the canonical and the non-canonical. NIK has a role in both but has been shown to be indispensable for the non-canonical signaling pathway where it phosphorylates IKKα, 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 (TRAF), 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

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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-κB 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.

The NF-κB 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. ibid* **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-κB 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-κB-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-κB 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).

NIK aberrantly accumulates in diffuse large B-cell lymphoma (DLBCL) cells due to constitutive activation of B-cell activation factor (BAFF) through interaction with

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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-κB pathway activation as having a significant role in DLBCL proliferation (Pham *et al. Blood* **2011**, *117*, 200-210).
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-κB, 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* **2011**, 1-13). A wealth of evidence showed that NF-κB 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.

In addition research has shown that NF-κB controls the expression of many genes involved in inflammation and that NF-κB 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-κB signaling pathway can have a therapeutic benefit for the treatment of diseases and disorders for which over-activation of NF-κB signaling is observed.

Dysregulated NF-κB 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-κB 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-κB 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).

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 a.l 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-IKKα 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 TNFα (Chung et al 2011). 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 a.l Toxicol. In Vitro* **2010**, *24*, 310-318).

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-IκB-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-κB 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-κB pathway activation, induced skeletal muscle insulin resistance *in vitro,* suggesting that NIK could be an important therapeutic target for the treatment of insulin resistance associated with inflammation in obesity and type 2 diabetes (Choudhary *et al. Endocrinology* **2011**, *152*, 3622-3627).

NF-κB 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-κB 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*, 1-9, e15383). Thus this group concluded that NIK is important in the immune and bone-destructive components of inflammatory arthritis and represents a possible therapeutic target for these diseases.

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

WO2010/042337 describes novel 6-azaindole aminopyrimidine derivatives having NIK inhibitory activity.
WO2009/158011 describes alkynyl alcohols as kinase inhibitors.

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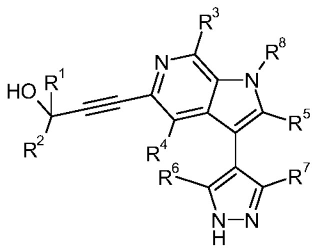
WO2012/123522 describes 6,5-heterocyclic propargylic alcohol compounds and uses therefor.

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

DESCRIPTION OF THE INVENTION

The present invention concerns novel compounds of Formula (I):



(I)

and tautomers and stereoisomeric forms thereof, wherein

R^1 is selected from the group of hydrogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^2 is selected from the group of hydrogen; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; C_{3-6}cycloalkyl; and Het^1;

Het^1 is a heteroaryl selected from the group of thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, and isothiazolyl, each of which may be optionally substituted with one or two substituents independently selected from halogen and C_{1-4}alkyl;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^3 is selected from the group of hydrogen; halogen; cyano; C_{3-6}cycloalkyl; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or more fluoro substituents; -OC_{1-6}alkyl; -OC_{1-6}alkyl substituted with one or more fluoro substituents; and C_{1-6}alkyl substituted with one substituent selected from -$NR^{3a}R^{3b}$, -OH, and -OC_{1-4}alkyl;

R^{3a} and R^{3b} are each independently selected from hydrogen, and C_{1-4}alkyl;

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R^4 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^5 is selected from the group of hydrogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^6 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; and $-NR^{7a}R^{7b}$; wherein

R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-4}alkyl;

R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with OH, $-OC_{1-4}$alkyl, and $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of
(i) fluoro,
(ii) Het^3,
(iii) Ar^1,
(iv) $-NR^{8a}R^{8b}$,
(v) $-NR^{8c}C(=O)R^{8d}$,
(vi) $-NR^{8c}C(=O)NR^{8a}R^{8b}$,
(vii) $-NR^{8c}C(=O)OR^{8e}$,
(viii) $-NR^{8c}S(=O)_2NR^{8a}R^{8b}$,
(ix) $-NR^{8c}S(=O)_2R^{8d}$,
(x) $-OR^{8f}$,
(xi) $-OC(=O)NR^{8a}R^{8b}$,
(xii) $-C(=O)NR^{8a}R^{8b}$,
(xiii) $-S(O)_2R^{8d}$, and
(xiv) $-S(O)_2NR^{8a}R^{8b}$;

R^{8a}, R^{8b}, R^{8c} and R^{8f} are each independently selected from the group of hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl; and C_{2-6}alkyl substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1-4}$alkyl;

R^{8d} is selected from the group of C_{1-6}alkyl, which may be optionally substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1-4}$alkyl; and C_{3-6}cycloalkyl;

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R^{8e} is selected from the group of C_{1-6}alkyl; C_{3-6}cycloalkyl; and C_{2-6}alkyl substituted with one substituent selected from -$NR^{8x}R^{8y}$, -OH, and -OC_{1-4}alkyl;

wherein R^{8x} and R^{8y} are each independently selected from hydrogen and C_{1-4}alkyl;

Ar^1 is selected from the group of phenyl, thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl, each of which may be optionally substituted with one or two substituents independently selected from halogen, cyano, C_{1-4}alkyl, C_{1-4}alkyl substituted with one or more fluoro substituents, -OC_{1-4}alkyl, and -OC_{1-4}alkyl substituted with one or more fluoro substituents;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, -OC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-4}alkyl substituted with one -OC_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, -OC_{1-4}alkyl, C_{1-4}alkyl substituted with one -OC_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

and the pharmaceutically acceptable salts and the solvates thereof.

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

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

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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.

The invention also relates to the use of a compound of Formula (I), a pharmaceutically acceptable 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 salt, or a solvate thereof.

The invention also relates to a product comprising a compound of Formula (I), a pharmaceutically acceptable 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, the invention relates to a method of treating or preventing a cell proliferative disease in a warm-blooded animal which comprises administering to the said animal an effective amount of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, as defined herein, or a pharmaceutical composition or combination as defined herein.

DETAILED DESCRIPTION OF THE INVENTION

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

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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 C_{1-6}alkyl group contains from 1 to 6 carbon atoms, a C_{3-6}cycloalkyl group contains from 3 to 6 carbon atoms, and so on.

The term ‘C_{1-4}alkyl’ 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.

The term ‘C_{1-6}alkyl’ 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 C_{1-4}alkyl and *n*-pentyl, *n*-hexyl, 2-methylbutyl and the like.

The term ‘C_{2-6}alkyl’ as used herein as a group or part of a group represents a straight or branched chain saturated hydrocarbon radical having from 2 to 6 carbon atoms such as ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, *t*-butyl, *n*-pentyl, *n*-hexyl, 2-methylbutyl and the like.

The term ‘C_{3-6}cycloalkyl’ 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.

The term ‘C_{1-6}alkyl substituted with one or more substituents’ as used herein as a group or part of a group refers to a C_{1-6}alkyl group as defined herein wherein one or more than one hydrogen atom is replaced with another group. The term therefore includes monosubstitutedC_{1-6}alkyl and also polysubstitutedC_{1-6}alkyl. There may be one, two, three or more hydrogen atoms replaced with a substituent, so the fully or partially substituted C_{1-6}alkyl may have one, two, three or more substituents. Examples of such groups wherein the substituent is for example, fluoro include fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, trifluoroethyl and the like.

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, preferably from 1 to 3 hydrogens, more preferably 1 hydrogen, on the atom or radical indicated in the expression using “substituted” are replaced with a selection from the indicated group, provided that the normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

Combinations of substituents and/or variables are permissible only if such combinations result in chemically stable compounds. "Stable compound" is meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

The term 'C_{3-6}cycloalkyl optionally substituted with OH, -OC_{1-4}alkyl, and -C_{1-4}alkylOH' as used herein refers to a C_{3-6}cycloalkyl group as defined herein, which is unsubstituted or substituted by 1 or more than 1, for example 1, 2 or 3, in particular 1, substituents independently selected from the group consisting of OH, -OC_{1-4}alkyl, and -C_{1-4}alkylOH.

In a particular embodiment, the expression "C_{3-6}cycloalkyl optionally substituted with -C_{1-4}alkylOH" is limited to "C_{3-6}cycloalkyl optionally substituted with one -C_{1-4}alkylOH".

In a particular embodiment, the expression "-SO_2C_{1-6}alkyl optionally substituted with phenyl" is limited to "-SO_2C_{1-6}alkyl optionally substituted with one phenyl".The term optionally substituted, for example as used in optionally substituted C_{1-6}alkyl, means that, unless otherwise is indicated or is clear from the context, the group is unsubstituted or substituted by one or more, for example 1, 2 or 3, substituents.

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

$S(O)_2$ or SO_2 represents a sulfonyl moiety.

Substituents covered by the term "Het^x", "heterocyclyl" or "heteroaryl" may be attached to the remainder of the molecule of Formula (I) through any available ring carbon or heteroatom as appropriate, if not otherwise specified.

"Ar^1" may be attached to the remainder of the molecule of Formula (I) through any available ring carbon atom or through a 'NH' group (e.g. in pyrrolyl, pyrazolyl, imidazolyl) as appropriate, if not otherwise specified.

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

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

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

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

The term “therapeutically effective amount” as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medicinal doctor or other clinician, which includes alleviation or reversal of the symptoms of the disease or disorder being treated.

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

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

The term “compounds of the invention” as used herein, is meant to include the compounds of Formula (I), and the salts and solvates thereof.

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

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

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

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

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

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.

Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, i.e. they are not related as mirror images. If a compound contains a double bond, the substituents may be in the *E* or the *Z* configuration.

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

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

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

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

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

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

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

R^1 is selected from the group of hydrogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^2 is selected from the group of hydrogen; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; C_{3-6}cycloalkyl; and Het^1;

Het^1 is a heteroaryl selected from the group of thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, and isothiazolyl, each of which may be optionally substituted with one or two substituents independently selected from halogen and C_{1-4}alkyl;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^3 is selected from the group of hydrogen; halogen; cyano; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or more fluoro substituents; $-OC_{1-6}$alkyl; $-OC_{1-6}$alkyl substituted with one or more fluoro substituents; and C_{1-6}alkyl substituted with one substituent selected from $-NR^{3a}R^{3b}$, -OH, and $-OC_{1-4}$alkyl;

R^{3a} and R^{3b} are each independently selected from hydrogen, and C_{1-4}alkyl;

R^4 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^5 is selected from the group of hydrogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^6 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; and $-NR^{7a}R^{7b}$; wherein

R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-4}alkyl;

R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with OH, $-OC_{1-4}$alkyl, and $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,

(ii) Het^3,

(iii) Ar^1,

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(iv) $-NR^{8a}R^{8b}$,
(v) $-NR^{8c}C(=O)R^{8d}$,
(vi) $-NR^{8c}C(=O)NR^{8a}R^{8b}$,
(vii) $-NR^{8c}C(=O)OR^{8e}$,
(viii) $-NR^{8c}S(=O)_2NR^{8a}R^{8b}$,
(ix) $-NR^{8c}S(=O)_2R^{8d}$,
(x) $-OR^{8f}$,
(xi) $-OC(=O)NR^{8a}R^{8b}$,
(xii) $-C(=O)NR^{8a}R^{8b}$,
(xiii) $-S(O)_2R^{8d}$, and
(xiv) $-S(O)_2NR^{8a}R^{8b}$;

R^{8a}, R^{8b}, R^{8c} and R^{8f} are each independently selected from the group of hydrogen; $C_{1\text{-}6}$alkyl; $C_{3\text{-}6}$cycloalkyl; and $C_{2\text{-}6}$alkyl substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1\text{-}4}$alkyl;

R^{8d} is selected from the group of $C_{1\text{-}6}$alkyl, which may be optionally substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1\text{-}4}$alkyl; and $C_{3\text{-}6}$cycloalkyl;

R^{8e} is selected from the group of $C_{1\text{-}6}$alkyl; $C_{3\text{-}6}$cycloalkyl; and $C_{2\text{-}6}$alkyl substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1\text{-}4}$alkyl;

wherein R^{8x} and R^{8y} are each independently selected from hydrogen and $C_{1\text{-}4}$alkyl;

Ar^1 is selected from the group of phenyl, thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl, each of which may be optionally substituted with one or two substituents independently selected from halogen, cyano, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkyl substituted with one or more fluoro substituents, $-OC_{1\text{-}4}$alkyl, and $-OC_{1\text{-}4}$alkyl substituted with one or more fluoro substituents;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one substituent selected from $C_{1\text{-}4}$alkyl, and $C_{1\text{-}4}$alkyl substituted with one or more fluoro substituents;

Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one substituent selected from $C_{1\text{-}4}$alkyl, and $C_{1\text{-}4}$alkyl substituted with one or more fluoro substituents;

and the pharmaceutically acceptable salts and the solvates thereof.

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

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

R^2 is C_{1-4}alkyl;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^3 is selected from the group of hydrogen, halogen, C_{3-6}cycloalkyl, C_{1-6}alkyl and C_{1-6}alkyl substituted with one or more fluoro substituents;

R^4 is selected from the group of hydrogen and halogen;

R^5 is selected from the group of hydrogen, cyano, C_{1-4}alkyl and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^6 is selected from the group of hydrogen and halogen;

R^7 is selected from the group of hydrogen, halogen, cyano, C_{1-4}alkyl, C_{1-4}alkyl substituted with one or more fluoro substituents and $-NR^{7a}R^{7b}$;

R^{7a} is selected from the group of hydrogen and C_{1-4}alkyl; and

R^{7b} is selected from the group of hydrogen and C_{1-4}alkyl;

R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl; Het^2; C_{3-6}cycloalkyl optionally substituted with OH, $-OC_{1-4}$alkyl, and $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,

(ii) Het^3,

(iv) $-NR^{8a}R^{8b}$, and

(x) $-OR^{8f}$;

R^{8a}, R^{8b} and R^{8f} are each independently selected from the group of hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl; and C_{2-6}alkyl substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1-4}$alkyl;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{3-6}cycloalkyl, C_{1-4}alkyl substituted with one $–OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents; and

Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one or two substituents independently

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selected from fluoro, C_{1-4}alkyl, -OC_{1-4}alkyl, C_{1-4}alkyl substituted with one –OC_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;
and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and tautomers and stereoisomeric forms thereof, wherein
R^1 is C_{1-4}alkyl;
R^2 is C_{1-4}alkyl;
or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;
R^3 is selected from the group of hydrogen, halogen, C_{1-6}alkyl and C_{1-6}alkyl substituted with one or more fluoro substituents;
R^4 is selected from the group of hydrogen and halogen;
R^5 is selected from the group of hydrogen, cyano, C_{1-4}alkyl and C_{1-4}alkyl substituted with one or more fluoro substituents;
R^6 is selected from the group of hydrogen and halogen;
R^7 is selected from the group of hydrogen, halogen, cyano, C_{1-4}alkyl, C_{1-4}alkyl substituted with one or more fluoro substituents and $-NR^{7a}R^{7b}$;
R^{7a} is selected from the group of hydrogen and C_{1-4}alkyl; and
R^{7b} is selected from the group of hydrogen and C_{1-4}alkyl;
R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl; Het^2; C_{3-6}cycloalkyl optionally substituted with OH, -OC_{1-4}alkyl, and -C_{1-4}alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of
(i) fluoro,
(ii) Het^3,
(iv) $-NR^{8a}R^{8b}$, and
(x) $-OR^{8f}$;
R^{8a}, R^{8b} and R^{8f} are each independently selected from the group of hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl; and C_{2-6}alkyl substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and -OC_{1-4}alkyl;
Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one substituent selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents; and
Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of

which may be optionally substituted with one substituent selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;
and the pharmaceutically acceptable salts and the solvates thereof.

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

R^1 is selected from the group of hydrogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^2 is selected from the group of C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; C_{3-6}cycloalkyl; and Het^1;

Het^1 is a heteroaryl selected from the group of thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, and isothiazolyl, each of which may be optionally substituted with one or two substituents independently selected from halogen and C_{1-4}alkyl;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^3 is selected from the group of hydrogen; halogen; cyano; C_{3-6}cycloalkyl; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or more fluoro substituents; -OC_{1-6}alkyl; -OC_{1-6}alkyl substituted with one or more fluoro substituents; and C_{1-6}alkyl substituted with one substituent selected from -$NR^{3a}R^{3b}$, -OH, and -OC_{1-4}alkyl;

R^{3a} and R^{3b} are each independently selected from hydrogen, and C_{1-4}alkyl;

R^4 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^5 is selected from the group of hydrogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^6 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; and -$NR^{7a}R^{7b}$; wherein

R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-4}alkyl;

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R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with OH, $-OC_{1-4}$alkyl, and $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,

(ii) Het^3,

(iii) Ar^1,

(x) $-OR^{8f}$,

R^{8f} is selected from the group of hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl; and C_{2-6}alkyl substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1-4}$alkyl;

Ar^1 is selected from the group of phenyl, thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl, each of which may be optionally substituted with one or two substituents independently selected from halogen, cyano, C_{1-4}alkyl, C_{1-4}alkyl substituted with one or more fluoro substituents, $-OC_{1-4}$alkyl, and $-OC_{1-4}$alkyl substituted with one or more fluoro substituents;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{3-6}cycloalkyl, C_{1-4}alkyl substituted with one $-OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{1-4}alkyl substituted with one $-OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

and the pharmaceutically acceptable salts and the solvates thereof.

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

R^1 is selected from the group of hydrogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

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R^2 is selected from the group of C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; C_{3-6}cycloalkyl; and Het^1;

Het^1 is a heteroaryl selected from the group of thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, and isothiazolyl, each of which may be optionally substituted with one or two substituents independently selected from halogen and C_{1-4}alkyl;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^3 is selected from the group of hydrogen and C_{1-6}alkyl;

R^4 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^5 is selected from the group of hydrogen and cyano;

R^6 is hydrogen;

R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; and $-NR^{7a}R^{7b}$; wherein

R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-4}alkyl;

R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with OH, $-OC_{1-4}$alkyl, and $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of
(i) fluoro,
(ii) Het^3,
(iii) Ar^1,
(x) $-OR^{8f}$,

R^{8f} is selected from the group of hydrogen and C_{1-6}alkyl;

Ar^1 is phenyl;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{3-6}cycloalkyl, C_{1-4}alkyl substituted with one -OC$_{1-4}$alkyl, and C$_{1-4}$alkyl substituted with one or more fluoro substituents;

Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C$_{1-4}$alkyl, -OC$_{1-4}$alkyl, C$_{1-4}$alkyl substituted with one -OC$_{1-4}$alkyl, and C$_{1-4}$alkyl substituted with one or more fluoro substituents;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and tautomers and stereoisomeric forms thereof, wherein
R^1 is selected from the group of hydrogen; C$_{1-4}$alkyl; and C$_{1-4}$alkyl substituted with one or more fluoro substituents;

R^2 is selected from the group of hydrogen; C$_{1-4}$alkyl; C$_{1-4}$alkyl substituted with one or more fluoro substituents; C$_{3-6}$cycloalkyl; and Het^1;
Het^1 is a heteroaryl selected from the group of thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, and isothiazolyl, each of which may be optionally substituted with one or two substituents independently selected from halogen and C$_{1-4}$alkyl;
or R^1 and R^2 together with the carbon atom to which they are attached form a C$_{3-6}$cycloalkyl;
R^3 is selected from the group of hydrogen; halogen; cyano; C$_{3-6}$cycloalkyl; C$_{1-6}$alkyl; C$_{1-6}$alkyl substituted with one or more fluoro substituents; -OC$_{1-6}$alkyl; -OC$_{1-6}$alkyl substituted with one or more fluoro substituents; and C$_{1-6}$alkyl substituted with one substituent selected from -NR^{3a}R^{3b}, -OH, and -OC$_{1-4}$alkyl;
R^{3a} and R^{3b} are each independently selected from hydrogen, and C$_{1-4}$alkyl;
R^4 is selected from the group of hydrogen; halogen; C$_{1-4}$alkyl; and C$_{1-4}$alkyl substituted with one or more fluoro substituents;
R^5 is selected from the group of hydrogen; cyano; C$_{1-4}$alkyl; and C$_{1-4}$alkyl substituted with one or more fluoro substituents;
R^6 is selected from the group of hydrogen; halogen; C$_{1-4}$alkyl; and C$_{1-4}$alkyl substituted with one or more fluoro substituents;
R^7 is selected from the group of hydrogen; halogen; cyano; C$_{1-4}$alkyl; and C$_{1-4}$alkyl substituted with one or more fluoro substituents;

R^8 is selected from the group of $-SO_2C_{1-6}$alkyl; Het^2; C_{3-6}cycloalkyl optionally substituted with $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,

(ii) Het^3,

(iii) Ar^1,

(x) $-OR^{8f}$,

R^{8f} is C_{1-6}alkyl;

Ar^1 is phenyl;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{3-6}cycloalkyl, C_{1-4}alkyl substituted with one $-OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, and azetidinyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{1-4}alkyl substituted with one $-OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

and the pharmaceutically acceptable salts and the solvates thereof.

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

R^1 is selected from the group of C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^2 is selected from the group C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; C_{3-6}cycloalkyl; and Het^1;

Het^1 is a heteroaryl selected from the group of thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, and isothiazolyl, each of which may be optionally substituted with one or two substituents independently selected from halogen and C_{1-4}alkyl;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^3 is selected from the group of hydrogen; halogen; cyano; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or more fluoro substituents; and C_{1-6}alkyl substituted with one substituent selected from $-NR^{3a}R^{3b}$, -OH, and $-OC_{1-4}$alkyl;

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R^{3a} and R^{3b} are each independently selected from hydrogen, and C_{1-4}alkyl;
R^4 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;
R^5 is selected from the group of hydrogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;
R^6 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;
R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; and $-NR^{7a}R^{7b}$; wherein
R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-4}alkyl;
R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with OH, $-OC_{1-4}$alkyl, and $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of
(i) fluoro,
(ii) Het^3,
(iii) Ar^1,
(x) $-OR^{8f}$;
R^{8f} is selected from the group of hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl; and C_{2-6}alkyl substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1-4}$alkyl;
wherein R^{8x} and R^{8y} are each independently selected from hydrogen and C_{1-4}alkyl;
Ar^1 is phenyl optionally substituted with one or two substituents independently selected from halogen, cyano, C_{1-4}alkyl, C_{1-4}alkyl substituted with one or more fluoro substituents, $-OC_{1-4}$alkyl, and $-OC_{1-4}$alkyl substituted with one or more fluoro substituents;
Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one substituent selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;
Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one substituent selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;
and the pharmaceutically acceptable salts and the solvates thereof.

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

R^1 is selected from the group of C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^2 is selected from the group C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; C_{3-6}cycloalkyl; and Het^1;

Het^1 is a heteroaryl selected from the group of thiazolyl optionally substituted with one or two substituents independently selected from halogen and C_{1-4}alkyl;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; and $-NR^{7a}R^{7b}$; wherein

R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-4}alkyl;

R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with OH, $-OC_{1-4}$alkyl, and $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,

(ii) Het^3,

(iii) Ar^1,

(x) $-OR^{8f}$;

R^{8f} is selected from the group of hydrogen; C_{1-6}alkyl; and C_{2-6}alkyl substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1-4}$alkyl;

wherein R^{8x} and R^{8y} are each independently selected from hydrogen and C_{1-4}alkyl;

Ar^1 is phenyl;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one substituent selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of

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which may be optionally substituted with one substituent selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;
and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein:
R^1 is selected from the group of hydrogen; and C_{1-4}alkyl;
R^2 is selected from the group of C_{1-4}alkyl; C_{3-6}cycloalkyl; and Het^1;
Het^1 is a heteroaryl selected from the group of thiazolyl and isoxazolyl, each of which may be optionally substituted with one or two C_{1-4}alkyl substituents;
or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;
R^3 is selected from the group of hydrogen and C_{1-6}alkyl;
R^4 is hydrogen;
R^5 is selected from the group of hydrogen and cyano;
R^6 is hydrogen;
R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; and $-NR^{7a}R^{7b}$; wherein R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-4}alkyl;
R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of
(i) fluoro,
(ii) Het^3,
(iii) Ar^1,
(x) $-OR^{8f}$,
R^{8f} is selected from the group of hydrogen and C_{1-6}alkyl;
Ar^1 is phenyl;
Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, pyrrolidinyl and azetidinyl, each of which may be optionally substituted with one or two substituents independently selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;
Het^3 is a heterocyclyl selected from the group of tetrahydrofuranyl and oxetanyl;
and the pharmaceutically acceptable salts and the solvates thereof.

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

R^1 is $C_{1\text{-}4}$alkyl;

R^2 is selected from the group of $C_{1\text{-}4}$alkyl and Het^1;

Het^1 is thiazolyl;

or R^1 and R^2 together with the carbon atom to which they are attached form a $C_{3\text{-}6}$cycloalkyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is selected from the group of hydrogen; cyano; amino; and $C_{1\text{-}4}$alkyl;

R^8 is selected from the group of hydrogen; $-SO_2C_{1\text{-}6}$alkyl optionally substituted with phenyl; Het^2; $C_{3\text{-}6}$cycloalkyl optionally substituted with $-C_{1\text{-}4}$alkylOH; and $C_{1\text{-}6}$alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,

(ii) Het^3,

(iii) Ar^1, and

(x) $-OR^{8f}$;

R^{8f} is selected from the group of hydrogen and $C_{1\text{-}6}$alkyl;

Ar^1 is phenyl;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of azetidinyl and piperidinyl, each of which may be optionally substituted with one $C_{1\text{-}4}$alkyl;

Het^3 is a heterocyclyl selected from the group of tetrahydrofuranyl and oxetanyl;

and the pharmaceutically acceptable salts and the solvates thereof.

Another embodiment of the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments wherein one or more, preferably all, of the following restrictions apply:

(a) R^1 is selected from the group of hydrogen; and $C_{1\text{-}4}$alkyl;

R^2 is selected from the group of $C_{1\text{-}4}$alkyl; $C_{3\text{-}6}$cycloalkyl; and Het^1;

or R^1 and R^2 together with the carbon atom to which they are attached form a $C_{3\text{-}6}$cycloalkyl;

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(b) Het^1 is a heteroaryl selected from the group of thiazolyl and isoxazolyl, each of which may be optionally substituted with one or two C_{1-4}alkyl substituents;
(c) R^3 is selected from the group of hydrogen and C_{1-6}alkyl;
(d) R^4 is hydrogen;
(e) R^5 is selected from the group of hydrogen and cyano;
(f) R^6 is hydrogen;
(g) R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; and $-NR^{7a}R^{7b}$; wherein R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-4}alkyl;
(h) R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of fluoro, Het^3, Ar^1, and $-OR^{8f}$;
(i) R^{8f} is selected from the group of hydrogen and C_{1-6}alkyl;
(j) Ar^1 is phenyl;
(k) Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, pyrrolidinyl and azetidinyl, each of which may be optionally substituted with one or two substituents independently selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;
(l) Het^3 is a heterocyclyl selected from the group of tetrahydrofuranyl and oxetanyl.

Another embodiment of the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments wherein one or more, preferably all, of the following restrictions apply:
(a) R^1 is C_{1-4}alkyl;
R^2 is selected from the group of C_{1-4}alkyl and Het^1;
or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;
(b) Het^1 is thiazolyl;
(c) R^3 is hydrogen;
(d) R^4 is hydrogen;
(e) R^5 is hydrogen;
(f) R^6 is hydrogen;
(g) R^7 is selected from the group of hydrogen; cyano; amino; and C_{1-4}alkyl;
(h) R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with $-C_{1-4}$alkylOH; and C_{1-6}alkyl

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optionally substituted with one or more substituents independently selected from the group of fluoro, Het^3, Ar^1, and -OR^{8f};

(i) R^{8f} is selected from the group of hydrogen and C_{1-6}alkyl;

(j) Ar^1 is selected from the group of phenyl;

(k) Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of azetidinyl and piperidinyl, each of which may be optionally substituted with one C_{1-4}alkyl;

(l) Het^3 is a heterocyclyl selected from the group of tetrahydrofuranyl and oxetanyl.

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

R^1 is methyl;

R^2 is selected from the group of methyl and thiazol-2-yl;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_5cycloalkyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is selected from the group of hydrogen; cyano; amino; and methyl;

R^8 is selected from the group of hydrogen; -SO_2C_{1-4}alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl substituted with -C_{1-4}alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,

(ii) Het^3,

(iii) Ar^1, and

(x) -OR^{8f};

R^{8f} is selected from the group of hydrogen and methyl;

Ar^1 is selected from the group of phenyl;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of 3-azetidinyl and 4-piperidinyl, each of which may be optionally substituted with one C_{1-4}alkyl; in particular Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of 3-azetidinyl and 4-piperidinyl, each of which are substituted with one C_{1-4}alkyl;

Het^3 is a heterocyclyl selected from the group of tetrahydrofuran-3-yl and 3-oxetanyl; and the pharmaceutically acceptable salts and the solvates thereof.

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In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein:
R^1 is C_{1-4}alkyl; in particular methyl;
R^2 is C_{1-4}alkyl; in particular methyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 is hydrogen;
R^6 is hydrogen;
R^7 is hydrogen;
R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; C_{3-6}cycloalkyl optionally substituted with $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of
(i) fluoro,
(iii) Ar^1, and
(x) $-OR^{8f}$;
R^{8f} is selected from the group of hydrogen and C_{1-6}alkyl;
Ar^1 is phenyl;
and the pharmaceutically acceptable salts and the solvates thereof.

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^6 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents; and
R^7 is hydrogen; or
R^6 is hydrogen; and
R^7 is selected from the group of hydrogen, cyano, amino and C_{1-4}alkyl.

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^6 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;
R^7 is hydrogen; or
R^6 is hydrogen; and
R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; and $-NR^{7a}R^{7b}$; wherein

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R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-4}alkyl.

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 is C_{1-4}alkyl;
R^2 is selected from the group C_{1-4}alkyl, and Het^1; wherein
Het^1 is a heteroaryl selected from the group of thiazolyl, pyrazolyl, and imidazolyl; in particular thiazolyl;
or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl group;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 is hydrogen;
R^6 is hydrogen;
R^7 is selected from the group of hydrogen, cyano, amino, and C_{1-4}alkyl;
R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of
(i) fluoro,
(ii) Het^3,
(iii) Ar^1, and
(x) $-OR^{8f}$;
R^{8f} is selected from the group of hydrogen and C_{1-6}alkyl;
Ar^1 is phenyl;
Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of azetidinyl and piperidinyl, each of which may be optionally substituted with one C_{1-4}alkyl;
Het^3 is a heterocyclyl selected from the group of tetrahydrofuranyl and oxetanyl, each of which may be optionally substituted with one substituent selected from C_{1-4}alkyl.

In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein:
R^1 is C_{1-4}alkyl;
R^2 is selected from the group C_{1-4}alkyl, C_{3-6}cycloalkyl and Het^1; wherein

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Het^1 is a heteroaryl selected from the group of thiazolyl, isoxazolyl, pyrazolyl, and imidazolyl; each of which may be optionally substituted with one or two $C_{1\text{-}4}$alkyl substituents;

or R^1 and R^2 together with the carbon atom to which they are attached form a $C_{3\text{-}6}$cycloalkyl group;

R^3 is hydrogen, $C_{1\text{-}6}$alkyl or $C_{3\text{-}6}$cycloalkyl;

R^4 is hydrogen;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is selected from the group of hydrogen, halogen, cyano, $C_{1\text{-}4}$alkyl and $-NR^{7a}R^{7b}$;

R^{7a} and R^{7b} are each independently selected from hydrogen and $C_{1\text{-}4}$alkyl;

R^8 is selected from the group of hydrogen; $-SO_2C_{1\text{-}6}$alkyl optionally substituted with phenyl; Het^2; $C_{3\text{-}6}$cycloalkyl optionally substituted with $-C_{1\text{-}4}$alkylOH; and $C_{1\text{-}6}$alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,

(ii) Het^3,

(iii) Ar^1, and

(x) $-OR^{8f}$;

R^{8f} is selected from the group of hydrogen and $C_{1\text{-}6}$alkyl;

Ar^1 is phenyl;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of azetidinyl and piperidinyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, $C_{1\text{-}4}$alkyl, $-OC_{1\text{-}4}$alkyl, $C_{3\text{-}6}$cycloalkyl, and $C_{1\text{-}4}$alkyl substituted with one $-OC_{1\text{-}4}$alkyl;

Het^3 is a heterocyclyl selected from the group of tetrahydrofuranyl and oxetanyl, each of which may be optionally substituted with one substituent selected from $C_{1\text{-}4}$alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

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 is $C_{1\text{-}4}$alkyl; in particular methyl;

R^2 is $C_{1\text{-}4}$alkyl; in particular methyl;

R^7 is hydrogen;

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R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; C_{3-6}cycloalkyl optionally substituted with $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,

(iii) Ar^1, and

(x) $-OR^{8f}$.

