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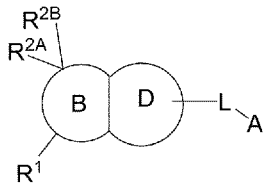

(I)

(57) **Abstract:** The present invention provides novel compounds of formula (I) and pharmaceutical compositions containing these compounds. The compounds of formula (I) can act as PAR-2 inhibitors, which renders these compounds highly advantageous for use in therapy, particularly in the treatment or prevention of pain, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a central nervous system disorder, spinal cord injury, a metabolic disorder, a gastrointestinal disorder, a cardiovascular disorder, a fibrotic disorder, a respiratory disorder, a skin disorder, an allergic disorder, or cancer (I).

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Novel PAR-2 inhibitors

The present invention provides novel compounds of formula (I) and pharmaceutical compositions containing these compounds. The compounds of formula (I) can act as PAR-2 inhibitors, which renders these compounds highly advantageous for use in therapy, particularly in the treatment or prevention of pain, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a central nervous system disorder, spinal cord injury, a metabolic disorder, a gastrointestinal disorder, a cardiovascular disorder, a fibrotic disorder, a respiratory disorder, a skin disorder, an allergic disorder, or cancer.

The protease-activated receptors (PARs) family

G Protein-Coupled Receptors (GPCRs) form the largest family of human membrane proteins (~ 800 members) and are involved in many physiological processes. Compounds targeting GPCRs also represent approximately 27% of the global market for therapeutic drugs (Hauser et al., *Nat. Rev. Drug Discov.*, 2017, 16(12):829-842).

2% of the human genome code for proteases (also called proteinases) which suggests their importance in the correct functioning of the body (Hollenberg et al., *Br. J. Pharmacol.*, 2014, 171(5):1180-94). Indeed, it has been shown that certain soluble and membrane-bound proteinases can regulate cell function by cleaving GPCRs at the cell surface to activate or inactivate receptors such as the Protease-Activated Receptors (PARs). The PARs family is composed of four members (PAR-1, PAR-2, PAR-3 and PAR-4) and belongs to the class A GPCR-receptor sub-family (Marcfarlane et al., *Pharmacological Reviews*, 2001, 475(7357):519-23). They are expressed in widely diverse cells such as platelets, immune cells, endothelial cells, myocytes, astrocytes, neurons, epithelial cells and fibroblasts and involved in a large set of physiological and pathophysiological functions (Ossovskaya et al., *Physiol. Rev.*, 2004, 84(2):579-621).

PAR-2: mechanism of action

Activation of PARs involves the cleavage of the extracellular N-terminal part of the receptor by proteases at a specific site. This unmasks an amino-acid sequence in the amino terminus that folds back to act as a “tethered ligand” (TL): it binds to a conserved region in the second extracellular loop of the cleaved receptor and triggers intra-cellular signalling (Ossovskaya et al., *Physiol. Rev.*, 2004, 84(2):579-621; Hollenberg et al., *Br. J. Pharmacol.*, 2014, 171(5):1180-94).

PAR-2 is activated by several host and pathogen-derived serine proteases such as trypsin, mast cell tryptase, kallikreins and members of the coagulation cascade TF-FVIIa and FVa-FXa. These proteases cleave at $R^{34}\downarrow S^{35}$LIGKV and unmask the tethered ligand SLIGKV in humans. Artificially, *in vitro*, synthetic peptides corresponding to the TL (SLIGKV) can activate the receptor without cleavage.

Activation of PAR-2 induces several signalling cascades involving a number of G proteins such as G_q, G_i, and $G_{12/13}$. The pathway best described so far involves its interaction with G_q and the mobilization of intracellular calcium that influences the function of several cell types. After repeated activations, PAR2 is rapidly desensitized via its endocytosis by a β-arrestin-dependent mechanism and its targeting to the lysosomes (Ossovskaya et al., *Physiol. Rev.*, 2004, 84(2):579-621).

PAR-2 in physiological conditions

PAR-2 has been shown to have a key function in multiple organs (Ossovskaya et al., *Physiol. Rev.*, 2004, 84(2):579-621). PAR-2 is expressed in the brain within neurons and glial cells. It is also found in the periphery in spinal afferent neurons and nociceptive DRG neurons. PAR-2 signalling has been involved in the survival, sensitization of these cells and their signal transmission, thereby controlling neuronal damage, inflammation and pain.

PAR-2 is involved in the function of the cardiovascular system. Indeed, its activation can induce the relaxation or contraction of some vessels such as pulmonary arteries, coronary and intramyocardial arteries, therefore regulating the blood flow. It also controls inflammation and repair of the endothelium which influences vascular permeability.

PAR-2 expression has been detected within the gastrointestinal system in the small intestine, colon, liver, pancreas and stomach. Its activation has been involved in the regulation of ion transport from the intestinal mucosa, contraction of gastric longitudinal muscle, pancreatic, salivary and gastric secretions, excitation of myenteric neurons, intestinal barrier integrity, release of prostaglandins from enterocytes. PAR-2 therefore plays a key role in controlling fluid secretion, intestinal inflammation, and gastro-intestinal hyperalgesia.

PAR-2 is involved in airways function since it is expressed by epithelial and endothelial cells in the lungs. Its activation has been shown to regulate bronchodilatation or bronchoconstriction (depending on the experimental system used), ion transport in the airway epithelium, proliferation and activation of airway smooth muscle cells and lung fibroblasts. PAR-2 can thus regulate airway resistance, lung inflammation and lung fibrosis.

In the skin, PAR-2 expression has been detected in keratinocytes, microvasculature and immune cells. Its activation has been involved in skin pigmentation, skin inflammation, and wound healing.

Finally, PAR-2 expression has been detected in immune cells such as macrophages where it influences cell maturation and cytokine secretion, thereby regulating inflammation.

PAR-2 in pathological conditions

Since PAR-2 regulates numerous and diverse biological processes, it is not surprising that its dysfunction is involved in as many pathological conditions.

PAR-2 is expressed in the brain, dorsal root ganglia, spinal afferent neurons and nociceptive DRG neurons. Its activation by proteases such as the tryptase released by mast cells leads to calcium and cAMP signalling (Steinhoff et al., *Nat Med*, 2000, 6(2):151-8; Zhao et al., *J Biol Chem.*, 2015, 290(22):13875-87). This promotes inflammation and hyperalgesia through the release of CGRP (calcitonine gene-related peptide) and SP (substance P) from spinal afferent neurons and the sensitization of Transient Receptors Potential Vanilloid (TRPV) TRPV1 and TRPV4 in sensory neurons (Vergnolle et al., *Nat Med*, 2001, 6(2):151-8; Steinhoff et al., *Nat Med*, 2000, 6(2):151-8; Amadesi et al., *J Neurosci*, 2004, 24(18):4300-12; Grant et al., *J Physiol*, 2007, 578 (Pt 3), 715-33; Jimenez Vargas et al., *Proc Natl Acad Sci USA*, 2018, 115(31):E7438-E7447). This is supported by the large amount *of in vivo* data available in the literature demonstrating that inhibition of PAR-2 reduces inflammatory pain, neuropathic pain, cancer pain and treatment-induced pain in animal models (Bao et al., *Expert Opin Ther Targets*, 2014; 18(1):15-27; Chen et al., *Neuroscience*, 2011, 193, 440-51). PAR-2 is therefore clearly involved in the generation and the transmission of the pain signal, neurogenic inflammation and nociception.

The expression of PAR-2 and proteases is elevated in the spinal cord after a contusion-compression injury (Radulovic et al., *Neurobiol Dis*, 2015, 83, 75-89; Li et al, *Physiol. Res.*, 2019, 68(2):305-316). Its activation can result in cAMP signalling in oligodendrocytes (Yoon et al., *Glia*, 2017, 65(12):2070-2086). Experiments *in vitro* and *in vivo* in rodents

have shown that the inhibition of PAR-2 signalling during experimental spinal cord injury reduces inflammation, scar formation and mechanical and thermal hyperalgesia and improves remyelination of oligodendrocytes and locomotor recovery (Radulovic et al., *Neurobiol Dis*, 2015, 83, 75-89; Li et al, *Physiol. Res.*, 2019, 68(2):305-316; Yoon et al., *Glia*, 2017, 65(12):2070-2086; Li et al, *Physiol. Res.*, 2019, 68(2):305-316 ; Wei et al, *Physiol. Res.*, 2016, 65(1):145-53). PAR-2 inhibitors can thus improve recovery from spinal cord injuries.

Disorders of the immune system are at the basis of numerous diseases. In all cases, the immune system attacks the normal constituents of the organism considering them as foreign. It becomes pathogenic and induces lesions on a specific organ (e.g., type 1 diabetes in the pancreas or multiple sclerosis in the brain) or systemically (e.g., rheumatoid arthritis or systemic lupus erythematosus, SLE).

Cytokines are small proteins involved in cell signalling that orchestrate the immune response. Their dysregulation is at the basis of the pathogenesis of autoinflammatory diseases. These conditions are characterized by immune activation, infiltration and abnormal cytokine production. They include conditions such as: rheumatologic inflammatory diseases, skin inflammatory diseases, lung inflammatory diseases, muscle inflammatory diseases, bowel inflammatory diseases, brain inflammatory diseases and autoimmune diseases.

While autoinflammatory diseases evolve chronically, some conditions can lead to an acute immune disorder. Indeed, a sudden excessive and uncontrolled release of pro-inflammatory cytokines, also called cytokine storm, has been observed in graft-versus-host disease, multiple sclerosis, pancreatitis, multiple organ dysfunction syndrome, viral diseases, bacterial infections, hemophagocytic lymphohistiocytosis, and sepsis (Gerlach H, *F1000Res,* 2016, 5, 2909; Tisoncik JR et al., *Microbiol Mol Biol Rev*, 2012, 76(1):16-32). In these conditions, a dysregulated immune response and subsequent hyperinflammation may lead to multiple organ failure that can be fatal.

Because PAR-2 influences the production of inflammatory cytokines and the function of diverse organs, numerous studies have demonstrated that it is a promising therapeutic target for various autoinflammatory diseases.

The expression of proteinases and PAR-2 is significantly increased in organs directly involved in autoinflammatory diseases such as the coronary arteries of atherosclerotic patients (Jones et al., *Arterioscler Thromb Vasc Biol*, 2018, 38(6):1271-1282), the skin of atopic dermatitis and psoriasis patients (Nattkemper et al., *Journal of Investigative Dermatology*, 2018, 138:1311-1317), the joints of rheumatoid arthritis and osteoarthritis patients (Tindell et al., *Rheum Int*, 2012, 32(10):3077-86), the colon of inflammatory bowel disease patients (Christerson et al., *J Crohns Colitis*, 2009, 3(1):15-24; Kim et al., *Inflamm Bowel Dis.*, 2003, 9(4):224-9), the lungs of idiopathic pulmonary fibrosis patients (Bardou et al., *Am J Respir Crit Care Med*, 2016, 193(8):847-60), the liver of non-alcoholic steatohepatitis patients (Rana et al., *Mol Metab*, 2019, 29:99-113), the area of active demyelination in the brain of multiple sclerosis patients (Noorbakhsh et al., *J Exp Med*, 2006, 203(2):425-35).

There, PAR-2 activation leads to calcium signalling in several cells such as osteoblasts, fibroblasts, monocytes, keratinocytes (Abraham et al, *Bone*, 2000, 26(1):7-14; Lin et al., *J. Cell. Mol. Med.*, 2015, 19(6):1346-56; Johansson et al., *J leukoc Biol,* 2005, 78(4):967-75; Joo et al., *Bio Mol Ther*, 2016, 24(5):529-535). This signalling is associated with cell maturation and/or migration, activation as well as the secretion of inflammatory cytokines such as IL-8, IL-6, TNFα and IL-1β in various cell types such as vascular smooth muscle cells, synovial cells, monocytes, keratinocytes, astrocytes, chondrocytes, adipocytes and fibroblasts (Demetz et al., *Atherosclerosis*, 2010, 212:466-471; Kelso et al., *Arthritis Rheum*, 2007, 56(3):765-71; Johansson et al., *J Leukoc Biol*, 2005, 78(4):967-75; Steven et al., *Innate Immun*, 2013, 19(6):663-72; Kim et al., *Bio Mol Ther*, 2012, 20(5):463-9; Radulovic et al., *Neurobiol Dis*, 2015, 83, 75-89; Lin et al., *J. Cell. Mol. Med.*, 2015, 19(6):1346-56; Bagher et al., *Cell Communi and Signal*, 2018, 16(1), 59;

Huang et al, *Aging*, 2019, 11(24):12532-12545; Bandeanlou et al., *Nat. Med.*, 2011, 17:1490-1497). PAR-2 signalling also influences tissue remodelling through its role in the survival of key cells such as neurons and chondrocytes in central nervous system disorders and rheumatologic inflammatory diseases respectively (Afkhami-Goli et al., *J Immunol*, 2007, 179(8):5493-503; Huang et al., *Aging*, 2019, 11(24):12532-12545), as well as the secretion of growth factors (e.g. CTGF) and extracellular components (e.g. collagen) (Lin et al., *Mol. Med.*, 2015, 21(1):576-83; Chung et al., *J Biol Chem*, 2013, 288(52):37319-31). It is important to note that other signalling pathways such as cyclic AMP in alveolar macrophages and Gi in hepatocytes seem important to regulate cytokine secretion and steatosis respectively (Rayees et al., *Cell Rep*, 2019, 27(3):793-805.e4; Rana et al., *Mol Metab*, 2019, 29, 99-113).

In vivo, it has clearly been shown that the inhibition of PAR-2 signaling, either pharmacologically or by genetic modification, significantly reduced the symptoms of atherosclerosis, idiopathic pulmonary fibrosis, atopic dermatitis, multiple sclerosis, arthritis, non-alcoholic steatohepatitis and inflammatory bowel disease in mouse models (Jones et al., *Arterioscler Thromb Vasc Biol*, 2018, 38(6):1271-1282; Borensztajn et al., *Am J Pathol*, 2010, 177(6):2753-64; Moniaga et al., *Am J Pathol*, 2013, 182: 841e851; Noorbakhsh et al., *J Exp Med*, 2006, 203(2):425-35, Ferrell et al., *J Clin Invest*, 2003, 111(1):35-41; Rana et al., *Mol Metab*, 2019, 29:99-113; Hyun et al., *Gut*, 2008, 57(9):1222-9). PAR-2 therefore plays a key role in the molecular and cellular mechanisms underlying the pathogenesis of autoinflammatory diseases.

PAR-2-dependent inflammation can also impair cellular metabolism and promote insulin resistance which then leads to the pathogenesis of diabetes, obesity and metabolic syndrome. Indeed, PAR-2 expression in adipocyte tissues has been correlated with the increasing BMI of volunteer people and the inhibition of PAR-2 signaling attenuates the symptoms of metabolic disorders in mice (Lim et al., *FASEB Journal*, 2013, 27(12):4757-4767; Badeanlou et al., *Nat. Med.*, 2011, 17(11):1490-1497).

Many airborne allergens from house dust mite and cockroach allergens contain protease activity. This protease activity can activate PAR-2 expressed on human airway epithelial cells, endothelial cells as well as immune cells and induce calcium signalling. This ultimately leads to the release of inflammatory cytokines and angiogenic response at the basis of the pathogenesis of cockroach allergy and allergic asthma (Do et al., *Allergy*, 2016, 71(4):463-74; Asosingh et al., *J Clin Invest*, 2018, 128(7):3116-3128). *In vivo*, functional blockade of PAR-2 in the airways during allergen challenge improves allergen-induced inflammation and airway hyperresponsiveness in mice (Asaduzzaman et al., *Clin Exp Allergy*, 2015, 45(12):1844-55).

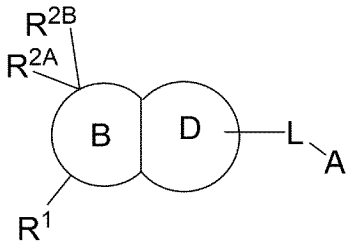
The expression of PAR-2 and proteases is also significantly increased in many cancer types such as cervical squamous cell carcinoma, endocervical adenocarcinoma, colon adenocarcinoma, esophageal carcinoma, glioblastoma multiforme, acute myeloid leukemia, lung adenocarcinoma, lung squamous cell carcinoma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, prostate adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, testicular germ cell tumors, uterine corpus endometrial carcinoma, uterine carcinosarcoma, hepatocellular carcinoma, and breast cancer, which can be associated to poor prognosis (Kaufmann et al., *Carcinogenesis*, 2009, 30(9):1487-96; Su et al., *Oncogene*, 2009, 28(34):3047-57; Arakaki et al., *Int. J. Mol. Sci.* 2018, 19, 1886). The activation of this receptor in cancer cells can lead to several signalling cascades such as calcium, β-arrestin and Gi signalling (Kaufmann et al., *J Cancer Res Clin Oncol*, 2011, 137(6):965-73; Wu et al, *Mol Med Rep*, 2014, 10(6):3021-6; Ge et al., *J Biol Chem*, 2004, 279(53):55419-24). This ultimately controls cancer cell migration, proliferation, survival, and expression of inflammatory cytokines (Jiang et al., *J Pharmacol Exp Ther*, 2018, 364(2):246-257; Darmoul et al., *British J Cancer*, 2001, 85(5):772-9; Quan et al., *Oncol Res.*, 2019, 27(7):779-788).

The expression of PAR-2 on other cells of the tumor microenvironment, such as immune cells, fibroblasts, endothelial cells and DRG neurons, can also control the immune response to cancer cells, fibrosis, as well as angiogenesis and cancer-induced pain (Mubbach et al., *Mol cancer*, 2016, 15(1):54; Uusitalo-Jarvinen et al., *Arteriocler Thromb Vasc Biol*, 2007, 27(6):1456-62; D'Andrea et al, *Am J Pathol*, 2001, 158(6):2031-41; Graf et al, *Sci Immunol*, 2019, 4(39):eaaw8405; Qian at al., *Oncol Lett*, 2018, 16(2):1513-20; Tu et al, *J Neurosci*, 2021, 41(1):193-210). *In vivo*, the inhibition of PAR-2 has been shown to be an efficient way of reducing tumor growth and increasing survival in mouse models of different cancers such as breast cancer, liver cancer and colon cancer (Versteeg et al., *Cancer Res*, 2008, 68(17):7219-27; Sun et al., *World J Gastroenterol*, 2018, 24(10):1120-1133; Quan et al., *Oncol Res.*, 2019, 27(7):779-788). Importantly, inhibition of PAR2 or one of its ligands led to reduced infiltration of immune-supressive Tumor Associated Macrophages and regulatory T cells while increasing cytotoxic T cells in the tumor as well as increasing antigen presenting cells in the draining lymph nodes in several syngeneic mouse models; this unleashed the anti-tumoral immune response and increased the potency of immune-checkpoint inhibitors currently used in the clinic (Graf et al, *Sci Immunol*, 2019, 4(39):eaaw8405). PAR-2 therefore constitutes a promising therapeutic target in oncology and immune-oncology.

Considering the role of PAR-2 in several pathophysiological conditions, inhibitors of this receptor can have therapeutic applications in a wide variety of human diseases. This has drawn a great interest from pharmaceutical industry to develop such compounds. Various PAR-2 inhibitors and therapeutic uses thereof have been proposed, for example, in: Yau et al., *Expert Opin Ther Pat*, 2016, 26(4):471-83; Jiang et al., *J Pharmacol Exp Ther*, 2018, 364(2):246-57; WO 2004/002418; WO 2005/030773; WO 2012/012843; WO 2012/026765; WO 2012/026766; WO 2012/101453; WO 2015/048245; WO 2016/154075; WO 2017/194716; WO 2017/197463; WO 2018/043461 (EP 3 508 487); WO 2018/057588; WO 2019/163956 (EP 3 760 631); WO 2019/199800; JP 2020/007262; and WO 2021/106864. However, despite the efforts made in the past 10 years, no PAR-2 inhibitor has reached the market yet (Yau et al., *Expert Opin Ther Pat.*, 2016, 26(4):471-83). There is therefore still an unmet need for novel and/or improved PAR-2 inhibitors with high potency, selectivity and bioavailability.

The present invention addresses this need and solves the problem of providing novel and highly potent PAR-2 inhibitors. In particular, it has surprisingly been found that the compounds of formula (I) as provided herein are potent inhibitors of PAR-2 signalling, which renders these compounds advantageous for use in therapy, including in particular in the treatment or prevention of pain, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a central nervous system disorder, spinal cord injury, a metabolic disorder, a gastrointestinal disorder, a cardiovascular disorder, a fibrotic disorder, a respiratory disorder, a skin disorder, an allergic disorder, or cancer.

Accordingly, the present invention provides a compound of the following formula (I)



(I)

or a pharmaceutically acceptable salt or solvate thereof.

In formula (I), ring B is a non-aromatic C_{4-8} carbocyclic ring or a non-aromatic 4- to 8-membered heterocyclic ring, which is fused to ring D, wherein said carbocyclic ring or said heterocyclic ring is: (i) substituted with a group R^1; (ii) substituted with the groups R^{2A} and R^{2B} which are attached to the same ring carbon atom of said carbocyclic ring or said heterocyclic ring; and (iii) optionally substituted with one or more groups R^Y.

Ring D is a 5- or 6-membered heteroaromatic ring, which is fused to ring B, wherein said heteroaromatic ring comprises at least one nitrogen ring atom, wherein said heteroaromatic ring is substituted with a group -L-A, and wherein said heteroaromatic ring is optionally substituted with one or more groups R^X.

R^1 is selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-5} alkylene)-carbocyclyl, and -(C_{0-5} alkylene)-heterocyclyl, wherein said alkyl, said alkenyl, said alkynyl, the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, and the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{12}, wherein one or more -CH_2- units comprised in said alkyl, said alkenyl, said alkynyl, in the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, or in the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally replaced by a group independently selected from -C(R^{L1})(R^{L1})-, -O-, -S-, -SO-, -SO_2-, -CO-, and -N(R^{L1})-, wherein each R^{L1} is independently hydrogen or C_{1-5} alkyl, wherein two groups R^{L1} which are attached to the same carbon atom may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or a heterocycloalkyl, and wherein the carbocyclyl group in said -(C_{0-5} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{11}.

Each R^{11} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3}

alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc}.

Each R^{12} is independently selected from -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), carbocyclyl, heterocyclyl, and -L^Z-R^Z, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more groups R^{Cyc}.

R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, wherein said cycloalkyl, said cycloalkenyl, said heterocycloalkyl or said heterocycloalkenyl is optionally substituted with one or more groups R^{21};
or R^{2A} and R^{2B} are each independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-5} alkylene)-carbocyclyl, and -(C_{0-5} alkylene)-heterocyclyl, wherein said alkyl, said alkenyl, said alkynyl, the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, and the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{22}, wherein one or more -CH_2- units comprised in said alkyl, said alkenyl, said alkynyl, in the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, or in the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-, and further wherein the carbocyclyl group in said -(C_{0-5} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc},
wherein R^{2A} and a group R^Y may also be mutually joined to form, together with the ring atoms that they are attached to, a carbocyclyl or heterocyclyl, wherein said carbocyclyl or said heterocyclyl is optionally substituted with one or more groups R^{Cyc}.

Each R^{21} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5}

alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc}.

Each R^{22} is independently selected from -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), carbocyclyl, heterocyclyl, and -L^Z-R^Z, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more groups R^{Cyc}.

Each R^X is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc}.

Each R^Y is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3}

alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc};

wherein any two groups R^Y which are attached to the same ring carbon atom (i) may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or a heterocycloalkyl, wherein said cycloalkyl or said heterocycloalkyl is optionally substituted with one or more groups R^{Cyc}, or (ii) may mutually form a group =O.

L is selected from -CO-, -SO- and -SO_2-.

The group A is -N(-R^N)-R^N or heterocyclyl, wherein said heterocyclyl is attached via a ring nitrogen atom to group L, and wherein said heterocyclyl is optionally substituted with one or more groups R^A.

Each R^N is independently selected from hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, -(C_{0-8} alkylene)-OH, -(C_{0-8} alkylene)-O(C_{1-5} alkyl), -(C_{0-8} alkylene)-SH, -(C_{0-8} alkylene)-S(C_{1-5} alkyl), -(C_{1-8} alkylene)-NH_2, -(C_{1-8} alkylene)-NH(C_{1-5} alkyl), -(C_{1-8} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-8} alkylene)-halogen, -(C_{1-8} alkylene)-C_{1-5} haloalkyl, -(C_{0-8} alkylene)-O-(C_{1-8} haloalkyl), -(C_{0-8} alkylene)-CN, -(C_{0-8} alkylene)-CHO, -(C_{0-8} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-8} alkylene)-COOH, -(C_{0-8} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-8} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-8} alkylene)-CO-NH_2, -(C_{0-8} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-8} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-8} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{1-8} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{1-8} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{1-8} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-8} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-8} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-8} alkylene)-SO_2-NH_2, -(C_{0-8} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-8} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-8} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{1-8} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-8} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-8} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-8} alkylene)-carbocyclyl, and -(C_{0-8} alkylene)-heterocyclyl, wherein one or more -CH_2- units comprised in said C_{1-8} alkyl, said C_{2-8} alkenyl, said C_{2-8} alkynyl, and in any of the aforementioned C_{0-8} alkylene and C_{1-8} alkylene groups are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-, wherein the carbocyclyl group in said -(C_{0-8} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-8} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc}, and wherein at least one group R^N is not hydrogen.

Each R^A is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3}

alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc}; and further wherein any two groups R^A, which are attached to the same carbon atom of group A, may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or a heterocycloalkyl, wherein said cycloalkyl or said heterocycloalkyl is optionally substituted with one or more groups R^{Cyc}.

Each R^{Cyc} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO(C_{1-5} alkyl), -COOH, -COO(C_{1-5} alkyl), -O-CO(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -P(=O)(-OH)(-OH), -P(=O)(-OH)(-O-C_{1-5} alkyl), -P(=O)(-O-C_{1-5} alkyl)(-O-C_{1-5} alkyl), -(C_{0-3} alkylene)-cycloalkyl, -(C_{0-3} alkylene)-heterocycloalkyl, and -L^Z-R^Z.

Each L^Z is independently selected from a covalent bond, C_{1-7} alkylene, C_{2-7} alkenylene, and C_{2-7} alkynylene, wherein said alkylene, said alkenylene and said alkynylene are each optionally substituted with one or more groups independently selected from halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), and -N(C_{1-5} alkyl)(C_{1-5} alkyl), and further wherein one or more -CH_2- units comprised in said alkylene, said alkenylene or said alkynylene are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-.

Each R^Z is independently selected from -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO(C_{1-5} alkyl), -COOH, -COO(C_{1-5} alkyl), -O-CO(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5}

alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, wherein said aryl, said heteroaryl, said cycloalkyl, and said heterocycloalkyl are each optionally substituted with one or more groups independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), carbocyclyl, and heterocyclyl, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more groups independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), and -SO_2-(C_{1-5} alkyl).

Preferably, the following proviso applies to the compounds of formula (I):

– if ring B is a pyrrolidinyl ring, ring D is a pyridinyl ring, R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a cyclopropyl, L is -CO-, and group A is morpholin-4-yl, then R^1 is not 5-R^{11}-pyrimidin-2-yl or acetyl;

– if ring B and ring D together are a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-c]pyridinyl ring or a 6-oxo-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazinyl ring, R^{2A} and R^{2B} are each methyl, R^1 is phenyl which is optionally substituted with one or more groups R^{11}, L is -CO-, and group A is -NH-R^N, then R^N is not a heterocycloalkyl which comprises one oxidized sulfur ring atom, in which all other ring atoms are carbon atoms, and which is substituted with a methyl group;

– if ring B and ring D together are a 3-R^X-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazinyl ring, R^X is -OH, one of R^{2A} and R^{2B} is methyl, the other one of R^{2A} and R^{2B} is -CON(-CH_3)$_2$, R^1 is methyl, L is -CO-, and group A is -NH-R^N, then R^N is not 4-fluorobenzyl; and

– if ring B and ring D together are a 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine ring or a 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine, L is -CO-, group A is -NH-R^N, and R^1 is -CH_2-phenyl or -CH_2-pyridinyl, wherein the phenyl in said -CH_2-phenyl and the pyridinyl in said -CH_2-pyridinyl are each optionally substituted with one or more groups R^{11}, then R^{2A} and R^{2B} are not methyl.

The present invention also relates to a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable excipient. Accordingly, the invention relates to a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising any of the aforementioned entities and a pharmaceutically acceptable excipient, for use as a medicament.

The invention further relates to a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising any of the aforementioned entities and a pharmaceutically acceptable excipient, for use in the treatment or prevention of a PAR-2 mediated disease or disorder. Thus, the invention in particular provides a pharmaceutical composition comprising, as an active ingredient, a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, for use in the treatment or prevention of a PAR-2 mediated disease or disorder.

Moreover, the present invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for the treatment or prevention of a PAR-2 mediated disease or disorder.

The invention likewise relates to a method of treating or preventing a PAR-2 mediated disease or disorder, the method comprising administering a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising any of the aforementioned entities in combination with a pharmaceutically acceptable excipient, to a subject (preferably a human) in need thereof. It will be understood that a therapeutically effective amount of the compound of formula (I) or the pharmaceutically acceptable salt or solvate thereof (or of the pharmaceutical composition) is to be administered in accordance with this method.

As explained above, the disease or disorder to be treated or prevented with a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof (or a corresponding pharmaceutical composition) in accordance with the present invention includes any PAR-2 mediated disease or disorder. It is preferred that the disease/disorder to be treated or prevented in accordance with the invention is pain (e.g., chronic pain), an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder (e.g., a rheumatologic inflammatory disorder, a skin inflammatory disorder, a lung inflammatory disorder, a muscle inflammatory disorder, a bowel inflammatory disorder, or a brain inflammatory disorder), a central nervous system disorder, spinal cord injury, a metabolic disorder, a gastrointestinal disorder, a cardiovascular disorder, a fibrotic disorder, a respiratory disorder, a skin disorder, an allergic disorder, or cancer. More preferably, the disease/disorder to be treated or prevented in accordance with the present invention is selected from neuropathic pain, inflammatory pain, cancer pain, post-operative incision pain, fracture pain, osteoporotic fracture pain, gout joint pain, chronic pain, spinal cord injury, atopic dermatitis, contact dermatitis, dry skin dermatitis, seborrhoeic dermatitis, arthritis, rheumatoid arthritis, osteoarthritis, psoriasis, psoriatic arthritis, multiple sclerosis, non-alcoholic steatohepatitis (NASH), obesity (e.g., diet-induced obesity), diabetes (e.g., type 1 diabetes or type 2 diabetes), adipose inflammation, pancreatitis, metabolic syndrome, PAR-2 associated metabolic dysfunction, periodontitis, gingivitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, peptic ulcer disease (e.g., gastric ulcer or duodenal ulcer), infectious enteritis, irritable bowel syndrome, atherosclerosis, asthma, interstitial lung disease, pulmonary fibrosis (e.g., idiopathic pulmonary fibrosis), rheumatoid arthritis-associated interstitial lung disease, liver fibrosis, cystic fibrosis, renal fibrosis, peritoneal fibrosis, pancreatic fibrosis, intestinal fibrosis, cardiac fibrosis, skin fibrosis, systemic lupus erythematosus (SLE), scleroderma, skin eczema, acne, rosacea, post-inflammatory hyperpigmentation, lichen planus, pruritus, polymyositis, vasculitis, Wegener's granulomatosis (or granulomatosis with polyangiitis), Netherton syndrome, dermatomyositis, uveitis, liver cirrhosis,

Alzheimer's disease, Parkinson's disease, dust mite allergy (e.g., house dust mite allergy), cockroach allergy, allergic asthma, colorectal cancer, colon cancer (e.g., colon adenocarcinoma), gastric cancer (e.g., stomach adenocarcinoma), rectal cancer (e.g., rectum adenocarcinoma), liver cancer (e.g., hepatocellular carcinoma), breast cancer, pancreatic cancer (e.g., pancreatic adenocarcinoma or pancreatic ductal adenocarcinoma), cervical cancer (e.g., cervical squamous cell carcinoma or endocervical adenocarcinoma), prostate cancer (e.g., prostate adenocarcinoma), ovarian cancer (e.g., ovarian serous cystadenocarcinoma), endometrial cancer (e.g., uterine corpus endometrial carcinoma), uterine sarcoma (e.g., uterine carcinosarcoma), germ cell cancer (e.g., testicular germ cell cancer), esophageal cancer, leukemia (e.g., acute myeloid leukemia), lung cancer (e.g., lung adenocarcinoma or lung squamous cell carcinoma), adrenal gland cancer (e.g., adrenocortical carcinoma), bile duct cancer (e.g., cholangio carcinoma), bladder cancer (e.g., bladder urothelial carcinoma), head and neck cancer, kidney cancer (e.g., kidney chromophobe, kidney renal cell carcinoma, kidney renal clear cell carcinoma, or kidney renal papillary cell carcinoma), lymphoma (e.g., lymphoid neoplasm diffuse large B-cell lymphoma), mesothelioma, sarcoma, melanoma (e.g., skin cutaneous melanoma, or uveal melanoma), thyroid carcinoma, thymus cancer (e.g., thymoma), or glioblastoma.

Accordingly, the present invention particularly relates to a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising any of the aforementioned entities and a pharmaceutically acceptable excipient, for use in the treatment or prevention of neuropathic pain, inflammatory pain, cancer pain, post-operative incision pain, fracture pain, osteoporotic fracture pain, gout joint pain, chronic pain, spinal cord injury, atopic dermatitis, contact dermatitis, dry skin dermatitis, seborrhoeic dermatitis, arthritis, rheumatoid arthritis, osteoarthritis, psoriasis, psoriatic arthritis, multiple sclerosis, non-alcoholic steatohepatitis (NASH), obesity (e.g., diet-induced obesity), diabetes, adipose inflammation, pancreatitis, metabolic syndrome, PAR-2 associated metabolic dysfunction, periodontitis, gingivitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, peptic ulcer disease (e.g., gastric ulcer or duodenal ulcer), infectious enteritis, irritable bowel syndrome, atherosclerosis, asthma, interstitial lung disease, pulmonary fibrosis (e.g., idiopathic pulmonary fibrosis), rheumatoid arthritis-associated interstitial lung disease, liver fibrosis, cystic fibrosis, renal fibrosis, peritoneal fibrosis, pancreatic fibrosis, intestinal fibrosis, cardiac fibrosis, skin fibrosis, systemic lupus erythematosus (SLE), scleroderma, skin eczema, acne, rosacea, post-inflammatory hyperpigmentation, lichen planus, pruritus, polymyositis, vasculitis, Wegener's granulomatosis (or granulomatosis with polyangiitis), Netherton syndrome, dermatomyositis, uveitis, liver cirrhosis, Alzheimer's disease, Parkinson's disease, dust mite allergy (e.g., house dust mite allergy), cockroach allergy, allergic asthma, or cancer (e.g., colorectal cancer, colon cancer (e.g., colon adenocarcinoma), gastric cancer (e.g., stomach adenocarcinoma), rectal cancer (e.g., rectum adenocarcinoma), liver cancer (e.g., hepatocellular carcinoma), breast cancer, pancreatic cancer (e.g., pancreatic adenocarcinoma or pancreatic ductal adenocarcinoma), cervical cancer (e.g., cervical squamous cell carcinoma or endocervical adenocarcinoma), prostate cancer (e.g., prostate adenocarcinoma), ovarian cancer (e.g., ovarian serous cystadenocarcinoma), endometrial cancer (e.g., uterine corpus endometrial carcinoma), uterine sarcoma (e.g., uterine carcinosarcoma), germ cell cancer (e.g., testicular germ cell cancer), esophageal cancer, leukemia (e.g., acute myeloid leukemia), lung cancer (e.g., lung adenocarcinoma or lung squamous cell carcinoma), adrenal gland cancer (e.g., adrenocortical carcinoma), bile duct cancer (e.g., cholangio carcinoma), bladder cancer (e.g., bladder urothelial carcinoma), head and neck cancer, kidney cancer (e.g., kidney chromophobe, kidney renal cell carcinoma, kidney renal clear cell carcinoma, or kidney renal

papillary cell carcinoma), lymphoma (e.g., lymphoid neoplasm diffuse large B-cell lymphoma), mesothelioma, sarcoma, melanoma (e.g., skin cutaneous melanoma, or uveal melanoma), thyroid carcinoma, thymus cancer (e.g., thymoma), or glioblastoma.

The present invention also relates to a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, wherein said compound is conjugated via a linker to a membrane anchor. The corresponding conjugate can be employed in place of the compound of formula (I) for any use or purpose described in the present specification, e.g., for use in the treatment or prevention of a PAR-2 mediated disease or disorder, including any of the diseases/disorders mentioned herein above. Such conjugates are advantageous in that they allow to tether the conjugated compound of formula (I) to a cell membrane in the proximity of PAR-2 and, thus, to facilitate its interaction with PAR-2.

The membrane anchor may be any moiety that is capable of inserting/partitioning into a lipid membrane (preferably a cell membrane), particularly a hydrophobic moiety or a lipid moiety; the conjugated compound of formula (I) is thereby "anchored" to the corresponding lipid membrane. For example, the membrane anchor may be a C_{12-20} alkanoyl group (e.g., a hexadecanoyl group, $-CO-(CH_2)_{14}-CH_3$), cholesterol, cholestanol, a sphingolipid, or glycophosphatidylinositol (GPI). The membrane anchor may also be, e.g., a moiety of formula (II), (III), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) or (XV) as described and defined in WO 2017/197463, particularly on pages 10 to 15 of WO 2017/197463 which is incorporated herein by reference. The membrane anchor may further be, e.g., a raftophile A or A', or a moiety of any one of the formulae 2, 200a to 200m, 3, 300a to 300g, 4a, 400aa to 400ap, 4b, 400ba, 5a, 500aa to 500ae, 5b, 500ba, 6, 600, 7, 700, 700a to 700c, 8a, 800a, 8b, 9, 900, 10, 1000, 11, 1100a, 1100b, 12, 1200a, 1200b, 13a, 1300aa to 1300ac, 13b, 1300b, 14a, 1400aa to 1400ae, 14b, 1400b, 14c, 15, 1500a, 16, 1600a, 18a, 1800a to 1800d, 18b, 19a, 1900a, 19b or 1900b, as described and defined in WO 2005/097199 which is incorporated herein by reference.

The linker is covalently bound to the membrane anchor and to the compound of formula (I) (or the pharmaceutically acceptable salt or solvate thereof). While the linker is not particularly limited, it preferably has a length of about 1 nm to about 50 nm, and/or it preferably provides a distance of at least 8 atoms between the compound of formula (I) and the membrane anchor. For example, the linker may comprise (or consist of) one or more polyethylene glycol (PEG) units, or may comprise (or consist of) a peptide (which may be composed of, e.g., 2 to 200 amino acid residues). The linker may also be, e.g., a moiety of formula (IV), (XX), (XXI) or (XXII) as described and defined in WO 2017/197463, particularly on pages 15 to 18 of WO 2017/197463 which is incorporated herein by reference. The linker may further be, e.g., a linker B or B', or a moiety of any one of the formulae 20, 2000, 2001, 21, 2100, 2101, 22, 23, 28 or 28a, as described and defined in WO 2005/097199 which is incorporated herein by reference. It will be understood that the linker may be attached to the membrane anchor via any suitable chemical linkage, e.g. via an amide linkage or via an ester linkage. Likewise, the linker may be attached to the compound of formula (I) (or the pharmaceutically acceptable salt or solvate thereof) via any suitable chemical linkage, e.g. via an amide linkage or via an ester linkage. While the linker may be attached at any position (or to any functional group) of the compound of formula (I) or the pharmaceutically acceptable salt or solvate thereof, it is preferred that the linker is attached to group A or to a substituent R^A on group A.

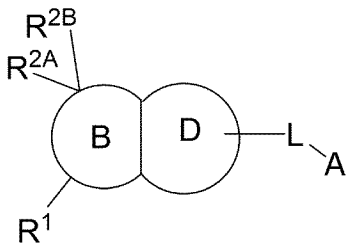
Moreover, the linker and the membrane anchor may together form, e.g., any one of the moieties described to be attached to a PAR-2 inhibitor in WO 2017/197463 (which is incorporated herein by reference), or to a PAR-2 modulating compound in WO 2017/173347 (which is incorporated herein by reference), or to a pharmacophore in WO 2005/097199 (which is incorporated herein by reference). Suitable protocols for the preparation of corresponding linkers and membrane anchors are also described in these documents.

An example of a corresponding conjugate, wherein a compound of formula (I) is conjugated via a linker to a membrane anchor, is described in Example 261.

Accordingly, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, wherein said compound is conjugated via a linker to a membrane anchor, wherein the membrane anchor is a C_{12-20} alkanoyl group (e.g., a hexadecanoyl group, -CO-$(CH_2)_{14}$-CH_3). The invention particularly provides the compound N-(37-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-3-methyl-4,17,30,37-tetraoxo-7,10,13,20,23,26-hexaoxa-3,16,29-triazaheptatriacontyl)-N-methylpalmitamide or a pharmaceutically acceptable salt or solvate thereof.

The present invention furthermore relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as an inhibitor of protease-activated receptor 2 (PAR-2) in research, particularly as a research tool compound for inhibiting PAR-2. Accordingly, the invention refers to the *in vitro* use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as a PAR-2 inhibitor and, in particular, to the *in vitro* use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as a research tool compound acting as a PAR-2 inhibitor. The invention likewise relates to a method, particularly an *in vitro* method, of inhibiting PAR-2, the method comprising the application of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof. The invention further relates to a method of inhibiting PAR-2, the method comprising applying a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof to a test sample (e.g., a biological sample) or a test animal (i.e., a non-human test animal). The invention also refers to a method, particularly an *in vitro* method, of inhibiting PAR-2 in a sample (e.g., a biological sample), the method comprising applying a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof to said sample. The present invention further provides a method of inhibiting PAR-2, the method comprising contacting a test sample (e.g., a biological sample) or a test animal (i.e., a non-human test animal) with a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof. The terms “sample”, “test sample” and “biological sample” include, without being limited thereto: a cell, a cell culture or a cellular or subcellular extract; biopsied material obtained from an animal (e.g., a human), or an extract thereof; or blood, serum, plasma, saliva, urine, feces, or any other body fluid, or an extract thereof. It is to be understood that the term “*in vitro*” is used in this specific context in the sense of “outside a living human or animal body”, which includes, in particular, experiments performed with cells, cellular or subcellular extracts, and/or biological molecules in an artificial environment such as an aqueous solution or a culture medium which may be provided, e.g., in a flask, a test tube, a Petri dish, a microtiter plate, etc.

The compounds of formula (I) as well as the pharmaceutically acceptable salts and solvates thereof will be described in more detail in the following.



(I)

In formula (I), ring B is a non-aromatic C_{4-8} carbocyclic ring or a non-aromatic 4- to 8-membered heterocyclic ring, which is fused to ring D, wherein said carbocyclic ring or said heterocyclic ring is: (i) substituted with a group R^1; (ii) substituted with the groups R^{2A} and R^{2B} which are attached to the same ring carbon atom of said carbocyclic ring or said heterocyclic ring; and (iii) optionally substituted with one or more (e.g., one, two or three) groups R^Y.

Ring D is a 5- or 6-membered heteroaromatic ring, which is fused to ring B, wherein said heteroaromatic ring comprises at least one nitrogen ring atom, wherein said heteroaromatic ring is substituted with a group -L-A, and wherein said heteroaromatic ring is optionally substituted with one or more (e.g., one, two or three) groups R^X.

Accordingly, as also depicted in formula (I), the rings B and D are fused, i.e., they share two adjacent ring atoms (which form part of both ring B and ring D) and thus form a fused bicyclic ring system. In this fused bicyclic ring system, only ring D is aromatic whereas ring B is non-aromatic.

As explained above, ring B is a non-aromatic C_{4-8} carbocyclic ring or a non-aromatic 4- to 8-membered heterocyclic ring, wherein said carbocyclic ring or said heterocyclic ring is optionally substituted with one or more groups R^Y. It will be understood that ring B is fused to ring D, is substituted with a group R^1, and is substituted with the groups R^{2A} and R^{2B} (which are attached to the same ring carbon atom of ring B); these features are also depicted in formula (I) and will not be repeated at every instance where ring B is further described herein below.

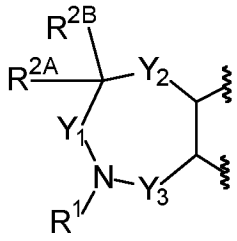
It is preferred that said non-aromatic C_{4-8} carbocyclic ring is a C_{4-8} cycloalkyl ring or a C_{4-8} cycloalkenyl ring, more preferably a C_{5-7} cycloalkyl ring or a C_{5-7} cycloalkenyl ring (e.g., a cyclohexenyl ring), even more preferably a cyclopentyl ring, a cyclohexyl ring, or a cycloheptyl ring.

Moreover, it is preferred that said non-aromatic 4- to 8-membered heterocyclic ring is a 4- to 8-membered heterocycloalkyl ring or a 4- to 8-membered heterocycloalkenyl ring, more preferably a 5- to 7-membered heterocycloalkyl ring (i.e., a heterocycloalkyl ring having 5, 6 or 7 ring atoms) or a 5- to 7-membered heterocycloalkenyl ring (i.e., a heterocycloalkenyl ring having 5, 6 or 7 ring atoms; e.g., a 3,4-dihydro-2H-pyranyl ring or a 3,6-dihydro-2H-pyranyl ring), even more preferably a 5- to 7-membered heterocycloalkyl ring (e.g., a pyrrolidinyl ring, a piperidinyl ring, a 1,3-diazinanyl ring, a piperazinyl ring, an azepanyl ring, a tetrahydropyranyl ring, a

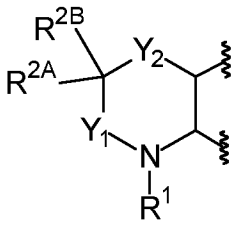
morpholino ring, a 1,4-oxazepanyl ring, or a 1,4-thiazepanyl ring). It is furthermore preferred that said non-aromatic heterocyclic ring (including also said heterocycloalkyl ring or said heterocycloalkenyl ring) has one or more (e.g., one or two) ring heteroatoms selected from nitrogen, oxygen and sulfur while all remaining ring atoms are carbon atoms, wherein any nitrogen ring atom (if present) and/or any sulfur ring atom (if present) is optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized (i.e., to form an oxo group). More preferably, said heterocyclic ring (including also said heterocycloalkyl ring or said heterocycloalkenyl ring) has one or more (e.g., one or two) nitrogen ring atoms while all remaining ring atoms are carbon atoms, wherein one or more carbon ring atoms are optionally oxidized; corresponding examples include, in particular, a pyrrolidinyl ring, a piperidinyl ring, a 1,3-diazinanyl ring, a piperazinyl ring, or an azepanyl ring. A particularly preferred example of said heterocyclic ring (or said heterocycloalkyl ring) is a pyrrolidinyl ring.

Preferably, ring B is a non-aromatic 4- to 8-membered heterocyclic ring (e.g., a 4- to 8-membered heterocycloalkyl ring or a 4- to 8-membered heterocycloalkenyl ring), wherein said heterocyclic ring is optionally substituted with one or more groups R^Y. More preferably, ring B is a non-aromatic 5- to 7-membered heterocyclic ring (e.g., a heterocycloalkyl ring having 5, 6 or 7 ring members, or a heterocycloalkenyl ring having 5, 6 or 7 ring members) which is optionally substituted with one or more R^Y. Even more preferably, ring B is a 5- to 7-membered heterocycloalkyl ring which is optionally substituted with one or more R^Y. Yet even more preferably, ring B is a 5- to 7-membered heterocycloalkyl ring which is optionally substituted with one or more R^Y, wherein said heterocycloalkyl ring has one or two ring heteroatoms selected from nitrogen, oxygen and sulfur (preferably one or two nitrogen ring atoms) while all remaining ring atoms are carbon atoms, wherein one or more carbon ring atoms are optionally oxidized. Corresponding preferred examples include a pyrrolidinyl ring, a piperidinyl ring, a 1,3-diazinanyl ring, a morpholinyl ring, or an azepanyl ring, particularly a pyrrolidinyl ring or a piperidinyl ring, even more preferably a pyrrolidinyl ring. For each of the aforementioned preferred definitions of ring B, it is furthermore preferred that ring B comprises at least one nitrogen ring atom and that the group R^1 is attached to said nitrogen ring atom. Accordingly, a particularly preferred example of ring B is a pyrrolidinyl ring or a piperidinyl ring, wherein said pyrrolidinyl ring or said piperidinyl ring is optionally substituted with one or more R^Y, and wherein the group R^1 is attached to the nitrogen ring atom of said pyrrolidinyl ring or said piperidinyl ring. An even more preferred example of ring B is a pyrrolidinyl ring (which is optionally substituted with one or more R^Y), wherein the group R^1 is attached to the nitrogen ring atom of said pyrrolidinyl ring.

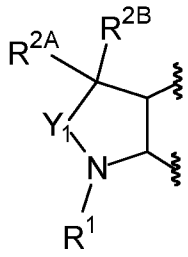
In accordance with the above general and preferred definitions of ring B, it is particularly preferred that ring B is a group of the following formula (B1), even more preferably a group of the following formula (B2), and still more preferably a group of the following formula (B3):



(B1)



(B2)



(B3)

It will be understood that the above-depicted groups of formulae (B1), (B2) and (B3) are fused to ring D via the two adjacent ring carbon atoms (i.e., the two ring carbon atoms between Y_2 and Y_3 in formula (B1), the two ring carbon atoms between Y_2 and N(-R^1) in formula (B2), or the two ring carbon atoms between C(-R^{2A})(-R^{2B}) and N(-R^1) in formula (B3)), which is reflected in formulae (B1), (B2) and (B3) by the bonds (cut by a wavy line) which extend from these adjacent ring carbon atoms.

Y_1, Y_2 (if present) and Y_3 (if present) are each independently selected from a bond, -CH_2-, -CH_2-CH_2-, -O-, -S-, -SO-, -SO_2-, -CO-, -NH-, and -N(C_{1-5} alkyl)-, wherein said -CH_2- and said -CH_2-CH_2- are each optionally substituted with one or more groups R^Y, wherein said -NH- is optionally substituted with a group R^Y, and further wherein one -CH_2- unit in said -CH_2-CH_2- is optionally replaced by a group selected from -O-, -S-, -SO-, -SO_2-, -CO-, -NH-, and -N(C_{1-5} alkyl)-; with the proviso that formula (B1) has 4 to 8 ring atoms (i.e., the options for Y_1, Y_2 and Y_3 in formula (B1) are limited by the additional requirement that the resulting ring B is a 4- to 8-membered ring). In particular, said -CH_2- may be optionally substituted with one or two groups R^Y, and said -CH_2-CH_2- may be optionally substituted with one, two, three or four groups R^Y. It will be understood that the definitions of Y_1, Y_2 and Y_3 only apply insofar as these groups are present in the compound of formula (I), regardless of whether this is explicitly reflected by the term "if present" in the definitions of Y_1, Y_2 and Y_3. Accordingly, the definition of Y_1 applies to each of formulae (B1), (B2) and (B3), the definition of Y_2 only applies to formulae (B1) and (B2), and the definition of Y_3 only applies to formula (B1).

Preferably, Y_1, Y_2 (if present) and Y_3 (if present) are each independently selected from a bond, -CH_2-, -CH_2-CH_2-, -O-, -S-, -CO-, and -NH-, wherein said -CH_2- and said -CH_2-CH_2- are each optionally substituted with one or more (e.g., one or two) groups R^Y, wherein said -NH- is optionally substituted with a group R^Y, and wherein one -CH_2- unit in said -CH_2-CH_2- is optionally replaced by a group selected from -O-, -S-, and -CO-; with the proviso that formula (B1) has 4 to 8 ring atoms. More preferably, Y_1, Y_2 (if present) and Y_3 (if present) are each independently selected from a bond, -CH_2-, -CH_2-CH_2-, -O-, -S-, and -CO-, wherein said -CH_2- and said -CH_2-CH_2- are each optionally substituted with one or more (e.g., one or two) groups R^Y; with the proviso that formula (B1) has 4 to 8 ring atoms. Even more preferably, Y_1, Y_2 (if present) and Y_3 (if present) are each independently selected from a bond, -CH_2-, and -CH_2-CH_2-, wherein said -CH_2- is optionally substituted with one or two groups R^Y, and wherein said -CH_2-CH_2- is optionally substituted with one, two, three or four groups R^Y; with the proviso that formula (B1) has 4 to 8 ring atoms.

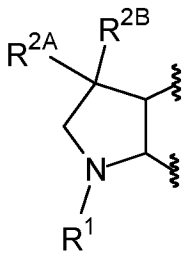
In formula (B1), it is particularly preferred that: Y_1 is selected from a bond, -CH_2-, -CH_2-CH_2-, -O-, -S-, -CO-, and -NH-, wherein said -CH_2- and said -CH_2-CH_2- are each optionally substituted with one or more (e.g., one or two) groups R^Y, wherein said -NH- is optionally substituted with a group R^Y, and wherein one -CH_2- unit in said -CH_2-CH_2- is

optionally replaced by a group selected from -O-, -S-, and -CO-; and that Y_2 and Y_3 are each independently selected from a bond, $-CH_2-$, -O-, -S-, and -CO-, wherein said $-CH_2-$ is optionally substituted with one or two groups R^Y. More preferably, Y_1 in formula (B1) is selected from a bond, $-CH_2-$, $-CH_2-CH_2-$, -O-, -S-, and -CO-, wherein said $-CH_2-$ and said $-CH_2-CH_2-$ are each optionally substituted with one or more (e.g., one or two) groups R^Y; and Y_2 and Y_3 in formula (B1) are each independently a bond or $-CH_2-$, wherein said $-CH_2-$ is optionally substituted with one or two groups R^Y.

In formula (B2), it is preferred that Y_1 and Y_2 are each independently selected from a bond, $-CH_2-$, $-CH_2-CH_2-$, -O-, -S-, -CO-, and -NH-, wherein said $-CH_2-$ and said $-CH_2-CH_2-$ are each optionally substituted with one or more (e.g., one or two) groups R^Y, wherein said -NH- is optionally substituted with a group R^Y, and wherein one $-CH_2-$ unit in said $-CH_2-CH_2-$ is optionally replaced by a group selected from -O-, -S-, and -CO-. More preferably, Y_1 and Y_2 in formula (B2) are each independently selected from a bond, $-CH_2-$, $-CH_2-CH_2-$, -O-, -S-, and -CO-, wherein said $-CH_2-$ and said $-CH_2-CH_2-$ are each optionally substituted with one or more (e.g., one or two) groups R^Y. Even more preferably, Y_1 and Y_2 in formula (B2) are each independently selected from a bond, $-CH_2-$, and $-CH_2-CH_2-$, wherein said $-CH_2-$ is optionally substituted with one or two groups R^Y, and wherein said $-CH_2-CH_2-$ is optionally substituted with one, two, three or four groups R^Y.

In formula (B3), it is preferred that Y_1 is selected from a bond, $-CH_2-$, $-CH_2-CH_2-$, -O-, -S-, -CO-, and -NH-, wherein said $-CH_2-$ and said $-CH_2-CH_2-$ are each optionally substituted with one or more (e.g., one or two) groups R^Y, wherein said -NH- is optionally substituted with a group R^Y, and wherein one $-CH_2-$ unit in said $-CH_2-CH_2-$ is optionally replaced by a group selected from -O-, -S-, and -CO-. More preferably, Y_1 in formula (B3) is selected from a bond, $-CH_2-$, $-CH_2-CH_2-$, -O-, -S-, and -CO-, wherein said $-CH_2-$ and said $-CH_2-CH_2-$ are each optionally substituted with one or more (e.g., one or two) groups R^Y. Even more preferably, Y_1 in formula (B3) is selected from a bond, $-CH_2-$, and $-CH_2-CH_2-$, wherein said $-CH_2-$ is optionally substituted with one or two groups R^Y, and wherein said $-CH_2-CH_2-$ is optionally substituted with one, two, three or four groups R^Y. Yet even more preferably, Y_1 in formula (B3) is $-CH_2-$ or $-CH_2-CH_2-$, wherein said $-CH_2-$ is optionally substituted with one or two groups R^Y, and wherein said $-CH_2-CH_2-$ is optionally substituted with one, two, three or four groups R^Y. Still more preferably, Y_1 in formula (B3) is $-CH_2-$ which is optionally substituted with one or two groups R^Y.

Accordingly, it is particularly preferred that ring B is a group of the following formula:



,

which is optionally substituted with one or two groups R^Y. While said formula (i.e., ring B) may be substituted with 0, 1 or 2 groups R^Y, it is preferably substituted with 0 or 1 group R^Y, and more preferably it is not substituted with any groups R^Y.

Thus, most preferably, ring B is a group of the following formula:

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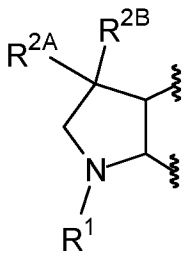


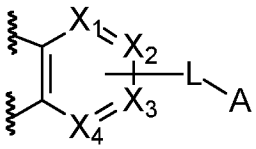
As explained above, ring D is a 5- or 6-membered heteroaromatic ring which comprises at least one nitrogen ring atom, wherein said heteroaromatic ring is optionally substituted with one or more groups R^X. It will be understood that ring D is fused to ring B, and that ring D is substituted with a group -L-A; these features are also depicted in formula (I) and will not be repeated at every instance where ring D is further described herein below.

Preferably, ring D is a 5- or 6-membered heteroaromatic ring having one, two or three ring heteroatoms independently selected from nitrogen, oxygen and sulfur, wherein at least one of said ring heteroatoms is a nitrogen ring atom (preferably all ring heteroatoms are nitrogen ring atoms), while all remaining ring atoms are carbon atoms, wherein said heteroaromatic ring is optionally substituted with one or more groups R^X. Corresponding preferred examples of ring D include a pyridinyl ring, a pyridazinyl ring, a pyrimidinyl ring, a pyrazinyl ring, an 1,2,4-triazinyl ring, a 1H-pyrrolyl ring, a pyrazolyl ring, an imidazolyl ring, a 1,2,3-triazolyl ring, a furanyl ring, a thiophenyl ring, an oxazolyl ring, an isoxazolyl ring, a thiazolyl ring, or an isothiazolyl ring. In particular, ring D may be, e.g., a 5- or 6-membered heteroaromatic ring which comprises one nitrogen ring atom and optionally one further ring heteroatom selected from nitrogen, oxygen and sulfur (preferably a further nitrogen ring atom), wherein all remaining ring atoms are carbon atoms, and wherein said heteroaromatic ring is optionally substituted with one or more groups R^X. More preferably, ring D is a 6-membered heteroaromatic ring which comprises one, two or three nitrogen ring atoms while all remaining ring atoms are carbon atoms, and wherein said heteroaromatic ring is optionally substituted with one or more groups R^X. Even more preferably, ring D is a 6-membered heteroaromatic ring which comprises one or two nitrogen ring atoms while all remaining ring atoms are carbon atoms, and wherein said heteroaromatic ring is optionally substituted with one or more groups R^X; corresponding examples include, in particular, a pyridinyl ring, a pyridazinyl ring, a pyrimidinyl ring, or a pyrazinyl ring. Even more preferably, ring D is a pyridinyl or pyrazinyl ring which is optionally substituted with one or more groups R^X. Yet even more preferably, ring D is a pyridinyl or pyrazinyl ring which is optionally substituted with one or more groups R^X, wherein said pyridinyl or pyrazinyl ring is fused via its ring carbon atoms 2 and 3 to ring B. Still more preferably, ring D is a pyrazinyl ring which is optionally substituted with one or more groups R^X, wherein said pyrazinyl ring is fused via its ring carbon atoms 2 and 3 to ring B. It is furthermore preferred that ring D is substituted with 0, 1 or 2 groups R^X, more preferably with 0 or 1 group R^X, even more preferably ring D is not substituted with any groups R^X.

The group -L-A is attached to ring D, as also depicted in formula (I). While the group -L-A may, in principle, be attached to any ring atom of ring D (other than the two ring atoms shared by ring B and ring D), in the case of a 5-membered heteroaromatic ring as ring D, it is preferred that -L-A is attached to the ring atom of said 5-membered heteroaromatic ring which is most distant to the two ring atoms shared by ring B and ring D. In the case of a 6-membered heteroaromatic ring as ring D, it is preferred that -L-A is attached to one of the two ring atoms of said 6-membered

heteroaromatic ring which are most distant to the two ring atoms shared by ring B and ring D, more preferably to that ring atom (among the aforementioned two ring atoms which are most distant to the two ring atoms shared by ring B and ring D) which is closer (i.e., more proximate) to the ring atom of ring B carrying the groups R^{2A} and R^{2B}.

In accordance with the above general and preferred definitions of ring D, it is particularly preferred that ring D is a group of the following formula (D1):



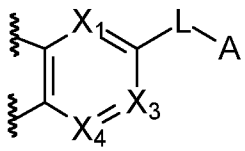
(D1)

wherein the ring atoms X_1, X_2, X_3 and X_4 are each independently a carbon atom or a nitrogen atom, wherein one among X_2 and X_3 is a carbon atom and carries the group -L-A, wherein at least one of the remaining ring atoms among X_1, X_2, X_3 and X_4 is a nitrogen atom, and wherein any among the ring atoms X_1, X_2, X_3 and X_4 that is a carbon atom (and that does not carry the group -L-A) is optionally substituted with a group R^X.

It will be understood that the above-depicted group of the formula (D1) is fused via the two adjacent ring carbon atoms (other than X_1 to X_4) to ring B, which is reflected in formula (D1) by the bonds that extend from these adjacent ring carbon atoms (and that are cut by a wavy line). It will further be understood that if any of X_1, X_2, X_3 and X_4 is a carbon atom which is substituted with a group R^X, the group R^X replaces a hydrogen atom that would otherwise (i.e., in the absence of the optional substituent R^X) be attached to the respective carbon atom. Moreover, it will be understood that any among the ring atoms X_1, X_2, X_3 and X_4 that is a nitrogen atom does not carry any optional substituent.

In formula (D1), it is preferred that one or two of the ring atoms X_1, X_2, X_3 and X_4 is/are each a nitrogen atom, and all remaining ring atoms (among X_1, X_2, X_3 and X_4) are carbon atoms, whereby one of X_2 and X_3 is a carbon atom that carries the group -L-A. For example, X_1 may be a nitrogen atom while all remaining ring atoms X_2, X_3 and X_4 are carbon atoms (whereby one of X_2 and X_3 is a carbon atom that carries the group -L-A); or X_4 may be a nitrogen atom while all remaining ring atoms X_1, X_2 and X_3 are carbon atoms (whereby one of X_2 and X_3 is a carbon atom that carries the group -L-A); or X_1 and X_4 may be nitrogen atoms while the remaining ring atoms X_2 and X_3 are carbon atoms (whereby one of X_2 and X_3 is a carbon atom that carries the group -L-A). More preferably, X_1 is a nitrogen atom, one of X_2, X_3 and X_4 is a nitrogen atom or a carbon atom, and the other two of X_2, X_3 and X_4 are each a carbon atom, whereby one of X_2 and X_3 is a carbon atom that carries the group -L-A. Even more preferably, X_1 is a nitrogen atom, X_4 is a nitrogen atom or a carbon atom, and X_2 and X_3 are each a carbon atom, whereby one of X_2 and X_3 is a carbon atom that carries the group -L-A. Yet even more preferably, X_1 and X_4 are each a nitrogen atom and X_2 and X_3 are each a carbon atom, whereby the carbon atom in either X_2 or X_3 carries the group -L-A. As explained above, it is preferred that the compound of formula (I) comprises zero, one or two groups R^X, more preferably zero or one group R^X, even more preferably zero (i.e., no) groups R^X. Accordingly, it is particularly preferred that X_1 and X_4 are each a nitrogen atom, one of X_2 and X_3 is C(-L-A), and the other one of X_2 and X_3 is C(-H).

Still more preferably, ring D is a group of the following formula (D2):

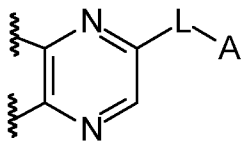


(D2)

wherein the ring atoms X_1, X_3 and X_4 are each independently a carbon atom or a nitrogen atom, wherein at least one among X_1, X_3 and X_4 is a nitrogen atom, and wherein any among the ring atoms X_1, X_3 and X_4 that is a carbon atom is optionally substituted with a group R^X.

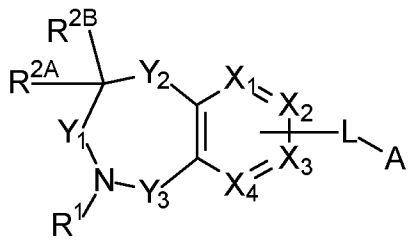
Preferably, one or two of the ring atoms X_1, X_3 and X_4 is/are each a nitrogen atom, and all remaining ring atoms (among X_1, X_3 and X_4) are carbon atoms. More preferably, X_1 is a nitrogen atom, one of X_3 and X_4 is a nitrogen atom or a carbon atom, and the other one of X_3 and X_4 is a carbon atom. Thus, for example, X_1 may be a nitrogen atom, and X_3 and X_4 may each be a carbon atom; or, alternatively, X_1 and X_3 may each be a nitrogen atom, and X_4 may be a carbon atom; or, alternatively, X_1 and X_4 may each be a nitrogen atom, and X_3 may be a carbon atom. It is particularly preferred that X_1 and X_4 are each a nitrogen atom, and X_3 is a carbon atom. As explained above, any among the ring atoms X_1, X_3 and X_4 that is a carbon atom is optionally substituted with a group R^X. Yet, it is preferred that the compound of formula (I) comprises zero, one or two groups R^X, more preferably zero or one group R^X, even more preferably zero groups R^X, so that any among the ring atoms X_1, X_3 and X_4 that is a carbon atom is preferably not substituted with a group R^X, i.e. is a ring atom C(-H). Accordingly, it is particularly preferred that X_1 and X_4 are each a nitrogen atom, and X_3 is a carbon atom optionally substituted with R^X; even more preferably, X_1 and X_4 are each N, and X_3 is C(-H).

Thus, even more preferably, ring D is a group of the following formula (D3):



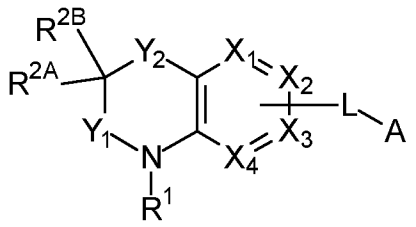
(D3)

In accordance with the above definitions of rings B and D, it is particularly preferred that the compound of formula (I) has the following structure:



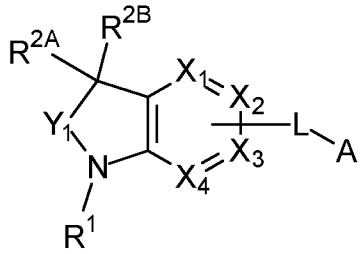
;

more preferably the compound of formula (I) has the following structure:



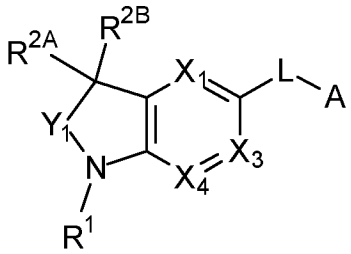
;

even more preferably the compound of formula (I) has the following structure:



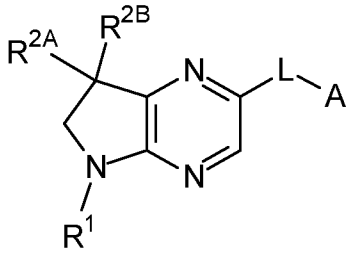
;

yet even more preferably the compound of formula (I) has the following structure:



;

still more preferably the compound of formula (I) has the following structure:



In formula (I), the group R^1 is selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-5} alkylene)-carbocyclyl, and -(C_{0-5} alkylene)-heterocyclyl, wherein said alkyl, said alkenyl, said alkynyl, the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, and the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{12}, wherein one or more (e.g., one, two, or three) -CH_2- units comprised in said alkyl, said alkenyl, said alkynyl, in the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, or in the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally replaced by a group independently selected from -$C(R^{L1})(R^{L1})$-, -O-, -S-, -SO-, -SO_2-, -CO-, and -$N(R^{L1})$-, wherein each R^{L1} is independently hydrogen or C_{1-5} alkyl, wherein two groups R^{L1} which are attached to the same carbon atom may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or a heterocycloalkyl, and wherein the carbocyclyl group

in said -(C_{0-5} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two, three, or four) groups R^{11}.

Preferably, R^1 is selected from C_{1-5} alkyl, -(C_{0-5} alkylene)-carbocyclyl, and -(C_{0-5} alkylene)-heterocyclyl, wherein said alkyl, the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, and the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{12}, wherein one or more -CH_2- units comprised in said alkyl, in the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, or in the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally replaced by a group independently selected from -$C(R^{L1})(R^{L1})$-, -O-, -S-, -SO-, -SO_2-, -CO-, and -$N(R^{L1})$-, wherein each R^{L1} is independently hydrogen or C_{1-5} alkyl, wherein two groups R^{L1} which are attached to the same carbon atom may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl (e.g., a C_{3-6} cycloalkyl) or a heterocycloalkyl (e.g., a 3 to 6-membered heterocycloalkyl), and wherein the carbocyclyl group in said -(C_{0-5} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{11}.