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^2 is selected from the group of C_{1-4}alkyl and thiazolyl; in particular methyl and thiazolyl; more in particular thiazolyl.

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^2 is methyl.

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 is selected from the group of hydrogen; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; R^2 is selected from the group of hydrogen; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; C_{3-6}cycloalkyl and Het^1.

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 is C_{1-4}alkyl; R^2 is selected from the group of C_{1-4}alkyl and Het^1.

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 is C_{1-4}alkyl; R^2 is selected from the group of C_{1-4}alkyl and Het^1; or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl.

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 is selected

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from the group of C_{1-4}alkyl and C_{1-4}alkyl substituted with one or more fluoro substituents;
R^2 is selected from the group of C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; C_{3-6}cycloalkyl and Het^1;
or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl.

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 is C_{1-4}alkyl; R^2 is selected from the group of C_{1-4}alkyl; or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl.

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 is C_{1-4}alkyl; R^2 is selected from the group of C_{1-4}alkyl.

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 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl.

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 is C_{1-4}alkyl; R^2 is selected from the group of C_{1-4}alkyl and Het^1; or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl.

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 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; R^6 is hydrogen.

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 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; R^6 is hydrogen; R^7 is hydrogen.

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 is methyl; R^2 is methyl; R^3 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; R^6 is hydrogen; R^7 is hydrogen.

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 Ar^1 is phenyl.

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 is other than $-NR^{7a}R^{7b}$.

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 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents.

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^6 is hydrogen; and R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents; in particular wherein R^6 is hydrogen; and R^7 is selected from the group of halogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents.

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^1 is thiazolyl optionally substituted with one or two substituents independently selected from halogen and C_{1-4}alkyl;
Ar^1 is phenyl optionally substituted with one or two substituents independently selected from halogen, cyano, C_{1-4}alkyl, C_{1-4}alkyl substituted with one or more fluoro substituents, $-OC_{1-4}$alkyl, and $-OC_{1-4}$alkyl substituted with one or more fluoro substituents;

Het[2] is a heterocyclyl, bound through any available carbon atom, selected from the group of azetidinyl and piperidinyl, each of which may be optionally substituted with one C_{1-4}alkyl; in particular Het[2] is a heterocyclyl, bound through any available carbon atom, selected from the group of azetidinyl and piperidinyl, each of which are substituted with one C_{1-4}alkyl;
Het[3] is selected from the group of tetrahydrofuranyl and oxetanyl, each of which may be optionally substituted with C_{1-4}alkyl.

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[1] is thiazolyl;
Ar[1] is phenyl;
Het[2] is a heterocyclyl, bound through any available carbon atom, selected from the group of azetidinyl and piperidinyl, each of which may be optionally substituted with one C_{1-4}alkyl; in particular Het[2] is a heterocyclyl, bound through any available carbon atom, selected from the group of azetidinyl and piperidinyl, each of which are substituted with one C_{1-4}alkyl;
Het[3] is selected from the group of tetrahydrofuranyl and oxetanyl.

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[1] is thiazolyl optionally substituted with one or two substituents independently selected from halogen and C_{1-4}alkyl;
Ar[1] is phenyl optionally substituted with one or two substituents independently selected from halogen, cyano, C_{1-4}alkyl, C_{1-4}alkyl substituted with one or more fluoro substituents, -OC_{1-4}alkyl, and -OC_{1-4}alkyl substituted with one or more fluoro substituents;
Het[2] is a heterocyclyl, bound through any available carbon atom, selected from the group of pyrrolidinyl, azetidinyl and piperidinyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, -OC_{1-4}alkyl, C_{3-6}cycloalkyl, and C_{1-4}alkyl substituted with one -OC_{1-4}alkyl; in particular Het[2] is a heterocyclyl, bound through any available carbon atom, selected from the group of pyrrolidinyl, azetidinyl and piperidinyl, each of which are substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, -OC_{1-4}alkyl, C_{3-6}cycloalkyl, and C_{1-4}alkyl substituted with one -OC_{1-4}alkyl;

Het^3 is selected from the group of tetrahydrofuranyl and oxetanyl, each of which may be optionally substituted with C_{1-4}alkyl.

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^1 is thiazolyl or isoxazolyl, each of which may be optionally substituted with C_{1-4}alkyl;
Ar^1 is phenyl;
Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of pyrrolidinyl, azetidinyl and piperidinyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, -OC_{1-4}alkyl, C_{3-6}cycloalkyl, and C_{1-4}alkyl substituted with one -OC_{1-4}alkyl; in particular Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of pyrrolidinyl, azetidinyl and piperidinyl, each of which are substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, -OC_{1-4}alkyl, C_{3-6}cycloalkyl, and C_{1-4}alkyl substituted with one -OC_{1-4}alkyl;
Het^3 is selected from the group of tetrahydrofuranyl and oxetanyl.

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 is hydrogen, halogen, cyano, amino or C_{1-4}alkyl.

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 is selected from the group of hydrogen and C_{1-4}alkyl;
R^2 is selected from the group of C_{1-4}alkyl; C_{3-6}cycloalkyl; and Het^1;
Het^1 is isoxazolyl which may be optionally substituted with one or two C_{1-4}alkyl substituents;
R^7 is selected from the group of hydrogen; halogen and C_{1-4}alkyl; preferably R^7 is hydrogen;
R^8 is selected from the group of -SO_2C_{1-6}alkyl; Het^2; C_{3-6}cycloalkyl optionally substituted with -C_{1-4}alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of
(i) fluoro,
(ii) Het^3,
(iii) Ar^1,

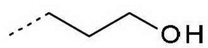
(x) -OR^{8f},
R^{8f} is C_{1-6}alkyl;
Ar^1 is phenyl;
Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, and pyrrolidinyl, each of which may be optionally substituted with one or two substituents independently selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;
Het^3 is tetrahydrofuranyl.

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 is selected from the group of hydrogen and C_{1-4}alkyl;
R^2 is selected from the group of C_{1-4}alkyl; C_{3-6}cycloalkyl; and Het^1;
Het^1 is isoxazolyl which may be optionally substituted with one or two C_{1-4}alkyl substituents;
R^7 is selected from the group of hydrogen; halogen and C_{1-4}alkyl; preferably R^7 is hydrogen;
R^8 is selected from the group of -SO_2C_{1-6}alkyl; Het^2; C_{3-6}cycloalkyl; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of
(i) fluoro,
(iii) Ar^1,
Ar^1 is phenyl;
Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, and pyrrolidinyl, each of which may be optionally substituted with one or two substituents independently selected from C_{3-6}cycloalkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents.

In an embodiment, the present invention concerns novel compounds of Formula (I), tautomers and stereoisomeric forms thereof, wherein:
R^1 is selected from the group of C_{1-4}alkyl;
R^2 is selected from the group of C_{1-4}alkyl and Het^1;
Het^1 is a heteroaryl selected from the group of thiazolyl and isoxazolyl, each of which may be optionally substituted with one or two C_{1-4}alkyl substituents;
or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;
R^3 is hydrogen;

R^4 is hydrogen;
R^5 is hydrogen;
R^6 is hydrogen;
R^7 is hydrogen;
R^8 is selected from the group of hydrogen, Het^2 and C_{1-6}alkyl optionally substituted with one or more OH substituents
Het^2 is piperidinyl, bound through any available carbon atom, substituted with one or two substituents independently selected from C_{1-4}alkyl and C_{3-6}cycloalkyl;
and the pharmaceutically acceptable salts and the solvates thereof.

Another embodiment of the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments wherein one or more, preferably all, of the following restrictions apply:

(a) R^1 is selected from the group of C_{1-4}alkyl;
R^2 is selected from the group of C_{1-4}alkyl and Het^1;
or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;
(b) Het^1 is a heteroaryl selected from the group of thiazolyl and isoxazolyl, each of which may be optionally substituted with one or two C_{1-4}alkyl substituents;
(c) R^3 is hydrogen;
(d) R^4 is hydrogen;
(e) R^5 is hydrogen;
(f) R^6 is hydrogen;
(g) R^7 is hydrogen;
(h) R^8 is selected from the group of hydrogen, Het^2 and C_{1-6}alkyl optionally substituted with one or more OH substituents;
in particular R^8 is selected from hydrogen, $-CH_2CH_3$, 

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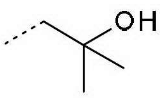
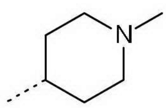
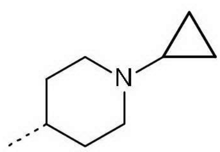


, 

, and 

;
(i) Het^2 is piperidinyl, bound through any available carbon atom, substituted with one or two substituents independently selected from C_{1-4}alkyl and C_{3-6}cycloalkyl.

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^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with OH, $-OC_{1-4}$alkyl, and $-C_{1-4}$alkylOH; C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of (ii) Het^3 and (iii) Ar^1; and C_{2-6}alkyl substituted with one or more substituents independently selected from the group of

(i) fluoro,
(iv) $-NR^{8a}R^{8b}$,
(v) $-NR^{8c}C(=O)R^{8d}$,
(vi) $-NR^{8c}C(=O)NR^{8a}R^{8b}$,
(vii) $-NR^{8c}C(=O)OR^{8e}$,
(viii) $-NR^{8c}S(=O)_2NR^{8a}R^{8b}$,
(ix) $-NR^{8c}S(=O)_2R^{8d}$,
(x) $-OR^{8f}$,
(xi) $-OC(=O)NR^{8a}R^{8b}$,
(xii) $-C(=O)NR^{8a}R^{8b}$,
(xiii) $-S(O)_2R^{8d}$, and
(xiv) $-S(O)_2NR^{8a}R^{8b}$.

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^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with $-C_{1-4}$alkylOH; C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of Het^3 and Ar^1; and C_{2-6}alkyl substituted with one or more substituents independently selected from the group of fluoro and $-OR^{8f}$.

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 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;
R^8 is selected from the group of $-SO_2C_{1-6}$alkyl; Het^2; C_{3-6}cycloalkyl optionally substituted with $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,
(ii) Het^3,
(iii) Ar^1,
(x) $-OR^{8f}$,
R^{8f} is C_{1-6}alkyl;
Ar^1 is phenyl;
Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{3-6}cycloalkyl, C_{1-4}alkyl substituted with one $-OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;
Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, and azetidinyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{1-4}alkyl substituted with one $-OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents.

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 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;
R^8 is selected from the group of $-SO_2C_{1-6}$alkyl; Het^2; C_{3-6}cycloalkyl; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of
(i) fluoro,
(ii) Het^3,
(iii) Ar^1,
(x) $-OR^{8f}$,
R^{8f} is C_{1-6}alkyl;
Ar^1 is phenyl;
Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{3-6}cycloalkyl, C_{1-4}alkyl substituted with one $-OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

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Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, and azetidinyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, $C_{1\text{-}4}$alkyl, -O$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkyl substituted with one -O$C_{1\text{-}4}$alkyl, and $C_{1\text{-}4}$alkyl substituted with one or more fluoro substituents.

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 is selected from the group of hydrogen; halogen; cyano; and $C_{1\text{-}4}$alkyl;

R^8 is selected from the group of -$SO_2C_{1\text{-}6}$alkyl; Het^2; $C_{3\text{-}6}$cycloalkyl; and $C_{1\text{-}6}$alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,

(ii) Het^3,

(iii) Ar^1,

(x) -OR^{8f},

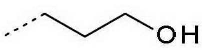
R^{8f} is $C_{1\text{-}6}$alkyl;

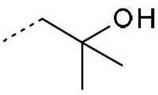
Ar^1 is phenyl;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, and pyrrolidinyl, each of which may be optionally substituted with one or two substituents independently selected from $C_{1\text{-}4}$alkyl, $C_{3\text{-}6}$cycloalkyl, and $C_{1\text{-}4}$alkyl substituted with one or more fluoro substituents;

Het^3 is tetrahydrofuranyl.

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^8 is selected from hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2-CH(CH_3)_2$,



, 

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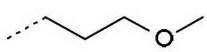
, 

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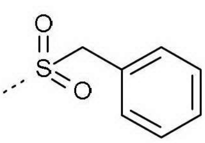
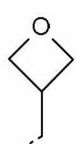
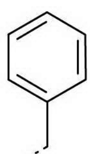
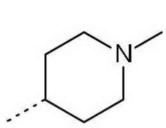
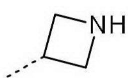
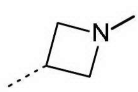


, 

, 
, 

, 

, 

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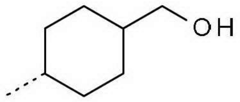
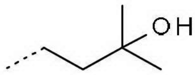
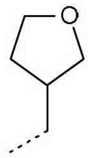
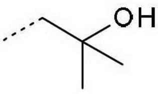
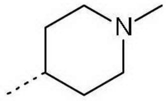
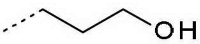
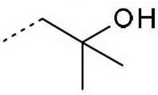
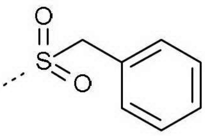
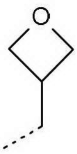
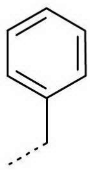
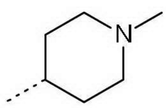
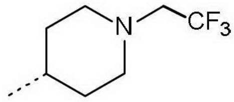
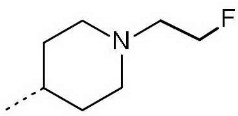
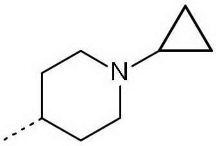
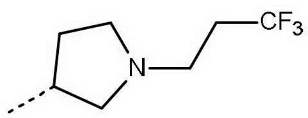
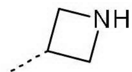
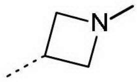
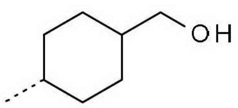
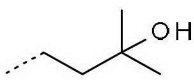
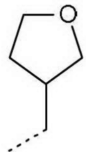
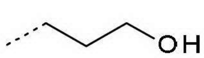
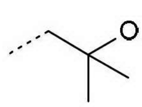
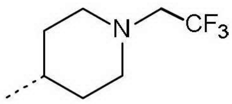
,  and . More in particular, R^8 is selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, , , and .

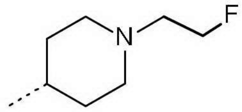
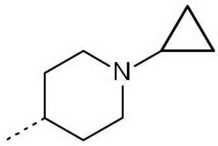
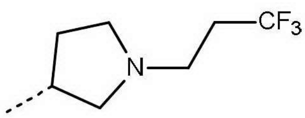
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^8 is selected from hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2-CH(CH_3)_2$,

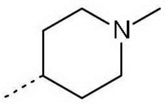
, , , , ,

, , , , ,

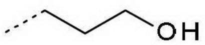
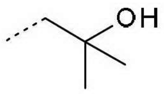
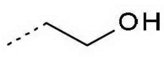
, , , ,

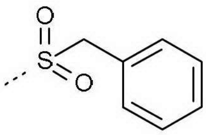
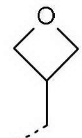
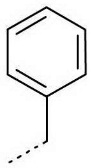
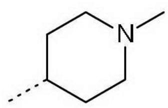
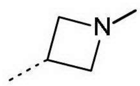
, ,  and . More in particular, R^8 is selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, , , ,

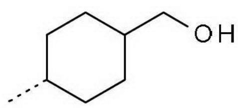
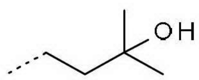
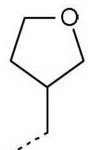
, ,  and

.

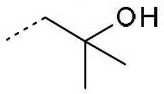
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^8 is selected from hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2-CH(CH_3)_2$,

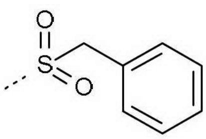
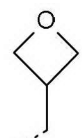
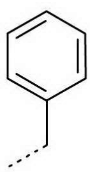
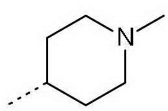
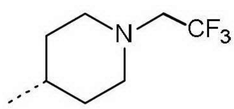
, , , , ,

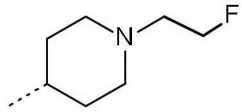
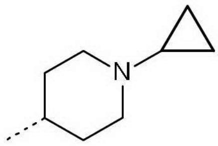
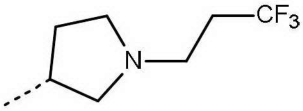
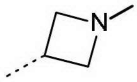
, , , , ,

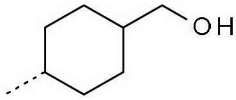
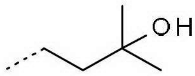
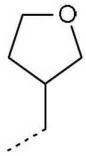
,  and .

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^8 is selected from hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2-CH(CH_3)_2$,

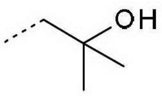
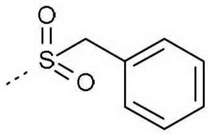
, , , , ,

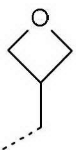
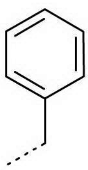
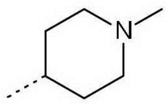
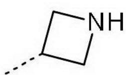
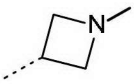
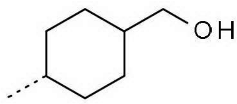
, , , , ,

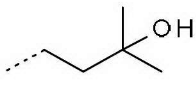
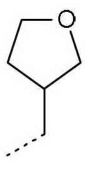
, , , ,

,  and .

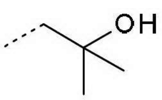
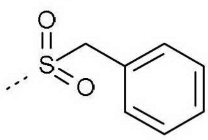
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^8 is selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2-CH(CH_3)_2$, ,

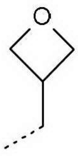
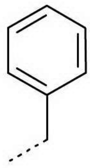
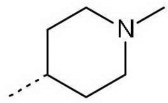
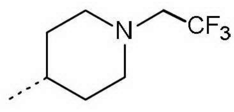
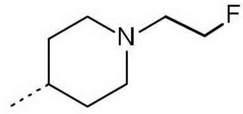
, , , , ,

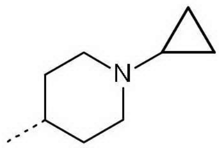
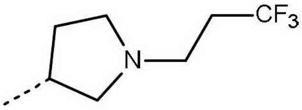
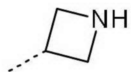
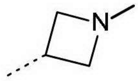
, , , , , ,

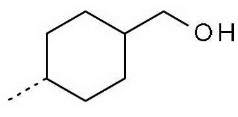
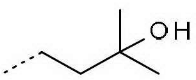
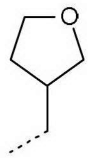
 and .

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^8 is selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2-CH(CH_3)_2$, ,

, , , , ,

, , , , ,

, , , ,

,  and .

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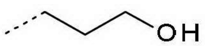
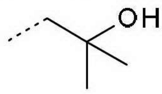
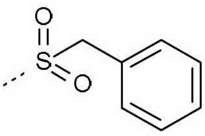
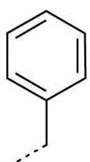
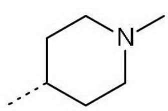
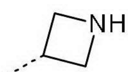
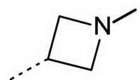
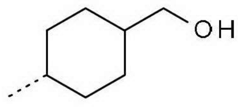
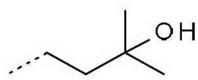
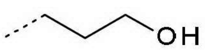
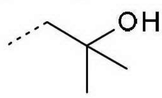
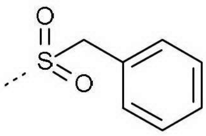
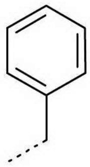
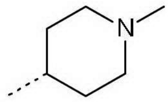
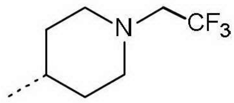
, , , , ,

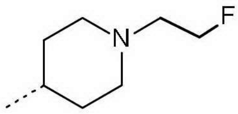
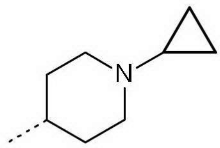
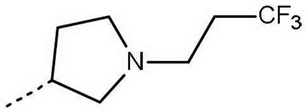
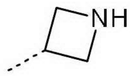
, , , , ,

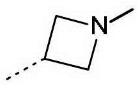
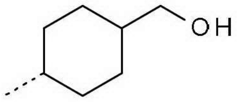
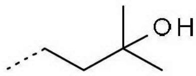
, and .

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^8 is selected from hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2-CH(CH_3)_2$,

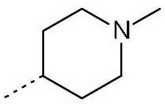
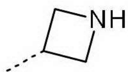
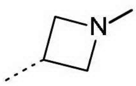
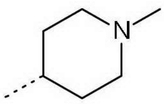
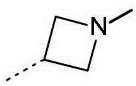
, , , , ,

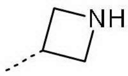
, , , ,

, , , ,

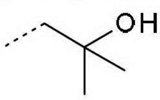
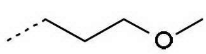
, , and .

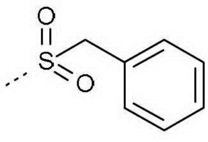
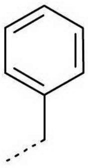
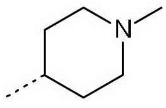
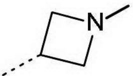
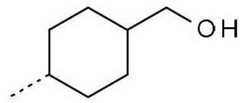
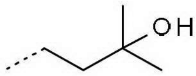
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^2 is selected from the group of

,  and ; in particular Het^2 is selected from the group of  and .

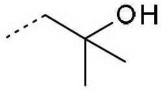
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^8 is other than .

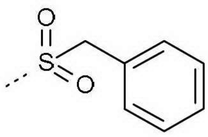
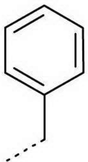
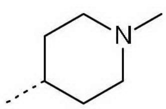
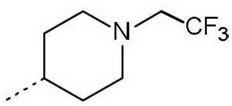
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^8 is selected from hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2-CH(CH_3)_2$,

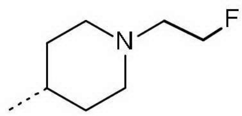
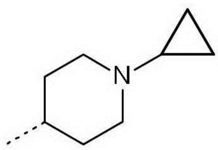
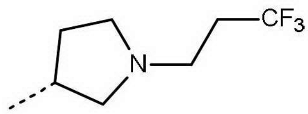
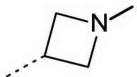
, , , , ,

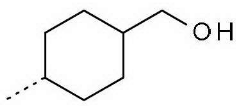
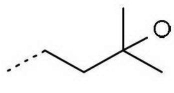
, , , , , and .

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^8 is selected from hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2-CH(CH_3)_2$,

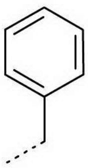
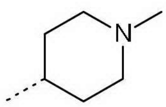
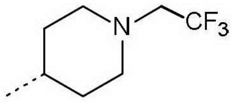
, , , , ,

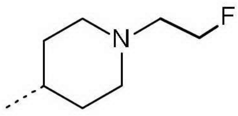
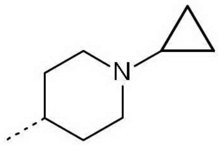
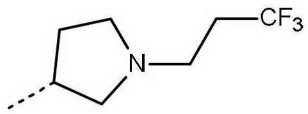
, , , ,

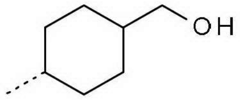
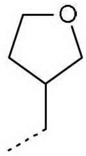
, , , ,

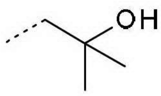
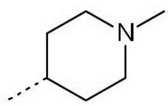
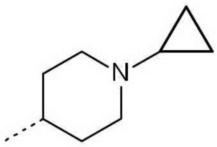
, and .

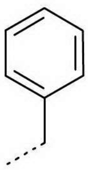
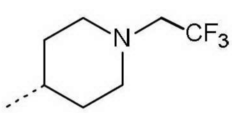
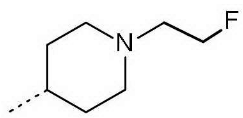
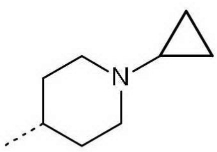
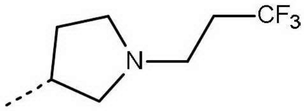
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^8 is selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2-CH(CH_3)_2$, ,

, , , ,

, , ,

 and .

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^8 is selected from hydrogen, $-CH_2CH_3$, , , , and .

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^8 is selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, , , ,  and .

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^8 is other than hydrogen.

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^{7a} and R^{7b} are each independently selected from C_{1-4}alkyl.

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 is C_{1-4}alkyl;
R^2 is selected from the group of C_{1-4}alkyl and Het[1], in particular R^2 is selected from the group of C_{1-4}alkyl and thiazolyl;
or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;
wherein R^3 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; R^6 is hydrogen;
R^8 is selected from hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2-CH(CH_3)_2$,

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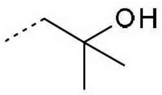

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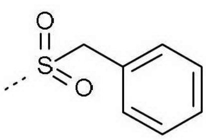

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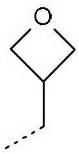

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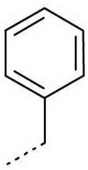
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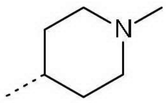

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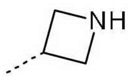

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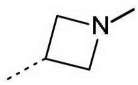

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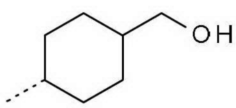

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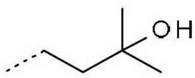

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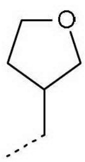
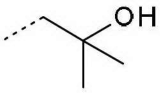


.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^1 is C_{1-4}alkyl;
R^2 is selected from the group of C_{1-4}alkyl and Het[1], in particular R^2 is selected from the group of C_{1-4}alkyl and thiazolyl;
or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;
wherein R^3 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; R^6 is hydrogen;

R^8 is selected from hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, $-CH(CH_2CH_3)_2$, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2-CH(CH_3)_2$,

, 

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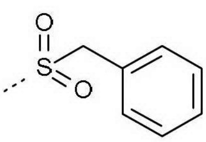
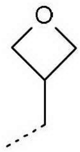
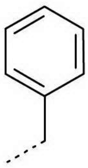
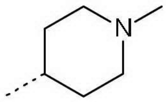
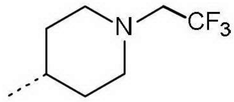


, 

, 
, 

, 

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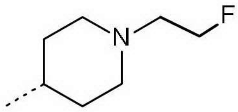
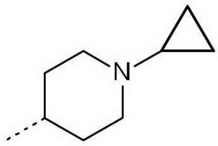
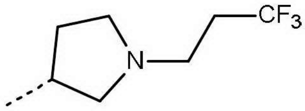
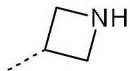


, 

, 

, 

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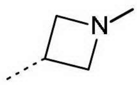
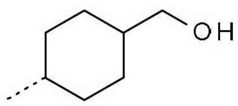
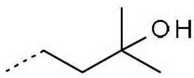
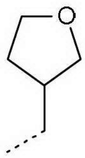


, 

, 

and 

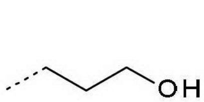
.

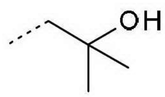
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable addition salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

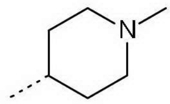
R^1 is methyl;

R^2 is methyl;

wherein R^3 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; R^6 is hydrogen; R^7 is hydrogen;

R^8 is selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2)_2CH_3$, 

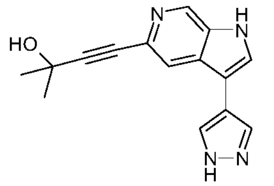
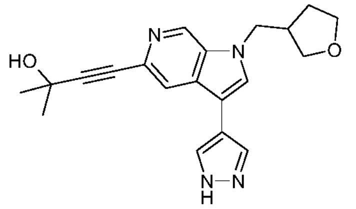
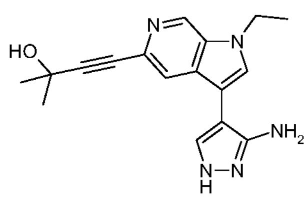
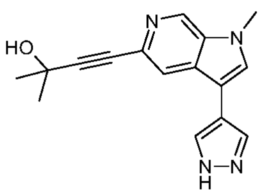
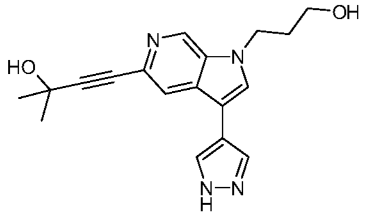
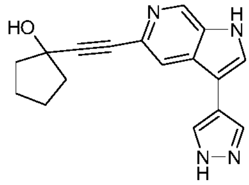
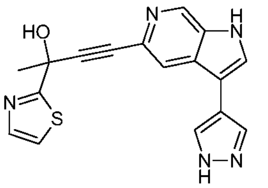
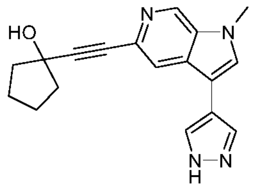
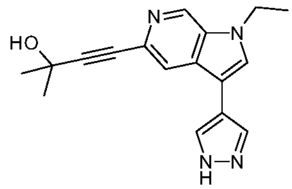
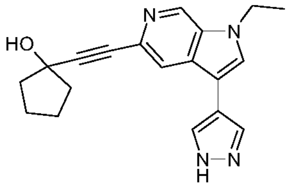
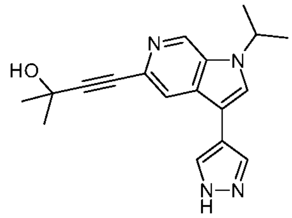
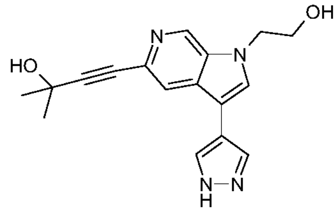
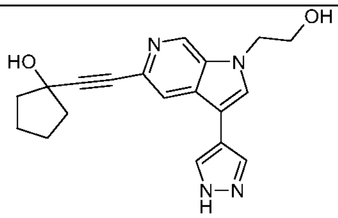
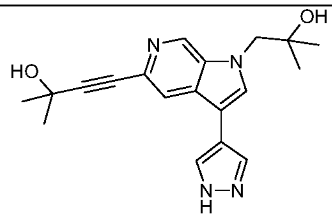
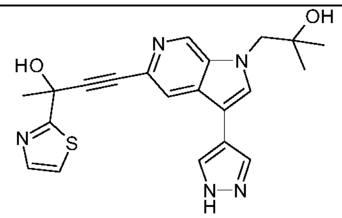
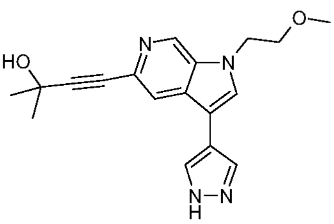
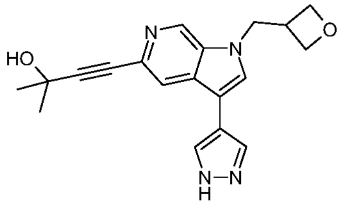
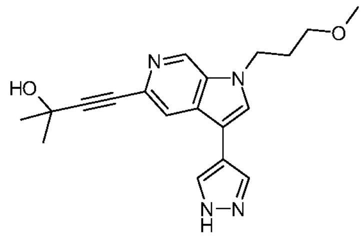
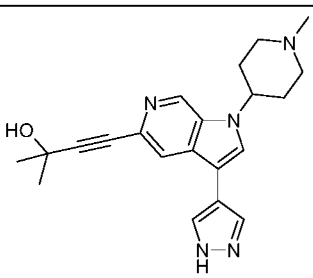
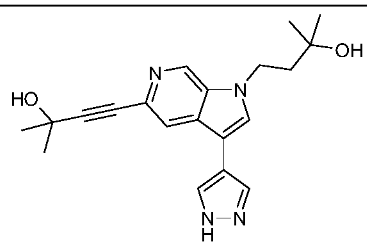
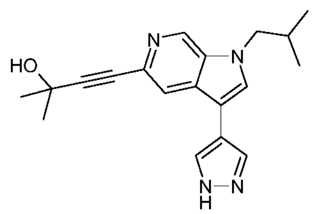
, 

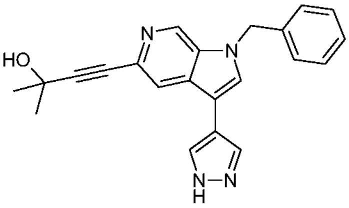
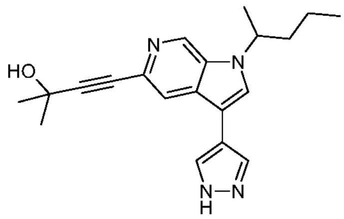
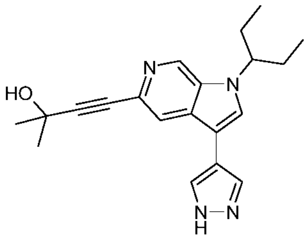
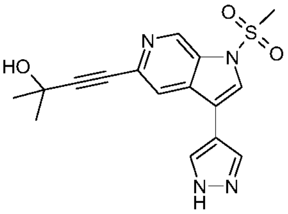
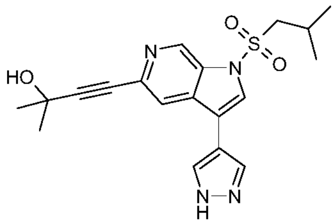
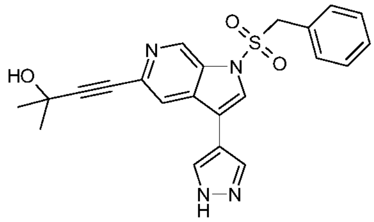
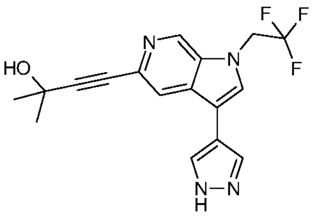
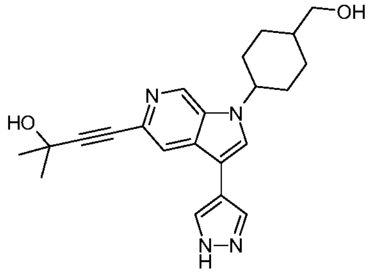
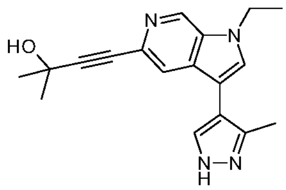
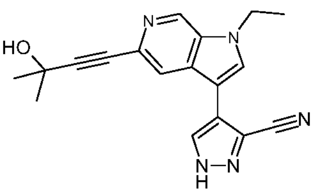
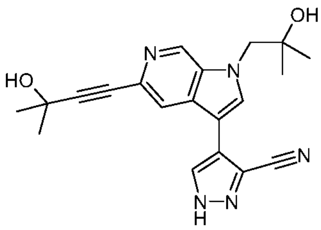
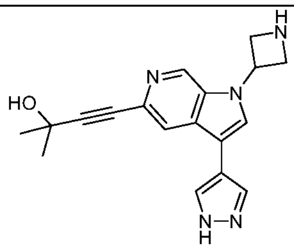
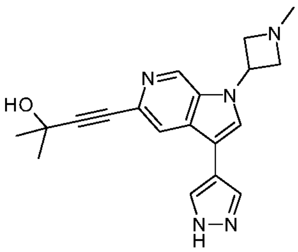
, and 

.