More preferably, R^1 is selected from C_{1-5} alkyl (e.g., isobutyl), -(C_{0-5} alkylene)-carbocyclyl, and -(C_{0-5} alkylene)-heterocyclyl, wherein the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl and the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{12}, wherein one or more -CH_2- units comprised in the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl or in the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally replaced by a group independently selected from -$C(R^{L1})(R^{L1})$-, -O-, -S-, -SO-, -SO_2-, -CO-, and -$N(R^{L1})$-, wherein each R^{L1} is independently hydrogen or C_{1-5} alkyl, wherein two groups R^{L1} which are attached to the same carbon atom may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or a heterocycloalkyl, and wherein the carbocyclyl group in said -(C_{0-5} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{11}.

Even more preferably, R^1 is -L^1-carbocyclyl or -L^1-heterocyclyl, wherein the carbocyclyl in said -L^1-carbocyclyl or the heterocyclyl in said -L^1-heterocyclyl is optionally substituted with one or more (e.g., one, two, three, or four) groups R^{11}.

For example, R^1 may be -L^1-aryl, -L^1-cycloalkyl, -L^1-cycloalkenyl, -L^1-heteroaryl, -L^1-heterocycloalkyl, or -L^1-heterocycloalkenyl, wherein the cyclic moiety in each of the aforementioned groups is optionally substituted with one or more groups R^{11}. It is particularly preferred that R^1 is -L^1-aryl, -L^1-cycloalkyl, -L^1-heteroaryl or -L^1-heterocycloalkyl, wherein the aryl in said -L^1-aryl, the cycloalkyl in said -L^1-cycloalkyl, the heteroaryl in said -L^1-heteroaryl or the heterocycloalkyl in said -L^1-heterocycloalkyl is optionally substituted with one or more groups R^{11}. More preferably, R^1 is -L^1-aryl, -L^1-cycloalkyl or -L^1-heteroaryl, wherein the aryl in said -L^1-aryl, the cycloalkyl in said -L^1-cycloalkyl or the heteroaryl in said -L^1-heteroaryl is optionally substituted with one or more groups R^{11}. In particular, it is preferred that R^1 is selected from -L^1-phenyl, -L^1-naphthyl (e.g., -L^1-naphthalen-1-yl or -L^1-naphthalen-2-yl), -L^1-(C_{3-7} cycloalkyl), -L^1-(monocyclic 5- or 6-membered heteroaryl), or -L^1-(bicyclic 9- or 10-membered heteroaryl), wherein the cyclic moiety in each of the aforementioned groups is optionally substituted with one or more groups R^{11}. By way of example, if R^1 is -L^1-heteroaryl [e.g., -L^1-(monocyclic 5- or 6-membered heteroaryl) or -L^1-(bicyclic 9- or 10-

membered heteroaryl)] wherein the heteroaryl in said -L^1-heteroaryl is optionally substituted with one or more groups R^{11}, then the heteroaryl in said -L^1-heteroaryl may be, e.g., selected from pyrrolyl (e.g., 1H-pyrrol-1-yl, 1H-pyrrol-2-yl,or 1H-pyrrol-3-yl), pyrazolyl (e.g., pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl), imidazolyl (e.g., imidazol-1-yl, imidazol-2-yl, or imidazol-4-yl), triazolyl (e.g., 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, or 4H-1,2,4-triazolyl; such as, e.g., 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, or 1H-1,2,4-triazol-5-yl), furanyl (e.g., furan-2-yl or furan-3-yl), thiophenyl (e.g., thiophen-2-yl or thiophen-3-yl), oxazolyl (e.g., oxazol-2-yl, oxazol-4-yl, or oxazol-5-yl), isoxazolyl (e.g., isoxazol-3-yl, isoxazol-4-yl, or isoxazol-5-yl), thiazolyl, isothiazolyl, pyridinyl (e.g., pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl), pyridazinyl, pyrimidinyl, pyrazinyl, 1H-indolyl, 2H-isoindolyl, indolizinyl (e.g., indolizin-1-yl or indolizin-2-yl), 1H-indazolyl, benzimidazolyl, benzofuranyl (e.g., benzofuran-2-yl, benzofuran-3-yl, benzofuran-4-yl, benzofuran-5-yl, benzofuran-6-yl, or benzofuran-7-yl), isobenzofuranyl, benzo[b]thiophenyl (e.g., benzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, benzo[b]thiophen-4-yl, benzo[b]thiophen-5-yl, benzo[b]thiophen-6-yl, or benzo[b]thiophen-7-yl), benzo[c]thiophenyl, quinolinyl, isoquinolinyl, quinoxalinyl, phthalazinyl, quinazolinyl, and cinnolinyl. If R^1 is -L^1-cycloalkyl [e.g., -L^1-(C_{3-7} cycloalkyl)] wherein the cycloalkyl in said -L^1-cycloalkyl is optionally substituted with one or more groups R^{11}, then the cycloalkyl in said -L^1-cycloalkyl may be, e.g., selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. Even more preferably, R^1 is selected from -L^1-phenyl, -L^1-(monocyclic 5- or 6-membered heteroaryl), or -L^1-(bicyclic 9- or 10-membered heteroaryl), wherein the phenyl in said -L^1-phenyl, the heteroaryl in said -L^1-(monocyclic 5- or 6-membered heteroaryl) and the heteroaryl in said -L^1-(bicyclic 9- or 10-membered heteroaryl) are each optionally substituted with one or more groups R^{11}. Yet even more preferably, R^1 is -L^1-phenyl, wherein the phenyl in said -L^1-phenyl is optionally substituted with one or more (e.g., one, two, or three) groups R^{11}.

Further examples of R^1 include any of the specific groups R^1 comprised in the compounds of formula (I) described in the examples section, particularly in any one of Examples 1 to 282.

L^1 is independently selected from a bond, -C(R^{L1})(R^{L1})-, -O-, -S-, -SO-, -SO_2-, -CO-, and -N(R^{L1})-, wherein each R^{L1} is independently hydrogen or C_{1-5} alkyl, and further wherein two groups R^{L1} which are attached to the same carbon atom may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl (e.g., a C_{3-6} cycloalkyl) or a heterocycloalkyl (e.g., a 3 to 6-membered heterocycloalkyl).

Preferably, L^1 is independently selected from a bond, -CH_2-, -CH(C_{1-5} alkyl)-, -C(C_{1-5} alkyl)(C_{1-5} alkyl)-, C_{3-6} cycloalkyl-1,1-ene, -O-, -S-, -SO-, -SO_2-, -CO-, -NH-, and -N(C_{1-5} alkyl)-. More preferably, L^1 is independently selected from a bond, -CH_2-, -CH(C_{1-5} alkyl)-, -C(C_{1-5} alkyl)(C_{1-5} alkyl)-, and C_{3-5} cycloalkyl-1,1-ene (e.g., cyclopropyl-1,1-ene). Even more preferably, L^1 is independently selected from a bond, -CH_2-, -CH(C_{1-3} alkyl)-, and -C(C_{1-3} alkyl)(C_{1-3} alkyl)-. Yet even more preferably, L^1 is a bond.

In accordance with the above definition of L^1, it is particularly preferred that R^1 is phenyl which is optionally substituted with one or more (e.g., one, two, or three) groups R^{11}. If said phenyl is optionally substituted with one group R^{11}, it is preferred that said group R^{11} is attached in meta or para position on the phenyl (preferably in para position), i.e., that R^1 is 3-R^{11}-phenyl or 4-R^{11}-phenyl (preferably 4-R^{11}-phenyl). If said phenyl is optionally substituted with two groups R^{11}, it is preferred that the two groups R^{11} are attached in meta and para position, i.e., that R^1 is 3-R^{11}-4-R^{11}-phenyl.

If said phenyl is optionally substituted with three groups R^{11}, it is preferred that two of the three groups R^{11} are attached in meta position and one group R^{11} is attached in para position, i.e., that R^1 is 3-R^{11}-4-R^{11}-5-R^{11}-phenyl. It is furthermore preferred that said phenyl is substituted with two or three (particularly with two) groups R^{11}. Accordingly, it is particularly preferred that R^1 is 3-R^{11}-4-R^{11}-phenyl or 3-R^{11}-4-R^{11}-5-R^{11}-phenyl, wherein each R^{11} is independently selected from halogen (e.g., -F, -Cl, -Br, or -I), C_{1-5} haloalkyl (e.g., $-CF_3$), and C_{1-5} alkyl (e.g., $-CH_3$), even more preferably wherein each R^{11} is independently selected from -F, -Cl, $-CF_3$, and $-CH_3$. Corresponding preferred examples of R^1 include 4-chloro-3-fluoro-phenyl, 3,4-dichloro-phenyl, 3,4-difluoro-phenyl, 3-chloro-4-fluoro-phenyl, 3-fluoro-4-trifluoromethyl-phenyl, 3-chloro-4-trifluoromethyl-phenyl, 3-fluoro-4-methyl-phenyl, 3-chloro-4-methyl-phenyl, 3,4,5-trifluoro-phenyl, or 4-chloro-3,5-difluoro-phenyl. Particularly preferred examples of R^1 are 4-chloro-3-fluoro-phenyl or 3,4-difluoro-phenyl.

Each R^{11} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two or three) groups R^{Cyc}.

Preferably, each R^{11} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc}. More preferably, each R^{11} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -(C_{0-3} alkylene)-carbocyclyl, and -(C_{0-3} alkylene)-heterocyclyl, wherein the carbocyclyl group in said -(C_{0-3}

alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN. Even more preferably, each R^{11} is independently selected from C_{1-5} alkyl, halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN. Yet even more preferably, each R^{11} is independently selected from halogen (e.g., -F, -Cl, -Br, or -I), C_{1-5} haloalkyl (e.g., -CF_3), and C_{1-5} alkyl (e.g., methyl). Still more preferably, each R^{11} is independently halogen (particularly -F or -Cl) or C_{1-5} haloalkyl (particularly -CF_3).

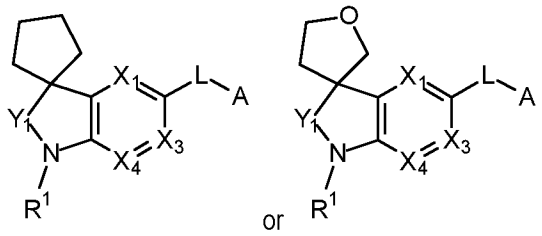
Each R^{12} is independently selected from -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), carbocyclyl, heterocyclyl, and -L^Z-R^Z, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more (e.g., one, two or three) groups R^{Cyc}.

Preferably, each R^{12} is independently selected from -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), and -SO_2-(C_{1-5} alkyl). More preferably, each R^{12} is independently selected from -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN.

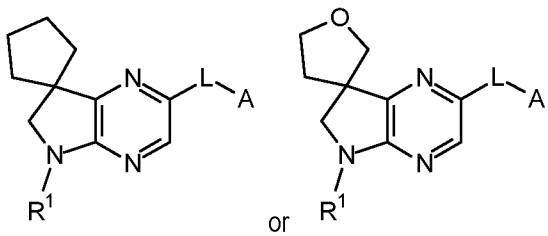
R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, wherein said cycloalkyl, said cycloalkenyl, said heterocycloalkyl or said heterocycloalkenyl is optionally substituted with one or more (e.g., one, two or three) groups R^{21};
alternatively, R^{2A} and R^{2B} are each independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-5} alkylene)-carbocyclyl, and -(C_{0-5} alkylene)-heterocyclyl, wherein said alkyl, said alkenyl, said alkynyl, the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, and the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{22}, wherein one or more -CH_2- units comprised in said alkyl, said alkenyl, said alkynyl, in the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, or in the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-, and further wherein the carbocyclyl group in said -(C_{0-5} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc},

wherein R^{2A} and a group R^{Y} (if present) may also be mutually joined to form, together with the ring atoms that they are attached to, a carbocyclyl or heterocyclyl, wherein said carbocyclyl or said heterocyclyl is optionally substituted with one or more (e.g., one, two or three) groups R^{Cyc}.

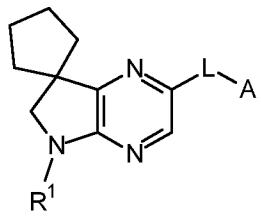
As explained above, R^{2A} and R^{2B} may be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, wherein said cycloalkyl, said cycloalkenyl, said heterocycloalkyl or said heterocycloalkenyl is optionally substituted with one or more groups R^{21}. It will be understood that said cycloalkyl, said cycloalkenyl, said heterocycloalkyl or said heterocycloalkenyl forms a spirocyclic ring system together with the fused rings B and D. Said cycloalkyl (which is formed from R^{2A}, R^{2B} and the carbon atom carrying R^{2A} and R^{2B}) is preferably a monocyclic cycloalkyl, more preferably a C_{3-7} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl); a particularly preferred example of said cycloalkyl is cyclopentyl. Said cycloalkenyl (which is formed from R^{2A}, R^{2B} and the carbon atom carrying R^{2A} and R^{2B}) is preferably a monocyclic cycloalkenyl, more preferably a C_{4-7} cycloalkenyl (e.g., cyclobutenyl, cyclopentenyl, cyclohexenyl, or cyclohepentyl); a particularly preferred example of said cycloalkenyl is cyclobutenyl or cyclopentenyl. Said heterocycloalkyl (which is formed from R^{2A}, R^{2B} and the carbon atom carrying R^{2A} and R^{2B}) is preferably a monocyclic heterocycloalkyl, more preferably a 3- to 7-membered heterocycloalkyl (e.g., containing one or two ring heteroatoms selected independently from oxygen, sulfur and nitrogen, wherein all remaining ring atoms are carbon atoms), even more preferably a 4- to 7-membered heterocycloalkyl having one ring heteroatom selected from oxygen, sulfur and nitrogen (wherein all other ring atoms are carbon atoms); corresponding examples of said heterocycloalkyl include tetrahydrofuranyl (which may be attached, e.g., via the carbon ring atom in 3-position), tetrahydropyranyl (which may be attached, e.g., via the carbon ring atom in 4-position), tetrahydrothiophenyl (which may be attached, e.g., via the carbon ring atom in 3-position), thianyl (which may be attached, e.g., via the carbon ring atom in 4-position), pyrrolidinyl (which may be attached, e.g., via the carbon ring atom in 3-position), or piperidinyl (which may be attached, e.g., via the carbon ring atom in 4-position); a particularly preferred example of said heterocycloalkyl is tetrahydrofuranyl (which may be attached, e.g., via the carbon ring atom in 3-position). Said heterocycloalkenyl (which is formed from R^{2A}, R^{2B} and the carbon atom carrying R^{2A} and R^{2B}) is preferably a monocyclic heterocycloalkenyl, more preferably a 4- to 7-membered heterocycloalkenyl (e.g., containing one or two ring heteroatoms selected independently from oxygen, sulfur and nitrogen, wherein all remaining ring atoms are carbon atoms), even more preferably a 4- to 7-membered heterocycloalkenyl having one ring heteroatom selected from oxygen, sulfur and nitrogen (wherein all other ring atoms are carbon atoms). It is particularly preferred that R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or heterocycloalkyl, wherein said cycloalkyl or said heterocycloalkyl is optionally substituted with one or more groups R^{21}. Even more preferably, R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a cyclopentyl or a tetrahydrofuranyl, wherein said cyclopentyl or said tetrahydrofuranyl is optionally substituted with one or more groups R^{21} (yet even more preferably, R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a cyclopentyl which is optionally substituted with one or more groups R^{21}); thus, in accordance with the above preferred definitions of ring B and ring D, it is particularly preferred that the compound of formula (I) has one of the following structures:



wherein the cyclopentyl ring and the tetrahydrofuran ring in the above-depicted formulae are each optionally substituted with one or more groups R^{21}. In this case, in accordance with the above preferred definitions of ring B and ring D, it is even more preferred that the compound of formula (I) has one of the following structures:



wherein the cyclopentyl ring and the tetrahydrofuran ring in the above-depicted formulae are each optionally substituted with one or more groups R^{21}; yet even more preferably, the compound of formula (I) has the following structure:



wherein the cyclopentyl ring in the above-depicted formula is optionally substituted with one or more groups R^{21}.

Alternatively (i.e., if R^{2A} and R^{2B} are not mutually joined), the groups R^{2A} and R^{2B} are each independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-5} alkylene)-carbocyclyl, and -(C_{0-5} alkylene)-heterocyclyl, wherein said alkyl, said alkenyl, said alkynyl, the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, and the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{22}, wherein one or more (e.g., one, two, or three) -CH_2- units comprised in said alkyl, said alkenyl, said alkynyl, in the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, or in the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-, and further wherein the carbocyclyl group in said -(C_{0-5} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{Cyc}.

If R^{2A} and R^{2B} are not mutually joined, it is preferred that R^{2A} and R^{2B} are each independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-5} alkylene)-carbocyclyl, and -(C_{0-5} alkylene)-heterocyclyl, wherein said alkyl, said alkenyl, said alkynyl, the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, and the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two, or three) groups independently selected from -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN, wherein one or more (e.g., one, two, or three) -CH_2- units comprised in said

alkyl, said alkenyl, said alkynyl, in the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, or in the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-, and further wherein the carbocyclyl group in said -(C_{0-5} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{Cyc}. More preferably, R^{2A} and R^{2B} are each independently selected from C_{1-5} alkyl, -(C_{0-5} alkylene)-cycloalkyl, -(C_{0-5} alkylene)-aryl, -(C_{0-5} alkylene)-heterocycloalkyl, and -(C_{0-5} alkylene)-heteroaryl, wherein said alkyl or the alkylene group in any of said -(C_{0-5} alkylene)-cycloalkyl, said -(C_{0-5} alkylene)-aryl, said -(C_{0-5} alkylene)-heterocycloalkyl, or said -(C_{0-5} alkylene)-heteroaryl is optionally substituted with one or more groups independently selected from -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN, wherein one or more -CH_2- units comprised in said alkyl or in the alkylene group in any of said -(C_{0-5} alkylene)-cycloalkyl, said -(C_{0-5} alkylene)-aryl, said -(C_{0-5} alkylene)-heterocycloalkyl, or said -(C_{0-5} alkylene)-heteroaryl are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-, and further wherein the cycloalkyl group in said -(C_{0-5} alkylene)-cycloalkyl, the aryl group in said -(C_{0-5} alkylene)-aryl, the heterocycloalkyl group in said -(C_{0-5} alkylene)-heterocycloalkyl, and the heteroaryl group in said -(C_{0-5} alkylene)-heteroaryl are each optionally substituted with one or more groups R^{Cyc}. Even more preferably, R^{2A} and R^{2B} are each independently selected from C_{1-5} alkyl, -(C_{0-5} alkylene)-cycloalkyl, -(C_{0-5} alkylene)-aryl (e.g., -(C_{0-5} alkylene)-phenyl, such as -CH_2-phenyl), -(C_{0-5} alkylene)-heterocycloalkyl, and -(C_{0-5} alkylene)-heteroaryl, wherein said alkyl or the alkylene group in any of said -(C_{0-5} alkylene)-cycloalkyl, said -(C_{0-5} alkylene)-aryl, said -(C_{0-5} alkylene)-heterocycloalkyl, or said -(C_{0-5} alkylene)-heteroaryl is optionally substituted with one or more groups independently selected from -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN, and further wherein the cycloalkyl group in said -(C_{0-5} alkylene)-cycloalkyl, the aryl group in said -(C_{0-5} alkylene)-aryl, the heterocycloalkyl group in said -(C_{0-5} alkylene)-heterocycloalkyl, and the heteroaryl group in said -(C_{0-5} alkylene)-heteroaryl are each optionally substituted with one or more groups independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN. Yet even more preferably, R^{2A} and R^{2B} are each independently selected from C_{1-5} alkyl, -(C_{0-3} alkylene)-cycloalkyl (e.g., cyclopropyl, -CH_2-cyclopropyl, cyclobutyl, -CH_2-cyclobutyl, cyclopentyl, or -CH_2-cyclopentyl), -(C_{0-3} alkylene)-heterocycloalkyl [e.g., oxetanyl (such as oxetan-2-yl or oxetan-3-yl), -CH_2-oxetanyl (such as oxetan-2-ylmethyl or oxetan-3-ylmethyl), tetrahydrofuranyl (such as tetrahydrofuran-3-yl), -CH_2-tetrahydrofuranyl (such as tetrahydrofuran-3-ylmethyl), tetrahydropyranyl (such as tetrahydropyran-4-yl), or -CH_2-tetrahydropyranyl (such as tetrahydropyran-4-ylmethyl)], or -(C_{0-3} alkylene)-heteroaryl [e.g., -CH_2-oxazolyl (such as oxazol-2-ylmethyl, oxazol-4-ylmethyl, or oxazol-5-ylmethyl), -CH_2-pyridinyl (such as pyridin-2-ylmethyl, pyridin-3-ylmethyl, or pyridin-4-ylmethyl), -C(-CH_3)(-CH_3)-pyridinyl (such as -C(-CH_3)(-CH_3)-(pyridin-2-yl)), -CH_2-pyrimidinyl (such as pyrimidin-2-ylmethyl), -CH_2-pyrazinyl (such as pyrazin-2-ylmethyl)], wherein said alkyl is optionally substituted with one or more groups independently selected from -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN, and further wherein the cycloalkyl group in said -(C_{0-3} alkylene)-cycloalkyl, the heterocycloalkyl group in said -(C_{0-3} alkylene)-heterocycloalkyl and the heteroaryl group in said -(C_{0-3} alkylene)-heteroaryl are each optionally substituted with one or more groups independently selected from C_{1-5} alkyl, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN. Thus, for example, R^{2A} and R^{2B}

may each be independently a C_{1-5} alkyl which is optionally substituted with one or more groups independently selected from -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN; a corresponding preferred example of R^{2A} and/or R^{2B} is C_{1-5} alkyl (e.g., tert-butyl) substituted with one or two groups -O(C_{1-5} alkyl), such as, e.g., -C(-CH_3)(-CH_3)-CH_2-O-CH_3, -C(-CH_3)(-CH_3)-CH_2-O-CH_2-CH_3, -CH(-CH_2-O-CH_3)(-CH_2-O-CH_3), -CH(-CH_3)-CH_2-O-CH_3, -CH_2CH_2-O-CH_3, or -CH_2CH_2-O-CH_2CH_3. A further example of R^{2A} and/or R^{2B} is -(C_{0-3} alkylene)-phenyl which is optionally substituted with one or more groups independently selected from C_{1-5} alkyl, halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN; particularly 4-chloro-3-fluorophenyl or 4-chloro-3-fluorophenylmethyl. Thus, for example, R^{2A} may be 4-chloro-3-fluorophenyl and R^{2B} may be C_{1-5} alkyl (e.g., methyl). Particularly preferred examples of each of R^{2A} and R^{2B} include methyl, ethyl, isopropyl, iso-butyl, sec-butyl (e.g., (*S*)-sec-butyl or (*R*)-sec-butyl), tert-butyl, cyclopropylmethyl, 1-methylcyclobutyl, 3-(methoxymethyl)cyclobutylmethyl, 2,2,2-trifluoroethyl, -C(-CH_3)(-CH_3)-CH_2-O-CH_3, -C(-CH_3)(-CH_3)-CH_2-O-CH_2-CH_3, -CH(-CH_3)-CH_2-O-CH_3 (e.g., (*S*)-CH(-CH_3)-CH_2-O-CH_3 or (*R*)-CH(-CH_3)-CH_2-O-CH_3), -CH_2CH_2-O-CH_3, -CH(-CH_2-O-CH_3)(-CH_2-O-CH_3), -CH_2-(cyclobut-1,3-diyl)-CH_2-O-CH_3, pyridin-2-ylmethyl, 6-methoxypyridin-2-ylmethyl, or 1-methyl-1-(pyridin-2-yl)ethyl. Still more preferably, R^{2A} and R^{2B} are each independently C_{1-5} alkyl (e.g., methyl, ethyl, isopropyl, iso-butyl, sec-butyl, or tert-butyl). Thus, as an especially preferred example, R^{2A} and R^{2B} may each be methyl. It will be understood that for each of the general and preferred definitions of R^{2A} and R^{2B} described herein above, the groups R^{2A} and R^{2B} may be the same or different.

Moreover, as explained above, the group R^{2A} may also be mutually joined with a group R^Y (if present; preferably with a group R^Y that is attached to a ring atom directly adjacent to the carbon ring atom carrying R^{2A}) to form, together with the ring atoms that said groups R^{2A} and R^Y are attached to, a carbocyclyl or heterocyclyl, wherein said carbocyclyl or said heterocyclyl is optionally substituted with one or more (e.g., one, two or three) groups R^{Cyc}. In particular, the group R^{2A} may be mutually joined with a group R^Y (if present), wherein said group R^Y is attached to a ring atom directly adjacent to the carbon ring atom carrying R^{2A}, to form, together with the ring atoms that said groups R^{2A} and R^Y are attached to, a carbocyclyl or heterocyclyl, wherein said carbocyclyl or said heterocyclyl is optionally substituted with one or more groups R^{Cyc}; it will be understood that the corresponding carbocyclyl or heterocyclyl is then fused to ring B, which together with ring D results in a fused tricyclic ring system. The carbocyclyl formed from said groups R^{2A} and R^Y (and from the ring atoms that these groups R^{2A} and R^Y are attached to) may be, e.g., a cycloalkyl, a cycloalkenyl, or an aryl; preferably, said carbocyclyl is a cycloalkyl, such as, e.g., cyclopentyl or cyclohexyl. The heterocyclyl formed from said groups R^{2A} and R^Y (and from the ring atoms that these groups R^{2A} and R^Y are attached to) may be, e.g., a heterocycloalkyl, a heterocycloalkenyl, or a heteroaryl; preferably, said heterocyclyl is a heterocycloalkyl, such as, e.g., tetrahydrofuranyl (which may be attached, e.g., via the ring carbon atoms in positions 2 and 3). Accordingly, if R^{2A} and a group R^Y (preferably a group R^Y that is attached to a ring atom directly adjacent to the carbon ring atom carrying R^{2A}) are mutually joined, it is particularly preferred that they are mutually joined to form, together with the ring atoms that they are attached to, a cycloalkyl or heterocycloalkyl, wherein said cycloalkyl or said heterocycloalkyl is optionally substituted with one or more groups R^{Cyc}. It will be understood that if R^{2A} and a group R^Y are mutually joined, then the group R^{2B} has the same meaning as described herein above (see the general and preferred meanings of R^{2B} in the case that R^{2A} and R^{2B} are not mutually joined).

Each R^{21} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{Cyc}.

Preferably, each R^{21} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc}. More preferably, each R^{21} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -(C_{0-3} alkylene)-carbocyclyl, and -(C_{0-3} alkylene)-heterocyclyl, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN. Even more preferably, each R^{21} is independently selected from C_{1-5} alkyl (e.g., methyl), halogen (e.g., -F, -Cl, -Br, or -I), C_{1-5} haloalkyl (e.g., -CF_3), -O-(C_{1-5} haloalkyl) (e.g., -OCF_3), and -CN.

Each R^{22} is independently selected from -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -

SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), carbocyclyl, heterocyclyl, and -L^Z-R^Z, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{Cyc}.

Preferably, each R^{22} is independently selected from -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), and -SO_2-(C_{1-5} alkyl). More preferably, each R^{22} is independently selected from -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN.

Each R^X is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two or three) groups R^{Cyc}.

Preferably, each R^X is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3}

alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc}. More preferably, each R^X is independently selected from C_{1-5} alkyl, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -(C_{0-3} alkylene)-cycloalkyl (e.g., cyclopropyl), and -(C_{0-3} alkylene)-heterocycloalkyl, wherein the cycloalkyl group in said -(C_{0-3} alkylene)-cycloalkyl and the heterocycloalkyl group in said -(C_{0-3} alkylene)-heterocycloalkyl are each optionally substituted with one or more groups R^{Cyc}.

Each R^Y is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two or three) groups R^{Cyc};
wherein any two groups R^Y (if present) which are attached to the same ring carbon atom (i) may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or a heterocycloalkyl, wherein said cycloalkyl or said heterocycloalkyl is optionally substituted with one or more (e.g., one, two or three) groups R^{Cyc}, or (ii) may mutually form a group =O.

Preferably, each R^Y is independently selected from C_{1-5} alkyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-aryl, -(C_{0-3} alkylene)-cycloalkyl (e.g., cyclopropyl), -(C_{0-3} alkylene)-heteroaryl (e.g., pyridinyl; such as pyridin-2-yl), and -(C_{0-3} alkylene)-heterocycloalkyl, wherein the aryl group in said -(C_{0-3} alkylene)-aryl, the cycloalkyl group in said -(C_{0-3} alkylene)-cycloalkyl, the heteroaryl group in said -(C_{0-3} alkylene)-heteroaryl, and the heterocycloalkyl group in said -(C_{0-3} alkylene)-heterocycloalkyl are each optionally

substituted with one or more groups R^{Cyc}; wherein any two groups R^Y (if present) which are attached to the same ring carbon atom (i) may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl (e.g., a C_{3-7} cycloalkyl) or a heterocycloalkyl (e.g., a 3- to 7-membered heterocycloalkyl), wherein said cycloalkyl or said heterocycloalkyl is optionally substituted with one or more groups R^{Cyc}, or (ii) may mutually form a group =O. More preferably, each R^Y is independently selected from C_{1-5} alkyl, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN. It is furthermore preferred that ring B is substituted with 0, 1, 2 or 3 groups R^Y, more preferably with 0, 1 or 2 groups R^Y, even more preferably with 0 or 1 group R^Y, yet even more preferably ring B is not substituted with any groups R^Y.

The group L is selected from -CO-, -SO- and -SO_2-. Preferably, L is -CO- or -SO_2-. More preferably, L is -CO-.

The group A is -N(-R^N)-R^N or heterocyclyl, wherein said heterocyclyl is attached via a ring nitrogen atom to group L, and wherein said heterocyclyl is optionally substituted with one or more (e.g., one, two, three, or four) groups R^A.

Each R^N is independently selected from hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, -(C_{0-8} alkylene)-OH, -(C_{0-8} alkylene)-O(C_{1-5} alkyl), -(C_{0-8} alkylene)-SH, -(C_{0-8} alkylene)-S(C_{1-5} alkyl), -(C_{1-8} alkylene)-NH_2, -(C_{1-8} alkylene)-NH(C_{1-5} alkyl), -(C_{1-8} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-8} alkylene)-halogen, -(C_{1-8} alkylene)-C_{1-5} haloalkyl, -(C_{0-8} alkylene)-O-(C_{1-8} haloalkyl), -(C_{0-8} alkylene)-CN, -(C_{0-8} alkylene)-CHO, -(C_{0-8} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-8} alkylene)-COOH, -(C_{0-8} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-8} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-8} alkylene)-CO-NH_2, -(C_{0-8} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-8} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-8} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{1-8} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{1-8} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{1-8} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-8} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-8} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-8} alkylene)-SO_2-NH_2, -(C_{0-8} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-8} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-8} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{1-8} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-8} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-8} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-8} alkylene)-carbocyclyl, and -(C_{0-8} alkylene)-heterocyclyl, wherein one or more (e.g., one, two, or three) -CH_2- units comprised in said C_{1-8} alkyl, said C_{2-8} alkenyl, said C_{2-8} alkynyl, and in any of the aforementioned C_{0-8} alkylene and C_{1-8} alkylene groups are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-, wherein the carbocyclyl group in said -(C_{0-8} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-8} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{Cyc}, and wherein at least one group R^N is not hydrogen.

Preferably, each R^N is independently selected from hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-5} alkylene)-OH, -(C_{0-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-5} alkylene)-SH, -(C_{0-5} alkylene)-S(C_{1-5} alkyl), -(C_{1-5} alkylene)-NH_2, -(C_{1-5} alkylene)-NH(C_{1-5} alkyl), -(C_{1-5} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-5} alkylene)-halogen, -(C_{1-5} alkylene)-C_{1-5} haloalkyl, -(C_{0-5} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-5} alkylene)-CN, -(C_{0-5} alkylene)-CHO, -(C_{0-5} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-5} alkylene)-COOH, -(C_{0-5} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-5} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-5} alkylene)-CO-NH_2, -(C_{0-5} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-5} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-5} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{1-5} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{1-5} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{1-5} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-5} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-5} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-5} alkylene)-SO_2-NH_2, -(C_{0-5} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-5} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-5}

alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{1-5} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-5} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-5} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-5} alkylene)-carbocyclyl, and -(C_{0-5} alkylene)-heterocyclyl, wherein one or more (e.g., one, two, or three) -CH_2- units comprised in said C_{1-5} alkyl, said C_{2-5} alkenyl, said C_{2-5} alkynyl, and in any of the aforementioned C_{0-5} alkylene and C_{1-5} alkylene groups are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-, wherein the carbocyclyl group in said -(C_{0-5} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{Cyc}, and wherein at least one group R^N is not hydrogen.

As explained above, if group A is -N(-R^N)-R^N, then at least one group R^N is not hydrogen. In particular, the group A may be, e.g., -NH-R^N, -N(C_{1-5} alkyl)-R^N, or -N[-(C_{1-5} alkylene)-O(C_{1-5} alkyl)]-R^N, wherein R^N is selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-5} alkylene)-OH, -(C_{0-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-5} alkylene)-SH, -(C_{0-5} alkylene)-S(C_{1-5} alkyl), -(C_{1-5} alkylene)-NH_2, -(C_{1-5} alkylene)-NH(C_{1-5} alkyl), -(C_{1-5} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-5} alkylene)-halogen, -(C_{1-5} alkylene)-C_{1-5} haloalkyl, -(C_{0-5} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-5} alkylene)-CN, -(C_{0-5} alkylene)-CHO, -(C_{0-5} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-5} alkylene)-COOH, -(C_{0-5} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-5} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-5} alkylene)-CO-NH_2, -(C_{0-5} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-5} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-5} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{1-5} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{1-5} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{1-5} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-5} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-5} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-5} alkylene)-SO_2-NH_2, -(C_{0-5} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-5} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-5} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{1-5} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-5} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-5} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-5} alkylene)-carbocyclyl, and -(C_{0-5} alkylene)-heterocyclyl, wherein one or more (e.g., one, two, or three) -CH_2- units comprised in said C_{1-5} alkyl, said C_{2-5} alkenyl, said C_{2-5} alkynyl, and in any of the aforementioned C_{0-5} alkylene and C_{1-5} alkylene groups are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-, and further wherein the carbocyclyl group in said -(C_{0-5} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{Cyc}. Corresponding preferred examples of group A include -NH-C(-CH_3)(-CH_3)-CH_2-N(-CH_3)-(5-carboxy-4,6-dimethyl-pyridin-2-yl), -NH-C(-CH_3)(-CH_3)-CH_2-N(-CH_3)-(5-carboxy-pyridin-2-yl), -NH-C(-CH_3)(-CH_3)-CO-N(-CH_3)-CH_2-CO-NH_2, -NH-C(-CH_3)(-CH_3)-CO-N(-CH_3)(-CH_3), -NH-C(-CH_3)(-CH_3)-CO-NH-CH_3, -NH-CH(-CH_3)-CH_2-COOH, -NH-CH_2-CH_2-CH(-CH_3)-COOH, -NH-CH_2-CH_2-CH(-CH_3)-CH_2-COOH, -NH-CH_2-CH_2-CH(-CH_3)-CH_2-CO-NH_2, -NH-CH_2-CH_2-CH(-CH_3)-CH_2-CO-N(-CH_3)-CH_3, -NH-(1-(aminocarbonyl)cyclopropan-1-yl), -N(C_{1-5} alkyl)-C(-CH_3)(-CH_3)-CH_2-N(-CH_3)-(5-carboxy-4,6-dimethyl-pyridin-2-yl), -N(C_{1-5} alkyl)-C(-CH_3)(-CH_3)-CH_2-N(-CH_3)-(5-carboxy-pyridin-2-yl), -N(C_{1-5} alkyl)-C(-CH_3)(-CH_3)-CO-N(-CH_3)-CH_2-CO-NH_2, -N(C_{1-5} alkyl)-C(-CH_3)(-CH_3)-CO-N(-CH_3)(-CH_3), -N(C_{1-5} alkyl)-C(-CH_3)(-CH_3)-CO-NH-CH_3, -N(C_{1-5} alkyl)-CH(-CH_3)-CH_2-COOH, -N(C_{1-5} alkyl)-CH_2-CH_2-CH(-CH_3)-COOH, -N(C_{1-5} alkyl)-CH_2-CH_2-CH(-CH_3)-CH_2-COOH, -N(C_{1-5} alkyl)-CH_2-CH_2-CH(-CH_3)-CH_2-CO-NH_2, -N(C_{1-5} alkyl)-CH_2-CH_2-CH(-CH_3)-CH_2-CO-N(-CH_3)-CH_3, -N(C_{1-5} alkyl)-(1-(aminocarbonyl)cyclopropan-1-yl), -N[-(C_{1-5} alkylene)-O(C_{1-5} alkyl)]-C(-CH_3)(-CH_3)-CH_2-N(-CH_3)-(5-carboxy-4,6-dimethyl-pyridin-2-yl), -N[-(C_{1-5} alkylene)-O(C_{1-5} alkyl)]-C(-CH_3)(-CH_3)-CH_2-N(-CH_3)-(5-carboxy-pyridin-2-yl), -N[-(C_{1-5} alkylene)-O(C_{1-5} alkyl)]-C(-CH_3)(-CH_3)-CO-N(-CH_3)-CH_2-CO-NH_2, -N[-(C_{1-5} alkylene)-O(C_{1-5} alkyl)]-C(-CH_3)(-CH_3)-CO-N(-CH_3)(-CH_3), -N[-(C_{1-5} alkylene)-O(C_{1-5} alkyl)]-C(-CH_3)(-CH_3)-CO-NH-CH_3, -N[-(C_{1-5} alkylene)-O(C_{1-5} alkyl)]-CH(-CH_3)-CH_2-COOH, -N[-(C_{1-5} alkylene)-O(C_{1-5} alkyl)]-CH_2-CH_2-CH(-CH_3)-COOH, -N[-(C_{1-5} alkylene)-O(C_{1-5} alkyl)]-CH_2-CH_2-CH(-CH_3)-CH_2-COOH, -N[-(C_{1-5} alkylene)-O(C_{1-5} alkyl)]-

CH_2-CH_2-CH(-CH_3)-CH_2-CO-NH_2, -N[-(C_{1-5} alkylene)-O(C_{1-5} alkyl)]-CH_2-CH_2-CH(-CH_3)-CH_2-CO-N(-CH_3)-CH_3, or -N[-(C_{1-5} alkylene)-O(C_{1-5} alkyl)]-(1-(aminocarbonyl)cyclopropan-1-yl). Particularly preferred examples of group A include -N(-CH_3)-C(-CH_3)(-CH_3)-CH_2-N(-CH_3)-(5-carboxy-4,6-dimethyl-pyridin-2-yl), -N(-CH_3)-C(-CH_3)(-CH_3)-CH_2-N(-CH_3)-(5-carboxy-pyridin-2-yl), -N(-CH_2CH_2-O-CH_3)-C(-CH_3)(-CH_3)-CH_2-N(-CH_3)-(5-carboxy-4,6-dimethyl-pyridin-2-yl), -N(-CH_2CH_2-O-CH_3)-C(-CH_3)(-CH_3)-CH_2-N(-CH_3)-(5-carboxy-pyridin-2-yl), -N(-CH_3)-C(-CH_3)(-CH_3)-CO-N(-CH_3)-CH_2-CO-NH_2, -N(-CH_3)-C(-CH_3)(-CH_3)-CO-N(-CH_3)(-CH_3), -N(-CH_3)-C(-CH_3)(-CH_3)-CO-NH-CH_3, -N(-CH_3)-CH(-CH_3)-CH_2-COOH, -N(-CH_3)-CH_2-CH_2-CH(-CH_3)-COOH, -N(-CH_3)-CH_2-CH_2-CH(-CH_3)-CH_2-COOH, -N(-CH_3)-CH_2-CH_2-CH(-CH_3)-CH_2-CO-NH_2, -N(-CH_3)-CH_2-CH_2-CH(-CH_3)-CH_2-CO-N(-CH_3)-CH_3, or -NH-(1-(aminocarbonyl)cyclopropan-1-yl).

Preferably, the group A is heterocyclyl which is attached via a ring nitrogen atom to group L, and wherein said heterocyclyl is optionally substituted with one or more groups R^A. Said heterocyclyl may be, e.g., a 5 to 14 membered heterocyclyl. More preferably, group A is heterocycloalkyl or heterocycloalkenyl, wherein said heterocycloalkyl or said heterocycloalkenyl is attached via a ring nitrogen atom to group L, and wherein said heterocycloalkyl or said heterocycloalkenyl is optionally substituted with one or more groups R^A. Said heterocycloalkyl or said heterocycloalkenyl may be, e.g., a 5 to 14 membered heterocycloalkyl or a 5 to 14 membered heterocycloalkenyl. Even more preferably, group A is heterocycloalkyl which is attached via a ring nitrogen atom to group L, wherein said heterocycloalkyl is optionally substituted with one or more groups R^A. Said heterocycloalkyl is preferably a 5 to 11 membered heterocycloalkyl containing one nitrogen ring atom (through which the heterocycloalkyl is attached to group L) and optionally containing one or more (e.g., one, two, or three) further ring heteroatoms independently selected from nitrogen, oxygen and sulfur, wherein all remaining ring atoms are carbon atoms, wherein any nitrogen ring atom (if present) and/or any sulfur ring atom (if present) is optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized (i.e., to form an oxo group). More preferably, said heterocycloalkyl is a 5 to 7 membered (even more preferably a 6-membered) monocyclic heterocycloalkyl containing one nitrogen ring atom (through which the heterocycloalkyl is attached to group L) and optionally containing one or two further ring heteroatoms independently selected from nitrogen, oxygen and sulfur, wherein all remaining ring atoms are carbon atoms, wherein any nitrogen ring atom (if present) and/or any sulfur ring atom (if present) is optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized. Moreover, the heterocycloalkyl may contain a lactam function, i.e. the heterocycloalkyl may contain a second nitrogen ring atom (in addition to the first nitrogen ring atom through which the group A is attached to group L) which is adjacent to an oxidized carbon ring atom (C=O). A corresponding preferred example of group A is 3-oxopiperazin-1-yl which is optionally substituted with one or more (e.g., one, two, three, or four) groups R^A; a corresponding particularly preferred example of group A is 2,2-dimethyl-piperazin-3-on-1-yl (which may optionally be further substituted with one or more R^A). A further preferred example of group A is 4-(5-carboxypyridin-2-yl)piperazin-1-yl which is optionally substituted with one or more (e.g., one, two, three, or four) groups R^A; corresponding preferred examples of group A include 2,2-dimethyl-4-(5-carboxy-4,6-dimethyl-pyridin-2-yl)piperazin-1-yl or 2,2-dimethyl-4-(5-carboxy-pyridin-2-yl)piperazin-1-yl (each of which may optionally be further substituted with one or more R^A), particularly 2,2-dimethyl-4-(5-carboxy-4,6-dimethyl-pyridin-2-yl)piperazin-1-yl. A further preferred example of group A is 4-(5-carboxymethylpyridin-2-yl)piperazin-1-yl which is optionally substituted with one or more (e.g., one, two, three, or four) groups R^A; a corresponding preferred example of group A includes 2,2-dimethyl-4-(5-carboxymethylpyridin-2-yl)piperazin-1-yl (which may optionally be further

substituted with one or more R^A). Further preferred examples of group A are 4-(4-carboxythiazol-2-yl)piperazin-1-yl or 4-(5-carboxythiazol-2-yl)piperazin-1-yl, which are each optionally substituted with one or more (e.g., one, two, three, or four) groups R^A; corresponding preferred examples of group A include 2,2-dimethyl-4-(4-carboxythiazol-2-yl)piperazin-1-yl or 2,2-dimethyl-4-(5-carboxythiazol-2-yl)piperazin-1-yl (each of which may optionally be further substituted with one or more R^A). A further preferred example of group A is 4-(carboxymethyl)piperidin-1-yl which is optionally substituted with one or more (e.g., one, two, three, or four) groups R^A; corresponding preferred examples of group A include 3-methoxy-4-(carboxymethyl)piperidin-1-yl, 3-methyl-4-(carboxymethyl)piperidin-1-yl, or 3-fluoro-4-(carboxymethyl)piperidin-1-yl (each of which may optionally be further substituted with one or more R^A).

Further examples of group A include any of the specific groups A comprised in the compounds of formula (I) described in the examples section, particularly in any one of Examples 1 to 282.

Each R^A is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more (e.g., one, two or three) groups R^{Cyc}; and further wherein any two groups R^A, which are attached to the same carbon atom of group A, may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or a heterocycloalkyl, wherein said cycloalkyl or said heterocycloalkyl is optionally substituted with one or more (e.g., one, two or three) groups R^{Cyc}.

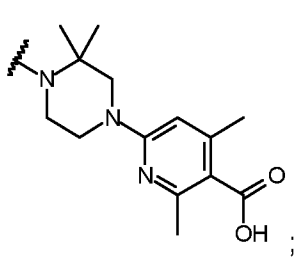
Preferably, each R^A is independently selected from C_{1-5} alkyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3}

alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-aryl, -(C_{0-3} alkylene)-cycloalkyl (e.g., cyclopropyl), -(C_{0-3} alkylene)-heteroaryl (e.g., pyridinyl; such as pyridin-2-yl), and -(C_{0-3} alkylene)-heterocycloalkyl, wherein the aryl group in said -(C_{0-3} alkylene)-aryl, the cycloalkyl group in said -(C_{0-3} alkylene)-cycloalkyl, the heteroaryl group in said -(C_{0-3} alkylene)-heteroaryl, and the heterocycloalkyl group in said -(C_{0-3} alkylene)-heterocycloalkyl are each optionally substituted with one or more groups R^{Cyc}; and further wherein any two groups R^A, which are attached to the same carbon atom of group A, may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl (e.g., a C_{3-7} cycloalkyl, such as cyclopropyl).

If group A is a heterocyclyl (as described herein above, including any of the corresponding preferred or exemplary cyclic groups A described herein; referred to as "ring A" in the following), it is particularly preferred that at least two substituents R^A are present, which are attached to the same carbon ring atom of ring A, and which are each independently a C_{1-5} alkyl group or which are mutually joined to form, together with the carbon ring atom that they are attached to, a C_{3-7} cycloalkyl group. Accordingly, it is particularly preferred that group A is a heterocycloalkyl (including any of the specific heterocycloalkyl groups described herein above) which is attached via a ring nitrogen atom to group L, wherein said heterocycloalkyl is either (i) substituted with two C_{1-5} alkyl groups which are attached to the same ring carbon atom or is (ii) substituted with two substituents R^A which are attached to the same ring carbon atom and are mutually joined to form, together with the ring carbon atom that they are attached to, a C_{3-7} cycloalkyl group (e.g. a cyclopropyl group), and wherein said heterocycloalkyl is optionally further substituted with one or more groups R^A. Even more preferably, group A is a heterocycloalkyl (including any of the specific heterocycloalkyl groups described herein above) which is attached via a ring nitrogen atom to group L, wherein said heterocycloalkyl is substituted with two C_{1-5} alkyl groups which are attached to the same ring carbon atom, and wherein said heterocycloalkyl is optionally further substituted with one or more groups R^A (e.g., with one group R^A which is 5-carboxy-4,6-dimethyl-pyridin-2-yl). The two C_{1-5} alkyl groups that are attached to the same ring carbon atom may be the same or different, and are preferably selected independently from methyl, ethyl, propyl and butyl; more preferably, the two C_{1-5} alkyl groups that are attached to the same ring carbon atom are each methyl. The C_{3-7} cycloalkyl group (which is formed from the two mutually joined substituents R^A) is preferably selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; more preferably, the C_{3-7} cycloalkyl group is a cyclopropyl group. The position, i.e. the specific carbon ring atom of ring A, at which the two C_{1-5} alkyl groups or the two mutually joined substituents R^A (which together form a C_{3-7} cycloalkyl group) are attached is not particularly limited. For example, the two C_{1-5} alkyl groups or the two mutually joined substituents R^A (which together form a C_{3-7} cycloalkyl group) may be attached to a carbon ring atom (of ring A) which is (i) directly adjacent to the nitrogen ring atom through which ring A is attached to group L, or is (ii) separated by one ring atom from said nitrogen ring atom (through which ring A is attached to group L), or is (iii) separated by two ring atoms from said nitrogen ring atom (through which ring A is attached to group L). Corresponding preferred examples of ring A include 2,2-dimethyl-piperazin-1-yl, 3,3-dimethyl-piperazin-1-yl, 2,2-dimethyl-piperazin-3-on-1-yl, 2,2,4-trimethyl-piperazin-3-on-1-yl, 4-ethyl-2,2-dimethyl-piperazin-3-on-1-yl, spiro[piperazin-2,1'-cyclopropane]-1-yl, spiro[piperazin-3,1'-cyclopropane]-1-yl, 2,2-dimethyl-piperidin-1-yl, 3,3-dimethyl-piperidin-1-yl, 4,4-dimethyl-piperidin-1-yl, spiro[piperidin-2,1'-cyclopropane]-1-yl, spiro[piperidin-3,1'-cyclopropane]-1-yl, or spiro[piperidin-4,1'-cyclopropane]-1-yl, wherein the piperazinyl moiety, the piperazinonyl moiety or the piperidinyl moiety in each of the aforementioned groups is optionally further substituted with one or

more (e.g., one or two) groups R^A (e.g., with one group R^A which is selected from 5-carboxypyridin-2-yl, 5-carboxy-4,6-dimethyl-pyridin-2-yl, 5-carboxymethyl-pyridin-2-yl, 5-carboxymethyl-4,6-dimethyl-pyridin-2-yl, 4-carboxythiazol-2-yl, and 5-carboxythiazol-2-yl). It is particularly preferred that the two C_{1-5} alkyl groups or the two mutually joined substituents R^A (which together form a C_{3-7} cycloalkyl group, preferably a cyclopropyl group) are attached to a carbon ring atom which is directly adjacent to the nitrogen ring atom through which ring A is attached to group L. A corresponding particularly preferred example of ring A is 2,2-dimethyl-piperazin-1-yl, wherein the piperazinyl group in said 2,2-dimethyl-piperazin-1-yl is optionally further substituted with one or more groups R^A; accordingly, ring A may be, e.g., 2,2-dimethyl-4-(5-carboxypyridin-2-yl)piperazin-1-yl, 2,2-dimethyl-4-(5-carboxy-4,6-dimethyl-pyridin-2-yl)piperazin-1-yl, 2,2-dimethyl-4-(5-carboxymethylpyridin-2-yl)piperazin-1-yl, 2,2-dimethyl-4-(5-carboxymethyl-4,6-dimethyl-pyridin-2-yl)piperazin-1-yl, 2,2-dimethyl-4-(4-carboxythiazol-2-yl)piperazin-1-yl, or 2,2-dimethyl-4-(5-carboxythiazol-2-yl)piperazin-1-yl. An even more preferred example of ring A is 2,2-dimethyl-4-(5-carboxy-4,6-dimethyl-pyridin-2-yl)piperazin-1-yl.

In accordance with the above, it is particularly preferred that group A is selected from any one of the following groups: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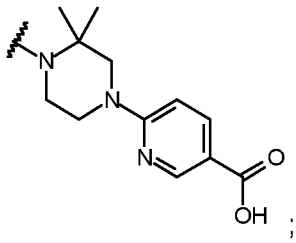
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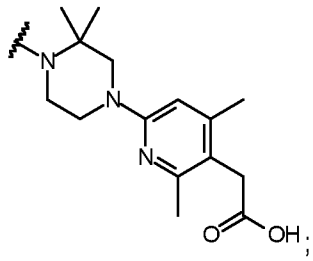
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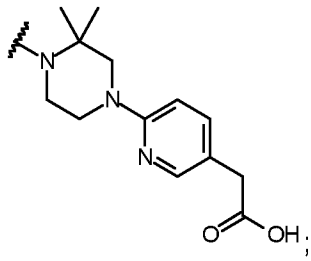
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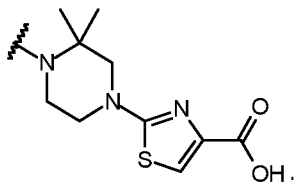
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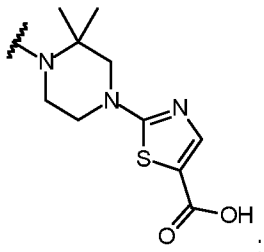
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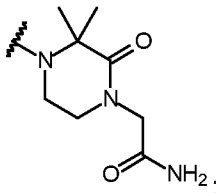
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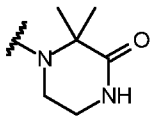
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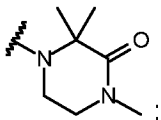
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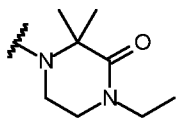
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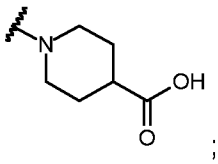
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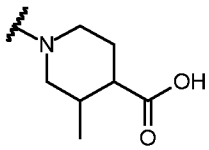
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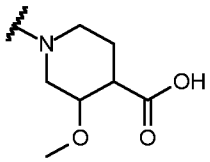
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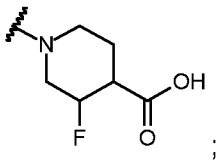
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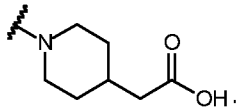
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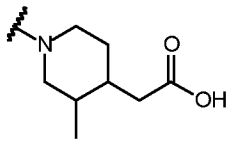
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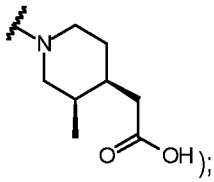
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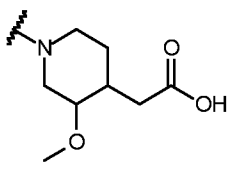
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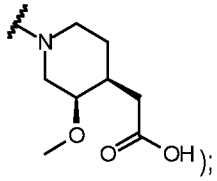
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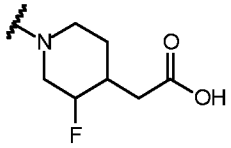
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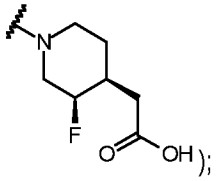
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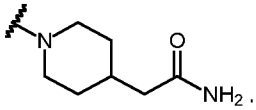
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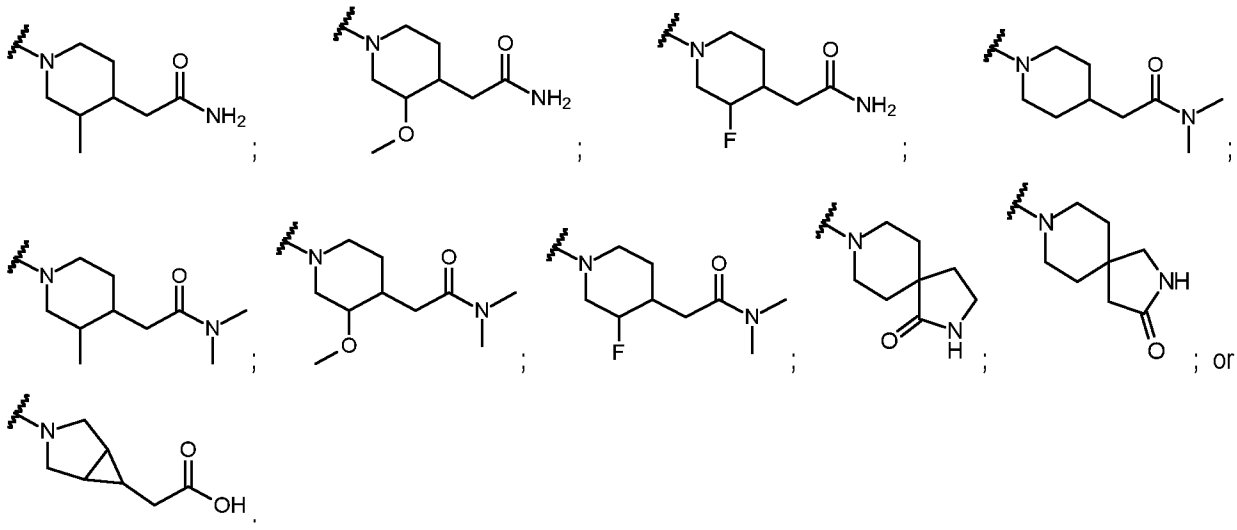
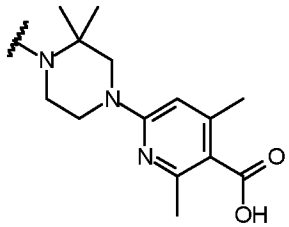
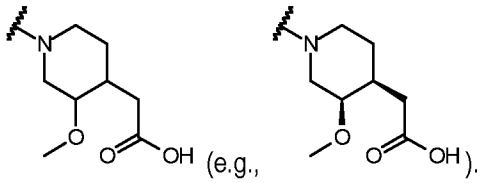


An especially preferred example of group A is 2,2-dimethyl-4-(5-carboxy-4,6-dimethyl-pyridin-2-yl)piperazin-1-yl:



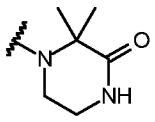
The present invention particularly relates to compounds of formula (I) as well as pharmaceutically acceptable salts and solvates thereof, wherein group A is 2,2-dimethyl-4-(5-carboxy-4,6-dimethyl-pyridin-2-yl)piperazin-1-yl, and R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a C_{3-7} cycloalkyl (preferably a cyclopentyl) which is optionally substituted with one or more groups R^{21}. The invention also specifically relates to compounds of formula (I) as well as pharmaceutically acceptable salts and solvates thereof, wherein group A is 2,2-dimethyl-4-(5-carboxy-4,6-dimethyl-pyridin-2-yl)piperazin-1-yl, and R^{2A} and R^{2B} are each independently C_{1-5} alkyl (e.g., R^{2A} and R^{2B} may each be methyl).

A further especially preferred example of group A is 3-methoxy-4-(carboxymethyl)piperidin-1-yl:



The invention particularly relates to compounds of formula (I) as well as pharmaceutically acceptable salts and solvates thereof, wherein group A is 3-methoxy-4-(carboxymethyl)piperidin-1-yl, and R^{2A} and R^{2B} are each independently C_{1-5} alkyl (e.g., R^{2A} and R^{2B} may each be methyl).

A further especially preferred example of group A is 2,2-dimethyl-3-oxo-piperazin-1-yl:



The invention particularly relates to compounds of formula (I) as well as pharmaceutically acceptable salts and solvates thereof, wherein group A is 2,2-dimethyl-3-oxo-piperazin-1-yl, and R^{2A} and R^{2B} are each independently C_{1-5} alkyl (e.g., R^{2A} and R^{2B} may each be methyl).

Each R^{Cyc} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), $-NH_2$, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO(C_{1-5} alkyl), -COOH, -COO(C_{1-5} alkyl), -O-CO(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), $-SO_2-NH_2$, $-SO_2$-NH(C_{1-5} alkyl), $-SO_2$-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), $-SO_2$-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -P(=O)(-OH)(-OH), -P(=O)(-OH)(-O-C_{1-5} alkyl), -P(=O)(-O-C_{1-5} alkyl)(-O-C_{1-5} alkyl), -(C_{0-3} alkylene)-cycloalkyl, -(C_{0-3} alkylene)-heterocycloalkyl, and -L^Z-R^Z.

Preferably, each R^{Cyc} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), $-NH_2$, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO(C_{1-5} alkyl), -COOH, -COO(C_{1-5} alkyl), -O-CO(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), $-SO_2-NH_2$, $-SO_2$-NH(C_{1-5} alkyl), $-SO_2$-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), $-SO_2$-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-cycloalkyl, -(C_{0-3} alkylene)-heterocycloalkyl, and -L^Z-R^Z. More preferably, each R^{Cyc} is independently selected from C_{1-5} alkyl, -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), $-NH_2$, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN.

Each L^Z is independently selected from a covalent bond, C_{1-7} alkylene, C_{2-7} alkenylene, and C_{2-7} alkynylene, wherein said alkylene, said alkenylene and said alkynylene are each optionally substituted with one or more (e.g., one, two, or three) groups independently selected from halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), $-NH_2$, -NH(C_{1-5} alkyl), and -N(C_{1-5} alkyl)(C_{1-5} alkyl), and further wherein one or more (e.g., one, two, or three) $-CH_2-$ units comprised in said alkylene, said alkenylene or said alkynylene are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and $-SO_2-$.

Preferably, each L^Z is independently selected from a covalent bond, C_{1-5} alkylene, C_{2-5} alkenylene, and C_{2-5} alkynylene, wherein said alkylene, said alkenylene and said alkynylene are each optionally substituted with one or more (e.g., one, two, or three) groups independently selected from halogen, C_{1-5} haloalkyl, -O-(C_{1-5}

haloalkyl), -CN, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), and -N(C_{1-5} alkyl)(C_{1-5} alkyl), and further wherein one or more (e.g., one, two, or three) -CH_2- units comprised in said alkylene, said alkenylene or said alkynylene are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-.

Each R^Z is independently selected from -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO(C_{1-5} alkyl), -COOH, -COO(C_{1-5} alkyl), -O-CO(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, wherein said aryl, said heteroaryl, said cycloalkyl, and said heterocycloalkyl are each optionally substituted with one or more (e.g., one, two or three) groups independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), carbocyclyl, and heterocyclyl, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more groups independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), and -SO_2-(C_{1-5} alkyl).

Preferably, each R^Z is independently selected from -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO(C_{1-5} alkyl), -COOH, -COO(C_{1-5} alkyl), -O-CO(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, wherein said aryl, said heteroaryl, said cycloalkyl, and said heterocycloalkyl are each optionally substituted with one or more (e.g., one, two or three) groups independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), and -N(C_{1-5} alkyl)(C_{1-5} alkyl).

It is preferred that at least one (more preferably all) of the following conditions apply to the compounds of formula (I):

– if ring B is a pyrrolidinyl ring, ring D is a pyridinyl ring, R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a cyclopropyl, L is -CO-, and group A is morpholin-4-yl, then R^1 is not 5-R^{11}-pyrimidin-2-yl or acetyl; and/or

– if ring B and ring D together are a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-c]pyridinyl ring or a 6-oxo-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazinyl ring, R^{2A} and R^{2B} are each methyl, R^1 is phenyl which is optionally substituted with one or more groups R^{11}, L is -CO-, and group A is -NH-R^N, then R^N is not a heterocycloalkyl which comprises one oxidized sulfur ring atom, in which all other ring atoms are carbon atoms, and which is substituted with a methyl group; and/or

– if ring B and ring D together are a 3-R^X-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazinyl ring, R^X is -OH, one of R^{2A} and R^{2B} is methyl, the other one of R^{2A} and R^{2B} is -CON(-CH_3)$_2$, R^1 is methyl, L is -CO-, and group A is -NH-R^N, then R^N is not 4-fluorobenzyl; and/or

– if ring B and ring D together are a 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine ring or a 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine, L is -CO-, group A is -NH-R^N, and R^1 is -CH_2-phenyl or -CH_2-pyridinyl, wherein the phenyl in said -CH_2-phenyl and the pyridinyl in said -CH_2-pyridinyl are each optionally substituted with one or more groups R^{11}, then R^{2A} and R^{2B} are not methyl.

Thus, as explained above, it is preferred that the following proviso applies to the compounds of formula (I): If ring B is a pyrrolidinyl ring, ring D is a pyridinyl ring, R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a cyclopropyl, L is -CO-, and group A is morpholin-4-yl, then R^1 is not 5-R^{11}-pyrimidin-2-yl or acetyl. Accordingly, if B is a pyrrolidinyl ring, if D is a pyridinyl ring, if R^{2A} and R^{2B} are mutually joined to form (together with the carbon atom that they are attached to) a cyclopropyl, if L is -CO-, and if group A is morpholin-4-yl, then it is preferred that the group R^1 is not 5-R^{11}-pyrimidin-2-yl or acetyl (i.e., it is preferred that R^1 is not a pyrimidin-2-yl group which carries one substituent R^{11} in the 5-position of the pyrimidine ring, and that R^1 is not acetyl). More preferably, if ring B is a pyrrolidinyl ring, ring D is a pyridinyl ring, L is -CO-, and group A is morpholin-4-yl, then R^1 is not 5-R^{11}-pyrimidin-2-yl or acetyl. Even more preferably, if ring B is a pyrrolidinyl ring, ring D is a pyridinyl ring, and L is -CO-, then R^1 is not 5-R^{11}-pyrimidin-2-yl or acetyl. Even more preferably, if ring B is a pyrrolidinyl ring and L is -CO-, then R^1 is not 5-R^{11}-pyrimidin-2-yl or acetyl. Even more preferably, if ring B is a pyrrolidinyl ring, then R^1 is not 5-R^{11}-pyrimidin-2-yl or acetyl. Yet even more preferably, R^1 is not 5-R^{11}-pyrimidin-2-yl (i.e., R^1 is a group different from 5-R^{11}-pyrimidin-2-yl) and/or R^1 is not acetyl. Still more preferably, R^1 is not 5-R^{11}-pyrimidin-2-yl and is not acetyl.

Moreover, as explained above, it is preferred that the following proviso applies to the compounds of formula (I): If ring B and ring D together are a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-c]pyridinyl ring or a 6-oxo-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazinyl ring, R^{2A} and R^{2B} are each methyl, R^1 is phenyl which is optionally substituted with one or more groups R^{11}, L is -CO-, and group A is -NH-R^N, then R^N is not a heterocycloalkyl which comprises one oxidized sulfur ring atom, in which all other ring atoms are carbon atoms, and which is substituted with a methyl group. Accordingly, if ring B and ring D are fused to form a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-c]pyridinyl ring or a 6-oxo-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazinyl ring, if R^{2A} and R^{2B} are each methyl, if R^1 is phenyl which is optionally substituted with one or more groups R^{11}, if L is -CO-, if group A is -N(-R^N)-R^N, and if one group R^N is hydrogen, then it is preferred that the other

group R^N is not a heterocycloalkyl which comprises one oxidized sulfur ring atom (particularly a ring atom -S(=O)$_2$-), in which all other ring atoms are carbon atoms, and which is substituted with a methyl group. More preferably, if ring B and ring D together are a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-c]pyridinyl ring or a 6-oxo-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazinyl ring, R^{2A} and R^{2B} are each methyl, L is -CO-, and group A is -NH-R^N, then R^N is not a heterocycloalkyl which comprises one oxidized sulfur ring atom, in which all other ring atoms are carbon atoms, and which is substituted with a methyl group. Even more preferably, if ring B and ring D together are a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-c]pyridinyl ring or a 6-oxo-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazinyl ring, L is -CO-, and group A is -NH-R^N, then R^N is not a heterocycloalkyl which comprises one oxidized sulfur ring atom, in which all other ring atoms are carbon atoms, and which is substituted with a methyl group. Even more preferably, if ring B is a 2-oxopyrrolidinyl ring, ring D is a pyridinyl ring or a pyridazinyl ring, L is -CO-, and group A is -NH-R^N, then R^N is not a heterocycloalkyl which comprises one oxidized sulfur ring atom, in which all other ring atoms are carbon atoms, and which is substituted with a methyl group. Even more preferably, if ring B is a 2-oxopyrrolidinyl ring and group A is -NH-R^N, then R^N is not a heterocycloalkyl which comprises one oxidized sulfur ring atom, in which all other ring atoms are carbon atoms, and which is substituted with a methyl group. Yet even more preferably, group A is not -NH-R^N, wherein R^N is a heterocycloalkyl which comprises one oxidized sulfur ring atom, in which all other ring atoms are carbon atoms, and which is substituted with a methyl group. Still more preferably, group A is not -NH-R^N, wherein R^N is heterocycloalkyl optionally substituted with one or more groups R^{Cyc}.

Furthermore, as explained above, it is preferred that the following proviso applies to the compounds of formula (I): If ring B and ring D together are a 3-R^X-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazinyl ring, R^X is -OH, one of R^{2A} and R^{2B} is methyl, the other one of R^{2A} and R^{2B} is -CON(-CH_3)$_2$, R^1 is methyl, L is -CO-, and group A is -NH-R^N, then R^N is not 4-fluorobenzyl. Accordingly, if ring B and ring D together are a 4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazinyl ring which is substituted in position 3 with one group R^X which is -OH, if one of R^{2A} and R^{2B} is methyl, if the other one of R^{2A} and R^{2B} is -CON(-CH_3)CH_3, if R^1 is methyl, if L is -CO-, and if group A is -NH-R^N, then it is preferred that R^N is not 4-fluorobenzyl (i.e., that R^N is not a group -CH_2-(4-fluorophenyl)). More preferably, if ring B and ring D together are a 3-R^X-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazinyl ring, and if L is -CO-, then R^X is not -OH. Even more preferably, if ring D is a pyrazolyl ring which is optionally substituted with one or more groups R^X, and if L is -CO-, then said one or more groups R^X are not -OH.

As also explained above, it is preferred that the following proviso applies to the compounds of formula (I): If ring B and ring D together are a 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine ring or a 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine, L is -CO-, group A is -NH-R^N, and R^1 is -CH_2-phenyl or -CH_2-pyridinyl, wherein the phenyl in said -CH_2-phenyl and the pyridinyl in said -CH_2-pyridinyl are each optionally substituted with one or more groups R^{11}, then R^{2A} and R^{2B} are not methyl. More preferably, if ring B and ring D together are a 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine ring or a 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine, L is -CO-, and group A is -NH-R^N, then R^{2A} and R^{2B} are not methyl. Even more preferably, if ring B and ring D together are a 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine or a 2-R^Y-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine ring, L is -CO-, and group A is -NH-R^N, then R^{2A} and R^{2B} are not methyl. Yet even more preferably, if ring

B is a 2-oxopyrrolidinyl ring or a 2-R^Y-pyrrolidinyl ring, ring D is a pyridinyl ring, L is -CO-, and group A is -NH-R^N, then R^{2A} and R^{2B} are not methyl.

Further to the above, it is preferred that the compound 1-(tert-butyl)-6-((4-fluorophenyl)carbamoyl)-2-oxo-1,2-dihydrospiro[pyrido[2,3-b][1,4]oxazine-3,3'-pyrrolidine] is excluded from formula (I). More preferably, if ring B is a non-aromatic 4- to 8-membered heterocyclic ring comprising a -C(=O)- ring atom adjacent to the ring carbon atom carrying R^{2A} and R^{2B}, wherein said ring B is optionally substituted with one or more groups R^Y, and if R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a pyrrolidin-3-yl group which is optionally substituted with one or more groups R^{21}, then R^1 is not tert-butyl. Even more preferably, if ring B is a non-aromatic 4- to 8-membered heterocyclic ring comprising a -C(=O)- ring atom adjacent to the ring carbon atom carrying R^{2A} and R^{2B}, wherein said ring B is optionally substituted with one or more groups R^Y, and if R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a heterocycloalkyl which is optionally substituted with one or more groups R^{21}, then said heterocycloalkyl is not pyrrolidin-3-yl.

It is particularly preferred that the compound of formula (I) is any one of the specific compounds of formula (I) described in the examples section of this specification, including any one of Examples 1 to 282 described further below, either in non-salt form and/or non-solvated form, or as a pharmaceutically acceptable salt or solvate of the respective compound.

Accordingly, it is particularly preferred that the compound of formula (I) is selected from:

1'-(4-chloro-3-fluorophenyl)-5'-(2,2-dimethyl-3-oxopiperazine-1-carbonyl)-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridin]-2'(1'H)-one;

1'-(4-chloro-3-fluorophenyl)-5'-(2,2-dimethyl-3-oxopiperazine-1-carbonyl)spiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridin]-2'(1'H)-one;

4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;

8-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-1,3,8-triazaspiro[4.5]decane-2,4-dione;

methyl 1-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperidine-4-carboxylate;

1-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperidine-4-carboxylic acid;

methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

4-(1'-(3-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;

4-(1'-(2-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;

4-(3,3-dimethyl-1-(thiophen-3-yl)-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;
4-(1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;
methyl 6-(4-(1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;
6-(4-(1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;
4-(1-(4-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;
methyl 6-(4-(1-(3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;
6-(4-(1-(3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;
4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;
4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-1-ethyl-3,3-dimethylpiperazin-2-one;
(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(3,3-dimethylmorpholino)methanone;
tert-butyl 4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate;
(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(2,2-dimethylpiperazin-1-yl)methanone;
(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(4-ethyl-2,2-dimethylpiperazin-1-yl)methanone;
1-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)ethan-1-one;
ethyl 4-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-oxobutanoate;
4-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-oxobutanoic acid;
ethyl 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-5-oxopentanoate;
5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-5-oxopentanoic acid;
8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-1-methyl-1,3,8-triazaspiro[4.5]decan-4-one;
2-(3-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-azabicyclo[3.1.0]hexan-6-yl)acetic acid;
methyl 2-(3-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-azabicyclo[3.1.0]hexan-6-yl)acetate;

methyl 2-((1R,5S,6S)-3-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-azabicyclo[3.1.0]hexan-6-yl)acetate;

2-((1R,5S,6S)-3-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-azabicyclo[3.1.0]hexan-6-yl)acetic acid;

ethyl 1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidine-4-carboxylate;

1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidine-4-carboxylic acid;

methyl 2-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-4-yl)acetate;

2-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-4-yl)acetic acid;

2-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid;

methyl 2-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate;

methyl 2-((3R,4S)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate;

2-((3R,4S)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid;

ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylpyrimidine-5-carboxylate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylpyrimidine-5-carboxylic acid;

ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyrimidine-5-carboxylate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-pyrimidine-5-carboxylic acid;

ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carboxylate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carboxylic acid;

methyl 6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

3-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)butanoic acid;

methyl 3-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)butanoate;

methyl (R)-3-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)butanoate;

(R)-3-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)butanoic acid;

N-(1-carbamoylcyclopropyl)-1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide;

methyl 6-((2-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)ethyl)(methyl)amino)-2,4-dimethylnicotinate;

6-((2-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)ethyl)(methyl)amino)-2,4-dimethylnicotinic acid;

1-(4-chloro-3-fluorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide;

1-(4-chloro-3-fluorophenyl)-N-(2-hydroxy-2-methylpropyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide;

4-(1-(4-chloro-3-fluorophenyl)-3-ethyl-3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;

N-(1-carbamoylcyclopropyl)-1-(4-chloro-3-fluorophenyl)-3-ethyl-3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide;

4-(1'-(4-chloro-3-fluorophenyl)-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;

6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;

4-(1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;

methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

4-(8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;

cis-4-(8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;

4-((3aR,8aR)-8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;

4-((3aS,8aS)-8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;

methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

ethyl 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-1,3,4-thiadiazole-2-carboxylate;

(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(2,2-dimethyl-4-(1,3,4-thiadiazol-2-yl)piperazin-1-yl)methanone;

ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazole-5-carboxylate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazole-5-carboxylic acid;

ethyl 2-(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazol-5-yl)acetate;

2-(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazol-5-yl)acetic acid;

methyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-5-methylthiazole-4-carboxylate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-5-methylthiazole-4-carboxylic acid;

1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-7,7-dimethyl-1,4-diazepan-5-one;

8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-2,8-diazaspiro[4.5]decan-1-one;

8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-2,8-diazaspiro[4.5]decan-3-one;

1-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-4-yl)imidazolidin-2-one;

ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-(trifluoromethyl)thiazole-5-carboxylate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-(trifluoromethyl)thiazole-5-carboxylic acid;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N,N-dimethylthiazole-4-carboxamide;

(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(4-(4-(4-hydroxypiperidine-1-carbonyl)thiazol-2-yl)-2,2-dimethylpiperazin-1-yl)methanone;

(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(2,2-dimethyl-4-(4-(morpholine-4-carbonyl)thiazol-2-yl)piperazin-1-yl)methanone;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carboxamide;

methyl 6-(4-(1-(3-fluoro-4-methylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(3-fluoro-4-methylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

methyl 6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-difluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-(1'-(4-chloro-3-fluorophenyl)-3-fluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridin]-2-en-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-((3S,4S)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate;

2-((3S,4S)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid;

methyl 2-((3R,4R)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate;

2-((3R,4R)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid;

ethyl (2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carbonyl)glycinate;

(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carbonyl)glycine;

methyl 2-((3S,4R)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate;

2-((3S,4R)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid;

methyl 6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(2,2-dimethyl-4-(4-(4-methylpiperazine-1-carbonyl)thiazol-2-yl)piperazin-1-yl)methanone;

methyl 6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)isonicotinate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)isonicotinic acid;

ethyl 3-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)isonicotinate;

3-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)isonicotinic acid;

ethyl 6-((1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-3-yl)amino)nicotinate;

6-((1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-3-yl)amino)nicotinic acid;

ethyl 6-((1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-3-yl)(methyl)amino)nicotinate;

6-((1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-3-yl)(methyl)amino)nicotinic acid hydrochloride;

methyl 6-(4-(1'-(3,4-difluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(3,4-difluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-4-yl)acetate;

2-(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-4-yl)acetic acid;

ethyl 2-(5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-2-yl)acetate;

2-(5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-2-yl)acetic acid;

methyl 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

1‘-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)spiro[indoline-3,3‘-pyrrolidin]-2-one;

8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one;

ethyl 6-(6-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-2,6-diazaspiro[3.3]heptan-2-yl)nicotinate;

6-(6-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-2,6-diazaspiro[3.3]heptan-2-yl)nicotinic acid;

methyl 2-(1-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)piperidin-4-yl)acetate;

2-(1-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)piperidin-4-yl)acetic acid;

4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;

methyl 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-difluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-difluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

ethyl 2-((1R,5S)-8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)acetate;

2-((1R,5S)-8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)acetic acid;

methyl 6-(4-(6-(5-(4-(5-(methoxycarbonyl)-4,6-dimethylpyridin-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)nicotinoyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

methyl 6-(4-(1-(5-chloropyridin-2-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(6-(5-(4-(5-carboxy-4,6-dimethylpyridin-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)nicotinoyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-(1-(5-chloropyridin-2-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(3,3-dimethyl-1-(pyridin-2-yl)-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

ethyl 1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-4-(pyridin-2-yl)piperidine-3-carboxylate;

(cis)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-4-(pyridin-2-yl)piperidine-3-carboxylic acid;

(trans)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-4-(pyridin-2-yl)piperidine-3-carboxylic acid;

methyl 6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-3-methylpicolinate;

6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-3-methylpicolinic acid;

methyl 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2-methoxynicotinate;

5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2-methoxynicotinic acid;

methyl 6-(4-((1S,3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

methyl 6-(4-((1R,3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

methyl 6-(4-((3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1S,3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-((1R,3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-((3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-((1S,3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

methyl 6-(4-((1R,3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

methyl 6-(4-((3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1S,3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-((1R,3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-((3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)nicotinate;

methyl 5-(4-(1-(3-fluoro-4-(4-(5-(methoxycarbonyl)pyridin-3-yl)-2,2-dimethylpiperazine-1-carbonyl)phenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)nicotinate;

5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)nicotinic acid;

5-(4-(4-(5-(4-(5-carboxypyridin-3-yl)-2,2-dimethylpiperazine-1-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-2-fluorobenzoyl)-3,3-dimethylpiperazin-1-yl)nicotinic acid;

methyl 2-(6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)propanoate;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)propanoic acid;

methyl 6-(4-(1-(4-cyanocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(4-carbamoylcyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(1-(4,4-difluorocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-(4,4-difluorocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

4-(5-(4-(4,6-dimethylpyridin-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)cyclohexane-1-carbonitrile;

methyl 2-(6-(4-(1-cyclopentyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-cyclopentyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(1-(4-cyanocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-(4-cyanocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)-2-methylpropanoate;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)-2-methylpropanoic acid;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-8,8-dimethyl-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-8,8-dimethyl-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(4-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(4-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-cyclopentyl-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-cyclopentyl-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(3-(4-chloro-3-fluorobenzyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(3-(4-chloro-3-fluorobenzyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(1,3-dihydroisobenzofuran-5-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

2-(6-(4-(5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(3,3-dimethyl-5'-(3,4,5-trifluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(3,3-dimethyl-5'-(3,4,5-trifluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

2-(6-(4-(5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-8-methoxy-7,7-dimethyl-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-8-methoxy-7,7-dimethyl-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-6-methoxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-6-methoxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(3-(4-chloro-3-fluorophenyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(3-(4-chloro-3-fluorophenyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-6-hydroxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 8-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-8-oxooctanoate;

8-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-8-oxooctanoic acid;;

N-(37-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-3-methyl-4,17,30,37-tetraoxo-7,10,13,20,23,26-hexaoxa-3,16,29-triazaheptatriacontyl)-N-methylpalmitamide;

methyl 4-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,6-dimethylnicotinate;

4-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,6-dimethylnicotinic acid;

methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

1-(1-((5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazin]-2'-yl)sulfonyl)piperidin-4-yl)imidazolidin-2-one;

methyl 2-(6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrazino[2,3-b][1,4]oxazine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrazino[2,3-b][1,4]oxazine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

tert-butyl 2-(4-(5-(2-methoxy-2-oxoethyl)pyridin-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-7,7-dimethyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(1-(4-cyclopropylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(4-cyclopropylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-3,7,7-trimethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-3,7,7-trimethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

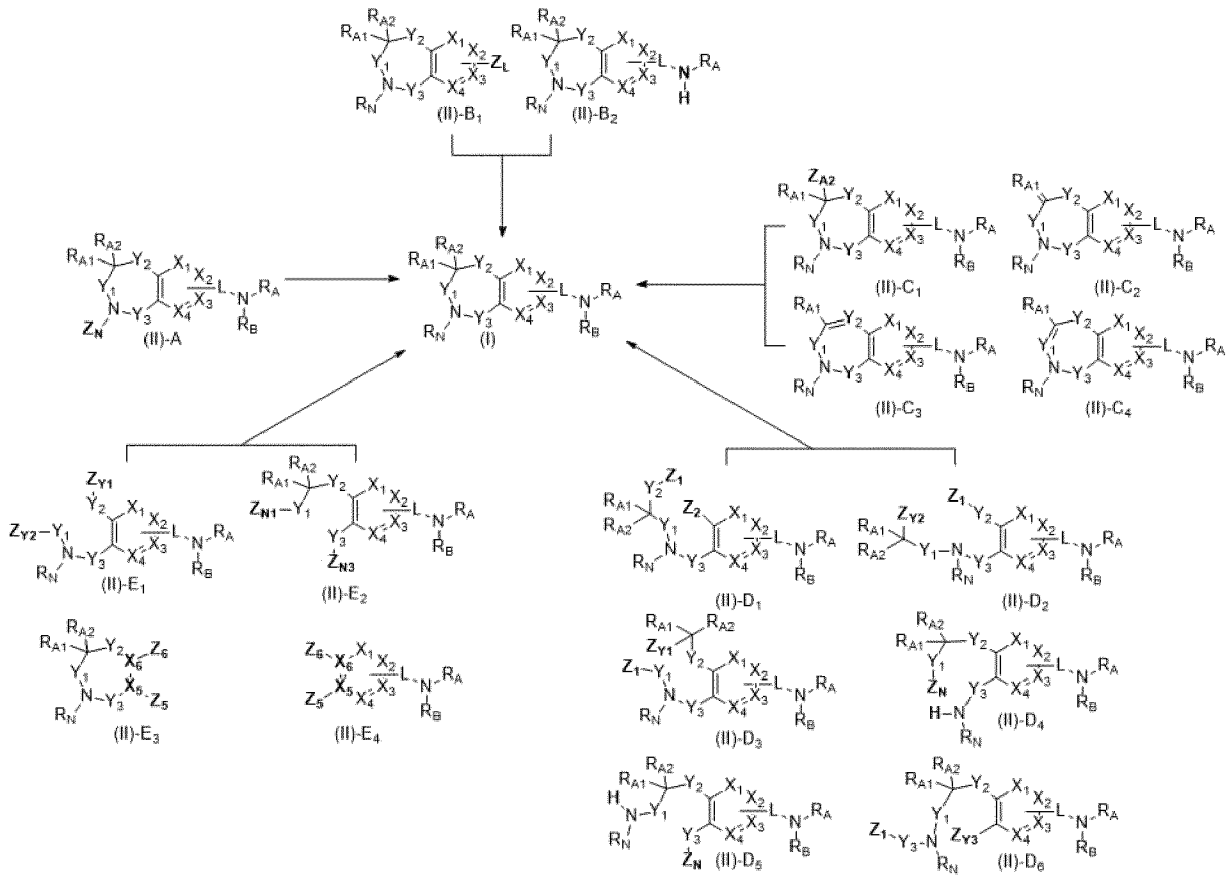
4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-2-one;

or a pharmaceutically acceptable salt or solvate of any one of the above-mentioned compounds.

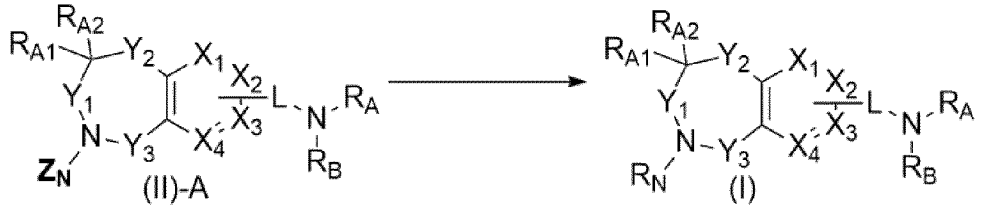
The present invention also relates to each of the intermediates described further below in the examples section of this specification, including any one of these intermediates in non-salt form and/or non-solvated form, or in the form of a salt or solvate (e.g., a pharmaceutically acceptable salt or solvate) of the respective compound. Such intermediates can be used, in particular, in the synthesis of the compounds of formula (I).

For a person skilled in the field of synthetic chemistry, various ways for the preparation of the compounds of general formula (I) and their pharmaceutically acceptable salts and solvates will be readily apparent. For example, the compounds of the invention can be prepared in accordance with, or in analogy to, the synthetic routes described in detail in the examples section. In particular, the compounds of formula (I) can be synthesized in accordance with the methods described in the following general schemes (general disconnections).

Schematic overview:



Compounds of formula (I) can be obtained from a precursor (II)-A according to the general disconnection A:



With Z_N being a hydrogen atom:

- By a N-derivation known to the person skilled in the art, with the appropriate partner (based on the works described in *Chem. Rev.*, **2016**, 116, 12564-12649, *Chem. Rev.* **2019**, 119, 11857–11911, *Chem. Rev.* **2019**, 119, 12491–12523, *Chem. Rev.* **2019**, 119, 11245–11290, *Chem. Soc. Rev.*, **2014**, 3525-3550, or Nature, **2020**, 581, 415–420)
- By aniline synthesis from the appropriate aldehyde or keto derivative (based on the works described in *Org. Lett.*, **2012**, *14*, 5606-5609 or *Nature,* ***2020***, 584**,** 75–81).

With Z_N being a methyl group:

- By N-arylation (based on the work described in *Org. Lett.*, **2013**, *15*, 5452-5455) with the apprioate aryne precursor.

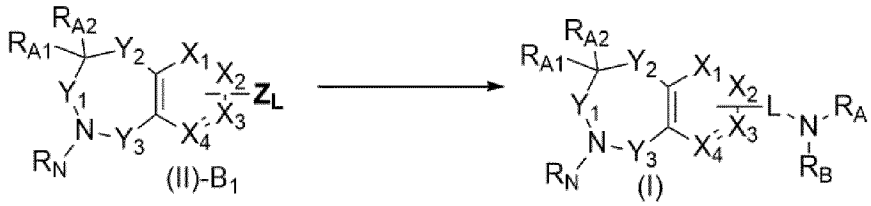
With Z_N being a benzoic group:

- By metal catalyzed debenzoylative N-arylation with the appropriate organometallic partner (based on the work described in *J. Org. Chem.*, **2006**, *71*, 219-224)

With Z_N being a substituted carbonyl group:

- By rearrangement of the corresponding amide derivative (based on the work described in *Synlett* **2013**, 24, 1448-1454), or by rearrangement of the corresponding carbamate derivative (based on the work described in *J. Am. Chem. Soc.*, **2019**, *141*, 7262-7265)
- By metal catalyzed deacylative N-arylation with the appropriate halogenated or pseudo-halogenated aryl (based on the works described in *Org. Lett.* **2021**, 23, 3, 687–691 or *J. Org. Chem.*, **2012**, *77*, 9236-9239)

Compounds of formula (I) can be obtained from a precursor (II)-B_1 according to the general disconnection B_1:



With Z_L being a hydrogen atom (based on the work described in *ARKIVOC* **2013**, 1, 154-174, *ARKIVOC* **2001**, 1, 242-268 or *Synthesis* **2011**, 20, 3209-3219):

- By N-oxidation followed by a sequence leading to the carboxylic, sulfonic or sulfinic acid and subsequent amide, sulfonamide or sulfinamide synthesis with the appropriate amine.

- By N-oxidation followed by a sequence leading to the conversion of Z_L into a halogen or a pseudo-halogen, followed by a transformation or a sequence described below.
- By carbon-hydrogen bond activation with a metal leading to the conversion of Z_L into a halogen, a pseudo-halogen, or an organometallic group, followed by a transformation or a sequence described below.

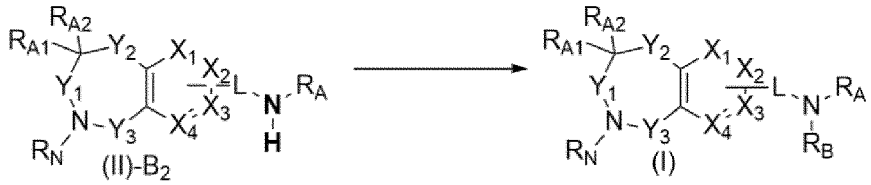
With Z_L being a hydroxy group (based on the work described in *Org. Process Res. Dev.* **2004**, 8, 62-71 or *Tet. Lett.*, **1992**, 33, 1181-1184):

- By a transformation or sequence known to the person skilled in the art of Z_L into a halogen or pseudo-halogen, followed by a transformation or a sequence described below.

With Z_L being a halogen or a pseudo-halogen, or an organometallic group:

- By a direct, metal catalyzed amino-carbonylation reaction, sulfinamide or sulfonamide synthesis with the appropriate amine (based on the work described in *RSC Adv.*, **2014**, 4, 10367-10389 or *Synthesis*, **2008**, 311-312)
- By a transformation or a sequence known to the person skilled in the art leading to a carboxylic, sulfonic or sulfinic acid, followed by amide, sulfonamide or sulfinimide synthesis with the appropriate amine (based on the work described in *J. Org. Chem.*, **2008**, *73*, 3967-3969)

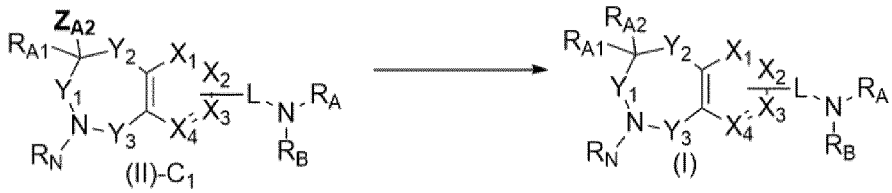
Compounds of formula (I) can be obtained from a precursor (II)-B_2 according to the general disconnection B_2:



(II)-B_2 (I)

By a transformation or a sequence known to the person skilled in the art leading to a tertiary amide, sulfonamide or sulfinimide by for example a sequence including deprotonation and N-substitution with the appropriate partner, or a metal catalyzed N-derivation.

Compounds of formula (I) can be obtained from a precursor (II)-C_1 according to the general disconnection C_1:



(II)-C_1 (I)

With Z_{A2} being a halogen or a pseudo-halogen and R_{A1}, Y_1 or Y_2 linked with a carbonyl (based on the works described in *ChemistryOpen*, **2020**, 9, 100–17, or *Acc. Chem. Res.* **2008**, 41, 11, 1545–1554):

- By halogen metal exchange, followed by derivation by metal catalysed coupling with the appropriate partner.
- By halogen metal exchange, followed by nucleophilic displacement or nucleophilic addition on the appropriate partner.

- By direct nucleophilic displacement of the halogen or pseudo-halogen with the appropriate nucleophile.

With Z_{A2} being a hydrogen atom and R_{A1}, Y_1 or Y_2 linked with a carbonyl (based on the works described in *ChemistryOpen*, **2020**, 9, 100–17, or *Acc. Chem. Res.* **2008**, 41, 11, 1545–1554):

- By metalation followed by derivation by metal catalysed coupling with the appropriate partner.
- By metalation followed by nucleophilic displacement or nucleophilic addition on the appropriate partner.
- By direct nucleophilic displacement of the halogen or pseudo-halogen with the appropriate nucleophile.
- By oxidative coupling (based on the work described in *Angew. Chem. Int. Ed.* **2017**, 56, 5921–5925)

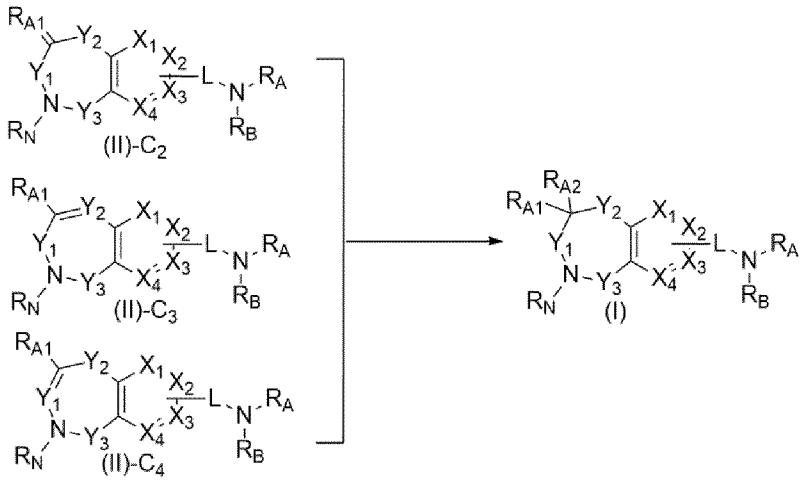
With Z_{A2} being a hydrogen atom and Y_1 being a bond:

- By photoredox catalysed alpha derivation of amine with the appropriate radical acceptor (based on the works described in *J. Am. Chem. Soc.* **2020,** 15, 142, 11972–11977, or Chem. Rev., **2013**, 113, 5322−5363).

With Z_{A2} being a halogen or a pseudo-halogen and Y_2 being a bond:

- By metal catalysed coupling with the appropriate partner (based on the works described in Org. Lett., **2009**, 11, 23, 5514-5517)

Compounds of formula (I) can be obtained from a precursor (II)-C_2, (II)-C_3 or (II)-C_4 according to general disconnection $C_{2/3/4}$:

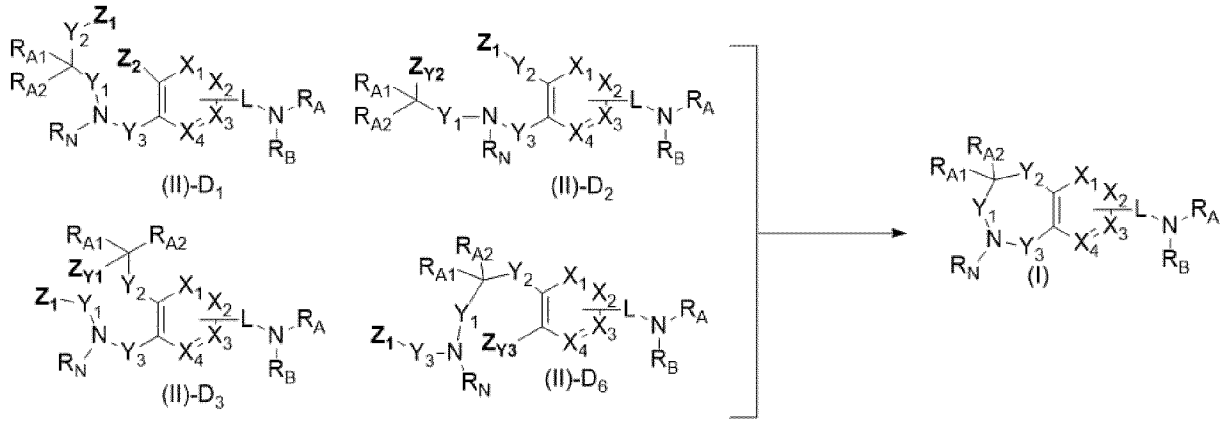


- By [2+1] cycloaddition with the appropriate partner (based on the works described in *Chem. Rev.* **2017**, 117, 18, 11651–11679).
- By epoxidation followed by epoxide opening with the appropriate partner (based on the works described in *Chem. Soc. Rev.*, **2011**, 40, 1722-1760, *J. Am. Chem. Soc.* **1993**, 115, 19, 8867–8868, or *Synlett,* **2005,** 8, 1199-1222).
- By [2+2] cycloaddition with the appropriate partner (based on the works described in *Eur. J. Org. Chem.*, **2020**, 10, 1310-1326, or *Chem. Rev.* **2016**, 116, 9748−9815).

- By [2+2] cycloaddition with the appropriate carbonyle, eventually followed with the corresponding oxetane opening with the approriate partner (based on the works described in *Molecules,* **2013**, 18, 11384-11428, or *Chem. Rev.*, **2016**, 116, 12150−12233).
- By [2+3] cycloaddition with the appropriate partner (based on the works described in *Beilstein J. Org. Chem.* **2020**, 16, 3015–3031, or *Chem. Rev.* **2005**, 105, 2765−2809).
- By [2+4] Diels-Alder cycloaddition with the appropriate diene or with the appropriate dienophile (based on the works described in *Chem. Rev.* **1942**, 31, 2, 319–523, or *Chem. Soc. Rev.*, **2018**, 47, 7926).
- By a nucleophilic addition known to the person skilled in the art with (II)-C_3 containing a conjugated double bond (Y_2 being -CZ-) or an imine (Y_2 being a N) or with (II)-C_4 containing an α,β-unsaturated carbonyl (Y_1 being -CZ_2-C(O)-) sulfononyl (Y_1 being -CZ_2-$S(O)_2$-) or an imine (Y_1 being a bond).
- By an electrophilic addition known to the person skilled in the art on the exo cyclic double bond on (II)-C_4 (Y_1 being -CZ-).

Additionally, specific intermediates (II)-C_2 (II)-C_3 and (II)-C_4 can be obtained, or can be precursors to obtain compounds of formula (I), using synthetic strategies residing on the dearomatization of respective aromatic compounds (based on the works described in *Synlett*, **2020**, 31, 1775-1788, *Org. Chem. Front.*, **2020**, 7, 3967-3998, *Tetrahedron*, **2015**, 71, 3549-359, *Org. Lett.* **2019**, 21, 4459–4463, *Synthesis,* **2022**, 54, 92-110, *Chem Sci.* **2017,** 8, 7112–7118, *Org. Biomol. Chem.*, **2014**,12, 4807-4815, or *Tetrahedron*, **2019**, 75, 2063-2097).

Compounds of formula (I) can be obtained from a precursor (II)-D_1 (II)-D_2, (II)-D_3, or (II)-D_6 according to general disconnection $D_{1/2/3/6}$:



With Z_1 being a hydrogen or an organometallic group, or a halogen or pseudo halogen and Z_2, Z_{Y1}, Z_{Y2}, Z_{Y3} being respectively a halogen or a pseudo halogen, or a hydrogen or an organometallic group:

- By a metal catalyzed coupling reaction known to the person skilled in the art.

With Z_1 being a hydrogen, or a halogen or pseudo halogen and Z_2 Z_{Y1}, Z_{Y2}, Z_{Y3}, being respectively a halogen or a pseudo halogen, or a hydrogen:

- By a guided metalation followed by an intramolecular nucleophilic substitution or nucleophilic aromatic substitution known to the person skilled in the art.

- By a nucleophilic substitution or nucleophilic aromatic substitution known to the person skilled in the art.

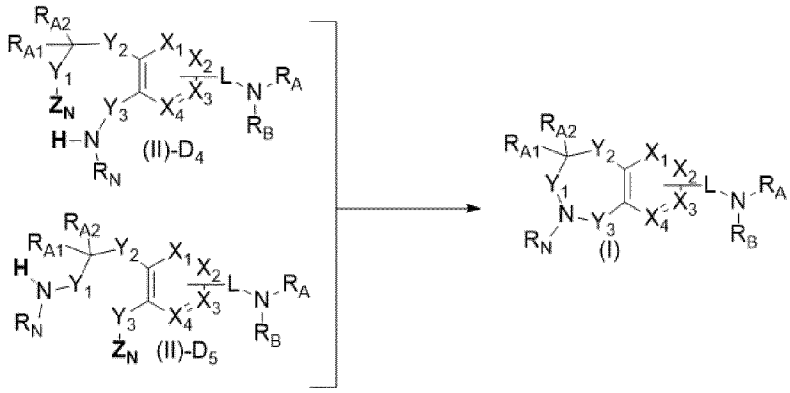
With Z_1 and Z_2, Z_{Y1}, Z_{Y2}, Z_{Y3} being both halogens or pseudo halogens:

- By a metal catalyzed reductive coupling (based on the works described in *Chem. Eur. J.* **2014**, 20, 15334–15338, or *Chem. Eur. J.* **2014**, 20, 6828 – 6842).

With Z_1 and Z_2, Z_{Y1}, Z_{Y2}, Z_{Y3} being the appropriate partners:

- By a suitable cycloaddition mentioned in general disconnection $C_{2/3/4}$

Compounds of formula (I) can be obtained from a precursor (II)-D_4 or (II)-D_5 according to general disconnection $D_{4/5}$:



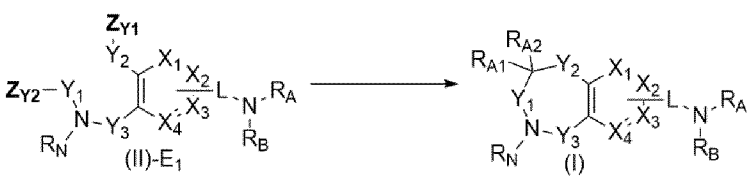
With Z_N being a carbonyl:

- By a reductive amination reaction or amide synthesis known to the person skilled in the art.
- By a Petasis reaction (based on the works described in *Chem. Rev.* **2019**, 119, 11245–11290, or *RSC Adv.*, **2015**, 5, 76337-76341).

With Z_N being a halogen or pseudo-halogen, or an organometallic group:

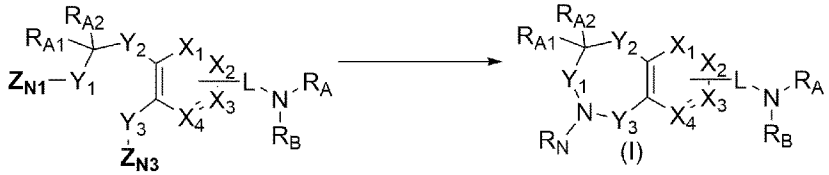
- By a nucleophilic substitution known to the person skilled in the art.
- By a metal catalyzed coupling reaction (based on the works described in *Chem. Rev.* **2016**, 116, 19, 12564–12649, Chem. Soc. Rev., **2014**, 43, 3525-3550 or *Chem. Rev.* **2019**, 119, 24, 12491–12523).

Compounds of formula (I) can be obtained from a precursor (II)-E_1 according to general disconnection E_1:



- By a cross-coupling reaction, reductive coupling or cross metathesis known to the person skilled in the art.
- By a Petasis or Mannich reaction (based respectively on the works described in *Chem. Rev.* **2019**, 119, 11245–11290, *RSC Adv.*, **2015**, 5, 76337-76341, *Org. Chem. Front.*, **2018**, 5, 1049-1066, or *Synthesis* **2013**, 45, 2769-2812).

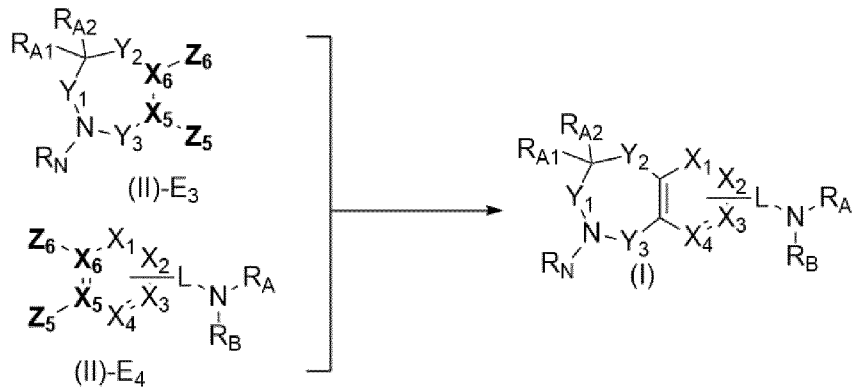
Compounds of formula (I) can be obtained from a precursor (II)-E_2 according to general disconnection E_2:



(II)-E_2 (I)

- By double reductive amination with R_N-NH_2
- By double nucleophilic (aromatic) substitution with R_N-NH_2
- By one pot reductive amination and nucleophilic substitution with R_N-NH_2

Compounds of formula (I) can be obtained from precursor (II)-E_3 and/or (II)-E_4 according to general disconnection $E_{3/4}$:



(II)-E_3 (II)-E_4 (I)

- By a heterocycle synthesis from precursor (II)-E_3 known to the person skilled in the art, and more specifically by specific methods described in *Topics in Current Chemistry,* **2019**, 377, 21, *Synthetic Communications*, **2020**, 50, 1251 – 1285, *Org. Chem. Front.*, 2019,6, 2120-2141, *Chem. Rev.* 2011, 111, 4, 2937–2980, or *Synlett*, **2011**, 2387-2391.
- By cycloaddition reactions leading to a heteroaromatic cycle synthesis known to the person skilled in the art, and more specifically sequences based on the works described in *Org. Chem. Front.*, **2014**, 1, 1010-1015, *J. Am. Chem. Soc.* **1999**, 121, 54-62, *Acc. Chem. Res.* **2020**, 53, 4, 773–781 or *C. R. Chimie,* **2017**, 20, 643-647.
- By cycloaddition leading to a non-aromatic heterocycle synthesis known to the person skilled in the art, and more specifically hetero-aryne transformations based on the works described in *Angew. Chem. Int. Ed.*, **2015**, 54, 11765 –11769, or *Chem. Rev.* **2021**, 121, 3892−4044.

Using and combining the above-mentioned general disconnections A, B_1, B_2, C_1, $C_{2/3/4}$, $D_{1/2/3/6}$, $D_{4/5}$, E_1, E_2, $E_{3/4}$, and available literature enables the synthesis of any compounds of formula (I) from commercially available compounds or from compounds whose synthesis is already described in the literature or compounds which are accessible with a method known in the art.

The following definitions apply throughout the present specification and the claims, unless specifically indicated otherwise.

The term "hydrocarbon group" refers to a group consisting of carbon atoms and hydrogen atoms.

The term "alicyclic" is used in connection with cyclic groups and denotes that the corresponding cyclic group is non-aromatic.

As used herein, the term "alkyl" refers to a monovalent saturated acyclic (i.e., non-cyclic) hydrocarbon group which may be linear or branched. Accordingly, an "alkyl" group does not comprise any carbon-to-carbon double bond or any carbon-to-carbon triple bond. A "C_{1-5} alkyl" denotes an alkyl group having 1 to 5 carbon atoms. Preferred exemplary alkyl groups are methyl, ethyl, propyl (e.g., n-propyl or isopropyl), or butyl (e.g., n-butyl, isobutyl, sec-butyl, or tert-butyl). Unless defined otherwise, the term "alkyl" preferably refers to C_{1-4} alkyl, more preferably to methyl or ethyl, and even more preferably to methyl.

As used herein, the term "alkenyl" refers to a monovalent unsaturated acyclic hydrocarbon group which may be linear or branched and comprises one or more (e.g., one or two) carbon-to-carbon double bonds while it does not comprise any carbon-to-carbon triple bond. The term "C_{2-5} alkenyl" denotes an alkenyl group having 2 to 5 carbon atoms. Preferred exemplary alkenyl groups are ethenyl, propenyl (e.g., prop-1-en-1-yl, prop-1-en-2-yl, or prop-2-en-1-yl), butenyl, butadienyl (e.g., buta-1,3-dien-1-yl or buta-1,3-dien-2-yl), pentenyl, or pentadienyl (e.g., isoprenyl). Unless defined otherwise, the term "alkenyl" preferably refers to C_{2-4} alkenyl.

As used herein, the term "alkynyl" refers to a monovalent unsaturated acyclic hydrocarbon group which may be linear or branched and comprises one or more (e.g., one or two) carbon-to-carbon triple bonds and optionally one or more (e.g., one or two) carbon-to-carbon double bonds. The term "C_{2-5} alkynyl" denotes an alkynyl group having 2 to 5 carbon atoms. Preferred exemplary alkynyl groups are ethynyl, propynyl (e.g., propargyl), or butynyl. Unless defined otherwise, the term "alkynyl" preferably refers to C_{2-4} alkynyl.

As used herein, the term "alkylene" refers to an alkanediyl group, i.e. a divalent saturated acyclic hydrocarbon group which may be linear or branched. A "C_{1-5} alkylene" denotes an alkylene group having 1 to 5 carbon atoms, and the term "C_{0-3} alkylene" indicates that a covalent bond (corresponding to the option "C_0 alkylene") or a C_{1-3} alkylene is present. Preferred exemplary alkylene groups are methylene (-CH_2-), ethylene (e.g., -CH_2-CH_2- or -CH(-CH_3)-), propylene (e.g., -CH_2-CH_2-CH_2-, -CH(-CH_2-CH_3)-, -CH_2-CH(-CH_3)-, or -CH(-CH_3)-CH_2-), or butylene (e.g., -CH_2-CH_2-CH_2-CH_2-). Unless defined otherwise, the term "alkylene" preferably refers to C_{1-4} alkylene (including, in particular, linear C_{1-4} alkylene), more preferably to methylene or ethylene, and even more preferably to methylene.

As used herein, the term "alkenylene" refers to an alkenediyl group, i.e. a divalent unsaturated acyclic hydrocarbon group which may be linear or branched and comprises one or more (e.g., one or two) carbon-to-carbon double bonds while it does not comprise any carbon-to-carbon triple bond. A "C_{2-5} alkenylene" denotes an alkenylene group having

2 to 5 carbon atoms. Unless defined otherwise, the term "alkenylene" preferably refers to C_{2-4} alkenylene (including, in particular, linear C_{2-4} alkenylene).

As used herein, the term "alkynylene" refers to an alkynediyl group, i.e. a divalent unsaturated acyclic hydrocarbon group which may be linear or branched and comprises one or more (e.g., one or two) carbon-to-carbon triple bonds and optionally one or more (e.g., one or two) carbon-to-carbon double bonds. A "C_{2-5} alkynylene" denotes an alkynylene group having 2 to 5 carbon atoms. Unless defined otherwise, the term "alkynylene" preferably refers to C_{2-4} alkynylene (including, in particular, linear C_{2-4} alkynylene).

As used herein, the term "carbocyclyl" (or "carbocyclic ring") refers to a hydrocarbon ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings), wherein said ring group may be saturated, partially unsaturated (i.e., unsaturated but not aromatic) or aromatic. Unless defined otherwise, "carbocyclyl" preferably refers to aryl, cycloalkyl or cycloalkenyl.

As used herein, the term "heterocyclyl" (or "heterocyclic ring") refers to a ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings), wherein said ring group comprises one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group), and further wherein said ring group may be saturated, partially unsaturated (i.e., unsaturated but not aromatic) or aromatic. For example, each heteroatom-containing ring comprised in said ring group may contain one or two O atoms and/or one or two S atoms (which may optionally be oxidized) and/or one, two, three or four N atoms (which may optionally be oxidized), provided that the total number of heteroatoms in the corresponding heteroatom-containing ring is 1 to 4 and that there is at least one carbon ring atom (which may optionally be oxidized) in the corresponding heteroatom-containing ring. Unless defined otherwise, "heterocyclyl" preferably refers to heteroaryl, heterocycloalkyl or heterocycloalkenyl.

As used herein, the term "aryl" refers to an aromatic hydrocarbon ring group, including monocyclic aromatic rings as well as bridged ring and/or fused ring systems containing at least one aromatic ring (e.g., ring systems composed of two or three fused rings, wherein at least one of these fused rings is aromatic; or bridged ring systems composed of two or three rings, wherein at least one of these bridged rings is aromatic). If the aryl is a bridged and/or fused ring system which contains, besides one or more aromatic rings, at least one non-aromatic ring (e.g., a saturated ring or an unsaturated alicyclic ring), then one or more carbon ring atoms in each non-aromatic ring may optionally be oxidized (i.e., to form an oxo group). "Aryl" may, e.g., refer to phenyl, naphthyl, dialinyl (i.e., 1,2-dihydronaphthyl), tetralinyl (i.e., 1,2,3,4-tetrahydronaphthyl), indanyl, indenyl (e.g., 1H-indenyl), anthracenyl, phenanthrenyl, 9H-fluorenyl, or azulenyl. Unless defined otherwise, an "aryl" preferably has 6 to 14 ring atoms, more preferably 6 to 10 ring atoms, even more preferably refers to phenyl or naphthyl, and most preferably refers to phenyl.

As used herein, the term "heteroaryl" (or "heteroaromatic ring") refers to an aromatic ring group, including monocyclic aromatic rings as well as bridged ring and/or fused ring systems containing at least one aromatic ring (e.g., ring

systems composed of two or three fused rings, wherein at least one of these fused rings is aromatic; or bridged ring systems composed of two or three rings, wherein at least one of these bridged rings is aromatic), wherein said aromatic ring group comprises one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, and further wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group). For example, each heteroatom-containing ring comprised in said aromatic ring group may contain one or two O atoms and/or one or two S atoms (which may optionally be oxidized) and/or one, two, three or four N atoms (which may optionally be oxidized), provided that the total number of heteroatoms in the corresponding heteroatom-containing ring is 1 to 4 and that there is at least one carbon ring atom (which may optionally be oxidized) in the corresponding heteroatom-containing ring. "Heteroaryl" may, e.g., refer to thienyl (i.e., thiophenyl), benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl (i.e., furanyl), benzofuranyl, isobenzofuranyl, chromanyl, chromenyl (e.g., 2H-1-benzopyranyl or 4H-1-benzopyranyl), isochromenyl (e.g., 1H-2-benzopyranyl), chromonyl, xanthenyl, phenoxathiinyl, pyrrolyl (e.g., 1H-pyrrolyl), imidazolyl, pyrazolyl, pyridyl (i.e., pyridinyl; e.g., 2-pyridyl, 3-pyridyl, or 4-pyridyl), pyrazinyl, pyrimidinyl, pyridazinyl, indolyl (e.g., 1H-indolyl), isoindolyl, indazolyl, indolizinyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl (e.g., [1,10]phenanthrolinyl, [1,7]phenanthrolinyl, or [4,7]phenanthrolinyl), phenazinyl, thiazolyl, isothiazolyl, phenothiazinyl, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl (i.e., furazanyl), or 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, or 1,3,4-thiadiazolyl), phenoxazinyl, pyrazolo[1,5-a]pyrimidinyl (e.g., pyrazolo[1,5-a]pyrimidin-3-yl), 1,2-benzoisoxazol-3-yl, benzothiazolyl, benzothiadiazolyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzo[b]thiophenyl (i.e., benzothienyl), triazolyl (e.g., 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, or 4H-1,2,4-triazolyl), benzotriazolyl, 1H-tetrazolyl, 2H-tetrazolyl, triazinyl (e.g., 1,2,3-triazinyl, 1,2,4-triazinyl, or 1,3,5-triazinyl), furo[2,3-c]pyridinyl, dihydrofuropyridinyl (e.g., 2,3-dihydrofuro[2,3-c]pyridinyl or 1,3-dihydrofuro[3,4-c]pyridinyl), imidazopyridinyl (e.g., imidazo[1,2-a]pyridinyl or imidazo[3,2-a]pyridinyl), quinazolinyl, thienopyridinyl, tetrahydrothienopyridinyl (e.g., 4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl), dibenzofuranyl, 1,3-benzodioxolyl, benzodioxanyl (e.g., 1,3-benzodioxanyl or 1,4-benzodioxanyl), or coumarinyl. Unless defined otherwise, the term "heteroaryl" preferably refers to a 5 to 14 membered (more preferably 5 to 10 membered) monocyclic ring or fused ring system comprising one or more (e.g., one, two, three or four) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized; even more preferably, a "heteroaryl" refers to a 5 or 6 membered monocyclic ring comprising one or more (e.g., one, two or three) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized. Moreover, unless defined otherwise, particularly preferred examples of a "heteroaryl" include pyridinyl (e.g., 2-pyridyl, 3-pyridyl, or 4-pyridyl), imidazolyl, thiazolyl, 1H-tetrazolyl, 2H-tetrazolyl, thienyl (i.e., thiophenyl), or pyrimidinyl.

As used herein, the term "cycloalkyl" refers to a saturated hydrocarbon ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings; such as, e.g., a fused ring system composed of two or three fused rings). "Cycloalkyl" may, e.g., refer to cyclopropyl, cyclobutyl,

cyclopentyl, cyclohexyl, cycloheptyl, decalinyl (i.e., decahydronaphthyl), or adamantyl. Unless defined otherwise, "cycloalkyl" preferably refers to a C_{3-11} cycloalkyl, and more preferably refers to a C_{3-7} cycloalkyl. A particularly preferred "cycloalkyl" is a monocyclic saturated hydrocarbon ring having 3 to 7 ring members. Moreover, unless defined otherwise, particularly preferred examples of a "cycloalkyl" include cyclohexyl or cyclopropyl, particularly cyclohexyl.

As used herein, the term "heterocycloalkyl" refers to a saturated ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings; such as, e.g., a fused ring system composed of two or three fused rings), wherein said ring group contains one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, and further wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group). For example, each heteroatom-containing ring comprised in said saturated ring group may contain one or two O atoms and/or one or two S atoms (which may optionally be oxidized) and/or one, two, three or four N atoms (which may optionally be oxidized), provided that the total number of heteroatoms in the corresponding heteroatom-containing ring is 1 to 4 and that there is at least one carbon ring atom (which may optionally be oxidized) in the corresponding heteroatom-containing ring. "Heterocycloalkyl" may, e.g., refer to aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, piperazinonyl (e.g., piperazin-2-on-1-yl or piperazin-3-on-1-yl), azepanyl, diazepanyl (e.g., 1,4-diazepanyl), oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, morpholinyl (e.g., morpholin-4-yl), thiomorpholinyl (e.g., thiomorpholin-4-yl), oxazepanyl, oxiranyl, oxetanyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, thiiranyl, thietanyl, tetrahydrothiophenyl (i.e., thiolanyl), 1,3-dithiolanyl, thianyl, thiepanyl, decahydroquinolinyl, decahydroisoquinolinyl, or 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl. Unless defined otherwise, "heterocycloalkyl" preferably refers to a 3 to 11 membered saturated ring group, which is a monocyclic ring or a fused ring system (e.g., a fused ring system composed of two fused rings), wherein said ring group contains one or more (e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized; more preferably, "heterocycloalkyl" refers to a 5 to 7 membered saturated monocyclic ring group containing one or more (e.g., one, two, or three) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized. Moreover, unless defined otherwise, particularly preferred examples of a "heterocycloalkyl" include tetrahydropyranyl, piperidinyl, piperazinyl, piperazinonyl, morpholinyl, pyrrolidinyl, or tetrahydrofuranyl.

As used herein, the term "cycloalkenyl" refers to an unsaturated alicyclic (non-aromatic) hydrocarbon ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings; such as, e.g., a fused ring system composed of two or three fused rings), wherein said hydrocarbon ring group comprises one or more (e.g., one or two) carbon-to-carbon double bonds and does not comprise any carbon-to-carbon triple bond. "Cycloalkenyl" may, e.g., refer to cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, or cycloheptadienyl. Unless defined otherwise, "cycloalkenyl" preferably refers to a C_{3-11} cycloalkenyl, and more preferably refers to a C_{3-7} cycloalkenyl. A particularly

preferred “cycloalkenyl” is a monocyclic unsaturated alicyclic hydrocarbon ring having 3 to 7 ring members and containing one or more (e.g., one or two; preferably one) carbon-to-carbon double bonds.

As used herein, the term “heterocycloalkenyl” refers to an unsaturated alicyclic (non-aromatic) ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings; such as, e.g., a fused ring system composed of two or three fused rings), wherein said ring group contains one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group), and further wherein said ring group comprises at least one double bond between adjacent ring atoms and does not comprise any triple bond between adjacent ring atoms. For example, each heteroatom-containing ring comprised in said unsaturated alicyclic ring group may contain one or two O atoms and/or one or two S atoms (which may optionally be oxidized) and/or one, two, three or four N atoms (which may optionally be oxidized), provided that the total number of heteroatoms in the corresponding heteroatom-containing ring is 1 to 4 and that there is at least one carbon ring atom (which may optionally be oxidized) in the corresponding heteroatom-containing ring. “Heterocycloalkenyl” may, e.g., refer to imidazolinyl (e.g., 2-imidazolinyl (i.e., 4,5-dihydro-1H-imidazolyl), 3-imidazolinyl, or 4-imidazolinyl), tetrahydropyridinyl (e.g., 1,2,3,6-tetrahydropyridinyl), dihydropyridinyl (e.g., 1,2-dihydropyridinyl or 2,3-dihydropyridinyl), pyranyl (e.g., 2H-pyranyl or 4H-pyranyl), thiopyranyl (e.g., 2H-thiopyranyl or 4H-thiopyranyl), dihydropyranyl, dihydrofuranyl, dihydropyrazolyl, dihydropyrazinyl, dihydroisoindolyl, octahydroquinolinyl (e.g., 1,2,3,4,4a,5,6,7-octahydroquinolinyl), or octahydroisoquinolinyl (e.g., 1,2,3,4,5,6,7,8-octahydroisoquinolinyl). Unless defined otherwise, “heterocycloalkenyl” preferably refers to a 3 to 11 membered unsaturated alicyclic ring group, which is a monocyclic ring or a fused ring system (e.g., a fused ring system composed of two fused rings), wherein said ring group contains one or more (e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, wherein one or more carbon ring atoms are optionally oxidized, and wherein said ring group comprises at least one double bond between adjacent ring atoms and does not comprise any triple bond between adjacent ring atoms; more preferably, “heterocycloalkenyl” refers to a 5 to 7 membered monocyclic unsaturated non-aromatic ring group containing one or more (e.g., one, two, or three) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, wherein one or more carbon ring atoms are optionally oxidized, and wherein said ring group comprises at least one double bond between adjacent ring atoms and does not comprise any triple bond between adjacent ring atoms.

As used herein, the term “halogen” refers to fluoro (-F), chloro (-Cl), bromo (-Br), or iodo (-I).

As used herein, the term “haloalkyl” refers to an alkyl group substituted with one or more (preferably 1 to 6, more preferably 1 to 3) halogen atoms which are selected independently from fluoro, chloro, bromo and iodo, and are preferably all fluoro atoms. It will be understood that the maximum number of halogen atoms is limited by the number of available attachment sites and, thus, depends on the number of carbon atoms comprised in the alkyl moiety of the

haloalkyl group. "Haloalkyl" may, e.g., refer to $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2-CH_3$, $-CH_2-CF_3$, $-CH_2-CHF_2$, $-CH_2-CF_2-CH_3$, $-CH_2-CF_2-CF_3$, or $-CH(CF_3)_2$. A particularly preferred "haloalkyl" group is $-CF_3$.

The terms "bond" and "covalent bond" are used herein synonymously, unless explicitly indicated otherwise or contradicted by context.

As used herein, the terms "optional", "optionally" and "may" denote that the indicated feature may be present but can also be absent. Whenever the term "optional", "optionally" or "may" is used, the present invention specifically relates to both possibilities, i.e., that the corresponding feature is present or, alternatively, that the corresponding feature is absent. For example, the expression "X is optionally substituted with Y" (or "X may be substituted with Y") means that X is either substituted with Y or is unsubstituted. Likewise, if a component of a composition is indicated to be "optional", the invention specifically relates to both possibilities, i.e., that the corresponding component is present (contained in the composition) or that the corresponding component is absent from the composition.

Various groups are referred to as being "optionally substituted" in this specification. Generally, these groups may carry one or more substituents, such as, e.g., one, two, three or four substituents. It will be understood that the maximum number of substituents is limited by the number of attachment sites available on the substituted moiety. Unless defined otherwise, the "optionally substituted" groups referred to in this specification carry preferably not more than two substituents and may, in particular, carry only one substituent. Moreover, unless defined otherwise, it is preferred that the optional substituents are absent, i.e. that the corresponding groups are unsubstituted.

A skilled person will appreciate that the substituent groups comprised in the compounds of the present invention may be attached to the remainder of the respective compound via a number of different positions of the corresponding specific substituent group. Unless defined otherwise, the preferred attachment positions for the various specific substituent groups are as illustrated in the examples.

As used herein, unless explicitly indicated otherwise or contradicted by context, the terms "a", "an" and "the" are used interchangeably with "one or more" and "at least one". Thus, for example, a composition comprising "a" compound of formula (I) can be interpreted as referring to a composition comprising "one or more" compounds of formula (I).

It is to be understood that wherever numerical ranges are provided/disclosed herein, all values and subranges encompassed by the respective numerical range are meant to be encompassed within the scope of the invention. Accordingly, the present invention specifically and individually relates to each value that falls within a numerical range disclosed herein, as well as each subrange encompassed by a numerical range disclosed herein.

As used herein, the term "about" preferably refers to ±10% of the indicated numerical value, more preferably to ±5% of the indicated numerical value, and in particular to the exact numerical value indicated. If the term "about" is used in connection with the endpoints of a range, it preferably refers to the range from the lower endpoint -10% of its indicated numerical value to the upper endpoint +10% of its indicated numerical value, more preferably to the range

from of the lower endpoint -5% to the upper endpoint +5%, and even more preferably to the range defined by the exact numerical values of the lower endpoint and the upper endpoint.

As used herein, the term "comprising" (or "comprise", "comprises", "contain", "contains", or "containing"), unless explicitly indicated otherwise or contradicted by context, has the meaning of "containing, inter alia", i.e., "containing, among further optional elements, ...". In addition thereto, this term also includes the narrower meanings of "consisting essentially of" and "consisting of". For example, the term "A comprising B and C" has the meaning of "A containing, inter alia, B and C", wherein A may contain further optional elements (e.g., "A containing B, C and D" would also be encompassed), but this term also includes the meaning of "A consisting essentially of B and C" and the meaning of "A consisting of B and C" (i.e., no other components than B and C are comprised in A).

The scope of the invention embraces all pharmaceutically acceptable salt forms of the compounds of formula (I) which may be formed, e.g., by protonation of an atom carrying an electron lone pair which is susceptible to protonation, such as an amino group, with an inorganic or organic acid, or as a salt of an acid group (such as a carboxylic acid group) with a physiologically acceptable cation. Exemplary base addition salts comprise, for example: alkali metal salts such as sodium or potassium salts; alkaline earth metal salts such as calcium or magnesium salts; zinc salts; ammonium salts; aliphatic amine salts such as trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine, procaine salts, meglumine salts, ethylenediamine salts, or choline salts; aralkyl amine salts such as N,N-dibenzylethylenediamine salts, benzathine salts, benethamine salts; heterocyclic aromatic amine salts such as pyridine salts, picoline salts, quinoline salts or isoquinoline salts; quaternary ammonium salts such as tetramethylammonium salts, tetraethylammonium salts, benzyltrimethylammonium salts, benzyltriethylammonium salts, benzyltributylammonium salts, methyltrioctylammonium salts or tetrabutylammonium salts; and basic amino acid salts such as arginine salts, lysine salts, or histidine salts. Exemplary acid addition salts comprise, for example: mineral acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate salts (such as, e.g., sulfate or hydrogensulfate salts), nitrate salts, phosphate salts (such as, e.g., phosphate, hydrogenphosphate, or dihydrogenphosphate salts), carbonate salts, hydrogencarbonate salts, perchlorate salts, borate salts, or thiocyanate salts; organic acid salts such as acetate, propionate, butyrate, pentanoate, hexanoate, heptanoate, octanoate, cyclopentanepropionate, decanoate, undecanoate, oleate, stearate, lactate, maleate, oxalate, fumarate, tartrate, malate, citrate, succinate, adipate, gluconate, glycolate, nicotinate, benzoate, salicylate, ascorbate, pamoate (embonate), camphorate, glucoheptanoate, or pivalate salts; sulfonate salts such as methanesulfonate (mesylate), ethanesulfonate (esylate), 2-hydroxyethanesulfonate (isethionate), benzenesulfonate (besylate), p-toluenesulfonate (tosylate), 2-naphthalenesulfonate (napsylate), 3-phenylsulfonate, or camphorsulfonate salts; glycerophosphate salts; and acidic amino acid salts such as aspartate or glutamate salts. Further pharmaceutically acceptable salts are described in the literature, e.g., in Stahl PH & Wermuth CG (eds.), "Handbook of Pharmaceutical Salts: Properties, Selection, and Use", Wiley-VCH, 2002 and in the references cited therein. Preferred pharmaceutically acceptable salts of the compounds of formula (I) include a hydrochloride salt, a hydrobromide salt, a mesylate salt, a sulfate salt, a tartrate salt, a fumarate salt, an acetate salt, a citrate salt, and a phosphate salt. A particularly preferred pharmaceutically acceptable salt of the compound of formula (I) is a hydrochloride salt. Accordingly, it is preferred that the compound of formula (I), including any one of the specific compounds of formula (I) described herein, is in the form of a hydrochloride salt, a hydrobromide salt, a mesylate salt, a sulfate salt, a tartrate salt, a fumarate salt, an

acetate salt, a citrate salt, or a phosphate salt, and it is particularly preferred that the compound of formula (I) is in the form of a hydrochloride salt.

The present invention also specifically relates to the compound of formula (I), including any one of the specific compounds of formula (I) described herein, in non-salt form.

Moreover, the scope of the invention embraces the compounds of formula (I) in any solvated form, including, e.g., solvates with water (i.e., as a hydrate) or solvates with organic solvents such as, e.g., methanol, ethanol, isopropanol, acetic acid, ethyl acetate, ethanolamine, DMSO, or acetonitrile. All physical forms, including any amorphous or crystalline forms (i.e., polymorphs), of the compounds of formula (I) are also encompassed within the scope of the invention. It is to be understood that such solvates and physical forms of pharmaceutically acceptable salts of the compounds of the formula (I) are likewise embraced by the invention.

Furthermore, the compounds of formula (I) may exist in the form of different isomers, in particular stereoisomers (including, e.g., geometric isomers (or cis/trans isomers), enantiomers and diastereomers) or tautomers (including, in particular, prototropic tautomers, such as keto/enol tautomers or thione/thiol tautomers). All such isomers of the compounds of formula (I) are contemplated as being part of the present invention, either in admixture or in pure or substantially pure form. As for stereoisomers, the invention embraces the isolated optical isomers of the compounds according to the invention as well as any mixtures thereof (including, in particular, racemic mixtures/racemates). The racemates can be resolved by physical methods, such as, e.g., fractional crystallization, separation or crystallization of diastereomeric derivatives, or separation by chiral column chromatography. The individual optical isomers can also be obtained from the racemates via salt formation with an optically active acid followed by crystallization. The present invention further encompasses any tautomers of the compounds of formula (I). It will be understood that some compounds may exhibit tautomerism. In such cases, the formulae provided herein expressly depict only one of the possible tautomeric forms. The formulae and chemical names as provided herein are intended to encompass any tautomeric form of the corresponding compound and not to be limited merely to the specific tautomeric form depicted by the drawing or identified by the name of the compound.

The scope of the invention also embraces compounds of formula (I), in which one or more atoms are replaced by a specific isotope of the corresponding atom. For example, the invention encompasses compounds of formula (I), in which one or more hydrogen atoms (or, e.g., all hydrogen atoms) are replaced by deuterium atoms (i.e., ^{2}H; also referred to as “D”). Accordingly, the invention also embraces compounds of formula (I) which are enriched in deuterium. Naturally occurring hydrogen is an isotopic mixture comprising about 99.98 mol-% hydrogen-1 (^{1}H) and about 0.0156 mol-% deuterium (^{2}H or D). The content of deuterium in one or more hydrogen positions in the compounds of formula (I) can be increased using deuteration techniques known in the art. For example, a compound of formula (I) or a reactant or precursor to be used in the synthesis of the compound of formula (I) can be subjected to an H/D exchange reaction using, e.g., heavy water (D_2O). Further suitable deuteration techniques are described in: Atzrodt J et al., *Bioorg Med Chem*, 20(18), 5658-5667, 2012; William JS et al., *Journal of Labelled Compounds and Radiopharmaceuticals*, 53(11-12), 635-644, 2010; Modvig A et al., *J Org Chem*, 79, 5861-5868, 2014. The content of deuterium can be determined, e.g., using mass spectrometry or NMR spectroscopy. Unless specifically

indicated otherwise, it is preferred that the compound of formula (I) is not enriched in deuterium. Accordingly, the presence of naturally occurring hydrogen atoms or ^{1}H hydrogen atoms in the compounds of formula (I) is preferred.

The present invention also embraces compounds of formula (I), in which one or more atoms are replaced by a positron-emitting isotope of the corresponding atom, such as, e.g., ^{18}F, ^{11}C, ^{13}N, ^{15}O, ^{76}Br, ^{77}Br, ^{120}I and/or ^{124}I. Such compounds can be used as tracers, trackers or imaging probes in positron emission tomography (PET). The invention thus includes (i) compounds of formula (I), in which one or more fluorine atoms (or, e.g., all fluorine atoms) are replaced by ^{18}F atoms, (ii) compounds of formula (I), in which one or more carbon atoms (or, e.g., all carbon atoms) are replaced by ^{11}C atoms, (iii) compounds of formula (I), in which one or more nitrogen atoms (or, e.g., all nitrogen atoms) are replaced by ^{13}N atoms, (iv) compounds of formula (I), in which one or more oxygen atoms (or, e.g., all oxygen atoms) are replaced by ^{15}O atoms, (v) compounds of formula (I), in which one or more bromine atoms (or, e.g., all bromine atoms) are replaced by ^{76}Br atoms, (vi) compounds of formula (I), in which one or more bromine atoms (or, e.g., all bromine atoms) are replaced by ^{77}Br atoms, (vii) compounds of formula (I), in which one or more iodine atoms (or, e.g., all iodine atoms) are replaced by ^{120}I atoms, and (viii) compounds of formula (I), in which one or more iodine atoms (or, e.g., all iodine atoms) are replaced by ^{124}I atoms. In general, it is preferred that none of the atoms in the compounds of formula (I) are replaced by specific isotopes.

The compounds provided herein may be administered as compounds *per se* or may be formulated as medicaments. The medicaments/pharmaceutical compositions may optionally comprise one or more pharmaceutically acceptable excipients, such as carriers, diluents, fillers, disintegrants, lubricating agents, binders, colorants, pigments, stabilizers, preservatives, antioxidants, and/or solubility enhancers.

The pharmaceutical compositions may comprise one or more solubility enhancers, such as, e.g., poly(ethylene glycol), including poly(ethylene glycol) having a molecular weight in the range of about 200 to about 5,000 Da (e.g., PEG 200, PEG 300, PEG 400, or PEG 600), ethylene glycol, propylene glycol, glycerol, a non-ionic surfactant, tyloxapol, polysorbate 80, macrogol-15-hydroxystearate (e.g., Kolliphor® HS 15, CAS 70142-34-6), a phospholipid, lecithin, dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, a cyclodextrin, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxyethyl-γ-cyclodextrin, hydroxypropyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, sulfobutylether-γ-cyclodextrin, glucosyl-α-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-α-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin, dimaltosyl-β-cyclodextrin, methyl-β-cyclodextrin, a carboxyalkyl thioether, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, a vinyl acetate copolymer, vinyl pyrrolidone, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, or any combination thereof.

The pharmaceutical compositions may also comprise one or more preservatives, particularly one or more antimicrobial preservatives, such as, e.g., benzyl alcohol, chlorobutanol, 2-ethoxyethanol, m-cresol, chlorocresol (e.g., 2-chloro-3-methyl-phenol or 4-chloro-3-methyl-phenol), benzalkonium chloride, benzethonium chloride, benzoic acid (or a pharmaceutically acceptable salt thereof), sorbic acid (or a pharmaceutically acceptable salt thereof), chlorhexidine, thimerosal, or any combination thereof.

The pharmaceutical compositions can be formulated by techniques known to the person skilled in the art, such as the techniques published in "Remington: The Science and Practice of Pharmacy", Pharmaceutical Press, 22nd edition. The pharmaceutical compositions can be formulated as dosage forms for oral, parenteral, such as intramuscular, intravenous, subcutaneous, intradermal, intraarterial, intracardial, rectal, nasal, topical, aerosol or vaginal administration. Dosage forms for oral administration include coated and uncoated tablets, soft gelatin capsules, hard gelatin capsules, lozenges, troches, solutions, emulsions, suspensions, syrups, elixirs, powders and granules for reconstitution, dispersible powders and granules, medicated gums, chewing tablets and effervescent tablets. Dosage forms for parenteral administration include solutions, emulsions, suspensions, dispersions and powders and granules for reconstitution. Emulsions are a preferred dosage form for parenteral administration. Dosage forms for rectal and vaginal administration include suppositories and ovula. Dosage forms for nasal administration can be administered via inhalation and insufflation, for example by a metered inhaler. Dosage forms for topical administration include creams, gels, ointments, salves, patches and transdermal delivery systems.