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 is hydrogen.

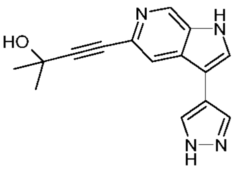
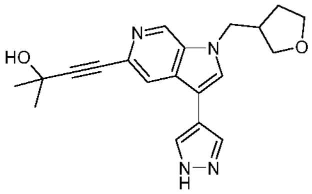
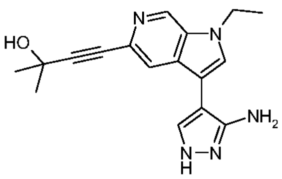
Specific compounds according to the invention include:

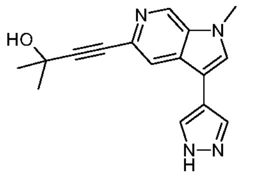
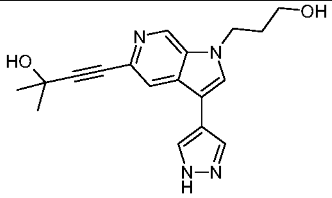
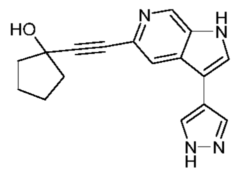
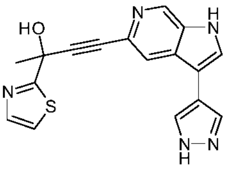
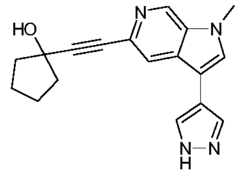
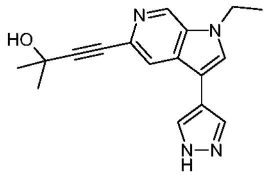
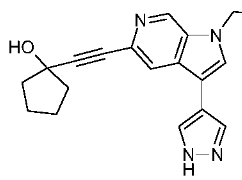
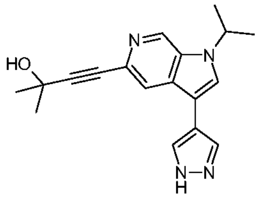
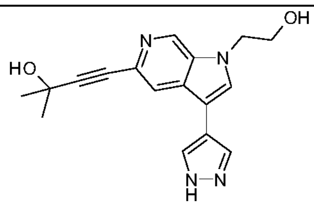
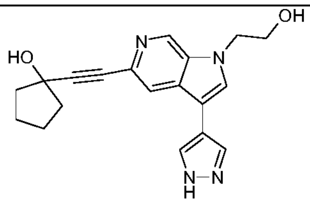
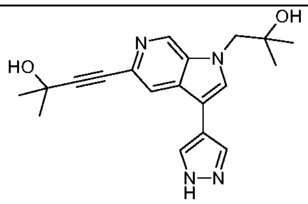
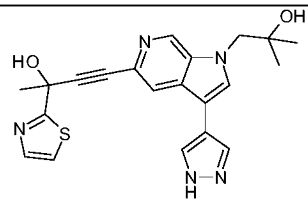
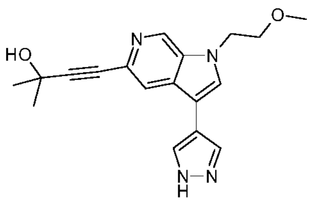
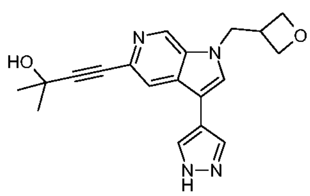
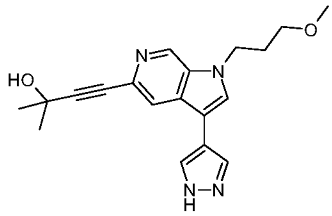
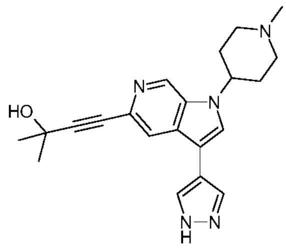
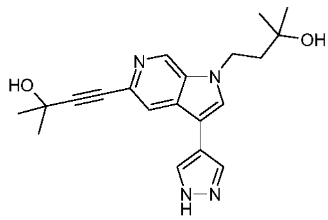
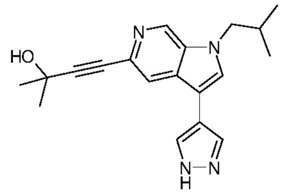
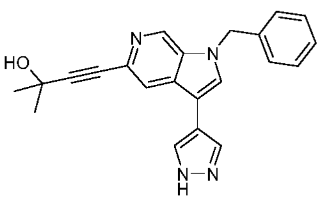
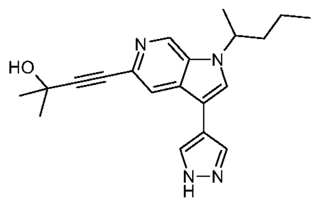
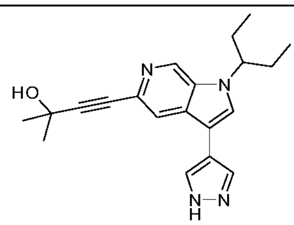
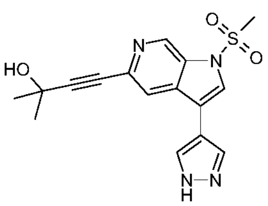
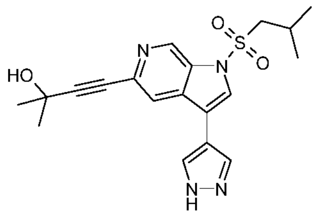
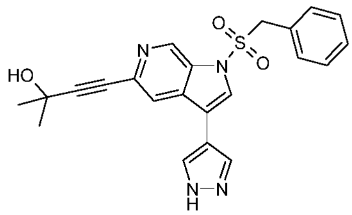
		
		
		
		
		
		
		

and the pharmaceutically acceptable salts and solvates forms of such compounds.

Specific compounds according to the invention include:

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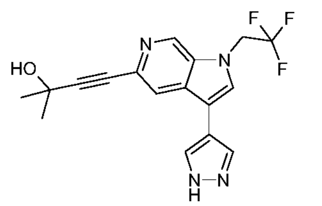
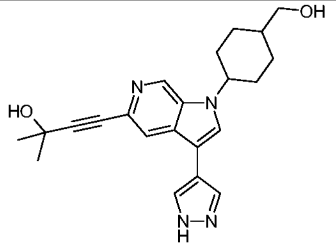
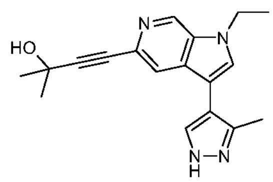
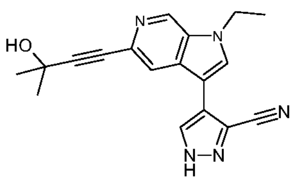
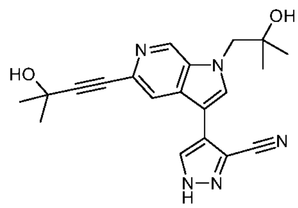
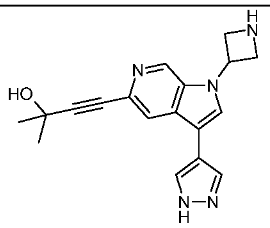
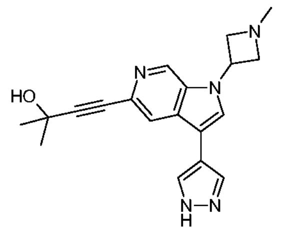
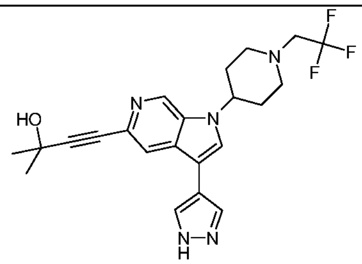
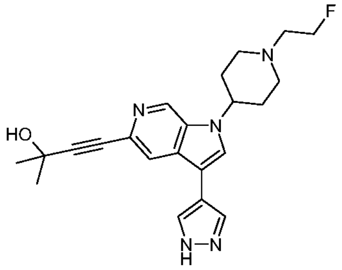
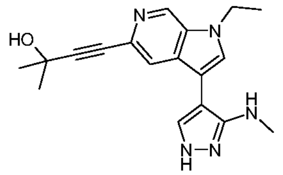
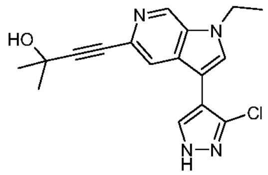
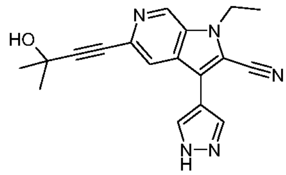
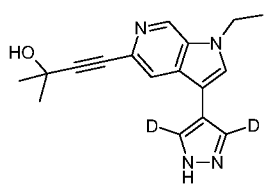
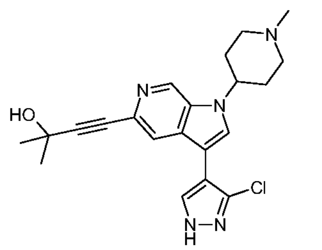
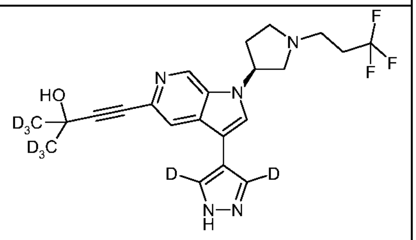
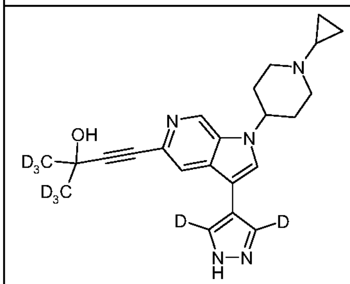
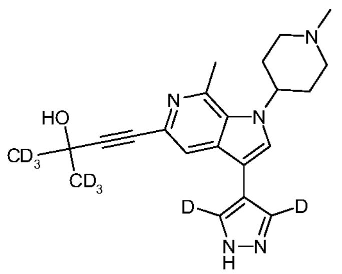
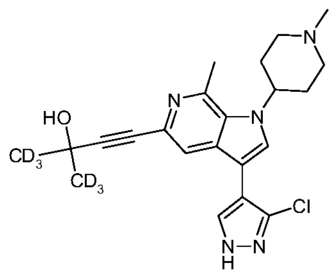
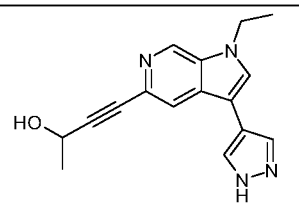
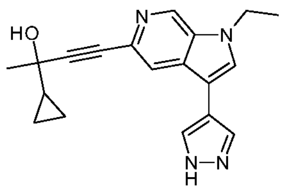
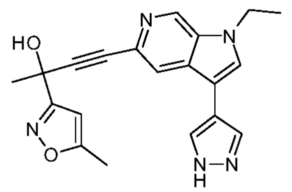
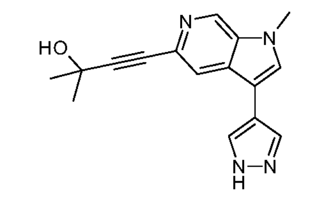
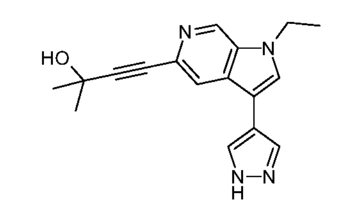
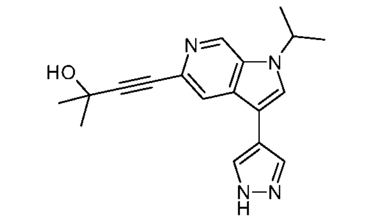
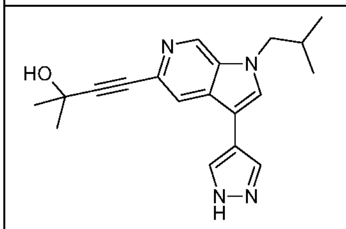
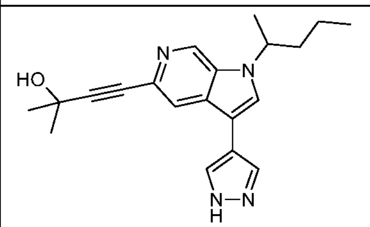
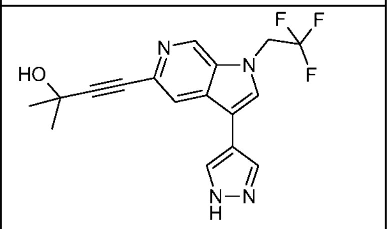
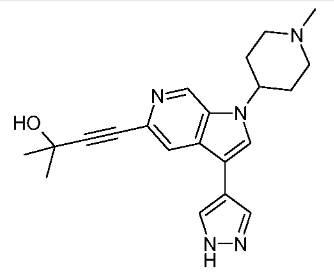
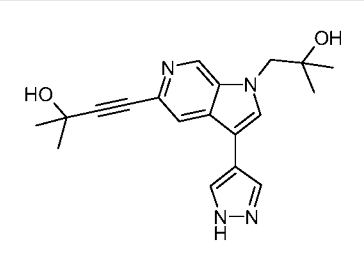
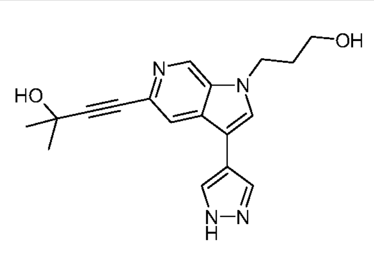
		
		
		
		
		 S-enantiomer
		
		

	R or S-enantiomer	

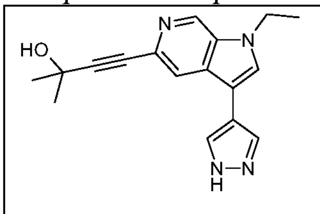
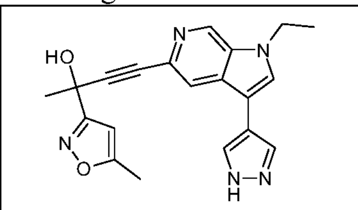
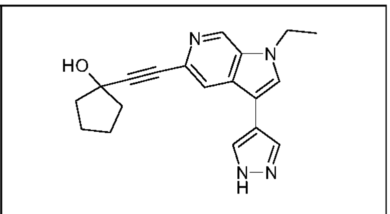
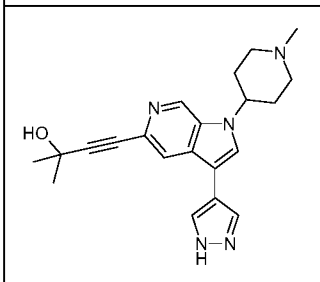
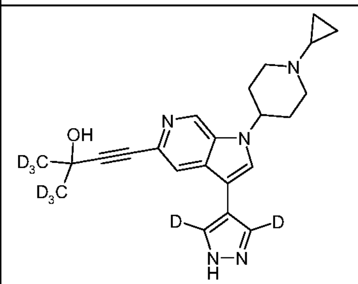
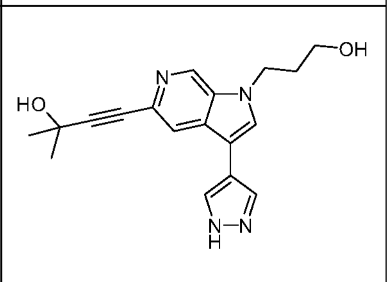
tautomers and stereoisomeric forms thereof,
and the pharmaceutically acceptable salts and the solvates thereof.

More specific compounds according to the invention include:

and the pharmaceutically acceptable salts and solvates forms of such compounds.

More specific compounds according to the invention include:

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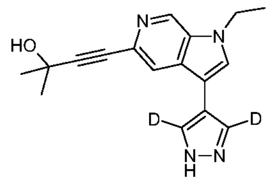
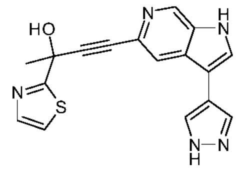
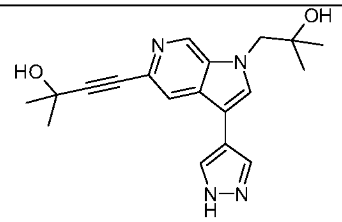
		

tautomers and stereoisomeric forms thereof,
and the pharmaceutically acceptable salts and the solvates thereof.

For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts". Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Conversely, said salt forms can be converted into the free base form by treatment with an appropriate base.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts.

Representative acids which may be used in the preparation of pharmaceutically acceptable salts include, but are not limited to, the following: acetic acid, 2,2-dichloroactic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, (+)-camphoric acid, camphorsulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucoronic acid, L-glutamic acid, beta-oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoromethylsulfonic acid, and undecylenic acid.

Representative bases which may be used in the preparation of pharmaceutically acceptable salts include, but are not limited to, the following: ammonia, L-arginine, benethamine, benzathine, calcium hydroxide, choline, dimethylethanolamine, diethanolamine, diethylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylene-diamine, *N*-methyl-glucamine, hydrabamine, 1*H*-imidazole, L-lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, secondary amine, sodium hydroxide, triethanolamine, tromethamine and zinc hydroxide.

Conversely, said salt forms can be converted into the free acid forms by treatment with an appropriate acid.

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.

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

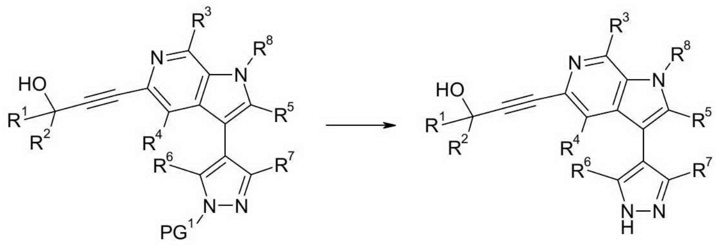
Methods of Synthesis

Compounds of Formula (I) can be prepared by methods known to those who are 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.

For clarity, only one specific regioisomer of the intermediates is shown in the general schemes. However, the skilled person will realize that some intermediates may appear as mixtures of regioisomers as is also clear from the examples in the specific experimental part.

Herein, the term ‘Me’ means methyl, ‘DMF’ means *N*,*N*-dimethylformamide, ‘$Pd(PPh_3)_4$’ means tetrakis(triphenylphosphine)palladium, ‘Boc’ means t-butoxycarbonyl, ‘$[Ir(OMe)cod]_2$’ means (1,5-cyclooctadiene)(methoxy) iridium(I) dimer (also bis(1,5-cyclooctadiene)di-μ-methoxydiiridium(I)), ‘Ts’ means tosyl, ‘THF’ means tetrahydrofuran, ‘TFA’ means trifluoroacetic acid, ‘SEM’ means 2-(trimethylsilyl)ethoxy]-methyl, **‘**TBAF’ means tetrabutylammonium fluoride, ‘$PdCl_2$(dppf)’ means [1,1'-bis(diphenylphosphino-κP)ferrocene]dichloropalladium, ‘KOAc’ means potassium acetate.

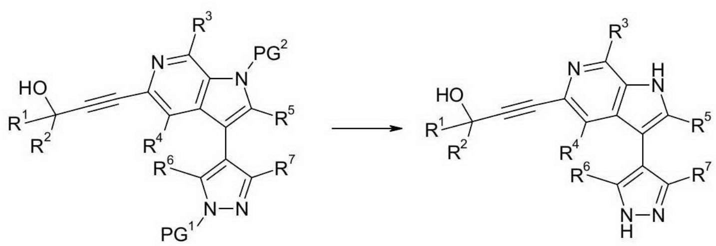
Scheme 1



(IIa) (Ia)

Scheme 1 illustrates methods of preparing compounds of Formula (Ia), wherein R^1-R^8 are as defined in Formula (I), except where R^8 is hydrogen. Intermediates (IIa), wherein PG^1 is a suitable protecting group, such as a t-butoxycarbonyl (Boc) or [2-(trimethylsilyl)ethoxy]methyl (SEM), can be treated with reagents, such as tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF), with heating, or TFA in dichloromethane (DCM), to furnish compounds of Formula (Ia).

Scheme 2



(IIb) (Ib)

Scheme 2 illustrates methods of preparing compounds of Formula (Ib), wherein R^1-R^7 are as defined in Formula (I) and R^8 is hydrogen. Intermediates (IIb), wherein PG^1 is a suitable protecting group, such as SEM, and PG^2 is a suitable protecting group, such as

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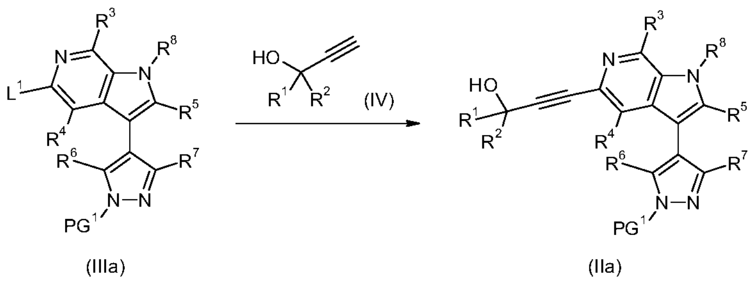
tosyl (Ts), can be treated with a suitable reagent, such as TBAF in THF, to furnish compounds of Formula (Ib).

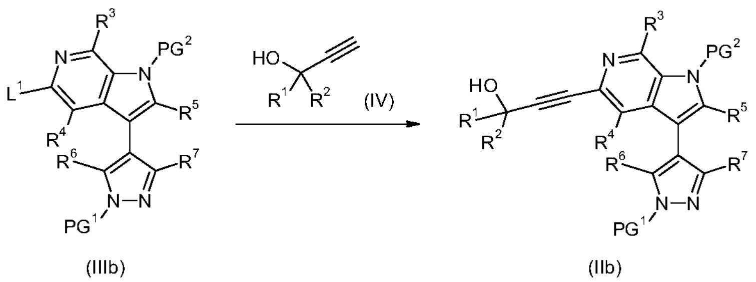
Additional compounds of Formula (I) can be prepared from compounds of Formula (Ia) and (Ib) by elaboration of functional groups present. Such elaboration includes, but is not limited to, hydrolysis, reduction, oxidation, alkylation, amidation and dehydration. Such transformations may in some instances require the use of protecting groups.

Scheme 3



Intermediates of Formula (IIa), wherein R^1-R^8 are as defined in Formula (I) and PG^1 is a suitable protecting group, can be prepared by reaction of intermediates of Formula (IIIa) wherein L^1 is a suitable leaving group such as chloro or bromo, with alkynes of Formula (IV) under palladium-catalyzed Sonogashira coupling conditions, using for example tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$), CuI and a base such as triethylamine in acetonitrile, with heating (Scheme 3).

Scheme 4



Intermediates of Formula (IIb), wherein R^1-R^7 are as defined in Formula (I), PG^1 and PG^2 are suitable protecting groups, can be prepared by means of a Sonogashira palladium-catalyzed coupling of intermediates of Formula (IIIb), wherein L^1 is a suitable leaving group such as chloro or bromo, with alkynes of Formula (IV), using a

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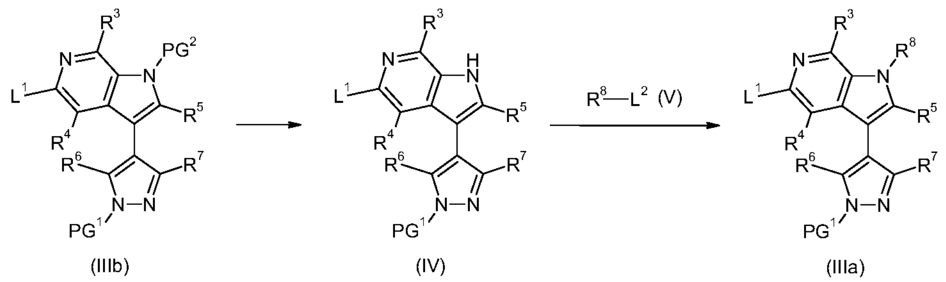
suitable palladium catalyst, copper catalyst, base and solvent (for example, $Pd(PPh_3)_4$, CuI, triethylamine and acetonitrile, respectively) (Scheme 4).

Alkynes of Formula (IV) are commercially available or can be prepared by known methods.

Scheme 5



Scheme 5 illustrates methods of preparing intermediates of Formula (IIIa) from intermediates of Formula (IIIb). Intermediates of Formula (IIIb), wherein R^3-R^7 are as defined above, PG^1 is Boc, PG^2 is Ts and L^1 is a suitable leaving group, can be selectively deprotected in the presence of a suitable reagent, such as TBAF in THF, to furnish intermediates of Formula (IV). Intermediates of Formula (IV) can be reacted in a variety of ways to yield intermediates of Formula (IIIa). For example, *N*-alkylation of (IV) by treatment with an appropriate alkylating agent of Formula (V) wherein L^2 is a suitable leaving group, for example sulfonate esters (e.g., mesylate, tosylate, or triflate), or alkyl halides (e.g., bromo or iodo), in the presence of a suitable base such as NaH or K_2CO_3, in an appropriate solvent such as *N*,*N*-dimethylformamide (DMF), yields intermediates of Formula (IIIa). Intermediates of Formula (IV) can also be alkylated by reacting with an epoxide, for example 1,2-epoxy-2-methylpropane, employing a suitable base such as NaH, in an appropriate solvent such DMF. Alternatively, intermediates (IV) can be reacted with alcohols, wherein R^8 is C_{1-6}alkyl or C_{2-6}alkyl optionally substituted as in R^8 in Formula (I), under standard Mitsunobu reaction conditions to yield intermediates of Formula (IIIa). Furthermore, intermediate Formula (IV) can be reacted with sulfonyl chlorides, in an appropriate solvent such as DMF, in the presence of a suitable base such as NaH, to yield intermediates of Formula (IIIa), wherein R^8 is $-SO_2C_{1-6}$alkyl optionally substituted as in R^8 in Formula (I).

Scheme 6

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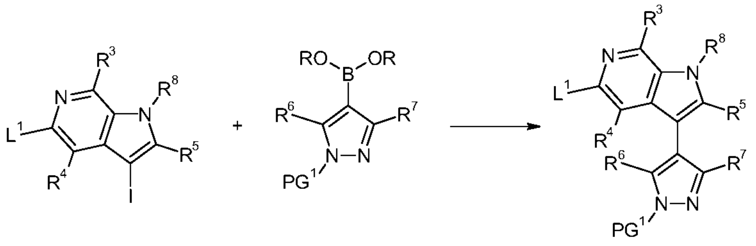
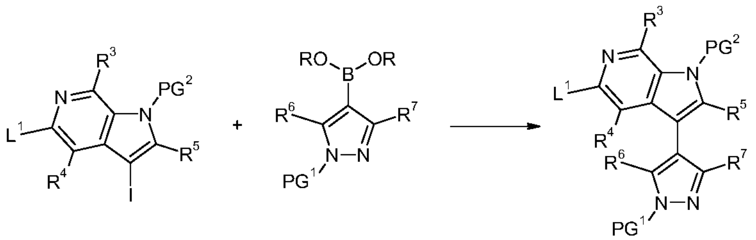


(VIa) (VII) (IIIa)

Intermediate of Formula (IIIa), wherein R^3-R^8 are as defined in Formula (I), PG^1 is a suitable protecting group and L^1 is a suitable leaving group, can also be prepared according to scheme 6. Heating intermediates of Formula (VIa) with the appropriate pyrazole boronate of Formula (VII), protected with a suitable protecting group, such as SEM, under palladium-catalyzed Suzuki coupling conditions, using for example [1,1'-bis(diphenylphosphino-κP)ferrocene]dichloropalladium ($PdCl_2(dppf)$), K_2CO_3 in water and DMF as a solvent, yields intermediates of Formula (IIIa).