The compounds of formula (I) or the pharmaceutically acceptable salts or solvates thereof, or the above described pharmaceutical compositions comprising any of the aforementioned entities, may be administered to a subject by any convenient route of administration, whether systemically/peripherally or at the site of desired action, including but not limited to one or more of: oral (e.g., as a tablet, capsule, or as an ingestible solution), topical (e.g., transdermal, intranasal, ocular, buccal, and sublingual), parenteral (e.g., using injection techniques or infusion techniques, and including, for example, by injection, e.g., subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, or intrasternal by, e.g., implant of a depot, for example, subcutaneously or intramuscularly), pulmonary (e.g., by inhalation or insufflation therapy using, e.g., an aerosol, e.g., through mouth or nose), gastrointestinal, intrauterine, intraocular, subcutaneous, ophthalmic (including intravitreal or intracameral), rectal, or vaginal administration.

If said compounds or pharmaceutical compositions are administered parenterally, then examples of such administration include one or more of: intravenously, intraarterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracardially, intracranially, intramuscularly or subcutaneously administering the compounds or pharmaceutical compositions, and/or by using infusion techniques. For parenteral administration, the compounds are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Said compounds or pharmaceutical compositions can also be administered orally in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavoring or coloring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications.

The tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycolate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included. Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the agent may be combined with various sweetening or flavoring agents, coloring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

For oral administration, the compounds or pharmaceutical compositions are preferably administered by oral ingestion, particularly by swallowing. The compounds or pharmaceutical compositions can thus be administered to pass through the mouth into the gastrointestinal tract, which can also be referred to as “oral-gastrointestinal” administration.

Alternatively, said compounds or pharmaceutical compositions can be administered in the form of a suppository or pessary, or may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of the present invention may also be dermally or transdermally administered, for example, by the use of a skin patch.

Said compounds or pharmaceutical compositions may also be administered by sustained release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include, e.g., polylactides, copolymers of L-glutamic acid and gamma-ethyl-L-glutamate, poly(2-hydroxyethyl methacrylate), ethylene vinyl acetate, or poly-D-(–)-3-hydroxybutyric acid. Sustained-release pharmaceutical compositions also include liposomally entrapped compounds. The present invention thus also relates to liposomes containing a compound of the invention.

Said compounds or pharmaceutical compositions may also be administered by the pulmonary route, rectal routes, or the ocular route. For ophthalmic use, they can be formulated as micronized suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

It is also envisaged to prepare dry powder formulations of the compounds of formula (I) for pulmonary administration, particularly inhalation. Such dry powders may be prepared by spray drying under conditions which result in a substantially amorphous glassy or a substantially crystalline bioactive powder. Accordingly, dry powders of the compounds of the present invention can be made according to an emulsification/spray drying process.

For topical application to the skin, said compounds or pharmaceutical compositions can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the

following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, 2-octyldodecanol, benzyl alcohol and water.

The present invention thus relates to the compounds or the pharmaceutical compositions provided herein, wherein the corresponding compound or pharmaceutical composition is to be administered by any one of: an oral route; topical route, including by transdermal, intranasal, ocular, buccal, or sublingual route; parenteral route using injection techniques or infusion techniques, including by subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, intrasternal, intraventricular, intraurethral, or intracranial route; pulmonary route, including by inhalation or insufflation therapy; gastrointestinal route; intrauterine route; intraocular route; subcutaneous route; ophthalmic route, including by intravitreal, or intracameral route; rectal route; or vaginal route. Preferred routes of administration are oral administration or parenteral administration. For each of the compounds or pharmaceutical compositions provided herein, it is particularly preferred that the respective compound or pharmaceutical composition is to be administered orally (particularly by oral ingestion).

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject. The specific dose level and frequency of dosage for any particular individual subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the individual subject undergoing therapy.

A proposed, yet non-limiting dose of the compounds according to the invention for oral administration to a human (of approximately 70 kg body weight) may be 0.05 to 2000 mg, preferably 0.1 mg to 1000 mg, of the active ingredient per unit dose. The unit dose may be administered, e.g., 1 to 3 times per day. The unit dose may also be administered 1 to 7 times per week, e.g., with not more than one administration per day. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient/subject as well as the severity of the condition to be treated. The precise dose and also the route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

The compound of formula (I) or the pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising any of the aforementioned entities, can be administered in monotherapy (e.g., without concomitantly administering any further therapeutic agents, or without concomitantly administering any further therapeutic agents against the same disease that is to be treated or prevented with the compound of formula (I)). However, the compound of formula (I) or the pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising any of the aforementioned entities, can also be administered in combination with one or more further therapeutic agents. If the compound of formula (I) is used in combination with a second therapeutic agent active against the same disease or condition, the dose of each compound may differ from that when the corresponding compound is used alone, in particular, a lower dose of each compound may be used. The combination of the

compound of formula (I) with one or more further therapeutic agents may comprise the simultaneous/concomitant administration of the compound of formula (I) and the further therapeutic agent(s) (either in a single pharmaceutical formulation or in separate pharmaceutical formulations), or the sequential/separate administration of the compound of formula (I) and the further therapeutic agent(s). If administration is sequential, either the compound of formula (I) according to the invention or the one or more further therapeutic agents may be administered first. If administration is simultaneous, the one or more further therapeutic agents may be included in the same pharmaceutical formulation as the compound of formula (I), or they may be administered in two or more different (separate) pharmaceutical formulations.

For the treatment or prevention of cancer, the one or more further therapeutic agents to be administered in combination with a compound of the present invention are preferably anticancer drugs. The anticancer drug(s) to be administered in combination with a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof may, e.g., be selected from: a tumor angiogenesis inhibitor (e.g., a protease inhibitor, an epidermal growth factor receptor kinase inhibitor, or a vascular endothelial growth factor receptor kinase inhibitor); a cytotoxic drug (e.g., an antimetabolite, such as purine and pyrimidine analog antimetabolites); an antimitotic agent (e.g., a microtubule stabilizing drug or an antimitotic alkaloid); a platinum coordination complex; an anti-tumor antibiotic; an alkylating agent (e.g., a nitrogen mustard or a nitrosourea); an endocrine agent (e.g., an adrenocorticosteroid, an androgen, an anti-androgen, an estrogen, an anti-estrogen, an aromatase inhibitor, a gonadotropin-releasing hormone agonist, or a somatostatin analog); a compound that targets an enzyme or receptor that is overexpressed and/or otherwise involved in a specific metabolic pathway that is deregulated (or misregulated) in the tumor cell (e.g., ATP and GTP phosphodiesterase inhibitors, histone deacetylase inhibitors, protein kinase inhibitors (such as serine, threonine and tyrosine kinase inhibitors, e.g., Abelson protein tyrosine kinase inhibitors) and the various growth factors, their receptors and corresponding kinase inhibitors (such as epidermal growth factor receptor kinase inhibitors, vascular endothelial growth factor receptor kinase inhibitors, fibroblast growth factor inhibitors, insulin-like growth factor receptor inhibitors and platelet-derived growth factor receptor kinase inhibitors)); methionine; an aminopeptidase inhibitor; a proteasome inhibitor; a cyclooxygenase inhibitor (e.g., a cyclooxygenase-1 inhibitor or a cyclooxygenase-2 inhibitor); a topoisomerase inhibitor (e.g., a topoisomerase I inhibitor or a topoisomerase II inhibitor); a poly ADP ribose polymerase inhibitor (PARP inhibitor); an epidermal growth factor receptor (EGFR) inhibitor/antagonist; an adenosine A_{2A} receptor antagonist; an adenosine A_{2B} receptor antagonist; a dual adenosine A_{2A}/A_{2B} receptor antagonist; and a prostaglandin E2 receptor 4 (EP4) antagonist.

An alkylating agent which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, a nitrogen mustard (such as cyclophosphamide, mechlorethamine (chlormethine), uramustine, melphalan, chlorambucil, ifosfamide, bendamustine, or trofosfamide), a nitrosourea (such as carmustine, streptozocin, fotemustine, lomustine, nimustine, prednimustine, ranimustine, or semustine), an alkyl sulfonate (such as busulfan, mannosulfan, or treosulfan), an aziridine (such as hexamethylmelamine (altretamine), triethylenemelamine, ThioTEPA (N,N'N'-triethylenethiophosphoramide), carboquone, or triaziquone), a hydrazine (such as procarbazine), a triazene (such as dacarbazine), or an imidazotetrazine (such as temozolomide).

A platinum coordination complex which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, cisplatin, carboplatin, nedaplatin, oxaliplatin, satraplatin, or triplatin tetranitrate.

A cytotoxic drug which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, an antimetabolite, including folic acid analogue antimetabolites (such as aminopterin, methotrexate, pemetrexed, or raltitrexed), purine analogue antimetabolites (such as cladribine, clofarabine, fludarabine, 6-mercaptopurine (including its prodrug form azathioprine), pentostatin, or 6-thioguanine), and pyrimidine analogue antimetabolites (such as cytarabine, decitabine, 5-fluorouracil (including its prodrug forms capecitabine and tegafur), floxuridine, gemcitabine, enocitabine, or sapacitabine).

An antimitotic agent which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, a taxane (such as docetaxel, larotaxel, ortataxel, paclitaxel/taxol, tesetaxel, or nab-paclitaxel (e.g., Abraxane®)), a Vinca alkaloid (such as vinblastine, vincristine, vinflunine, vindesine, or vinorelbine), an epothilone (such as epothilone A, epothilone B, epothilone C, epothilone D, epothilone E, or epothilone F) or an epothilone B analogue (such as ixabepilone/azaepothilone B).

An anti-tumor antibiotic which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, an anthracycline (such as aclarubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, amrubicin, pirarubicin, valrubicin, or zorubicin), an anthracenedione (such as mitoxantrone, or pixantrone) or an anti-tumor antibiotic isolated from Streptomyces (such as actinomycin (including actinomycin D), bleomycin, mitomycin (including mitomycin C), or plicamycin).

A tyrosine kinase inhibitor which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, axitinib, bosutinib, cediranib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, semaxanib, sorafenib, sunitinib, axitinib, nintedanib, ponatinib, vandetanib, or vemurafenib.

A topoisomerase inhibitor which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, a topoisomerase I inhibitor (such as irinotecan, topotecan, camptothecin, belotecan, rubitecan, or lamellarin D) or a topoisomerase II inhibitor (such as amsacrine, etoposide, etoposide phosphate, teniposide, or doxorubicin).

A PARP inhibitor which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, niraparib, olaparib, rucaparib, talazoparib, veliparib, pamiparib (BGB-290), BMN-673, CEP 9722, MK 4827, E7016, or 3-aminobenzamide.

An EGFR inhibitor/antagonist which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, gefitinib, erlotinib, lapatinib, afatinib, neratinib, osimertinib, brigatinib, dacomitinib, vandetanib, pelitinib, canertinib, icotinib, poziotinib, ABT-414, AV-412, PD 153035, PKI-166, BMS-690514, CUDC-101, AP26113, XL647, cetuximab, panitumumab, zalutumumab, nimotuzumab, or matuzumab.

An adenosine A_{2A} receptor antagonist which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, ciforadenant, imaradenant, inupadenant, istradefylline, preladenant, SCH-58261, SCH-442416, ST 1535, or ZM241385.

An adenosine A_{2B} receptor antagonist which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, LAS38096 or LAS101057.

A dual adenosine A_{2A}/A_{2B} receptor antagonist which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, M1069, etrumadenant, or INCB106385.

A prostaglandin E2 receptor 4 (EP4) antagonist which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, DT-9081, grapiprant, palupiprant, BAY-1316957, CJ-42794, ER-819762, GW627368, L-161982, MF498, MF-766, MK-2894, or ONO-AE3-208.

Further anticancer drugs may also be used in combination with a compound of the present invention. The anticancer drugs may comprise biological or chemical molecules, like TNF-related apoptosis-inducing ligand (TRAIL), tamoxifen, amsacrine, bexarotene, estramustine, irofulven, trabectedin, cetuximab, panitumumab, tositumomab, alemtuzumab, bevacizumab, edrecolomab, gemtuzumab, alvocidib, seliciclib, aminolevulinic acid, methyl aminolevulinate, efaproxiral, porfimer sodium, talaporfin, temoporfin, verteporfin, alitretinoin, tretinoin, anagrelide, arsenic trioxide, atrasentan, bortezomib, carmofur, celecoxib, demecolcine, elesclomol, elsamitrucin, etoglucid, lonidamine, lucanthone, masoprocol, mitobronitol, mitoguazone, mitotane, oblimersen, omacetaxine, sitimagene, ceradenovec, tegafur, testolactone, tiazofurine, tipifarnib, vorinostat, iniparib, or copanlisib.

Also biological drugs, like antibodies, antibody fragments, antibody constructs (for example, single-chain constructs), and/or modified antibodies (like CDR-grafted antibodies, humanized antibodies, “fully human” antibodies, etc.) directed against cancer or tumor markers/factors/cytokines involved in proliferative diseases can be employed in cotherapy approaches with the compounds of the invention. Examples of such biological molecules are anti-HER2 antibodies (e.g. trastuzumab, Herceptin®), anti-CD20 antibodies (e.g. Rituximab, Rituxan®, MabThera®, Reditux®), anti-CD19/CD3 constructs, and anti-TNF antibodies (see, e.g., Taylor PC, *Curr Opin Pharmacol*, 2003, 3(3):323-328).

An anticancer drug which can be used in combination with a compound of the present invention may be, in particular, an immunooncology therapeutic (such as an antibody (e.g., a monoclonal antibody or a polyclonal antibody), an antibody fragment, an antibody construct (e.g., a single-chain construct), or a modified antibody (e.g., a CDR-grafted antibody, a humanized antibody, or a “fully human” antibody) or a small molecule) targeting any one of CTLA-4, PD-1, PD-L1, TIGIT, TIM3, LAG3, OX40, CSF1R, IDO, CD40, adenosine A_{2A} receptor (A2A), adenosine A_{2B} receptor (A2B), A2A/A2B, prostaglandin E2 receptor 4 (EP4), or chemokine (C-C motif) receptor 8 (CCR8). Such immunooncology therapeutics include, e.g., an anti-CTLA-4 antibody (e.g., ipilimumab or tremelimumab), an anti-PD-1 antibody (e.g., nivolumab (BMS-936558), pembrolizumab (MK-3475), pidilizumab (CT-011), cemiplimab, dostarlimab, spartalizumab, camrelizumab, sintilimab, tislelizumab, toripalimab, zimberelimab, AMP-224, AMP-514 (or MEDI0680), JTX-4014, INCMGA00012 (or MGA012), or APE02058), an anti-PD-L1 antibody (e.g., atezolizumab, avelumab, durvalumab, KN035, CK-301, BMS-936559, MEDI4736, MPDL3280A (RG7446), MDX-1105, MEDI6469, or bintrafusp alfa), an anti-TIGIT antibody (e.g., tiragolumab, vibostolimab, domvanalimab, etigilimab, BMS-986207, EOS-448, COM902, ASP8374, SEA-TGT, BGB-A1217, IBI-939, or M6223), an anti-TIM3 antibody, an anti-LAG3 antibody (e.g., relatlimab (or BMS-986016), ieramilimab (or LAG525), encelimab (or TSR-033), tebotelimab (or MGD013), REGN3767 (or R3767), FS118, IMP701, or IMP731), an anti-OX40 antibody (e.g., MEDI0562), an anti-CSF1R antibody (e.g., IMC-CS4 or RG7155), an anti-IDO antibody, an anti-CD40 antibody (e.g., CP-870,893 or Chi Lob 7/4), or an anti-CCR8 antibody (e.g., DT-7012, BMS-986340, S-531011, BAY-3375968, GS-1811 (or JTX-1811), FPA157, SRF114, HBM1022, or LM-108). Further immunooncology therapeutics are known in the art and are described, e.g., in: Kyi C et al., *FEBS Lett*, 2014, 588(2):368-76; Intlekofer AM et al., *J Leukoc Biol*, 2013, 94(1):25-39; Callahan MK et al., *J Leukoc Biol*, 2013, 94(1):41-53; Ngiow SF et al., *Cancer Res*, 2011, 71(21):6567-71; and Blattman JN et al., *Science*, 2004, 305(5681):200-5.

In particular, a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising any of the aforementioned entities, may be administered in combination with an immune checkpoint inhibitor, preferably an antibody (or an antigen-binding fragment thereof, or an antibody construct) directed against CTLA-4, PD-1, PD-L1, TIGIT, or LAG3. Corresponding preferred examples include, but are not limited to, any one of the anti-CTLA-4 antibodies ipilimumab or tremelimumab, any one of the anti-PD-1 antibodies nivolumab,

pembrolizumab, pidilizumab, cemiplimab, dostarlimab, spartalizumab, camrelizumab, sintilimab, tislelizumab, toripalimab, zimberelimab, AMP-224, AMP-514, JTX-4014, INCMGA00012, or APE02058, any one of the anti-PD-L1 antibodies atezolizumab, avelumab, durvalumab, KN035, CK-301, BMS-936559, MEDI4736, MPDL3280A, MDX-1105, MEDI6469 or bintrafusp alfa, any one of the anti-TIGIT antibodies tiragolumab, vibostolimab, domvanalimab, etigilimab, BMS-986207, EOS-448, COM902, ASP8374, SEA-TGT, BGB-A1217, IBI-939 or M6223, and/or any one of the anti-LAG3 antibodies relatlimab, ieramilimab, encelimab, tebotelimab, REGN3767, FS118, IMP701, or IMP731.

The present invention thus relates to a compound of formula (I) or a pharmaceutically acceptable salt or solvates thereof, or a pharmaceutical composition comprising any of the aforementioned entities optionally in combination with a pharmaceutically acceptable excipient, for use in the treatment or prevention of cancer, wherein the compound or the pharmaceutical composition is to be administered in combination with one or more immune checkpoint inhibitors, wherein said one or more immune checkpoint inhibitors are preferably selected from anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-TIGIT antibodies, and/or anti-LAG3 antibodies (for example, said one or more immune checkpoint inhibitors may be selected from anti-CTLA-4 antibodies, anti-PD-1 antibodies and/or anti-PD-L1 antibodies, such as, e.g., ipilimumab, tremelimumab, nivolumab, pembrolizumab, cemiplimab, spartalizumab, camrelizumab, sintilimab, tislelizumab, AMP-224, AMP-514, atezolizumab, avelumab, durvalumab, KN035, or CK-301); more preferably, said one or more immune checkpoint inhibitors are selected from ipilimumab, tremelimumab, nivolumab, pembrolizumab, pidilizumab, cemiplimab, dostarlimab, spartalizumab, camrelizumab, sintilimab, tislelizumab, toripalimab, zimberelimab, AMP-224, AMP-514, JTX-4014, INCMGA00012, APE02058, atezolizumab, avelumab, durvalumab, KN035, CK-301, BMS-936559, MEDI4736, MPDL3280A, MDX-1105, MEDI6469, bintrafusp alfa, tiragolumab, vibostolimab, domvanalimab, etigilimab, BMS-986207, EOS-448, COM902, ASP8374, SEA-TGT, BGB-A1217, IBI-939, M6223, relatlimab, ieramilimab, encelimab, tebotelimab, REGN3767, FS118, IMP701, and IMP731.

Moreover, a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising any of the aforementioned entities, may also be administered in combination with an anti-CCR8 antibody (particularly an antagonistic anti-CCR8 antibody), such as, e.g., DT-7012, BMS-986340, S-531011, BAY-3375968, GS-1811 (or JTX-1811), FPA157, SRF114, HBM1022, or LM-108. Accordingly, the present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt or solvates thereof, or a pharmaceutical composition comprising any of the aforementioned entities optionally in combination with a pharmaceutically acceptable excipient, for use in the treatment or prevention of cancer, wherein the compound or the pharmaceutical composition is to be administered in combination with one or more anti-CCR8 antibodies (which may be selected, e.g., from DT-7012, BMS-986340, S-531011, BAY-3375968, GS-1811 (or JTX-1811), FPA157, SRF114, HBM1022, and LM-108).

The present invention thus particularly relates to a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising any of the aforementioned entities optionally in combination with a pharmaceutically acceptable excipient, for use in the treatment or prevention of cancer, wherein the compound or the pharmaceutical composition is to be administered in combination with one or more anticancer drugs (including any one or more of the specific anticancer drugs described herein above).

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation. The individual components of such combinations may be administered either sequentially or

simultaneously/concomitantly in separate or combined pharmaceutical formulations by any convenient route. When administration is sequential, either the compound of the present invention (i.e., the compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof) or the further therapeutic agent(s) may be administered first. When administration is simultaneous, the combination may be administered either in the same pharmaceutical composition or in different pharmaceutical compositions. When combined in the same formulation, it will be appreciated that the two or more compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately, they may be provided in any convenient formulation and may be administered by any convenient route. For the combinations described above, it is preferred that the individual components of such combinations are provided in separate pharmaceutical formulations.

The subject or patient to be treated in accordance with the present invention may be an animal (e.g., a non-human animal). Preferably, the subject/patient is a mammal. More preferably, the subject/patient is a human (e.g., a male human or a female human) or a non-human mammal (such as, e.g., a guinea pig, a hamster, a rat, a mouse, a rabbit, a dog, a cat, a horse, a monkey, an ape, a marmoset, a baboon, a gorilla, a chimpanzee, an orangutan, a gibbon, a sheep, cattle, or a pig). Most preferably, the subject/patient to be treated in accordance with the invention is a human.

The term “treatment” of a disorder or disease, as used herein, is well known in the art. “Treatment” of a disorder or disease implies that a disorder or disease is suspected or has been diagnosed in a patient/subject. A patient/subject suspected of suffering from a disorder or disease typically shows specific clinical and/or pathological symptoms which a skilled person can easily attribute to a specific pathological condition (i.e., diagnose a disorder or disease).

The “treatment” of a disorder or disease may, for example, lead to a halt in the progression of the disorder or disease (e.g., no deterioration of symptoms) or a delay in the progression of the disorder or disease (in case the halt in progression is of a transient nature only). The “treatment” of a disorder or disease may also lead to a partial response (e.g., amelioration of symptoms) or complete response (e.g., disappearance of symptoms) of the subject/patient suffering from the disorder or disease. Accordingly, the “treatment” of a disorder or disease may also refer to an amelioration of the disorder or disease, which may, e.g., lead to a halt in the progression of the disorder or disease or a delay in the progression of the disorder or disease. Such a partial or complete response may be followed by a relapse. It is to be understood that a subject/patient may experience a broad range of responses to a treatment (such as the exemplary responses as described herein above). The treatment of a disorder or disease may, *inter alia*, comprise curative treatment (preferably leading to a complete response and eventually to healing of the disorder or disease) and palliative treatment (including symptomatic relief).

The term “prevention” of a disorder or disease, as used herein, is also well known in the art. For example, a patient/subject suspected of being prone to suffer from a disorder or disease may particularly benefit from a prevention of the disorder or disease. The subject/patient may have a susceptibility or predisposition for a disorder or disease, including but not limited to hereditary predisposition. Such a predisposition can be determined by standard methods or assays, using, e.g., genetic markers or phenotypic indicators. It is to be understood that a disorder or disease to be prevented in accordance with the present invention has not been diagnosed or cannot be diagnosed in the patient/subject (for example, the patient/subject does not show any clinical or pathological symptoms). Thus, the term

"prevention" comprises the use of a compound of the present invention before any clinical and/or pathological symptoms are diagnosed or determined or can be diagnosed or determined by the attending physician.

It is to be understood that the present invention specifically relates to each and every combination of features and embodiments described herein, including any combination of general and/or preferred features/embodiments. In particular, the invention specifically relates to each combination of meanings (including general and/or preferred meanings) for the various groups and variables comprised in formula (I).

In this specification, a number of documents including patent applications and scientific literature are cited. The disclosure of these documents, while not considered relevant for the patentability of this invention, is herewith incorporated by reference in its entirety. More specifically, all referenced documents are incorporated by reference to the same extent as if each individual document was specifically and individually indicated to be incorporated by reference.

The reference in this specification to any prior publication (or information derived therefrom) is not and should not be taken as an acknowledgment or admission or any form of suggestion that the corresponding prior publication (or the information derived therefrom) forms part of the common general knowledge in the technical field to which the present specification relates.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

The compounds of formula (I) described in the following examples section are defined by their chemical formulae and their corresponding chemical names. In case of conflict between any chemical formula and the corresponding chemical name indicated herein, the present invention relates to both the compound defined by the chemical formula and the compound defined by the chemical name, and particularly relates to the compound defined by the chemical formula.

EXAMPLES

General experimental procedures

General conditions

All reagents were commercial grade and used without further purification. Reactions were typically run using commercial anhydrous solvents under argon atmosphere.

Column chromatography was generally performed with a Biotage Isolera® Four apparatus using, unless stated otherwise, Biotage® KP-Sil cartridge pre-filled with 50 µm irregular silica gel. Alternatively, Interchim® PURIFLASH jumbo pack silica HP cartridges pre-filed with 50 µm silica gel (mentioned as Interchim® 50 µm), Interchim®

PURIFLASH jumbo pack silica SDT cartridges pre-filed with 20 µm silica gel (mentioned as Interchim® 20 µm), or Biotage Sfär® KP-Amino D cartridges pre-filed with 50 µm silica gel (mentioned as Biotage® KPNH) could be used when necessary. Alternatively, column chromatography was performed with a Biotage Isolera Spektra One® using Silica gel 60® (40-63 µm, Merck) (mentioned as Merck 60®).

Thin layer chromatography (TLC) was carried out using pre-coated silica gel F-254 plates or Biotage KP-NH TLC plates.

Releasing of free bases from the corresponding salts was carried out using Biotage ISOLUTE® SCX-2 cation exchange cartridges.

^{1}H-NMR spectra were recorded on a Bruker AV-300 spectrometer or on a Bruker AMX-400 spectrometer. Proton chemical shifts are listed relative to residual CD_3OD (3.31 ppm), DMSO (2.50 ppm), D_2O (4.78 ppm) or $CDCl_3$ (7.26 ppm). Splitting patterns are designated as s (singlet), d (doublet), dd (doublet-doublet), t (triplet), tt (triplet-triplet), td (triplet-doublet), q (quartet), quint (quintuplet), sex (sextuplet), sept (septuplet), m (multiplet), bs (broad).

UPLC-MS analyses were recorded with an UPLC Waters Aquity platform with a photodiode array detector (210-400 nm) using an Acquity CSH C_{18} 1.7 µm (2.1 x 30 mm) column. The mobile phase consisted in a gradient of water with 0.025% of trifluoroacetic acid (TFA) and acetonitrile with 0.025% of TFA. The flow rate was 0.8 mL per min. All analyses were performed at 55 °C. The UPLC system was coupled with a Waters SQD2 platform. All mass spectra were full-scan experiments (mass range 100-800 amu) and were obtained using electrospray ionization.

HPLC-MS were recorded using an HPLC Waters platform with a 2767 sample manager, a 2525 pump, a photodiode array detector (200-400 nm). This HPLC system was coupled with a Waters Acquity QDa detector. Mass spectra were full-scan experiments (mass range 110-850 amu) and were obtained using electro spray ionization. For analytical samples, the selected column was a XSelect CSH C_{18} 3.5 µm (2.1x30 mm) column. For preparative purifications, the selected column was, unless otherwise stated, an XSelect CSH prep C_{18} 5 µm (19 x 100 mm) column. The mobile phase consisted in an appropriate gradient of water with 0.1% of formic acid and acetonitrile with 0.1% of formic acid. The flow rate was 1 mL/min in analytical mode, and in preparative mode 25 mL/min.
Alternatively, HPLC-MS were recorded using a Thermo LC/MS-Ultimate 3000-Ion Trap HCT Brucker. Mass spectra were performed on a Brucker Ion Trap and were obtained using electrospray ionization. For analytical samples, the selected column was a Nucleodur 3 µm 4.6 x 100 mm reverse-phase column. The mobile phase consisted in a linear gradient with a flow rate of 1.3 mL/min from 95% A and 5% B to 5% A and 95% B in 8.5 min (solvent A, H_2O with 0.1% formic acid; solvent B, acetonitrile with 0.1% formic acid). Preparative purifications were performed on a Gilson PLC 2020 apparatus using a column C8 Princeton SPHER.60-10 µm, mentioned as Column B. The mobile phase consisted in a gradient of acetonitrile (5 to 100%) in water + 0.1% formic acid with a flow rate of 30 mL/min.
After preparative HPLC, the fractions were combined, eventually partially concentrated under reduced pressure, then freeze dried from a water acetonitrile mixture.

All HPLC-MS were performed at room temperature.

Melting points were measured on a Barnstead Electrothermal 9100 or an Electrothermal 1002 and are not corrected.

Unless mentioned otherwise all compounds isolated by filtration or centrifugation were dried overnight in high vacuum at 50-70 °C.

General procedures

General procedure (I): Nucleophilic aromatic substitution

To a solution of haloheteroaryl (1.0 eq.) in toluene (0.15 M) at 0°C, was added alkylnitrile (1.0 eq.) and sodium hexamethyldisilazide (NaHMDS) 2M in tetrahydrofuran (THF) (1.0 eq.). The reaction mixture was stirred at 0°C for 2 hours, then hydrolysed with ice and NH_4Cl (sat. aq.) and extracted with ethyl acetate (EtOAc). The organic layer was washed with brine, dried over magnesium sulfate then concentrated to dryness to obtain the corresponding heteroaryl acetonitrile.

General procedure (Ib): Nucleophilic aromatic substitution

To a solution of haloheteroaryl (1.0 eq.) in toluene (0.45 M, 1V) at 0°C, was added ester (1.0 eq.) then Lithium hexamethyldisilazide (LiHMDS) 1M in tetrahydrofuran (THF) (2.0 eq.) was added dropwise. The reaction mixture was stirred at 25°C for 24 hours, then hydrolysed with NH_4Cl (sat. aq., 4V), diluted with water (2V) and extracted with ethyl acetate (EtOAc 2* 4V). The organic layer was washed with brine, dried over magnesium sulfate then concentrated to dryness to obtain the corresponding heteroaryl ester.

General procedure (IIa): nitrile hydration

To a solution of nitrile (1.0 eq.) in dimethyl sulfoxide (DMSO) (0.2 M) was added potassium carbonate (2.0 - 4.0 eq.), and hydrogen peroxide aqueous 30% (3.0 - 10 eq.). The reaction was stirred at 25 °C for 1 to 16 hours. The reaction mixture was diluted with water then extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to dryness. The crude was purified by flash chromatography to afford the corresponding amide.

General procedure (IIb): nitrile hydration

To a solution of nitrile (1.0 eq.) in DMSO (0.2 M, 1 V) was added potassium carbonate (2.0 - 4.0 eq.), and hydrogen peroxide aqueous 30% (3.0 - 10 eq.). The reaction was stirred at 25 °C for 1 to 16 hours. The reaction mixture was diluted with water (50 V), the obtained precipitate was collected by filtration, and washed with water (20 V) to afford the corresponding amide.

General procedure (III): Cyclisation

To a solution of amide (1.0 eq.) in *t*-BuOH (0.1 M) were added NaOtBu (3.0 eq.) and benzene-1,2-diamine (0.2 eq.). The mixture was sparged with Argon for 10 min before addition of CuO (0.1 equiv). The reaction mixture was heated at 100 °C for 18 hours. The reaction mixture was filtered through a pad of Celite, the pad was washed with EtOAc

and dichloromethane (DCM) then the filtrate was concentrated to dryness. The crude residue was purified by flash chromatography to afford the corresponding dihydro-pyrroloheteroaryl.

General procedure (IV): aryl cyanation

Under inert atmosphere, to a solution of aryl halide (1.0 eq.) in DMA (0.3M) was added Zinc(II) cyanide (1.5 eq.). The mixture was sparged with argon for 10 min before addition of Bis(tri-tert-butylphosphine)palladium (0.1 eq.). The reaction mixture was heated at 130 °C for 18 hours. The reaction mixture was filtered through a pad of Celite and washed with EtOAc and DCM. then the filtrate was concentrated to dryness. The residue was dissolved in EtOAc, washed with $NaHCO_3$ sat. aq., brine, dried over magnesium sulfate and concentrated to dryness. The crude was purified by flash chromatography to afford the corresponding nitrile.

General procedure (V): Ullmann coupling

Under inert atmosphere, to a solution of amide (1.0 eq.) in dioxane (0.1 M) were added potassium carbonate (3.0 eq.), (1R,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (0.2 eq.), and aryl halide (1.1 eq.). The mixture was sparged with argon for 10 min before addition of CuI (0.1 eq.). The reaction mixture was heated at 100 °C for 18 hours. The reaction mixture was filtered through a pad of Celite and washed with EtOAc and DCM, then the filtrate was concentrated to dryness. The crude was purified by flash chromatography to afford the corresponding N-arylamide.

General procedure (VI): formation of methyl ester from amide

Under inert atmosphere, to a solution of amide (1.0 eq.) in MeOH (0.1 M) was added 1,1-dimethoxy-N,N-dimethylmethanamine (6 eq.). The reaction mixture was heated at 60 °C for 16 to 24 hours. The reaction mixture was concentrated to dryness. The crude was purified by flash chromatography to afford the corresponding methyl ester.

General procedure (VII): ester hydrolysis

To a solution of methyl ester (1.0 equiv) in THF (0.1 M) was added lithium hydroxide 1M aq. (1.5 equiv). The reaction was stirred at 25 °C for 1 to 18 hours. The reaction mixture was acidified with HCl 1M aq. to pH = 1 then extracted with EtOAc. The organic layer was dried over magnesium sulfate and concentrated to dryness to afford the corresponding acid.

General procedure (VIIIa): peptidic coupling

To a mixture of acid in DCM (0.1 M) or in DCM/THF (1:1, 0.1 M) or in Propylene carbonate (0.1 M) was added ((1H-benzo[d][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate(V) (1.3 eq.), N,N-diisopropylethylamine (1.0 to 5.0 eq) and the amine (1.0 to 2.0 eq.). The reaction mixture was stirred at 25 °C for 3 to 18 hours. The reaction mixture was hydrolysed with NH_4Cl sat. aq. then extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate then concentrated to dryness to afford the corresponding crude amide.

General procedure (VIIIb): peptidic coupling

To a mixture of acid in THF (0.1 M) or in MeTHF (0.1 M) was added N-[1-(Cyano-2-ethoxy-2-oxoethylideneaminooxy)dimethylamino(morpholino)uronium Hexafluorophosphate (1.2 eq.), triethylamine (1.0 to 5.0

eq) and the amine (1.0 to 2.0 eq.). The reaction mixture was stirred at 25 °C for 3 to 18 hours. The reaction mixture was hydrolysed with NH_4Cl sat. aq. then extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate then concentrated to dryness to afford the corresponding crude amide.

General procedure (IX): amide reduction

To a solution of amide in THF (0.1 M) at 0°C were added sodium borohydride (5.0 eq.) and dropwise boron trifluoride diethyl etherate (7.0 eq.). The reaction mixture was stirred at 25 °C for 5 hours. At 0°C, the reaction mixture was hydrolysed with cooled water, stirred at 25°C for 18 hours then extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to dryness. The crude was purified by flash chromatography to afford the corresponding amine.

General procedure (X): Buchwald coupling

Under inert atmosphere, to a solution of amine (1.0-2.0 equiv) and halide or pseudo halide (1.0-2.0 equiv) in toluene (0.1-0.2 M) was added sodium tert-butoxide (1.5 equiv). The mixture was sparged with Argon for 10 min before addition of RuPhos PdG4 (0.05 equiv). The reaction mixture was heated at 80 °C for 16 hours. The reaction mixture was filtered through a pad of Celite, the pad was washed with EtOAc then the filtrate was concentrated to dryness. The crude residue was purified by flash chromatography to afford the corresponding N-Aryl amine.

General procedure (Xb): Buchwald coupling

Under inert atmosphere, to a solution of amine (1.0-2.0 equiv) and halide or pseudo halide (1.0-2.0 equiv) in Dioxane (0.1 M) was added Cesium Carbonate (3 equiv). The mixture was sparged with Argon for 10 min before addition of RuPhos PdG4 (0.10 equiv). The reaction mixture was heated at 100 °C for 16 hours. The reaction mixture was filtered through a pad of Celite, the pad was washed with EtOAc then the filtrate was concentrated to dryness. The crude residue was purified by flash chromatography to afford the corresponding N-Aryl amine.

General procedure (Xc): Buchwald coupling

Under inert atmosphere, to a solution of amine (1.0 equiv) in Dioxane (0.1 M) was added Cesium Carbonate (3 equiv). The mixture was sparged with Argon for 10 min before addition of RuPhos PdG4 (0.10 equiv). The reaction mixture was heated at 100 °C for 4 hours, then halide or pseudo halide (2.0 equiv) was added and the reaction mixture was further heated for 20 hours. The reaction mixture was filtered through a pad of Celite, the pad was washed with EtOAc then the filtrate was concentrated to dryness. The crude residue was purified by flash chromatography to afford the corresponding N-Aryl aza-indoline.

General procedure (Xd): Buchwald coupling

Under inert atmosphere, to a solution of precursor (1.0 equiv) in Dioxane (0.1 M) was added Cesium Carbonate (3 equiv). The mixture was sparged with Argon for 10 min before addition of SPhos PdG4 (0.10 equiv). The reaction mixture was heated at 100 °C for 20 hours. The reaction mixture was filtered through a pad of Celite, the pad was washed with EtOAc then the filtrate was concentrated to dryness. The crude residue was purified by flash chromatography to afford the corresponding cyclised product.

General procedure (XI): methyl ester cleavage

To a solution of methyl ester in ^{t}BuOH (0.05 M) was added Sodium ^{t}Butoxide (10 eq). The reaction was stirred at 60°C for 18 hours. The reaction mixture was diluted with water and acidified with HCl aq. 1M to pH = 3 then extracted with EtOAc. The organic layer was dried over magnesium sulfate and concentrated to dryness to afford the corresponding acid.

General procedure (XII): amine boc deprotection

A solution of boc protected amine in DCM (0.2 M, 1 V) or in dioxane (0.2 M, 1 V) was treated with TFA (1 V) or HCl (2M in Et_2O, 1 V) or HCl (4N in dioxane, 0.5 V). The reaction mixture was stirred at 25°C for 1 hour then concentrated under reduced pressure to obtain the corresponding crude amine.

General procedure (XIII): nucleophilic displacement

To a solution of nucleophile (alcohol, amide) in THF or in DMF or in DMA or in NMP (0.2 M, 1 V) was added NaH (sodium hydride 60% in mineral oil) (1.0 – 5.0 eq) at 0°C. The mixture was stirred at 0°C for 20 minutes then the electrophile was added (1.0 – 3.0 eq.). The reaction mixture was stirred at 25°C for 18 hours then quenched in NH_4Cl (sat.aq. 10 V) extracted with EtOAc. The organic layer was dried over magnesium sulfate and concentrated to dryness to afford the corresponding substituted product.

General procedure (XIV): aminocarbonylation

In the first chamber of a two-chamber reactor (2*20 mL) was prepared a solution of halide or pseudo-halide, amine (1.0 - 2.0 eq), and triethyl amine (3.0 - 5.0 eq) in dioxane (0.12 M, 1 V). In the second chamber a suspension of $Mo(CO)_6$ (1.0-2.5 eq) in dioxane (1V) was prepared. Both chambers were sparged with argon for 10 minutes then XantPhos Pd G4 (0.10 eq) was added in the first chamber, and DBU (2.0-5.0 eq) was added in the second chamber. The set up was crimped and heated at 110°C for 16 hours. The mixture in the first chamber was filtered over a Celite pad, rinsed with DCM (3 V), the filtrate was washed with NH_4Cl (3 V, sat.aq.), brine (3 V) then dried over magnesium sulfate and concentrated under reduced pressure to obtain crude aminocarbonylated product.

General procedure (XVa): Nitrile reduction

To a solution of nitrile in MeOH (0.1 M, 1 V) was added Cobalt$^{(II)}$ chloride hexahydrate (1 equiv.) and di-tert-butyl dicarbonate (2 equiv.), the solution was cooled at -78°C for 15 minutes, then Sodium borohydride (7 equiv.) was added. The reaction mixture was let warm up at -20°C for 4 hours, then at 25°C for 30 minutes. The reaction mixture was quenched with NH_4Cl (1 V, sat. aq.), diluted with water (1V) and extracted with EtOAc (2*1 V). Combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was dissolved in DCM (0.25 M) and treated with trifluoroacetic acid (10 equiv.) at 25°C for 16 hours. The reaction mixture was concentrated under reduced pressure, then purified by Ion Exchange chromatography (Isolute SCX-2, load in DCM, elution with NH_3 1N in MeOH). The eluate was concentrated under reduced pressure to obtain the corresponding amine.

General procedure (XVb): Nitrile reduction

To a solution of nitrile in EtOH (0.15 M, 1 V) was added ammonium hydroxide (20 equiv.). The reaction mixture was sparged with Argon for 10 min then Raney Nickel (type 2800, 1 equiv.) was added and the solution was sparged with Hydrogen for 5 minutes then the reaction mixture was heated at 50°C under a hydrogen atmosphere (1 Bar) for 18 hours. The reaction mixture was sparged with Argon for 10 minutes then treated with Sodium nitrate (10% aq. 1 V) and the mixture was stirred at 25°C for 1 hour. The mixture was filtered over a Celite pad which was rinsed with EtOH (2 V). The filtrate was partially concentrated under reduced pressure, treated with NaOH (1N, 0.5 V) and extracted with EtOAc (3 * 1 V). The combined organic layers were washed with brine (1 V), dried over $MgSO_4$, and concentrated under reduced pressure to obtain the corresponding amine.

General procedure (XVI): Aromatic bromination

To a solution of aromatic in MeCN or EtOAc (0.1 M, 1 V) was added N-bromosuccinimide (1.0 equiv.) followed by acetic acid (1.0 equiv.). The reaction mixture was stirred at 25°C for 1 hour, then washed with K_2CO_3 (sat. aq., 1 V), with Brine (0.3 V), dried over $MgSO_4$, and concentrated under reduced pressure to obtain the crude corresponding brominated aromatic compound.

General procedure (XVII): N-aryl N-allyl amino-pyrazine synthesis

To a solution of 2,3-dichloropyrazine and aniline (1.0 equiv) in MeTHF (0.2 M, 1 V) was added Potassium tert-butoxide (3 equiv.). The reaction mixture was stirred at 25°C for 2 hours then 3-bromo-2-methylprop-1-ene was added (1.2 equiv.) and the reaction mixture was heated at 40°C for 18 hours. The reaction mixture was quenched with NH_4Cl (sat.aq. 0.3 V), diluted with water (0.2 V) and extracted with EtOAc (2*0.3 V). The combined organic layers were washed with brine (0.3 V) dried over $MgSO_4$ then concentrated under reduced pressure to afford the crude corresponding N-aryl N-allyl amino-pyrazine.

General procedure (XVIII): Pseudo-heck cyclisation

To a solution of N-aryl N-allyl amino-aryl in a DMSO/water mixture (95:5, 0.5 M, 1 V) was added Sodium formate (1.2 equiv.), the reaction mixture was sparged with Argon for 5 minutes then Palladium$^{(II)}$ acetate (0.05 equiv.) was added and the mixture was heated at 100°C for 30 minutes. The reaction mixture was filtered over a celite pad, which was rinsed with water (3 V) then with EtOAc (1 V) and the filtrate was extracted with EtOAc (2 * 1 V). The combined organic layers were washed with brine (1 V) dried over $MgSO_4$ then concentrated under reduced pressure to afford the crude corresponding cyclised product.

General procedure (XIX): methoxycarbonylation

In the first chamber of a two-chamber reactor (2*20 mL) was prepared a solution of halide or pseudo-halide, and triethyl amine (2.0 eq) in a dioxane/methanol mixture (1:1 0.15 M, 1 V). In the second chamber a suspension of $Mo(CO)_6$ (0.5 eq) in dioxane (1V) was prepared. Both chambers were sparged with argon for 10 minutes then XantPhos Pd G4 (0.10 eq) was added in the first chamber, and DBU (1.5 eq) was added in the second chamber. The set up was crimped and heated at 80°C for 16 hours. The mixture in the first chamber was filtered over a Celite pad and rinsed with DCM (3 V). The filtrate was concentrated under reduced pressure to obtain the crude corresponding methoxycarbonylated product.

General procedure (XX): Ester reduction

To a solution of ester in THF (0.2 M, 1 V) at 0°C was added dropwise Diisobutylaluminium hydride (1M in THF, 6 equiv.). The reaction mixture was stirred at 25°C for 4 hours, then quenched with NaOH (4N aq. 2 V) at 0°C. The mixture was stirred for another 20 minutes then extracted with EtOAc (3*1 V). The combined oganic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to obtain the crude corresponding alcohol.

General procedure (XXI): Alcohol oxidation

To a solution of alcohol in DCM (0.1 M, 1 V) at 0°C was added portionwise Dess-martin Periodinane (1.5 equiv.). The reaction mixture was stirred at 25°C for 1 hour, then quenched with $Na_2S_2O_3$ (sat. Aq. 1 V) and extracted with DCM (2*1 V). The combined oganic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to obtain the crude corresponding aldehyde.

General procedure (XXII): Reductive amination

To a solution of aldehyde in DCM (0.1 M, 1 V) at 25°C was added the amine (1.5 equiv.) and Sodium triacetoxyhydroborate (1.5 equiv.). The reaction mixture was stirred at 60°C for 18 hour, then quenched with $NaHCO_3$ (sat. Aq. 2 V) and extracted with DCM (2*8 V). The combined oganic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to obtain the crude corresponding aldehyde.

General procedure (XXIII): Intramolecular Nucleophilic aromatic substitution

To a solution of amino-haloheteroaryl (1.0 eq.) in Me-THF (0.1 M, 1V) at 0°C, was added Potassium ^{t}butoxide (1.5 equiv.). The reaction mixture was stirred at 25°C for 1 hour, then hydrolysed with NH_4Cl (sat. aq., 4V), diluted with water (2V) and extracted with ethyl acetate (EtOAc 2* 4V). The organic layer was washed with brine, dried over magnesium sulfate then concentrated to dryness to obtain the corresponding cyclised product.

The synthesis and characterization of various exemplary compounds of formula (I) as well as corresponding synthetic intermediates are described in the following (where they are referred to as “Examples” and “Compounds”, respectively).

Compound **1**: ethyl 2-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylpyrimidine-5-carboxylate

To a solution of ethyl 2-chloro-4-methylpyrimidine-5-carboxylate (300 mg) in MeCN (15 mL) was added Potassium carbonate (1.5 eq.) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The reaction mixture was heated at 80°C for 16 hours then diluted with EtOAc (100 mL), washed with water (100 mL), brine (100 mL), the organic layer was dried over $MgSO_4$ and concentrated to dryness. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **1** (560 mg, 99%) as a white solid.

M/Z $(M+H)^+$: 379.3

Compound **2**: ethyl 2-(3,3-dimethylpiperazin-1-yl)-4-methylpyrimidine-5-carboxylate hydrochloride

Compound **2** was prepared according to general procedure (XII) starting from Compound **1** (560 mg) in DCM with TFA. The crude was dissolved in DCM (5 mL), treated with HCl (2N in Et_2O, 5 mL), concentrated under reduced pressure, then dissolved in HCl (1M in MeOH, 5 mL) and concentrated under reduced pressure to obtain Compound **2** (450 mg, 97%) as a white solid.

M/Z $(M+H)^+$: 279.3

Compound **3**: ethyl 2-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)pyrimidine-5-carboxylate

To a solution of ethyl 2-chloropyrimidine-5-carboxylate (250 mg) in MeCN (15 mL) was added Potassium carbonate (1.5 eq.) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The reaction mixture was heated at 80°C for 16 hours then diluted with EtOAc (100 mL), washed with water (100 mL), brine (100 mL), the organic layer was dried over $MgSO_4$ and concentrated to dryness. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **3** (478 mg, 98%) as a white solid.

M/Z $(M-^tBu+H)^+$: 309.2

Compound **4**: ethyl 2-(3,3-dimethylpiperazin-1-yl)pyrimidine-5-carboxylate hydrochloride

Compound **4** was prepared according to general procedure (XII) starting from Compound **3** (475 mg) in DCM with TFA. The crude was dissolved in DCM (5 mL), treated with HCl (2N in Et_2O, 5 mL), concentrated under reduced pressure, then dissolved in HCl (1M in MeOH, 5 mL) and concentrated under reduced pressure to obtain Compound **4** (420 mg, quant.) as a white solid.

M/Z $(M+H)^+$: 265.3

Compound **5**: ethyl 2-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carboxylate

Compound **5** was prepared according to general procedure (X) starting from ethyl 2-bromothiazole-4-carboxylate (300 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **5** (344 mg, 73%) as a yellow solid.

M/Z $(M[+H)^+$: 370.3

Compound **6**: ethyl 2-(3,3-dimethylpiperazin-1-yl)thiazole-4-carboxylate

Compound **6** was prepared according to general procedure (XII) starting from Compound **5** (344 mg) in dioxane with HCl in dioxane at 70°C for 16 hours. The crude was treated with K_2CO_3 (sat.aq., 50 mL) and extracted with EtOAc (2*50 mL). Combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to obtain Compound **6** (217 mg, 87%) as an orange oil.

M/Z $(M+H)^+$: 270.2

Compound **7**: methyl 6-((2-((tert-butoxycarbonyl)(methyl)amino)ethyl)(methyl)amino)-2,4-dimethylnicotinate

Compound **7** was prepared according to general procedure (X) starting from methyl 6-chloro-2,4-dimethylnicotinate (250 mg) and tert-butyl methyl(2-(methylamino)ethyl)carbamate (1.1 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **7** (328 mg, 75%) as a white solid.

M/Z (M[+H)$^+$: 352.2

Compound **8**: methyl 2,4-dimethyl-6-(methyl(2-(methylamino)ethyl)amino)nicotinate hydrochloride

Compound **8** was prepared according to general procedure (XII) starting from Compound **7** (328 mg) in dioxane with HCl in dioxane for 4 hours. The crude was triturated in Et_2O (20 mL) and further washed with Et_2O (3*15 mL) to obtain Compound **8** (254 mg, 95%) as a beige solid.

M/Z (M+H)$^+$: 252.1

Compound **9**: tert-butyl 4-(5-(methoxycarbonyl)-4,6-dimethylpyridin-2-yl)-2,2-dimethylpiperazine-1-carboxylate

Compound **9** was prepared according to general procedure (X) starting from methyl 6-chloro-2,4-dimethylnicotinate (1.80 g) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.1 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **9** (3.27 g, 96%) as a white solid.

M/Z (M[+H)$^+$: 378.3

Compound **10**: methyl 6-(3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate hydrochloride

Compound **10** was prepared according to general procedure (XII) starting from Compound **9** (3.40 g) in dioxane with HCl in dioxane for 4 hours. The crude was triturated in a mixture of Et_2O (100 mL) and EtOH (3 mL) and further washed with Et_2O (3*15 mL) to obtain Compound **10** (2.80 g, 99%) as a white solid.

M/Z (M+H)$^+$: 278.2

Compound **11**: 6-(3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid

Compound **11** was prepared according to general procedure (XI) starting from Compound **10** (100 mg). The reaction mixture was concentrated under reduced pressure, the residue was treated with HCl (4N in dioxane, 20 mL), and the mixture was concentrated under reduced pressure. The crude was dissolved in MeOH and the methanolic solution was charged on an Isolute SCX-2 cartridge (2 g), the cartridge was rinsed with MeOH then eluted with triethylamine (1M in methanol) to obtain Compound **11** (53 mg, 64%) as a white solid.

M/Z (M+H)$^+$: 264.2

Compound **12**: tert-butyl (1-carbamoylcyclopropyl)(methyl)carbamate

To a solution of 1-((tert-butoxycarbonyl)(methyl)amino)cyclopropane-1-carboxylic acid (250 mg) in THF (15 mL) was added N,N-diisopropylethylamine (3.0 eq.), then at 0°C Methyl chlorocarbonate (1.5 eq.) was added dropwise. The reaction mixture was stirred at 0°C for 30 minutes, ammonia was added (0.4 M in dioxane, 3.0 eq.) and the mixture was let warm up at 25°C over 18 hours, then concentrated under reduced pressure. The residue was treated with $NaHCO_3$ (sat. aq., 50 mL) and extracted with EtOAc (3*100 mL). Combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain Compound **12** (238 mg, 96%) as a white solid.

M/Z (M+Na)$^+$: 237.1

Compound **13**: 1-(methylamino)cyclopropane-1-carboxamide hydrochloride

Compound **13** was prepared according to general procedure (XII) starting from Compound **12** (258 mg) in dioxane with HCl in dioxane for 18 hours at 60°C. The crude was triturated in Et_2O (20 mL) to obtain Compound **13** (150 mg, 90%) as a beige solid.

M/Z $(M+H)^+$: 115.0

Compound **14**: 4-(3-bromo-6-chloropyridin-2-yl)tetrahydro-2H-pyran-4-carbonitrile

Compound **14** was prepared according to general procedure (I) starting from 3-bromo-6-chloro-2-fluoropyridine (1.50 g) and tetrahydro-2H-pyran-4-carbonitrile (759 µL). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **14** (1.67 g, 83%) as a white solid.

M/Z $(M[^{35}Cl][^{81}Br]+H)^+$: 303.0

Compound **15**: 4-(3-bromo-6-chloropyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide

Compound **15** was prepared according to general procedure (IIa) starting from Compound **14** (500 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 20:80) to obtain Compound **15** (477 mg, 90%) as a white solid.

M/Z $(M[^{35}Cl^{81}Br]+H)^+$:321.0

Compound **16**: 5'-chloro-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridin]-2'(1'H)-one

Compound **16** was prepared according to general procedure (III) starting from Compound **15** (477 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **16** (330 mg, 93%) as a brown solid.

M/Z $(M[^{35}Cl]+H)^+$:239.0

Compound **17**: 2'-oxo-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **17** was prepared according to general procedure (IV) starting from Compound **16** (330 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **17** (263 mg, 83%) as a brown solid.

M/Z $(M+H)^+$: 230.1.

Compound **18**: 1'-(4-chloro-3-fluorophenyl)-2'-oxo-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **18** was prepared according to general procedure (V) starting from Compound **17** (260 mg) and 4-bromo-1-chloro-2-fluorobenzene (261 mg, 1.1 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **17** (239 mg, 59%) as a purple solid.

M/Z $(M[^{35}Cl]+H)^+$:358.1 .

Compound **19**: 1'-(4-chloro-3-fluorophenyl)-2'-oxo-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carboxamide

Compound **19** was prepared according to general procedure (IIa) starting from Compound **18** (239 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **19** (203 mg, 81%) as a purple solid.

M/Z (M[^{35}Cl]+H)$^{+}$: 376.2

Compound **20**: methyl 1'-(4-chloro-3-fluorophenyl)-2'-oxo-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylate

Compound **20** was prepared according to general procedure (VI) starting from Compound **19** (203 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **20** (205 mg, 97%) as a white solid.

M/Z (M [^{35}Cl] +H)$^{+}$: 391.2 .

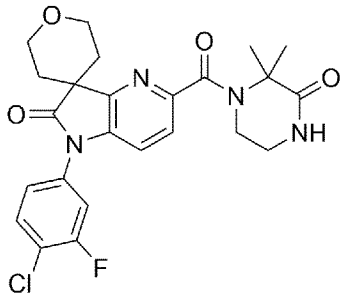
Compound **21**: 1'-(4-chloro-3-fluorophenyl)-2'-oxo-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylic acid and 6-(4-carboxytetrahydro-2H-pyran-4-yl)-5-((4-chloro-3-fluorophenyl)amino)picolinic acid mixture

Compound **20** (205 mg) was hydrolysed according to general procedure (VII) to obtain Compound **21** (204 mg) as a white solid.

M/Z (M [^{35}Cl]+H)$^{+}$: 377.2

M/Z (M [^{35}Cl]+H)$^{+}$: 395.1

Example **1**: 1'-(4-chloro-3-fluorophenyl)-5'-(2,2-dimethyl-3-oxopiperazine-1-carbonyl)-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridin]-2'(1'H)-one



To a solution of Compound **21** (204 mg) in DCM/THF (1:1, 30 mL) was added ((1H-benzo[d][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate(V) (2.3 eq.), N,N-diisopropylethylamine (3.8 eq) and 3,3-dimethylpiperazin-2-one (1.5 eq.). The reaction mixture was stirred at 25 °C for 18 hours. The reaction mixture was hydrolysed then extracted with EtOAc. The organic layer was dried over $MgSO_4$. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to EtOAc 100%) then further purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried with water to obtain Example **1** (137 mg, 54% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.69 (s, 6H, 2 CH_3); 1.83-2.00 (m, 4H, 2 CH_2, **CH_2**CH_2O); 3.52-3.58 (m, 2H, CH_2); 3.93-4.09 (m, 4H, 2 CH_2, CH_2**CH_2**O); 7.38 (d, *J* 8.4 Hz, 1H, Ar); 7.43 (ddd, *J* 8.4, 2.1, 0.9 Hz, 1H, Ar); 7.57 (d, *J* 8.4 Hz, 1H, Ar); 7.69 (dd, *J* 8.4, 2.1 Hz, 1H, Ar); 7.83 (t, *J* 8.4 Hz, 1H, Ar); 8.13-8.16 (m, 1H, NH). One CH_2 signal not observed.

M/Z (M[^{35}Cl]+H)$^{+}$: 487.0,

Mp: 162-164 °C

Compound **22**: 1-(3-bromo-6-chloropyridin-2-yl)cyclopentane-1-carbonitrile

Compound **22** was prepared according to general procedure (I) starting from 3-bromo-6-chloro-2-fluoropyridine (5.00 g) and cyclopentanecarbonitrile. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/Et_2O 80:20) to obtain Compound **22** (5.57 g, 82%) as a white solid.

M/Z(M[^{35}Cl][^{81}Br]+H)$^+$: 287.0

Compound **23**: 1-(3-bromo-6-chloropyridin-2-yl)cyclopentane-1-carboxamide

Compound **23** was prepared according to general procedure (IIa) starting from Compound **22** (5.57 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **23** (5.96 g) as a white solid.

M/Z (M[^{35}Cl^{81}Br]+H)$^+$:305.1

Compound **24**: 5'-chlorospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridin]-2'(1'H)-one

Compound **24** was prepared according to general procedure (III) starting from Compound **23** (5.96 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **24** (3.37 g, 77% over 2 steps) as a beige solid.

M/Z (M[^{35}Cl]+H)$^+$:223.0

Compound **25**: 2'-oxo-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **25** was prepared according to general procedure (IV) starting from Compound **24** (200 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **25** (184 mg, 96%) as a white solid.

M/Z (M+H)$^+$: 214.1.

Compound **26**: 1'-(4-chloro-3-fluorophenyl)-2'-oxo-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **26** was prepared according to general procedure (V) starting from Compound **25** (184 mg) and 4-bromo-1-chloro-2-fluorobenzene (199 mg, 1.1 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **26** (250 mg, 89%) as a beige solid.

M/Z (M[^{35}Cl]+H)$^+$:342.1 .

Compound **27**: 1'-(4-chloro-3-fluorophenyl)-2'-oxo-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxamide

Compound **27** was prepared according to general procedure (IIa) starting from Compound **26** (220 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **27** (240 mg) as a white solid.

M/Z (M[^{35}Cl]+H)$^+$: 360.2

Compound **28**: methyl 1'-(4-chloro-3-fluorophenyl)-2'-oxospiro[cyclopentane-1,3'-indoline]-5'-carboxylate

Compound **28** was prepared according to general procedure (VI) starting from Compound **27** (240 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **28** (212 mg, 88% over 2 steps) as a white solid.

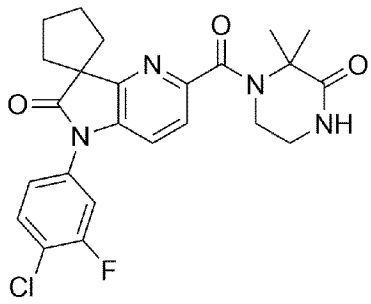
M/Z (M [^{35}Cl] +H)$^{+}$: 375.2 .

Compound **29**: 1'-(4-chloro-3-fluorophenyl)-2'-oxo-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylic acid

Compound **29** was prepared according to general procedure (VII) starting from Compound **28** (212 mg). The crude was purified by flash chromatography (Merck 60®, DCM 100% to DCM/MeOH 80:20), then further purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze-dried to obtain Compound **29** (55 mg, 27%) as a white solid.

M/Z (M ^{35}Cl+H)$^{+}$ 361.2.

Example **2**: 1'-(4-chloro-3-fluorophenyl)-5'-(2,2-dimethyl-3-oxopiperazine-1-carbonyl)spiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridin]-2'(1'H)-one



Example **2** was prepared according to general procedure (VIIIa) starting from Compound **29** (55 mg), 3,3-dimethylpiperazin-2-one (1.3 eq.) and N,N-diisopropylethylamine (3.0 eq.) in a mixture DCM/THF. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to EtOAc 100%) then freeze dried with MeOH/water to obtain Example **2** (30 mg, 42%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.67 (s, 6H, 2 CH_3); 1.64-2.15 (m, 8H, 4 CH_2); 3.47-3.53 (m, 2H, CH_2); 7.33 (d, *J* 8.1 Hz, 1H, Ar); 7.39-7.73 (m, 1H, Ar); 7.50 (d, *J* 8.1 Hz, 1H, Ar); 7.69 (dd, *J* 10.2, *J* 2.4 Hz, 1H, Ar); 7.80 (t, *J* 8.4 Hz, 1H, Ar); 8.06-8.09 (m, 1H, N**H**CO), one CH_2 signal not observed.

M/Z (M[^{35}Cl]+H)$^{+}$: 471.3.

Mp: 143 145 °C

Compound **30**: 5'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **30** was prepared according to general procedure (IX) starting from Compound **24** (1.60 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **30** (850 mg, 56%) as a beige solid.

M/Z (M[^{35}Cl]+H)$^{+}$: 209.2

Compound **31**: 1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **31** was prepared according to general procedure (IV) starting from Compound **30** (850 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **31** (602 mg, 74%) as a brown solid

M/Z $(M+H)^+$: 200.2

Compound **32**: 1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **32** was prepared according to general procedure (X) starting from Compound **31** (195 mg) and 4-bromo-1-chloro-2-fluorobenzene (1.1 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **32** (220 mg) as a yellow solid.

M/Z $(M[^{35}Cl]+H)^+$: 328.2

Compound **33:** 1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxamide

Compound **33** was prepared according to general procedure (IIa) starting from Compound **32** (220 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **33** (200 mg, 60% over 2 steps) as a beige solid.

M/Z $(M[^{35}Cl]+H)^+$: 346.2

Compound **34:** methyl 1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylate

Compound **34** was prepared according to general procedure (VI) starting from Compound **33** (200 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **34** (197 mg, 94%) as a beige solid.

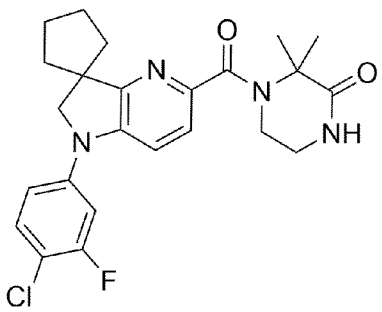
M/Z $(M[^{35}Cl]+H)^+$: 361.3

Compound **35**: 1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylic acid

Compound **35** was obtained (255 mg) as a yellow solid according to general procedure (VII) starting from Compound **34** (251 mg).

M/Z $(M[^{35}Cl]+H)^+$: 347.3

Example **3**: 4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one



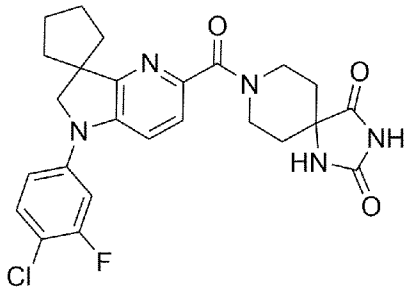
Example **3** was prepared according to general procedure (VIIIa) starting from Compound **35** (99 mg), 3,3-dimethylpiperazin-2-one (2.0 eq.) and N,N-diisopropylethylamine (3.0 eq.) in a THF/DCM mixture (5:2). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to EtOAc 100%) then triturated in 12 mL of a DCM/Pentane mixture (1:5) to obtain Example **3** (48 mg, 32% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.66 (s, 6H, 2 CH_3); 1.81-1.93 (m, 8H, 4 CH_2); 3.56-3.51 (m, 2H, CH_2); 3.93 (s, 2H, CH_2); 7.19 (ddd, *J* 8.7, 2.7, 1.0 Hz, 1H, Ar), 7.33 (dd, *J* 11.8, 2.7 Hz, 1H, Ar); 7.40 (d, *J* 8.4 Hz, 1H, Ar); 7.51-7.57 (m, 2H, 2 Ar), 8.02-8.06 (m, 1H, NH).

M/Z (M[^{35}Cl]+H)$^+$: 457.3.

Mp: 198:200 °C.

Example **4**: 8-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-1,3,8-triazaspiro[4.5]decane-2,4-dione



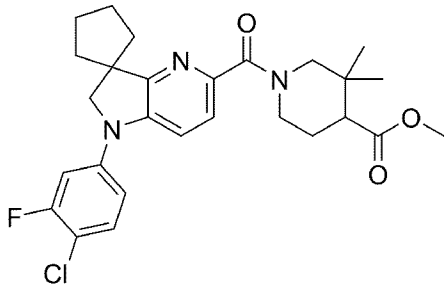
Example **4** was prepared according to general procedure (VIIIa) starting from Compound **35** (50 mg), 1,3,8-triazaspiro[4.5]decane-2,4-dione (2.0 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 95:05 to 0:100) then freeze dried to obtain Example **4** (16 mg, 22% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.54-2.01 (m, 12H, 4 **CH_2** cyclopentyl+2 (N-CH_2-**CH_2**); 3.17-3.27 (m, 1H, N-**CH_2**-CH_2); 3.39-3.51 (m, 1H, N-**CH_2**-CH_2); 3.93 (s, 2H, C-**CH_2**-N); 3.97-4.09 (m, 1H, N-**CH_2**-CH_2); 4.18-4.32 (m, 1H, N-**CH_2**-CH_2); 7.17-7.21 (dd,*J* 8.9, 2.0 Hz, 1H, Ar); 7.30-7.35 (dd, *J* 11.9, 2.5 Hz, 1H, Ar); 7.40 (d, *J* 8.4 Hz, 1H, Ar); 7.49-7.59 (m, 2H, 2 Ar); 8.58 (s, 1H, NH); 10.74 (bs, 1H, NH).

M/Z (M[^{35}Cl]+H)$^+$: 498.2.

Mp: 280-285 °C.

Example **5**: methyl 1-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperidine-4-carboxylate



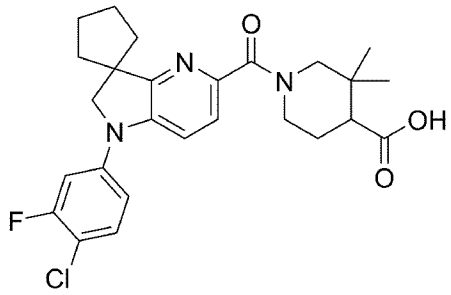
Example **5** was prepared according to general procedure (VIIIa) starting from Compound **35** (80 mg), methyl 3,3-dimethylpiperidine-4-carboxylate (2.0 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified

by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **5** (100 mg) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.81-1.12 (m, 6H, 2**CH_3**); 1.40-1.45 (m, 4H, 2**CH_2** cyclopentyl); 1.69-2.22 (m, 6H, 2**CH_2** cyclopentyl + N-CH_2-**CH_2**), 2.36-2.48 (1H, m, CH), 2.81-3.23 (m, 2H, NCH_2), 3.70 (s, 3H, OCH_3), 3.83 (s, 2H,N-CH_2), 4.26-4.61 (m, 2H, N-CH_2), 6.92-7.02 (m, 2H, 2 Ar), 7.28-7.37 (m, 2H, 2 Ar), 7.51 (d, *J* 8.4 Hz, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 500.3.

Example **6**: 1-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperidine-4-carboxylic acid



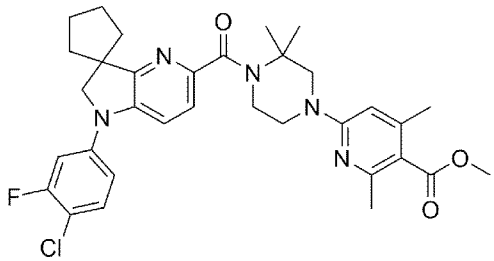
Example **6** was prepared according to general procedure (VII) starting from Example **5** (100 mg). The crude was purified by flash chromatography (Merck 60®, DCM 100% to DCM/MeOH 80:20) then further purified by preparative HPLC (Column B, (H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 95:05 to 0:100) and freeze dried to obtain Example **6** (20 mg, 18% over 3 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 0.77-1.10 (m, 6H, 2**CH3**); 1.53-2.03 (m, 10H, 4**CH2** cyclopentyl+N-CH2-**CH2**); 2.28-2.41 (m, 1H, CO-**CH**-C(CH3)2); 2.77-3.14 (m, 2H, N-**CH2**), 3.86-4.12 (m, 3.5H, N-**CH2**+N-**CH2**-cyclopentyl); 4.33-4.45 (m, 0.5H, N-**CH2**); 7.19 (dd, *J* 8.4, 2.0 Hz, 1H, Ar); 7.28-7.41 (m, 2H, 2 Ar); 7.49-7.58 (m, 2H, 2 Ar); One signal not observed (COOH).