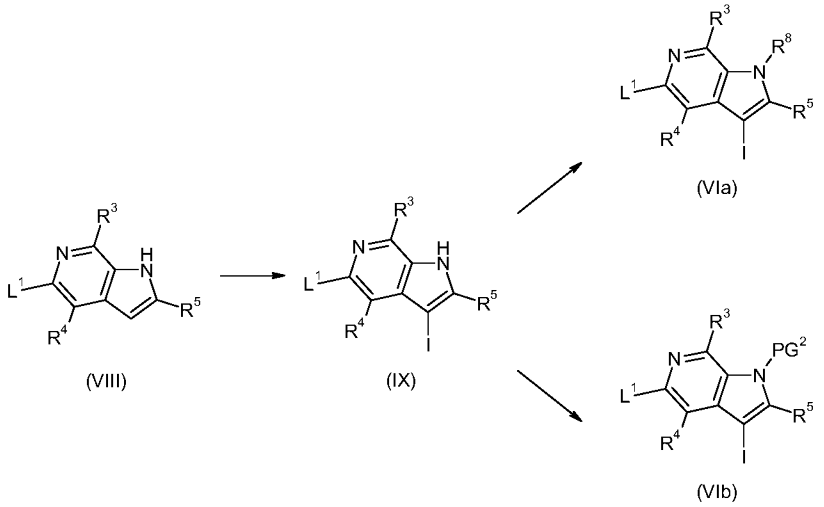
Scheme 7



(VIb) (VII) (IIIb)

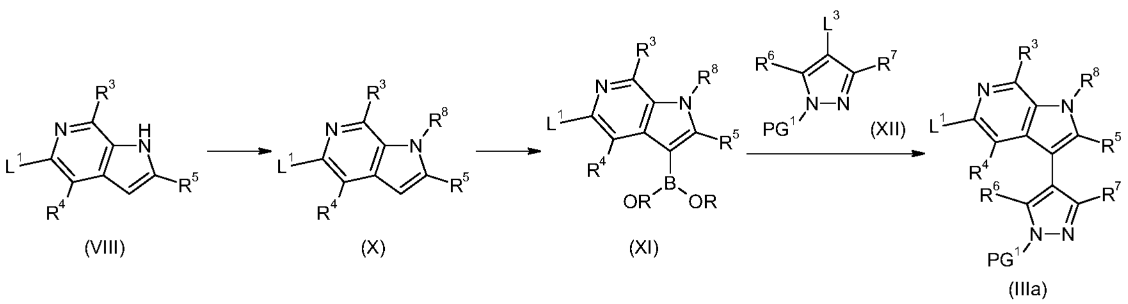
Intermediates of Formula (IIIb), wherein R^3-R^7 are as defined in Formula (I), PG^1 and PG^2 are suitable protecting groups, and L^1 is a suitable leaving group, can be prepared from intermediates of Formula (VIb) and (VII), using the methods described above for the preparation of intermediates of Formula (IIIa) from intermediates of Formula (VIa) and (VII) (Scheme 7).

Scheme 8



Scheme 8 illustrates methods of preparing intermediates of Formula (VIa) and (VIb), wherein R^3-R^5 and R^8 are as defined in Formula (I), PG^2 is a suitable protecting group and L^1 is a suitable leaving group. Treatment of intermediates of Formula (VIII) with a mixture of iodine and potassium hydroxide in a suitable solvent such as DMF yields intermediates of Formula (IX). Intermediates of Formula (VIa) can be prepared from intermediates of Formula (IX), using the methods described above for the preparation of intermediates of Formula (IIIa) from intermediates of Formula (IIIb) and (IV). Intermediates of Formula (IX) can be converted to intermediates of Formula (VIb), wherein R^3-R^5 and L^1 are as define above, and PG^2 is Ts, by reaction with tosyl chloride, in an appropriate solvent such as DMF, in the presence of a suitable base such as NaH.

Scheme 9



Scheme 9 illustrates a further method for preparing intermediates of Formula (IIIa), wherein R^3-R^8 are as defined in Formula (I), PG^1 is a suitable protecting group and L^1 is a suitable leaving group. Intermediates of Formula (X) can be prepared from intermediates of Formula (VIII), using the methods described above for the preparation

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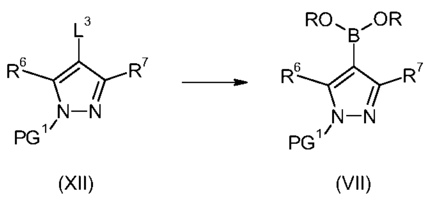
of intermediates of Formula (IIIa) from intermediates of Formula (IIIb) and (IV). Heating intermediates of Formula (X) with an appropriate borane species, such as 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, under Iridium-catalyzed conditions using for example bis(1,5-cyclooctadiene)di-μ-methoxydiiridium(I) ([Ir(OMe)cod]$_2$) with an appropriate ligand, and cyclohexane as solvent, yields boronates of Formula (XI). In turn, heating boronates of Formula (XI) with pyrazoles of Formula (XII), wherein L^3 is a suitable leaving group such as chloro or bromo and PG^1 is a suitable protecting group such as SEM, under palladium-catalyzed Suzuki coupling conditions using for example $PdCl_2$(dppf), K_2CO_3 in water and DMF as solvent, furnishes intermediates of Formula (IIIa).

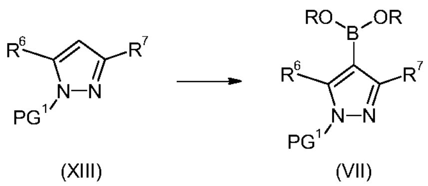
Azaindoles of Formula (VIII) are commercially available or can be prepared by known methods (e.g., Merour *et al. Tetrahedron* **2013**, *69* 4767-4834).

Scheme 10



Scheme 10 illustrates a method of preparing intermediates of Formula (VII), wherein R^6 and R^7 are as defined in Formula (I) and PG^1 is a suitable protecting group. Heating pyrazoles of Formula (XII), wherein L^3 is a suitable leaving group such as chloro or bromo, with the appropriate borane species, such as bis(pinacolato)diborane, under palladium-catalyzed conditions using for example $PdCl_2$(dppf), potassium acetate (KOAc) base, in DMF as a solvent, furnishes pyrazole boronates of Formula (VII).

Scheme 11



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Scheme 11 illustrates a further method for preparing pyrazole boronates of Formula (VII). Heating of intermediates of Formula (XIII), wherein R^6 and R^7 are as defined in Formula (I) and PG^1 is a suitable protecting group, with an appropriate borane species, such as 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, under Iridium-catalyzed conditions using for example $[Ir(OMe)cod]_2$ with an appropriate ligand, and cyclohexane as solvent yields pyrazole boronates of Formula (VII).

One skilled in the art will appreciate that alternative methods may be applicable for preparing compounds of Formula (VII), for example halogen-metal exchange and subsequent quench with boron electrophiles such as tri-isopropyl borate. Pyrazoles of Formula (XII) and (XIII) can be sourced from commercial suppliers or synthesized by those skilled in the art employing methods described in the literature [J. Elguero, 'Comprehensive Heterocyclic Chemistry II', Pergamon Press: Oxford, 1996, Vol. 3, Editors: A. R. Katritzky, C. W. Rees and E. F. V. Scriven; Fustero *et al. Chem. Rev.*, **2011**, 111, 6984-7034].

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.

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) 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.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary.

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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-fluorenylmethyleneoxycarbonyl (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.

Compounds of the invention may be prepared from commercially available starting materials using the general methods illustrated herein.

Pharmacology

It has been found that the compounds of the present invention inhibit NF-κB-inducing kinase (NIK - also known as MAP3K14). 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, 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.

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

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cell lymphoma), T-cell leukaemia/lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumour of myeloid lineage, for example leukemias, acute and chronic myelogenous leukemias, chronic myelomonocytic leukemia (CMML), myeloproliferative disorder, myeloproliferative syndrome, myelodysplastic syndrome, or promyelocytic leukemia; multiple myeloma; thyroid follicular cancer; hepatocellular cancer, a tumour of mesenchymal origin (e.g. Ewing's sarcoma), for example fibrosarcoma or rhabdomyosarcoma; a tumour of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma (such as glioblastoma multiforme) or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

Hence, the invention relates to compounds of Formula (I), the tautomers and the stereoisomeric forms thereof, and the pharmaceutically acceptable salts and the solvates thereof, for use as a medicament.

The invention also relates to the use of a compound of Formula (I), a tautomer or a stereoisomeric form thereof or a pharmaceutically acceptable salt or a solvate thereof, or a pharmaceutical composition according to the invention for the manufacture of a medicament.

The present invention also relates to a compound of Formula (I), a tautomer or a stereoisomeric form thereof or a pharmaceutically acceptable 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-κB-inducing kinase dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by inhibition of NF-κB-inducing kinase. Also, the present invention relates to the use of a compound of Formula (I), a tautomer or a stereoisomeric form thereof or a pharmaceutically acceptable 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-κB-inducing kinase dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by inhibition of NF-κB-inducing kinase.

The invention also relates to a compound of Formula (I), a tautomer or a stereoisomeric form thereof or a pharmaceutically acceptable 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 salt or a solvate thereof, for use in treating or preventing any one of the diseases mentioned hereinbefore.

The invention also relates to the use of a compound of Formula (I), a tautomer or a stereoisomeric form thereof or a pharmaceutically acceptable 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.

The compounds of the present invention can be administered to mammals, preferably humans, for the treatment or prevention of any one of the diseases mentioned hereinbefore.

In view of the utility of the compounds of Formula (I), a tautomer or a stereoisomeric form thereof or a pharmaceutically acceptable 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.

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 salt or a solvate thereof, to warm-blooded animals, including humans.

Therefore, the invention also relates to a method for the treatment of any one of the diseases mentioned hereinbefore comprising administering a therapeutically effective amount of compound according to the invention to a patient in need thereof.

One skilled in the art will recognize that a therapeutically effective amount of the compounds of the present invention is the amount sufficient to have therapeutic activity and that this amount varies *inter alias*, depending on the type of disease, the concentration of the compound in the therapeutic formulation, and the condition of the patient. Generally, the amount of a compound of the present invention to be administered as a therapeutic agent for treating the disorders referred to herein will be determined on a case by case by an attending physician.

Those of skill in the treatment of such diseases could determine the effective therapeutic daily amount from the test results presented hereinafter. An effective therapeutic daily 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

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from about 0.01 mg/kg to about 10 mg/kg, even more preferably from about 0.01 mg/kg to about 1 mg/kg, most preferably from about 0.05 mg/kg to about 1 mg/kg body weight. The amount of a compound according to the present invention, also referred to here as the active ingredient, which is required to achieve a therapeutically effect 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.

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 salt or a solvate thereof and a pharmaceutically acceptable carrier or diluent.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition. Accordingly, the present invention further provides a pharmaceutical composition comprising a compound according to the present invention, together with a pharmaceutically acceptable carrier or diluent. The carrier or diluent must be “acceptable” in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The pharmaceutical compositions of this invention may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro et al. Remington’s Pharmaceutical Sciences (18th ed., Mack Publishing Company, 1990, see especially Part 8 : Pharmaceutical preparations and their Manufacture). A therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as oral, percutaneous or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel,

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shampoo or the like. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The present compounds can be used for systemic administration such as oral, percutaneous or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. The compounds are preferably orally administered. The exact dosage and frequency of administration depends on the particular compound of Formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

The compounds of the present invention may be administered alone or in combination with one or more additional therapeutic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound according to the present invention and one or more additional therapeutic agents, as well as administration of the compound according to the present invention and each additional therapeutic agent in its own separate pharmaceutical dosage formulation. For example, a compound according to the present invention and a therapeutic agent may be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent may be administered in separate oral dosage formulations.

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

- platinum coordination compounds for example cisplatin optionally combined with amifostine, carboplatin or oxaliplatin;
- taxane compounds for example paclitaxel, paclitaxel protein bound particles (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;
- glucocorticoïden for example prednisone;
- antibodies for example trastuzumab (HER2 antibody), rituximab (CD20 antibody), gemtuzumab, gemtuzumab ozogamicin, cetuximab, pertuzumab, bevacizumab, alemtuzumab, eculizumab, ibritumomab tiuxetan, nofetumomab, panitumumab, tositumomab, CNTO 328;
- estrogen receptor antagonists or selective estrogen receptor modulators or inhibitors of estrogen synthesis for example tamoxifen, fulvestrant, toremifene, droloxifene, faslodex, raloxifene or letrozole;
- aromatase inhibitors such as exemestane, anastrozole, letrazole, testolactone and vorozole;
- differentiating agents such as retinoids, vitamin D or retinoic acid and retinoic acid metabolism blocking agents (RAMBA) for example accutane;
- DNA methyl transferase inhibitors for example azacytidine or decitabine;
- antifolates for example premetrexed disodium;
- antibiotics for example antinomycin D, bleomycin, mitomycin C, dactinomycin, carminomycin, daunomycin, levamisole, plicamycin, mithramycin;
- antimetabolites for example clofarabine, aminopterin, cytosine arabinoside or methotrexate, azacitidine, cytarabine, floxuridine, pentostatin, thioguanine;
- apoptosis inducing agents and antiangiogenic agents such as Bcl-2 inhibitors for example YC 137, BH 312, ABT 737, gossypol, HA 14-1, TW 37 or decanoic acid;
- tubuline-binding agents for example combrestatin, colchicines or nocodazole;
- kinase inhibitors (e.g. EGFR (epithelial growth factor receptor) inhibitors, MTKI (multi target kinase inhibitors), mTOR inhibitors) for example flavoperidol, imatinib mesylate, erlotinib, gefitinib, dasatinib, lapatinib, lapatinib ditosylate, sorafenib, sunitinib, sunitinib maleate, temsirolimus;
- farnesyltransferase inhibitors for example tipifarnib;
- histone deacetylase (HDAC) inhibitors for example sodium butyrate, suberoylanilide hydroxamic acid (SAHA), depsipeptide (FR 901228), NVP-LAQ824, R306465, quisinostat, trichostatin A, vorinostat;

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- Inhibitors of the ubiquitin-proteasome pathway for example PS-341, MLN .41 or bortezomib;
- Yondelis;
- Telomerase inhibitors for example telomestatin;
- Matrix metalloproteinase inhibitors for example batimastat, marimastat, prinostat or metastat;
- Recombinant interleukins for example aldesleukin, denileukin diftitox, interferon alfa 2a, interferon alfa 2b, peginterferon alfa 2b;
- MAPK inhibitors;
- Retinoids for example alitretinoin, bexarotene, tretinoin;
- Arsenic trioxide;
- Asparaginase;
- Steroids for example dromostanolone propionate, megestrol acetate, nandrolone (decanoate, phenpropionate), dexamethasone;
- Gonadotropin releasing hormone agonists or antagonists for example abarelix, goserelin acetate, histrelin acetate, leuprolide acetate;
- Thalidomide, lenalidomide;
- Mercaptopurine, mitotane, pamidronate, pegademase, pegaspargase, rasburicase;
- BH3 mimetics for example ABT-737;
- MEK inhibitors for example PD98059, AZD6244, CI-1040;
- colony-stimulating factor analogs for example filgrastim, pegfilgrastim, sargramostim; erythropoietin or analogues thereof (e.g. darbepoetin alfa); interleukin 11; oprelvekin; zoledronate, zoledronic acid; fentanyl; bisphosphonate; palifermin;
- a steroidal cytochrome P450 17alpha-hydroxylase-17,20-lyase inhibitor (CYP17), e.g. abiraterone, abiraterone acetate.

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 anticancer agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

The one or more other medicinal agents and the compound according to the present invention may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two or more compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective

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dosage amounts and regimes for each component of the combination will depend on the particular other medicinal agent and compound of the present invention being administered, their route of administration, the particular tumour being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.
The weight ratio of the compound according to the present invention and the one or more other anticancer agent(s) when given as a combination may be determined by the person skilled in the art. Said ratio and the exact dosage and frequency of administration depends on the particular compound according to the invention and the other anticancer agent(s) used, the particular condition being treated, the severity of the condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. A particular weight ratio for the present compound of Formula (I) and another anticancer agent may range from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

The platinum coordination compound is advantageously administered in a dosage of 1 to 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.

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.

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.

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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.

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.

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.

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.

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.

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

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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.

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.

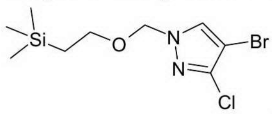
The following examples further illustrate the present invention.

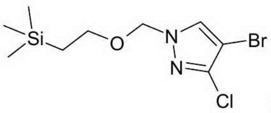
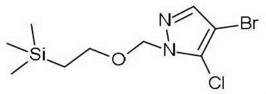
Examples

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.

Herein, the term ‘Boc’ means *tert*-butoxycarbonyl, ‘DCE’ means 1,2-dichloroethane, ‘Cs_2CO_3’ means cesium carbonate, ‘DCM’ means dichloromethane, ‘BEH’ means bridged ethylsiloxane/silica hybrid, ‘DIAD’ means diisopropylazodicarboxylate, ‘DIPEA’ means diisopropylethylamine, ‘DMAP’ means *N*,*N*-dimethylpyridin-4-amine, ‘DMF’ means *N*,*N*-dimethylformamide, ‘DMSO’ means dimethylsulfoxide, ‘UPLC’ means ultra performance liquid chromatography, ‘LC’ means liquid chromatography, ‘EtOAc’ means ethyl acetate, ‘flash-NH_2’ means ISOLUTE® silica polypropylamino weak anion exchange column, ‘HPLC’ means high performance liquid chromatography, ‘LCMS’ means liquid chromatography/mass spectrometry, ‘MeCN’ means acetonitrile, ‘MeOH’ means methanol, ‘R_t’ means retention time, ‘ISOLUTE® SCX-2 SPE’ means ISOLUTE® silica propylsulfonic acid strong cation exchange column, ‘SEM’ means 2-(trimethylsilyl)ethoxy]-methyl, ‘TBAF’ means tetrabutylammonium fluoride, ‘TFA’ means trifluoroacetic acid, ‘Na_2SO_4’ means sodium sulfate, ‘HATU’ means 1-[bis(dimethylamino)methylene]-1H-[1,2,3]triazolo[4,5-b]pyridin-1-ium 3-oxide hexafluorophosphate and ‘THF’ means tetrahydrofuran.

In the structures of the intermediates and the compounds of the present invention, deuterium (^2H) is represented by the chemical symbol D.

Some intermediates are indicated in the experimental part to appear as mixtures of regioisomers (position isomers). This means that there are two or more positions in the intermediate to which the substituent may be attached, and that the intermediate referred to actually is a mixture of different potential products formed during the synthesis. For example, intermediate 76  , which is indicated as a mixture of regioisomers, is a mixture of

 and  .

Some intermediates are indicated in the experimental part with the comment ‘Regiochemistry of Boc-group not determined’. This means that one specific regio-isomer was formed or isolated, but that the exact postion of the Boc group was not determined.

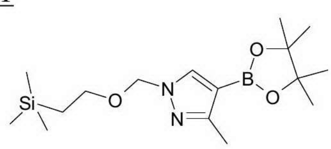
Intermediates were obtained as mixtures of regioisomers or as single regioisomers. The skilled person will realize that mixtures of regioisomers can be easily separated into single regioisomers if desired by methods well-known by the skilled person and as illustrated for some intermediates in the sections below.

When in the Examples below, intermediates or compounds were prepared according to the reaction protocol of a fully described Example, this means that the intermediate or compound was prepared by an analogous reaction protocol (but not necessarily identical) as the Example referred to.

Preparation of intermediates

Example A1

a) Preparation of intermediate 1

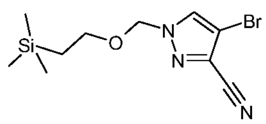
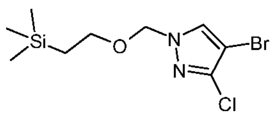
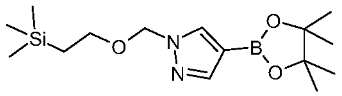
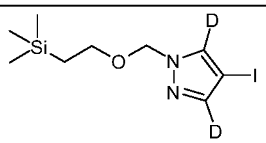


A mixture of 3-methylpyrazole-4-boronic acid pinacol ester (0.50 g, 2.40 mmol), 2-(trimethylsilyl)ethoxymethyl chloride (0.53 ml, 3.00 mmol) and DIPEA (1.3 ml, 7.21 mmol) in DCM (10 ml) was stirred at ambient temperature for 1.5 hours. The mixture

was partitioned between DCM and water. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the desired product as a pale brown oil (0.81 g, 100%, mixture of two regioisomers).
LCMS (Method D): R_t = 4.21 and 4.32 min, m/z $[M+H]^+$ = 339.

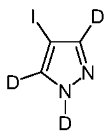
Intermediates 2 and 76 to 78 were prepared according to the reaction protocol of intermediate 1 using the appropriate starting materials (Table 1).

Table 1:

Intermediate	Structure	Starting Material	LCMS Data
2		4-Bromo-1*H*-pyrazole-3-carbonitrile	Mixture of regioisomers: R_t = 4.03 and 4.11 min, m/z $[M+H]^+$ = 302/304 (Method D)
76		4-Bromo-5-chloro-1*H*-pyrazole	Mixture of regioisomers: R_t = 4.44 min, m/z $[M+H]^+$ = 311/313 (Method C)
77		4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazole	
78		Intermediate 79	

Example A10

a) Preparation of intermediate 79

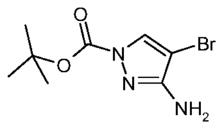


A stirred mixture of iodine (1.06 g, 8.32 mmol), pyrazole-*d₄* (1.0 g, 13.8 mmol) and MeCN (12 ml) at ambient temperature was treated with ammonium ceric nitrate (1.06 g, 8.32 mmol) and the resulting mixture stirred for 3 hours. The mixture was concentrated *in vacuo* and the residue partitioned between 5% aqueous sodium bisulphite solution and EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with a mixture of EtOAc and pentane (0:1 to 7:3 by volume), to afford the desired product as an off-white solid (1.3 g, 47%).

LCMS (Method C): R_t = 2.13 min, m/z $[M+H]^+$ = 197.

Example A2

a) Preparation of intermediate 3

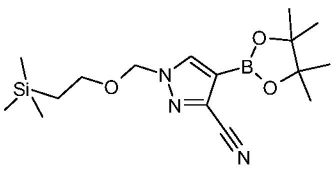


A stirred solution of 3-amino-4-bromo-1*H*-pyrazole (1.00 g, 6.17 mmol) and DMAP (0.15 g, 1.23 mmol) in THF (17 ml) at ambient temperature was treated with di-*tert*-butyl dicarbonate (1.48 g, 6.79 mmol), and the resulting mixture was stirred for 2 hours. The mixture was partitioned between DCM and water. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and EtOAc (4:1 to 2:3 by volume) to afford the desired product (1.56 g, 96%, mixture of two regioisomers).

LCMS (Method D): R_t = 2.74 and 2.76 min, m/z $[M+H\text{-}tert\text{-butyl}]^+$ = 206/208.

Example A3

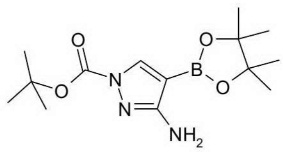
a) Preparation of intermediate 4



A degassed suspension of intermediate 2 (1.84 g, 5.78 mmol), *bis*(pinacolato)diboron (1.84 g, 7.23 mmol), potassium acetate (1.70 g, 17.4 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.47 g, 0.58 mmol) in DMF (57 ml) was heated at 70 ºC for 3.5 hours. The mixture was cooled to ambient temperature and partitioned between DCM and water. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the desired product as a brown oil (2.02 g, 100%) as a mixture of two regioisomers.

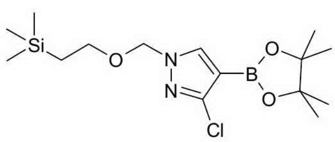
Intermediate 5 was prepared according to the reaction protocol of intermediate 4 using the appropriate starting material (Table 2).

Table 2:

Intermediate	**Structure**	**Starting Material**	**LCMS Data**
5		Intermediate 3 (Intermediate 3 was separated in single regioisomers before using a single regioisomer as starting material for Intermediate 5)	Regiochemistry of the Boc group assumed; R_t = 2.84 min, m/z $[M+H]^+$ = 309 (Method D)

Example A11

a) Preparation of intermediate 80

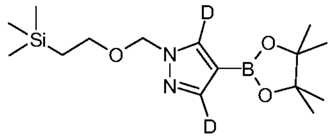


A degassed solution of intermediate 76 (0.03 g, 0.10 mmol) in anhydrous THF (1.6 ml) under an argon atmosphere at ambient temperature was treated dropwise with a 2.0 M solution of isopropylmagnesium chloride in THF (0.16 ml, 0.318 mmol). After stirring for 1 hour, 2-methoxy-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (0.07 ml, 0.424 mmol) was added dropwise and the resulting mixture stirred for 1 hour. The mixture was diluted with saturated aqueous ammonium chloride solution and partitioned between water and DCM. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*.

The residue was purified by column chromatography on silica gel, eluting with a mixture of EtOAc and pentane (0:1 to 1:1 by volume), to afford the desired product as a colourless oil (0.04 g, 100%, mixture of two regioisomers).

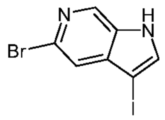
Intermediate 81 was prepared according to the reaction protocol of intermediate 80 using the appropriate starting material (Table 3).

Table 3:

Intermediate	Structure	Starting Material
81		Intermediate 78

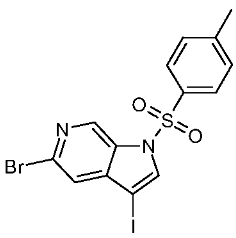
Example A4

a) Preparation of intermediate 6



A stirred solution of 5-bromo-1*H*-pyrrolo[2,3-*c*]pyridine (4.00 g, 20.3 mmol) in DMF (150 ml) at ambient temperature was treated with potassium hydroxide (4.32 g, 77.2 mmol). After 10 minutes, iodine (5.67 g, 22.3 mmol) was added and the resulting mixture was stirred for 3 hours. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was triturated with water, filtered and dried *in vacuo* to afford the desired product as an orange solid (5.71 g, 87%).
LCMS (Method C): R_t = 3.23 min, m/z $[M+H]^+$ = 323/325.

b) Preparation of intermediate 7

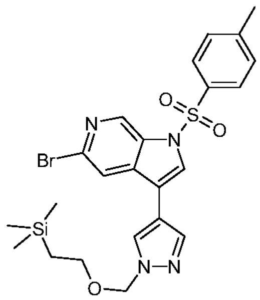


A stirred solution of intermediate 6 (3.00 g, 9.29 mmol), *p*-toluenesulfonyl chloride (2.13 g, 11.2 mmol) and DIPEA (3.6 ml, 20.4 mmol) in DCM (20 ml) at ambient temperature was treated with DMAP (0.023 g, 0.19 mmol), and the resulting mixture was stirred for 4 hours. The mixture was diluted with water and extracted with DCM.

The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and EtOAc (1:9 to 1:1 by volume), to afford the desired product as a white solid (3.20 g, 72%).

LCMS (Method C): R_t = 4.43 min, m/z $[M+H]^+$ = 477/479.

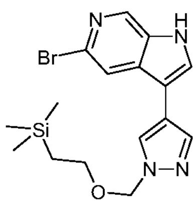
c) Preparation of intermediate 8



A degassed suspension of intermediate 7 (3.13 g, 6.56 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1-(2-trimethylsilanylethoxymethyl)-1*H*-pyrazole (3.19 g, 9.84 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.54 g, 0.66 mmol) and potassium carbonate (1.81 g, 13.1 mmol) in DMF (28 ml) and water (7.0 ml) was heated at 50 °C for 5.5 hours. The mixture was cooled to ambient temperature, diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of DCM and EtOAc (1:0 to 1:1 by volume), to afford the desired product as a pale brown oil (2.70 g, 75%).

LCMS (Method B): R_t = 2.95 min, m/z $[M+H]^+$ = 547/549.

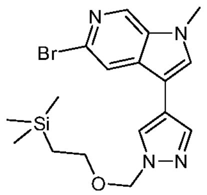
d) Preparation of intermediate 9



A stirred mixture of intermediate 8 (3.53 g, 6.45 mmol) in THF (30 ml) at ambient temperature was treated with 1.0 M TBAF solution in THF (16.0 ml, 16.0 mmol), and the resulting mixture was stirred for 20 hours. The mixture was partitioned between EtOAc and brine. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel,

eluting with a mixture of DCM and EtOAc (1:0 to 1:1 by volume), and triturated with DCM to afford the desired product as a fawn solid (1.91 g, 75%).
LCMS (Method D): R_t = 3.50 min, m/z $[M+H]^+$ = 393/395.

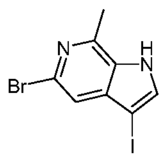
e) Preparation of intermediate 10



A stirred mixture of intermediate 9 (0.33 g, 0.84 mmol), potassium carbonate (0.23 g, 1.68 mmol) and iodomethane (0.062 ml, 1.00 mmol) in DMF (5.0 ml) was heated at 110 °C for 1 hour. A second portion of iodomethane (0.010 ml, 0.16 mmol) was added and heating was continued for a further 30 minutes. The mixture was cooled to ambient temperature and partitioned between EtOAc and brine. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of DCM and EtOAc (1:0 to 4:1 by volume), to afford the desired product as a pale brown solid (0.24 g, 70%).
LCMS (Method D): R_t = 3.73 min, m/z $[M+H]^+$ = 407/409.

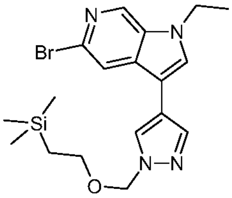
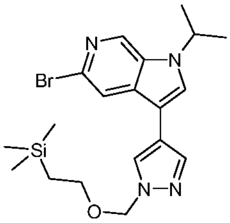
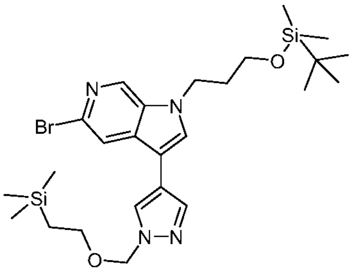
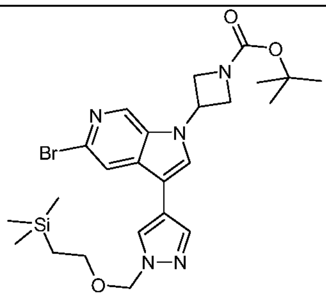
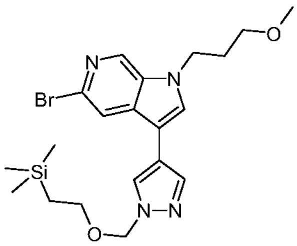
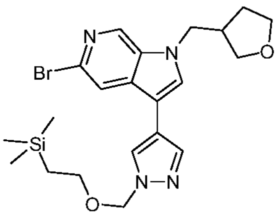
Intermediate 122 was prepared according to the reaction protocol of intermediate 6 using the appropriate starting material (Table 4).

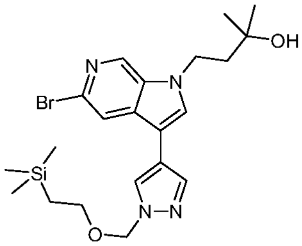
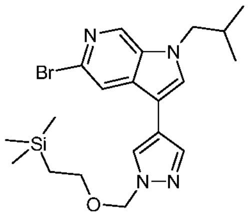
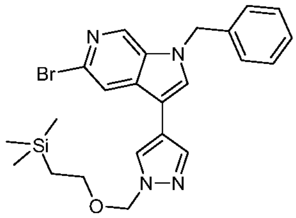
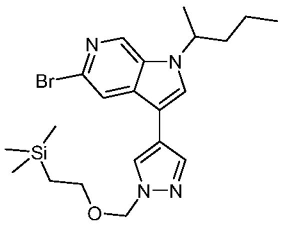
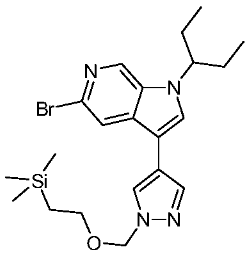
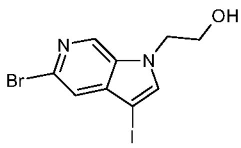
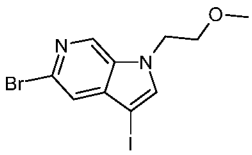
Table 4:

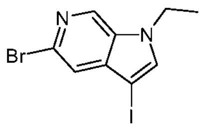
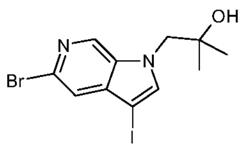
Intermediate	Structure	Starting Material	LCMS Data
122		Intermediate 130	R_t = 3.03 min, m/z $[M+H]^+$ = 337/339 (Method D)

Intermediates 11 to 25 were prepared according to the reaction protocol of intermediate 10 using the appropriate starting materials (Table 5).

Table 5:

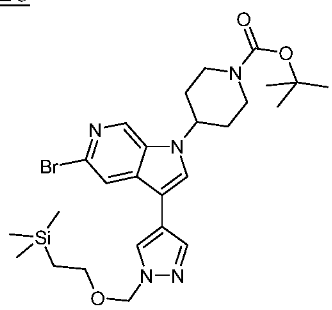
Intermediate	Structure	Starting Materials	LCMS Data
11		a) Intermediate 9 b) Iodoethane	R_t = 4.07 min, m/z $[M+H]^+$ = 421/423 (Method A)
12		a) Intermediate 9 b) 2-Iodopropane	R_t = 4.04 min, m/z $[M+H]^+$ = 435/437 (Method D)
13		a) Intermediate 9 b) (3-Bromopropoxy)-*tert*-butyldimethylsilane	R_t = 5.04 min, m/z $[M+H]^+$ = 565/567 (Method D)
14		a) Intermediate 9 b) 3-Iodoazetidine-1-carboxylic acid *tert*-butyl ester	R_t = 4.36 min, m/z $[M+H]^+$ = 548/550 (Method A)
15		a) Intermediate 9 b) 1-Bromo-3-methoxypropane	R_t = 3.88 min, m/z $[M+H]^+$ = 465/467 (Method D)
16		a) Intermediate 9 b) 3-Bromomethyltetrahydrofuran	R_t = 3.75 min, m/z $[M+H]^+$ = 477/479 (Method D)

Intermediate	Structure	Starting Materials	LCMS Data
17		a) Intermediate 9 b) 4-Bromo-2-methylbutanol	R_t = 3.84 min, m/z $[M+H]^+$ = 479/481 (Method C)
18		a) Intermediate 9 b) 1-Bromo-2-methylpropane	R_t = 4.41 min, m/z $[M+H]^+$ = 449/451 (Method A)
19		a) Intermediate 9 b) Benzyl bromide	R_t = 4.34 min, m/z $[M+H]^+$ = 483/485 (Method A)
20		a) Intermediate 9 b) 2-Bromopentane	R_t = 4.52 min, m/z $[M+H]^+$ = 463/465 (Method A)
21		a) Intermediate 9 b) 3-Bromopentane	R_t = 4.52 min, m/z $[M+H]^+$ = 463/465 (Method A)
22		a) Intermediate 6 b) 2-Bromoethanol	R_t = 2.97 min, m/z $[M+H]^+$ = 367/369 (Method B)
23		a) Intermediate 6 b) 2-Bromo-1-methoxyethane	R_t = 3.55 min, m/z $[M+H]^+$ = 381/383 (Method B)

Intermediate	Structure	Starting Materials	LCMS Data
24		a) Intermediate 6 b) Iodoethane	R_t = 3.56 min, m/z $[M+H]^+$ = 351/353 (Method D)
25		a) Intermediate 6 b) 1,2-Epoxy-2-methylpropane	R_t = 3.31 min, m/z $[M+H]^+$ = 395/397 (Method C)

Example A5

a) Preparation of intermediate 26



A stirred solution of intermediate 9 (0.19 g, 0.48 mmol) in DMF (4.8 ml) at 0 °C was treated with sodium hydride (0.039 g, 0.97 mmol, 60% in mineral oil). After 30 minutes, 4-methanesulfonyloxypiperidine-1-carboxylic acid *tert*-butyl ester (0.24 g, 0.85 mmol) was added and the resulting mixture was warmed to ambient temperature and stirred for 30 minutes. The reaction mixture was heated at 70 °C for 20 hours before allowing to cool to ambient temperature. A second portion of sodium hydride (0.020 g, 0.50 mmol, 60% in mineral oil) was added and the reaction mixture was stirred at ambient temperature for 10 minutes. After this time, 4-methanesulfonyloxypiperidine-1-carboxylic acid *tert*-butyl ester (0.24 g, 0.85 mmol) was added and the resulting mixture was heated at 100 °C for 5.5 hours. The mixture was cooled to ambient temperature and partitioned between EtOAc and brine. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of DCM and EtOAc (1:0 to 1:1 by volume), to afford the desired product as a pale yellow oil (0.14 g, 50%).

LCMS (Method A): R_t = 4.53 min, m/z $[M+H]^+$ = 576/578.

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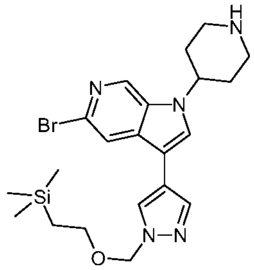
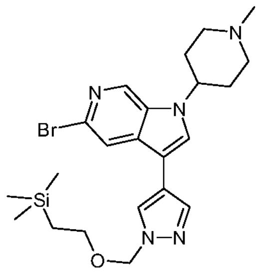
b) Preparation of intermediate 27



A stirred solution of intermediate 26 (0.14 g, 0.24 mmol) in DCM (3.2 ml) at ambient temperature was treated with TFA (0.28 ml, 3.65 mmol). After stirring for 45 minutes, a second portion of TFA (0.093 ml, 1.22 mmol) was added and the resulting mixture was stirred for a further 2 hours. The mixture was diluted with DCM and purified by column chromatography on a flash-NH_2 cartridge, eluting with a mixture of DCM and MeOH (9:1 by volume), to afford the desired product as a yellow gum (0.088 g, 76%).
LCMS (Method D): R_t = 2.46 min, m/z $[M+H]^+$ = 476/478.

c) Preparation of intermediate 28



A stirred solution of intermediate 27 (0.088 g, 0.19 mmol), 37% aqueous formaldehyde (0.055 ml, 0.74 mmol) and sodium acetate (0.015 g, 0.19 mmol) in MeOH (2.6 ml) and DCE (1.6 ml) at 0 °C was treated with sodium triacetoxyborohydride (0.16 g, 0.74 mmol). The resulting mixture was stirred at 0 °C for 5 minutes, then warmed to ambient temperature and stirred for a further 22 hours. The mixture was partitioned between EtOAc and saturated aqueous sodium hydrogen carbonate solution. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford the desired product as a pale yellow gum (0.086 g, 96%).
LCMS (Method D): R_t = 2.55 min, m/z $[M+H]^+$ = 490/492.

Intermediates 29 and 30 were prepared according to the reaction protocol of intermediate 26 using the appropriate starting materials (Table 6).

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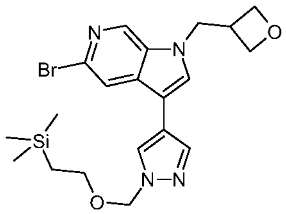
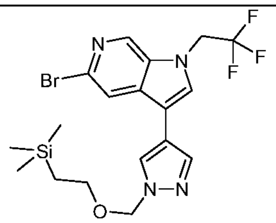
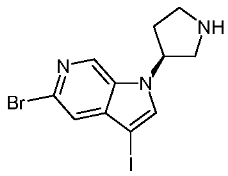
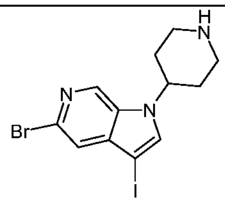
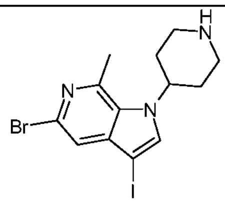
Table 6:

Intermediate	Structure	Starting Materials	LCMS Data
29		a) Intermediate 9 b) Toluene-4-sulfonic acid oxetan-3-ylmethyl ester	R_t = 3.59 min, m/z $[M+H]^+$ = 463/465 (Method D)
30		a) Intermediate 9 b) Trifluoromethanesulfonic acid 2,2,2-trifluoroethyl ester	R_t = 4.14 min, m/z $[M+H]^+$ = 475/477 (Method A)

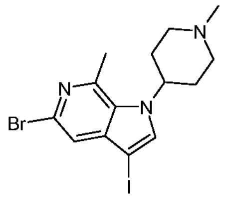
Intermediates 82,83 and 123 were prepared according to the reaction protocol of intermediate 27 using the appropriate starting material (Table 7).

Table 7:

Intermediate	Structure	Starting Material	LCMS Data
82	 S-enantiomer	Intermediate 107	R_t = 2.12 min, m/z $[M+H]^+$ = 392/394 (Method C)
83		Intermediate 108	R_t = 2.28 min, m/z $[M+H]^+$ = 406/408 (Method B)
123		Intermediate 125	R_t = 2.11 min, m/z $[M+H]^+$ = 420/422 (Method B)

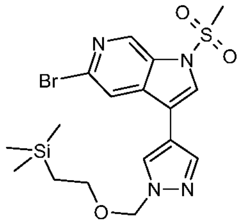
Intermediate 124 was prepared according to the reaction protocol of intermediate 28 using the appropriate starting material (Table 8).

Table 8:

Intermediate	Structure	Starting Material	LCMS Data
124		Intermediate 123	R_t = 2.16 min, m/z $[M+H]^+$ = 434/436 (Method B)

Example A6

a) Preparation of intermediate 31

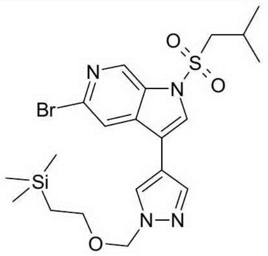
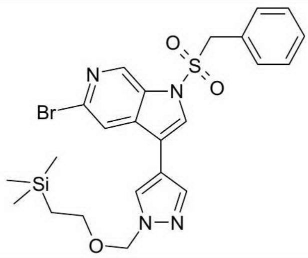


A stirred solution of intermediate 9 (0.060 g, 0.15 mmol) in DMF (1.4 ml) at 0 ºC was treated with sodium hydride (0.013 g, 0.34 mmol, 60% in mineral oil). After 30 minutes, the mixture was treated with methanesulfonyl chloride (0.026 ml, 0.34 mmol) and the resulting mixture was heated at 70 ºC for 1 hour. The mixture was partitioned between EtOAc and brine. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and EtOAc (1:0 to 1:4 by volume), to afford the desired product as an off-white solid (0.057 g, 95%).

LCMS (Method D): R_t = 3.94 min, m/z $[M+H]^+$ = 471/473.

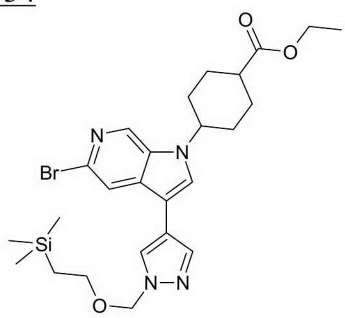
Intermediates 32 and 33 were prepared according to the reaction protocol of intermediate 31 using the appropriate starting materials (Table 9).

Table 9:

Intermediate	Structure	Starting Materials	LCMS Data
32		a) Intermediate 9 b) Isobutylsulfonyl chloride	R_t = 4.37 min, m/z $[M+H]^+$ = 513/515 (Method D)
33		a) Intermediate 9 b) Benzylsulfonyl chloride	R_t = 4.28 min, m/z $[M+H]^+$ = 547/549 (Method D)

Example A7

a) Preparation of intermediate 34

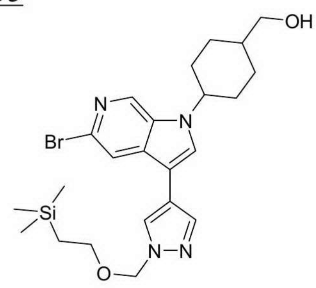


mixture of diastereoisomers

A stirred solution of intermediate 9 (0.25 g, 0.63 mmol), ethyl 4-hydroxycyclohexanecarboxylate (0.26 ml, 1.59 mmol) and triphenylphosphine (0.42 g, 1.59 mmol) in THF at ambient temperature was treated dropwise with DIAD (0.31 ml, 1.59 mmol). After stirring for 18 hours, the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and EtOAc (1:0 to 0:1 by volume), to afford the desired product as a white solid (0.078 g, 21%) (mixture of diastereoisomers).

LCMS (Method A): R_t = 4.44 min, m/z $[M+H]^+$ = 547/549.

b) Preparation of intermediate 35



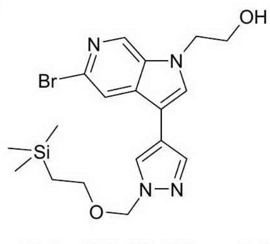
mixture of diastereoisomers

A solution of intermediate 34 (0.078 g, 0.14 mmol) and 2.0 M lithium borohydride solution in THF (0.21 ml, 0.43 mmol) in THF (2.6 ml) was heated at 50 ºC for 2 hours. The mixture was cooled to ambient temperature, concentrated *in vacuo* and partitioned between EtOAc and water. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of DCM and EtOAc (1:0 to 1:9 by volume), to afford the desired product as an off-white solid (0.058 g, 69%) (mixture of diastereoisomers).

LCMS (Method B): R_t = 3.84 min, m/z $[M+H]^+$ = 505/507.

Example A8

a) Preparation of intermediate 36



A degassed suspension of intermediate 22 (0.62 g, 1.70 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1-(2-trimethylsilanylethoxymethyl)-1*H*-pyrazole (0.83 g, 2.55 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.14 g, 0.17 mmol) and potassium carbonate (0.47 g, 3.40 mmol) in DMF (7.0 ml) and water (1.8 ml) was heated at 50 ºC for 5.5 hours. The mixture was cooled to ambient temperature, diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and EtOAc (1:1 to 0:1 by volume), to afford the desired product (0.48 g, 64%).

LCMS (Method C): R_t = 3.53 min, m/z $[M+H]^+$ = 437/439.

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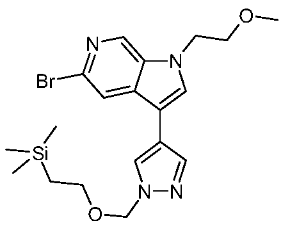
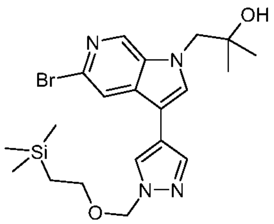
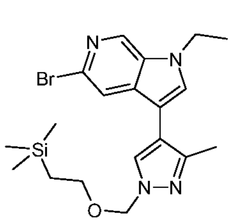
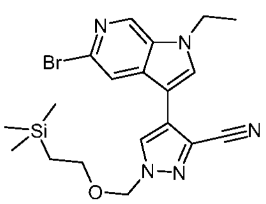
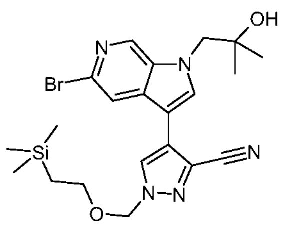
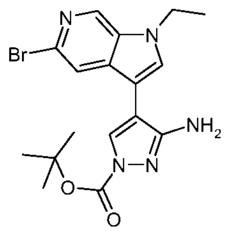
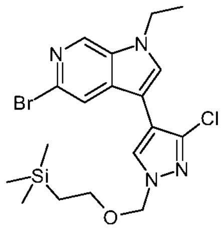
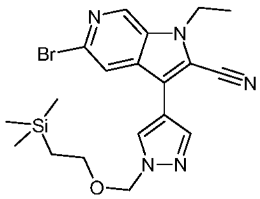
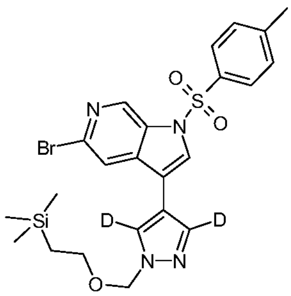
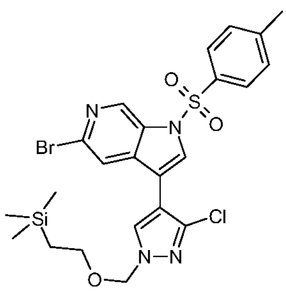
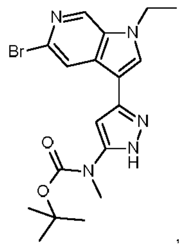
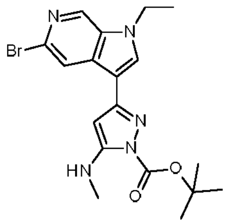
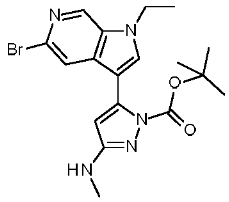
Intermediates 37 to 42 and 84 to 88 were prepared according to the reaction protocol of intermediate 36 using the appropriate starting materials (Table 10).

Table 10:

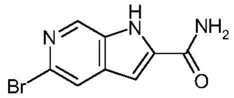
Intermediate	Structure	Starting Materials	LCMS Data
37		a) Intermediate 23 b) 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1-(2-trimethylsilanylethoxymethyl)-1*H*-pyrazole	R_t = 3.97 min, m/z $[M+H]^+$ = 451/453 (Method C)
38		a) Intermediate 25 b) 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1-(2-trimethylsilanylethoxymethyl)-1*H*-pyrazole	R_t = 3.80 min, m/z $[M+H]^+$ = 465/467 (Method C)
39		a) Intermediate 24 b) Intermediate 1	Mixture of two regioisomers: R_t = 4.53 and 4.61 min, m/z $[M-SiMe_3+OH+H]^+$ = 376/378 (Method D)
40		a) Intermediate 24 b) Intermediate 4	Mixture of two regioisomers: R_t = 4.26 min, m/z $[M+H]^+$ = 446/448 (Method D)
41		a) Intermediate 25 b) Intermediate 4	Mixture of two regioisomers: R_t = 4.13 min, m/z $[M+H]^+$ = 490/492 (Method C)

Intermediate	Structure	Starting Materials	LCMS Data
42		a) Intermediate 24 b) Intermediate 5	Regiochemistry of Boc-group not determined: R_t = 3.11 min, m/z $[M+H]^+$ = 406/408 (Method D)
84		a) Intermediate 24 b) Intermediate 80	Mixture of regioisomers: R_t = 4.53 min, m/z $[M+H]^+$ = 455/457 (Method C)
85		a) Intermediate 93 b) Intermediate 77	R_t =4.35 min, m/z $[M+H]^+$ = 446/448 (Method D)
86		a) Intermediate 7 b) Intermediate 81	R_t = 4.64 min, m/z $[M+H]^+$ = 549/551 (Method D)
87		a) Intermediate 7 b) Intermediate 80 (Intermediate 80 was separated in single regioisomers before using a single regioisomer as starting material for Intermediate 87)	Regiochemistry of the SEM group assumed; R_t = 4.96 min, m/z $[M+H]^+$ = 581/583 (Method C)

Intermediate	Structure	Starting Materials	LCMS Data
88	mixture of 2 structures from the following group:  ,  and  (exact composition of the mixture not determined)	a) Intermediate 24 b) Intermediate 97	R_t = 2.95 min, m/z $[M+H]^+$ = 420/422 (Method C)

Example A12

a) Preparation of intermediate 89

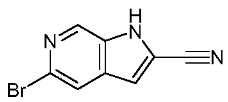


A stirred mixture of 5-bromo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylic acid (0.66 g, 2.73 mmol), HATU (1.14 g, 3.00 mmol) and DMF (30 ml) under a nitrogen atmosphere at ambient temperature was treated with 4-methylmorpholine (0.48 ml, 4.37 mmol). After stirring for 1 hour, 2.0 M ammonia solution in MeOH (11 ml, 21.8 mmol) was added and the resulting mixture stirred for 18 hours. The mixture was concentrated *in vacuo* and the residue triturated with MeOH to afford the desired product as a tan solid (0.07 g, 11%). The filtrate was concentrated *in vacuo* and the residue purified by ISOLUTE®

SCX-2 SPE column, eluting with a mixture of MeOH and 2.0 M ammonia solution in MeOH (1:0 to 0:1 by volume). Further purification by trituration with DCM afforded the desired product as a tan solid (0.39 g, 60%).

LCMS (Method C): R_t = 2.11 min, m/z $[M+H]^+$ = 240/242.

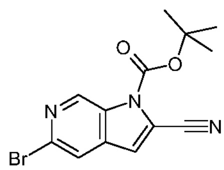
b) Preparation of intermediate 90



A stirred mixture of intermediate 89 (0.36 g, 1.50 mmol) and phosphorus oxychloride (4.1 ml, 43.6 mmol) under a nitrogen atmosphere was heated at 106 °C for 1 hour. The mixture was cooled to ambient temperature, poured onto a mixture of 30 % aqueous ammonium hydroxide solution and ice. After stirring for 15 minutes, the mixture was partitioned between brine and EtOAc. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford the desired product as a pale yellow solid (0.19 g, 57%).

LCMS (Method C): R_t = 2.83 min, m/z $[M+H]^+$ = 222/224.

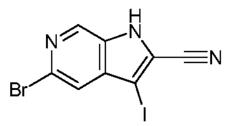
c) Preparation of intermediate 91



A stirred suspension of intermediate 90 (0.19 g, 0.86 mmol) in DCM (4.0 ml) at 0 °C was treated sequentially with DMAP (0.0063 g, 0.05 mmol), triethylamine (0.24 ml, 1.7 mmol) and di-*tert*-butyldicarbonate (0.22 g, 1.03 mmol). The resulting mixture was warmed to ambient temperature and stirred for 1 hour. The mixture was partitioned between DCM and water. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with a mixture of EtOAc and pentane (0:1 to 1:1 by volume), to afford the desired product as a white solid (0.21 g, 76%).

LCMS (Method C): R_t = 3.90 min, m/z $[M+H- (\textit{tert}\text{-butyl})]^+$ = 266/268.

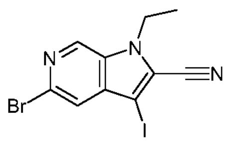
d) Preparation of intermediate 92



A stirred solution of intermediate 91 (0.13 g, 0.41 mmol) in DMF (2.2 ml) at ambient temperature was treated with powdered potassium hydroxide (0.09 g, 1.46 mmol). After stirring for 5 minutes, a solution of iodine (0.18 g, 0.57 mmol) in DMF (1.2 ml) was added and the resulting mixture was stirred for 24 hours. The mixture was partitioned between EtOAc and water. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the desired product as a white solid (0.15 g, 98%).

LCMS (Method C): R_t = 3.37 min, m/z $[M+H]^+$ = 348/350.

e) Preparation of intermediate 93

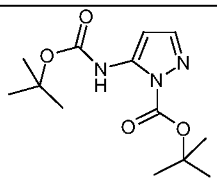
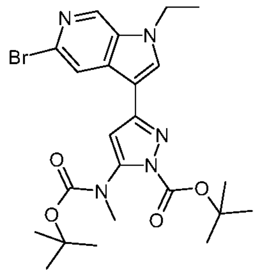


A stirred solution of intermediate 92 (0.15 g, 0.42 mmol) in anhydrous DMF (3.3 ml) under a nitrogen atmosphere at ambient temperature was treated portionwise with sodium hydride (0.04 g, 0.9 mmol, 60% in mineral oil). After stirring for 30 minutes, iodoethane (0.07 ml, 0.87 mmol) was added dropwise and the resulting mixture stirred at 90 °C for 1 hour. The mixture was cooled to ambient temperature, quenched with water and partitioned between water and EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with a mixture of EtOAc and cyclohexane (0:1 to 1:4 by volume), to afford the desired product as a white solid (0.12 g, 74%).

LCMS (Method C): R_t = 3.83 min, m/z $[M+H]^+$ = 376/378.

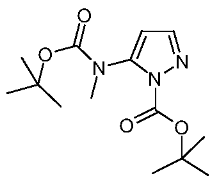
Intermediates 94 and 95 were prepared according to the reaction protocol of intermediate 91 using the appropriate starting material (Table 11).

Table 11:

Intermediate	Structure	Starting Material	LCMS Data
94		1*H*-Pyrazol-3-ylamine	Mixture of regioisomers
95		Intermediate 88	Mixture of regioisomers R_t = 4.06 min, m/z $[M+H]^+$ = 520/522 (Method C)

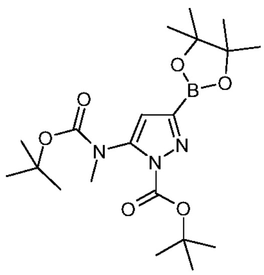
Intermediate 96 was prepared according to the reaction protocol of intermediate 93 using the appropriate starting materials (Table 12).

Table 12:

Intermediate	Structure	Starting Materials
96	 Regiochemistry of the Boc group assumed;	a) Intermediate 94 (Intermediate 94 was separated in single regioisomers before using a single regioisomer as starting material for Intermediate 96) b) Iodomethane

<u>Example A13</u>

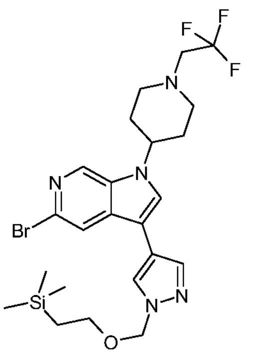
<u>a) Preparation of intermediate 97</u>



A degassed mixture of intermediate 96 (0.48 g, 1.63 mmol) 4,4,-di-*tert*-butyl-2,2-dipyridyl (0.044 g, 3.26 mmol) and cyclohexane (4.8 ml) under an argon atmosphere at ambient temperature was treated sequentially with di-μ-methoxobis(1,5-cyclooctadiene)diiridium (0.054 g, 0.08 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.47 ml, 3.26 mmol). The resulting mixture was stirred at 60 °C for 4 hours. The mixture was cooled to ambient temperature and concentrated in *vacuo* to afford the desired product as a light brown solid (0.69 g, 100%, mixture of two regioisomers).

<u>Example A14</u>

<u>a) Preparation of intermediate 98</u>

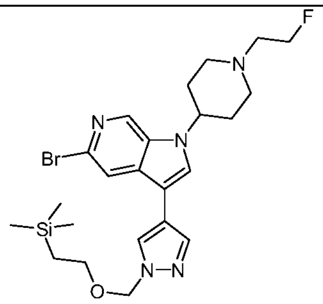
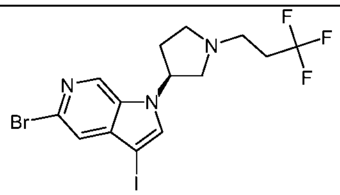


A stirred mixture of intermediate 27 (0.09 g, 0.180 mmol) DIPEA (0.06 ml, 0.36 mmol) and DMF (1.9 ml) under a nitrogen atmosphere at ambient temperature was treated with trifluoromethanesulfonic acid 2,2,2-trifluoroethyl ester (0.08 g, 0.36 mmol). After stirring for 3 hours, the resulting mixture was partitioned between water and EtOAc. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with a mixture of EtOAc and DCM (0:1 to 4:1 by volume) to afford the desired product as a colourless oil.

LCMS (Method D): R_t = 4.27 min, m/z $[M+H]^+$ = 558/560.

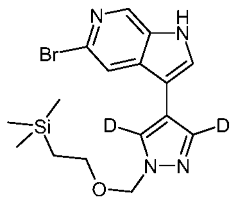
Intermediates 99 and 100 were prepared according to the reaction protocol of intermediate 98 using the appropriate starting materials (Table 13).

Table 13:

Intermediate	Structure	Starting Materials	LCMS Data
99		a) Intermediate 27 b) 1-Fluoro-2-iodo-ethane	R_t = 2.65 min, m/z $[M+H]^+$ = 522 (Method D)
100	 S-enantiomer	a) Intermediate 82 b) 1,1,1-Trifluoro-3-iodopropane	R_t = 2.69 min, m/z $[M+H]^+$ = 488/490 (Method B)

Example A15

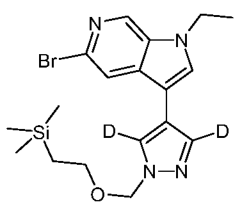
a) Preparation of intermediate 101



A suspension of intermediate 86 (0.41 g, 0.75 mmol) and Cs_2CO_3 (0.73 g, 2.22 mmol) in a mixture of MeOH (6.0 ml) and THF (12 ml) was stirred at ambient temperature for 1 hour. The mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and water. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo.* Trituration of the residue with DCM afforded the desired product as an off-white solid (0.10 g, 34%). The filtrate was concentrated *in vacuo* and the residue purified by column chromatography on silica gel, eluting with a mixture of EtOAc and pentane (0:1 to 1:0 by volume), to afford the desired product as an off-white solid (0.12 g, 39%).

LCMS (Method B): R_t = 3.48 min, m/z $[M+H]^+$ = 395/397.

b) Preparation of intermediate 102



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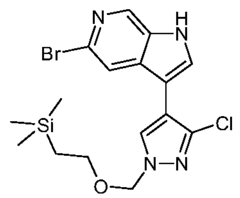
A stirred mixture of intermediate 101 (0.12 g, 0.29 mmol), iodoethane (0.025 ml, 0.32 mmol), Cs_2CO_3 (0.19 g, 0.58 mmol) and DMF (2.0 ml) was heated by microwave irradiation at 110 °C for 1 hour. The mixture was cooled to ambient temperature and partitioned between water and EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with a mixture of EtOAc and DCM (0:1 to 1:1 by volume), to afford the desired product as a pale yellow oil (0.15 g, 66%).
LCMS (Method B): R_t = 4.04 min, m/z $[M+H]^+$ = 423/425.

Example A16

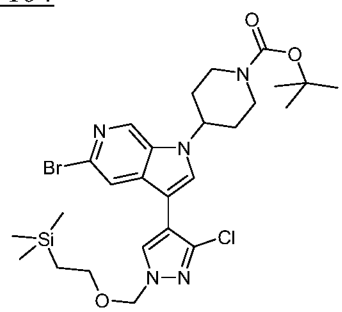
a) Preparation of intermediate 103



Regiochemistry of the SEM group assumed

A stirred solution of intermediate 87 (1.4 g, 2.41 mmol) in MeOH (12 ml) and THF (12 ml) at ambient temperature was treated with sodium methoxide (25% wt. in MeOH, 5.5 ml, 24.0 mmol) and the resulting mixture was stirred for 30 minutes. The mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and water. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the desired product as a pale yellow solid (0.89 g, 86%; Regiochemistry of the SEM group assumed).
LCMS (Method A): R_t = 3.95 min, m/z $[M+H]^+$ = 427/429.

b) Preparation of intermediate 104

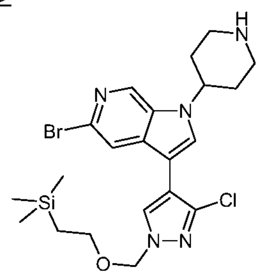


Regiochemistry of the SEM group assumed

A stirred mixture of intermediate 103 (0.40 g, 0.94 mmol), Cs_2CO_3 (1.37 g, 4.21 mmol), 4-methanesulfonyloxypiperidine-1-carboxylic acid *tert*-butyl ester (0.78 g, 2.81 mmol) and DMF (16.5 ml) was heated at 90 °C for 21 hours. A second aliquot of

Cs_2CO_3 (0.46 g, 1.40 mmol) and 4-methanesulfonyloxypiperidine-1-carboxylic acid *tert*-butyl ester (0.26 g, 94 mmol) was added and the reaction mixture stirred at 90 ºC for 12 hours. The mixture was cooled to ambient temperature and partitioned between EtOAc and water. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of DCM and EtOAc (1:0 to 4:1 by volume), to afford the desired product as a pale yellow oil (0.20 g, 35%; Regiochemistry of the SEM group assumed). LCMS (Method A): R_t = 4.80 min, m/z $[M+H]^+$ = 610/612.

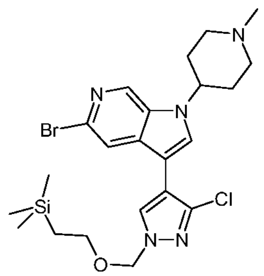
c) Preparation of intermediate 105



Regiochemistry of the SEM group assumed

A stirred solution of intermediate 104 (0.20 g, 0.33 mmol) in DCM (7.4 ml) at ambient temperature was treated with TFA (0.25 ml, 3.32 mmol) and the resulting mixture was stirred for 27 hours. The mixture was partitioned between DCM and saturated aqueous sodium hydrogen carbonate solution. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the desired product as a cream solid (0.14 g, 81%; Regiochemistry of the SEM group assumed).
LCMS (Method D): R_t = 2.79 min, m/z $[M+H]^+$ = 510/512.

d) Preparation of intermediate 106



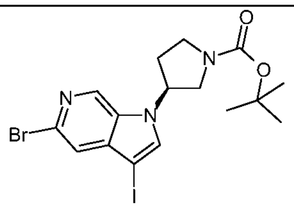
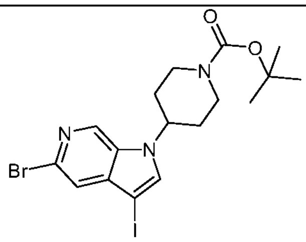
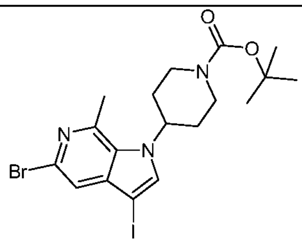
Regiochemistry of the SEM group assumed

A stirred mixture of intermediate 105 (0.14 g, 0.27 mmol), 37% aqueous formaldehyde (0.08 ml, 1.08 mmol), sodium acetate (0.02 g, 0.27 mmol), MeOH (6.2 ml) and DCE (3.6 ml) at 0 ºC was treated with sodium triacetoxyborohydride (0.23 g, 1.08 mmol). The resulting mixture was warmed to ambient temperature and stirred for 18 hours. The

mixture was partitioned between EtOAc and saturated aqueous sodium hydrogen carbonate solution. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of DCM and MeOH (1:0 to 9:1 by volume) to afford the desired product as a cream solid (0.07 g, 53%; Regiochemistry of the SEM group assumed).
LCMS (Method A): R_t = 2.73 min, m/z $[M+H]^+$ = 524/526.