M/Z (M[^{35}Cl]+H)$^+$: 486.3.

Mp: 280-285 °C.

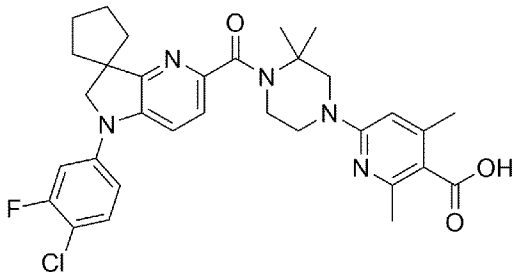
Example **7**: methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



Example **7** was prepared according to general procedure (VIIIa) starting from Compound **35** (105 mg), Compound **10** (1.2 eq.) and N,N-diisopropylethylamine (4.0 eq.) in THF/DCM mixture (1:1). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **7** (155 mg, 84%) as a white solid.

M/Z (M[^{35}Cl]+H)$^+$: 606.5

Example **8**: 6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **8** was prepared according to general procedure (XI) starting from Example **7** (155 mg). The crude was purified by flash chromatography (Merck 60®, DCM 100% to DCM/MeOH 80:20) and freeze dried to obtain Example **8** (10 mg, 6%) as a white solid.

^{1}H-NMR (DMSO-d_6 300 MHz) δ: 1.47 (s, 6H, 2 CH_3); 1.74-2.01 (m, 8H, 4 CH_2); 2.25 (s, 3H, CH_3); 2.36 (s, 3H, CH_3); 3.52-3.59 (m, 2H, CH_2); 3.77-3.95 (m, 6H, 3 CH_2); 6.30 (s, 1H, Ar), 7.18 (dd, *J* 2.1, 8.7 Hz, 1H, Ar); 7.29-7.35 (m, 2H, 2 Ar); 7.50-7.57 (m, 2H, 2 Ar). COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 592.4.

Mp: 265 - 267 °C.

Compound **36**: 1'-(3-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **36** was prepared according to general procedure (X) starting from Compound **31** (100 mg) and 1-bromo-3-chlorobenzene (1.1 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **36** (110 mg) as a yellow oil.

M/Z (M[^{35}Cl]+H)$^+$: 310.7

Compound **37:** 1'-(3-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxamide

Compound **37** was prepared according to general procedure (IIa) starting from Compound **36** (110 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 20:80) to obtain Compound **37** (70 mg) as a white solid.

M/Z (M[^{35}Cl]+H)$^+$: 328.3

Compound **38:** methyl 1'-(3-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylate

Compound **38** was prepared according to general procedure (VI) starting from Compound **36** (70 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 40:60) to obtain Compound **38** (40 mg) as a white solid.

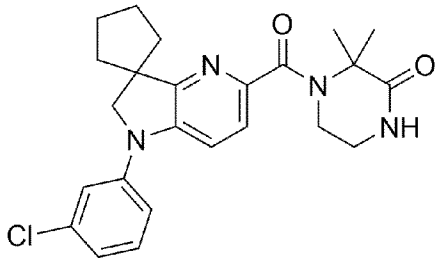
M/Z (M[^{35}Cl]+H)$^+$: 343.1

Compound **39**: 1'-(3-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylic acid

Compound **39** was obtained (40 mg) as a yellow solid according to general procedure (VII) starting from Compound **38** (40 mg).

M/Z (M[^{35}Cl]+H)$^+$: 329.0

Example **9**: 4-(1'-(3-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one



Example **9** was prepared according to general procedure (VIIIa) starting from Compound **39** (40 mg), 3,3-dimethylpiperazin-2-one (2.0 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to Cyhex/EtOAc 70:30) to obtain Example **9** (50 mg, 22% over 5 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.66 (s, 6H, 2 CH_3); 1.73-2.00 (m, 8H, 4 CH_2); 3.51-3.59 (m, 2H, CH_2); 3.94 (s, 2H, CH_2); 7.07 (d, *J* 7.5 Hz, 1H, Ar); 7.28-7.33 (m, 2H, 2 Ar); 7.38-7.42 (m, 2H, 2 Ar); 7.48 (d, *J* 7.5 Hz, 1H, Ar); 8.04 (bs, 1H, CON**H**R), one CH_2 signal not observed.

M/Z (M[^{35}Cl]+H)$^+$: 439.4.

Mp: 188-192 °C.

Compound **40**: 1'-(2-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **40** was prepared according to general procedure (X) starting from Compound **31** (100 mg) and 1-bromo-2-chlorobenzene (1.1 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **40** (90 mg) as a yellow oil.

M/Z (M[^{35}Cl]+H)$^+$: 310.2

Compound **41:** 1'-(2-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxamide

Compound **41** was prepared according to general procedure (IIa) starting from Compound **40** (90 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 20:80) to obtain Compound **41** (70 mg) as a white solid.

M/Z (M[^{35}Cl]+H)$^+$: 328.3

Compound **42:** methyl 1'-(2-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylate

Compound **42** was prepared according to general procedure (VI) starting from Compound **41** (90 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **42** (50 mg) as a white solid.

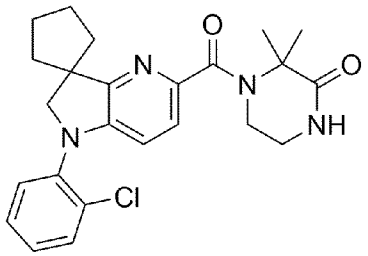
M/Z (M[^{35}Cl]+H)$^+$: 343.1

Compound **43**: 1'-(2-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylic acid

Compound **43** was prepared according to general procedure (VII) starting from Compound **42** (50 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 30:70) to obtain Compound **43** (44 mg) as a white solid.

M/Z (M[^{35}Cl]+H)$^+$: 329.1

Example **10**: 4-(1'-(2-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one



Example **10** was prepared according to general procedure (VIIIa) starting from Compound **43** (44 mg), 3,3-dimethylpiperazin-2-one (2.0 eq.) and N,N-diisopropylethylamine (5.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to Cyhex/EtOAc 70:30) to obtain Example **10** (14 mg, 6% over 5 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.64 (s, 6H, 2 CH_3); 1.63-2.03 (m, 8H, 4 CH_2); 3.53-3.62 (m, 2H, CH_2); 3.88 (s, 2H, CH_2); 6.55 (d, *J* 8.5 Hz, 1H, Ar); 7.30-7.36 (m, 2H, 2 Ar); 7.44 (td, *J* 8.0, 1.2 Hz, 1H, Ar); 7.55 (dd, *J* 8.0, 1.2 Hz, 1H, Ar); 7.61 (dd, *J* 8.0, 1.2 Hz, 1H, Ar); 8.04 (bs, 1H, CON**H**R); one CH_2 signal not observed.

M/Z (M[^{35}Cl]+H)$^+$: 439.3.

Mp: 206-210 °C.

Compound **44**: 2-(3-bromo-6-chloropyridin-2-yl)-2-methylpropanenitrile

Compound **44** was prepared according to general procedure (I) starting from 3-bromo-6-chloro-2-fluoropyridine (5.00 g) and isobutyronitrile (2.13 mL). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **44** (4.14 g) as a clear oil.

M/Z(M[^{35}Cl][^{81}Br]+H)$^+$: 261.0

Compound **45**: 2-(3-bromo-6-chloropyridin-2-yl)-2-methylpropanamide

Compound **45** was prepared according to general procedure (IIa) starting from Compound **44** (4.14 g). The crude was triturated in a mixture DCM/n-pentane (20/80). The precipitate was recovered by filtration to obtain Compound **45** (2.77 g, 42% over 2 steps) as a white solid.

M/Z (M[^{35}Cl^{81}Br]+H)$^+$: 279.0

Compound **46**: 5-chloro-3,3-dimethyl-1,3-dihydro-2H-pyrrolo[3,2-b]pyridin-2-one

Compound **46** was prepared according to general procedure (III) starting from Compound **45** (2.77 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **46** (1.57 g, 80%) as a beige solid.

M/Z (M[^{35}Cl]+H)$^+$: 197.0

Compound **47**: 5-chloro-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

Compound **47** was prepared according to general procedure (IX) starting from Compound **46** (1.57 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **47** (1.09 g, 75%) as a beige solid.

M/Z (M[^{35}Cl]+H)$^{+}$: 182.9

Compound **48**: 3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonitrile

Compound **48** was prepared according to general procedure (IV) starting from Compound **47** (1.09 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 20:80) to obtain Compound **48** (460 mg, 45%) as a beige solid

M/Z (M+H)$^{+}$: 174.2

Compound **49**: 3,3-dimethyl-1-(thiophen-3-yl)-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonitrile

Compound **49** was prepared according to general procedure (X) starting from Compound **48** (100 mg) and 3-bromothiophene (1.6 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **49** (100 mg, 68%) as a yellow solid.

M/Z (M+H)$^{+}$: 256.2

Compound **50:** 3,3-dimethyl-1-(thiophen-3-yl)-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide

Compound **50** was prepared according to general procedure (IIa) starting from Compound **49** (100 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **50** (120 mg) as a beige solid.

M/Z (M+H)$^{+}$: 274.2

Compound **51:** methyl 3,3-dimethyl-1-(thiophen-3-yl)-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylate

Compound **51** was prepared according to general procedure (VI) starting from Compound **50** (120 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **51** (60 mg) as a yellow solid.

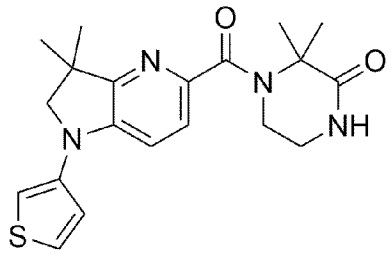
M/Z (M+H)$^{+}$: 289.2

Compound **52**: 3,3-dimethyl-1-(thiophen-3-yl)-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylic acid

Compound **52** was obtained (60 mg) as a yellow solid according to general procedure (VII) starting from Compound **51** (60 mg).

M/Z (M+H)$^{+}$: 275.1

Example **11**: 4-(3,3-dimethyl-1-(thiophen-3-yl)-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one



Example **11** was prepared according to general procedure (VIIIa) starting from Compound **52** (60 mg), 3,3-dimethylpiperazin-2-one (2.0 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) then further purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried to obtain Example **11** (11 mg, 8% over 4 steps) as a beige solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.33 (s, 6H, 2 CH_3); 1.66 (s, 6H, 2 CH_3); 3.34-3.38 (m, 2H, CH_2); 3.50-3.57 (m, 2H, CH_2); 3.84 (s, 2H, CH_2); 7.07 (dd, J 3.1, 1.6 Hz, 1H, Ar); 7.30 (dd, J 5.1, 1.6 Hz, 1H, Ar); 7.39 (s, 2H, 2 Ar); 7.64 (dd, J 5.1, 3.1 Hz, 1H, Ar); 8.04 (bs, 1H, CONHR).

M/Z $(M+H)^+$: 385.2.

Mp: 208-212 °C.

Compound **53**: 1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonitrile

Compound **53** was prepared according to general procedure (X) starting from Compound **48** (85 mg) and 4-bromo-1,2-difluorobenzene (1.0 eq). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **53** (110 mg, 79%) as a yellow oil.

M/Z $(M+H)^+$: 286.2

Compound **54:** 1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide

Compound **54** was prepared according to general procedure (IIa) starting from Compound **53** (110 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **54** (100 mg) as a white solid.

M/Z $(M+H)^+$: 304.2

Compound **55:** methyl 1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylate

Compound **55** was prepared according to general procedure (VI) starting from Compound **54** (120 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 20:80) to obtain Compound **55** (85 mg, 81%) as a yellow solid.

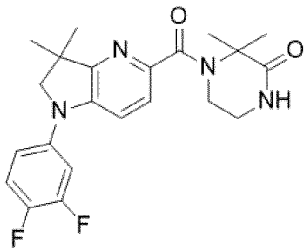
M/Z $(M+H)^+$: 319.1

Compound **56**: 1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylic acid

Compound **56** was obtained (80 mg, 98%) as a yellow solid according to general procedure (VII) starting from Compound **55** (85 mg).

M/Z $(M+H)^+$: 305.1

Example **12:** 4-(1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one



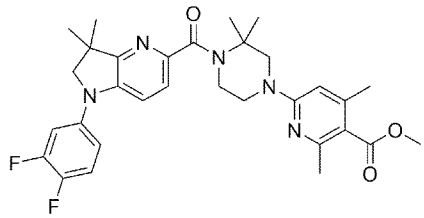
Example **12** was prepared according to general procedure (VIIIa) starting from Compound **56** (40 mg), 3,3-dimethylpiperazin-2-one (1.2 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) then triturated in Et_2O to obtain Example **12** (30 mg, 55%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.33 (s, 6H, 2 CH_3); 1.66 (s, 6H, 2 CH_3); 3.31-3.35 (m, 2H, CH_2); 3.51-3.54 (m, 2H, CH_2); 3.84 (s, 2H, CH_2); 7.12-7.17 (m, 1H, Ar); 7.33-7.50 (m, 4H, 4 Ar); 8.05 (bs, 1H, NH).

M/Z $(M+H)^+$: 415.2.

Mp: 217-220°C

Example **13**: methyl 6-(4-(1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

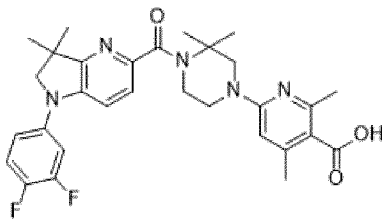


Example **13** was prepared according to general procedure (VIIIa) starting from Compound **56** (47 mg), Compound **10** (1.2 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Example **13** (77 mg, 88%) as a white solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.43 (s, 6H, 2 CH_3); 1.63 (s, 6H, 2 CH_3); 2.34 (s, 3H, CH_3); 2.49 (s, 3H, CH_3); 3.61-3.67 (m, 2H, CH_2); 3.77 (s, 2H, N-CH_2); 3.89 (s, 3H, O-CH_3); 3.96-4.02 (m, 4H, 2 N-CH_2); 6.11 (s, 1H, Ar); 6.90-6.96 (m, 1H, Ar); 7.00-7.07 (m, 1H, Ar); 7.14-7.24 (m, 1H, Ar); 7.28 (d, J 8.4 Hz, 1H, Ar); 7.50 (d, J 8.4 Hz, 1H, Ar).

M/Z $(M+H)^+$: 564.4

Example **14**: 6-(4-(1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **14** was prepared according to general procedure (XI) starting from Example **13** (77 mg). The crude was purified by flash chromatography (Merck 60®, DCM 100% to DCM/MeOH 80:20) and freeze dried to obtain Example **14** (40 mg, 53%) as a white solid.

^{1}H-NMR (DMSO-d_6 300 MHz) δ: 1.34 (s, 6H, 2 CH_3); 1.48 (s, 6H, 2 CH_3); 2.25 (s, 3H, CH_3); 2.36 (s, 3H, CH_3); 3.52-3.55 (m, 2H, CH_2); 3.80-3.86 (m, 6H, 3 CH_2); 6.32 (s, 1H, Ar); 7.11-7.16 (m, 1H, Ar); 7.31-7.40 (m, 2H, 2 Ar); 7.43-7.48 (m, 2H, 2 Ar), 12.68 (bs, 1H, CO_2H).

M/Z $(M+H)^+$: 550.3

Compound **57**: 1-(4-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonitrile

Compound **57** was prepared according to general procedure (X) starting from Compound **48** (85 mg) and 1-bromo-4-fluorobenzene (1.0 eq). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **57** (86 mg, 66%) as a yellow solid.

M/Z $(M+H)^+$: 268.2

Compound **58:** 1-(4-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide

Compound **58** (90 mg, 99%) was obtained as a white solid from Compound **57** (85 mg) according to general procedure (IIb).

M/Z $(M+H)^+$: 286.2

Compound **59:** methyl 1-(4-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylate

Compound **59** was prepared according to general procedure (VI) starting from Compound **58** (120 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **59** (85 mg, 81%) as a white solid.

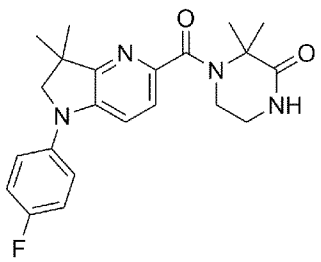
M/Z $(M+H)^+$: 301.2

Compound **60**: 1-(4-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylic acid

Compound **60** was obtained (80 mg) as a yellow solid according to general procedure (VII) starting from Compound **59** (85 mg).

M/Z $(M+H)^+$: 287.2

Example **15:** 4-(1-(4-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one



Example **15** was prepared according to general procedure (VIIIa) starting from Compound **60** (33 mg), 3,3-dimethylpiperazin-2-one (1.2 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash

chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) then triturated in Et_2O to obtain Example **15** (20 mg, 44%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.32 (s, 6H, 2 CH_3); 1.65 (s, 6H, 2 CH_3); 3.32-3.35 (m, 2H, CH_2); 3.51-3.54 (m, 2H, CH_2); 3.82 (s, 2H, CH_2); 7.20-7.26 (m, 2H, 2 Ar); 7.30-7.38 (m, 4H, 4 Ar); 8.04 (bs, 1H, NH).

M/Z $(M+H)^+$: 397.2 .

Mp: 234-236 °C.

Compound **61**: 1-(3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonitrile

Compound **61** was prepared according to general procedure (X) starting from Compound **48** (150 mg) and 1-bromo-3-fluorobenzene (1.0 eq). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **61** (205 mg, 89%) as a white solid.

M/Z $(M+H)^+$: 268.2

Compound **62:** 1-(3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide

Compound **62** (210 mg, 98%) was obtained as a white solid from Compound **61** (200 mg) according to general procedure (IIb).

M/Z $(M+H)^+$: 286.2

Compound **63:** methyl 1-(3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylate

Compound **63** was prepared according to general procedure (VI) starting from Compound **62** (210 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **63** (160 mg, 72%) as a white solid.

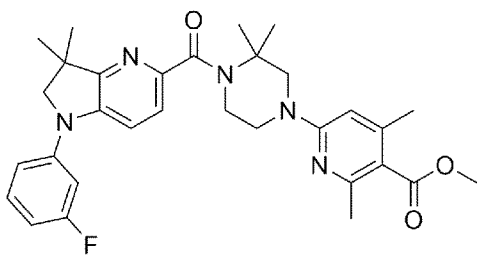
M/Z $(M+H)^+$: 301.2

Compound **64**: 1-(3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylic acid

Compound **64** was obtained (140 mg, 92%) as a yellow solid according to general procedure (VII) starting from Compound **63** (160 mg).

M/Z $(M+H)^+$: 287.2

Example **16**: methyl 6-(4-(1-(3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



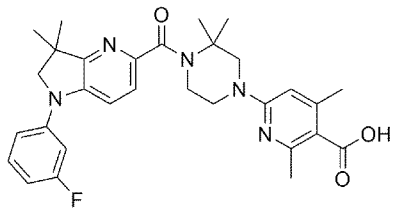
Example **16** was prepared according to general procedure (VIIIb) starting from Compound **64** (50 mg), Compound **10** (1.3 eq.) and Triethylamine (4.7 eq.) in THF. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to Et_2O 0:100). The product was further purified by dissolution in Et_2O (10 mL), extraction with HCl

(aq. 1N, 3*10 mL), aqueous layers were basified with Na_2CO_3 (sat. aq.) and extracted with Et_2O (3*10 mL) to obtain Example **16** (60 mg, 63%) as a white solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.43 (s, 6H, 2 CH_3); 1.63 (s, 6H, 2 CH_3); 2.34 (s, 3H, CH_3); 2.49 (s, 3H, CH_3); 3.61-3.67 (m, 2H, CH_2); 3.81 (s, 2H, N-CH_2); 3.89 (s, 3H, O-CH_3); 3.97 (s, 2H, N-CH_2); 3.99-4.03 (m, 2H, N-CH_2); 6.11 (s, 1H, Ar); 6.71-6.78 (m, 1H, Ar); 6.89-6.95 (m, 1H, Ar); 6.98-7.01 (m, 1H, Ar); 7.27-7.38 (m, 1H, Ar); 7.40 (d, J 8.4 Hz, 1H, Ar); 7.51 (d, J 8.4 Hz, 1H, Ar).

M/Z $(M+H)^+$: 546.4

Example **17**: 6-(4-(1-(3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **17** was prepared according to general procedure (XI) starting from Example **16** (60 mg). The crude was purified by flash chromatography (Merck 60®, DCM 100% to DCM/MeOH 80:20) and freeze dried to obtain Example **17** (41 mg, 70%) as a white solid.

^{1}H-NMR (DMSO-d_6 300 MHz) δ: 1.35 (s, 6H, 2 CH_3); 1.48 (s, 6H, 2 CH_3); 2.24 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 3.51-3.54 (m, 2H, CH_2); 3.79-3.85 (m, 6H, 3 CH_2); 6.28 (bs, 1H, Ar); 6.84 (dt, *J* 6.3, 2.1 Hz, 1H, Ar); 7.06-7.17 (m, 2H, 2 Ar); 7.33 (d, *J* 8.2 Hz, 1H, Ar); 7.37-7.45 (m, 1H, Ar); 7.53 (d, *J* 8.2 Hz, 1H, Ar). COOH was not observed.

M/Z $(M+H)^+$: 532.4

Compound **65**: 1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonitrile

Compound **65** was prepared according to general procedure (X) starting from Compound **48** (100 mg) and 4-bromo-1-chloro-2-fluorobenzene (1.1 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **65** (230 mg, 88%) as a yellow solid.

M/Z $(M[^{35}Cl]+H)^+$: 302.2.

Compound **66:** 1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide

Compound **66** was prepared according to general procedure (IIa) starting from Compound **65** (230 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **66** (300 mg) as a yellow solid.

M/Z $(M[^{35}Cl]+H)^+$: 320.2.

Compound **67:** methyl 1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylate

Compound **67** was prepared according to general procedure (VI) starting from Compound **66** (300 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 40:60) to obtain Compound **67** (140 mg, 55% over 2 steps) as a white solid.

M/Z $(M[^{35}Cl]+H)^+$: 335.2.

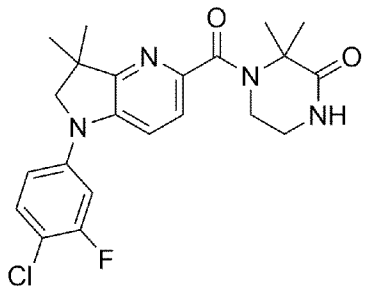
Compound **68**: 1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylic acid
Compound **68** was obtained (140 mg) as a yellow solid according to general procedure (VII) starting from Compound **67** (140 mg).
M/Z ($M[^{35}Cl]+H)^+$: 321.2.

Compound **69**: 6-chloro-2-iodo-N-(2-methylallyl)pyridin-3-amine
To a solution of 6-chloro-2-iodopyridin-3-amine (5.00 g) in THF, ^{t}BuOK (1.2 eq) was added at 0°C. The reaction mixture was stirred at 0°C for 10 minutes then 3-Bromo-2-methylpropene (1.1 eq) was added and the reaction was stirred at 25°C for 16 hours. The reaction mixture was quenched with NH4Cl (150 mL, sat. aq.), extracted with EtOAc (2*100 mL). Combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and concentrated under reduced presure. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **69** (4.54 g, 75%) as an orange oil.
M/Z ($M[^{35}Cl]+H)^+$: 309.1.

Compound **70**: 5-chloro-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine
To a solution of Compound **69** (1.51 g) in a DMSO/water mixture (16.5 mL, 9:1) was added tetrabutylammonium chloride (1.2 eq), sodium formate (1.2 eq) and triethylamine (3.0 eq). The reaction mixture was sparged with argon for 10 minutes then Palladium acetate (0.15 eq) was added and the reaction vial was crimped and heated at 120°C for 1 hour. The reaction mixture was filtered over a Celite pad that was further rinsed with EtOAc (50 mL). The filtrate was washed with NH4Cl (50 mL, sat.aq.) then with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70/30) to obtain Compound **70** (0.70 g, 78%) as a yellow solid.
M/Z ($M[^{35}Cl]+H)^+$: 183.1.

Compound **71**: 5-chloro-1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine
Compound **71** was prepared according to general procedure (X) starting from Compound **70** (600 mg) and 4-bromo-1-chloro-2-fluorobenzene (2.0 eq) with ^{t}BuONa (3.0 eq) at 100°C for 16 hours. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/DCM 70:30) to obtain Compound **71** (925 mg, 91%) as a beige solid.
M/Z ($M[^{35}Cl]_2+H)^+$: 311.17.

Example **18**: 4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one



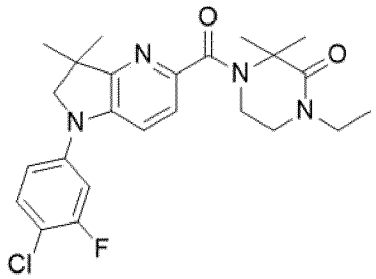
Example **18** was prepared according to general procedure (VIIIa) starting from Compound **68** (70 mg), 3,3-dimethylpiperazin-2-one (2.0 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) then further purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried to obtain Example **18** (39 mg, 43% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.32 (s, 6H, 2 CH_3); 1.66 (s, 6H, 2 CH_3); 3.48-3.55 (m, 2H , CH_2); 3.86 (s, 2H, CH_2); 7.18 (dd, *J* 8.5, 2.5 Hz, 1H, Ar); 7.37 (dd, *J* 1.7, 2.5 Hz, 1H, Ar); 7.40 (d, *J* 8.2 Hz, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar); 8.06 (bs, 1H, CONHR); one CH_2 signal not observed.

M/Z (M[^{35}Cl]+H)$^+$: 431.2.

Mp: 249-253 °C.

Example **19**: 4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-1-ethyl-3,3-dimethylpiperazin-2-one



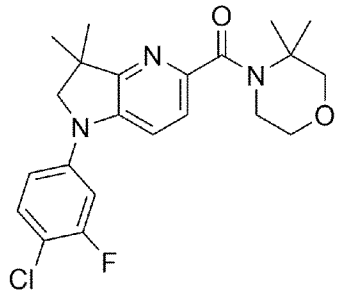
Example **19** was prepared according to general procedure (XIII) starting from Example **18** (70 mg), and bromoethane (1.8 eq.) in THF. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Example **19** (45 mg, 60%) as a white solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.05 (t, *J* 6.9 Hz, 3H, CH_3); 1.33 (s, 6H, $(CH_3)_2$); 1.66 (s, 6H, $(CH_3)_2$); 3.35 (d, *J* 6.9 Hz, 2H, CH_2); 3.47-3.51 (m, 2H, CH_2); 3.56-3.59 (m, 2H, CH_2); 3.86 (s, 2H, CH_2); 7.18 (m, 1H, Ar); 7.33 (dd, *J* 11.7, 2.4 Hz, 1H, Ar); 7.41 (d, J 8.4 Hz, 1H); 7.52-7.58 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 459.5.

Mp: 224-226 °C.

Example **20**: (1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(3,3-dimethylmorpholino)methanone



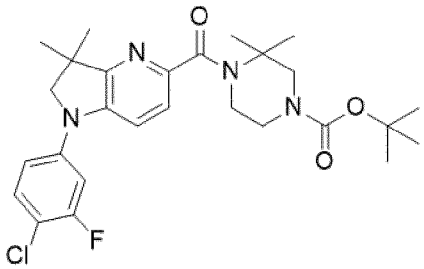
Example **20** was prepared according to general procedure (VIIIa) starting from Compound **68** (70 mg), 3,3-dimethylmorpholine (2.0 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) then freeze dried to obtain Example **20** (39 mg, 45% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.32 (s, 6H, 2 CH_3); 1.39 (s, 6H, 2 CH_3); 3.41 (s, 2H, CH_2); 3.46-3.50 (m, 2H, CH_2); 3.69-3.73 (m, 2H, CH_2); 3.85 (s, 2H, CH_2); 7.18 (dd, *J* 8.7, 2.4 Hz, 1H, Ar); 7.29-7.36 (m, 2H, 2 Ar); 7.51-7.58 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 418.3.

Mp: 173-177 °C.

Example **21**: tert-butyl 4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate

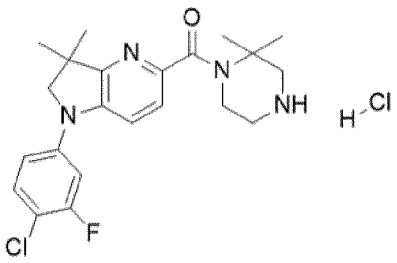


Example **21** was prepared according to general procedure (VIIIa) starting from Compound **68** (500 mg), tert-butyl 3,3-dimethylpiperazine-1-carboxylate (1.0 eq.) and N,N-diisopropylethylamine (4.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **21** (740 mg, 92%) as a clear oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.32 (s, 6H, $(CH_3)_2$); 1.41 (s, 9H, $(CH_3)_3$); 1.45 (s, 6H, $(CH_3)_2$); 3.35-3.45 (m, 4H, $(CH_2)_2$); 3.46-3.55 (m, 2H, CH_2); 3.84 (s, 2H, CH_2); 7.16 (dd, *J* 9.0, 2.1 Hz, 1H, Ar); 7.27-7.35 (m, 2H, 2 Ar); 7.51-7.57 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 517.3.

Example **22**: (1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(2,2-dimethylpiperazin-1-yl)methanone hydrochloride

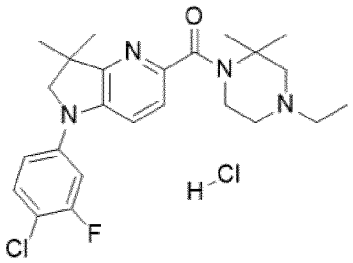


Example **22** was prepared according to general procedure (XII) starting from Example **21** (690 mg) in dioxane with HCl in dioxane. The crude was purified by trituration in Et_2O (30 mL) to obtain Example **22** (600 mg, 99%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.32 (s, 6H, $(CH_3)_2$); 1.54 (s, 6H, $(CH_3)_2$); 3.13-3.17 (m, 2H, N-CH_2); 3.25-3.30 (m, 2H, N-CH_2); 3.64-3.68 (m, 2H, N-CH_2); 7.16-7.20 (m, 1H, Ar); 7.33 (dd, *J* 12.0, 2.7 Hz, 1H, Ar); 7.43 (d, *J* 8.4 Hz, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar); 9.24 (bs, 2H, NH_2^+). One N-CH_2 was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 417.2.

Example **23**: (1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(4-ethyl-2,2-dimethylpiperazin-1-yl)methanone hydrochloride

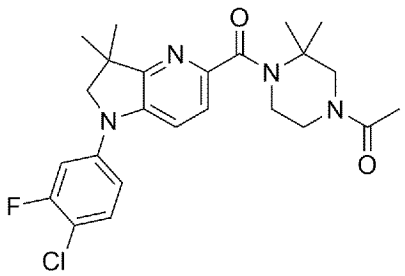


To a suspension of Example **22** (70 mg) in MeTHF (2.0 mL) was added triethylamine (2.0 eq), acetaldehyde (1.0 eq), sodium triacetoxyborohydride (2.0 eq). The reaction mixture was stirred at 25°C for 18 hours, then quenched with $NaHCO_3$ (sat. aq. 10 mL) and extracted with EtOAc (10 mL). The crude was purified by preparative HPLC (H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 40:60) and freeze dried with aqueous HCl to obtain Example **23** (22 mg, 30%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.29 (t, *J* 7.2 Hz, 3H, CH_3); 1.32 (s, 3H, CH_3); 1.36 (s, 3H, CH_3); 1.55 (s, 3H, CH_3); 1.60 (s, 3H, CH3); 3.05-3.22 (m, 4H, $(CH_2)_2$); 3.36-3.46 (m, 2H, CH_2); 3.52-3.56 (m, 1H, CH); 3.83-3.90 (m, 2H, CH_2); 4.06-4.11 (m, 1H, CH); 7.17-7.21 (m, 1H, Ar); 7.33 (dd, J 11.7; 2.7 Hz, 1H, Ar); 7.46 (d, J 8.4 Hz, 1H, Ar); 7.53-7.58 (m, 2H, 2 Ar); 10.21 (bs, 1H, NH^+).

M/Z (M[^{35}Cl]+H)$^+$: 445.4

Example **24**: 1-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)ethan-1-one

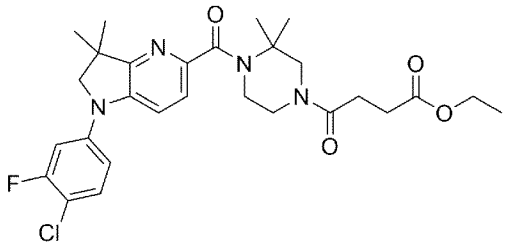


Example **24** was prepared according to general procedure (VIIIa) starting from Example **22** (75 mg), acetic acid (1.0 eq.) and N,N-diisopropylethylamine (4.0 eq.) in DCM. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 0:100) then further purified by preparative HPLC (H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 40:60) and freeze dried with aqueous HCl to obtain Example **24** (30 mg, 42%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.32-1.34 (m, 6H, $(CH_3)_2$); 1.45 (s, 3H, CH_3); 1.49 (s, 3H, CH_3); 1.97-2.03 (m, 3H, CH_3); 3.43-3.47 (m, 1H, CH); 3.56 (d, *J* 6.3 Hz, 2H, CH_2); 3.60-3.67 (m, 2H, CH_2); 3.69-3.72 (m, 1H, CH); 3.84 (s, 2H, CH_2); 7.17(dd, *J* 8.7, 2.4 Hz, 1H, Ar); 7.28-7.36 (m, 2H, 2 Ar); 7.51-7.58 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 459.4

Example **25**: ethyl 4-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-oxobutanoate

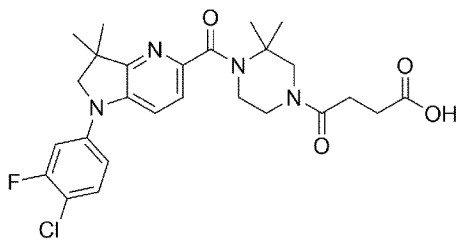


Example **25** was prepared according to general procedure (VIIIa) starting from Example **22** (75 mg), 4-ethoxy-4-oxobutanoic acid (1.0 eq.) and N,N-diisopropylethylamine (4.0 eq.) in DCM. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 0:100) and freeze dried to obtain Example **25** (65 mg, 77%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1-13-1.18 (m, 3H, OCH_2-CH_3); 1.32-1.33 (m, 6H, $(CH_3)_2$); 1.44 (s, 3H, CH_3); 1.50 (s, 3H, CH_3); 2.53-2.61 (m, 4H, 2 CH_2); 3.45-3.99 (m, 6H, 3 N-CH_2); 3.84 (s, 2H, N-CH_2); 3.98-4.06 (m, 2H, O-CH_2); 7.15-7.19 (m, 1H, Ar). 7.29-7.36 (m, 2H, 2 Ar) 7.51-7.57 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 545.5.

Example **26**: 4-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-oxobutanoic acid

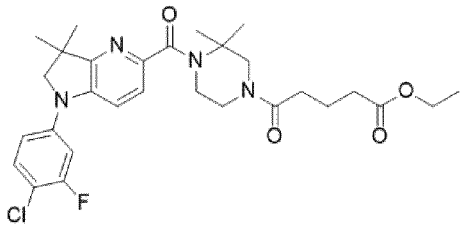


Example **26** was prepared according to general procedure (VII) starting from Example **25** (65 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried with aqueous HCl to obtain Example **26** (35 mg, 57%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.32-1.33 (m, 6H, $(CH_3)_2$); 1.45 (s, 3H, CH_3); 1.50 (s, 3H, CH_3); 2.42-2.48 (m, 2H, CH_2); 2.54-2.63 (m, 2H, CH_2); 3.56-3.59 (m, 2H, CH_2); 3.64-3.72 (m, 4H, $(CH_2)_2$); 3.64 (s, 2H, CH_2); 7.15-7.19 (m, 1H, Ar). 7.29-7.36 (m, 2H, 2 Ar) 7.51-7.57 (m, 2H, 2 Ar). COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 545.5

Example **27**: ethyl 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-5-oxopentanoate

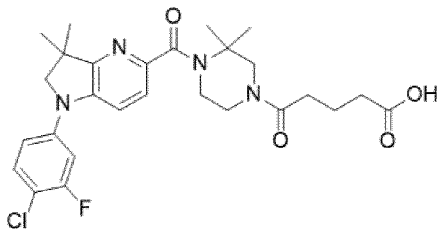


Example **27** was prepared according to general procedure (VIIIa) starting from Example **22** (75 mg), 5-ethoxy-5-oxopentanoic acid (1.0 eq.) and N,N-diisopropylethylamine (4.0 eq.) in DCM. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 0:100) and freeze dried to obtain Example **27** (66 mg, 77%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.13-1.19 (m, 3H, CH_3); 1.32 (s, 3H, CH_3); 1.32 (s, 3H, CH_3); 1.44 (s, 3H, CH_3); 1.48 (s, 3H, CH_3); 1.73-1.79 (m, 2H, CH_2); 2.31-2.34 (m, 4H, $(CH_2)_2$; 3.43-3.47 (m, 1H, CH); 3.55-3.70 (m, 5H, $(CH_2)_2$, CH); 3.84 (s, 2H, CH_2); 3.99-4.08 (m, 2H, CH_2); 7.17 (dd, *J* 9.0, 2.1 Hz, 1H, Ar); 7.29-7.36 (m, 2H, 2 Ar); 7.51-7.59 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 559.5

Example **28**: 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-5-oxopentanoic acid

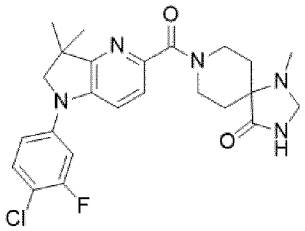


Example **28** was prepared according to general procedure (VII) starting from Example **27** (59 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried with aqueous HCl to obtain Example **28** (30 mg, 54%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.32 (s, 3H, CH_3); 1.33 (s, 3H, CH_3); 1.45 (s, 3H, CH_3); 1.46 (s, 3H, CH_3); 1.70-1.76 (m, 2H, CH_2); 2.23-2.37 (m, 4H, $(CH_2)_2$); 3.44-3.47 (m, 1H, CH); 3.56-3.70 (m, 5H, $(CH_2)_2$ + CH); 3.04 (s, 2H, CH_2); 7.17 (dd, *J* 9.0, 2.4 Hz, 1H, Ar); 7.29-7.37 (m, 2H, 2 Ar); 7.51-7.57 (m, 2H, 2 Ar). COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 531.5.

Example **29**: 8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-1-methyl-1,3,8-triazaspiro[4.5]decan-4-one

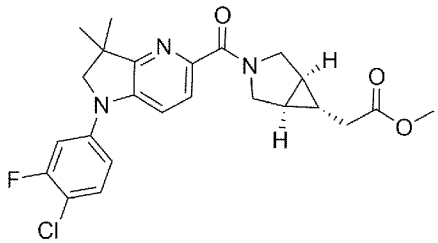


Example **29** was prepared according to general procedure (VIIIa) starting from Compound **68** (75 mg), 1-methyl-1,3,8-triazaspiro[4.5]decan-4-one hydrochloride (1.5 eq.) and N,N-diisopropylethylamine (4.0 eq.) in DCM. The crude was purified by preparative HPLC (H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 40:60) and freeze dried with water to obtain Example **29** (40 mg, 36%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.33 (s, 6H, 2*CH_3); 1.51-1.88 (m, 4H, 2*CH_2); 2.20-2.38 (m, 3H, N-**CH_3**); 3.44-3.58 (m, 1H, N-C**H_a**H_b); 3.64-3.77 (m, 1H, N-CH_a**H_b**); 3.80-3.92 (m, 3H, 3*N-$CH_a$$H_b$); 3.94-4.08 (m, 2H, 2*N-$CH_a$$H_b$); 4.16-4.29 (m, 1H, N-$CH_a$$H_b$); 7.15-7.22 (m, 1H, Ar); 7.33 (dd, *J* 11.9 2.6 Hz, 1H, Ar); 7.40 (d, J 8.4 Hz, 1H, Ar); 7.51-7.59 (m, 2H, 2 Ar); 8.28 (bs, 1H, NH).

M/Z (M[^{35}Cl]+H)$^+$: 472.3.

Example **30**: methyl 2-((1R,5S,6S)-3-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-azabicyclo[3.1.0]hexan-6-yl)acetate

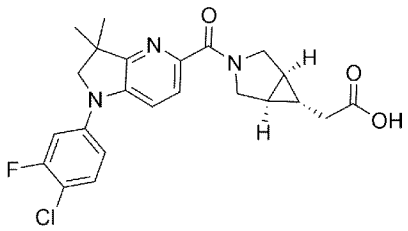


Example **30** was prepared according to general procedure (VIIIa) starting from Compound **68** (62 mg), methyl 2-((1R,5S,6S)-3-azabicyclo[3.1.0]hexan-6-yl)acetate hydrochloride (44 mg, 1.2 eq) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 20:80) to obtain Example **30** (75 mg, 85%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 0.63-0.70 (m, 1H, CH); 1.33 (s, 3H, CH_3); 1.36 (s, 3H, CH_3); 1.43-1.53 (m, 2H, 2*CH); 2.28-2.33 (m, 2H, CH_2); 3.4-3.48 (m, 1H, CHaHb); 3.59 (s, 3H, O-CH_3); 3.87 (s, 2H, N-CH_2); 3.88-3.98 (m, 3H, N-CH_2 + N-CHaHb); 7.16-7.21 (m, 1H, Ar); 7.31-7.35 (m, 1H, Ar); 7.50-7.59 (m, 3H, 3 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 458.3

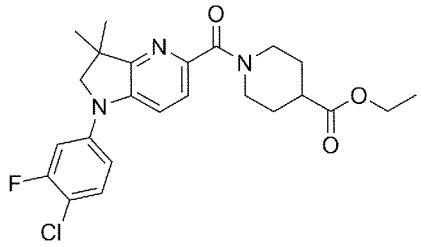
Example **31**: 2-((1R,5S,6S)-3-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-azabicyclo[3.1.0]hexan-6-yl)acetic acid



Example **31** was prepared according to general procedure (VII) starting from Example **30** (72 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 20:80 to 0:100) and freeze dried to obtain Example **31** (48 mg, 69%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 0.60-0.70 (m, 1H, CH); 1.33 (s, 3H, CH_3); 1.36 (s, 3H, CH_3); 1.42-1.54 (m, 2H, 2*CH); 2.18-2.24 (m, 2H, CH_2); 3.40-3.48 (m, 1H, CHaHb); 3.87 (s, 2H, N-CH_2); 3.88-3.98 (m, 3H, N-CH_2 + N-CHaHb); 7.16-7.21 (m, 1H, Ar); 7.33 (dd, *J* 11.9, 2.6 Hz, 1H, Ar); 7.50-7.59 (m, 3H, 3 Ar); 12.09 (bs, 1H, COOH).
M/Z (M[^{35}Cl]+H)$^+$: 444.3

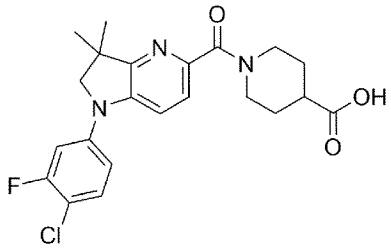
Example **32**: ethyl 1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidine-4-carboxylate



Example **32** was prepared according to general procedure (VIIIa) starting from Compound **68** (62 mg), ethyl piperidine-4-carboxylate (37 mg, 1.2 eq) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 20:80) to obtain Example **32** (38 mg, 43%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.19 (t, *J* 6.9 Hz, 3H, O-CH_2-CH_3); 1.33 (s, 6H, 2*CH_3); 1.42-1.66 (m, 2H, CH_2); 1.78-2.00 (m, 2H, CH_2); 2.58-2.66 (m, 1H, CH); 2.88-3.04 (m, 1H, N-CH_aH_b); 3.05-3.20 (m, 1H, N-CH_aH_b); 3.86 (s, 2H, N-CH_2); 3.90-4.03 (m, 1H, N-CH_aH_b); 4.06 (q, *J* 6.9 Hz, 2H, O-CH_2); 4.24-4.38 (m, 1H, N-CH_aH_b); 7.15-7.22 (m, 1H, Ar); 7.29-7.39 (m, 2H, 2 Ar); 7.50-7.60 (m, 2H, 2 Ar).
M/Z (M[^{35}Cl]+H)$^+$: 460.3

Example **33:** 1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidine-4-carboxylic acid

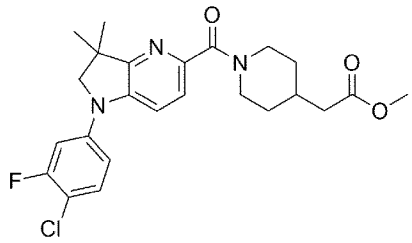


Example **33** was prepared according to general procedure (VII) starting from Example **32** (36 mg). The crude was purified by preparative HPLC (H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 60:40 to 20:80) and freeze dried to obtain Example **33** (25 mg, 74%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.33 (s, 6H, 2*CH_3); 1.42-1.66 (m, 2H, CH_2); 1.78-2.00 (m, 2H, CH_2); 2.50-2.60 (m, 1H, CH); 2.88-3.04 (m, 1H, N-CH_aH_b); 3.05-3.20 (m, 1H, N-CH_aH_b); 3.86 (s, 2H, N-CH_2); 3.90-4.05 (m, 1H, N-CH_aH_b); 4.24-4.38 (m, 1H, N-CH_aH_b); 7.15-7.22 (m, 1H, Ar); 7.29-7.39 (m, 2H, 2 Ar); 7.50-7.60 (m, 2H, 2 Ar); 12.32 (bs, 1H, COOH).

M/Z (M[^{35}Cl]+H)$^+$: 432.3

Example **34**: methyl 2-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-4-yl)acetate

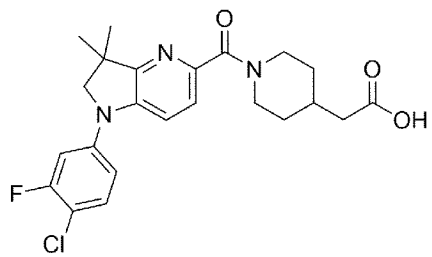


Example **34** was prepared according to general procedure (VIIIa) starting from Compound **68** (70 mg), methyl 2-(piperidin-4-yl)acetate (1.0 eq) and N,N-diisopropylethylamine (4.0 eq.) in DCM. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 20:80) to obtain Example **34** (68 mg) as a white solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.29-1.45 (m, 10H, 2 CH_3 + 2 N-CH_2-CH_aH_b); 1.68-1.87 (m, 2H, 2 N-CH_2-CH_aH_b); 2.04-2.13 (m, 1H, CH); 2.26-2.34 (m, 2H, CH_2CO); 2.76-2.88 (m, 1H, N-CH_aH_b); 3.02-3.12 (m, 1H, N-CH_aH_b); 3.68 (s, 3H, OCH_3); 3.76 (s, 2H, N-CH_2); 4.20-4.28 (m, 1H, N-CH_aH_b); 4.65-4.73 (m, 1H, N-CH_aH_b); 6.91-7.01 (m, 2H, 2 Ar); 7.32-7.38 (m, 2H, 2 Ar); 7.47 (d, *J* 8.5 Hz, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 460.3

Example **35**: 2-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-4-yl)acetic acid



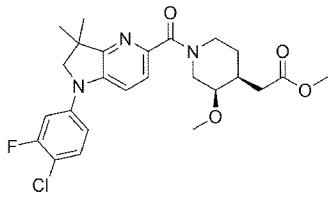
Example **35** was prepared according to general procedure (VII) starting from Example **34** (72 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 20:80 to 0:100) and freeze dried to obtain Example **35** (48 mg, 69%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.13-1.23 (m, 2H, CH_2); 1.31 (s, 6H, $(CH_3)_2$); 1.62-1.76 (m, 2H, CH_2); 1.89-1.99 (m, 1H, CH_2); 2.15-2.20 (m, 2H, CH_2); 2.77-2.83 (m, 1H, CH); 2.92-3.20 (m, 1H, CH); 3.85 (s, 2H, (CH_2); 3.97-4.02 (m,

1H, CH); 4.40-4.45 (m, 1H, CH); 7.15-7.18 (m, 1H, Ar); 7.29-7.34 (m, 2H, 2 Ar); 7.50-7.56 (m, 2H, 2 Ar); 12.13 (bs, 1H, CO_2H).

M/Z ($M[^{35}Cl]+H)^+$: 446.3

Example **36**: methyl 2-((3R,4S)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate

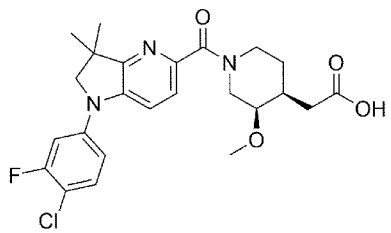


Example **36** was prepared according to general procedure (VIIIa) starting from Compound **68** (70 mg), methyl 2-((3R,4S)-3-methoxypiperidin-4-yl)acetate (1.0 eq) and N,N-diisopropylethylamine (4.0 eq.) in DCM. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 20:80) to obtain Example **36** (80 mg) as a white solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.40-1.58 (m, 7H, $(CH_3)_2$ + N-$CH_2CH_aH_b$); 1.75-1.78 (m, 1H, N-$CH_2CH_aH_b$); 2.20-2.31 (m, 2H, CH_2-CO); 2.51-2.56 (m, 1H, CH); 2.89-2.97 (m, 2H, 2 N-CH_aH_b); 3.20-3.25 (m, 1H, CH-OCH_3); 3.38-3.42 (m, 2H, N-CH_2); 3.62-3.65 (m, 3H, O-CH_3); 3.67-3.72 (m, 3H, $COOCH_3$); 4.14-4.22 (m, 0.5H, one rotamer of N-CH_aH_b); 4.49-4.60 (m, 1H, N-CH_aH_b); 4.82-4.94 (m, 0.5H, one rotamer of N-CH_aH_b); 6.91-7.00 (m, 2H, 2 Ar); 7.33-7.39 (m, 2H, 2 Ar); 7.50-7.58 (m, 1H, Ar).

M/Z ($M[^{35}Cl]+H)^+$: 490.3

Example **37**: 2-((3R,4S)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid

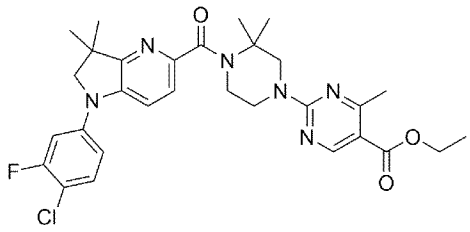


Example **37** was prepared according to general procedure (VII) starting from Example **36** (80 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 20:80 to 0:100) and freeze dried to obtain Example **37** (55 mg, 53% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.31-1.36 (m, 6H, $(CH_3)_2$); 1.43-1.60 (m, 2H, CH_2); 2.03-2.36 (m, 2H, CH_2); 2.80-2.89 (m, 3H, CH_3); 3.13-3.28 (m, 3H, CH_3); 3.38-3.42 (m, 1H, CH); 3.80-3.86 (m, 2H, CH_2); 3.88-4.05 (m, 0.5H, one rotamer of C**H$_a$**H$_b$); 4.25-4.34 (m, 0.5H, other rotamer of C**H$_a$**H$_b$); 4.37-4.45 (m, 0.5H, one rotamer of CH$_a$**H$_b$**); 4.63-4.70 (m, 0.5H, one rotamer of CH$_a$**H$_b$**); 7.16 (dd, *J* 9.0, 2.1 Hz, 1H, Ar); 7.28-7.38 (m, 2H, 2 Ar); 7.51-7.59 (m, 2H, 2 Ar). COOH was not observed.

M/Z ($M[^{35}Cl]+H)^+$: 476.3.

Example **38**: ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylpyrimidine-5-carboxylate

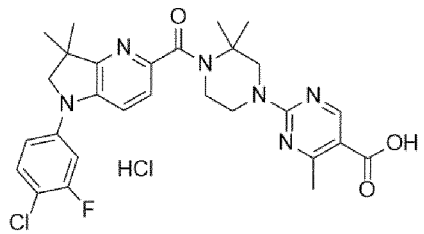


Example **38** was prepared according to general procedure (VIIIb) starting from Compound **68** (80 mg), Compound **2** (1.2 eq.) and triethylamine (3 eq.) in THF. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex /EtOAc 70:30) to obtain Example **38** (103 mg, 71%) as a clear oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.36 (t, *J* 7.2 Hz, 3H, OCH_2-CH_3); 1.42 (s, 6H, 2*CH_3); 1.63 (s, 6H, 2*CH_3); 2.68 (s, 3H, CH_3), 3.77 (s, 2H, N-**CH_2**); 3.90-4.08 (m, 6H, 3 N-**CH_2**); 4.31 (q, *J* 7.2 Hz, 2H, O-**CH_2**); 6.84-7.00 (m, 2H, 2 Ar); 7.31-7.38 (m, 2H, 2 Ar); 7.49 (d, *J* 8.4 Hz, Ar); 8.86 (s, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 581.4

Example **39**: 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylpyrimidine-5-carboxylic acid hydrochloride

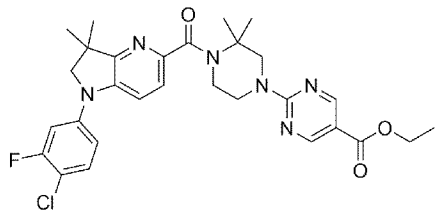


Example **39** was prepared according to general procedure (VII) starting from Example **38** (103 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) then freeze-dried with aqueous HCl to obtain Example **39** (45 mg, 43%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.34 (s, 6H, 2*CH_3); 1.49 (s, 6H, 2*CH_3); 2.58 (s, 3H, CH_3), 3.75-3.83 (m, 2H, N-**CH_2**-CH_2-N); 3.84 (s, 2H, N-**CH_2**-C-N); 4.05 (s, 2H, N-**CH_2**); 7.17 (dd, *J* 8.7, 2.1 Hz, 1H, Ar); 7.27-7.37 (m, 2H, 2 Ar), 7.48-7.58 (m, 2H, 2 Ar); 8.74 (s, 1H, Ar). One CH_2 signal, HCl and COOH were not observed.

M/Z (M[^{35}Cl]+H)$^+$: 553.4.

Example **40**: ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyrimidine-5-carboxylate

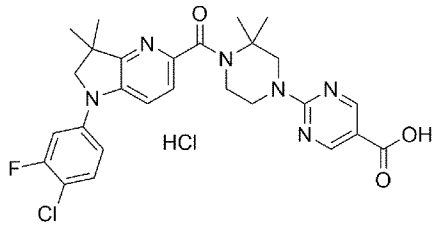


Example **40** was prepared according to general procedure (VIIIb) starting from Compound **68** (80 mg), Compound **4** (1.2 eq.) and triethylamine (3 eq.) in THF. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex /EtOAc 70:30) to obtain Example **40** (98 mg, 69%) as a white solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.37 (t, *J* 7.2 Hz, 3H, OCH_2-CH_3); 1.42 (s, 6H, 2*CH_3); 1.64 (s, 6H, 2*CH_3); 3.77 (s, 2H, N-**CH_2**); 3.90-3.99 (m, 4H, 2 N-**CH_2**); 4.07 (s, 2H, N-CH_2); 4.35 (q, *J* 7.2 Hz, 2H, O-**CH_2**); 6.86-7.02 (m, 2H, 2 Ar); 7.33-7.39 (m, 2H, 2 Ar); 7.51 (d, *J* 8.4 Hz, Ar); 8.90 (s, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^{+\cdot}$: 567.4

Example **41**: 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-pyrimidine-5-carboxylic acid hydrochloride

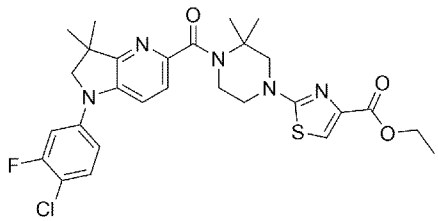


Example **41** was prepared according to general procedure (VII) starting from Example **40** (103 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) then freeze-dried with aqueous HCl to obtain Example **41** (39 mg, 40%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, 2*CH_3); 1.51 (s, 6H, 2*CH_3); 3.75-3.80 (m, 2H, N-**CH_2**-CH_2-N); 3.82-3.88 (m, 4H, N-CH_2-**CH_2**-N + N-**CH_2**-C-N); 4.05 (s, 2H, N-CH_2) 7.18 (dd, *J* 9.0, 2.1 Hz, 1H, Ar); 7.27-7.37 (m, 2H, 2 Ar), 7.50-7.60 (m, 2H, 2 Ar); 8.77-8.84 (m, 2H, 2 Ar). HCl and COOH were not observed.

M/Z (M[^{35}Cl]+H)$^{+\cdot}$: 539.4.

Example **42**: ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carboxylate

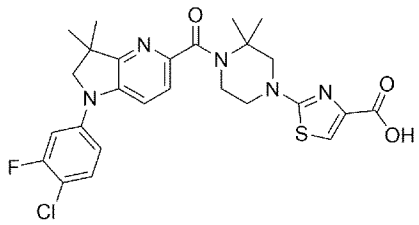


Example **42** was prepared according to general procedure (VIIIa) starting from Compound **68** (62 mg), Compound **6** (1.2 eq.) and N,N-diisopropylethylamine (3 eq.) in DCM. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 15:85) to obtain Example **42** (86 mg, 78%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.27 (t, *J* 7.2 Hz, 3H, OCH_2-CH_3); 1.35 (s, 6H, 2*CH_3); 1.54 (s, 6H, 2*CH_3); 3.53-3.60 (m, 2H, N-**CH_2**-CH_2-N); 3.72 (s, 2H, N-**CH_2**); 3.78-3.86 (m, 2H, N-CH_2-**CH_2**-N); 3.87 (s, 2H, N-**CH_2**); 4.23 (q, *J* 7.2 Hz, 2H, O-CH_2); 7.19 (dd, *J* 8.7, 1.9 Hz, 1H, Ar); 7.30 (d, *J* 8.7 Hz, 1H, Ar); 7.33 (dd, *J* 11.9, 2.6 Hz, 1H, Ar); 7.51-7.60 (m, 2H, 2 Ar); 7.65 (s, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^{+\cdot}$: 572.4

Example **43**: 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carboxylic acid

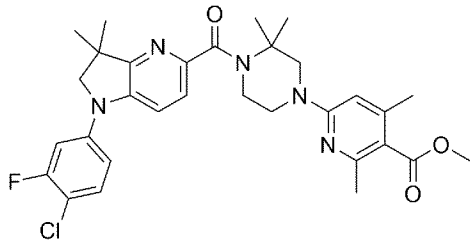


Example **43** was prepared according to general procedure (VII) starting from Example **42** (83 mg). The crude was purified by preparative HPLC (H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 50:50 to 10:90) then freeze-dried to obtain Example **43** (50 mg, 63%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, 2*CH_3); 1.53 (s, 6H, 2*CH_3); 3.52-3.60 (m, 2H, N-**CH_2**-CH_2-N); 3.72 (s, 2H, N-**CH_2**); 3.78-3.86 (m, 2H, N-CH_2-**CH_2**-N); 3.87 (s, 2H, N-**CH_2**); 7.19 (dd, *J* 8.7, 1.9 Hz, 1H, Ar); 7.30 (d, *J* 8.7 Hz, 1H, Ar); 7.33 (dd, *J* 11.9, 2.6 Hz, 1H, Ar); 7.51-7.60 (m, 3H, 3 Ar); 12.62 (bs, 1H, COOH).

M/Z (M[^{35}Cl]+H)$^+$: 544.5.

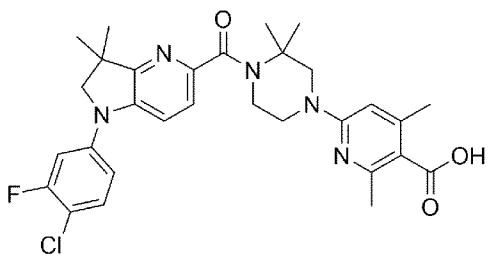
Example **44**: methyl 6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



Example **44** was prepared according to general procedure (XIV) starting from Compound **71** (600 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **44** (755 mg, 68%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.42 (s, 6H, $C(CH_3)_2$); 1.60 (s, 6H, $C(CH_3)_2$); 2.32 (s, 3H, $ArCH_3$); 2.47 (s, 3H, $ArCH_3$); 3.58-3.64 (m, 2H, N-CH_2-CH_2); 3.76 (s, 2H, N-CH_2); 3.85 (s, 3H, OCH_3); 3.93 (s, 2H, N-CH_2); 3.95-4.02 (m, 2H, N-CH_2-CH_2); 6.10 (s, 1H, Ar); 6.83-7.02 (m, 2H, 2 Ar); 7.31-7.36 (m, 2H, 2 Ar); 7.48 (d, *J* 8.4Hz, 1H, Ar). M/Z (M[^{35}Cl]+H$^+$): 580.4.

Example **45**: 6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid

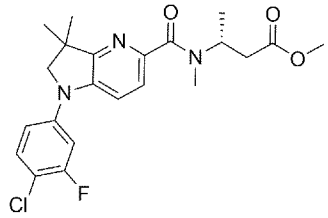


Example **45** was prepared according to general procedure (XI) starting from Example **44** (275 mg). The crude was purified by flash chromatography (Interchim® 50 µm, DCM 100% to DCM/MeOH 90:10), then freeze-dried with water/Ethanol (9:1) to obtain Example **45** (160 mg, 60%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.36 (s, 6H, $C(CH_3)_2$); 1.49 (s, 6H, $C(CH_3)_2$); 2.27 (s, 3H, $ArCH_3$); 2.38 (s, 3H, $ArCH_3$); 3.53-3.56 (m, 2H, CH_2); 3.80-3.88 (m, 6H, 3*CH_2); 6.34 (s, 1H, Ar); 7.18 (dd, *J 1.7, 7.5* Hz, 1H, Ar); 7.30-7.36 (m, 2H, 2*Ar); 7.52-7.58 (m, 2H, 2*Ar); 12.65 (bs, 1H, COOH).

M/Z ($M[^{35}Cl]+H)^+$: 566.4

Example **46**: methyl (R)-3-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)butanoate

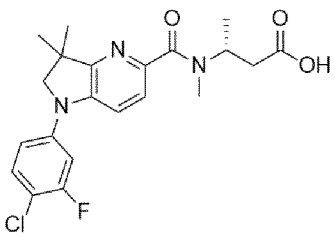


Example **46** was prepared according to general procedure (VIIIa) starting from Compound **68** (50 mg), methyl (R)-3-(methylamino)butanoate hydrochloride (32 mg, 1.2 eq) and N,N-diisopropylethylamine (4.0 eq.) in DCM. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **46** (56 mg, 83%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.16-1.41 (m, 9H, 3*CH_3); 2.55-2.78 (m, 2H, **CH_2**-COOH); 2.80 (s, 2.3H, one rotamer of N-**CH_3**); 2.89 (s, 0.7H, one rotamer of N-**CH_3**); 3.52-3.61 (m, 3H, OCH_3); 3.80-3.90 (m, 2H, N-**CH_2**); 4.31-4.49 (m, 0.8H, one rotamer of N-**CH**); 4.82-4.95 (m, 0.2H, one rotamer of N-**CH**); 7.15-7.21 (m, 1H, Ar); 7.28-7.36 (m, 2H, 2 Ar); 7.50-7.60 (m, 2H, 2 Ar).

M/Z ($M[^{35}Cl]+H)^+$: 434.2

Example **47**: (R)-3-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)butanoic acid

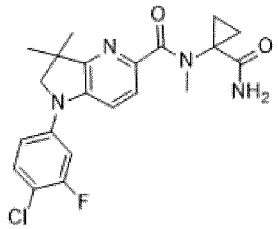


Example **47** was prepared according to general procedure (VII) starting from Example **46** (160 mg). The crude was purified by trituration in MeCN (2 mL) then freeze dried to obtain Example **47** (33 mg, 57%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.16-1.38 (m, 9H, 3*CH_3); 2.55-2.75 (m, 2H, **CH_2**-COOH); 2.81 (s, 2.3H, one rotamer of N-**CH_3**); 2.90 (s, 0.7H, one rotamer of N-**CH_3**); 3.80-3.90 (m, 2H, N-**CH_2**); 4.32-4.45 (m, 0.8H, one rotamer of N-**CH**); 4.82-4.95 (m, 0.2H, one rotamer of N-**CH**); 7.15-7.21 (m, 1H, Ar); 7.28-7.32 (m, 1H, Ar); 7.32-7.36 (m, 1H, Ar); 7.50-7.60 (m, 2H, 2 Ar); 12.20 (m, 1H, COOH).

M/Z ($M[^{35}Cl]+H)^+$: 420.2.

Example **48**: N-(1-carbamoylcyclopropyl)-1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide

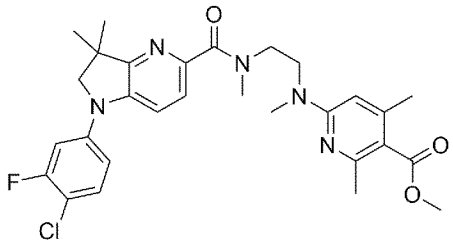


Example **48** was prepared according to general procedure (VIIIa) starting from Compound **68** (70 mg), Compound **13** (33 mg) and N,N-diisopropylethylamine (5.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100 to EtOAc/MeOH 80:20) then further purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried to obtain Example **48** (42 mg, 46%) as a white solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 0.43-0.60 (m, 1H, CH_2); 0.96-1.05 (m, 1H, CH_2); 1.11-1.20 (m, 2H, , CH_2); 1.31-1.39 (m, 6H, 2 CH_3); 2.95-3.16 (m, 3H, CH_3); 3.77-3.90 (m, 2H, CH_2); 7.15-7.23 (m, 2H, CO-**NH_2**); 7.31 (dd, *J* 12.1, 2.3 Hz, 1H, Ar); 7.47-7.60 (m, 4H, 4 Ar).

M/Z (M[^{35}Cl]+H)$^{+\cdot}$: 417.2

Example **49**: methyl 6-((2-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)ethyl)(methyl)amino)-2,4-dimethylnicotinate

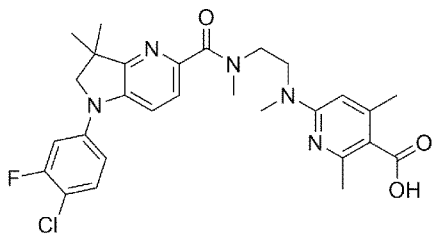


Example **49** was prepared according to general procedure (VIIIa) starting from Compound **68** (62 mg), Compound **8** (1.2 eq.) and N,N-diisopropylethylamine (3 eq.) in DCM. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 20:80) to obtain Example **49** (87 mg) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.24-1.32 (m, 6H, 2*CH_3); 2.05 (s, 3H, CH_3); 2.18 (s, 3H, CH_3); 2.80 (s, 3H, N-CH_3); 3.02 (s, 3H, N-CH_3); 3.04-3.08 (m, 2H, N-CH_2); 3.63-3.67 (m, 2H, N-CH_2); 3.76 (s, 2H, N-CH_3); 3.83 (s, 3H, O-CH_3); 6.02 (s, 1H, Ar); 7.02-7.40 (m, 4H, 4 Ar); 7.50-7.60 (m, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^{+\cdot}$: 554.4

Example **50**: 6-((2-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)ethyl)(methyl)amino)-2,4-dimethylnicotinic acid

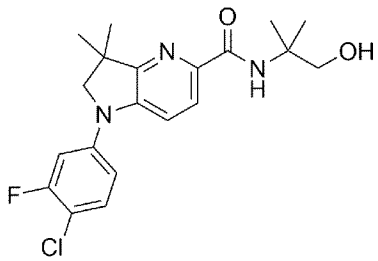


Example **50** was prepared according to general procedure (XI) starting from Example **49** (193 µmol). The crude was purified by preparative HPLC (H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70). The white solid was dissolved in 2 mL of HCl 1.25M in MeOH then concentrated to dryness. The yellow residue was dissolved in 1 mL of DCM then poured into 15 mL of Et_2O. The precipitate was filtered, dissolved in MeCN then freeze-dried with water to obtain Example **50** (23 mg, 21% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.24-1.32 (m, 6H, 2*CH_3); 2.14 (s, 2H, one rotamer of CH_3); 2.33 (s, 3H, CH_3); 2.40-2.50 (m, 1H, one rotamer of CH_3); 2.80-2.95 (m, 2H, N-CH_2); 3.04 (s, 2H, N-CH_2); 3.12-3.17 (m, 1H, N-CHaHb); 3.17-3.24 (m, 1H, N-CHaHb); 3.77 (m, 3H, N-CH_3); 3.82-3.88 (m, 1H, one rotamer of N-CH_3); 3.88-3.98 (m, 2H, one rotamer of N-CH_3); 6.10-6.50 (m, 0.6H, one rotamer of Ar); 6.70-6.95 (m, 0.4H, one rotamer of Ar); 7.05-7.40 (m, 4H, 4 Ar); 7.50-7.60 (m, 1H, Ar). COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 540.5.