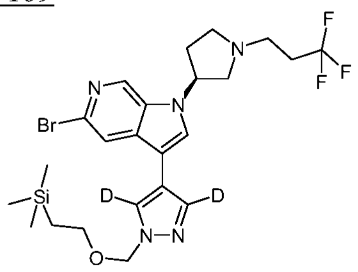
Intermediates 107,108 and 125 were prepared according to the reaction protocol of intermediate 104 using the appropriate starting materials (Table 14).

Table 14:

Intermediate	**Structure**	**Starting Materials**	**LCMS Data**
107	 S-enantiomer	a) Intermediate 6 b) (*R*)-3-Methanesulfonyloxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester	R_t = 4.08 min, m/z $[M+H]^+$ = 492/494 (Method B)
108		a) Intermediate 6 b) 4-Methanesulfonyloxy-piperidine-1-carboxylic acid *tert*-butyl ester	R_t = 4.26 min, m/z $[M+H]^+$ = 506/508 (Method B)
125		a) Intermediate 122 b) 4-Methanesulfonyloxy-piperidine-1-carboxylic acid *tert*-butyl ester	R_t = 4.34 min, m/z $[M+H]^+$ = 520/522 (Method B)

Example A17

a) Preparation of intermediate 109



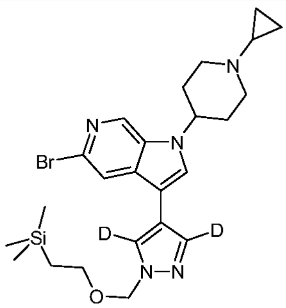
S-enantiomer

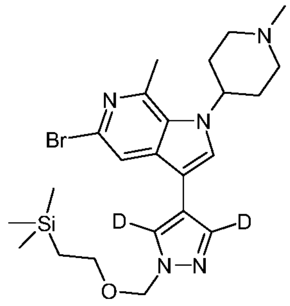
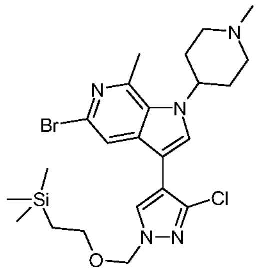
A degassed suspension of intermediate 100 (0.23 g, 0.48 mmol), intermediate 81 (0.16 g, 0.48 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.04 g, 0.05 mmol) and Cs_2CO_3 (0.47 g, 1.43 mmol) in 1,4-dioxane (4.0 ml) and water (1.0 ml) was heated at 80 °C for 18 hours. The mixture was cooled to ambient temperature and partitioned between saturated aqueous sodium hydrogen carbonate solution and EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with a mixture of DCM and 2.0 M ammonia solution in MeOH (1:0 to 9:1 by volume). Further purification by column chromatography, eluting with a mixture of DCM and MeOH (1:0 to 19:1 by volume), afforded the desired product as a yellow gum (0.14 g, 51%).

LCMS (Method C): R_t = 3.08 min, m/z $[M+H]^+$ = 560/562.

Intermediates 110, 126 and 127 were prepared according to the reaction protocol of intermediate 109 using the appropriate starting materials (Table 15).

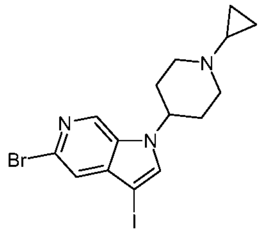
Table 15:

Intermediate	Structure	Starting Materials	LCMS Data
110		a) Intermediate 111 b) Intermediate 81	R_t = 2.54 min, m/z $[M+H]^+$ = 518/520 (Method B)

Intermediate	Structure	Starting Materials	LCMS Data
126		a) Intermediate 124 b) Intermediate 81	R_t = 2.51 min, m/z $[M+H]^+$ = 506/508 (Method B)
127		a) Intermediate 124 b) Intermediate 80	R_t = 2.65 min, m/z $[M+H]^+$ = 538/540/542 (Method B)

Example A18

a) Preparation of intermediate 111

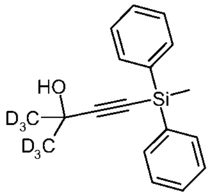


A stirred solution of intermediate 83 (0.32 g, 0.79 mmol) in a mixture of MeOH (7.2 ml) and acetic acid (3.6 ml) under a nitrogen atmosphere at ambient temperature was treated with (1-ethoxycyclopropoxy)trimethylsilane (0.48 ml, 2.75 mmol). After 10 minutes, the mixture was treated with sodium cyanoborohydride (0.30 g, 4.77 mmol) and the resulting mixture was stirred at 50 °C for 7.0 hours. The mixture was cooled to ambient temperature, concentrated *in vacuo* and partitioned between saturated aqueous sodium carbonate solution and EtOAc. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with a mixture of 2.0 M ammonia solution in MeOH and DCM (0:1 to 1:9 by volume), to afford the desired product as a pale yellow oil (0.29 g, 83%).

LCMS (Method B): R_t = 2.44 min, m/z $[M+H]^+$ = 446/448

Example A19

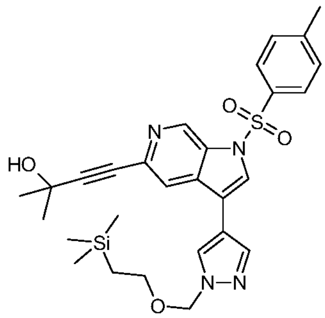
a) Preparation of intermediate 112



A stirred solution of (methyldiphenylsilyl)acetylene (2.0 ml, 9.08 mmol) in anhydrous THF (40 ml) under an argon atmosphere at -78 °C was treated with 1.6 M solution of *n*-butyllithium in hexanes (6.25 ml, 10.0 mmol) maintaining the temperature below -70 °C. After stirring for 1 hour, the mixture was treated with acetone-d_6 (0.79 ml, 10.91 mmol) and the resulting mixture stirred at 0 °C for 1.5 hours. The mixture was quenched by the addition of water and partitioned between water and EtOAc. The organic phase was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with a mixture of EtOAc and cyclohexane (0:1 to 3:7 by volume), to afford the desired product as a colourless oil (2.51 g, 96%).

Example A9

a) Preparation of intermediate 43

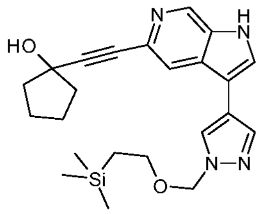
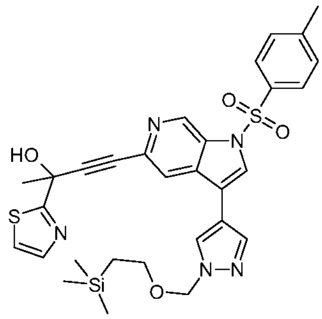
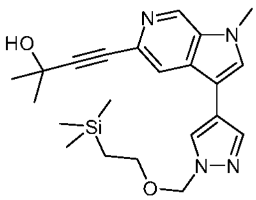
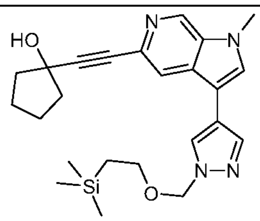
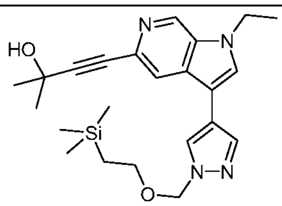
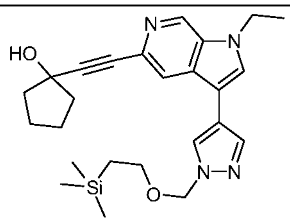


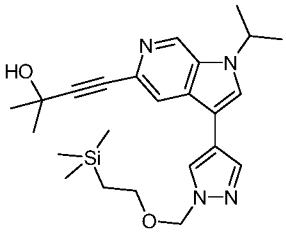
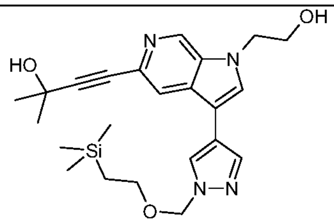
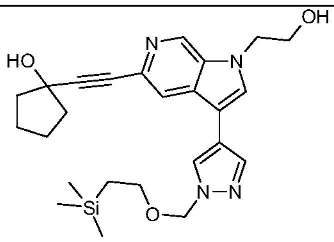
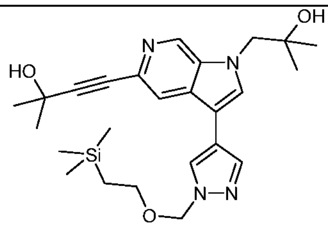
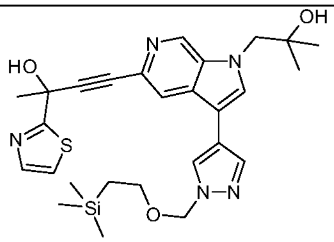
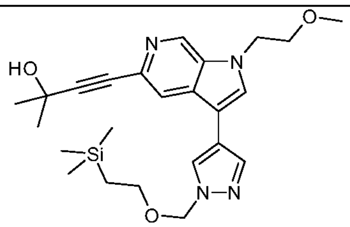
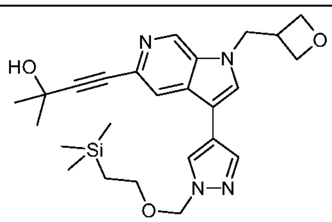
A degassed suspension of intermediate 8 (0.33 g, 0.60 mmol), 2-methyl-3-butyn-2-ol (0.07 ml, 0.72 mmol), tetrakis(triphenylphosphine)palladium(0) (0.14 g, 0.12 mmol), copper(I) iodide (0.011 g, 0.06 mmol) and triethylamine (0.60 ml, 4.22 mmol) in MeCN (12 ml) was heated at 100 °C under microwave irradiation for 2 hours. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and EtOAc (1:0 to 1:1 by volume), to afford the desired product (0.17 g, 52%).

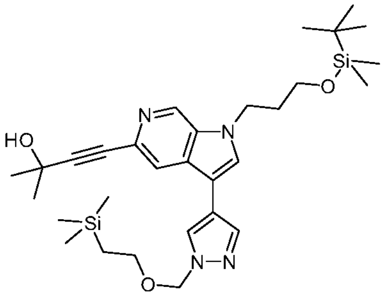
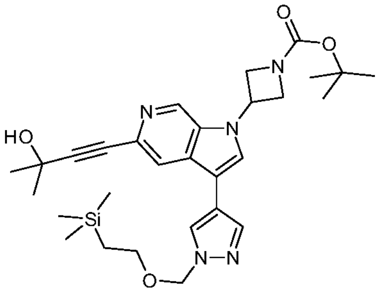
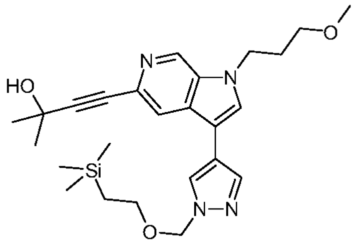
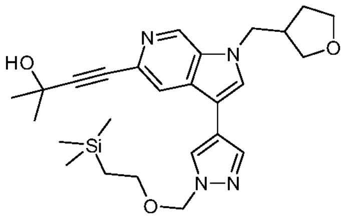
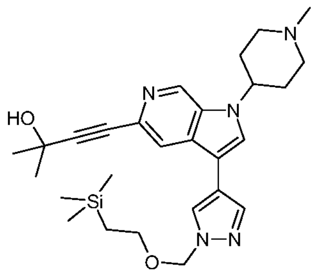
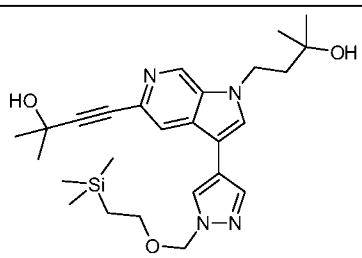
LCMS (Method C): R_t = 4.22 min, m/z $[M+H]^+$ = 551.

Intermediates 44 to 75 and 113 to 119 were prepared according to the reaction protocol of intermediate 43 using the appropriate starting materials (Table 16).

Table 16:

Intermediate	Structure	Starting Materials	LCMS Data
44		a) Intermediate 9 b) 1-Ethynylcyclopentanol	R_t = 2.69 min, m/z $[M+H]^+$ = 423 (Method C)
45		a) Intermediate 8 b) 2-Thiazol-2-ylbut-3-yn-2-ol	R_t = 4.16 min, m/z $[M+H]^+$ = 620 (Method B)
46		a) Intermediate 10 b) 2-Methyl-3-butyn-2-ol	R_t = 2.48 min, m/z $[M+H]^+$ = 411 (Method D)
47		a) Intermediate 10 b) 1-Ethynylcyclopentanol	R_t = 2.62 min, m/z $[M+H]^+$ = 437 (Method D)
48		a) Intermediate 11 b) 2-Methyl-3-butyn-2-ol	R_t = 2.55 min, m/z $[M+H]^+$ = 425 (Method D)
49		a) Intermediate 11 b) 1-Ethynylcyclopentanol	R_t = 2.71 min, m/z $[M+H]^+$ = 451 (Method D)

Intermediate	Structure	Starting Materials	LCMS Data
50		a) Intermediate 12 b) 2-Methyl-3-butyn-2-ol	R_t = 2.65 min, m/z $[M+H]^+$ = 439 (Method D)
51		a) Intermediate 36 b) 2-Methyl-3-butyn-2-ol	R_t = 2.51 min, m/z $[M+H]^+$ = 441 (Method C)
52		a) Intermediate 36 b) 1-Ethynylcyclopentanol	R_t = 2.66 min, m/z $[M+H]^+$ = 467 (Method C)
53		a) Intermediate 38 b) 2-Methyl-3-butyn-2-ol	R_t = 2.64 min, m/z $[M+H]^+$ = 469 (Method B)
54		a) Intermediate 38 b) 2-Thiazol-2-ylbut-3-yn-2-ol	R_t = 2.73 min, m/z $[M+H]^+$ = 538 (Method C)
55		a) Intermediate 37 b) 2-Methyl-3-butyn-2-ol	R_t = 2.69 min, m/z $[M+H]^+$ = 455 (Method C)
56		a) Intermediate 29 b) 2-Methyl-3-butyn-2-ol	R_t = 2.51 min, m/z $[M+H]^+$ = 467 (Method D)

Intermediate	Structure	Starting Materials	LCMS Data
57		a) Intermediate 13 b) 2-Methyl-3-butyn-2-ol	R_t = 3.56 min, m/z $[M+H]^+$ = 569 (Method D)
58		a) Intermediate 14 b) 2-Methyl-3-butyn-2-ol	R_t = 3.05 min, m/z $[M+H]^+$ = 552 (Method D)
59		a) Intermediate 15 b) 2-Methyl-3-butyn-2-ol	R_t = 2.61 min, m/z $[M+H]^+$ = 469 (Method D)
60		a) Intermediate 16 b) 2-Methyl-3-butyn-2-ol	R_t = 2.57 min, m/z $[M+H]^+$ = 481 (Method D)
61		a) Intermediate 28 b) 2-Methyl-3-butyn-2-ol	R_t = 2.08 min, m/z $[M+H]^+$ = 494 (Method D)
62		a) Intermediate 17 b) 2-Methyl-3-butyn-2-ol	R_t = 2.72 min, m/z $[M+H]^+$ = 483 (Method A)

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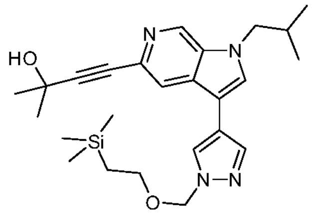
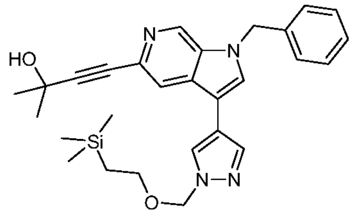
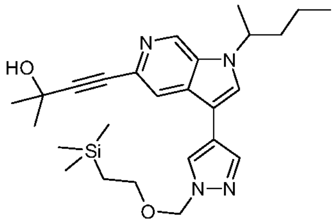
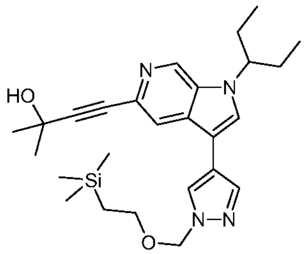
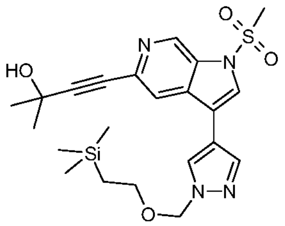
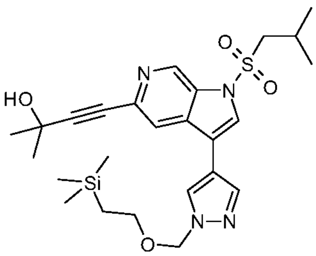
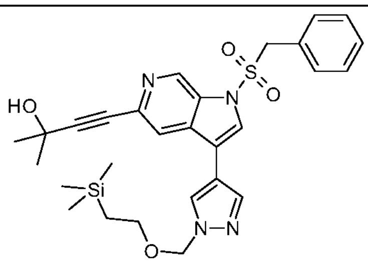
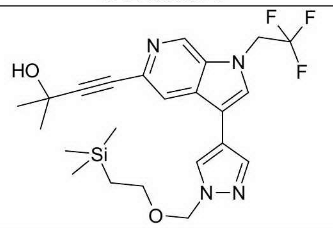
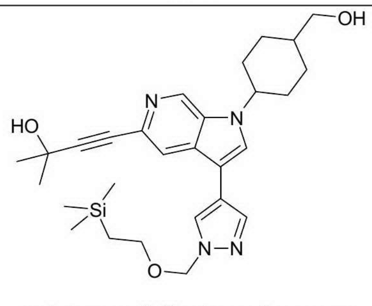
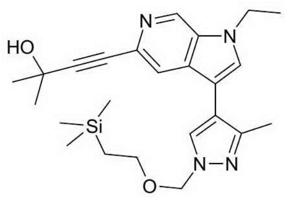
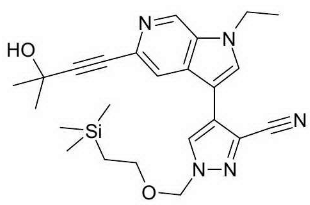
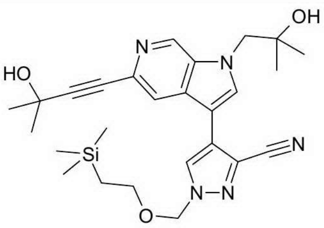
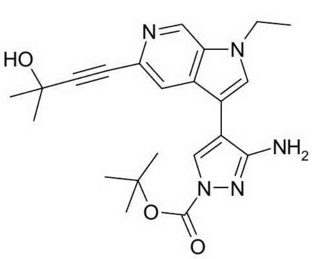
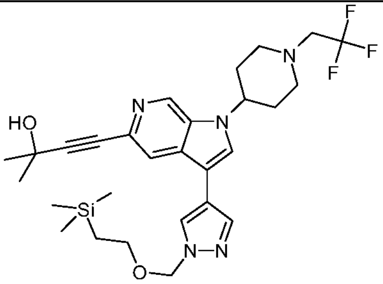
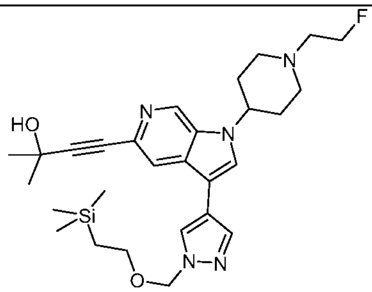
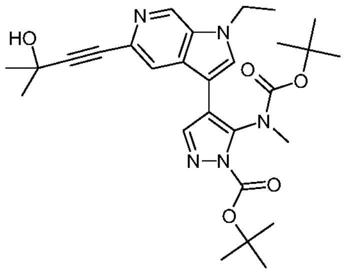
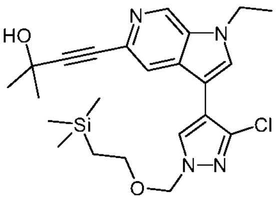
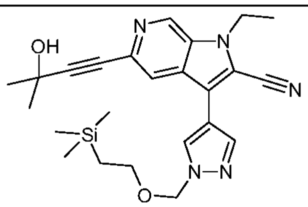
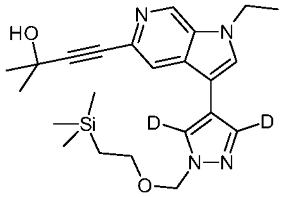
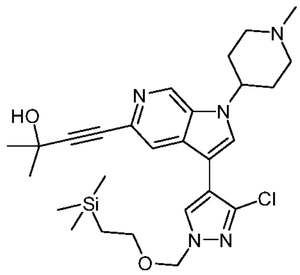
Intermediate	Structure	Starting Materials	LCMS Data
63		a) Intermediate 18 b) 2-Methyl-3-butyn-2-ol	R_t = 2.97 min, m/z $[M+H]^+$ = 453 (Method A)
64		a) Intermediate 19 b) 2-Methyl-3-butyn-2-ol	R_t = 2.96 min, m/z $[M+H]^+$ = 487 (Method D)
65		a) Intermediate 20 b) 2-Methyl-3-butyn-2-ol	R_t = 3.00 min, m/z $[M+H]^+$ = 467 (Method A)
66		a) Intermediate 21 b) 2-Methyl-3-butyn-2-ol	R_t = 4.52 min, m/z $[M+H]^+$ = 463/465 (Method A)
67		a) Intermediate 31 b) 2-Methyl-3-butyn-2-ol	R_t = 3.58 min, m/z $[M+H]^+$ = 475 (Method A)
68		a) Intermediate 32 b) 2-Methyl-3-butyn-2-ol	R_t = 3.88 min, m/z $[M+H]^+$ = 517 (Method D)
69		a) Intermediate 33 b) 2-Methyl-3-butyn-2-ol	R_t = 3.91 min, m/z $[M+H]^+$ = 551 (Method A)

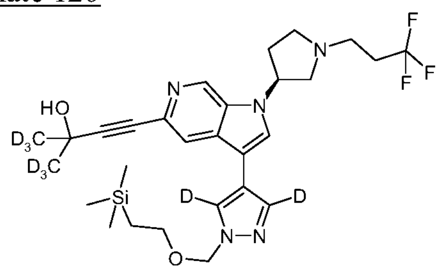
Intermediate	Structure	Starting Materials	LCMS Data
70		a) Intermediate 30 b) 2-Methyl-3-butyn-2-ol	R_t = 3.08 min, m/z $[M+H]^+$ = 479 (Method A)
71	 mixture of diastereoisomers	a) Intermediate 35 b) 2-Methyl-3-butyn-2-ol	R_t = 2.85 min, m/z $[M+H]^+$ = 509 (Method B)
72		a) Intermediate 39 b) 2-Methyl-3-butyn-2-ol	Mixture of regioisomers: R_t = 2.63 min, m/z $[M+H]^+$ = 439 (Method D)
73		a) Intermediate 40 b) 2-Methyl-3-butyn-2-ol	Mixture of regioisomers: R_t = 3.04 min, m/z $[M+H]^+$ = 450 (Method D)
74		a) Intermediate 41 b) 2-Methyl-3-butyn-2-ol	Mixture of regioisomers: R_t = 2.95 min, m/z $[M+H]^+$ = 494 (Method A)
75		a) Intermediate 42 b) 2-Methyl-3-butyn-2-ol	Regiochemistry of Boc-group not determined: R_t = 2.13 min, m/z $[M+H]^+$ = 410 (Method D)

Intermediate	Structure	Starting Materials	LCMS Data
113		a) Intermediate 98 b) 2-Methyl-3-butyn-2-ol	R_t = 2.99 min, m/z $[M+H]^+$ = 562 (Method D)
114		a) Intermediate 99 b) 2-Methyl-3-butyn-2-ol	R_t = 2.22/2.31 min, m/z $[M+H]^+$ = 526 (Method D)
115		a) Intermediate 95 b) 2-Methyl-3-butyn-2-ol	Mixture of regioisomers: R_t = 2.72 min, m/z $[M+H]^+$ = 524 (Method C)
116		a) Intermediate 84 b) 2-Methyl-3-butyn-2-ol	Mixture of regioisomers: R_t = 3.03 min, m/z $[M+H]^+$ = 459/461 (Method A)
117		a) Intermediate 85 b) 2-Methyl-3-butyn-2-ol	R_t = 3.83 min, m/z $[M+H]^+$ = 450 (Method C)

Intermediate	Structure	Starting Materials	LCMS Data
118		a) Intermediate 102 b) 2-Methyl-3-butyn-2-ol	R_t = 2.69 min, m/z $[M+H]^+$ = 427 (Method B)
119		a) Intermediate 106 b) 2-Methyl-3-butyn-2-ol	Regiochemistry of the SEM group assumed; R_t = 2.46 min, m/z $[M+H]^+$ = 528/530 (Method A)

Example A20

a) Preparation of intermediate 120



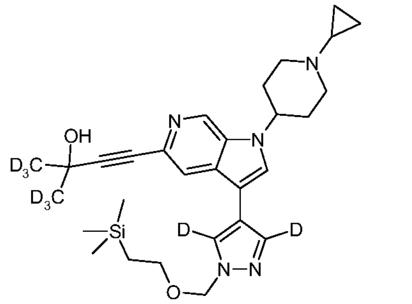
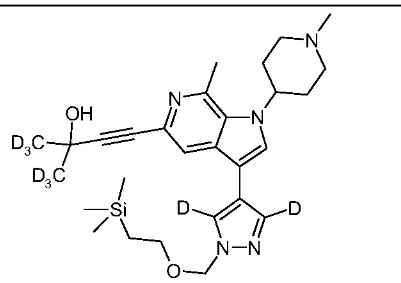
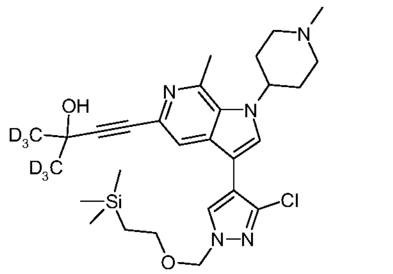
S-enantiomer

A degassed mixture of intermediate 109 (0.14 g, 0.24 mmol), intermediate 112 (0.10 g, 0.36 mmol), tetrakis(triphenylphosphine) palladium (0.06 g, 0.05 mmol), copper iodide (4.6 mg, 0.02 mmol), triethylamine (0.24 ml, 1.71 mmol) and MeCN (4.0 ml) was treated with 1.0 M solution of TBAF in THF (0.24 ml, 0.24 mmol), and the resulting mixture was heated by microwave irradiation at 100 °C for 1 hour. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with a mixture of MeOH and DCM (0:1 to 2:23 by volume) to afford the desired product as a yellow oil (0.05 g, 37%).

LCMS (Method B): R_t = 2.55 min, m/z $[M+H]^+$ = 570

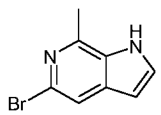
Intermediates 121, 128 and 129 were prepared according to the reaction protocol of intermediate 120 using the appropriate starting materials (Table 17).

Table 17:

Intermediate	Structure	Starting Materials	LCMS Data
121		a) Intermediate 110 b) Intermediate 112	R_t =2.36 min, m/z $[M+H]^+$ = 528 (Method A)
128		a) Intermediate 126 b) Intermediate 112	R_t = 2.32 min, m/z $[M+H]^+$ = 516 (Method C)
129		a) Intermediate 127 b) Intermediate 112	R_t = 2.27 min, m/z $[M+H]^+$ = 549/551 (Method B)

Example A21

a) Preparation of intermediate 130



A stirred solution of 6-bromo-2-methyl-3-nitro-pyridine (5.24 g, 24.1 mmol) in anhydrous THF (200 ml) under an argon atmosphere at -78 °C was treated with 1.0 M solution of vinylmagnesium bromide in THF (3.46 ml, 3.46 mmol), and the resulting mixture was stirred at -40 °C for 2 hours. The mixture was diluted with saturated aqueous ammonium chloride solution (11.5 ml) and partitioned between water and EtOAc. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with a mixture of EtOAc and cyclohexane (0:1 to 1:1 by volume), to afford the desired product as an orange oil (2.94 g, 57%).

LCMS (Method B): Rt = 1.83 min, m/z $[M+H]^+$ = 211/213

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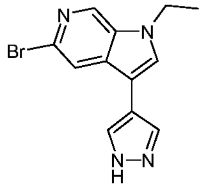
Example A22

a) Preparation of intermediate 131

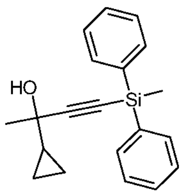


A mixture of intermediate 11 (0.10 g, 0.25 mmol), 1.0 M TBAF solution in THF (5.0 ml, 5 mmol) and 1,2-ethylenediamine (0.10 ml, 1.48 mmol) was heated at reflux for 24 hours. The mixture was cooled to ambient temperature and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel, eluting with a mixture of DCM and MeOH (1:0 to 9:1 by volume), to afford the desired product as a white solid (0.085 g, 95%).

LCMS (Method B): Rt = 2.47 min, m/z $[M+H]^+$ = 291/293

Example A23

a) Preparation of intermediate 133



(R or S enantiomer)

A stirred solution of (methyldiphenylsilyl)acetylene (80.0 g, 359.8 mmol) in anhydrous THF (1200 ml) under an argon atmosphere at -78 °C was treated with *n*-butyllithium (23.5 g, 367 mmol) maintaining the temperature below -70 °C. After stirring for 1 hour, the mixture was treated with 1-cyclopropyl-ethanone (36.3 g, 432 mmol) and the resulting mixture stirred at 0 °C for 1.5 hours. The mixture was quenched by the addition of water and partitioned between water and EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by chiral preparative SFC with the following conditions: column, ChiralPak IC, 300 x 50 mm, 10 µm; mobile phase, CO_2 (90%) and a mixture of heptane and isopropanol (1:1 by volume) (10%); flow rate 200 ml/min, back pressure 100 bar; detector, UV 220 nm; column temperature 38 °C. The first eluting enantiomer was isolated as an off-white solid (20.2 g, 47.5%). The second eluting enantiomer (intermediate 133; R or S enantiomer) was isolated as an off-white solid (20.2 g, 47.5%).

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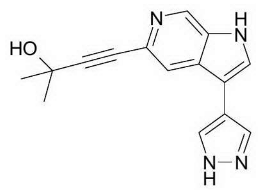
Preparation of compounds

The values of acid content (e.g. formic acid or acetic acid) in the compounds as provided herein, are those obtained experimentally and may vary when using different analytical methods. The content of formic acid or acetic acid reported herein was determined by ^{1}H NMR integration and is reported together with the ^{1}H NMR results. Compounds with an acid content of below 0.5 equivalents may be considered as free bases.