Example **51**: 1-(4-chloro-3-fluorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide

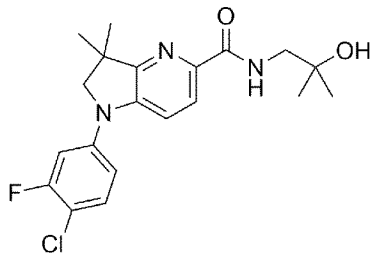


To a solution of Compound **65** (50 mg) in Chlorobenzene (2 mL) was added 2-amino-2-methylpropan-1-ol (1.5 eq) and zinc chloride (0.1 eq). The mixture was heated at 140°C for 18 hours then concentrated under reduced pressure. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Example **51** (37 mg, 57%) as a white solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.34 and 1.35 (2s, 12H, 4 x C**H$_3$**); 3.45 (d, *J* 5.4 Hz, 2H, C**H$_2$**OH); 3.88 (s, 2H, NC**H$_2$**); 5,15 (t, *J* 5.4 Hz, 1H, CH_2O**H**); 7.18-7.22 (m, 1H, Ar); 7.34 (dd, *J* 11.7, 2.7 Hz, 1H, Ar); 7.53-7.60 (m, 2H, 2 Ar); 7.75 (d, *J* 8.4 Hz, 1H, Ar); 8.06 (s, 1H, N**H**)

M/Z (M[^{35}Cl]+H)$^+$: 392.3

Example **52**: 1-(4-chloro-3-fluorophenyl)-N-(2-hydroxy-2-methylpropyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide



To a solution of Compound **65** (50 mg) in Chlorobenzene (2 mL) was added 1-amino-2-methylpropan-2-ol (24 µL, 1.5 eq) and zinc chloride (2.3 mg, 0.1 eq). The mixture was heated at 140°C for 18 hours then concentrated under reduced pressure. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Example **52** (45 mg, 69%) as a white solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.11 (s, 6H, NHCH$_2$C**Me$_2$**); 1.37 (s, 6H, ArNCH$_2$C**Me$_2$**); 3.27 (d, *J* 6.3 Hz, 2H, C**H$_2$**NH); 3.89 (s, 2H, NC**H$_2$**); 4.70 (s, 1H, O**H**); 7.21 (dd, *J* 8.7, 2.1 Hz, 1H, Ar); 7.35 (dd, *J* 11.7, 2.7 Hz, 1H, Ar); 7.54-7.60 (m, 2H, 2 Ar); 7.78 (d, *J* 8.1 Hz, 1H, Ar); 8.23 (t, *J* 6.3 Hz, 1H, N**H**).

M/Z (M[^{35}Cl]+H)$^+$: 392.3

Compound **72**: 2-(3-bromo-6-chloropyridin-2-yl)-2-methylbutanenitrile

Compound **72** was prepared according to general procedure (I) starting from 3-bromo-6-chloro-2-fluoropyridine (5.00 g) and 2-methylbutanenitrile (2.40 mL). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/Et$_2$O 80:20) to obtain Compound **72** (2.44 g, 38%) as a clear oil.

M/Z (M[^{81}Br^{35}Cl]+H)$^+$: 274.9

Compound **73**: 2-(3-bromo-6-chloropyridin-2-yl)-2-methylbutanamide

Compound **73** (2.54 g, 98%) was obtained as a white solid from Compound **72** (2.44 g) according to general procedure (IIb).

M/Z (M[^{35}Cl][^{81}Br]+H)$^+$: 292.9 .

Compound **74**: 5-chloro-3-ethyl-3-methyl-1,3-dihydro-2H-pyrrolo[3,2-b]pyridin-2-one

Compound **74** was prepared according to general procedure (III) starting from Compound **73** (2.50 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **74** (1.35 g, 75%) as a brown solid.

M/Z (M[^{35}Cl]+H)$^+$: 210.9

Compound **75**: 5-chloro-3-ethyl-3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

Compound **75** was prepared according to general procedure (IX) starting from Compound **74** (1.35 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100 then DCM 100% to DCM/MeOH: 90/10) to obtain Compound **75** (864 mg, 68%) as a beige solid.

M/Z (M[^{35}Cl]+H)$^+$ 197.1

Compound **76**: 3-ethyl-3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonitrile

Compound **76** was prepared according to general procedure (IV) starting from Compound **75** (629 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 20:80) to obtain Compound **76** (210 mg, 35%) as a yellow oil.

M/Z $(M+H)^+$: 188.1.

Compound **77**: 1-(4-chloro-3-fluorophenyl)-3-ethyl-3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonitrile

Compound **77** was prepared according to general procedure (X) starting from Compound **76** (210 mg) and 4-bromo-1-chloro-2-fluorobenzene (1.1 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **77** (250 mg) as a yellow oil.

M/Z $(M[^{35}Cl]+H)^+$ = 316.2.

Compound **78:** 1-(4-chloro-3-fluorophenyl)-3-ethyl-3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide

Compound **78** was prepared according to general procedure (IIa) starting from Compound **77** (250 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **78** (190 mg, 51% over 2 steps) as a white solid.

M/Z $(M[^{35}Cl]+H)^+$: 334.2

Compound **79:** methyl 1-(4-chloro-3-fluorophenyl)-3-ethyl-3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylate

Compound **79** was prepared according to general procedure (VI) starting from Compound **77** (190 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 40:60) to obtain Compound **79** (140 mg, 70%) as a white solid.

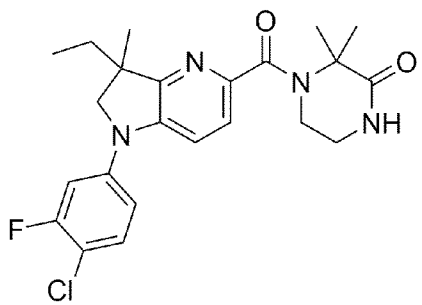
M/Z $(M[^{35}Cl]+H)^+$: 349.2

Compound **80**: 1-(4-chloro-3-fluorophenyl)-3-ethyl-3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylic acid

Compound **80** was obtained (70 mg) as a yellow solid according to general procedure (VII) starting from Compound **79** (80 mg).

M/Z $(M[^{35}Cl]+H)^+$: 335.0

Example **53**: 4-(1-(4-chloro-3-fluorophenyl)-3-ethyl-3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one



Example **53** was prepared according to general procedure (VIIIa) starting from Compound **80** (70 mg), 3,3-dimethylpiperazin-2-one (2.0 eq.) and N,N-diisopropylethylamine (2.0 eq.) in DCM. The crude was purified by flash

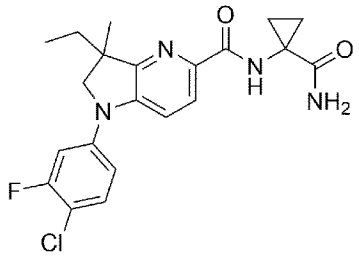
chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) then further purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried to obtain Example **53** (50 mg, 49% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 0.80 (t, *J* 7.5 Hz, 3H, CH3); 1.30 (s, 3H, CH3); 1.64-1.71 (m, 8H, CH2 + 2 CH3); 3.49-3.54 (m, 2H, CH2); 3.79 (d, *J* 10.0 Hz, 1H, CH2); 3.94 (d, *J* 10.0 Hz, 1H, CH2); 7.20 (dd, *J* 8.8, 2.6 Hz, 1H, Ar); 7.34 (dd, *J* 11.9, 2.6 Hz, 1H, Ar); 7.41 (d, *J* 7.9 Hz, 1H, Ar); 7.51-7.58 (m, 2H, 2 Ar); 8.05 (bs, 1H, CON**H**R); one CH_2 signal not observed.

M/Z (M[^{35}Cl]+H)$^+$: 445.4.

Mp: 213-217 °C.

Example **54**: N-(1-carbamoylcyclopropyl)-1-(4-chloro-3-fluorophenyl)-3-ethyl-3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide



Example **54** was prepared according to general procedure (VIIIa) starting from Compound **80** (58 mg), 1-aminocyclopropane-1-carboxamide (1.5 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) then further purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried to obtain Example **54** (65 mg, 91% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6 300 MHz) δ: 0.82 (t, *J* 7.6 Hz, 3H, CH_3); 1.00-1.04 (m, 2H, CH_2); 1.33-1.39 (m, 5H, CH_2 + CH_3); 1.68-1.81 (m, 2H, CH_2); 3.81 (d, *J* 9.8 Hz, 1H, CH_2); 3.95 (d, *J* 9.8 Hz, 1H, CH_2); 7.00 (bs, 1H, CO-**NH_2**); 7.09 (bs, 1H, CO-**NH_2**); 7.21 (dd, *J* 8.8, 2.6 Hz, 1H, Ar); 7.35 (dd, *J* 11.8, 2.6 Hz, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar); 7.76 (d, *J* 8.5 Hz, 1H, Ar); 8.74 (s, 1H, CO-**NH**). M/Z (M[^{35}Cl]+H)$^+$: 417.3.

Compound **81**: 5'-chloro-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]

Compound **81** was prepared according to general procedure (IX) starting from Compound **16** (2.00 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **81** (1.32 g, 70%) as a brown solid.

M/Z (M[^{35}Cl]+H)$^+$: 225.0

Compound **82**: 1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **82** was prepared according to general procedure (IV) starting from Compound **81** (500 mg). The reaction mixture was submitted to microwave irradiation at 150°C for 1 hour. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **82** (300 mg, 63%) as a white solid.

M/Z (M+H)$^+$: 216.2

Compound **83**: 1'-(4-chloro-3-fluorophenyl)-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **83** was prepared according to general procedure (X) starting from Compound **82** (400 mg) and 4-bromo-1-chloro-2-fluorobenzene (1.0 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **83** (420 mg, 66%) as a white solid.

M/Z $(M[^{35}Cl]+H)^+$: 344.2

Compound **84:** 1'-(4-chloro-3-fluorophenyl)-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carboxamide

Compound **84** (414 mg, 96%) was obtained as a white solid from Compound **83** (410 mg) according to general procedure (IIb).

M/Z$(M[^{35}Cl]+H)^+$: 362.2.

Compound **85:** methyl 1'-(4-chloro-3-fluorophenyl)-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylate

Compound **85** was prepared according to general procedure (VI) starting from Compound **84** (414 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 40:60) to obtain Compound **85** (354 mg, 82%) as a white solid.

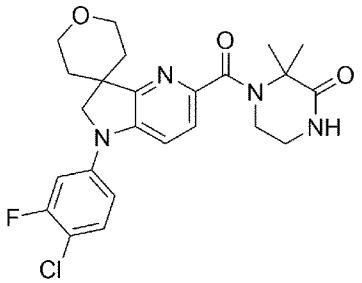
M/Z $(M[^{35}Cl]+H)^+$: 377.2

Compound **86**: 1'-(4-chloro-3-fluorophenyl)-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylic acid

Compound **86** was obtained (314 mg, 93%) as a white solid according to general procedure (VII) starting from Compound **85** (350 mg).

M/Z $(M[^{35}Cl]+H)^+$: 363.2

Example **55**: 4-(1'-(4-chloro-3-fluorophenyl)-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one



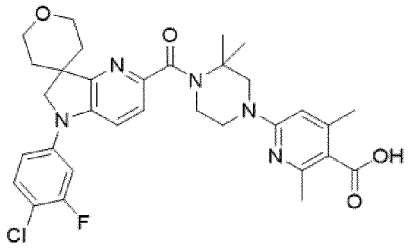
Example **55** was prepared according to general procedure (VIIIa) starting from Compound **86** (80 mg), 3,3-dimethylpiperazin-2-one (2.0 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, DCM 100% to DCM/MeOH 80:20) then further purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 95:05 to 0:100) and freeze dried to obtain Example **55** (43 mg, 41%) as a white solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.60-1.64 (m, 2H, CH_2); 1.89 (s, 6H, $(CH_3)_2$); 2.13-2.23 (m, 2H, CH_2); 3.59-3.64 (m, 4H, 2 CH_2); 3.76-3.80 (m, 2H, CH_2); 3.98 (s, 2H, CH_2); 4.07-4.13 (m, 2H, CH_2); 6.10 (bs, 1H, NH); 6.98-7.07 (m, 2H, 2 Ar); 7.37-7.44 (m, 2H, 2 Ar); 7.63 (d, *J* 8.3 Hz, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$ 473.3.

Mp: 245-248 °C.

Example **56**: 6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



To a solution of Compound **86** (50 mg) in DMF (5 mL) was added 1,8-Diazabicyclo[5.4.0]undec-7-ene (62 µL) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (61 mg). The mixture was stirred at 25°C for 5 minutes then a suspension of Compound **11** (1.0 eq) in DMF (5 mL) was added and the mixture was stirred at 25°C for 72 hours, then at 80°C for 8 hours. The reaction mixture was filtered and the filtrate was hydrolysed (100 mL) and extracted with Et_2O (3*50 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash chromatography (Merck 60®, DCM 100% to DCM/MeOH 80:20) then further purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried to obtain Example **56** (30 mg, 36%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.48 (s, 6H, $(CH_3)_2$); 1.60-1.64 (m, 2H, CH_2); 1.94-2.04 (m, 2H, CH_2); 2.24 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 3.54-3.61(m, 4H $(CH_2)_2$); 3.81-3.94 (m, 6H, $(CH_2)_3$); 4.08 (s, 2H, CH_2); 6.30 (s, 1H, Ar); 7.24 (dd, *J* 8.7, 2.1 Hz, 1H, Ar); 7.35-7.40 (m, 2H, 2 Ar); 7.52-7.60 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 608.5.

Compound **87**: 1-(3-bromo-6-chloropyridin-2-yl)cyclopropane-1-carbonitrile

Compound **87** was prepared according to general procedure (I) starting from 3-bromo-6-chloro-2-fluoropyridine (1.00 g) and cyclopropanecarbonitrile (350 µL). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **87** (370 mg, 30%) as a white solid.

M/Z(M[^{35}Cl][^{81}Br]+H)$^+$: 259.0

Compound **88**: 1-(3-bromo-6-chloropyridin-2-yl)cyclopropane-1-carboxamide

Compound **88** was prepared according to general procedure (IIa) starting from Compound **87** (680 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **88** (740 mg) as a white solid.

M/Z (M[^{35}Cl^{81}Br]+H)$^+$: 277.1

Compound **89**: 5'-chlorospiro[cyclopropane-1,3'-pyrrolo[3,2-b]pyridin]-2'(1'H)-one

Compound **89** was prepared according to general procedure (III) starting from Compound **88** (740 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **89** (400 mg) as a brown solid.

M/Z ($M[^{35}Cl]+H)^+$: 195.0

Compound **90**: 5'-chloro-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **90** was prepared according to general procedure (IX) starting from Compound **89** (1.60 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to EtOAc 100% to EtOAc/MeOH 80:20) to obtain Compound **90** (210 mg 44% over 3 steps) as a brown solid.

M/Z ($M[^{35}Cl]+H)^+$: 181.0

Compound **91**: 1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **91** was prepared according to general procedure (IV) starting from Compound **90** (210 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **91** (80 mg, 40%) as a yellow solid

M/Z $(M+H)^+$: 172.0

Compound **92**: 1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **92** was prepared according to general procedure (X) starting from Compound **91** (80 mg) and 4-bromo-1-chloro-2-fluorobenzene (1.1 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 20:80) to obtain Compound **92** (110 mg) as a yellow solid.

M/Z ($M[^{35}Cl]+H)^+$: 300.1

Compound **93:** 1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxamide

Compound **93** was prepared according to general procedure (IIa) starting from Compound **92** (110 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **93** (60 mg, 40% over 2 steps) as a white solid.

M/Z ($M[^{35}Cl]+H)^+$: 318.2

Compound **94:** methyl 1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylate

Compound **94** was prepared according to general procedure (VI) starting from Compound **93** (60 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 40:60) to obtain Compound **94** (30 mg) as a white solid.

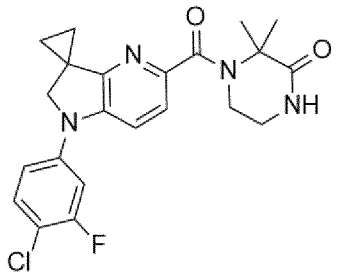
M/Z ($M[^{35}Cl]+H)^+$: 333.2

Compound **95:** 1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylic acid

Compound **95** was obtained (30 mg) as a yellow solid according to general procedure (VII) starting from Compound **94** (29 mg).

M/Z (M[^{35}Cl]+H)$^+$: 319.2

Example **57**: 4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one



Example **57** was prepared according to general procedure (VIIIa) starting from Compound **95** (29 mg), 3,3-dimethylpiperazin-2-one (2.0 eq.) and N,N-diisopropylethylamine (2.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Example **57** (13 mg, 32% over 3 steps) as a white solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.07-1.02 (m, 2H, CH_2); 1.30-1.35 (m, 2H, CH_2); 1.83 (s, 6H, 2 CH_3); 3.51-3.55 (m, 2H, CH_2); 3.65-3.70 (m, 2H, CH_2); 4.10 (s, 2H, CH_2); 6.10 (bs, 1H, CO-**NH_2**); 6.93-7.03 (m, 2H, 2 Ar); 7.28 (d, *J* 8.4 Hz, 1H, Ar); 7.37 (t, *J* 8.5 Hz, 1H, Ar); 7.51 (d, *J* 8.4 Hz, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 429.3.

Mp: 165-170 °C.

Compound **96**: 3-(3-bromo-6-chloropyridin-2-yl)tetrahydrofuran-3-carbonitrile

Compound **96** was prepared according to general procedure (I) starting from 3-bromo-6-chloro-2-fluoropyridine (2.17 g) and tetrahydrofuran-3-carbonitrile (958 µL). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/Et_2O 40:60) to obtain Compound **96** (1.11 g, 38%) as a white solid.

M/Z(M[^{35}Cl][^{81}Br]+H)$^+$: 289.0

Compound **97**: 3-(3-bromo-6-chloropyridin-2-yl)tetrahydrofuran-3-carboxamide

Compound **97** was prepared according to general procedure (IIa) starting from Compound **96** (2.00 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **97** (1.53 g 72%) as a white solid.

M/Z (M[^{35}Cl^{81}Br]+H)$^+$: 307.0

Compound **98**: 5'-chloro-4,5-dihydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridin]-2'(1'H)-one

Compound **98** was prepared according to general procedure (III) starting from Compound **97** (1.53 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **98** (0.78 g, 69%) as a beige solid.

M/Z (M[^{35}Cl]+H)$^+$: 225.1

Compound **99**: 5'-chloro-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]

Compound **99** was prepared according to general procedure (IX) starting from Compound **98** (780 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to EtOAc 100%) to obtain Compound **99** (725 mg, 99%) as a brown solid.

M/Z $(M[^{35}Cl]+H)^+$: 211.0

Compound **100**: 1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **100** was prepared according to general procedure (IV) starting from Compound **99** (725 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Compound **100** (496 mg, 72%) as a yellow solid

M/Z $(M+H)^+$: 202.1

Compound **101**: 1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carbonitrile

Compound **101** was prepared according to general procedure (X) starting from Compound **100** (490 mg) and 4-bromo-1-chloro-2-fluorobenzene (1.0 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **101** (476 mg) as a white solid.

M/Z $(M[^{35}Cl]+H)^+$: 330.2

Compound **102:** 1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carboxamide

Compound **102** (388 mg, 75%) was obtained as a white solid from Compound **101** (490 mg) according to general procedure (IIb).

M/Z $(M[^{35}Cl]+H)^+$: 348.2

Compound **103:** methyl 1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylate

Compound **103** was prepared according to general procedure (VI) starting from Compound **102** (680 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 20:80) to obtain Compound **103** (436 mg, 62%) as a white solid.

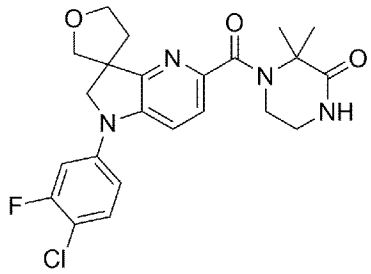
M/Z $(M[^{35}Cl]+H)^+$: 363.2

Compound **104:** 1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylic acid

Compound **104** was obtained (380 mg, 92%) as a white solid according to general procedure (VII) starting from Compound **103** (430 mg).

M/Z $(M[^{35}Cl]+H)^+$: 349.2

Example **58**: 4-(1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one



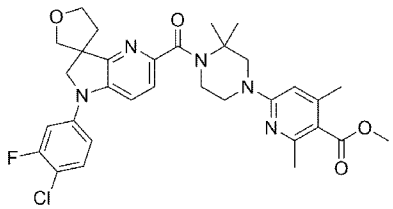
Example **58** was prepared according to general procedure (VIIIa) starting from Compound **104** (80 mg), 3,3-dimethylpiperazin-2-one (2.0 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100 to EtOAc/MeOH 90:10) then further purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried to obtain Example **58** (42 mg, 40%) as a white solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.87 (d, *J* 7.2 Hz, 6H); 2.11-2.19 (m, 1H, CH); 2.51-2.60 (m, 1H, CH); 3.54-3.84 (m, 4H, 2 CH_2); 3.90-4.19 (m, 6H, 3 CH_2); 6.17 (bs, 1H, NH); 6.95-7.05 (m, 2H, 2 Ar); 7.37-7.44 (m, 2H, 2 Ar); 7.63 (d, *J* 8.4 Hz, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 459.2.

Mp: 202-205 °C.

Example **59**: methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

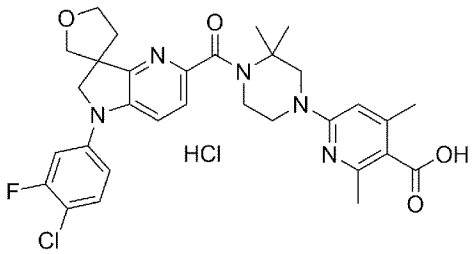


Example **59** was prepared according to general procedure (VIIIa) starting from Compound **104** (40 mg), Compound **10** (38 mg, 1.2 eq) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 0:100) to obtain Example **59** (65 mg) as a white solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.63 (s, 6H, 2 CH_3); 2.11-2.22 (m, 1H, OCH_2-CH_aH_b); 2.35 (s, 3H, CH_3); 2.50 (s, 3H, CH_3); 2.59-2.64 (m, 1H, OCH_2-CH_aH_b); 3.64-3.67 (m, 2H, OCH_2); 3.86-4.20 (m, 13H, 4 NCH_2, O-CH_2, $COOCH_3$); 6.14 (s, 1H, Ar); 6.94-7.04 (m, 2H, 2 Ar); 7.36-7.43 (m, 2H, 2 Ar); 7.55 (d, *J* 8.4 Hz, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 608.5.

Example **60**: 6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid hydrochloride



Example **60** was prepared according to general procedure (XI) starting from Example **59** (80 mg). The crude was purified by flash chromatography (Merck 60®, DCM 100% to DCM/MeOH 80:20) then further purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried with aqueous HCl to obtain Example **60** (15 mg, 22% over 3 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.49 (s, 6H, 2 CH_3); 2.15-2.22 (m, 1H, CH); 2.26 (s, 3H, CH_3); 2.31-2.36 (m, 1H, CH); 2.40 (s, 3H, CH_3); 3.51-3.54 (m, 2H, CH_2); 3.81-4.10 (m, 12H, 6 CH_2); 6.44 (bs, 1H, Ar); 7.20 (dd, *J* 8.7, 2.1 Hz, 1H, Ar); 7.33-7.40 (m, 2H, 2 Ar); 7.56-7.60 (m, 2H, 2 Ar).

M/Z ($M[^{35}Cl]+H)^+$: 594.4.

Compound **105**: cis-5-chloro-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine

In a screw cap vial, to a solution of 3-methyltetrahydrofuran-2-ol (1.10 g) in 35 mL H_2SO_4 (4% aqueous) was added 2-chloro-5-hydrazineylpyridine hydrochloride (1.5 eq). The reaction mixture was heated at 120°C for 1 hour, then neutralized in 200 mL $NaHCO_3$ (sat. aq.). The mixture was extracted with EtOAc (4*50 mL), dried over $MgSO_4$ and concentrated to dryness. The crude was purified by column chromatography (Merck 60®, CyHex 100% to EtOAc 100%) to obtain Compound **105** (1.31 g, 54%) as a brown solid.

M/Z ($M[^{35}Cl]+H)^+$: 211.1.

Compound **106**: cis-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carbonitrile

Compound **106** was prepared according to general procedure (IV) starting from Compound **105** (1.01 g). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 30:70) to obtain Compound **106** (886 mg, 92%) as a brown solid

M/Z $(M+H)^+$: 202.0

Compound **107**: cis-8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carboxamide

Compound **107** was prepared according to general procedure (X) starting from Compound **106** (300 mg) and 4-bromo-1-chloro-2-fluorobenzene (1.1 eq.). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to EtOAc 100%) to obtain Compound **107** (304 mg, 59%) as a yellow solid.

M/Z ($M[^{35}Cl]+H)^+$: 348.1

Compound **108:** methyl cis-8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carboxylate

Compound **108** was prepared according to general procedure (VI) starting from Compound **107** (304 mg). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 25:75) to obtain Compound **108** (292 mg, 92%) as a white solid.

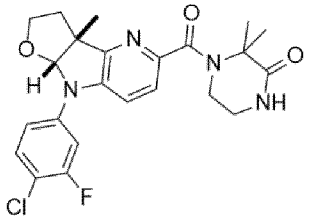
M/Z (M[^{35}Cl]+H)$^+$: 363.2

Compound **109:** cis-8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carboxylic acid

Compound **109** was obtained (264 mg, 94%) as a white solid according to general procedure (VII) starting from Compound **108** (292 mg).

M/Z (M[^{35}Cl]+H)$^+$: 349.0

Example **61**: cis-4-(8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one



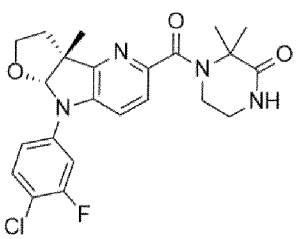
Example **61** was prepared according to general procedure (VIIIa) starting from Compound **109** (258 mg), 3,3-dimethylpiperazin-2-one (1.3 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM/THF (1:1). The crude was purified by flash chromatography (Merck 60®, CyHex 100% to EtOAc 100%) then further purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried with MeOH/water to obtain Example **61** (210 mg, 62%) as a white solid.

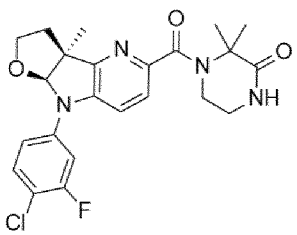
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.48 (s, 3H, CH_3); 1.67 (s, 6H, 2 CH_3); 2.04-2.15 (m, 1H, **CH_2**-CH_2-O); 2.29-2.30 (m, 1H, **CH_2**-CH_2-O); 3.37-3.52 (m, 3H, CH_2-**CH_2**-O, CH_2); 3.96-4.03 (m, 1H, CH_2-**CH_2**-O); 5.72 (s, 1H, CH); 7.32 (dd, 1H, *J* 8.7, *J* 2.1 Hz, 1H, Ar); 7.42-7.51 (m, 3H, 3 Ar); 7.61 (t, *J* 8.7 Hz, 1H, Ar); 8.04-8.06 (m, 1H, NHCO). One CH_2 signal not observed.

M/Z(M[^{35}Cl]+H)$^+$:459.2

MP: 243-245°C

Example **62** and Example **63**: 4-((3aR,8aR)-8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one and 4-((3aS,8aS)-8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one





Example **61** was purified by SFC, using ChiralPak IG 5µm (250*20 mm) as the stationary phase and CO_2/Ethanol (70:30, 120 mL/min) as the mobile phase, to obtain:

Example **62** (105 mg, 50%, ee > 99.5%), first eluting enantiomer (T_R = 6.25 min)

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.47 (s, 3H, CH_3); 1.66 (s, 6H, 2 CH_3); 2.04-2.14 (m, 1H, **CH_2**-CH_2-O); 2.25-2.31 (m, 1H, **CH_2**-CH_2-O); 3.38-3.44 (m, 3H, CH_2-**CH_2**-O, CH_2); 3.48-3.50 (m, 2H, CH_2); 3.96-4.01 (m, 1H, CH_2-**CH_2**-O); 5.70 (s, 1H, CH); 7.31 (dd, *J* 9.0, *J* 2.1 Hz, 1H, Ar); 7.42-7.45 (m, 2H, 2 Ar); 7.48 (d, *J* 8.4 Hz, 1H, Ar); 7.58 (t, *J* 8.7 Hz, 1H, Ar); 8.03-8.06 (m, 1H, NHCO).

M/Z(M[^{35}Cl]+H)$^+$:459.3

MP: 245°C

Example **63** (105 mg, 50%, ee > 99.5%), second eluting enantiomer (T_R = 7.08 min)

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.48 (s, 3H, CH_3); 1.67 (s, 6H, 2 CH_3); 2.04-2.15 (m, 1H, **CH_2**-CH_2-O); 2.26-2.31 (m, 1H, **CH_2**-CH_2-O); 3.36-3.43 (m, 3H, CH_2-**CH_2**-O, CH_2); 3.49-3.52 (m, 2H, CH_2); 3.97-4.02 (m, 1H, CH_2-**CH_2**-O); 5.71 (s, 1H, CH); 7.34-7.30 (m, 1H, Ar); 7.42-7.41 (m, 2H, 2 Ar); 7.49 (d, *J* 8.4 Hz, 1H, Ar); 7.59 (t, *J* 9.0 Hz, 1H, Ar); 8.03-8.06 (m, 1H, NHCO).

M/Z(M[^{35}Cl]+H)$^+$:459.3

MP: 245°C

Compound **110**: tert-butyl 4-(5-(2-methoxy-2-oxoethyl)pyridin-2-yl)-2,2-dimethylpiperazine-1-carboxylate

Compound **110** was prepared according to general procedure (Xb), starting from methyl 2-(6-chloropyridin-3-yl)acetate (200 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **110** (236 mg, 60%) as a clear oil.

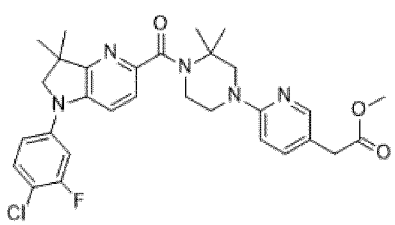
M/Z (M+H)$^+$:364.3

Compound **111**: methyl 2-(6-(3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate hydrochloride

Compound **111** was obtained as a white solid (188 mg, 98%) according to general procedure (XII) starting from Compound **110** (233 mg) in DCM using HCl in Et_2O.

M/Z (M+H)$^+$:264.1

Example **64**: methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

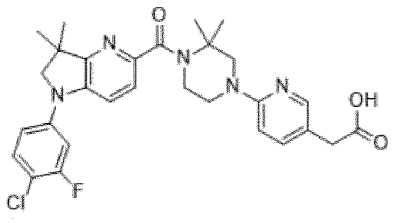


Example **64** was prepared according to general procedure (VIIIa) starting from Compound **68** (55 mg), Compound **111** (1.2 eq.), and N,N-diisopropylethylamine (4.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **64** (66 mg, 68%) as a yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.36 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 3.48-3.54 (m, 4H, 2 N-CH_2);3.61 (s, 3H, OCH_3); 3.83-3.86 (m, 6H, 2 N-CH_2 + $CH_2C(O)$); 6.60 (d, 1H, *J* 2.7 Hz, Ar); 7.17-7.21 (m, 1H, Ar); 7.30-7.37 (m; 2H, 2 Ar); 7.43-7.47 (m, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar); 7.96-7.97 (m, 1H, Ar).

M/Z(M[^{35}Cl]+H)$^{+\cdot}$:566.5

Example **65**: 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid

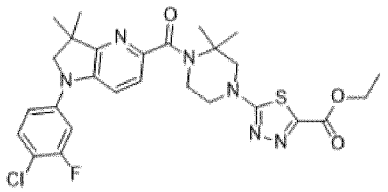


Example **65** was prepared according to general procedure (VII) starting from Example **64** (66 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 95:5 to 0:100) and freeze dried with water to obtain Example **65** (37 mg, 58%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.36 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 3.42 (s, 2H, $CH_2C(O)$); 3.49-3.53 (m, 2H, N-CH_2); 3.81-3.86 (m, 6H, 3 N-CH_2); 6.59 (d, *J* 8.7 Hz, 1H Ar); 7.17-7.21 (m, 1H, Ar); 7.30-7.37 (m, 2H, 2 Ar); 7.44 (dd, *J* 8.7, 2.3 Hz, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar); 7.95 (d, *J* 2.3 Hz, 1H, Ar). COOH was not observed.

M/Z (M[^{35}Cl]+H)$^{+\cdot}$: 552.5.

Example **66**: ethyl 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-1,3,4-thiadiazole-2-carboxylate

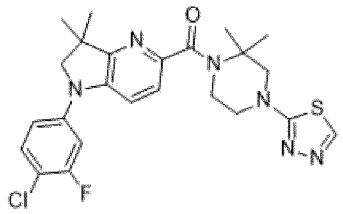


A suspension of Example **22** (75 mg), Ethyl 5-chloro-1,3,4-thiadiazole-2-carboxylate (1.5 eq.) and Potassium Carbonate (3 eq.) in DMF (0.1 M) was heated at 80°C for 16 hours. The reaction mixture was quenched in NH_4Cl (sat. aq., 50 mL), extracted with EtOAc (50 mL). The organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **66** (70 mg, 74%) as a clear oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.29-1.35 (m, 9H, 2 CH_3 +CH_2-**CH_3**); 1.54 (s, 6H, 2 CH_3); 3.67-3.70 (m, 2H, N-CH_2); 3.84-3.89 (m, 6H, 3 N-CH_2); 4.35 (q, 2H, *J* 4.2 Hz, **CH_2**-CH_3); 7.17-7.21 (m, 1H, Ar); 7.30-7.35 (m, 1H, Ar); 7.37-7.40 (m, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^{+\cdot}$: 573.4

Example **67**: (1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(2,2-dimethyl-4-(1,3,4-thiadiazol-2-yl)piperazin-1-yl)methanone



Example **67** was prepared according to general procedure (VII) starting from Example **66** (67 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried with water to obtain Example **67** (36 mg, 62%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, 2*CH_3); 1.53 (s, 6H, 2*CH_3); 3.58-3.66 (m, 2H, N-**CH_2**); 3.75 (s, 2H, N-**CH_2**); 3.78-3.86 (m, 2H, N-**CH_2**); 3.85 (s, 2H, N-**CH_2**); 7.19 (dd, *J* 8.9, 1.9 Hz, 1H, Ar); 7.32 (dd, *J* 12.0, 2.4 Hz, 1H, Ar); 7.38 (d, *J* 8.4 Hz, 1H, Ar); 7.50-7.60 (m, 2H, 2 Ar); 8.75 (s, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 501.3.

Compound **112**: ethyl 2-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazole-5-carboxylate

Compound **112** was prepared according to general procedure (Xb), starting from ethyl 2-bromo-4-methylthiazole-5-carboxylate (200 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **112** (307 mg, 80%) as an orange oil.

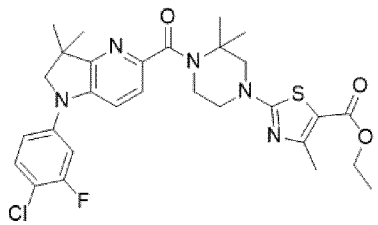
M/Z (M+H)$^+$:384.3

Compound **113**: ethyl 2-(3,3-dimethylpiperazin-1-yl)-4-methylthiazole-5-carboxylate

Compound **113** was obtained as a yellow oil (300 mg) according to general procedure (XII) starting from Compound **112** (233 mg) in DCM using TFA.

M/Z (M+H)$^+$:284.2

Example **68**: ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazole-5-carboxylate



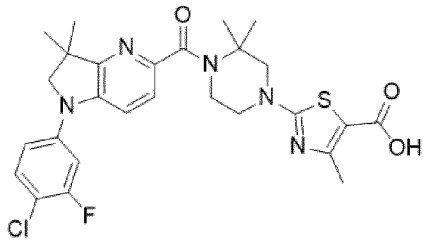
Example **68** was prepared according to general procedure (VIIIa) starting from Compound **68** (55 mg), Compound **113** (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **68** (42 mg, 42%) as a yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.24 (t, 3H, *J* 7.2 Hz, CH_2**CH_3**); 1.35 (s, 6H, 2 CH_3); 1.52 (s, 6H, 2 CH_3);

3.54-3.59 (m, 2H, N-CH_2); 3.76-3.86 (m, 6H, 3 N-CH_2); 4.18 (q, 2H, *J* 7.2 Hz, **CH_2CH_3**); 7.17-7.21 (m, 1H, Ar); 7.30-7.35 (m; 2H, 2 Ar); 7.35-7.40 (m, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar). One CH_3 was not observed

M/Z(M[^{35}Cl]+H)$^+$:586.4

Example **69**: 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazole-5-carboxylic acid



Example **69** was prepared according to general procedure (VII) starting from Example **68** (42 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried with water to obtain Example **69** (10 mg, 25%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, 2 CH_3); 1.52 (s, 6H, 2 CH_3); 2.44 (s, 3H, CH_3); 3.53-3.57 (m, 2H, NCH_2); 3.76 (s, 2H, NCH_2); 3.81-3.86 (m, 4H, 2 NCH_2); 7.17-7.21 (m, 1H, Ar); 7.33 (dd, *J* 12.1, 2.5 Hz, 1H, Ar); 7.38 (d, *J* 8.4 Hz, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar). COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 558.4.

Compound **114**: ethyl 2-(2-bromo-4-methylthiazol-5-yl)acetate

To a solution of ethyl 2-(2-amino-4-methylthiazol-5-yl)acetate (225 mg) and Copper$^{(II)}$ bromide (1.2 eq.) in MeCN (0.1 M) was added tert-butyl nitrite (1.5 eq.). The reaction mixture was sealed and heated at 60°C for 2 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **114** (191 mg, 64%) as an orange oil.

M/Z ([^{81}Br]M+H)$^+$:266.0

Compound **115**: tert-butyl 4-(5-(2-ethoxy-2-oxoethyl)-4-methylthiazol-2-yl)-2,2-dimethylpiperazine-1-carboxylate

Compound **115** was prepared according to general procedure (Xb), starting from Compound **114** (191 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **115** (106 mg, 37%) as a yellow oil.

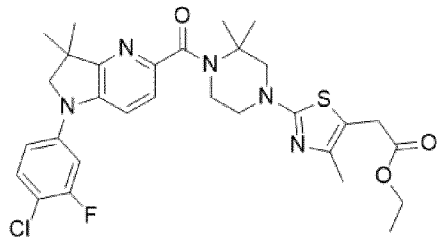
M/Z (M+H)$^+$: 398.3

Compound **116**: ethyl 2-(2-(3,3-dimethylpiperazin-1-yl)-4-methylthiazol-5-yl)acetate

Compound **116** was obtained as an orange oil (70 mg) according to general procedure (XII) starting from Compound **115** (106 mg) in DCM using TFA.

M/Z (M+H)$^+$:298.2

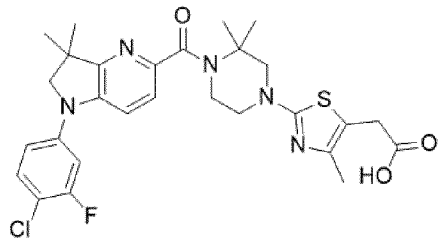
Example **70**: ethyl 2-(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazol-5-yl)acetate



Example **70** was prepared according to general procedure (VIIIa) starting from Compound **68** (55 mg), Compound **115** (1.4 eq.), and N,N-diisopropylethylamine (4.0 eq.) in DCM. The crude was purified by flash chromatography (Merck 60®, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **70** (78 mg, 76%) as a yellow oil.

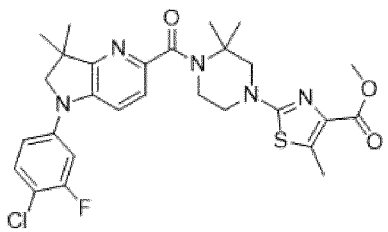
^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.18 (t, 3H, *J* 7.2 Hz, CH_2**CH_3**), 1.34 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 2.05 (s, 3H, CH_3); 3.49-3.64 (m, 6H, 3 N-CH_2); 3.77-3.81 (m, 2H, N-CH_2); 3.84 (s, 2H, $CH_2C(O)$); 4.07 (q, 2H, *J* 7.2 Hz, **CH_2**CH_3); 7.16-7.20 (m, 1H, Ar); 7.27-7.32 (m, 1H, Ar); 7.35-7.37 (m, 1H, Ar); 7.51-7.57 (m, 2H, 2 Ar).
M/Z(M[^{35}Cl]+H)$^+$:600.4

Example **71**: 2-(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazol-5-yl)acetic acid



Example **71** was prepared according to general procedure (VII) starting from Example **70** (78 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried with water to obtain Example **71** (30 mg, 40%) as a beige solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, 2 CH_3); 1.51 (s, 6H, 2 CH_3); 2.06 (s, 3H, CH_3); 3.46-3.50 (m, 2H, CH_2); 3.56 (s, 2H, CH_2); 3.63 (s, 2H, CH_2); 3.77-3.81 (m, 2H, CH_2); 3.86 (s, 2H, CH_2); 7.16-7.21 (m, 1H, Ar); 7.32 (dd, *J* 12.5, 2.6 Hz, 1H, Ar); 7.37 (d, *J* 8.4 Hz, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar). COOH was not observed.
M/Z (M[^{35}Cl]+H)$^+$: 572.4.

Example **72**: methyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-5-methylthiazole-4-carboxylate

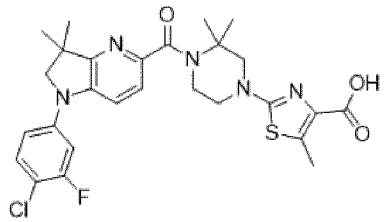


Example **72** was prepared according to general procedure (Xb), starting from Example **22** (75 mg) methyl 2-bromo-5-methylthiazole-4-carboxylate (1.5 eq.). The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **72** (57 mg) as a brown solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.41 (s, 6H, $(CH_3)_2$); 1.65 (s, 6H, $(CH_3)_2$); 2.63 (s, 3H, CH_3); 3.64-3.70 (m, 4H, 2 N-CH_2); 3.77 (s, 2H, N-CH_2); 3.88 (s, 3H, OCH_3); 3.89-3.96 (m, 2H, CH_2); 6.92-6.98 (m, 2H, 2 Ar); 7.32-7.38 (m, 2H, 2 Ar); 7.50-7.52 (m, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 572.4.

Example **73**: 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-5-methylthiazole-4-carboxylic acid hydrochloride

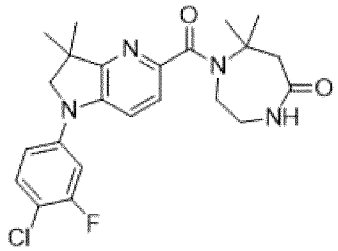


Example **73** was prepared according to general procedure (VII) starting from Example **72** (57 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried with HCl (aq. 0.1 N) to obtain Example **73** (30 mg, 30%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.34 (s, 6H, $(CH_3)_2$); 1.51 (s, 6H, $(CH_3)_2$); 2.53 (s, 3H, CH_3); 3.49-3.54 (m, 2H, CH_2); 3.63-3.68 (m, 2H, CH_2); 3.77-3.88 (m, 4H, 2*CH_2); 7.18 (dd, *J* 9.0, 2.1 Hz, 1H, Ar); 7.30-7.38 (m, 2H, 2 Ar); 7.52-7.59 (m, 2H, 2 Ar). COOH and Hydrochloric salt are not observed.

M/Z (M[^{35}Cl]+H)$^+$: 558.5.

Example **74**: 1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-7,7-dimethyl-1,4-diazepan-5-one

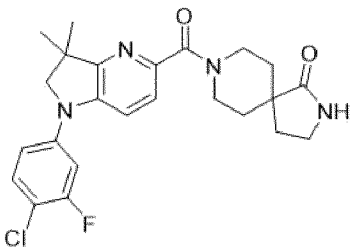


Example **74** was prepared according to general procedure (VIIIa) starting from Compound **68** (80 mg), 7,7-dimethyl-1,4-diazepan-5-one (1.0 eq.), and N,N-diisopropylethylamine (3.0 eq.) in DMF. The crude was purified by flash chromatography (Merck 60®, DCM 100% to DCM/MeOH 90:10), then precipitated from DMSO (5 mL) with water (30 mL) and washed with water to obtain Example **74** (45 mg, 41%) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.33 (s, 6H, $(CH_3)_2$); 1.59 (s, 6H, $(CH_3)_2$); 2.60-2.65 (m, 2H, CH_2); 3.40-3.47 (m, 2H, CH_2); 3.66-3.73 (m, 2H, CH_2); 3.84 (s, 2H, CH_2); 7.16-7.19 (m, 1H, Ar); 7.29-7.40 (m, 3H, NH + Ar); 7.52-7.57 (m, 2H, 2 Ar).

M/Z(M[^{35}Cl]+H)$^+$: 445.9

Example **75**: 8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-2,8-diazaspiro[4.5]decan-1-one

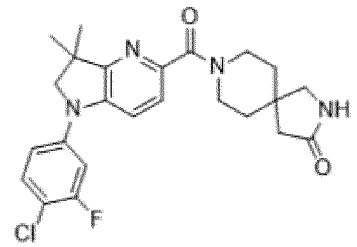


Example **75** was prepared according to general procedure (VIIIa) starting from Compound **68** (80 mg), 2,8-diazaspiro[4.5]decan-1-one hydrochloride (1.1 eq.), and N,N-diisopropylethylamine (5.0 eq.) in DMF. The crude was purified by flash chromatography (Merck 60®, DCM 100% to DCM/MeOH 90:10), then precipitated from DMSO (5 mL) with water (30 mL) and washed with water to obtain Example **75** (70 mg, 61%) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.33-1.50 (m, 8H, CH_2 + $(CH_3)_2$); 1.62-1.79 (m, 2H, CH_2); 1.97-2.12 (m, 2H, CH_2); 2.97-3.10 (m, 1H, C**H$_a$**H$_b$); 3.14-3.24 (m, 3H, CH$_a$**H$_b$** + CH_2); 3.86 (s, 2H, CH_2); 3.94-4.08 (m, 1H, CH); 4.26-4.37 (m, 1H, CH); 7.18 (dd, 1H, *J* 2.4, 8.7 Hz, Ar); 7.30-7.39 (m, 2H, 2 Ar); 7.51-7.61 (m, 3H, NH + Ar).

M/Z (M[^{35}Cl]+H)$^+$: 457.9.

Example **76**: 8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-2,8-diazaspiro[4.5]decan-3-one

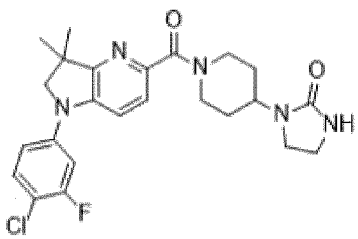


Example **76** was prepared according to general procedure (VIIIa) starting from Compound **68** (80 mg), 2,8-diazaspiro[4.5]decan-3-one hydrochloride (1.1 eq.), and N,N-diisopropylethylamine (5.0 eq.) in DMF. The crude was purified by flash chromatography (Merck 60®, DCM 100% to DCM/MeOH 90:10), then precipitated from DMSO (5 mL) with water (30 mL) and washed with water to obtain Example **76** (59 mg, 48%) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.33 (s, 6H, $(CH_3)_2$); 1.54-1.63 (m, 4H, 2*CH_2); 2.12 (s, 2H, CH_2); 3.10 (s, 2H, CH_2); 3.43-3.77 (m, 4H, 2*N-CH_2); 3.85 (s, 2H, N-CH_2); 7.17 (dd, 1H, *J* 1.8, 8.7 Hz, Ar); 7.29-7.37 (m, 2H, 2 Ar); 7.51-7.57 (m, 3H, Ar + NH).

M/Z (M[^{35}Cl]+H)$^+$: 457.9.

Example **77**: 1-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-4-yl)imidazolidin-2-one

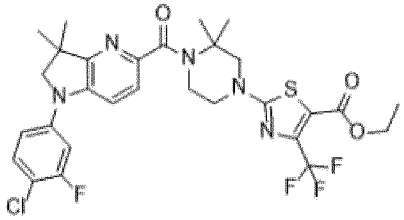


Example **77** was prepared according to general procedure (VIIIa) starting from Compound **68** (80 mg), 1-(piperidin-4-yl)imidazolidin-2-one (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in DMF. The crude was purified by flash chromatography (Merck 60®, DCM 100% to DCM/MeOH 90:10), then precipitated from DMSO (5 mL) with water (30 mL) and washed with water to obtain Example **77** (28 mg, 24%) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.34 (s, 6H, $(CH_3)_2$); 1.49-1.75 (m, 4H, 2*CH_2); 2.77-2.88 (m, 1H, C**H$_a$**H$_b$); 3.00-3.15 (m, 1H, C**H$_a$**H$_b$); 3.17-3.30 (m, 4H, 2*CH_2); 3.73-3.86 (m, 3H, CH_2, CH_a**H$_b$**); 4.07-4.18 (m, 1H, CH_a**H$_b$**); 4.47-4.62 (m, 1H, N-CH); 6.27 (s, 1H, NH), 7.15-7.21 (m, 1H, Ar); 7.30-7.40 (m, 2H, 2 Ar); 7.51-7.58 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 472.8.

Example **78**: ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-(trifluoromethyl)thiazole-5-carboxylate

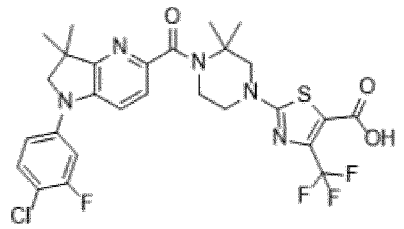


Example **78** was prepared according to general procedure (Xb), starting from Example **22** (100 mg) ethyl 2-bromo-4-(trifluoromethyl)thiazole-5-carboxylate (1.5 eq.). The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to EtOAc 100%) to obtain Example **78** (120 mg, 85%) as a clear oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.35 (t, 3H, *J* 7.2 Hz, CH_2**CH_3**); 1.43 (s, 6H, $(CH_3)_2$); 1.65 (s, 6H, $(CH_3)_2$); 3.65-3.68 (m, 2H, N-CH_2); 3.73-3.83 (m, 4H, 2*N-CH_2); 4.00-4.03 (m, 2H, N-CH_2); 4.32 (q, 2H, *J* 7.2 Hz, **CH_2**CH_3); 6.92-7.01 (m, 2H, 2 Ar); 7.34-7.40 (m, 2H, 2 Ar); 7.54 (d, 1H, *J* 8.4 Hz, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 640.9.

Example **79**: 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-(trifluoromethyl)thiazole-5-carboxylic acid

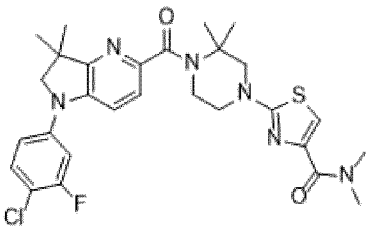


Example **79** was prepared according to general procedure (VII) starting from Example **78** (57 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 0:100) and freeze dried with HCl (aq. 0.1 N) to obtain Example **78** (30 mg, 30%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, $(CH_3)_2$); 1.53 (s, 6H, $(CH_3)_2$); 3.77-3.82 (m, 2H, N-CH_2); 3.84-3.89 (m, 4H, 2*N-CH_2); 7.18 (dd, 1H, dd, *J* 8.7 2.1 Hz, Ar); 7.27 (dd, 1H, *J* 2.4, 1.8 Hz, Ar); 7.38 (d, 1H, *J* 8.4, Ar); 7.52-7.58 (m, 2H, 2 Ar). COOH and one CH_2 were not observed.

M/Z (M[^{35}Cl]+H)$^+$: 612.3.

Example **80**: 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N,N-dimethylthiazole-4-carboxamide

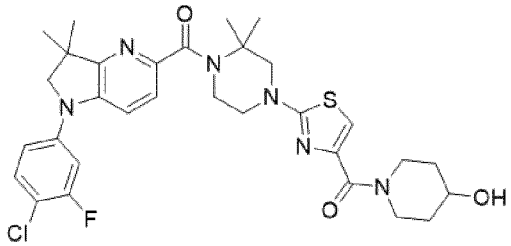


Example **80** was prepared according to general procedure (VIIIb) starting from Example **43** (50 mg), dimethylamine hydrochloride (1.1 eq.), and N,N-diisopropylethylamine (4.0 eq.) in PC. The reaction mixture was directly purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 50:50 to 10:90) and freeze dried with water to obtain Example **80** (37 mg, 71%) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, 2 CH_3); 1.52 (s, 6H, 2 CH_3); 2.93 (bs, 3H, N-CH_3); 3.11 (bs, 3H, N-CH_3); 3.55-3.58 (m, 2H, CH_2); 3.73 (s, 2H, CH_2); 3.81-3.84 (m, 2H, CH_2); 3.86 (s, 2H, CH_2); 7.11 (s, 1H, Ar); 7.19 (dd, *J* 8.9, 2.2 Hz, 1H, Ar); 7.33 (dd, *J* 11.8, 2.6 Hz, 1H, Ar); 7.38 (d, *J* 8.4 Hz, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 572.0.

Example **81**: (1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(4-(4-(4-hydroxypiperidine-1-carbonyl)thiazol-2-yl)-2,2-dimethylpiperazin-1-yl)methanone

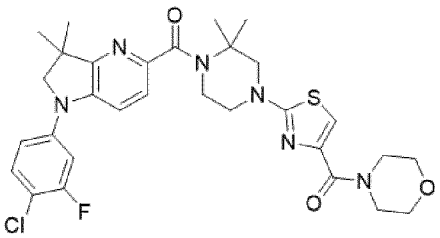


Example **81** was prepared according to general procedure (VIIIb) starting from Example **43** (50 mg), piperidin-4-ol (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in PC. The reaction mixture was directly purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 60:40 to 20:80) and freeze dried with water to obtain Example **81** (35 mg, 61%) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 8H, 2 CH_3 + CH_2); 1.52 (s, 6H, 2 CH_3); 1.72-1.80 (m, 2H, CH_2); 3.09-3.27 (m, 2H, CH_2); 3.55-3.60 (m, 2H, CH_2); 3.72 (bs, 3H, CH + CH_2); 3.80-3.84 (m, 2H, CH_2); 3.87 (s, 2H, CH_2); 3.92-3.98 (m, 2H, CH_2); 4.76 (d, *J* 4.2 Hz, 1H, OH); 7.09 (s, 1H, Ar); 7.17-7.21 (m, 1H, Ar); 7.33 (dd, *J* 11.8, 2.5 Hz, 1H, Ar); 7.39 (d, *J* 8.4 Hz, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 628.0.

Example **82**: (1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(2,2-dimethyl-4-(4-(morpholine-4-carbonyl)thiazol-2-yl)piperazin-1-yl)methanone

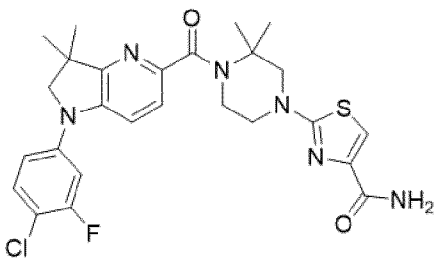


Example **82** was prepared according to general procedure (VIIIa) starting from Example **43** (50 mg), morpholine (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in PC. The reaction mixture was directly purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 50:50 to 10:90) and freeze dried with water to obtain Example **82** (31 mg, 55%) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, 2 CH_3); 1.52 (s, 6H, 2 CH_3); 3.55-3.59 (m, 8H, 4 CH_2); 3.71 (m, 4H, 2 CH_2); 3.80-3.84 (m, 2H, CH_2); 3.86 (s, 2H, CH_2); 7.17-7.21 (m, 2H, 2 Ar); 7.33 (dd, *J* 11.9, 2.6 Hz, 1H, Ar); 7.38 (d, *J* 8.4 Hz, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 614.0.

Example **83**: 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carboxamide



To a solution of Example **43** and ammonia (5.5 eq.), in dioxane (0.1M) was added ((1H-benzo[d][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate (1.5 eq.) and the mixture was heated at 80°C for 16 hours. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (2*40 mL). The organics were washed with brine (40 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Interchim® 50 µm, DCM 100% to DCM/MeOH 98:02) then further purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 50:50 to 10:90) and freeze dried with water to obtain Example **83** (20 mg, 40%) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, 2 CH_3); 1.53 (s, 6H, 2 CH_3); 3.52-3.57 (m, 2H, CH_2); 3.80-3.87 (m, 6H, 3 CH_2); 7.17-7.21 (m, 1H, Ar); 7.31-7.34 (m, 2H, 2 Ar); 7.38 (d, *J* 8.5 Hz, 1H, Ar); 7.41-7.47 (m, 2H, NH_2); 7.53-7.58 (m, 2H, 2 Ar).

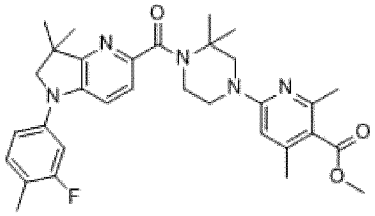
M/Z (M[^{35}Cl]+H)$^+$: 543.8.

Compound **117**: 5-chloro-1-(3-fluoro-4-methylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

Compound **117** was prepared according to general procedure (X) starting from Compound **70** (350 mg) and 4-bromo-2-fluoro-1-methylbenzene (2.0 eq) with ^{t}BuONa (3.0 eq) at 100°C for 18 hours. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **117** (340 mg, 61%) as a beige solid.

M/Z (M[^{35}Cl]+H)$^{+}$: 291.3.

Example **84**: methyl 6-(4-(1-(3-fluoro-4-methylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

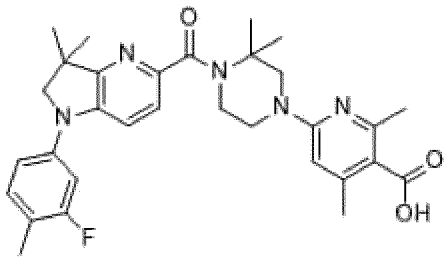


Example **84** was prepared according to general procedure (XIV) starting from Compound **117** (100 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 20:80) to obtain Example **84** (128 mg, 67%) as a beige solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.42 (m, 6H, $C(CH_3)_2$); 1.62 (s, 6H, $C(CH_3)_2$); 2.25 (s, 3H, $ArCH_3$); 2.32 (s, 3H, $ArCH_3$); 2.55 (bs, 3H, $ArCH_3$); 3.59-3.67 (m, 2H, N-CH_2); 3.76 (s, 2H, N-CH_2); 3.87 (s, 3H, OCH_3); 3.93-4.06 (m, 4H, 2 N-CH_2); 6.10 (s, 1H, Ar); 6.85-6.92 (m, 2H, 2 Ar); 7.14-7.20 (m, 1H, Ar); 7.29 (d, *J* 8.4Hz, 1H, Ar); 7.47 (d, *J* 8.4Hz, 1H, Ar).

M/Z (M+H^{+}): 561.0.

Example **85**: 6-(4-(1-(3-fluoro-4-methylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **85** was prepared according to general procedure (XI) starting from Example **84** (125 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) and freeze dried with HCl (0.1 N in water) to obtain Example **85** (88 mg, 68%) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, $(CH_3)_2$); 1.52 (s, 6H, $(CH_3)_2$); 2.21 (s, 3H, CH_3); 2.34 (s, 3H, CH_3); 3.59-3.72 (m, 2H, NCH_2); 3.83 (s, 2H, NCH_2); 3.92-3.97 (m, 4H, 2*CH_2); 6.61-6.69 (m, 1H, Ar); 7.05-7.09 (m, 2H, 2 Ar); 7.26-7.32 (m, 1H, Ar;) 7.35 (d, *J* 8.4, 1H, Ar); 7.47 (d, *J* 8.4, 1H, Ar). One CH3 and COOH are not observed.

M/Z (M+H^{+}): 547.0.

Compound **118**: 1-((4-chloro-3-fluorophenyl)amino)-2-methylpropan-2-ol

Under inert atmosphere, to a solution of 4-bromo-1-chloro-2-fluorobenzene (1.0 g) and 1-amino-2-methylpropan-2-ol (1.1 eq.) in Dioxane (0.1 M) was added Cesium Carbonate (2 eq.). The mixture was sparged with Argon for 10 min before addition of BrettPhos Pd G4 (0.05 equiv). The reaction mixture was heated at 100 °C for 1 hour. The reaction mixture was filtered through a pad of Celite, the pad was washed with EtOAc (20 mL) then the filtrate was

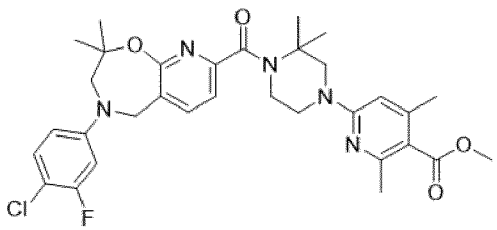
concentrated to dryness. The residue was purified by flash chromatography (Interchim® 50 µm, DCM 100% to DCM/MeOH 99:01) to obtain Compound **118** (710 mg, 68%) as a brown oil.
M/Z (M[^{35}Cl] - OH)$^{+}$: 200.6.

Compound **119**: 2,6-dichloro-N-(4-chloro-3-fluorophenyl)-N-(2-hydroxy-2-methylpropyl)nicotinamide
To a solution of 2,6-dichloronicotinic acid (626 mg) and Compound **118** (1.0 eq.) in DCM (0.1 M) was added pyridine (10 eq) and $POCl_3$ (2 eq.) at 0°C. The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with HCl (1N aq., 5 mL), diluted with water (15 mL) and extracted with DCM (3*20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **119** (910 mg, 71%) as a yellow oil.
M/Z (M[$^{35}Cl_3$] - OH)$^{+}$: 373.6

Compound **120**: 8-chloro-4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-3,4-dihydropyrido[3,2-f][1,4]oxazepin-5(2H)-one
To a solution of Compound **119** (300 mg) in THF (0.1 M) at 0°C was added Sodium Hydride (60% in mineral oil, 1.1 eq.). The reaction mixture was heated at 50°C for 21 hours. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2*20 mL). The combined organic layers were washed with brine (10 mL) dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **120** (143 mg, 53%) as a white solid.
M/Z (M[$^{35}Cl_2$]+H)$^{+}$: 355.6

Compound **121**: 8-chloro-4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine
To a solution of Compound **120** (253 mg) in THF (0.1 M) at 0°C was added Borane (dimethyl sulfide complexe, 5.0 eq.). The reaction mixture was heated at 50°C for 1.5 hour. The reaction mixture was quenched with MeOH (3 mL), heatd at 40°C for 20 min and concentrated under reduced pressure. The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **121** (195 mg, 80%) as a white solid.
M/Z (M[$^{35}Cl_2$]+H)$^{+}$: 341.1

Example **86**: methyl 6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



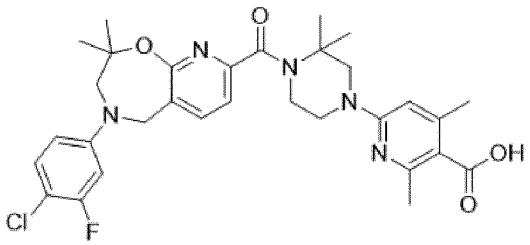
Example **86** was prepared according to general procedure (XIV) starting from Compound **121** (90 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The

crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Example **86** (91 mg, 57%) as a yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.15 (s, 6H, 2 CH_3); 1.47 (s, 6H, 2 CH_3); 2.22 (s, 3H, CH_3); 2.37 (s, 3H, CH_3); 3.32-3.39 (m, 2H, N-CH_2); 3.50-3.59 (m, 2H, N-CH_2); 3.78 (s, 3H, O-CH_3); 3.86-3.89 (m, 4H, 2 N-CH_2); 4.55 (s, 2H, N-CH_2); 6.32 (s, 1H, Ar); 6.81-6.85 (m, 1H, Ar); 7.00-7.06 (m, 1H, Ar); 7.20-7.28 (m, 2H, 2 Ar); 8.17 (d, *J* 7.7 Hz, 1H, Ar).

M/Z (M[^{35}Cl]+H$^+$): 610.9.

Example **87**: 6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **87** was prepared according to general procedure (XI) starting from Example **86** (91 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) and freeze dried with water to obtain Example **87** (12 mg, 14%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.16 (s, 6H, 2 CH_3); 1.47 (s, 6H, 2 CH_3); 2.25 (s, 3H, CH_3); 2.36 (s, 3H, CH_3); 3.39-3.44 (m, 2H, N-CH_2); 3.51-3.57 (m, 2H, N-CH_2); 3.86-3.89 (m, 4H, 2 N-CH_2); 4.55 (s, 2H, N-CH_2); 6.30 (s, 1H, Ar); 6.81-6.85 (m, 1H, Ar); 7.01-7.06 (m, 1H, Ar); 7.20-7.28 (m, 2H, 2 Ar); 8.17 (d, *J* 7.7 Hz, 1H, Ar); 12.68 (bs, 1H, COOH).

M/Z (M[^{35}Cl]+H$^+$): 596.9.

Compound **122**: 1-(3-chloropyridin-2-yl)-3,3-difluorocyclobutane-1-carbonitrile

Compound **122** was prepared according to general procedure (I) from 3-chloro-2-fluoropyridine (1.0 g) and 3,3-difluorocyclobutane-1-carbonitrile. The crude was purified by flash chromatography (Merck® 60 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **122** (1.29 g, 74%) as a clear oil.

M/Z (M[^{35}Cl]+H$^+$): 229.6.

Compound **123**: (1-(3-chloropyridin-2-yl)-3,3-difluorocyclobutyl)methanamine

Compound **123** (850 mg, 65%) was obtained as a clear oil following general procedure (XVa), starting from Compound **122** (1.29 g).

M/Z (M[^{35}Cl]+H$^+$): 233.4.

Compound **124**: 1'-(4-chloro-3-fluorophenyl)-3,3-difluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **124** was prepared according to general procedure (Xc) from Compound **123** (900 mg) and 4-bromo-1-chloro-2-fluorobenzene. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 75:25) to obtain Compound **124** (355 mg, 28%) as a white solid.

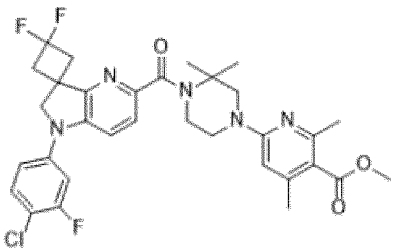
M/Z (M[^{35}Cl]+H$^+$): 325.6.

Compound **125**: 5'-bromo-1'-(4-chloro-3-fluorophenyl)-3,3-difluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **125** (431 mg, 99%) was obtained as an off-white solid following general procedure (XVI) in MeCN without further purification, starting from Compound **124** (350 mg).

M/Z ($M[^{35}Cl][^{81}Br]+H)^+$: 405.7 .

Example **88**: methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-difluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

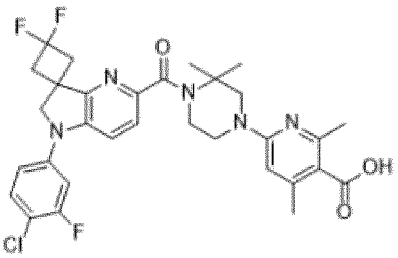


Example **88** was prepared according to general procedure (XIV) starting from Compound **125** (100 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Example **88** (85 mg) as a white solid.

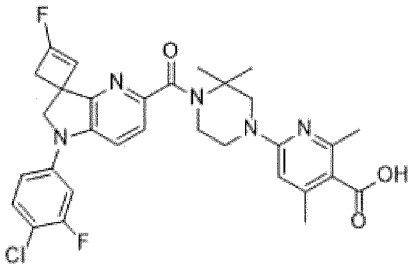
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.62 (s, 6H, 2 CH_3); 2.32 (s, 3H, CH_3); 2.47 (s, 3H, CH_3); 2.75-2.85 (m, 2H, (CH_aH_b)$_2$-CF_2); 3.15-3.30 (m, 2H, (CH_aH_b)$_2$-CF_2); 3.65-3.70 (m, 2H, N-CH_2); 3.87 (s, 3H, O-CH_3); 3.98-4.00 (m, 4H, 2 N-CH_2); 4.20 (s, 2H, N-CH_2); 6.11 (s, 1H, Ar); 6.91-7.03 (m, 2H, 2 Ar); 7.34-7.40 (m, 2H, 2 Ar); 7.58 (d, *J* 8.4 Hz, 1H, Ar).

M/Z ($M[^{35}Cl]+H^+$): 628.3.

Example **89**: 6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-difluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **90**: 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-fluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridin]-2-en-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **89** and Example **90** were prepared according to general procedure (XI) starting from Example **88** (80 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and the corresponding fractions were freeze dried with HCl (0.1 N in water) to obtain Example **89** (35 mg, 22% over 2 steps) as a yellow solid and Example **90** (10 mg, 14% over 2 steps) as a white solid.

Example **89:**

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.51 (s, 6H, $(CH_3)_2$); 2.30 (s, 3H, CH_3); 2.45 (s, 3H, CH_3); 2.93-3.12 (m, 4H, $(CH_2)_2$); 3.65-3.69 (m, 2H, CH_2); 3.88-3.94 (m, 4H, $(CH_2)_2$); 4.33 (s, 2H, CH_2); 6.56 (bs, 1H, Ar); 7.16-7.22 (dd, *J* 8.7 Hz, 2.7 Hz, 1H, Ar); 7.36 (dd, *J* 11.7 Hz, 2.7 Hz, 1H, Ar); 7.44 (d, *J* 8.7 Hz, 1H, Ar); 7.54-7.60 (m, 2H, 2 Ar). COOH was not observed.

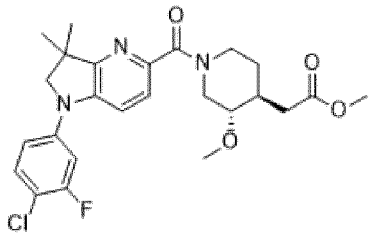
M/Z (M[^{35}Cl]+H)$^+$: 614.5

Example **90:**

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.48 (s, 6H, $(CH_3)_2$); 2.25 (s, 3H, CH_3); 2.37 (s, 3H, CH_3); 3.01-3.07 (m, 1H, CH); 3.15-3.22 (m, 1H, CH); 3.52-3.58 (m, 2H, CH_2); 3.68 (bs, 2H, CH_2); 3.74-3.79 (m, 2H, CH_2); 4.19-4.33 (m, 2H, CH_2); 5.30 (d, J 8.1 HZ, 1H, CH); 6.27 (bs, 1H, Ar); 7.18-7.22 (m, 1H, Ar); 7.32-7.40 (m, 2H, 2 Ar); 7.53-7.61 (m, 2H, 2 Ar); 12.65 (bs, 1H, CO_2H).

M/Z (M[^{35}Cl]+H)$^+$: 595.0.

Example **91**: methyl 2-((3S,4S)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate

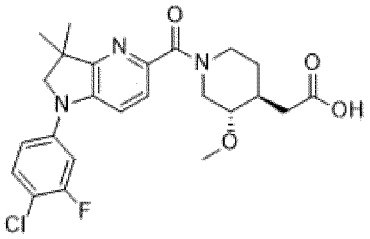


Example **91** was prepared according to general procedure (VIIIb) starting from Compound **68** (100 mg), methyl 2-((3S,4S)-3-methoxypiperidin-4-yl)acetate hydrochloride (1.1 eq.) and triethylamine (3 eq.) in THF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 0:100) to obtain Example **91** (139 mg, 91%) as a beige solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.34 (broad s, 7H, $(CH_3)_2$, CH); 1.68-2.03 (m, 2H, CH_2); 2.56-2.67 (m, 2H, CH_2); 2.76-3.09 (m, 3H, CH_2, CH); 3.12-3.24 (m, 2H, N-CH_2); 3.58 (s, 3H, O-CH_3); 3.81-3.88 (m, 3H, CH-O + N-CH_2); 3.89-4.01 (m, 0.5H, one rotamer of N-C**H$_a$**H$_b$); 4.23-4.40 (m, 0.5H, other rotamer of N-C**H$_a$**H$_b$); 4.45-4.60 (m, 0.5H, one rotamer of N-CH$_a$**H$_b$**); 4.63-4.76 (m, 0.5H, one rotamer of N-CH$_a$**H$_b$**); 7.18 (dd, 8.7 1.8 Hz, 1H, Ar); 7.32 (dd, 2.4, 1.8 Hz, 1H, Ar); 7.33-7.44 (m, 1H, Ar), 7.49-7.58 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 490.9

Example **92**: 2-((3S,4S)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid

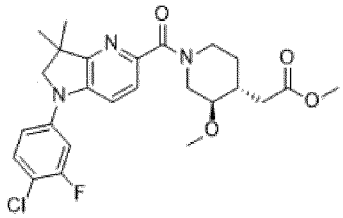


Example **92** was prepared according to general procedure (VII) starting from Example **91** (139 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 60:40 to 20:80) then freeze dried with HCl (0.1 N in water) to obtain Example **92** (83 mg, 57%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.30 (broad s, 7H, $(CH_3)_2$, CH); 1.68-1.97 (m,2H, CH_2); 2.07-2.18 (m, 1H, CH); 2.60-2.68 (m, 1H, CH); 2.77-3.01 (m, 3H, CH_2, CH); 3.14-3.33 (s, 3H, rotamer OCH_3); 3.82-3.87 (m, 2H, CH_2); 3.87-3.95 (m, 0.5H, one rotamer of C**H$_a$**H$_b$); 4.19-4.29 (m, 0.5H, other rotamer of C**H$_a$**H$_b$); 4.36-4.47 (m, 0.5H, one rotamer of CH$_a$**H$_b$**; 4.57-4.67 (0.5H, other rotamer of CH$_a$**H$_b$**); 7.16 (dd, 8.7 1.8 Hz, 1H, Ar); 7.27 (dd, 2.4, 1.8 Hz, 1H, Ar); 7.33-7.41 (m, 1H, Ar), 7.49-7.56 (m, 2H, 2 Ar). COOH was not observed

M/Z (M[^{35}Cl]+H)$^+$: 476.3

Example **93**: methyl 2-((3R,4R)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate

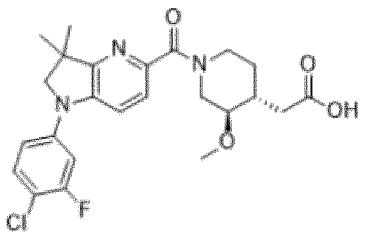


Example **93** was prepared according to general procedure (VIIIb) starting from Compound **68** (100 mg), methyl 2-((3R,4R)-3-methoxypiperidin-4-yl)acetate hydrochloride (1.1 eq.) and triethylamine (3 eq.) in THF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 0:100) to obtain Example **91** (121 mg, 79%) as a beige solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.34 (broad s, 7H, $(CH_3)_2$, CH); 1.68-2.03 (m, 2H, CH_2); 2.56-2.67 (m, 2H, CH_2); 2.76-3.09 (m, 3H, CH_2, CH); 3.12-3.24 (m, 2H, N-CH_2); 3.58 (s, 3H, O-CH_3); 3.81-3.88 (m, 3H, CH-O + N-CH_2); 3.89-4.01 (m, 0.5H, one rotamer of N-C**H$_a$**H$_b$); 4.23-4.40 (m, 0.5H, other rotamer of N-C**H$_a$**H$_b$); 4.45-4.60 (m, 0.5H, one rotamer of N-CH$_a$**H$_b$**); 4.63-4.76 (m, 0.5H, one rotamer of N-CH$_a$**H$_b$**); 7.18 (dd, 8.7 1.8 Hz, 1H, Ar); 7.32 (dd, 2.4, 1.8 Hz, 1H, Ar); 7.33-7.44 (m, 1H, Ar), 7.49-7.58 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 490.9

Example **94**: 2-((3R,4R)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid

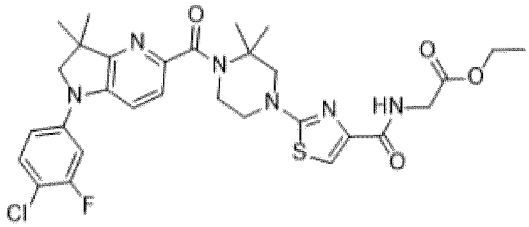


Example **94** was prepared according to general procedure (VII) starting from Example **93** (121 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 60:40 to 20:80) then freeze dried with HCl (0.1 N in water) to obtain Example **94** (77 mg, 61%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.32 (broad s, 7H, $(CH_3)_2$, CH); 1.70-1.96 (m, 2H, CH_2); 2.05-2.18 (m, 1H, CH); 2.57-2.67 (m, 1H, CH); 2.78-3.10 (m, 3H, CH, CH_2); 3.16-3.34 (2 d, 3H, rotamer OCH_3); 3.84 (s, 2H, CH_2); 3.89-3.97 (m, 0.5H, one rotamer of C**H$_a$**H$_b$); 4.21-4.31 (m, 0.5H, other rotamer of C**H$_a$**H$_b$); 4.39-4.51 (m, 0.5H, one rotamer of CH$_a$**H$_b$**); 4.59-4.72 (0.5H, other rotamer of CH$_a$**H$_b$**); 7.17(dd, *J* 8.7 2.1 Hz, 1H, Ar); 7.27 (dd, *J* 2.4, 1.8 Hz, 1H, Ar); 7.28-7.43 (m, 2H, 2 Ar), 7.50-7.58 (m, 2H, 2 Ar). COOH was not observed

M/Z (M[^{35}Cl]+H)$^+$: 476.3

Example **95**: ethyl (2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carbonyl)glycinate

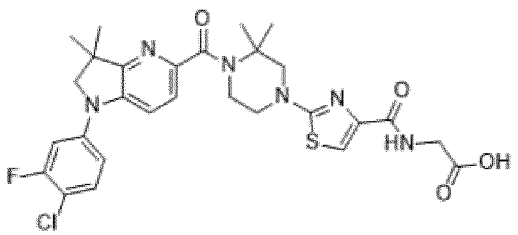


Example **95** was prepared according to general procedure (VIIIa) starting from Example **43** (75 mg), ethyl glycinate hydrochloride (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in PC. The crude was purified by flash chromatography (Interchim® 50 µm, DCM 100% to DCM/MeOH 98:02) to obtain Example **95** (80 mg, 92%) as an orange solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.20 (t, 3H, *J* 7.8 Hz, CH_2**CH_3**); 1.36 (s, 6H, 2 CH_3); 1.54 (s, 6H, 2 CH_3); 3.55-3.59 (m, 2H, N-CH_2); 3.83-3.87 (m, 6H, 3 N-CH_2); 3.96-3.98 (m, 2H, N-CH_2); 4.12 (q, 2H, J 7.8 Hz, **CH_2**CH_3); 7.17-7.21 (m, 1H, Ar); 7.30-7.40 (m, 3H, 3 Ar); 7.52-7.58 (m, 2H, 2 Ar), 8.37-8.42 (m, 1H, NH).

M/Z (M[^{35}Cl]+H)$^+$: 630.0

Example **96**: (2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carbonyl)glycine.

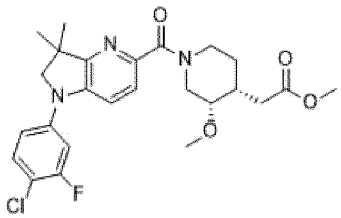


Example **96** was prepared according to general procedure (VII) starting from Example **95** (80 mg). The crude was suspended in DMSO (2 mL) and precipitated in water (40 mL). The precipitate was recovered by filtration and freeze dried in HCl (0.1 N in water) to obtain Example **96** (43 mg, 53%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, 2 CH_3); 1.54 (s, 6H, 2 CH_3); 3.59-3.66 (m, 2H, CH_2); 3.82-3.91 (m, 8H, 4 CH_2); 7.17-7.21 (m, 1H, Ar); 7.33 (dd, *J* 11.9, 2.6 Hz, 1H, Ar); 7.37-7.40 (m, 2H, 2 Ar); 7.53-7.59 (m, 2H, 2 Ar); 8.28-8.32 (m, 1H, NH). COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 602.0.

Example **97**: methyl 2-((3S,4R)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate

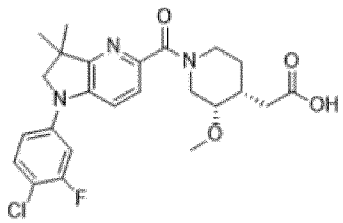


Example **97** was prepared according to general procedure (VIIIb) starting from Compound **68** (100 mg), methyl 2-((3S,4R)-3-methoxypiperidin-4-yl)acetate hydrochloride (1.1 eq.) and triethylamine (3 eq.) in THF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 0:100) to obtain Example **91** (135 mg) as a beige solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.38-1.57 (m, 7H, $(CH_3)_2$ + N-$CH_2CH_aH_b$); 1.74-1.78 (m, 1H, N-$CH_2CH_aH_b$); 2.19-2.38 (m, 2H, CH_2-CO); 2.51-2.61 (m, 1H, CH); 2.89-2.97 (m, 2H, 2 N-CH_aH_b); 3.20-3.25 (m, 1H, CH-OCH_3); 3.38-3.42 (m, 2H, N-CH_2); 3.62-3.65 (m, 3H, O-CH_3); 3.67-3.72 (m, 3H, $COOCH_3$); 4.14-4.22 (m, 0.5H, one rotamer of N-CH_aH_b); 4.49-4.60 (m, 1H, N-CH_aH_b); 4.82-4.94 (m, 0.5H, one rotamer of N-CH_aH_b); 6.91-7.05 (m, 2H, 2 Ar); 7.31-7.41 (m, 2H, 2 Ar); 7.47-7.61 (m, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 490.3

Example **98**: 2-((3S,4R)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid



Example **98** was prepared according to general procedure (VII) starting from Example **97** (121 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 60:40 to 20:80) then freeze dried with HCl (0.1 N in water) to obtain Example **98** (66 mg, 47% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.31-1.58 (m, 8H, $(CH_3)_2$, CH_2); 2.04-2.23 (m, 2H, CH_2); 2.30-2.41 (m, 1H, CH); 2.78-2.94 (m, 2.5 H, CH_2 and one rotamer of CH**a**H**b**); 3.06-3.46 (m, 3.5H, CH_3 other rotamer of CH_aH_b); 3.79-3.91 (m, 2H, CH_2); 3.96-4.10 (m, 0.5H, one rotamer of CH_aH_b); 4.26-4.47 (m, 2*0.5H, other rotamer of CH_aH_b and one

rotamer of $CH_a\mathbf{H_b}$); 4.62-4.74 (0.5H, other rotamer of $CH)_a\mathbf{H}_b$; 7.17 (dd, *J* 9.0, 2.1 Hz, 1H, Ar); 7.2-7.39 (m, 2H, 2 Ar); 7.51-7.59 (m, 2H, 2 Ar). COOH was not observed

M/Z $(M[^{35}Cl]+H)^+$: 476.3

Compound **126**: 3-chloro-N-(4-chloro-3-fluorophenyl)-N-(2-methylallyl)pyrazin-2-amine

Crude Compound **126** (10.0 g) was obtained as a brown oil according to general procedure (XVII) on a 5.0 g scale, using 4-chloro-3-fluoroaniline.

M/Z $(M[^{35}Cl]_2+H)^+$: 312.2.

Compound **127**: 5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **127** was prepared according to general procedure (XVIII) starting from crude Compound **126** (10.0 g). The crude was precipitated from a water/ethanol mixture (1:2, about 4 V) to obtain Compound 127 (3.32 g, 36% over 2 steps) as a beige solid.

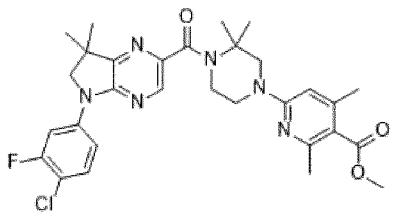
M/Z $(M[^{35}Cl]+H)^+$: 278.0.

Compound **128**: 2-bromo-5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **128** (4.20 g, 99%) was obtained as an off-white solid following general procedure (XVI) in MeCN without further purification, starting from Compound **127** (3.32 g).

M/Z $(M[^{81}Br^{35}Cl]+H)^+$: 358.1.

Example **99**: methyl 6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

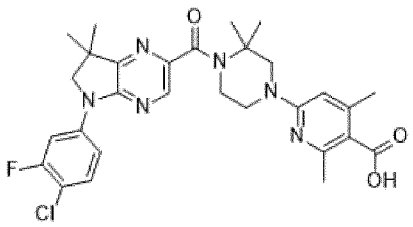


Example **99** was prepared according to general procedure (XIV) starting from Compound **128** (1.0 g) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **99** (0.82 g, 51%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.40 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 2.24 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 3.53-3.57 (m, 2H, N-$\mathbf{CH_2}$-CH_2-N); 3.77-3.84 (m, 5H, N-CH_2-$\mathbf{CH_2}$-N + O-CH_3); 3.88 (s, 2H, N-CH_2); 3.99 (s, 2H, N-CH_2); 6.37 (s, 1H, Ar); 7.62 (t, *J* 8.7 Hz, 1H, Ar); 7.73 (dd, *J* 8.7, 2.3 Hz, 1H, Ar); 8.09 (dd, *J* 12.4, 2.3 Hz, 1H, Ar); 8.22 (s, 1H, Ar).

M/Z $(M[^{35}Cl]+H)^+$: 581.4.

Example **100**: 6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid

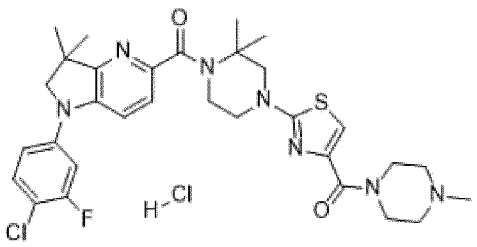


Example **100** was prepared according to general procedure (XI) starting from Example **99** (824 mg). The reaction mixture was quenched in water (50 mL), washed with Et_2O (2*40 mL), acidified with HCl (pH = 5) and extracted with DCM (2*50 mL). The combined DCM layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. To the residue was added DCM (20 mL) and the solid was recovered by filtration to obtain Example **100** (480 mg, 60%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.40 (s, 6H, CH_3 x2); 1.50 (s, 6H, CH_3 x2); 2.27 (s, 3H, CH_3); 2.37 (s, 3H, CH_3); 3.52-3.55 (m, 2H, N-**CH_2**-CH_2-N); 3.79-3.82 (m, 2H, N-CH_2-**CH_2**-N); 3.88 (s, 2H, CH_2); 3.99 (s, 2H, CH_2); 6.35 (s, 1H, Ar); 7.62 (t, *J* 8.7 Hz, 1H, Ar); 7.73 (dd, *J* 8.7, 2.3 Hz, 1H, Ar); 8.09 (dd, *J* 12.4, 2.3 Hz, 1H, Ar); 8.22 (s, 1H, Ar), 12.70 (bs, 1H, COOH).

M/Z (M[^{35}Cl]+H)$^+$: 567.4.

Example **101**: (1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(2,2-dimethyl-4-(4-(4-methylpiperazine-1-carbonyl)thiazol-2-yl)piperazin-1-yl)methanone hydrochloride



Example **101** was prepared according to general procedure (VIIIa) starting from Example **43** (50 mg), 1-methylpiperazine (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in PC. The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) then freeze dried with HCl (0.1 N in water) to obtain Example **101** (7 mg, 12%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, 2 CH_3); 1.53 (s, 6H, 2 CH_3); 2.79 (s, 1.5H, one rotamer of CH_3); 2.80 (s, 1.5H, other rotamer of CH_3); 3.00-3.12 (m, 3H, CH_2 + one rotamer of CH_2); 3.43-3.48 (m, 5H, 2 CH_2 + other rotamer of CH_2); 3.73 (s, 2H, CH_2); 3.82-3.85 (m, 2H, CH_2); 3.87 (s, 2H, CH_2); 4.49-4.77 (m, 2H, CH_2) 7.17-7.21 (m, 1H, Ar); 7.31-7.36 (m, 2H, 2 Ar); 7.39 (d, *J* 8.4 Hz, 1H, Ar); 7.53-7.59 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 626.9.

Compound **129**: 2-(3-chloropyridin-2-yl)-2-ethylbutanenitrile

Compound **129** was prepared according to general procedure (I) from 3-chloro-2-fluoropyridine (1.0 g) and 2-ethylbutanenitrile. The crude was purified by flash chromatography (Merck® 60 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **129** (1.31 g, 83%) as a clear oil.

M/Z (M[^{35}Cl]+H$^+$): 209.6.

Compound **130**: 2-(3-chloropyridin-2-yl)-2-ethylbutan-1-amine

Compound **130** (0.92 g, 69%) was obtained as a clear oil following general procedure (XVa), starting from Compound **129** (1.30 g).

M/Z (M[^{35}Cl]+H$^+$): 213.6.

Compound **131**: 1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

Compound **131** was prepared according to general procedure (Xc) from Compound **130** (900 mg) and 4-bromo-1-chloro-2-fluorobenzene. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 75:25) to obtain Compound **131** (644 mg, 50%) as a yellow oil.

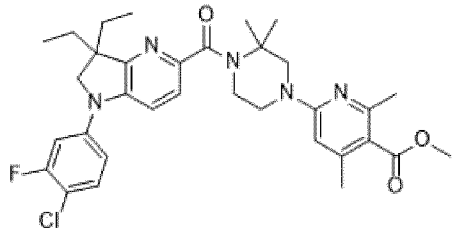
M/Z (M[^{35}Cl]+H$^+$): 305.7.

Compound **132**: 5-bromo-1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

Compound **132** was prepared according to general procedure (XVI) in MeCN from Compound **131** (630 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 90:10) to obtain Compound **132** (623 mg, 79%) as a brown oil.

M/Z (M[^{35}Cl][^{81}Br]+H)$^+$: 385.7.

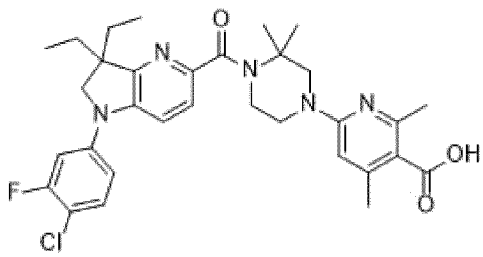
Example **102**: methyl 6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



Example **102** was prepared according to general procedure (XIV) starting from Compound **132** (100 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **102** (82 mg) as a yellow solid.

M/Z (M[^{35}Cl]+H$^+$): 608.4.

Example **103**: 6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **103** was prepared according to general procedure (XI) starting from Example **102** (80 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **103** (17 mg, 11% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 0.76 (t, *J* 7.2 Hz, 6H, $(CH_2\mathbf{CH_3})_2$); 1.52 (s, 6H, $(CH_3)_2$); 1.73 (q, 4H, *J* 7.2 Hz ($\mathbf{CH_2}CH_3)_2$); 2.33 (s, 3H, CH_3); 3.62-3.69 (m, 2H, CH_2); 3.84-3.94 (m, 6H, $(CH_2)_3$); 6.77 (bs, 1H, Ar); 7.22 (dd, J 9.0, 2.1 Hz, 1H, Ar); 7.33-7.39 (m, 2H, 2 Ar); 7.51-7.57 (m, 2H, 2 Ar). COOH and one CH_3 were not observed.

M/Z (M[^{35}Cl]+H)$^+$: 594.9.

Compound **133**: tert-butyl 4-(5-(2-methoxy-2-oxoethyl)pyridin-2-yl)-2,2-dimethylpiperazine-1-carboxylate

Compound **133** was prepared according to general procedure (Xb), starting from methyl 2-chloroisonicotinate (200 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The crude was directly engaged in the following step.

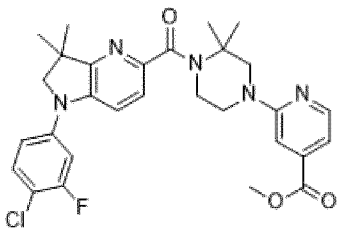
M/Z (M+H)$^+$:350.8

Compound **134**: methyl 2-(3,3-dimethylpiperazin-1-yl)isonicotinate

Compound **134** was obtained as a brown solid (261 mg, 78% over 2 steps) according to general procedure (XII) starting from Compound **133** in DCM using TFA.

M/Z (M+H)$^+$:250.7

Example **104**: methyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)isonicotinate

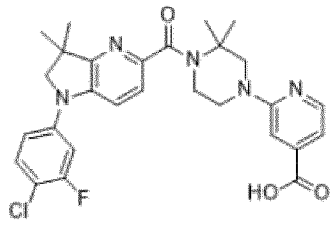


Example **104** was prepared according to general procedure (VIIIb) starting from Compound **68** (75 mg), Compound **134** (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in THF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **104** (95 mg, 74%) as a beige solid.

^{1}H-NMR (DMSO-d_6 +D_2O, 300 MHz) δ: 1.36 (s, 6H, $C(CH_3)_2$); 1.51 (s, 6H, $C(CH_3)_2$); 3.57-3.60 (m, 2H, N-CH_2); 3.81-3.94 (m, 9H, 3 N-CH_2 + O-CH_3); 7.00-7.04 (m, 2H, 2 Ar); 7.18 (dd, *J* 8.9, 2.0 Hz, 1H, Ar); 7.30-7.38 (m, 2H, 2 Ar); 7.52-7.58 (m, 2H, 2 Ar); 8.26 (d, *J* 5.7 Hz, 1H).

M/Z (M[^{35}Cl]+H)$^+$: 553.0.

Example **105**: 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)isonicotinic acid



Example **105** was prepared according to general procedure (VII) starting from Example **104** (95 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 60:40 to 20:80) freeze dried with HCl (0.1 N in water) to obtain Example **105** (80 mg, 81%) as a yellow solid.

^{1}H-NMR (DMSO-d_6 +D_2O, 300 MHz) δ: 1.35 (s, 6H, $C(CH_3)_2$); 1.53 (s, 6H, $C(CH_3)_2$); 3.65-3.67 (m, 2H, N-CH_2); 3.85 (s, 2H, N-CH_2); 3.88-3.91 (m, 2H, N-CH_2); 3.95 (s, 2H, CH_2), 7.11 (dd, *J* 5.7, 0.7 Hz, 1H, Ar); 7.18 (dd, *J* 8.9, 2.0 Hz, 1H, Ar); 7.29-7.39 (m, 3H, 3Ar); 7.52-7.58 (m, 2H, 2Ar); 8.19 (d, *J* 5.7 Hz, 1H). COOH was not observed.

M/Z ($M[^{35}Cl]+H)^+$: 538.9.

Compound **135**: tert-butyl 4-(4-(ethoxycarbonyl)pyridin-3-yl)-2,2-dimethylpiperazine-1-carboxylate

Compound **135** was prepared according to general procedure (Xb), starting from ethyl 3-chloroisonicotinate (217 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The crude was directly engaged in the following step.

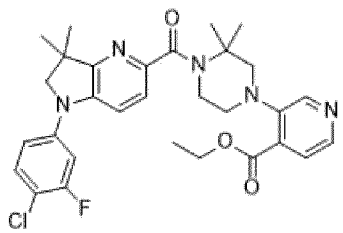
M/Z $(M+H)^+$: 364.8

Compound **136**: ethyl 3-(3,3-dimethylpiperazin-1-yl)isonicotinate

Compound **136** was obtained as a brown solid (209 mg, 60% over 2 steps) according to general procedure (XII) starting from Compound **135** (261 mg) in DCM using TFA.

M/Z $(M+H)^+$: 264.7

Example **106**: ethyl 3-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)isonicotinate

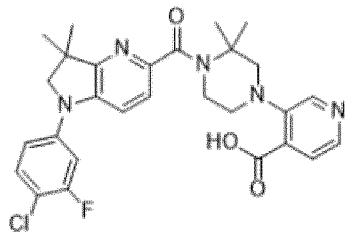


Example **106** was prepared according to general procedure (VIIIb) starting from Compound **68** (75 mg), Compound **136** (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in THF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 0:100) to obtain Example **106** (65 mg, 50%) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.28-1.33 (m, 9H, CH_2CH_3 + $C(CH_3)_2$); 1.55 (s, 6H, $C(CH_3)_2$); 3.23-3.31 (m, 2H, N-CH_2); 3.33-3.38 (m, 2H, N-CH_2); 3.71-3.74 (m, 2H, N-CH_2); 3.85 (s, 2H, N-CH_2); 4.31 (q, 2H, 7.2 Hz, CH_2CH_3); 7.18 (dd, *J* 8.9, 2.1 Hz, 1H, Ar); 7.35-7.40 (m, 2H, 2 Ar); 7.52-7.58 (m, 2H, 2 Ar); 8.09 (d, *J* 5.2 Hz, 1H, Ar); 8.43 (s, 1H, Ar).

M/Z $(M[^{35}Cl]+H)^+$: 567.0.

Example **107**: 3-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)isonicotinic acid



Example **107** was prepared according to general procedure (VII) starting from Example **106** (65 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) and freeze dried with HCl (0.1 N in water) to obtain Example **107** (45 mg, 68%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.34 (s, 6H, $C(CH_3)_2$); 1.55 (s, 6H, $C(CH_3)_2$); 3.38-3.46 (m, 4H, $2CH_2$); 3.75-3.81 (m, 2H, CH_2); 3.85 (s, 2H, CH_2), 7.18 (dd, *J* 8.9, 2.1 Hz, 1H, Ar); 7.32 (dd, *J* 11.9, 2.5 Hz, 1H, Ar); 7.38 (d, *J* 8.4 Hz, 1H, Ar); 7.55 (m, 2H, 2Ar); 7.73 (d, *J* 5.3 Hz, 1H, Ar), 8.19 (d, *J* 5.2 Hz, 1H, Ar); 8.51 (s, 1H, Ar).
M/Z (M[^{35}Cl]+H)$^+$: 538.9.

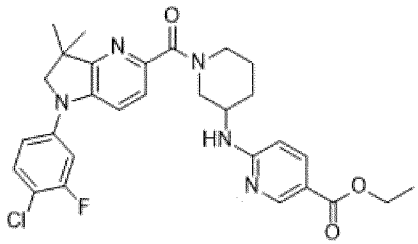
Compound **137**: ethyl 6-((1-((benzyloxy)carbonyl)piperidin-3-yl)amino)nicotinate

Compound **137** was prepared according to general procedure (Xb), starting from ethyl 6-chloronicotinate (300 mg) and benzyl 3-aminopiperidine-1-carboxylate (1.2 eq.). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **137** (330 mg, 53%) as a yellow oil.
M/Z (M+H)$^+$: 384.9

Compound **138**: ethyl 6-(piperidin-3-ylamino)nicotinate

A solution of of Compound **137** (330 mg) in EtOH (8.6 mL) was sparged with Argon for 5 minutes then Palladium on Charcoal (10% w/w, 0.1 eq) was added. The reaction mixture was stirred under a hydrogen atmosphere (1 Bar) for 16 hours, then filtered over a Celite pad which was rinsed with EtOAc (50 mL). The filtrate was concentrated under reduced pressure to obtain Compound 138 (207 mg, 97%) as a yellow oil.
M/Z (M+H)$^+$: 250.7.

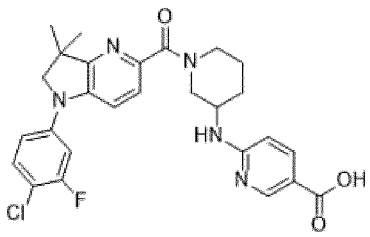
Example **108**: ethyl 6-((1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-3-yl)amino)nicotinate



Example **108** was prepared according to general procedure (VIIIb) starting from Compound **68** (75 mg), Compound **138** (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in MeTHF to obtain crude Example **108** (133 mg) as a beige solid.

M/Z (M[^{35}Cl]+H)$^{+}$: 553.0.

Example **109**: 6-((1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-3-yl)amino)nicotinic acid



Example **109** was prepared according to general procedure (VII) starting from Example **108** (187 µmol). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) and freeze dried with water to obtain Example **109** (73 mg, 75% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.23-1.27 (m, 6H, 2 CH_3); 1.56-1.70 (m, 2H, CH_2); 1.78-1.86 (m, 1H, C**H$_a$**H$_b$); 1.98-2.04 (m, 1H, CH$_a$**H$_b$**); 3.37-3.46 (m, 2H, CH_2); 3.71-3.78 (m, 3H, CH_2 + C**H$_a$**H$_b$); 3.88-3.95 (m, 1H, CH$_a$**H$_b$**); 3.97-4.09 (m, 1H, CH); 6.53-6.55 (d, *J* 8.1 Hz, 1H, Ar); 7.07-7.09 (m, 1H, Ar); 7.13-7.16 (m, 1H, Ar); 7.27-7.29 (m, 1H, Ar); 7.33-7.35 (m, 1H, Ar); 7.44-7.49 (m, 1H, Ar); 7.79 (d, *J* 8.3 Hz, 1H, Ar); 8.37 (bs, 1H, Ar). COOH and NH were not observed.

M/Z (M[^{35}Cl]+H)$^{+}$: 524.9.

Compound **139**: ethyl 6-((1-(tert-butoxycarbonyl)piperidin-3-yl)(methyl)amino)nicotinate

Compound **139** was prepared according to general procedure (Xb), starting from ethyl 6-chloronicotinate (300 mg) and tert-butyl 3-(methylamino)piperidine-1-carboxylate (1.2 eq.) to obtain crude Compound **139** (937 mg) as a brown oil.

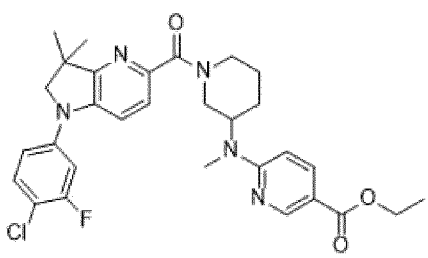
M/Z (M+H)$^{+}$: 364.8

Compound **140**: ethyl 6-(methyl(piperidin-3-yl)amino)nicotinate

Compound **140** was prepared according to general procedure (XII) starting from Compound **139** (1.62 mmol) in DCM using HCl in Et_2O. The crude was purified by flash chromatography (Biotage® KPNH, CyHex 100% to EtOAc 100%) to obtain Compound **140** (44 mg, 10% over 2 steps) as a yellow oil.

M/Z (M+H)$^{+}$: 264.7

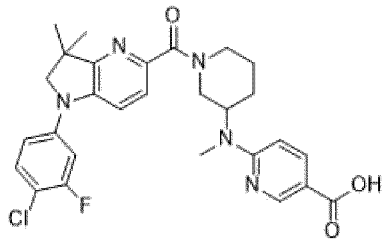
Example **110**: ethyl 6-((1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-3-yl)(methyl)amino)nicotinate



Example **110** was prepared according to general procedure (VIIIb) starting from Compound **68** (49 mg), Compound **140** (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in MeTHF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50/50) to obtain Example **110** (73 mg, 84%) as a yellow solid.

M/Z (M[^{35}Cl]+H)$^+$: 567.0.

Example **111**: 6-((1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-3-yl)(methyl)amino)nicotinic acid hydrochloride



Example **111** was prepared according to general procedure (VII) starting from Example **110** (73 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 60:40 to 40:60) and freeze dried with HCl (0.1 N in water) to obtain Example **111** (30 mg, 40%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) presence of rotamers δ: 0.98 (s, 1.5H, one rotamer of CH_3); 1.11 (s, 1.5H, other rotamer of CH_3); 1.34-1.36 (m, 3H, CH_3); 1.65-1.95 (m, 4H, 2 CH_2); 2.54-2.59 (m, 0.5H, one rotamer of C**H$_a$**H$_b$); 2.70-2.78 (m, 0.5H, other rotamer of C**H$_a$**H$_b$); 2.95-3.06 (m, 3.5H, CH_3 + one rotamer of CH$_a$**H$_b$**); 3.24-3.32 (m, 0.5H, other rotamer of CH$_a$**H$_b$**); 3.74 (s, 1H, C**H$_a$**H$_b$); 3.87 (s, 1H, CH$_a$H$_b$); 4.05-4.09 (m, 0.5H, one rotamer of C**H$_a$**H$_b$); 4.19-4.23 (m, 0.5H, other rotamer of CH$_a$H$_b$); 4.40-4.52 (m, 1H, CH$_a$**H$_b$**); 4.57-4.73 (m, 1H, CH); 6.73-6.77 (m, 0.5H, one rotamer of Ar); 6.90-6.93 (m, 0.5H, other rotamer of Ar); 7.12-7.21 (m, 1H, Ar); 7.24-7.26 (m, 1H, Ar); 7.41-7.44 (m, 1H, Ar); 7.50-7.59 (m, 2H, 2 Ar); 7.90-8.05 (m, 1H, Ar); 8.50-8.59 (m, 1H, Ar). COOH and HCl were not observed.

M/Z (M[^{35}Cl]+H)$^+$: 538.9.

Compound **141**: 2-(3-chloropyridin-2-yl)-2-ethylbutanenitrile

Compound **141** was prepared according to general procedure (I) from 3-chloro-2-fluoropyridine (1.0 g) and cyclopentanecarbonitrile. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **141** (1.28 g, 82%) as a clear oil.

M/Z (M[^{35}Cl]+H$^+$): 207.6.

Compound **142**: (1-(3-chloropyridin-2-yl)cyclopentyl)methanamine

Compound **142** (1.10 g, 85%) was obtained as a clear oil following general procedure (XVa), starting from Compound **141** (1.28 g).

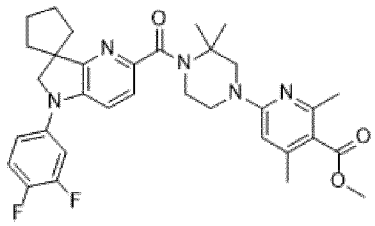
M/Z (M[^{35}Cl]+H$^+$): 211.6.

Compound **143**: 1'-(3,4-difluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **143** was prepared according to general procedure (Xc) from Compound **142** (400 mg) and 4-bromo-1,2-difluorobenzene. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 85:15) to obtain Compound **143** (181 mg, 33%) as a clear oil.
M/Z ($M+H^+$): 287.7.

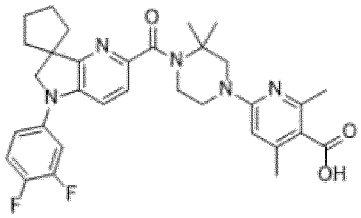
Compound **144**: 5'-bromo-1'-(3,4-difluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]
Compound **144** was prepared according to general procedure (XVI) in MeCN from Compound **143** (175 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **144** (150 mg, 67%) as a clear oil.
M/Z ($M[^{81}Br]+H)^+$: 367.6.

Example **112**: methyl 6-(4-(1'-(3,4-difluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



Example **112** was prepared according to general procedure (XIV) starting from Compound **144** (100 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to EtOAc 100%) to obtain Example **112** (145 mg) as a white solid.
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.80 (s, 6H, $(CH_3)_2$); 1.68-1.87 (m, 4H, 2 CH_2); 1.90-2.23 (m, 4H, 2 CH_2); 2.32 (s, 3H, CH_3); 2.48 (s, 3H, CH_3); 3.58-3.66 (m, 2H, N-CH_2); 3.80 (s, 2H, N-CH_2); 4.87 (s, 3H, O-CH_3); 3.93 (s, 2H, N-CH_2); 3.94-3.3.98 (m, 2H, N-CH_2); 6.08 (s, 1H, Ar); 6.88-6.94 (m, 1H, Ar); 6.97-7.04 (m, 1H, Ar); 7.08-7.23 (m, 1H, Ar); 7.26 (d, 1H, J 8.4 Hz, Ar); 7.48 (d, 1H, J 8.4 Hz, Ar).
M/Z ($M+H^+$): 591.0.

Example **113**: 6-(4-(1'-(3,4-difluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **113** was prepared according to general procedure (XI) starting from Example **112** (140 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **113** (45 mg, 19% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.52 (s, 6H, $(CH_3)_2$); 1.74-1.91 (m, 8H, $(CH_2)_4$); 2.34 (s, 3H, CH_3); 3.63-3.72 (m, 2H, CH_2); 3.85-3.91 (m, 4H, $(CH_2)_2$); 3.94 (s, 2H, CH_2); 6.76-6.90 (m, 1H, Ar); 7.13-7.17 (m, 1H, Ar); 7.34-7.41 (m, 2H, 2 Ar); 7.43-7.49 (m, 2H, 2 Ar). One CH_3 and COOH were not observed.

M/Z $(M+H)^+$: 577.0.

Compound **145**: tert-butyl 4-(4-(2-methoxy-2-oxoethyl)pyridin-2-yl)-2,2-dimethylpiperazine-1-carboxylate

Compound **145** was prepared according to general procedure (Xb), starting from methyl 2-(2-bromopyridin-4-yl)acetate (300 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The crude was directly engaged in the following step.

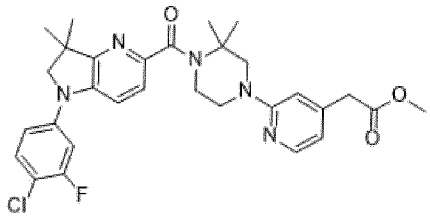
M/Z $(M+H)^+$: 364.6

Compound **146**: methyl 2-(2-(3,3-dimethylpiperazin-1-yl)pyridin-4-yl)acetate

Compound **146** was obtained as a brown solid (159 mg, 46% over 2 steps) according to general procedure (XII) starting from Compound **145** (261 mg) in DCM using TFA.

M/Z $(M+H)^+$: 264.6

Example **114**: methyl 2-(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-4-yl)acetate

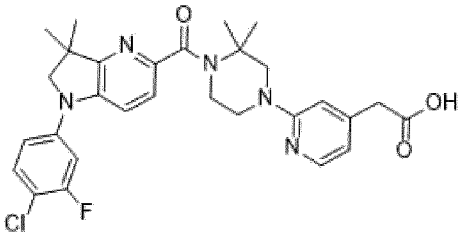


Example **114** was prepared according to general procedure (VIIIb) starting from Compound **68** (60 mg), Compound **146** (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in THF. The crude was purified by flash chromatography (Interchim® 50 µm, DCM 100% to DCM/MeOH 98:02) to obtain Example **114** (70 mg) as a yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.36 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 3.50-3.53 (m, 2H, N-CH_2); 3.60-3.63 (m, 5H, O-CH_3 + N-CH_2); 3.81-3.91 (m, 6H, $CH_2C(O)$ + 2 N-CH_2); 6.49-6.54 (m, 2H, 2 Ar); 7.17-7.21 (m, 1H, Ar); 7.30-7.37 (m, 2H, 2 Ar); 7.52-7.59 (m, 2H, 2 Ar); 8.01 (d, *J* 6.3 Hz, 1H, Ar).

M/Z $(M[^{35}Cl]+H)^+$: 567.0.

Example **115**: 2-(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-4-yl)acetic acid



Example **115** was prepared according to general procedure (VII) starting from Example **114** (65 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) and freeze dried with HCl (0.1 N in water) to obtain Example **115** (45 mg, 68%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.37 (s, 6H, 2 CH_3); 1.56 (s, 6H, 2 CH_3); 3.69-3.73 (m, 2H, CH_2); 3.76 (s, 2H, CH_2); 3.87 (s, 2H, CH_2); 3.94-3.98 (m, 4H, 2 CH_2); 6.91 (d, *J* 6.3 Hz, 1H, Ar); 7.17-7.21 (m, 1H, Ar); 7.33 (dd, *J* 11.7, 2.6 Hz, 2H, 2 Ar); 7.40 (d, *J* 8.4 Hz, 1H, Ar); 7.53-7.59 (m, 2H, 2 Ar); 7.99 (d, *J* 6.3 Hz, 1H, Ar). COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 553.0.

Compound **147**: tert-butyl 4-(6-(2-ethoxy-2-oxoethyl)pyridin-3-yl)-2,2-dimethylpiperazine-1-carboxylate

Compound **147** was prepared according to general procedure (Xb), starting ethyl 2-(5-bromopyridin-2-yl)acetate (300 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 65:35) to obtain Compound **147** (273 mg) as a brown solid which was directly engaged in the following step.

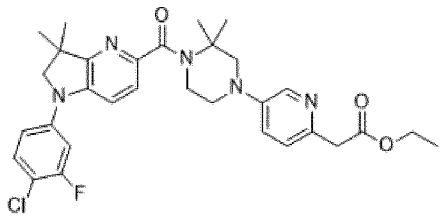
M/Z (M+H)$^+$: 378.9

Compound **148**: ethyl 2-(5-(3,3-dimethylpiperazin-1-yl)pyridin-2-yl)acetate hydrochloride

Compound **148** was prepared according to general procedure (XII) starting from Compound **147** (273 mg) in DCM using TFA. The crude product was dissolved in DCM (5 mL) and treated with HCl (2M in Et_2O, 3 mL) and concentrated under reduced pressure to obtain Compound **148** as a brown solid (149 mg, 41% over 2 steps)

M/Z (M+H)$^+$: 278.5

Example **116**: ethyl 2-(5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-2-yl)acetate

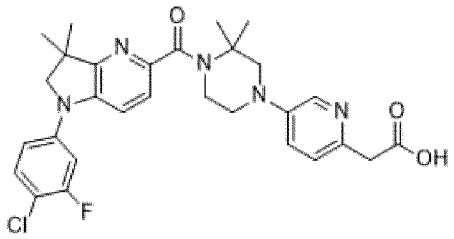


Example **116** was prepared according to general procedure (VIIIb) starting from Compound **68** (60 mg), Compound **148** (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in THF. The crude was purified by flash chromatography (Interchim® 50 µm, DCM 100% to DCM/MeOH 98:02) to obtain Example **116** (60 mg, 55%) as a yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.17 (t, 3H, *J* 7.2 Hz, CH_2CH_3); 1.35 (s, 6H, 2 CH_3); 1.52 (s, 6H, 2 CH_3); 3.33-3.44 (m, 2H, N-CH_2); 3.54 (s, 2H, $CH_2C(O)$); 3.66 (s, 2H, N-CH_2); 3.79-3.86 (m, 4H, 2 N-CH_2); 4.05 (q, 2H, *J* 7.2 Hz, CH_2CH_3); 7.14-7.21 (m, 3H, 3 Ar); 7.30-7.37 (m, 2H, 2 Ar); 7.53-7.59 (m, 2H, 2 Ar); 8.05 (s, 1H, Ar). COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 581.0.

Example **117**: 2-(5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-2-yl)acetic acid



Example **117** was prepared according to general procedure (VII) starting from Example **116** (60 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) and freeze dried with HCl (0.1 N in water) to obtain Example **117** (42 mg, 69%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.36 (s, 6H, 2 CH_3); 1.54 (s, 6H, 2 CH_3); 3.51-3.54 (m, 2H, CH_2); 3.74 (s, 2H, CH_2); 3.87-3.93 (m, 4H, 2 CH_2); 4.00 (s, 2H, CH_2); 7.17-7.21 (m, 1H, Ar); 7.33 (dd, *J* 11.9, 2.5 Hz, 1H, Ar); 7.38 (d, *J* 8.4 Hz, 1H, Ar); 7.53-7.59 (m, 2H, 2 Ar); 7.74 (d, *J* 9.0 Hz, 1H, Ar); 7.88-7.92 (m, 1H, Ar); 8.23-8.24 (m, 1H, Ar). COOH was not observed.

M/Z ($M[^{35}Cl]+H)^{+\cdot}$: 552.9.

Compound **149**: 1-(3-chloropyridin-2-yl)cyclobutane-1-carbonitrile

Compound **149** was prepared according to general procedure (I) from 3-chloro-2-fluoropyridine (1.0 g) and cyclobutanecarbonitrile. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **149** (0.76 g, 52%) as a clear oil.

M/Z ($M[^{35}Cl]+H^+$): 193.6

Compound **150**: (1-(3-chloropyridin-2-yl)cyclobutyl)methanamine

Compound **150** (293 mg, 38%) was obtained as a yellow oil following general procedure (XVa), starting from Compound **149** (756 mg).

M/Z ($M[^{35}Cl]+H^+$): 197.6.

Compound **151**: 1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **150** was prepared according to general procedure (Xc) from Compound **149** (293 mg) and 4-bromo-1-chloro-2-fluorobenzene. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **151** (187 mg, 43%) as a yellow oil.

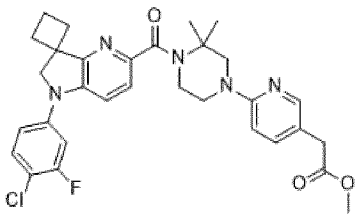
M/Z ($M[^{35}Cl]+H^+$): 287.7.

Compound **152**: 5'-bromo-1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **152** was prepared according to general procedure (XVI) in MeCN from Compound **151** (187 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 90:10) to obtain Compound **152** (151 mg, 63%) as a yellow oil.

M/Z ($M[^{35}Cl][^{81}Br]+H)^{+\cdot}$: 369.6.

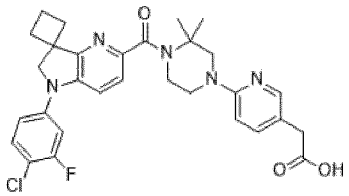
Example **118**: methyl 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



Example **118** was prepared according to general procedure (XIV) starting from Compound **152** (70 mg) and Compound **111** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Example **118** (51 mg) as a white solid.

M/Z $(M[^{35}Cl]+H)^+$: 579.0

Example **119**: 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **119** was prepared according to general procedure (VII) starting from Example **118** (50 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 95:05 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **119** (28 mg, 24% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6 + D_2O, 300 MHz) δ: 1.53 (s, 6H, $(CH_3)_2$); 1.98-2.08 (m, 3H, CH+CH_2); 2.19-2.23 (m, 3H, CH+CH_2); 2.41-2.44 (m, 2H, $CH_2C(O)$); 3.56 (s, 2H, N-CH_2); 3.63-3.66 (m, 2H, N-CH_2); 3.93-3.99 (m, 2H, N-CH_2); 4.14 (bs, 2H, N-CH_2); 7.14-7.18 (m, 2H, 2 Ar); 7.24-7.27 (m, 1H, Ar); 7.34-7.37 (m, 1H, Ar); 7.48-7.53 (m, 2H, 2 Ar); 7.92-7.95 (m, 2H, 2 Ar). COOH was not observed.

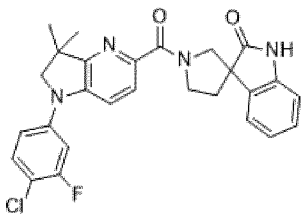
M/Z $(M[^{35}Cl]+H)^+$: 564.9

Compound **153**: spiro[indoline-3,3'-pyrrolidin]-2-one hydrochloride

Compound **153** was prepared according to general procedure (XII) starting from tert-butyl 2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carboxylate (100 mg) in DCM using TFA. The crude product was dissolved in DCM (5 mL) and treated with HCl (2M in Et_2O, 3 mL) and concentrated under reduced pressure to obtain Compound **153** as a yellow solid (77 mg, 99%)

M/Z $(M+H)^+$: not observed

Example **120**: 1'-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)spiro[indoline-3,3'-pyrrolidin]-2-one



Example **120** was prepared according to general procedure (VIIIb) starting from Compound **68** (60 mg), Compound **153** (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in MeTHF. The crude was purified by flash chromatography (Interchim® 50 µm, DCM 100% to DCM/MeOH 98:02) then further purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 50:50 to 10:90) and freeze dried with HCl (0.1 N in water) to obtain Example **120** (63 mg, 64%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.24-1.25 (m, 3H, CH_3); 1.38-1.39 (m, 3H, CH_3); 2.11-2.34 (m, 2H, CH_2); 3.74-3.84 (m, 2H, N-CH_2); 3.90-3.95 (m, 2H, N-CH_2); 3.99-4.07 (m, 1H, N-C$\mathbf{H_a}H_b$); 4.21-4.36 (m, 1H, N-$CH_a\mathbf{H_b}$); 6.84-6.90 (m, 1H, Ar); 6.95-7.03 (m, 1H, Ar); 7.15-7.39 (m, 4H, 4 Ar); 7.51-7.59 (m, 3H, 3 Ar); 10.51-10.56 (m, 1H, NH).

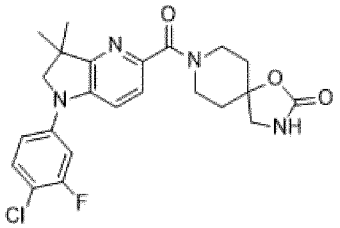
M/Z (M[^{35}Cl]+H)$^+$: 491.8.

Compound **154**: 1-oxa-3,8-diazaspiro[4.5]decan-2-one hydrochloride

Compound **154** was prepared according to general procedure (XII) starting tert-butyl 2-oxo-1-oxa-3,8-diazaspiro[4.5]decane-8-carboxylate (100 mg) in DCM using TFA. The crude product was dissolved in DCM (5 mL) and treated with HCl (2M in Et_2O, 3 mL) and concentrated under reduced pressure to obtain Compound **154** as a yellow oil (74 mg, 99%)

M/Z (M+H)$^+$: not observed

Example **121**: 8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one



Example **121** was prepared according to general procedure (VIIIb) starting from Compound **68** (60 mg), Compound **154** (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in MeTHF. The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 60:40 to 20:80) and freeze dried with HCl (0.1 N in water) to obtain Example **121** (20 mg, 22%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.33 (s, 6H, 2 CH_3); 1.77-1.90 (m, 4H, 2 CH_2); 3.31 (s, 2H, CH_2); 3.45-3.56 (m, 2H, CH_2); 3.75-4.00 (m, 4H, 2 CH_2); 7.17-7.20 (m, 1H, Ar); 7.31-7.36 (m, 1H, Ar); 7.39-7.42 (m, 1H, Ar); 7.52-7.59 (m, 3H, Ar + NH).

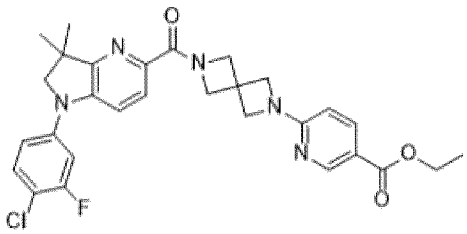
M/Z (M[^{35}Cl]+H)$^+$: 459.7.

Compound **155**: tert-butyl 6-(5-(ethoxycarbonyl)pyridin-2-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate

Compound **155** was prepared according to general procedure (Xb), starting from ethyl 6-chloronicotinate (200 mg) and tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (1.2 eq.). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **155** (242 mg, 65%) as a yelow oil.
M/Z $(M+H)^+$: 348.8

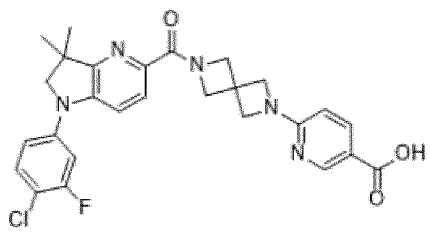
Compound **156**: ethyl 6-(2,6-diazaspiro[3.3]heptan-2-yl)nicotinate
Compound **156** was prepared according to general procedure (XII) starting from Compound **155** (242 mg) in DCM using TFA. The reaction mixture was concentrated under reduced pressure to obtain the crude Compound **156** (135 mg) as a brown solid.
M/Z $(M+H)^+$: 248.7

Example **122**: ethyl 6-(6-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-2,6-diazaspiro[3.3]heptan-2-yl)nicotinate



Example **122** was prepared according to general procedure (VIIIb) starting from Compound **68** (60 mg), Compound **156** (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in THF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **122** (85 mg, 83%) as a yellow solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.28 (t, *J* 7.2 Hz, 3H, CH_2CH_3); 1.36 (s, 6H, 2 CH_3); 3.88 (s, 2H, N-CH_2); 4.21-4.30 (m, 8H, CH_2CH_3 + 3 N-CH_2); 4.86 (s, 2H, N-CH_2); 6.37 (d, *J* 8.8 Hz, 1H, Ar); 7.18-7.22 (m, 1H, Ar); 7.32-7.37 (m, 1H, Ar); 7.53-7.59 (m, 2H, 2 Ar); 7.72 (d, *J* 8.4 Hz, 1H, Ar); 7.92-7.96 (m, 1H, Ar); 8.61 (m, 1H, Ar).
M/Z $(M[^{35}Cl]+H)^+$: 551.0.

Example **123**: 6-(6-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-2,6-diazaspiro[3.3]heptan-2-yl)nicotinic acid



Example **123** was prepared according to general procedure (VII) starting from Example **122** (60 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) and freeze dried with HCl (0.1 N in water) to obtain Example **123** (42 mg, 69%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.36 (s, 6H, 2 CH_3); 3.88 (s, 2H, CH_2); 4.20-4.28 (m, 6H, 3 CH_2); 4.86 (s, 2H, CH_2); 6.37 (d, *J* 8.8 Hz, 1H, Ar); 7.18-7.22 (m, 1H, Ar); 7.32-7.37 (m, 1H, Ar); 7.53-7.59 (m, 2H, 2 Ar); 7.72 (d, *J* 8.4 Hz, 1H, Ar); 7.90-7.94 (m, 1H, Ar); 8.59 (m, 1H, Ar). COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 522.8.

Compound **157**: methyl 1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylate

Compound **157** was prepared according to general procedure (XIX) starting from Compound **152** (230 mg). The crude Compound **157** (217 mg) was obtained as a red solid and was directly engaged in the following step.

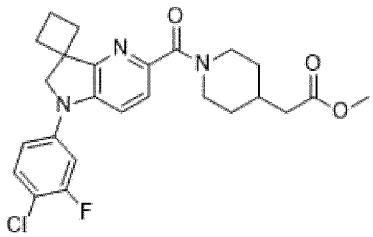
M/Z (M[^{35}Cl]+H)$^+$: 347.7

Compound **158**: 1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carboxylic acid

Compound **158** was prepared according to general procedure (VII) starting from Compound **157** (217 mg). The crude Compound **158** (160 mg, 72%) was obtained as an orange solid.

M/Z (M[^{35}Cl]+H)$^+$: 333.6

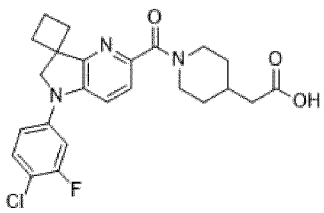
Example **124**: methyl 2-(1-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)piperidin-4-yl)acetate



Example **124** was prepared according to general procedure (VIIIb) starting from Compound **158** (100 mg), methyl 2-(piperidin-4-yl)acetate (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in MeTHF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to EtOAc 100%) to obtain Example **124** (69 mg, 49%) as a clear oil.

M/Z (M[^{35}Cl]+H)$^+$: 472.7

Example **125**: 2-(1-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)piperidin-4-yl)acetic acid

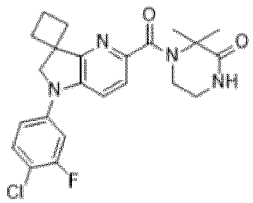


Example **125** was prepared according to general procedure (VII) starting from Example **124** (65 mg). The crude was suspended in Et_2O (5 mL), the solid was isolated by filtration then freeze dried in HCl (0.1 N in water) to obtain Example **125** (40 mg, 59%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.15-1.33 (m, 2H, CH_2); 1.66-1.82 (m, 2H, CH_2); 1.90-2.02 (m, 2H, CH_2); 2.04-2.15 (m, 1H, CH); 2.19-2.21 (m, 2H, CH_2); 2.24-2.31 (m, 2H, CH_2); 2.36-2.43 (m, 2H, CH_2); 2.74-2.84 (m, 1H, CH); 3.03-3.12 (m, 1H, CH); 4.11-4.17 (m, 3H, CH_2, CH); 4.42-4.47 (m, 1H, CH); 7.17 (dd, *J* 8.7, 2.1 Hz, 1H, Ar); 7.30 (dd, *J* 11.7, 2.1 Hz, 1H, Ar); 7.35 (d, *J* 8.7 Hz, 1H, Ar); 7.50-7.56 (m, 2H, 2 Ar); 12.10 (bs, 1H, CO_2H).

M/Z (M[^{35}Cl]+H)$^+$: 458.8.

Example **126**: 4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one

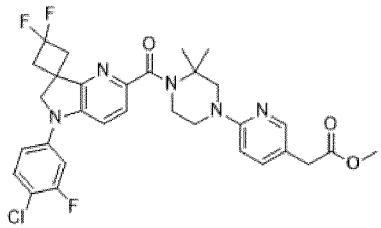


Example **126** was prepared according to general procedure (VIIIb) starting from Compound **158** (50 mg), 3,3-dimethylpiperazin-2-one (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in MeTHF. The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with water to obtain Example **126** (15 mg, 22%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.67 (s, 6H, $(CH_3)_2$); 1.97-2.10 (m, 2H, CH_2); 2.25-2.31 (m, 2H, CH_2); 2.30-2.35 (m, 2H, CH_2); 3.34-3.39 (m, 2H, CH_2); 3.56-3.60 (m, 2H, CH_2); 4.18 (s, 2H, CH_2); 7.17 (dd, *J* 8.7, 2.4 Hz, 1H, Ar); 7.31 (dd, *J* 11.7, 2.4 Hz, 1H, Ar); 7.41 (d, J 8.7 Hz, 1H, Ar); 7.51-7.57 (m, 2H, 2 Ar), 8.08 (bs, 1H, NH).

M/Z (M[^{35}Cl]+H)$^+$: 443.7

Example **127**: methyl 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-difluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

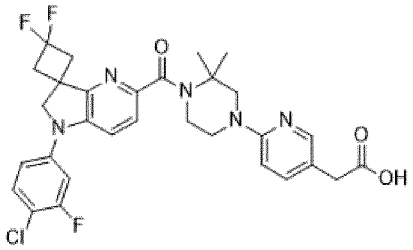


Example **127** was prepared according to general procedure (XIV) starting from Compound **125** (70 mg) and Compound **111** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Example **127** (106 mg, 51%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.52 (s, 6H, $(CH_3)_2$); 2.92-3.14 (m, 4H, $(CH_2)_2$); 3.45-3.58 (m, 4H, 2 N-CH_2); 3.61 (s, 2H, $CH_2C(O)$); 3.80-3.87 (m, 5H, N-CH_2 + OCH_3); 4.32 (s, 2H, N-CH_2); 6.54 (d, *J* 8.7 Hz, 1H, Ar); 7.19-7.21 (m, 1H, Ar); 7.33-7.45 (m, 3H, 3 Ar); 7.53-7.60 (m, 2H, 2 Ar); 7.90-7.94 (m, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 614.9

Example **128**: 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-difluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **128** was prepared according to general procedure (VII) starting from Example **127** (50 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 95:05 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **128** (40 mg, 39%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.56 (s, 6H, $(CH_3)_2$); 2.92-3.17 (m, 4H, $(CH_2)_2$); 3.60-3.65 (m, 2H, $CH_2C(O)$); 3.65-3.69 (m, 2H, N-CH_2); 3.75-3.91 (m, 4H, 2 N-CH_2); 4.33 (s, 2H, N-CH_2); 7.19-7.29 (m, 2H, 2 Ar); 7.34-7.37 (m, 1H, Ar); 7.43-7.46 (m, 1H, Ar); 7.54-7.61 (m, 2H, 2 Ar); 7.90-7.94 (m, 2H, 2 Ar). COOH was not observed

M/Z (M[^{35}Cl]+H)$^+$: 600.4

Compound **159**: benzyl (1R,5S)-3-(2-ethoxy-2-oxoethylidene)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a solution of Sodium Hydride (60% in mineral oil, 154 mg) in THF (2 mL) at 0°C was added dropwise a solution of ethyl 2-(diethoxyphosphoryl)acetate (865 mg) in THF (5 mL) the reaction mixture was stirred at 0°C for 10 minutes then a solution of Benzyl (1S,5R)-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (500 mg) in THF (5 mL) was added and the reaction mixture was stirred at 25°C for 5 hours. The reaction mixture was quenched with water (50 mL) then extracted with EtOAc (50 mL). The organic layer was washed with brine (50 mL), dried over $MgSO_4$ then concentrated under reduced pressure. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **159** (488 mg, 77%) as a clear oil.

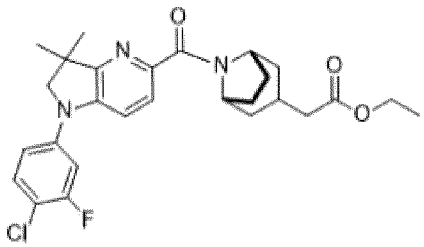
M/Z (M+H)$^+$: 330.8.

Compound **160**: ethyl 2-((1R,5S)-8-azabicyclo[3.2.1]octan-3-yl)acetate

A solution of of Compound **159** (488 mg) in EtOH (4 mL) was sparged with Argon for 5 minutes then Palladium on Charcoal (10% w/w, 0.1 eq) was added. The reaction mixture was stirred under a hydrogen atmosphere (1 Bar) for 16 hours, then filtered over a Celite pad which was rinsed with EtOAc (50 mL). The filtrate was concentrated under reduced pressure. The crude was purified by flash chromatography (Interchim® 50 µm, DCM 100% to DCM/MeOH 80:20) to obtain Compound **160** (190 mg, 65%) as a yellow oil.

M/Z (M+H)$^+$: 198.7.

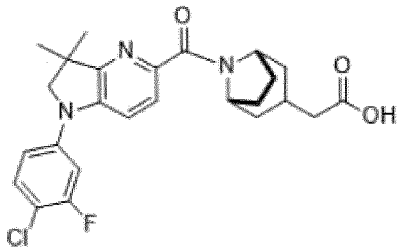
Example **129**: ethyl 2-((1R,5S)-8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)acetate



Example **129** was prepared according to general procedure (VIIIb) starting from Compound **68** (90 mg), and Compound **160** (1.1 eq.), and N,N-diisopropylethylamine (3.0 eq.) in MeTHF. The crude Example **129** (180 mg) was obtained as yellow oil and directly engaged in the following step.

M/Z (M[^{35}Cl]+H)$^{+}$: 500.9

Example **130**: 2-((1R,5S)-8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)acetic acid



Example **130** was prepared according to general procedure (VII) starting from Example **129** (141 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain the diasteroisomere mixture (85:15) Example **130** (74 mg, 56% over 2 steps) as a white solid.

^{1}H-NMR (MeOD-d_4, 300 MHz) δ: 1.42 (s, 6H, CH_3 x2); 1.48-1.57 (m, 1.5H); 1.72-1.82 (m, 0.5H); 1.83-2.12 (m, 4H); 2.13-2.52 (m, 4H); 2.52-2.67 (m, 1H); 3.86 (s, 2H, CH_2); 4.69-4.86 (m, 2H); 7.11-7.19 (m, 1H, Ar); 7.20 (dd, *J* 11.7, 2.5 Hz, 1H, Ar); 7.46 (t, *J* 8.7, 1H, Ar); 7.48-7.62 (m, 2H, 2 Ar); COOH was not observed.

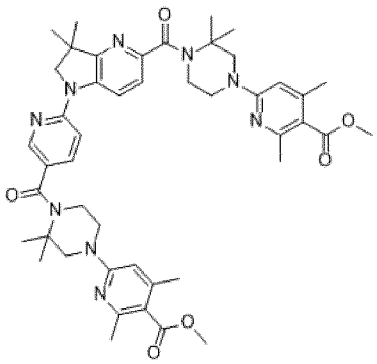
M/Z (M[^{35}Cl]+H)$^{+}$: 472.3

Compound **161**: 5-chloro-1-(5-chloropyridin-2-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

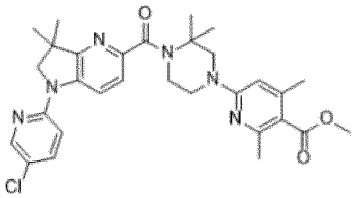
Compound **161** was prepared according to general procedure (X) starting from Compound **70** (350 mg) and 2-bromo-5-chloropyridine (2.0 eq) with ^{t}BuONa (3.0 eq) at 100°C for 18 hours. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/DCM 0:100) to obtain Compound **161** (150 mg, 62%) as a beige solid.

M/Z (M[^{35}Cl]+H)$^{+}$: 294.6.

Example **131**: methyl 6-(4-(6-(5-(4-(5-(methoxycarbonyl)-4,6-dimethylpyridin-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)nicotinoyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



And Example **132**: methyl 6-(4-(1-(5-chloropyridin-2-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



Example **131** and Example **132** were prepared according to general procedure (XIV) starting from Compound **161** (75 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 20:80) to obtain Example **131** (76 mg, 36%) as a white solid and Example **132** (40 mg, 28%) as a white solid.

Example **131**:

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.39 (s, 6H, 2 CH_3); 1.49 (s, 12H, 4 CH_3); 2.23 (s, 6H, 2 CH_3); 2.33 (s, 6H, 2 CH_3); 3.47-3.59 (m, 6H, 3 N-CH_2); 3.76-3.83 (m, 4H, 2 N-CH_2); 3.87-3.92 (m, 4H, 2 N-CH_2); 3.98 (s, 2H, N-CH_2); 6.36 (s, 2H, 2 Ar); 6.97 (d, *J* 8.9 Hz, 1H, Ar); 7.43 (d, *J* 8.4 Hz, 1H, Ar); 7.85 (dd, *J* 8.9, 2.2 Hz, 1H, Ar); 8.43 (d, *J* 2.2 Hz, 1H, Ar); 8.59 (d, *J* 8.4 Hz, 1H, Ar);

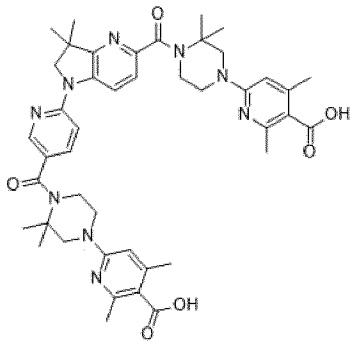
M/Z $(M+H)^+$: 833.7

Example **132**:

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.39 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 2.24 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 3.53-3.60 (m, 2H, N-CH_2); 3.76-3.84 (m, 5H, O-CH_3 + N-CH_2); 3.89 (s, 2H, N-CH_2); 3.93 (s, 2H, N-CH_2); 6.37 (s, 1H, Ar); 7.00 (d, *J* 9.1 Hz, 1H, Ar); 7.42 (d, *J* 8.5 Hz, 1H, Ar); 7.88 (dd, *J* 9.1, 2.5 Hz, 1H, Ar); 8.39 (d, *J* 2.5 Hz, 1H, Ar); 8.47 (d, *J* 8.5 Hz, 1H, Ar);

M/Z $(M[^{35}Cl]+H)^+$: 549.3.