Example B1

a) Preparation of compound 1



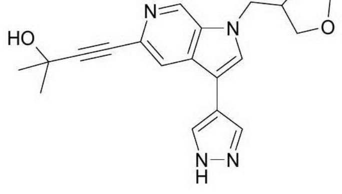
A mixture of intermediate 43 (0.17 g, 0.31 mmol), 1.0 M TBAF solution in THF (3.1 ml, 3.12 mmol) and 1,2-ethylenediamine (0.10 ml, 1.56 mmol) in THF (10 ml) was heated at reflux for 24 hours. The mixture was cooled to ambient temperature, concentrated *in vacuo* and the residue partitioned between EtOAc and brine. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with a mixture of DCM and MeOH (1:0 to 9:1 by volume), followed by trituration with DCM to afford the desired product (0.036 g, 43%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.84 (s, 1H), 11.76 (s, 1H), 8.64 (s, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.82 (d, J = 2.4 Hz, 1H), 7.79 (s, 1H), 5.40 (s, 1H), 1.46 (s, 6H).

LCMS (Method E): R_t = 1.93 min, m/z $[M+H]^+$ = 267.

Example B2

a) Preparation of compound 2



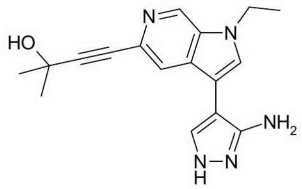
A stirred solution of intermediate 60 (0.13 g, 0.26 mmol) in DCM (4.0 ml) at ambient temperature was treated with TFA (0.80 ml, 10.5 mmol). After 3 hours, a second portion of TFA (0.2 ml) was added and the resulting mixture was stirred for a further 3 hours. The mixture was diluted with DCM and purified by column chromatography on a flash-NH_2 cartridge, eluting with a mixture of DCM and MeOH (4:1 by volume). The filtrate was concentrated *in vacuo* and triturated with MeCN to afford the desired product as a fawn solid (0.064 g, 67%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.87 (s, 1H), 8.84 (d, J = 0.9 Hz, 1H), 8.14 (s, 1H), 7.88 (s, 1H), 7.82 (s, 1H), 7.78 (d, J = 1.0 Hz, 1H), 5.41 (s, 1H), 4.24 (dd, J = 3.0, 7.6 Hz, 2H), 3.82-3.76 (m, 1H), 3.64-3.56 (m, 2H), 3.42 (dd, J = 5.5, 8.6 Hz, 1H), 2.81-2.71 (m, 1H), 1.91-1.81 (m, 1H), 1.63-1.53 (m, 1H), 1.45 (s, 6H).

LCMS (Method E): R_t = 2.13 min, m/z $[M+H]^+$ = 351.

Example B3

a) Preparation of compound 3



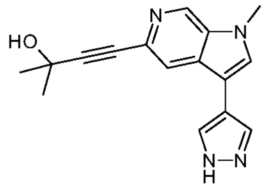
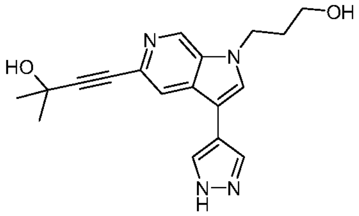
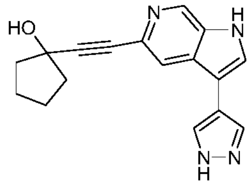
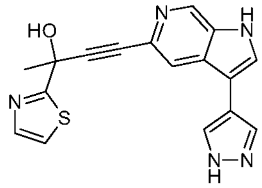
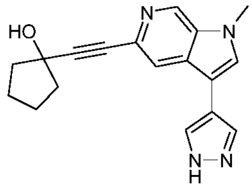
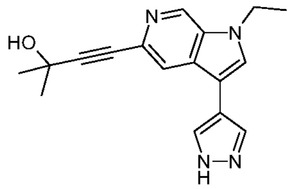
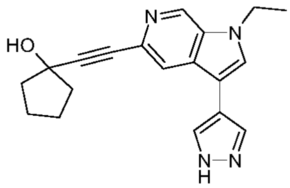
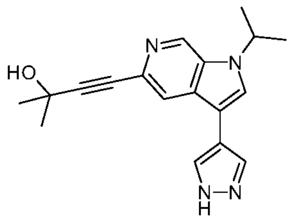
A suspension of intermediate 75 (0.062 g, 0.15 mmol) in MeCN (4.0 ml) was heated by microwave irradiation at 150 ºC for 2 hours. The mixture was cooled to ambient temperature and purified by ISOLUTE® SCX-2 SPE column, washing with MeOH, followed by 2.0 M ammonia in MeOH. Further purification by flash chromatography on silica gel, eluting with a mixture of DCM and MeOH (1:0 to 9:1 by volume), afforded the desired product as a pale yellow solid (0.012 g, 26%).

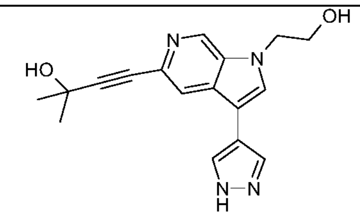
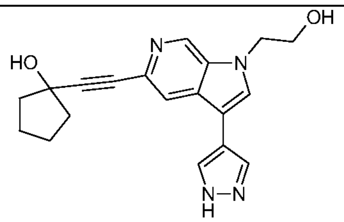
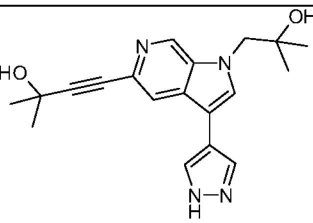
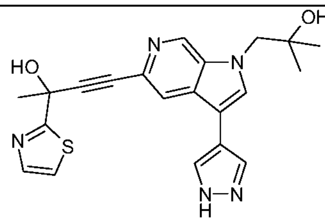
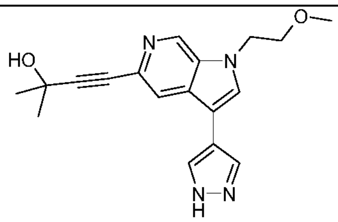
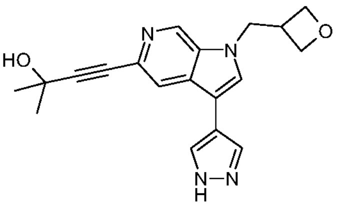
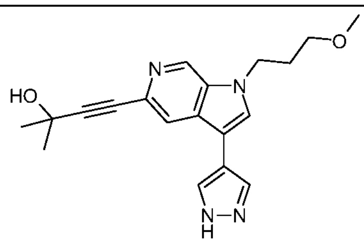
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.89 (s, 1H), 7.87 (s, 1H), 7.79 (s, 1H), 7.78 (s, 1H), 5.47 (s, 1H), 4.31 (q, J = 7.2 Hz, 2H), 1.45 (s, 6H), 1.40 (t, J = 7.2 Hz, 3H).

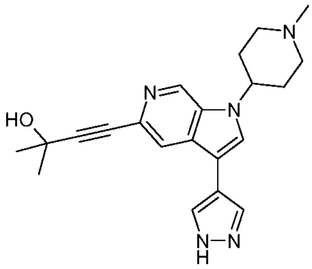
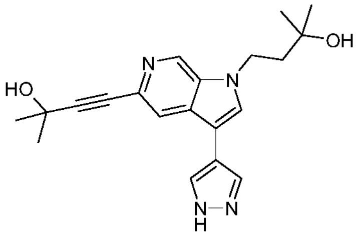
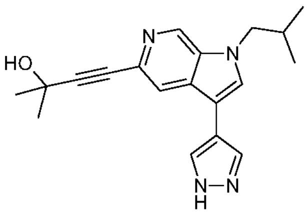
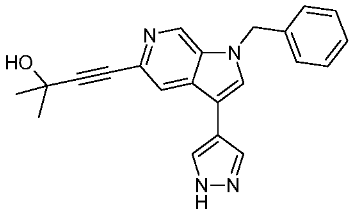
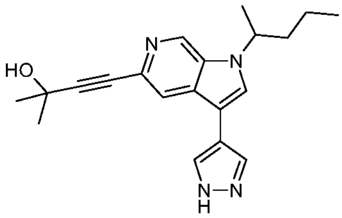
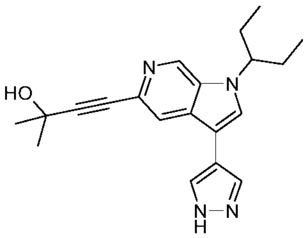
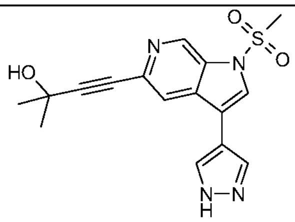
LCMS (Method E): R_t = 1.84 min, m/z $[M+H]^+$ = 310.

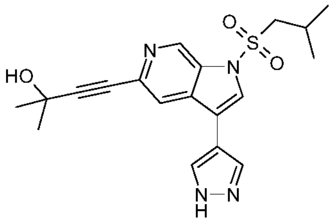
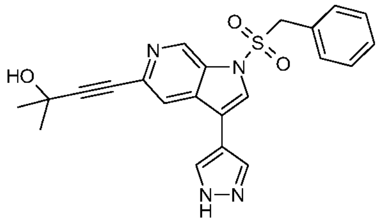
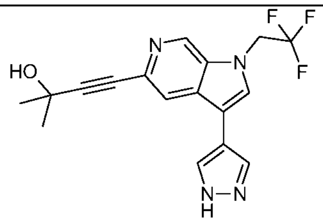
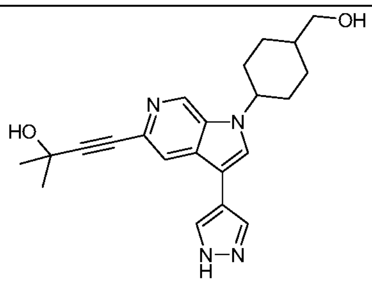
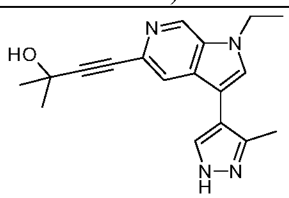
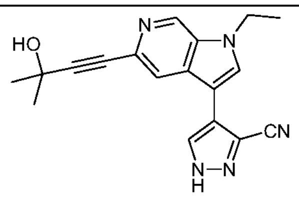
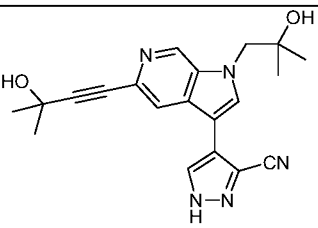
Compounds 4 to 33 and 35 to 45 were prepared according to the reaction protocol of Example B1 or B2 using the appropriate starting material (Table 18).

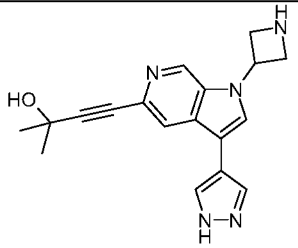
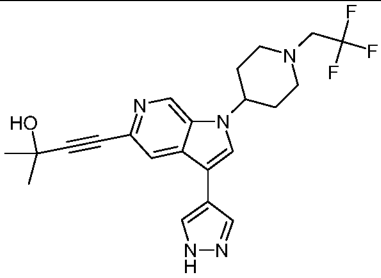
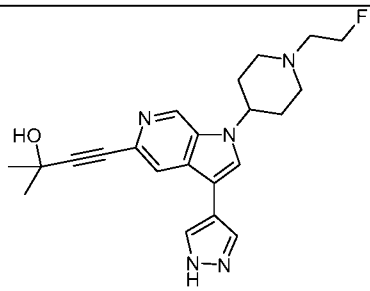
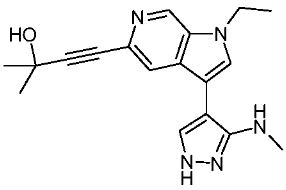
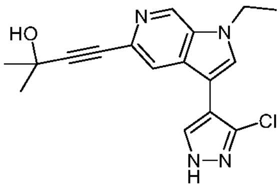
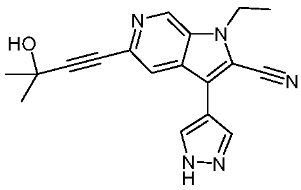
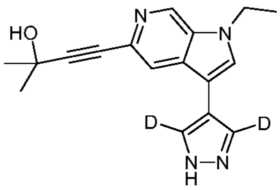
Table 18:

Compound	Structure	Method	Starting Material
4		B1	Intermediate 46
5		B1	Intermediate 57
6		B1	Intermediate 44
7		B1	Intermediate 45
8		B1	Intermediate 47
9		B1	Intermediate 48
10		B1	Intermediate 49
11		B1	Intermediate 50

Compound	Structure	Method	Starting Material
12		B1	Intermediate 51
13		B1	Intermediate 52
14		B1	Intermediate 53
15		B1	Intermediate 54
16		B1	Intermediate 55
17		B1	Intermediate 56
18		B1	Intermediate 59

Compound	Structure	Method	Starting Material
19		B2	Intermediate 61
20		B2	Intermediate 62
21		B2	Intermediate 63
22		B2	Intermediate 64
23		B2	Intermediate 65
24		B2	Intermediate 66
25		B2	Intermediate 67

Compound	Structure	Method	Starting Material
26		B2	Intermediate 68
27		B2	Intermediate 69
28		B2	Intermediate 70
29	 (3/7 mixture of diastereomers A/B)	B2	Intermediate 71
30		B1	Intermediate 72
31		B1	Intermediate 73
32		B1	Intermediate 74

Compound	Structure	Method	Starting Material
33		B2	Intermediate 58
35		B2	Intermediate 113
36		B2	Intermediate 114
37		B2	Intermediate 115
38		B2	Intermediate 116
39		B2	Intermediate 117
40		B2	Intermediate 118

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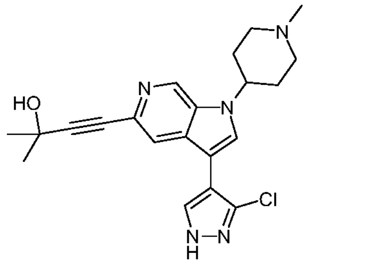
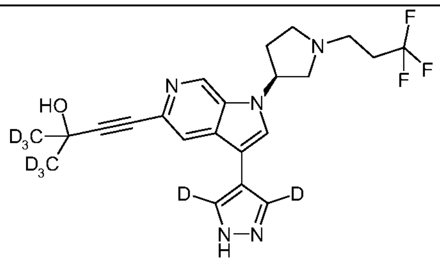
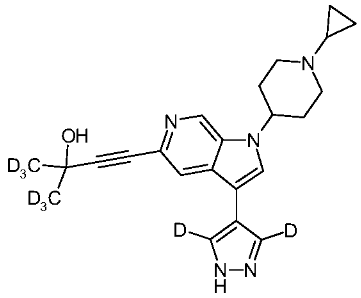
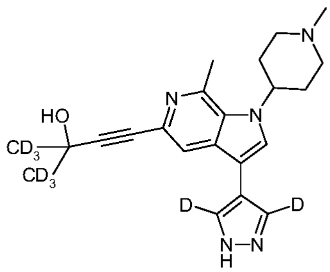
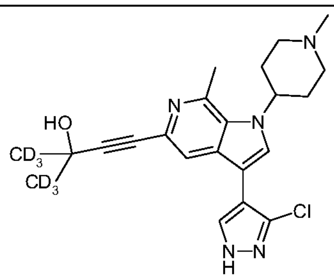
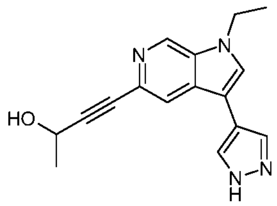
Compound	Structure	Method	Starting Material
41		B2	Intermediate 119
42	 S-enantiomer	B2	Intermediate 120
43		B2	Intermediate 121
44		B1	Intermediate 128
45		B1	Intermediate 129

Example B4

a) Preparation of compound 46



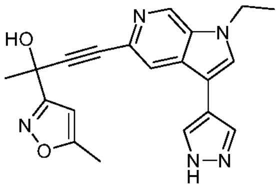
A degassed suspension of intermediate 131 (0.085 g, 0.23 mmol), but-3-yn-2-ol (0.04 ml, 0.47 mmol), tetrakis(triphenylphosphine)palladium(0) (0.05 g, 0.04 mmol), copper(I) iodide (0.005 g, 0.03 mmol) and triethylamine (0.10 ml, 0.72 mmol) in MeCN (5.0 ml) was heated at 100 °C under microwave irradiation for 2 hours. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by HPLC on C18 column, eluting with a mixture of MeCN and water containing 0.1% ammonia (1:9 to 19:1 by volume), to afford the desired product (0.02 g, 30%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.75 (s, 1H), 8.85 (d, J = 1.0 Hz, 1H), 8.02 (s, 2H), 7.91 (s, 1H), 7.85 (d, J = 1.0 Hz, 1H), 5.45 (s, 1H), 4.65-4.58 (q, J = 6.6 Hz, 1H), 4.33 (q, J = 7.3 Hz, 2H), 1.45-1.40 (m, 6H).

LCMS (Method C): R_t = 1.96 min, m/z $[M+H]^+$ = 281.

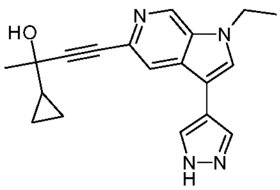
Compound 48 was prepared according to the reaction protocol of Example B4 using the appropriate starting materials (Table 19).

Table 19:

Compound	Structure	Starting Materials
48		a) Intermediate 131 b) 2-(5-Methyl-isoxazol-3-yl)-but-3-yn-2-ol

Example B5

a) Preparation of compound 49



(R or S enantiomer)

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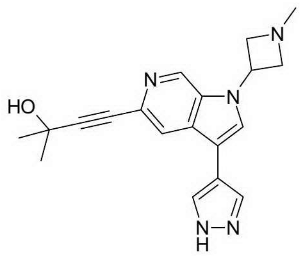
A degassed mixture of intermediate 131 (0.09 g, 0.31 mmol), intermediate 133 (0.19 g, 0.62 mmol), tetrakis(triphenylphosphine) palladium (0.07 g, 0.06 mmol), copper iodide (6.0 mg, 0.03 mmol), triethylamine (0.13 ml, 0.93 mmol) and MeCN (5.0 ml) under an argon atmosphere at ambient temperature was treated with 1.0 M solution of TBAF in THF (0.45 ml, 0.45 mmol). The resulting mixture was heated at 100 °C for 2 hours. The mixture was cooled to ambient temperature, filtered and the filtrate concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC, eluting with a mixture of acetonitrile and water containing 0.1% ammonium hydroxide (1:9 to 19:1 by volume over 22 min), to afford the desired product as a pale yellow solid (0.02 g, 20%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 13.00 (s, 1H), 9.05-9.05 (m, 1H), 8.17 (d, J = 70.3 Hz, 4H), 5.46 (s, 1H), 4.41 (q, J = 7.2 Hz, 2H), 1.56 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H), 1.23-1.15 (m, 1H), 0.62-0.48 (m, 2H), 0.47-0.40 (m, 2H).
LCMS (Method E): R_t = 2.32 min, m/z $[M+H]^+$ = 321

Example C1
Preparation of compound 34



A stirred mixture of compound 33 (0.47 g, 0.14 mmol), 37% aqueous formaldehyde (0.043 ml, 0.57 mmol), sodium acetate (0.012 g, 0.14 mmol), MeOH (2.0 ml) and DCE (1.2 ml) at 0 ºC was treated with sodium triacetoxyborohydride (0.12 g, 0.57 mmol). The resulting mixture was warmed to ambient temperature and stirred for 22 hours. The mixture was partitioned between EtOAc and saturated aqueous sodium hydrogen carbonate solution. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a mixture of DCM and MeOH (1:0 to 9:1 by volume). Further purification by HPLC on C18 column, eluting with a mixture of MeCN and water containing 0.1% ammonia (1:9 to 3:2 by volume), afforded the desired product as a white solid (0.010 g, 21%).
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.86 (s, 1H), 8.82 (d, J = 1.0 Hz, 1H), 8.18 (s, 1H), 8.13 (s, 1H), 7.88 (s, 1H), 7.79 (d, J = 1.0 Hz, 1H), 5.41 (s, 1H), 5.25-5.20 (m, 1H), 3.76 (t, J = 7.8 Hz, 2H), 3.38 (t, J = 7.8 Hz, 2H), 2.34 (s, 3H), 1.45 (s, 6H).
LCMS (Method E): R_t = 1.53 min, m/z $[M+H]^+$ = 336.

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Analytical Part

LCMS

Mass Spectrometry (LCMS) experiments to determine retention times and associated mass ions were performed using the following methods:

Method A: Experiments were performed on a Waters ZMD quadrupole mass spectrometer linked to a Waters 1525 LC system with a diode array detector. The spectrometer had an electrospray source operating in positive and negative ion mode. Additional detection was achieved using a Sedex 85 evaporative light scattering detector. LC was carried out using a Luna 3micron 30 x 4.6mm C18 column and a 2 mL/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.5 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 min. The final solvent system was held constant for a further 1 minute.

Method B: Experiments were performed on a Waters VG Platform II quadrupole spectrometer linked to a Hewlett Packard 1050 LC system with a diode array detector. The spectrometer had an electrospray source operating in positive and negative ion mode. Additional detection was achieved using a Sedex 85 evaporative light scattering detector. LC was carried out using a Luna 3micron 30 x 4.6mm C18 column and a 2 mL/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.3 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 min. The final solvent system was held constant for a further 1 minute.

Method C: Experiments were performed on a Waters Platform LC quadrupole mass spectrometer linked to a Hewlett Packard HP1100 LC system with diode array detector. The spectrometer had an electrospray source operating in positive and negative ion mode. Additional detection was achieved using a Sedex 85 evaporative light scattering detector. LC was carried out using a Phenomenex Luna 3micron 30 x 4.6mm C18 column and a 2 mL/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.5 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 min. The final solvent system was held constant for a further 1 minute.

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Method D: Experiments were performed on a Waters ZQ quadrupole mass spectrometer linked to a Hewlett Packard HP1100 LC system with quaternary pump and PDA detector. The spectrometer had an electrospray source operating in positive and negative ion mode. Additional detection was achieved using a Sedex 65 evaporative light scattering detector. LC was carried out using a Phenomenex Luna 3micron 30 x 4.6mm C18 column and a 2 mL/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.3 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 min. The final solvent system was held constant for a further 1 minute.

Method E: Experiments were performed on a Waters Micromass ZQ2000 quadrupole mass spectrometer linked to a Waters Acquity UPLC system with a PDA UV detector. The spectrometer had an electrospray source operating in positive and negative ion mode. LC was carried out using an Acquity BEH 1.7micron C18 column, an Acquity BEH Shield 1.7micron RP18 column or an Acquity HST 1.8micron column. Each column has dimensions of 100 x 2.1mm and was maintained at 40^{o}C with a flow rate of 0.4 mL/minute. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.4 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 5.2 min. The final solvent system was held constant for a further 0.8 min.

NMR Data

The NMR experiments herein were carried out using a Varian Unity Inova spectrometer with standard pulse sequences, operating at 400 MHz at ambient temperature. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard.

The values of acid content (e.g. formic acid or acetic acid) in the compounds as provided herein, are those obtained experimentally and may vary when using different analytical methods. The content of formic acid or acetic acid reported herein was determined by ^{1}H NMR integration. Compounds with an acid content of below 0.5 equivalents may be considered as free bases.

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Compound 4

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.87 (s, 1H), 8.74 (d, J = 1.0 Hz, 1H), 8.12 (s, 1H), 7.80 (s, 1H), 7.77 (d, J = 1.1 Hz, 1H), 7.76 (s, 1H), 5.40 (s, 1H), 3.87 (s, 3H), 1.45 (s, 6H).

LCMS (Method E): R_t = 1.99 min, m/z $[M+H]^+$ = 281.

Compound 5

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.92 (s, 1H), 8.83 (d, J = 1.0 Hz, 1H), 8.16 (s, 1H), 7.86 (s, 2H), 7.82 (d, J = 1.0 Hz, 1H), 5.45 (s, 1H), 4.65 (t, J = 5.0 Hz, 1H), 4.35 (t, J = 7.0 Hz, 2H), 3.42-3.36 (m, 2H), 2.00-1.91 (m, 2H), 1.50 (s, 6H).

LCMS (Method E): R_t = 1.93 min, m/z $[M+H]^+$ = 325.

Compound 6

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.85 (s, 1H), 11.71 (s, 1H), 8.65 (s, 1H), 7.98 (s, 2H), 7.79 (s, 1H), 7.78 (d, J = 1.0 Hz, 1H), 5.24 (s, 1H), 1.90-1.84 (m, 4H), 1.74-1.62 (m, 4H).

LCMS (Method E): R_t = 2.21 min, m/z $[M+H]^+$ = 293.

Compound 7

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.21 (s, 1H), 8.66 (s, 1H), 7.98 (s, 2H), 7.83-7.81 (m, 2H), 7.73 (d, J = 3.2 Hz, 1H), 7.63 (d, J = 3.3 Hz, 1H), 1.86 (s, 3H).

LCMS (Method E): R_t = 2.08 min, m/z $[M+H]^+$ = 336.

Compound 8

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.85 (s, 1H), 8.74 (d, J = 1.0 Hz, 1H), 8.13 (s, 1H), 7.81 (s, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.75 (s, 1H), 5.25 (s, 1H), 3.87 (s, 3H), 1.91-1.85 (m, 4H), 1.73-1.63 (m, 4H).

LCMS (Method E): R_t = 2.27 min, m/z $[M+H]^+$ = 307.

Compound 9

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.85 (s, 1H), 8.79 (d, J = 1.0 Hz, 1H), 8.12 (s, 1H), 7.85 (s, 1H), 7.80 (s, 1H), 7.77 (d, J = 1.0 Hz, 1H), 5.40 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H), 1.45 (s, 6H), 1.38 (t, J = 7.3 Hz, 3H).

LCMS (Method E): R_t = 2.15 min, m/z $[M+H]^+$ = 295.

Compound 10

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.85 (s, 1H), 8.79 (d, J = 1.0 Hz, 1H), 8.12 (s, 1H), 7.85 (s, 1H), 7.81 (s, 1H), 7.78 (d, J = 1.0 Hz, 1H), 5.25 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H), 1.91-1.85 (m, 4H), 1.73 -1.62 (m, 4H), 1.38 (t, J = 7.2 Hz, 3H).

LCMS (Method E): R_t = 2.42 min, m/z $[M+H]^+$ = 321.

Compound 11

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.85 (s, 1H), 8.82 (d, J = 0.9 Hz, 1H), 8.15 (s, 1H), 7.97 (s, 1H), 7.81 (s, 1H), 7.76 (d, J = 1.0 Hz, 1H), 5.39 (s, 1H), 4.93-4.84 (m, 1H), 1.47 (d, J = 6.5 Hz, 6H), 1.45 (s, 6H).

LCMS (Method E): R_t = 2.29 min, m/z $[M+H]^+$ = 309.

Compound 12

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.85 (s, 1H), 8.78 (d, J = 1.0 Hz, 1H), 7.97 (s, 2H), 7.79 (s, 1H), 7.76 (d, J = 1.0 Hz, 1H), 5.40 (s, 1H), 4.89 (s, 1H), 4.29 (t, J = 5.3 Hz, 2H), 3.72 (t, J = 5.0 Hz, 2H), 1.45 (s, 6H).

LCMS (Method E): R_t = 1.85 min, m/z $[M+H]^+$ = 311.

Compound 13

H NMR (400 MHz, DMSO-d_6) δ ppm: 12.85 (s, 1H), 8.77 (d, J = 0.9 Hz, 1H), 8.12 (s, 1H), 7.81 (s, 1H), 7.78 (s, 1H), 7.77 (d, J = 0.8 Hz, 1H), 5.24 (s, 1H), 4.91 (t, J = 5.3 Hz, 1H), 4.28 (t, J = 5.2 Hz, 2H), 3.71 (q, J = 5.2 Hz, 2H), 1.90-1.84 (m, 4H), 1.73 - 1.62 (m, 4H).

LCMS (Method E): R_t = 2.18 min, m/z $[M+H]^+$ = 337.

Compound 14

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.84 (s, 1H), 8.82 (d, J = 0.9 Hz, 1H), 8.12 (s, 1H), 7.79 (s, 1H), 7.74 (d, J = 0.8 Hz, 1H), 7.70 (s, 1H), 5.38 (s, 1H), 4.70 (s, 1H), 4.13 (s, 2H), 1.44 (s, 6H), 1.07 (s, 6H).

LCMS (Method E): R_t = 2.21 min, m/z $[M+H]^+$ = 339.

Compound 15

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.85 (s, 1H), 8.84 (d, J = 0.8 Hz, 1H), 8.14 (s, 1H), 7.79 (d, J = 0.9 Hz, 2H), 7.72 (s,1H), 7.63 (d, J = 3.3 Hz, 1H), 6.95 (s, 1H), 4.70 (s, 1H), 4.14 (s, 2H), 1.86 (s, 3H), 1.06 (s, 6H).

LCMS (Method E): R_t = 2.26 min, m/z $[M+H]^+$ = 408.

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Compound 16 (0.4 equivalents formic acid)
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.84 (s, 1H), 8.79 (d, J = 1.0 Hz, 1H), 8.13 (s, 0.4H), 7.95 (s, 2H), 7.78 (s, 1H), 7.77 (d, J = 0.9 Hz, 1H), 5.40 (s, 1H), 4.41 (t, J = 5.1 Hz, 2H), 3.66 (t, J = 5.2 Hz, 2H), 3.18 (s, 3H), 1.45 (s, 6H).
LCMS (Method E): R_t = 2.12 min, m/z $[M+H]^+$ = 325.

Compound 17
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.87 (s, 1H), 8.85 (d, J = 1.0 Hz, 1H), 8.13 (s, 1H), 7.86 (s, 1H), 7.80 (s, 1H), 7.77 (d, J = 1.0 Hz, 1H), 5.40 (s, 1H), 4.62-4.55 (m, 4H), 4.39 (t, J = 6.1 Hz, 2H), 3.52 - 3.40 (m, 1H), 1.45 (s, 6H).
LCMS (Method E): R_t = 2.05 min, m/z $[M+H]^+$ = 337.

Compound 18
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.86 (s, 1H), 8.75 (d, J = 1.0 Hz, 1H), 8.14 (s, 1H), 7.81 (s, 2H), 7.78 (d, J = 1.0 Hz, 1H), 5.40 (s, 1H), 4.29 (t, J = 6.9 Hz, 2H), 3.21 (t, J = 6.3 Hz, 2H), 3.17 (s, 3H), 2.04-1.95 (m, 2H), 1.45 (s, 6H).
LCMS (Method E): R_t = 2.20 min, m/z $[M+H]^+$ = 339.

Compound 19
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.85 (s, 1H), 8.86 (d, J = 0.9 Hz, 1H), 8.13 (s, 1H), 8.00 (s, 1H), 7.84 (s, 1H), 7.77 (d, J = 1.0 Hz, 1H), 5.40 (s, 1H), 4.53-4.44 (m, 1H), 2.87 (d, J = 11.3 Hz, 2H), 2.20 (s, 3H), 2.17-1.90 (m, 6H), 1.45 (s, 6H).
LCMS (Method E): R_t = 1.60 min, m/z $[M+H]^+$ = 364.

Compound 20
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.86 (s, 1H), 8.75 (d, J = 0.9 Hz, 1H), 8.13 (s, 1H), 7.84 (s, 1H), 7.81 (s, 1H), 7.78 (d, J = 1.0 Hz, 1H), 5.40 (s, 1H), 4.48 (s, 1H), 4.34-4.28 (m, 2H), 1.90-1.84 (m, 2H), 1.45 (s, 6H), 1.13 (s, 6H).
LCMS (Method E): R_t = 2.18 min, m/z $[M+H]^+$ = 353.

Compound 21
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.86 (s, 1H), 8.81 (s, 1H), 8.14 (s, 1H), 7.82 (s, 2H), 7.78 (s, 1H), 5.40 (s, 1H), 4.06 (d, J = 7.4 Hz, 2H), 2.18-2.06 (m, 1H), 1.45 (s, 6H), 0.83 (d, J = 6.6 Hz, 6H).
LCMS (Method E): R_t = 2.51 min, m/z $[M+H]^+$ = 323.

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Compound 22

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.88 (s, 1H), 8.79 (s, 1H), 8.15 (s, 1H), 7.96 (s, 1H), 7.83 (s, 1H), 7.80 (s, 1H), 7.29-7.22 (m, 5H), 5.50 (s, 2H), 5.40 (s, 1H), 1.44 (s, 6H).

LCMS (Method E): R_t = 2.66 min, m/z $[M+H]^+$ = 357.

Compound 23

^{1}H NMR (400 MHz, CD_3OD) δ ppm: 8.72 (s, 1H), 7.94 (s, 2H), 7.86 (s, 1H), 7.85 (s, 1H), 4.76-4.67 (m, 1H), 2.00-1.79 (m, 2H), 1.57 (s, 6H), 1.55 (d, J = 6.7 Hz, 3H), 1.31-1.05 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H).

LCMS (Method E): R_t = 2.69 min, m/z $[M+H]^+$ = 337.

Compound 24

^{1}H NMR (400 MHz, CD_3OD) δ ppm: 8.73 (s, 1H), 7.95 (s, 2H), 7.87 (s, 1H), 7.84 (s, 1H), 4.40-4.31 (m, 1H), 2.00-1.90 (m, 4H), 1.57 (s, 6H), 0.75 (t, J = 7.4 Hz, 6H).

LCMS (Method E): R_t = 2.60 min, m/z $[M+H]^+$ = 337.

Compound 25

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 13.12 (s, 1H), 9.07 (d, J = 1.0 Hz, 1H), 8.43 (s, 1H), 8.11 (s, 1H), 8.06 (s, 1H), 8.00 (d, J = 1.0 Hz, 1H), 5.54 (s, 1H), 3.61 (s, 3H), 1.52 (s, 6H).

LCMS (Method E): R_t = 2.75 min, m/z $[M+H]^+$ = 345.

Compound 26

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 13.05 (s, 1H), 9.02 (d, J = 1.0 Hz, 1H), 8.38 (s, 1H), 8.08 (s, 1H), 8.00 (s, 1H), 7.95 (d, J = 1.0 Hz, 1H), 5.49 (s, 1H), 3.61 (d, J = 6.7 Hz, 2H), 2.05-1.97 (m, 1H), 1.46 (s, 6H), 0.92 (d, J = 6.8 Hz, 6H).

LCMS (Method E): R_t = 3.54 min, m/z $[M+H]^+$ = 387.

Compound 27

^{1}H NMR (400 MHz, CD_3OD) δ ppm: 8.51 (d, J = 0.9 Hz, 1H), 8.10 (s, 1H), 7.87 (s, 1H), 7.84 (d, J = 1.0 Hz, 1H), 7.69 (s, 1H), 7.22-7.16 (m, 1H), 7.12-7.06 (m, 2H), 6.99-6.94 (m, 2H), 4.88 (s, 2H), 1.56 (s, 6H).

LCMS (Method E): R_t = 3.44 min, m/z $[M+H]^+$ = 421.

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Compound 28
^{1}H NMR (400 MHz, CD_3OD) δ ppm: 8.78 (s, 1H), 7.96 (s, 2H), 7.90 (d, J = 1.0 Hz, 1H), 7.76 (s, 1H), 5.19-5.11 (q, J = 8.8 Hz, 2H), 1.57 (s, 6H).
LCMS (Method E): R_t = 2.46 min, m/z $[M+H]^+$ = 349.

Compound 29 (3/7 mixture of diastereomers A/B)
^{1}H NMR (400 MHz, CD_3OD) δ ppm: 8.74-8.71 (m, $1H^{A+B}$), 8.03-7.87 (m, $3H^{A+B}$), 7.85-7.84 (m, $1H^{A+B}$), 4.58-4.42 (m, $1H^{A+B}$), 3.69 (d, J = 6.4 Hz, $2H^{A}$), 3.44 (d, J = 7.0 Hz, $2H^{B}$), 2.19-2.11 (m, $2H^{B}$), 2.04-1.75 (m, $5H^{A}$+$3H^{B}$), 1.67-1.60 (m, $2H^{A}$), 1.58 (s, $6H^{A+B}$), 1.37-1.22 (m, $4H^{B}$), 0.94-0.80 (m, $2H^{A}$).
LCMS (Method E): R_t = 2.27 min, m/z $[M+H]^+$ = 379.

Compound 30
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.57 (s, 1H), 8.80 (d, J = 1.0 Hz, 1H), 7.92 (s, 1H), 7.66 (s, 1H), 7.58 (s, 1H), 5.38 (s, 1H), 4.30 (q, J = 7.2 Hz, 2H), 2.26 (s, 3H), 1.43 (s, 6H), 1.38 (t, J = 7.2 Hz, 3H).
LCMS (Method E): R_t = 2.19 min, m/z $[M+H]^+$ = 309.

Compound 31
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.88 (d, J = 1.0 Hz, 1H), 8.48 (s, 1H), 7.94 (s, 1H), 7.75 (d, J = 1.0 Hz, 1H), 5.42 (s, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.45 (s, 6H), 1.39 (t, J = 7.2 Hz, 3H).
LCMS (Method E): R_t = 2.40 min, m/z $[M+H]^+$ = 320.

Compound 32
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 14.07 (s, 1H), 8.91 (d, J = 0.9 Hz, 1H), 8.50 (s, 1H), 7.87 (s, 1H), 7.75 (d, J = 0.9 Hz, 1H), 5.41 (s, 1H), 4.75 (s, 1H), 4.22 (s, 2H), 1.45 (s, 6H), 1.08 (s, 6H).
LCMS (Method E): R_t = 2.30 min, m/z $[M+H]^+$ = 364.

Compound 33
LCMS (Method D): R_t= 1.16 min, m/z $[M+H]^+$ = 322.

Compound 35
^{1}H NMR (400 MHz, CD_3OD) δ ppm: 8.79 (s, 1H), 7.98 (br. s, 2H), 7.94 (s, 1H), 7.88 (d, J=1.3 Hz, 1H), 4.61-4.51 (m, 1H), 3.22-3.13 (m, 4H), 2.76-2.68 (m, 2H), 2.28-2.16 (m, 2H), 2.11-2.04 (m, 2H), 1.60 (s, 6H).

LCMS (Method E): R_t = 2.71 min, m/z $[M+H]^+$ = 432.

Compound 36

^{1}H NMR (400 MHz, CD_3OD) δ ppm: 8.82 (s, 1H), 7.98 (br.s, 1H), 7.92 (s, 1H), 7.88 (d, J = 0.9 Hz, 1H), 4.70 (t, J = 5.2 Hz, 1H), 4.63-4.55 (m, 2H), 3.22 (d, J = 12.0 Hz, 2H), 2.89 (t, J = 4.7 Hz, 1H), 2.82 (t, J = 4.7 Hz, 1H), 2.49 (t, J = 11.4 Hz, 2H), 2.29-2.09 (m, 4H), 1.60 (s, 6H).

LCMS (Method E): R_t = 1.67 min, m/z $[M+H]^+$ = 396.

Compound 37

^{1}H NMR (400 MHz, CD_3OD) δ ppm: 8.70 (s, 1H), 7.75 (s, 1H), 7.75 (s, 1H), 7.68 (s, 1H), 4.36 (q, J = 7.3 Hz, 2H), 2.86 (s, 3H), 1.59 (s, 6H), 1.51 (t, J = 7.3 Hz, 3H).

LCMS (Method E): R_t = 1.92 min, m/z $[M+H]^+$ = 324.

Compound 38

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 13.20 (br.s, 1H), 8.87 (d, J = 1.0 Hz, 1H), 8.27 (s, 1H), 7.91 (s, 1H), 7.71 (d, J = 1.0 Hz, 1H), 5.45 (s, 1H), 4.38 (q, J = 7.2 Hz, 2H), 1.48 (s, 6H), 1.42 (t, J = 7.2 Hz, 3H).

LCMS (Method E): R_t = 2.44 min, m/z $[M+H]^+$ = 329/331.

Compound 39

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 13.34 (s, 1H), 9.11 (d, J = 1.1 Hz, 1H), 8.43 (s, 1H), 8.05 (s, 1H), 7.94 (d, J = 1.0 Hz, 1H), 5.51 (s, 1H), 4.51 (q, J = 7.2 Hz, 2H), 1.50 (s, 6H), 1.43 (t, J = 7.2 Hz, 3H).

LCMS (Method E): R_t = 2.98 min, m/z $[M+H]^+$ = 320.

Compound 40

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.88 (s, 1H), 8.89 (s, 1H), 7.97 (s, 1H), 7.87 (s, 1H), 5.47 (s, 1H), 4.34 (q, J = 7.2 Hz, 2H), 1.50 (s, 6H), 1.44 (t, J = 6.8 Hz, 3H).

LCMS (Method E): R_t = 2.13 min, m/z $[M+H]^+$ = 297.

Compound 41

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 13.21 (s, 1H), 8.96 (d, J = 0.9 Hz, 1H), 8.24 (s, 1H), 7.94 (s, 1H), 7.69 (d, J = 1.0 Hz, 1H), 5.46 (s, 1H), 4.63-4.53 (m, 1H), 2.91 (d, J = 11.4 Hz, 2H), 2.24 (s, 3H), 2.22-1.95 (m, 6H), 1.49 (s, 6H).

LCMS (Method E): R_t = 1.82 min, m/z $[M+H]^+$ = 398/400.

Compound 42
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.91 (br.s, 1H), 8.95 (d, J = 1.0 Hz, 1H), 7.96 (s, 1H), 7.81 (d, J = 0.9 Hz, 1H), 5.42 (s, 1H), 5.32-5.26 (m, 1H), 3.15-2.99 (m, 2H), 2.84-2.66 (m, 3H), 2.62-2.40 (m, 4H), 2.04-1.94 (m, 1H).
LCMS (Method E): R_t = 2.00 min, m/z $[M+H]^+$ = 440.

Compound 43
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.87 (s, 1H), 8.91 (s, 1H), 8.07 (s, 1H), 7.81 (s, 1H), 5.44 (s, 1H), 4.64-4.54 (m, 1H), 3.11-3.04 (m, 2H), 2.46-2.40 (m, 2H), 2.01-1.92 (m, 4H), 1.74-1.67 (m, 1H), 0.49-0.43 (m, 2H), 0.35-0.29 (m, 2H).
LCMS (Method E): R_t = 1.69 min, m/z $[M+H]^+$ = 398.

Compound 44
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.37 (s, 1H), 7.99 (s, 1H), 7.64 (s, 1H), 5.41 (s, 1H), 4.71-4.61 (m, 1H), 2.92 (d, J = 9.2 Hz, 2H), 2.84 (s, 3H), 2.23 (s, 3H), 2.17-1.93 (m, 6H).
LCMS (Method E): R_t = 1.60 min, m/z $[M+H]^+$ = 386.

Compound 45
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 13.19 (s, 1H), 8.17 (s, 1H), 7.87 (s, 1H), 7.49 (s, 1H), 5.41 (s, 1H), 4.75-4.65 (m, 1H), 2.92 (d, J = 11.2 Hz, 2H), 2.87 (s, 3H), 2.23 (s, 3H), 2.16-1.98 (m, 6H).
LCMS (Method E): R_t = 1.77 min, m/z $[M+H]^+$ = 418/420.

Compound 48
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.91 (s, 1H), 8.86 (s, 1H), 8.02 (br. s, 2H), 7.92 (s, 1H), 7.87 (d, J = 1.0 Hz, 1H), 6.49 (s, 1H), 6.38 (d, J = 0.9 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 2.41 (d, J = 0.8 Hz, 3H), 1.83 (s, 3H), 1.43 (t, J = 7.2, 3H).
LCMS (Method E): R_t = 2.38 min, m/z $[M+H]^+$ = 362

Pharmacological Part

Biological assay A

Inhibition of recombinant human NF-kappaB-inducing kinase (NIK/MAP3K14) activity

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%

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Tween® 20. Assays were carried out in 384 well Mesoscale high binding plates which had been coated with myelin basic protein (MBP) and blocked with bovine serum albumin to prevent non-specific protein binding. 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. Incubations consisted of compound (1% DMSO in control and blank wells), 25 μM Adenosine-5'-triphosphate (ATP), and 10 nM NIK/MAP3K14 substituting enzyme with buffer in the blank wells. Incubations were carried out for 1h at 25°C and were followed by washing and sequential incubation with rabbit anti-phospho-MBP and anti-rabbit Ig Sulfotag antibody before reading bound Sulfotag on a Mesoscale Discovery. 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 A2

Inhibition of auto-phosphorylation of recombinant human NF-kappaB-inducing kinase (NIK/MAP3K14) activity (AlphaScreen®)

NIK/MAP3K14 auto-phosphorylation activity was measured using the AlphaScreen® (αscreen) format (Perkin Elmer). All compounds tested were dissolved in dimethyl sulfoxide (DMSO) and further dilutions were made in assay buffer. Final DMSO concentration was 1% (v/v) in assays. Assay buffer was 50 mM Tris pH 7.5 containing 1 mM EGTA (ethylene glycol tetraacetic acid), 1 mM DTT (dithiothreitol), 0.1 mM Na_3VO_4, 5 mM $MgCl_2$, 0.01% Tween® 20. Assays were carried out in 384 well Alphaplates (Perkin Elmer). Incubations consisted of compound, 25 microM Adenosine-5'-triphosphate (ATP), and 0.2 nM NIK/MAP3K14. Incubations were initiated by addition of GST-tagged NIK/MAP3K14 enzyme, carried out for 1h at 25 °C and terminated by addition of stop buffer containing anti-phospho-IKK Ser176/180 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-IKKα levels in L363 cells

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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 $0.2x10^6$ cells per ml – $1x10^6$ cells per ml at 37°C in a humidified 5% CO_2 atmosphere. Cells were passaged twice a week splitting back to obtain the low density. Cells were seeded in 96 well plates (Nunc 167008) at $2x10^6$ per ml media in a volume of 75 µl per well plus 25 µl 1 µg/ml recombinant human B-cell activating factor (BAFF/BLyS/TNFSF13B). Seeded cells were incubated at 37°C in a humidified 5% CO_2 atmosphere for 24 hr. Drugs and/or solvents were added (20 µl) to a final volume of 120 µl. Following 2 hr treatment plates were removed from the incubator and cell lysis was achieved by the addition of 30 µl 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-IKKα 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 10µM ADS125117, a test concentration known to give full inhibition) were run in parallel. The blank incubation value was subtracted from all control and sample values. To determine the IC_{50} a sigmoidal curve was fitted to the plot of % inhibition of control P-IKKα levels versus Log_{10} compound concentration.

Biological assay C

Determination of antiproliferative activity on LP-1, L-363 and JJN-3 cells

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 LP-1, L-363 and JJN-3 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% CO_2 atmosphere. Cells were passaged at a seeding density of $0.2x10^6$ /ml twice a week. Cells were seeded in black tissue culture treated 96-well plates (Perkin Elmer). Densities used for plating ranged from 2,000 to 6,000 cells per well in a total volume of 75 µl medium. After twenty four hours, drugs and/or solvents were added (25 µl) to a final volume of 100 µl.

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Following 72 hr of treatment plates were removed from the incubator and allowed to equilibrate to room temperature for approx 10 min. 100 µl CellTiter-Glo reagent was added to each well that was then covered (Perkin Elmer Topseal) and shaken on plate shaker for 10 min. Luminescence was measured on a HTS Topcount (Perkin Elmer). Within an experiment, the results for each treatment were the mean of 2 replicate wells. For initial screening purposes, compounds were tested using a 9 point dilution curve (serial 1:3 dilutions). For each experiment, controls (containing no drug) and a blank incubation (containing cells read at the time of compound addition) were run in parallel. The blank value was subtracted from all control and sample values. For each sample, the mean value for cell growth (in relative light units) was expressed as a percentage of the mean value for cell growth of the control.

Data for the compounds of the invention in the above assays are provided in Table 20 (the values in Table 20 are averaged values over all measurements on all batches of a compound).

Table 20:

Compound	**Biochemical (MSD MBP) IC_{50} (nM)**	**Alpha-Screen IC50 (nM)**	**IKKα Cellular IC_{50} (nM)**	**JJN-3 EC_{50} (nM)**	**L-363 EC_{50} (nM)**	**LP-1 EC_{50} (nM)**
1	60	53	736	3337	6976	>30000
2	129	83	829	3949	4342	21344
3	58	28	173	2374	4037	7238
4	28	11	210	1151	1030	4718
5	16	14	71	1204	791	18811
6	19	26	1121	6876	10655	>30000
7	9	9	882	>30000	5393	>30000
8	21	7	406	3329	5856	9540
9	9	n.c.	89	526	553	3057
10	9	23	113	1214	3181	5073
11	6	21	20	258	283	916
12	47	22	185	1503	2449	8501
13	14	17	242	23780	11032	>30000

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Compound	Biochemical (MSD MBP) IC_{50} (nM)	Alpha-Screen IC50 (nM)	IKKα Cellular IC_{50} (nM)	JJN-3 EC_{50} (nM)	L-363 EC_{50} (nM)	LP-1 EC_{50} (nM)
14	18	108	132	1400	1329	12074
15	10	43	47	3846	>30000	>30000
16	92	99	523	4053	3143	20353
17	88	69	418	5859	11922	>30000
18	45	41	167	1867	2538	6822
19	65	98	602	704	570	11636
20	29	30	187	2652	2260	>30000
21	55	25	119	629	427	1118
22	224	232	1767	6075	5531	5227
23	57	43	302	848	625	1082
24	48	65	191	744	519	647
25	14	55	460	1898	2265	4981
26	n.c.	141	n.c.	3869	3334	5022
27	n.c.	290	n.c.	n.c.	n.c.	n.c.
28	n.c.	43	338	1527	1025	7381
29	n.c.	4	632	4174	2434	27150
30	29	23	149	1692	2410	8233
31	9	35	214	2378	3935	4902
32	68	44	1009	5671	22571	>30000
33	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
34	76	171	377	3660	2198	>30000
35	n.c.	23	n.c.	820	439	2667
36	n.c.	63	n.c.	1624	565	9589
37	n.c.	274	n.c.	5663	4908	>30000
38	n.c.	13	n.c.	1658	1323	3199
39	n.c.	47	n.c.	4607	3925	7998

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Compound	Biochemical (MSD MBP) IC_{50} (nM)	Alpha-Screen IC50 (nM)	IKKα Cellular IC_{50} (nM)	JJN-3 EC_{50} (nM)	L-363 EC_{50} (nM)	LP-1 EC_{50} (nM)
40	n.c.	38	n.c.	547	260	1946
41	n.c.	79	n.c.	1314	478	6111
42	n.c.	63	n.c.	2217	1026	2672
43	n.c.	44	n.c.	354	127	976
44	n.c.	84	n.c.	391	269	1539
45	n.c.	111	n.c.	415	277	1451
46	n.c.	13	n.c.	530	343	709
48	n.c.	14	n.c.	621	350	6093
49	n.c.	14	n.c.	1296	861	1696

n.c.: not calculated

Prophetic composition examples

"Active ingredient" (a.i.) as used throughout these examples relates to a compound of Formula (I), including any tautomer or stereoisomeric form thereof, or a pharmaceutically acceptable addition salt or a solvate thereof; in particular to any one of the exemplified compounds.

Typical examples of recipes for the formulation of the invention are as follows:

1. Tablets

Active ingredient	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg
Talcum	10 mg
Magnesium stearate	5 mg
Potato starch	ad 200 mg

2. Suspension

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

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A parenteral composition is prepared by stirring 1.5 % (weight/volume) of active ingredient in 0.9 % NaCl solution or in 10 % by volume propylene glycol in water.

4. Ointment

Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

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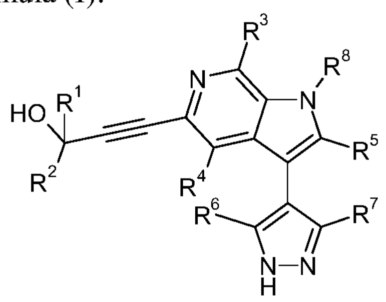
CLAIMS

1. A compound of Formula (I):



(I)

or a tautomer or a stereoisomeric form thereof, wherein

R^1 is selected from the group of hydrogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^2 is selected from the group of hydrogen; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; C_{3-6}cycloalkyl; and Het^1;

Het^1 is a heteroaryl selected from the group of thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, and isothiazolyl, each of which may be optionally substituted with one or two substituents independently selected from halogen and C_{1-4}alkyl;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^3 is selected from the group of hydrogen; halogen; cyano; C_{3-6}cycloalkyl; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or more fluoro substituents; $-OC_{1-6}$alkyl; $-OC_{1-6}$alkyl substituted with one or more fluoro substituents; and C_{1-6}alkyl substituted with one substituent selected from $-NR^{3a}R^{3b}$, -OH, and $-OC_{1-4}$alkyl;

R^{3a} and R^{3b} are each independently selected from hydrogen, and C_{1-4}alkyl;

R^4 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^5 is selected from the group of hydrogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^6 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

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R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; and $-NR^{7a}R^{7b}$; wherein

R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-4}alkyl;

R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with OH, $-OC_{1-4}$alkyl, and $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,
(ii) Het^3,
(iii) Ar^1,
(iv) $-NR^{8a}R^{8b}$,
(v) $-NR^{8c}C(=O)R^{8d}$,
(vi) $-NR^{8c}C(=O)NR^{8a}R^{8b}$,
(vii) $-NR^{8c}C(=O)OR^{8e}$,
(viii) $-NR^{8c}S(=O)_2NR^{8a}R^{8b}$,
(ix) $-NR^{8c}S(=O)_2R^{8d}$,
(x) $-OR^{8f}$,
(xi) $-OC(=O)NR^{8a}R^{8b}$,
(xii) $-C(=O)NR^{8a}R^{8b}$,
(xiii) $-S(O)_2R^{8d}$, and
(xiv) $-S(O)_2NR^{8a}R^{8b}$;

R^{8a}, R^{8b}, R^{8c} and R^{8f} are each independently selected from the group of hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl; and C_{2-6}alkyl substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1-4}$alkyl;

R^{8d} is selected from the group of C_{1-6}alkyl, which may be optionally substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1-4}$alkyl; and C_{3-6}cycloalkyl;

R^{8e} is selected from the group of C_{1-6}alkyl; C_{3-6}cycloalkyl; and C_{2-6}alkyl substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1-4}$alkyl;

wherein R^{8x} and R^{8y} are each independently selected from hydrogen and C_{1-4}alkyl;

Ar^1 is selected from the group of phenyl, thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl, each of which may be optionally substituted with one or two substituents independently selected from halogen, cyano, C_{1-4}alkyl, C_{1-4}alkyl substituted with one or more fluoro substituents, $-OC_{1-4}$alkyl, and $-OC_{1-4}$alkyl substituted with one or more fluoro substituents;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{3-6}cycloalkyl, C_{1-4}alkyl substituted with one $-OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{1-4}alkyl substituted with one $-OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

or a pharmaceutically acceptable addition salt or a solvate thereof.

2. The compound according to claim 1 wherein

R^3 is selected from the group of hydrogen; halogen; cyano; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or more fluoro substituents; $-OC_{1-6}$alkyl; $-OC_{1-6}$alkyl substituted with one or more fluoro substituents; and C_{1-6}alkyl substituted with one substituent selected from $-NR^{3a}R^{3b}$, -OH, and $-OC_{1-4}$alkyl;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one substituent selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one substituent selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents.

3. The compound according to claim 1 wherein

R^1 is selected from the group of hydrogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

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R^2 is selected from the group of C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; C_{3-6}cycloalkyl; and Het^1;

Het^1 is a heteroaryl selected from the group of thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, and isothiazolyl, each of which may be optionally substituted with one or two substituents independently selected from halogen and C_{1-4}alkyl;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^3 is selected from the group of hydrogen; halogen; cyano; C_{3-6}cycloalkyl; C_{1-6}alkyl; C_{1-6}alkyl substituted with one or more fluoro substituents; $-OC_{1-6}$alkyl; $-OC_{1-6}$alkyl substituted with one or more fluoro substituents; and C_{1-6}alkyl substituted with one substituent selected from $-NR^{3a}R^{3b}$, -OH, and $-OC_{1-4}$alkyl;

R^{3a} and R^{3b} are each independently selected from hydrogen, and C_{1-4}alkyl;

R^4 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^5 is selected from the group of hydrogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^6 is selected from the group of hydrogen; halogen; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; C_{1-4}alkyl substituted with one or more fluoro substituents; and $-NR^{7a}R^{7b}$; wherein

R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-4}alkyl;

R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with OH, $-OC_{1-4}$alkyl, and $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,
(ii) Het^3,
(iii) Ar^1,
(x) $-OR^{8f}$,

R^{8f} is selected from the group of hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkyl; and C_{2-6}alkyl substituted with one substituent selected from $-NR^{8x}R^{8y}$, -OH, and $-OC_{1-4}$alkyl;

Ar^1 is selected from the group of phenyl, thienyl, thiazolyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl, each of which may be optionally substituted with one or two substituents independently selected from halogen, cyano, C_{1-4}alkyl, C_{1-4}alkyl substituted with one or more fluoro substituents, $-OC_{1-4}$alkyl, and $-OC_{1-4}$alkyl substituted with one or more fluoro substituents;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{3-6}cycloalkyl, C_{1-4}alkyl substituted with one $-OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{1-4}alkyl substituted with one $-OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents.

4. The compound according to claim 1 wherein

R^1 is selected from the group of hydrogen; and C_{1-4}alkyl;

R^2 is selected from the group of C_{1-4}alkyl; C_{3-6}cycloalkyl; and Het^1;

Het^1 is a heteroaryl selected from the group of thiazolyl and isoxazolyl, each of which may be optionally substituted with one or two C_{1-4}alkyl substituents;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^3 is selected from the group of hydrogen and C_{1-6}alkyl;

R^4 is hydrogen;

R^5 is selected from the group of hydrogen and cyano;

R^6 is hydrogen;

R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; and $-NR^{7a}R^{7b}$; wherein R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-4}alkyl;

R^8 is selected from the group of hydrogen; $-SO_2C_{1-6}$alkyl optionally substituted with phenyl; Het^2; C_{3-6}cycloalkyl optionally substituted with $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,

(ii) Het^3,

(iii) Ar^1,

(x) $-OR^{8f}$,

R^{8f} is selected from the group of hydrogen and C_{1-6}alkyl;

Ar^1 is phenyl;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, pyrrolidinyl and azetidinyl, each of which may be optionally substituted with one or two substituents independently selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

Het^3 is a heterocyclyl selected from the group of tetrahydrofuranyl and oxetanyl.

5. The compound according to claim 1 wherein

R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents;

R^8 is selected from the group of $-SO_2C_{1-6}$alkyl; Het^2; C_{3-6}cycloalkyl optionally substituted with $-C_{1-4}$alkylOH; and C_{1-6}alkyl optionally substituted with one or more substituents independently selected from the group of

(i) fluoro,

(ii) Het^3,

(iii) Ar^1,

(x) $-OR^{8f}$,

R^{8f} is C_{1-6}alkyl;

Ar^1 is phenyl;

Het^2 is a heterocyclyl, bound through any available carbon atom, selected from the group of piperidinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, and oxetanyl, each of which may be optionally substituted with one or two substituents independently selected from fluoro, C_{1-4}alkyl, $-OC_{1-4}$alkyl, C_{3-6}cycloalkyl, C_{1-4}alkyl substituted with one $-OC_{1-4}$alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents;

Het^3 is a heterocyclyl selected from the group of morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranyl, and azetidinyl, each of which may be optionally substituted with one or two substituents independently selected from

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fluoro, C_{1-4}alkyl, -OC_{1-4}alkyl, C_{1-4}alkyl substituted with one -OC_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro substituents.

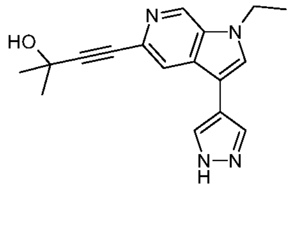
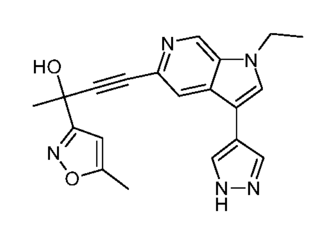
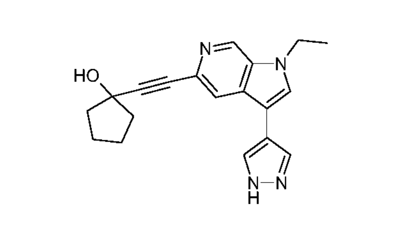
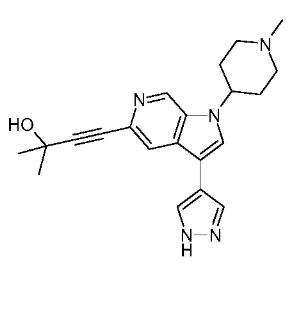
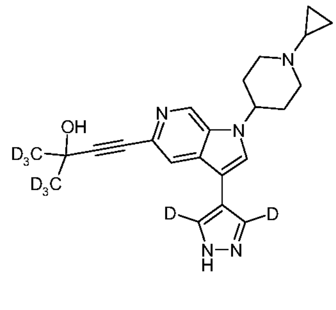
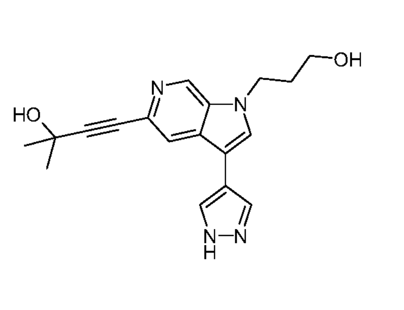
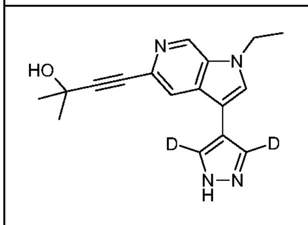
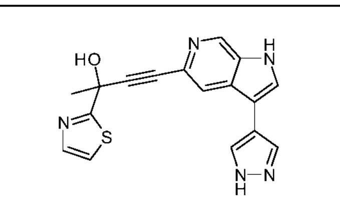
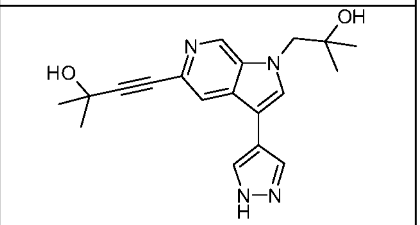
6. The compound according to claim 1 wherein
R^1 is selected from the group of C_{1-4}alkyl;
R^2 is selected from the group of C_{1-4}alkyl and Het^1;
Het^1 is a heteroaryl selected from the group of thiazolyl and isoxazolyl, each of which may be optionally substituted with one or two C_{1-4}alkyl substituents;
or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 is hydrogen;
R^6 is hydrogen;
R^7 is hydrogen;
R^8 is selected from the group of hydrogen, Het^2 and C_{1-6}alkyl optionally substituted with one or more OH substituents
Het^2 is piperidinyl, bound through any available carbon atom, substituted with one or two substituents independently selected from C_{1-4}alkyl and C_{3-6}cycloalkyl.

7. The compound according to any one of claims 1, 2, 3 or 4, wherein R^1 is C_{1-4}alkyl; R^2 is selected from the group of C_{1-4}alkyl and Het^1; or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl.

8. The compound according to claim 7, wherein R^1 is C_{1-4}alkyl; R^2 is selected from the group of C_{1-4}alkyl and Het^1.

9. The compound according to any one of claims 1, 2 or 3 wherein R^6 is hydrogen; and R^7 is selected from the group of hydrogen; halogen; cyano; C_{1-4}alkyl; and C_{1-4}alkyl substituted with one or more fluoro substituents

10. The compound according to claim 1, wherein the compound is selected from

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

11. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 10 and a pharmaceutically acceptable carrier or diluent.

12. A compound as claimed in any one of claims 1 to 10 for use as a medicament.

13. A compound as claimed in any one of claims 1 to 10 for use in the prevention or treatment of cancer.

14. A pharmaceutical composition as claimed in claim 11 for use in the prevention or treatment of cancer.

15. A method of treating or preventing a cell proliferative disease modulated by NIK/MAP3K14, P-IKKα, LP-1, L-363 or JN-3 inhibition in a warm-blooded animal which comprises administering to the said animal an effective amount of a compound as claimed in any one of claims 1 to 10.

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16. Use of a compound according to any one of claims 1-10 in the manufacture of a medicament for the treatment or prevention of a cell proliferative disease modulated by NIK/MAP3K14, P-IKKα, LP-1, L-363 or JN-3 inhibition.