Example **133**: 6-(4-(6-(5-(4-(5-carboxy-4,6-dimethylpyridin-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)nicotinoyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid

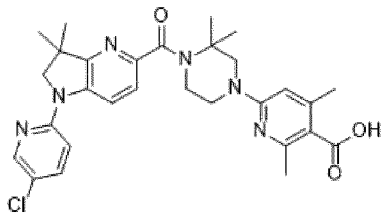


Example **133** was prepared according to general procedure (XI) starting from Example **131** (76 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 90:10 to 50:50) and freeze dried with HCl (0.1 N in water) to obtain Example **133** (3 mg, 4%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.40 (s, 6H, 2 CH_3); 1.50 (s, 12H, 4 CH_3); 2.26 (s, 6H, 2 CH_3); 2.37 (s, 6H, 2 CH_3); 3.49-3.58 (m, 4H, 2 N-CH_2); 3.76-3.83 (m, 4H, 2 N-CH_2); 3.87-3.89 (m, 4H, 2 N-CH_2); 3.97 (s, 2H, N-CH_2); 6.34 (s, 2H, 2 Ar); 6.99 (d, *J* 8.9 Hz, 1H, Ar); 7.44 (d, *J* 8.4 Hz, 1H, Ar); 7.86 (dd, *J* 8.9, 2.2 Hz, 1H, Ar); 8.45 (d, *J* 2.2 Hz, 1H, Ar); 8.6 (d, *J* 8.4 Hz, 1H, Ar). 2 COOH signals were not observed.

M/Z (M+2H)/2$^+$: 403.0.

Example **134**: 6-(4-(1-(5-chloropyridin-2-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid

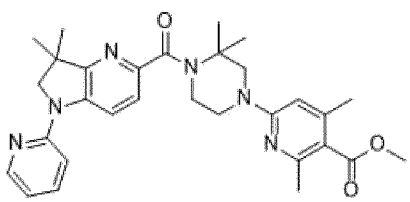


Example **134** was prepared according to general procedure (XI) starting from Example **132** (70 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) and freeze dried with HCl (0.1 N in water) to obtain Example **133** (25 mg, 36%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.38 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 2.26 (s, 3H, CH_3); 2.37 (s, 3H, CH_3); 3.53-3.56 (m, 2H, N-CH_2); 3.79-3.82 (m, 2H, N-CH_2); 3.89 (s, 2H, N-CH_2); 3.92 (s, 2H, N-CH_2); 6.34 (s, 1H, Ar); 7.00 (d, *J* 9.1 Hz, 1H, Ar); 7.42 (d, *J* 8.5 Hz, 1H, Ar); 7.88 (dd, *J* 9.1, 2.5 Hz, 1H, Ar); 8.39 (d, *J* 2.5 Hz, 1H, Ar); 8.47 (d, *J* 8.5 Hz, 1H, Ar). COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 549.3.

Example **135**: methyl 6-(4-(3,3-dimethyl-1-(pyridin-2-yl)-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



To a solution of Example **132** (20 mg) in dioxane (1 mL), was added potassium trifluoro(vinyl)borate (6 mg) and potassium carbonate (1.2 M in water, 89 µL). The reaction mixture was sparged with Argon for 10 minutes then Bis(tri-tert-butylphosphine)palladium (2 mg) was added and the reaction mixture was heated at 130°C for 96 hours, then filtered over celite, and concentrated under reduced pressure. The residue was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) and freeze dried with water to obtain Example **135** (3 mg, 17%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.39 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 2.24 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 3.54-3.59 (m, 2H, N-CH_2); 3.78 (s, 3H, CH_3); 3.81-3.85 (m, 2H, N-CH_2); 3.90-3.92 (m, 4H, 2 N-CH_2); 6.37 (s, 1H, Ar); 694-6.98 (m, 2H, 2 Ar); 7.42 (d, *J* 8.4 Hz, 1H, Ar); 7.75-7.81 (m, 1H, Ar); 8.35-8.38 (m, 1H, Ar); 8.55 (d, *J* 8.4 Hz, 1H, Ar).

M/Z $(M+H)^+$: 529.5.

Compound **162**: 1'-(tert-butyl) 3'-ethyl 5',6'-dihydro-[2,4'-bipyridine]-1',3'(2'H)-dicarboxylate

To a solution of 1-(tert-butyl) 3-ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1,3(2H)-dicarboxylate (579 mg) in dioxane (12 mL) was added 2-bromopyridine (200 mg) and potassium carbonate (1.2 M in water, 3.16 mL). The reaction was sparged with argon for 10 min then $Pd(dppf)Cl_2$ (93 mg) was added and the reaction mixture was heated at 100 °C for 16 hour. The reaction mixture was quenched with NH4Cl sat. (50 mL) then extracted with EtOAc (2*50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash chromatography (Interchim® 50 µm, DCM 100% to DCM/MeOH 98:2) to obtain Compound **162** (250 mg, 60%) as a yellow oil.

M/Z $(M+H)^+$: 333.7.

Compound **163**: ethyl 1',2',5',6'-tetrahydro-[2,4'-bipyridine]-3'-carboxylate hydrochloride

Compound **163** was prepared according to general procedure (XII) starting from Compound **162** (250 mg) using HCl in Et_2O. The crude Compound 163 was obtained as a yellow solid (250 mg) and diretcly engaged in the following step.

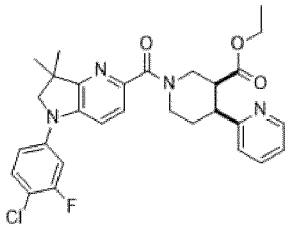
M/Z $(M+H)^+$: 233.7.

Compound **164**: ethyl (cis)-4-(pyridin-2-yl)piperidine-3-carboxylate

A solution of of Compound **163** (250 mg) in EtOH (7.5 mL) was sparged with Argon for 5 minutes then Palladium on Charcoal (10% w/w, 0.1 eq) was added. The reaction mixture was stirred under a hydrogen atmosphere (1 Bar) for 48 hours, then filtered over a Celite pad which was rinsed with MeOH (50 mL). The filtrate was concentrated under reduced pressure to obtain Compound **164** (280 mg) as a yellow oil.

M/Z $(M+H)^+$: 235.1.

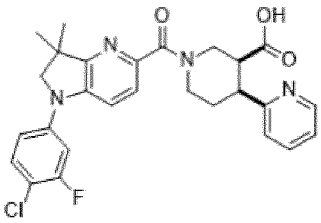
Example **136**: ethyl 1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-4-(pyridin-2-yl)piperidine-3-carboxylate



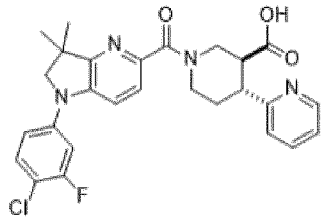
Example **136** was prepared according to general procedure (VIIIb) starting from Compound **68** (93 mg), and Compound **164** (1.1 eq.), and N,N-diisopropylethylamine (5.0 eq.) in MeTHF. The crude Example **136** (30 mg) was obtained as yellow solid and directly engaged in the following step.

M/Z (M[^{35}Cl]+H)$^{+\cdot}$: 537.9

Example **137** (cis)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-4-(pyridin-2-yl)piperidine-3-carboxylic acid



And Example **138**: (trans)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-4-(pyridin-2-yl)piperidine-3-carboxylic acid



Example **137** and Example **138** were prepared according to general procedure (VII) starting from Example **136** (30 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 40:60) and freeze dried with water to obtain Example **137** (3 mg, 2% over 4 steps) as a white solid and Example **138** (5 mg, 4% over 4 steps) as a white solid.

Example **137**:

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.34 (s, 6H, CH_3 x2); 1.94-2.10 (m, 1H); 2.24-2.39 (m, 1H); 3.05-3.22 (m, 2H); 3.57-3.66 (m, 1H); 3.68-3.93 (m, 4H); 4.24-4.55 (m, 1H); 7.15-7.17 (m, 1H, Ar); 7.18-7.36 (m, 3H, 3 Ar); 7.36-7.51 (m, 1H, Ar); 7.52-7.58 (m, 2H, 2 Ar); 7.71-7.86 (bs, 1H, Ar); 8.41-8.54 (bs, 1H, Ar); COOH was not observed.

M/Z (M[^{35}Cl]+H)$^{+\cdot}$: 509.4

Example **138**:

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.18-1.42 (m, 6H, CH_3 x2); 1.57-1.95 (m, 2H, pyr-CH-CH_2-CH_2); 2.80-3.10 (m, 2H); 3.10-3.22 (m, 2H); 3.79-3.93 (m, 2H, Me_2C-CH_2-N-Ar); 4.13-4.26 (m, 0.5H); 4.53-4.72 (m, 1H); 4.72-4.85 (m, 0.5H); 6.41-6.66 (bs, 0.3H); 7.14-7.27 (m, 2H, Ar x2); 7.27-7.39 (m, 2H, Ar x2); 7.39-7.50 (m, 1H, Ar); 7.50-7.62 (m, 2H, Ar x2); 7.73 (t, *J* 7.4 Hz, 1H, Ar); 8.48-8.50 (m, 2H, 2 Ar); 11.86-12.66 (bs, 1H, COOH).

M/Z (M[^{35}Cl]+H)$^{+\cdot}$: 509.3

Compound **165**: tert-butyl 4-(6-(methoxycarbonyl)-5-methylpyridin-2-yl)-2,2-dimethylpiperazine-1-carboxylate

Compound **165** was prepared according to general procedure (Xb), starting from methyl 6-chloro-3-methylpicolinate (217 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The crude Compound **165** (585 mg) was obtained as a yellow oil and engaged directly in the following step.

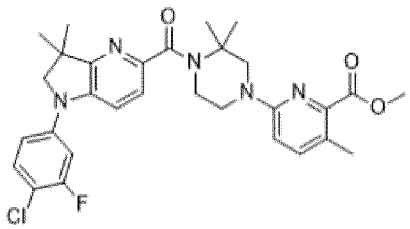
M/Z $(M+H)^+$: 364.2

Compound **166**: methyl 6-(3,3-dimethylpiperazin-1-yl)-3-methylpicolinate

Compound **166** was prepared according to general procedure (XII) starting from Compound **165** (585 mg) in DCM using TFA. The reaction mixture was concentrated under reduced pressure to obtain the crude Compound **166** (522 mg) as a brown oil.

M/Z $(M+H)^+$: 264.7

Example **139**: methyl 6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-3-methylpicolinate

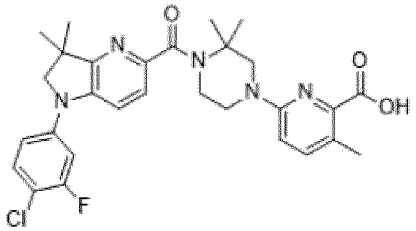


Example **139** was prepared according to general procedure (XIV) starting from Compound **71** (100 mg) and Compound **166** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **139** (106 mg) as an orange solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, 2 CH_3); 1.49 (s, 6H, 2 CH_3); 2.25 (s, 3H, CH_3); 3.51-3.57 (m, 2H N-CH_2); 3.81-3.86 (m, 9H, OCH_3 + 3 N-CH_2); 6.79 (d, *J* 8.7 Hz, 1H, Ar); 7.18 (dd, *J* 8.7, 2.9 Hz, 1H, Ar); 7.30-7.37 (m, 2H, 2 Ar); 7.37-7.58 (m, 3H, 3 Ar);

M/Z $(M[^{35}Cl]+H)^+$: 566.4.

Example **140**: 6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-3-methylpicolinic acid



Example **140** was prepared according to general procedure (XI) starting from Example **139** (106 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **140** (39 mg, 21%) as a yellow solid.

^{1}H-NMR (DMSO-d_6 +D_2O, 300 MHz) δ: 1.33 (s, 6H, 2 CH_3); 1.48 (s, 6H, 2 CH_3); 2.31 (s, 3H, CH_3); 3.52-3.59 (m, 2H N-CH_2); 3.78-3.81 (m, 6H, 3 N-CH_2); 6.84 (d, *J* 8.8 Hz, 1H, Ar); 7.16 (dd, *J* 8.8, 2.9 Hz, 1H, Ar); 7.25-7.35 (m, 2H, 2 Ar); 7.52-7.56 (m, 3H, 3 Ar); COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 552.4.

Compound **167**: tert-butyl 4-(6-methoxy-5-(methoxycarbonyl)pyridin-3-yl)-2,2-dimethylpiperazine-1-carboxylate

Compound **167** was prepared according to general procedure (Xb), starting from methyl 5-chloro-2-methoxynicotinate (287 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The crude Compound **167** (630 mg) was obtained as a brown oil and engaged directly in the following step.

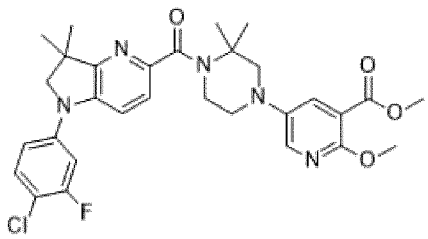
M/Z (M+H)$^+$: 364.2

Compound **168**: methyl 5-(3,3-dimethylpiperazin-1-yl)-2-methoxynicotinate

Compound **168** was prepared according to general procedure (XII) starting from Compound **167** (585 mg) in DCM using TFA. The reaction mixture was concentrated under reduced pressure to obtain the crude Compound **168** (198 mg) as a brown oil.

M/Z (M+H)$^+$: 264.7

Example **141**: methyl 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2-methoxynicotinate

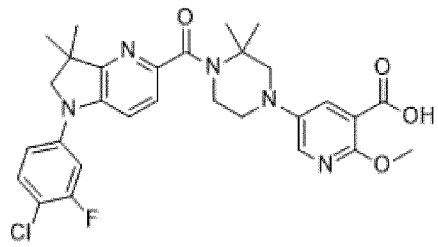


Example **141** was prepared according to general procedure (XIV) starting from Compound **71** (100 mg) and Compound **168** (1.9 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 45:55) to obtain Example **141** (80 mg) as a yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.34 (s, 6H, 2 CH_3); 1.51 (s, 6H, 2 CH_3); 3.32-3.40 (m, 4H, 2 N-CH_2); 3.73-3.78 (m, 2H, N-CH_2); 3.77 (s, 3H, O-CH_3); 3.79 (s, 3H, O-CH_3); 3.82-3.85 (s, 2H, N-CH_2); 7.16-7.20 (m, 1H, Ar); 7.30-7.36 (m, 2H, 2 Ar); 7.51-7.59 (m, 3H, 3 Ar); 7.93-7.94 (m, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 582.5.

Example **142**: 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2-methoxynicotinic acid



Example **142** was prepared according to general procedure (XI) starting from Example **141** (80 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **142** (29 mg, 15%) as a yellow solid.

^{1}H-NMR (DMSO-d_6 +D_2O, 300 MHz) δ: 1.35 (s, 6H, 2 CH_3); 1.52 (s, 6H, 2 CH_3); 3.20-3.25 (m, 1H, N-CH_aH_b); 3.34-3.42 (m, 3H, N-CH_aH_b + O-CH_3); 3.72-3.78 (m, 2H, N-CH_2); 3.82 (s, 2H, N-CH_2); 3.86 (s, 2H, N-CH_2); 7.16-7.22 (m, 1H, Ar); 7.30-7.38 (m, 2H, 2 Ar); 7.52-7.59 (m, 3H, 3 Ar); 7.91-8.20 (m, 1H, Ar); COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 568.4.

Compound **169**: (3R)1-(3-chloropyridin-2-yl)-3-methoxycyclopentane-1-carbonitrile

To a solution of 2-(3-chloropyridin-2-yl)acetonitrile (935 mg) and (R)-2-methoxybutane-1,4-diyl dimethanesulfonate (1.0 eq) in THF (30 mL) at 0°C was added Potassium tert-butoxide (2.0 eq).The reaction mixture was stirred at 25°C for 18 hours, quenched with NH_4Cl (sat. aq. 10 mL), diluted with water (5 mL) and extracted with EtOAc (3*10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **169** (510 mg) as a clear oil.

M/Z (M[^{35}Cl]+H)$^+$: 237.1

Compound **170**: ((3R)-1-(3-chloropyridin-2-yl)-3-methoxycyclopentyl)methanamine

Compound **170** (263 mg, 51%) was obtained as a clear oil following general procedure (XVa), starting from Compound **169** (510 mg).

M/Z (M[^{35}Cl]+H$^+$): 241.1

Compound **171**: (3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **171** was prepared according to general procedure (Xc) from Compound **170** (450 mg) and 4-bromo-1-chloro-2-fluorobenzene. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **171** (440 mg, 71%) as a yellow oil.

M/Z (M[^{35}Cl]+H$^+$): 333.2

Compound **172**: (major diastereoisomere) (3R)-5'-bromo-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]

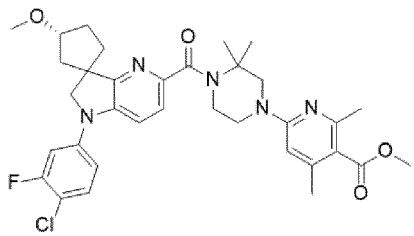
And Compound **173**: (minor diastereoisomere) (3R)-5'-bromo-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **172** and Compound **173** were prepared according to general procedure (XVI) in MeCN from Compound **171** (440 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 85:15) to obtain Compound **172** (330 mg, 61%) as a white solid and Compound **173** (140 mg, 26%) as a yellow oil.

Compound **172**: M/Z (M[^{35}Cl][^{81}Br]+H)$^+$: 413.1.

Compound **173**: M/Z (M[^{35}Cl][^{81}Br]+H)$^+$: 413.1.

Example **143**: (major diastereoisomere) methyl 6-(4-((3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

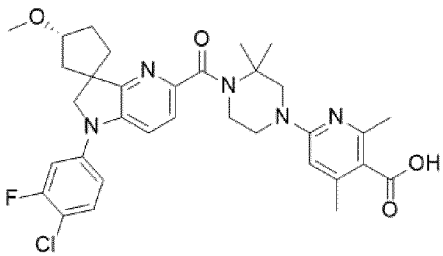


Example **143** was prepared according to general procedure (XIV) starting from Compound **172** (100 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 20:80) to obtain Example **143** (78 mg, 51%) as a white solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.58 (s, 6H, $(CH_3)_2$); 1.80-2.31 (m, 6H, 3 CH_2); 2.36 (s, 3H, CH_3); 2.51 (s, 3H, CH_3); 3.35 (s, 3H, $C(O)OCH_3$); 3.61-3.65 (m, 2H, N-CH_2); 3.88 (s, 3H, OCH_3); 3.89-4.06 (m, 6H, 3 N-CH_2); 4.10-4.13 (m, 1H, CH-OMe); 6.10 (s, 1H, Ar); 6.92-7.03 (m, 2H, 2 Ar); 7.27-7.41 (m, 2H, 2 Ar); 7.50 (d, *J* 7.2 Hz, 1H).

M/Z (M[^{35}Cl]+H)$^+$: 636.3.

Example **144**: (major diastereoisomere) 6-(4-((3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **144** was prepared according to general procedure (XI) starting from Example **143** (75 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **144** (58 mg, 75%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.51 (s, 6H, $(CH_3)_2$); 1.80-2.02 (m, 4H, $(CH_2)_2$); 2.08-2.22 (m, 2H, CH_2); 2.32 (s, 3H, CH_3); 3.23 (s, 3H, CH_3); 3.60-3.66 (m, 2H, CH_2); 3.83-3.91 (m, 4H, $(CH_2)_2$); 3.95-4.09 (m, 4H, 2 N-CH_2); 6.65 (bs, 1H, Ar); 7.16 (dd, *J* 9.0, 2.1 Hz, 1H, Ar); 7.30-7.38 (m, 2H, 2 Ar); 7.52-7.58 (m, 2H, 2 Ar). One CH_3 and COOH were not observed.

M/Z (M[^{35}Cl]+H)$^{+}$: 622.4

Compound **174**: (3S)1-(3-chloropyridin-2-yl)-3-methoxycyclopentane-1-carbonitrile

To a solution of 2-(3-chloropyridin-2-yl)acetonitrile (1.74 g) and (S)-2-methoxybutane-1,4-diyl dimethanesulfonate (1.0 eq) in THF (30 mL) at 0°C was added Potassium tert-butoxide (2.0 eq).The reaction mixture was stirred at 25°C for 18 hours, quenched with NH_4Cl (sat. aq. 10 mL), diluted with water (5 mL) and extracted with EtOAc (3*10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **174** (760 mg, 28%) as a clear oil.

M/Z (M[^{35}Cl]+H)$^{+}$: 237.6

Compound **175**: ((3S)-1-(3-chloropyridin-2-yl)-3-methoxycyclopentyl)methanamine

Compound **175** (540 mg, 70%) was obtained as a clear oil following general procedure (XVa), starting from Compound **174** (760 mg).

M/Z (M[^{35}Cl]+H^{+}): 241.1

Compound **176**: (3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **176** was prepared according to general procedure (Xc) from Compound **175** (520 mg) and 4-bromo-1-chloro-2-fluorobenzene. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **176** (350 mg, 48%) as a yellow oil.

M/Z (M[^{35}Cl]+H^{+}): 333.2

Compound **177**: (major diastereoisomere) (3S)-5'-bromo-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]

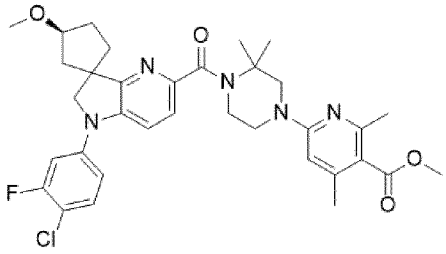
And Compound **178**: (minor diastereoisomere) (3S)-5'-bromo-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **177** and Compound **178** were prepared according to general procedure (XVI) in MeCN from Compound **176** (335 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 85:15) to obtain Compound **177** (250 mg, 60%) as a yellow oil and Compound **178** (90 mg, 22%) as a yellow oil.

Compound **177**: M/Z (M[^{35}Cl][^{81}Br]+H)$^{+}$: 413.1.

Compound **178**: M/Z (M[^{35}Cl][^{81}Br]+H)$^{+}$: 413.1.

Example **145**: (major diastereoisomere) methyl 6-(4-((3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

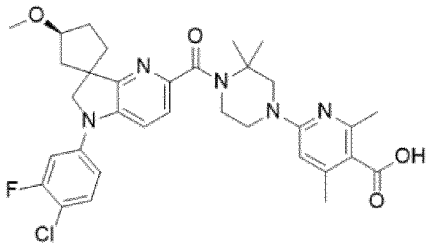


Example **145** was prepared according to general procedure (XIV) starting from Compound **177** (100 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 20:80) to obtain Example **145** (104 mg, 67%) as a white solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.58 (s, 6H, $(CH_3)_2$); 1.80-2.31 (m, 6H, 3 CH_2); 2.36 (s, 3H, CH_3); 2.50 (s, 3H, CH_3); 3.35 (s, 3H, $C(O)OCH_3$); 3.61-3.65 (m, 2H, N-CH_2); 3.88 (s, 3H, OCH_3); 3.89-4.06 (m, 6H, 3 N-CH_2); 4.10-4.13 (m, 1H, CH-OMe); 6.10 (s, 1H, Ar); 6.92-7.03 (m, 2H, 2 Ar); 7.27-7.41 (m, 2H, 2 Ar); 7.50 (d, *J* 7.2 Hz, 1H).

M/Z $(M[^{35}Cl]+H)^+$: 636.3.

Example **146**: (major diastereoisomere) 6-(4-((3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid

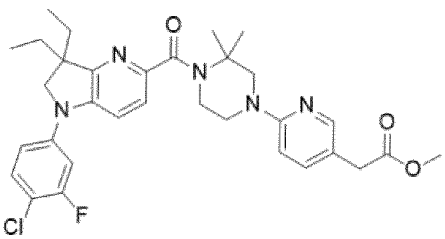


Example **146** was prepared according to general procedure (XI) starting from Example **145** (100 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **146** (65 mg, 63%) as a yellow solid.

^{1}H-NMR (DMSO-d_6 +D_2O, 300 MHz) δ: 1.50 (s, 6H, $(CH_3)_2$); 1.80-2.02 (m, 4H, $(CH_2)_2$); 2.08-2.22 (m, 2H, CH_2); 2.32 (s, 3H, CH_3); 2.49 (s, 3H, CH_3); 3.23 (s, 3H, CH_3); 3.60-3.66 (m, 2H, CH_2); 3.83-3.91 (m, 4H, 2 N-CH_2); 3.95-4.09 (m, 4H, 2 N-CH_2); 6.65 (bs, 1H, Ar); 7.16 (dd, *J* 9.0, 2.1 Hz, 1H, Ar); 7.30-7.38 (m, 2H, 2 Ar); 7.52-7.58 (m, 2H, 2 Ar). COOH was not observed.

M/Z $(M[^{35}Cl]+H)^+$: 622.4

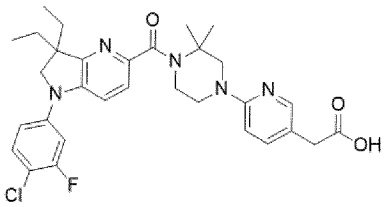
Example **147**: methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



Example **147** was prepared according to general procedure (XIV) starting from Compound **132** (100 mg) and Compound **111** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **147** (93 mg) as a yellow oil.

M/Z $(M[^{35}Cl]+H)^+$: 594.6.

Example **148**: 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **148** was prepared according to general procedure (VII) starting from Example **147** (90 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **148** (38 mg, 26% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 0.76 (t, *J* 7.2 Hz, 6H, 2 CH_2-CH_3); 1.53 (s, 6H, 2 CH_3); 1.68-1.76 (m, 4H, 2 CH_2CH_3); 3.55-3.65 (m, 4H, 2-N-CH_2); 3.82-3.93 (m, 6H, CH_2-CO, 2 N-CH_2); 6.90-7.23 (m, 2H, 2 Ar); 7.33-7.40 (m, 2H, 2 Ar); 7.51-7.56 (m, 2H, 2 Ar); 7.81 (bs, 1H, Ar); 7.94 (s, 1H, Ar); 12.53 (bs, 1H, CO_2H).

M/Z $(M[^{35}Cl]+H)^+$: 580.4

Compound **179**: tert-butyl 4-(5-(methoxycarbonyl)pyridin-3-yl)-2,2-dimethylpiperazine-1-carboxylateCompound **179** was prepared according to general procedure (Xb), starting from methyl 5-chloronicotinate (296 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The crude Compound **179** (550 mg) was obtained as a yellow oil and engaged directly in the following step.

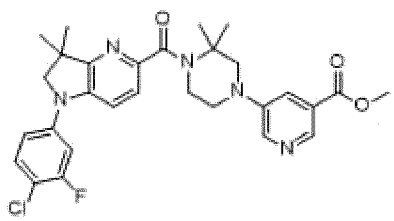
M/Z $(M+H)^+$: 350.2

Compound **180**: methyl 5-(3,3-dimethylpiperazin-1-yl)nicotinate

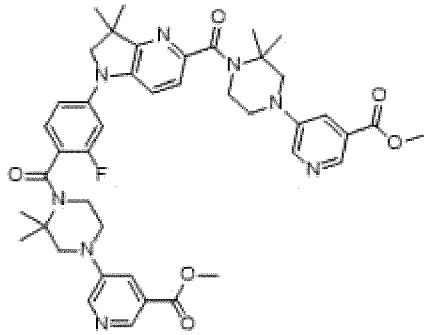
Compound **180** was prepared according to general procedure (XII) starting from Compound **179** (550 mg) in DCM using TFA. The reaction mixture was concentrated under reduced pressure to obtain the crude Compound **180** (477 mg) as a brown oil.

M/Z $(M+H)^+$: 250.2

Example **149**: methyl 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)nicotinate



And Example **150**: methyl 5-(4-(1-(3-fluoro-4-(4-(5-(methoxycarbonyl)pyridin-3-yl)-2,2-dimethylpiperazine-1-carbonyl)phenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)nicotinate



Example **149** and Example **150** were prepared according to general procedure (XIV) starting from Compound **71** (100 mg) and Compound **180** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, DCM 100% to DCM/MeOH 98:2) to obtain Example **149** (30 mg, 17%) as a yellow oil and Example **150** as a yellow solid (89 mg, 35%).

Example **149**:

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.34 (s, 6H, 2 CH_3); 1.53 (s, 6H, 2 CH_3); 3.34-3.52 (m, 4H, N-CH_2); 3.62-3.66 (m, 2H, N-CH_2); 3.80-3.88 (m, 5H, O-CH_3 + N-CH_2); 7.16-7.21 (m, 1H, Ar); 7.33-7.38 (m, 2H, 2 Ar); 7.38-7.42 (m, 2H, 2 Ar); 7.44-7.52 (m, 1H, Ar); 7.57 (d, J 8.4 Hz, 1H, Ar); 8.37-8.42 (m, 1H, Ar).

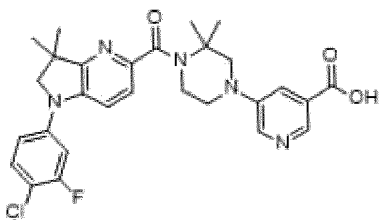
M/Z (M[^{35}Cl]+H)$^+$: 552.4.

Example **150**:

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.37 (s, 6H, 2 CH_3); 1.53 (s, 12H, 2*2 CH_3); 3.33-3.52 (m, 4H, 2 N-CH_2); 3.62-3.72 (m, 6H, 3 N-CH_2); 3.83-3.93 (m, 10H, 2 O-CH_3 + 2 N-CH_2); 7.14-7.23 (m, 2H, 2 Ar); 7.37-7.43 (m, 2H, 2 Ar); 7.48-7.52 (m, 2H, 2 Ar); 7.63 (d, J 8.4 Hz, 1H, Ar); 8.38-8.42 (m, 4H, 4 Ar).

M/Z (M+H)$^+$: 765.6.

Example **151**: 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)nicotinic acid



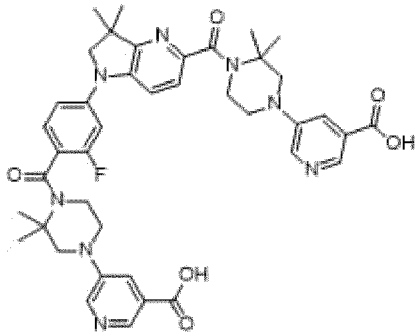
Example **151** was prepared according to general procedure (XI) starting from Example **149** (90 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 95:05 to 60:40) and freeze dried with HCl (0.1 N in water) to obtain Example **151** (21 mg, 23%) as a yellow solid.

^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.33 (s, 6H, 2 CH_3); 1.56 (s, 6H, 2 CH_3); 3.55 (t, *J* 5.5 Hz, 2H, N-CH_2); 3.72 (s, 2H, N-CH_2); 3.76 (s, 2H, N-CH_2); 3.92 (t, *J* 5.5 Hz, 2H, N-CH_2); 7.02-7.06 (m, 1H, Ar); 7.08-7.13 (m, 1H, Ar); 7.30-7.39 (m,

2H, 2 Ar); 7.44 (d, J 8.5 Hz, 1H, Ar); 8.21-8.22 (m, 1H, Ar); 8.31-8.32 (m, 1H, Ar); 8.38 (s, 1H, Ar). COOH was not observed.

M/Z ($M[^{35}Cl]+H)^+$: 538.3.

Example **152**: 5-(4-(4-(5-(4-(5-carboxypyridin-3-yl)-2,2-dimethylpiperazine-1-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-2-fluorobenzoyl)-3,3-dimethylpiperazin-1-yl)nicotinic acid



Example **152** was prepared according to general procedure (XI) starting from Example **150** (89 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **152** (40 mg, 43%) as a yellow solid.

^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.37 (s, 6H, 2 CH_3); 1.54-1.55 (m, 12H, 4 CH_3); 3.49 (t, J 5.5 Hz, 2H, N-CH_2); 3.55 (t, *J* 5.5 Hz, 2H, N-CH_2); 3.70-3.85 (m, 8H, 4 N-CH_2); 3.93 (t, *J* 5.5 Hz, 2H, N-CH_2); 7.05 (dd, *J* 12.2 2.2 Hz, 1H, Ar); 7.16 (dd, *J* 8.4 2.2 Hz, 1H, Ar); 7.32-7.37 (m, 1H, Ar); 7.41 (d, *J* 8.4 Hz, 1H, Ar); 7.6 (d, *J* 8.4 Hz, 1H, Ar); 8.18-8.20 (m, 2H, 2 Ar); 8.30-8.33 (m, 2H, 2 Ar); 8.38 (bs, 2H, 2 Ar). 2 COOH were not observed.

M/Z $(M+H)^+$: 765.6.

Compound **181**: 1-(3-chloropyridin-2-yl)-3-methylenecyclobutane-1-carbonitrile

Compound **181** was prepared according to general procedure (I) from 3-chloro-2-fluoropyridine (1.0 g) and 3-methylenecyclobutane-1-carbonitrile. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **181** (0.98 g, 63%) as a clear oil.

M/Z ($M[^{35}Cl]+H^+$): 205.6

Compound **182**: (1-(3-chloropyridin-2-yl)-3-methylcyclobutyl)methanamine

Compound **182** (587 mg, 59%) was obtained as a yellow oil following general procedure (XVa), starting from Compound **181** (978 mg).

M/Z ($M[^{35}Cl]+H^+$): 211.6.

Compound **183**: 1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **183** was prepared according to general procedure (Xc) from Compound **182** (585 mg) and 4-bromo-1-chloro-2-fluorobenzene. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to EtOAc 100%) to obtain Compound **183** (301 mg, 36%) as a white solid.

M/Z ($M[^{35}Cl]+H^+$): 303.3

Compound **184**: (major diastereoisomere) 5'-bromo-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

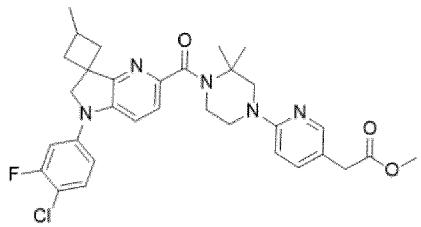
And Compound **185**: (minor diastereoisomere) 5'-bromo-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **184** and Compound **185** were prepared according to general procedure (XVI) in MeCN from Compound **183** (301 mg). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 85:15) to obtain Compound **184** (231 mg, 61%) as a white solid and Compound **185** (71 mg, 19%) as a white solid.

Compound **184**: M/Z (M[^{35}Cl][^{81}Br]+H)$^{+}$: 383.1

Compound **185**: M/Z (M[^{35}Cl][^{81}Br]+H)$^{+}$: 383.1

Example **153**: (major diastereoisomere) methyl 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

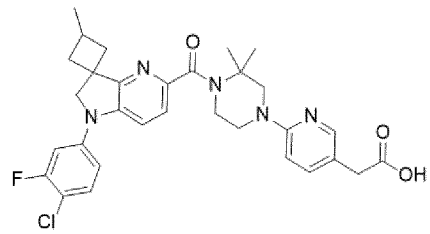


Example **153** was prepared according to general procedure (XIV) starting from Compound **184** (115 mg) and Compound **111** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 20:80) to obtain Example **153** (49 mg) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.15-1.23 (m, 3H, CH_3); 1.51 (s, 6H, 2 CH_3); 1.90-1.98 (m, 2H, 2 C**H$_a$**H$_b$); 2.53-2.72 (m, 3H, CHMe + 2 CH$_a$**H$_b$**); 3.49-3.66 (m, 8H, $CH_2C(O)$ + 3 N-CH_2); 3.86 (s, 3H, O-CH_3); 4.12 (m, 2H, N-CH_2); 6.52-6.61 (m, 1H, Ar); 7.15-7.19 (m, 1H, Ar); 7.22-7.60 (m, 5H, Ar); 7.93-7.97 (m, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^{+}$: 592.4

Example **154**: (major diastereoisomere) 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



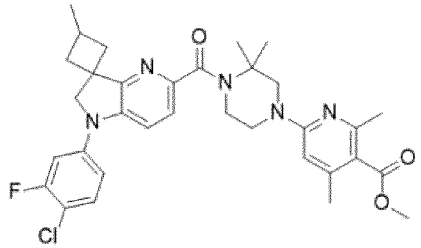
Example **154** was prepared according to general procedure (VII) starting from Example **153** (49 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **154** (7 mg, 4% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.17 (d, *J* 6.7 Hz, 3H, CH_3); 1.54 (s, 6H, 2 CH_3); 1.87-2.00 (m, 2H, C**Ha**Hb-CHMe-C**Ha'**Hb'); 2.55-2.64 (m, 2H, CHa**Hb**-CHMe-CHa'**Hb'**); 2.65-2.80 (m, 1H, C**H**Me); 3.50-3.60 (m, 2H, N-CH_2); 3.60-3.71 (m, 2H, N-CH_2); 3.82-4.02 (m, 2H, N-CH_2); 3.91 (s, 2H, **CH_2**-COOH); 4.13 (s, 2H, N-CH_2); 6.74-7.11 (m, 1H, Ar);

7.14-7.20 (m, 1H, Ar); 7.30-7.35 (m, 1H, Ar); 7.39 (d, *J* 8.9 Hz, 1H, Ar); 7.51-7.68 (m, 2H, 2 Ar); 7.61-7.90 (m, 1H, Ar); 7.93-7.97 (m, 1H, Ar); 12.10-12.70 (m, 1H, COOH).

M/Z (M[^{35}Cl]+H)$^{+}$: 578.5.

Example **155**: (major diastereoisomere) methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

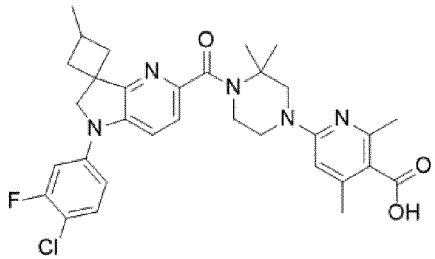


Example **155** was prepared according to general procedure (XIV) starting from Compound **184** (115 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **155** (79 mg) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.15-1.23 (m, 3H, CH_3); 1.51 (s, 6H, 2 CH_3); 1.90-1.98 (m, 2H, 2 C**H$_a$**H$_b$); 2.22 (s, 3H, CH_3); 2.33 (s, 3H, CH_3); 2.53-2.72 (m, 3H, CHMe + 2 CH$_a$**H$_b$**); 3.59-3.68 (m, 2H, N-CH_2); 3.77 (s, 3H, O-CH_3); 3.87-3.89 (m, 4H, 2 N-CH_2); 4.11 (s, 2H, N-CH_2); 6.33 (s, 1H, Ar); 7.15-7.19 (m, 1H, Ar); 7.24-7.45 (m, 3H, 3 Ar); 7.48-7.57 (m, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^{+}$: 606.5.

Example **156**: (major diastereoisomere) 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid

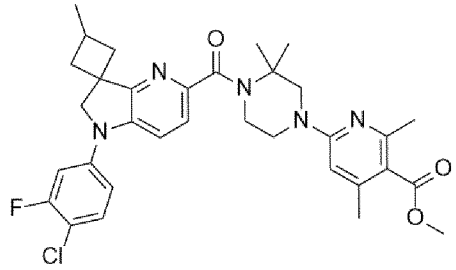


Example **156** was prepared according to general procedure (XI) starting from Example **155** (79 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **156** (37 mg, 20%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.17 (d, *J* 7.0 Hz, 3H, CH-CH_3); 1.52 (s, 6H, 2 CH_3); 1.88-2.00 (m, 2H, CH$_a$H$_b$); 2.28 (s, 3H, Ar-CH_3); 2.42 (s, 3H, Ar-CH_3); 2.54-2.62 (m, 2H, CH$_a$H$_b$); 2.68-2.84 (m, 1H, CH-Me); 3.59-3.72 (m, 2H, N-CH_2); 3.91-4.00 (m, 4H, 2 N-CH_2); 4.12 (s, 2H, N-CH_2); 6.27-6.62 (m, 1H, Ar); 7.18 (dd, *J* 9.2, 2.3 Hz, 1H, Ar); 7.32 (dd, *J* 11.8, 2.3 Hz, 1H, Ar); 7.39 (d, *J* 8.67 Hz, 1H, Ar); 7.50-7.59 (m, 2H, 2 Ar); COOH was not observed.

M/Z (M[^{35}Cl]+H)$^{+}$: 592.4

Example **157**: (minor diastereoisomere) methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

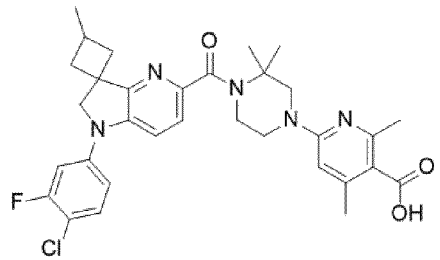


Example **157** was prepared according to general procedure (XIV) starting from Compound **185** (71 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **157** (48 mg) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.20 (d, *J* 6.4 Hz, 3H, CH-CH_3); 1.38 (s, 6H, 2 CH_3); 2.02-2.16 (m, 2H, 2 C**H$_a$**H$_b$); 2.22 (s, 3H, CH_3); 2.31-2.38 (m, 5H, CH_3 + 2 C**H$_a$**H$_b$); 3.42-3.49 (m, 1H, CHMe); 3.59-3.70 (m, 2H, N-CH_2); 3.77 (s, 3H, O-CH_3); 3.83-3.89 (m, 4H, 2 N-CH_2); 4.23 (s, 2H, N-CH_2); 6.34 (s, 1H, Ar); 7.15-7.19 (m, 1H, Ar); 7.24-7.45 (m, 3H, 3 Ar); 7.48-7.57 (m, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 606.5.

Example **158**: (minor diastereoisomere) 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **158** was prepared according to general procedure (XI) starting from Example **157** (79 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **158** (37 mg, 20%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.20 (d, *J* 6.4 Hz, 3H, CH-CH_3); 1.53 (s, 6H, 2 CH_3); 2.08-2.16 (m, 2H, CH_aH_b); 2.30 (s, 3H, Ar-CH_3); 2.34-2.40 (m, 2H, CH_aH_b); 2.46 (s, 3H, Ar-CH_3); 2.53-2.61 (m, 1H, CH-Me); 3.67-3.79 (m, 2H, N-CH_2); 3.88-3.99 (m, 4H, 2 N-CH_2); 4.25 (s, 2H, N-CH_2); 6.45-6.74 (m, 1H, Ar); 7.20 (dd, *J* 9.1, 2,5 Hz, 1H, Ar); 7.34 (dd, *J* 12.0, 2,5 Hz, 1H, Ar); 7.39 (d, *J* 8.5 Hz, 1H, Ar); 7.51-7.59 (m, 2H, 2 Ar); COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 592.4.

Compound **186**: methyl 2-(6-chloropyridin-3-yl)propanoate

Compound **186** (410 mg, 76%) was obtained without further purification as a yellow oil, from methyl 2-(6-chloropyridin-3-yl)acetate (500 mg), according to general procedure (XIII) in THF with NaH (1.0 eq.) and MeI (1.0 eq).

M/Z (M[^{35}Cl]+H)$^+$: 200.1

Compound **187**: tert-butyl 4-(5-(1-methoxy-1-oxopropan-2-yl)pyridin-2-yl)-2,2-dimethylpiperazine-1-carboxylate

Compound **187** was prepared according to general procedure (Xb), starting from Compound **186** (600 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The crude Compound **187** (780 mg) was obtained as a yellow solid and engaged directly in the following step.

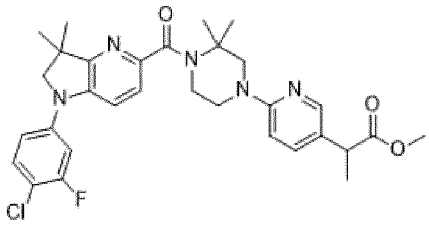
M/Z $(M+H)^+$: 378.1

Compound **188**: methyl 2-(6-(3,3-dimethylpiperazin-1-yl)pyridin-3-yl)propanoate hydrochloride

Compound **188** was prepared according to general procedure (XII) starting from Compound **187** (780 mg) in DCM using TFA. The reaction mixture was concentrated under reduced pressure then purified by Ion Exchange chromatography (Isolute SCX-2, load in DCM, elution with NH_3 1N in MeOH), and freeze dried with HCl (0.1N, aq.) to obtain Compound **188** (265 mg, 28%) as an orange solid.

M/Z $(M+H)^+$: 278.1

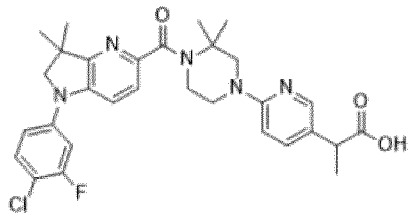
Example **159**: methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)propanoate



Example **159** was prepared according to general procedure (XIV) starting from Compound **71** (130 mg) and Compound **188** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **159** (154 mg) as a yellow oil.

M/Z $(M[^{35}Cl]+H)^+$: 580.4

Example **160**: 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)propanoic acid



Example **160** was prepared according to general procedure (XI) starting from Example **158** (154 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 60:40 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **160** (98 mg, 39%) as a yellow solid.

^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.45 (s, 6H, 2 CH_3); 1.53 (d, *J* 7.3 Hz, 3H, CH-**CH_3**); 1.69 (s, 6H, 2 CH_3); 3.77-3.84 (m, 3H, N-**CH_2** + Ar-CH); 3.88 (s, 2H, N-**CH_2**); 3.94 (s, 2H, N-**CH_2**); 4.09 (t, *J* 5.5 Hz, 2H, N-**CH_2**); 7.14-7.18 (m, 1H, Ar); 7.22 (dd, *J* 11.4 2.5 Hz, 1H, Ar); 7.41-7.51 (m, 3H, 3 Ar); 7.56 (d, *J* 8.4 Hz, 1H, Ar); 7.88 (d, *J* 2.0 Hz, 1H, Ar); 8.12 (dd, *J* 9.9 1.9Hz, 1H, Ar).

M/Z(M[^{35}Cl]+H)$^{+}$: 566.4.

Compound **189**: 2-(3-chloropyridin-2-yl)-2-methylpropanenitrile

Compound **189** (4.13 g, 90%) was obtained without further purification as a yellow oil, from 3-chloro-2-fluoropyridine (3.3 g) and isobutyronitrile, according to general procedure (I).

M/Z (M[^{35}Cl]+H^{+}): 181.4

Compound **190**: 2-(3-chloropyridin-2-yl)-2-methylpropan-1-amine

Compound **190** (2.07 g, 49%) was obtained as a yellow oil following general procedure (XVa), starting from Compound **189** (4.10 g).

M/Z (M[^{35}Cl]+H^{+}): 185.2

Compound **191**: 4-((2-(3-chloropyridin-2-yl)-2-methylpropyl)amino)cyclohexane-1-carbonitrile

To a solution of Compound **190** (100 mg) in THF (5 mL), was added a solution of 4-Oxo-cyclohexanecarbonitrile (100 mg) in THF (5 mL), Acetic acid (31 µL) and Sodium triacetoxyborohydride (230 mg). The reaction mixture was stirred at 25°C for 18 hours, then quenched with $NaHCO_3$ (sat. aq. 50 mL), and extracted with EtOAc (3*80 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash chromatography (KPNH, CyHex 100% to CyHex/EtOAc 75:25) to obtain Compound **191** (89 mg, 56%) as a clear oil.

M/Z (M[^{35}Cl]+H^{+}): 292.2

Compound **192**: 4-(3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)cyclohexane-1-carbonitrile

Compound **192** was prepared according to general procedure (Xd) starting from Compound **191** (158 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Compound **192** (75 mg, 54%) as a yellow oil.

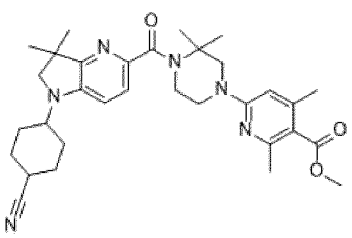
M/Z (M+H)$^{+}$: 256.2.

Compound **193**: 4-(5-bromo-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)cyclohexane-1-carbonitrile

Compound **193** (395 mg, 96%) was obtained without further purification as a beige solid following general procedure (XVI) in MeCN, starting from Compound **192** (316 mg).

M/Z (M[^{35}Cl][^{81}Br]+H)$^{+}$: 334.2

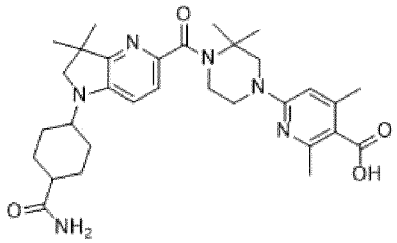
Example **161**: methyl 6-(4-(1-(4-cyanocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



Example **161** was prepared according to general procedure (XIV) starting from Compound **193** (200 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **161** (125 mg) as a clear oil.

M/Z $(M+H)^+$: 559.5

Example **162**: 6-(4-(1-(4-carbamoylcyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **162** was prepared according to general procedure (XI) starting from Example **161** (58 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 95:05 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **162** (8 mg, 2% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.66 (s, 6H, 2 CH_3); 1.36-1.57 (m, 10H, 2 CH_2 +2 CH_3); 1.73-1.85 (m, 4H, 2 CH_2); 2.02-2.11 (m, 1H, CH); 2.34 (s, 3H, CH_3); 3.26-3.29 (m, 2H, N-**CH_2**); 3.42-3.51 (m, 1H, N-**CH**); 3.67(bs, 2H, N-**CH_2**); 3.92-3.94 (m, 4H, 2 N-**CH_2**); 6.72-6.78 (m, 2H, NH_2); 7.84 (d, *J* 8.4 Hz, 1H, Ar); 7.25 (bs, 1H, Ar); 7.31 (d, *J* 8.4 Hz, 1H, Ar); COOH was not observed.

M/Z $(M+H)^+$: 563.5

Compound **194**: N-(2-(3-chloropyridin-2-yl)-2-methylpropyl)-4,4-difluorocyclohexan-1-amine

To a solution of Compound **190** (200 mg) in THF (8 mL), was added a solution of 4,4-difluorocyclohexan-1-one (218 mg), Acetic acid (62 µL) and Sodium triacetoxyborohydride (460 mg). The reaction mixture was stirred at 25°C for 18 hours, then quenched with $NaHCO_3$ (sat. aq. 50 mL), and extracted with EtOAc (3*80 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to obtain crude Compound **194** (344 mg) as a clear oil.

M/Z $(M[^{35}Cl]+H^+)$: 303.3

Compound **195**: 1-(4,4-difluorocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

Compound **195** was prepared according to general procedure (Xd) starting from Compound **194** (328 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **195** (198 mg, 69% over 2 steps) as a beige solid.

M/Z $(M+H)^+$: 267.2.

Compound **196**: 5-bromo-1-(4,4-difluorocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

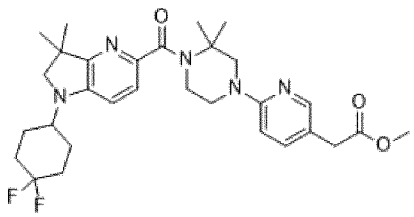
Compound **196** (230 mg, 90%) was obtained without further purification as a beige solid following general procedure (XVI) in MeCN, starting from Compound **195** (198 mg).

M/Z (M[^{81}Br]+H)$^+$: 345.4.

Compound **197**: methyl 1-(4,4-difluorocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylate
Compound **197** was prepared according to general procedure (XIX) starting from Compound **196** (230 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **197** (144 mg, 67%) as an orange solid.
M/Z (M+H)$^+$: 325.3.

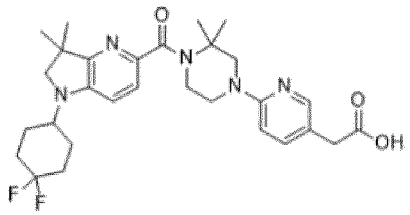
Compound **198**: 1-(4,4-difluorocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylic acid
Compound **198** was prepared according to general procedure (VII) starting from Compound **197** (144 mg). The crude Compound **198** (118 mg, 85%) was obtained as a white solid.
M/Z (M+H)$^+$: 311.3

Example **163**: methyl 2-(6-(4-(1-(4,4-difluorocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



Example **163** was prepared according to general procedure (VIIIb) starting from Compound **198** (118 mg), Compound **10** (1.1 eq.) and N,N-diisopropylethylamine (3.0 eq.) in MeTHF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **163** (159 mg, 75%) as a yellow solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.25 (s, 6H, 2 CH_3); 1.47 (s, 6H, 2 CH_3); 1.61-1.80 (m, 4H, 2 CH_2); 1.91-2.11 (m, 4H, 2 CH_2); 3.27 (s, 2H, Ar-CH_2); 3.48-3.53 (m, 4H, 2 N-CH_2); 3.60 (s, 3H, O-CH_3); 3.67-3.75 (m, 1H, N-CH); 3.78-3.86 (m, 4H, 2 N-CH_2); 6.58 (d, *J* 8.7 Hz, 1H, Ar); 6.83 (d, *J* 8.4 Hz, 1H, Ar); 7.28 (d, *J* 8.4 Hz, 1H, Ar); 7.43 (dd, *J* 2.4, 8.7 Hz, 1H, Ar); 7.95 (d, *J* 2.4 Hz, 1H, Ar);
M/Z (M+H)$^+$: 556.5

Example **164**: 2-(6-(4-(1-(4,4-difluorocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid

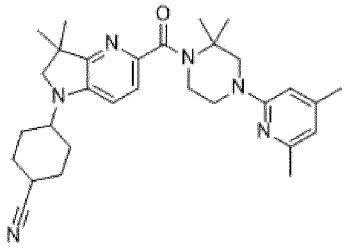


Example **164** was prepared according to general procedure (VII) starting from Example **163** (58 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 95:05 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **164** (8 mg, 2% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.25 (s, 6H, 2 CH_3); 1.48 (s, 6H, 2 CH_3); 1.61-1.71 (m, 2H, CH_2); 1.76-1.80 (m, 2H, CH_2); 1.91-2.10 (m, 4H, 2 CH_2); 2.28 (s, 2H, Ar-CH_2); 3.48-3.56 (m, 4H, 2 N-CH_2); 3.67-3.75 (m, 1H, N-CH); 3.84-3.89 (m, 4H, 2 N-CH_2); 6.75-6.85 (m, 2H, 2 Ar); 7.30 (d, *J* 8.2 Hz, 1H, Ar); 7.57 (bs, 1H, Ar); 7.93-7.94 (m, 1H, Ar); 12.39 (bs, 1H, COOH);

M/Z $(M+H)^+$: 542.4.

Example **165**: 4-(5-(4-(4,6-dimethylpyridin-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)cyclohexane-1-carbonitrile



To a solution of Example **161** (58 mg), in Pyridine (1 mL) was added Lithium Iodide (42 mg). The reaction mixture was sealed and heated at 120°C for 48 hours then concentrated under reduced pressure. The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 40:60) and freeze dried with HCl water to obtain Example **165** (5 mg, 2% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.24-1.26 (m, 6H, 2 CH_3); 1.49 (s, 6H, 2 CH_3); 1.58-1.80 (m, 6H, 3 CH_2); 1.94-2.34 (m, 8H, CH_2 + 2 CH_3); 3.1-3.24 (m, 1H, CH); 3.31 (s, 2H, CH_2); 3.54-3.56 (m, 3H, N-CH + N-CH_2); 3.83-3.84 (m, 4H, 2 N-CH_2); 6.27-6.57 (m, 2H, 2 Ar); 6.81 (d, *J* 8.1 Hz, 1H, Ar); 7.29 (d, *J* 8.1 Hz, 1H, Ar).

M/Z $(M+H)^+$: 501.4.

Compound **199**: N-(2-(3-chloropyridin-2-yl)-2-methylpropyl)cyclopentanamine

To a solution of Compound **190** (150 mg) in THF (8 mL), was added a solution of cyclopentanone (102 mg), Acetic acid (47 µL) and Sodium triacetoxyborohydride (344 mg). The reaction mixture was stirred at 25°C for 18 hours, then quenched with $NaHCO_3$ (sat. aq. 50 mL), and extracted with EtOAc (3*80 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to obtain crude Compound **199** (167 mg) as a clear oil.

M/Z $(M[^{35}Cl]+H^+)$: 253.1

Compound **200**: 1-cyclopentyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

Compound **200** was prepared according to general procedure (Xd) starting from Compound **199** (220 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 55:45) to obtain Compound **200** (114 mg, 39% over 2 steps) as a beige solid.

M/Z $(M+H)^+$: 217.2.

Compound **201**: 5-bromo-1-cyclopentyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

Compound **201** (138 mg, 89%) was obtained without further purification as a brown solid following general procedure (XVI) in MeCN, starting from Compound **200** (114 mg).

M/Z (M[^{81}Br]+H)$^+$: 295.2.

Compound **202**: methyl 1-cyclopentyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylate

Compound **202** was prepared according to general procedure (XIX) starting from Compound **201** (138 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **202** (88 mg, 69%) as a yellow oil.

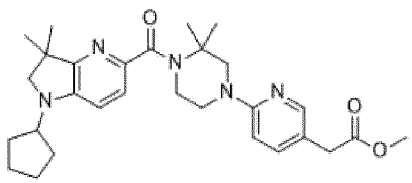
M/Z (M+H)$^+$: 275.1.

Compound **203**: 1-cyclopentyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylic acid

Compound **203** was prepared according to general procedure (VII) starting from Compound **202** (88 mg). The crude Compound **203** (68 mg, 81%) was obtained as a beige solid.

M/Z (M[^{35}Cl]+H)$^+$: 261.1

Example **166**: methyl 2-(6-(4-(1-cyclopentyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

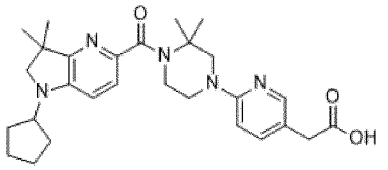


Example **166** was prepared according to general procedure (VIIIb) starting from Compound **203** (68 mg), Compound **111** (1.1 eq.) and N,N-diisopropylethylamine (3.0 eq.) in MeTHF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **166** (92 mg, 70%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.25 (s, 6H, 2 CH_3); 1.47 (s, 6H, 2 CH_3); 1.58-1.68 (m, 6H, 3 CH_2); 1.78-1.87 (m, 2H, CH_2); 3.27 (s, 2H, Ar-CH_2); 3.42-3.55 (m, 4H, 2 N-CH_2); 3.53 (s, 3H, O-CH_3); 3.78-3.85 (m, 5H, N-CH + 2 N-CH_2); 6.58 (d, *J* 8.7 Hz, 1H, Ar); 6.79 (d, *J* 8.4 Hz, 1H, Ar); 7.25 (d, *J* 8.4 Hz, 1H, Ar); 7.43 (dd, *J* 2.4, 8.7 Hz, 1H, Ar); 7.95 (d, *J* 2.4 Hz, 1H, Ar);

M/Z (M+H)$^+$: 506.5

Example **167**: 2-(6-(4-(1-cyclopentyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **167** was prepared according to general procedure (VII) starting from Example **166** (97 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 40:60) and freeze dried with HCl (0.1 N in water) to obtain Example **167** (44 mg, 43%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.25 (s, 6H, 2 CH_3); 1.48 (s, 6H, 2 CH_3); 1.61-1.71 (m, 2H, CH_2); 1.76-1.80 (m, 2H, CH_2); 1.91-2.10 (m, 4H, 2 CH_2); 2.28 (s, 2H, Ar-CH_2); 3.48-3.56 (m, 4H, 2 N-CH_2); 3.67-3.75 (m, 1H, N-CH); 3.84-

3.89 (m, 4H, 2 N-CH_2); 6.75-6.85 (m, 2H, 2 Ar); 7.30 (d, *J* 8.2 Hz, 1H, Ar); 7.57 (bs, 1H, Ar); 7.93-7.94 (m, 1H, Ar); 12.39 (bs, 1H, COOH);

M/Z $(M+H)^+$: 542.4.

Compound **204**: methyl 1-(4-cyanocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylate

Compound **204** was prepared according to general procedure (XIX) starting from Compound **193** (100 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **204** (68 mg, 73%) as a beige solid.

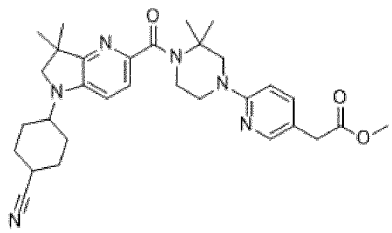
M/Z $(M+H)^+$: 314.3.

Compound **205**: methyl 1-(4-cyanocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylate

Compound **205** was prepared according to general procedure (VII) starting from Compound **204** (117 mg). The crude Compound **205** (92 mg, 82%) was obtained as a white solid.

M/Z $(M+H)^+$: 300.2

Example **168**: methyl 2-(6-(4-(1-(4-cyanocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

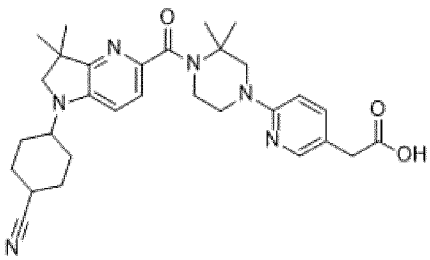


Example **168** was prepared according to general procedure (VIIIb) starting from Compound **205** (92 mg), Compound **111** (1.1 eq.) and N,N-diisopropylethylamine (4.0 eq.) in MeTHF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 25:75) to obtain Example **168** (143 mg, 85%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.24-1.26 (m, 6H, 2 CH_3); 1.47-1.53 (m, 6H, 2 CH_3); 1.53-1.77 (m, 6H, 3 CH_2); 1.95-2.13 (m, 2H, CH_2); 3.18-3.31 (m, 3H, 3 CH); 3.49-3.55 (m, 5H, N-CH_2 + CH_2C(O) + N-CH); 3.60 (s, 3H, O-CH_3); 3.82-3.87 (m, 4H, 2 N-CH_2); 6.59 (d, *J* 8.7 Hz, 1H, Ar); 6.80 (d, *J* 8.4 Hz, 1H, Ar); 7.27 (d, *J* 8.4 Hz, 1H, Ar); 7.44 (dd, *J* 2.1, 8.7 Hz, 1H, Ar); 7.95 (d, *J* 2.1 Hz, 1H, Ar);

M/Z $(M+H)^+$: 545.5

Example **169**: 2-(6-(4-(1-(4-cyanocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **169** was prepared according to general procedure (VII) starting from Example **168** (143 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 90:10 to 50:50) and freeze dried with HCl (0.1 N in water) to obtain Example **169** (17 mg, 12%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.24-1.26 (m, 6H, 2 CH_3); 1.47-1.53 (m, 7H, C**Ha**Hb + 2 CH_3); 1.58-1.77 (m, 6H, 3 CH_2); 1.95-2.13 (m, 2H, CH_2); 3.20-3.24 (m, 1H, CHa**Hb**); 3.30 (m, 1H, CH); 3.45 (s, 2H, N-**CH_2**); 3.53-3.54 (m, 3H, **CH**-N + N-**CH_2**); 3.82-3.87 (m, 4H, 2 N-**CH_2**); 6.68-6.72 (m, 1H, Ar); 6.79-6.82 (m, 1H, Ar); 7.25-7.29 (m, 1H, Ar); 7.50 (bs, 1H, Ar); 7.93-7.95 (m, 1H, Ar); 12.33 (m, 1H, COOH).

M/Z $(M+H)^+$: 531.4.

Compound **206**: 3-chloro-N-(3,4-difluorophenyl)-N-(2-methylallyl)pyrazin-2-amine

Crude Compound **206** (970 mg) was obtained as a brown oil according to general procedure (XVII) on a 500 mg scale, using 4-chloro-3-fluoroaniline.

M/Z $(M[^{35}Cl]+H)^+$: 296.2.

Compound **207**: 5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **207** was prepared according to general procedure (XVIII) starting from crude Compound **206** (970 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **207** (482 mg, 55% over 2 steps) as a yellow solid.

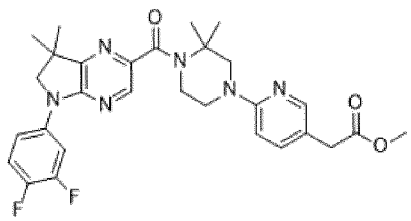
M/Z $(M+H)^+$: 262.2

Compound **208**: 2-bromo-5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **208** (476 mg, 76%) was obtained as a brown solid following general procedure (XVI) in MeCN without further purification, starting from Compound **207** (482 mg).

M/Z $(M[^{81}Br]+H)^+$: 340.1.

Example **170**: methyl 2-(6-(4-(5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

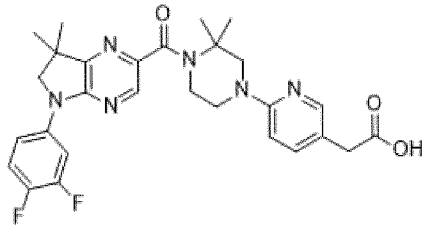


Example **170** was prepared according to general procedure (XIV) starting from Compound **208** (75 mg) and Compound **111** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **170** (60 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.39 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 3.46-3.53 (m, 4H, N-CH_2 + CH_2C(O)); 3.60 (s, 3H, O-CH_3); 3.76-3.90 (m, 4H, 2 N-CH_2); 3.98 (s, 2H, N-CH_2); 6.58-6.61 (m, 1H, Ar); 7.39-7.55 (m, 3 H, Ar); 7.63-7.70 (m, 1H, Ar); 7.96 (s,1H, Ar); 8.06 - 8.16 (m, 1H, Ar); 8.19 (s, 1H, Ar).

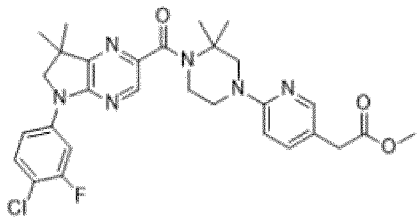
M/Z $(M+H)^+$: 551.4.

Example **171**: 2-(6-(4-(5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



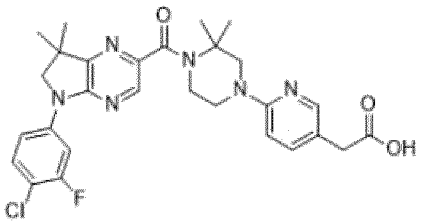
Example **171** was prepared according to general procedure (VII) starting from Example **170** (60 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **171** (28 mg, 22% over 2 steps) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.40 (s, 6H, 2 CH_3); 1.56 (s, 6H, 2 CH_3); 3.66 (s, 2H, $CH_2C(O)$); 3.69-3.77 (m, 2H, N-CH_2); 3.87-3.96 (m, 2H, N-CH_2); 3.98 (bs, 4H, 2 N-CH_2); 7.26-7.44 (m, 1H, Ar); 7.48-7.55 (m, 1H, Ar); 7.61-7.70 (m, 1H, Ar); 7.91-8.03 (m, 2H, 2 Ar); 8.08-8.13 (m, 1H, Ar); 8.23 (s, 1H, Ar); 12.25-14.14 (s, 1H, COOH).
M/Z $(M+H)^+$: 537.3.

Example **172**: methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



Example **172** was prepared according to general procedure (XIV) starting from Compound **128** (1.0 g) and Compound **111** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **172** (0.82 g, 51%) as a yellow solid.
M/Z $(M[^{35}Cl]+H)^+$: 567.3

Example **173**: 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **173** was prepared according to general procedure (VII) starting from Example **172** (84 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **173** (50 mg, 54% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.40 (s, 6H, 2 CH_3); 1.56 (s, 6H, 2 CH_3); 3.64 (s, 2H, $CH_2C(O)$); 3.66-3.75 (m, 2H, N-CH_2); 3.86-3.95 (m, 2H, N-CH_2); 3.98 (s, 2H, N-CH_2); 3.99 (s, 2H); 7.15-7.43 (m, 1H, Ar); 7.63 (t, *J* 8.8 Hz, 1H, Ar); 7.73 (dd, *J* 9.0, 2.6 Hz,1H, Ar); 7.85-8.00 (m, 2H, 2 Ar); 8.10 (dd, *J* 12.5, 2.6 Hz, 1H, Ar); 8.25 (s, 1H, Ar); 12.08-14.53 (s, 1H, COOH).

M/Z (M[^{35}Cl]+H)$^+$: 553.3.

Compound **209**: methyl 2-(6-chloropyridin-3-yl)-2-methylpropanoate

Compound **209** (210 mg, 37%) was obtained without further purification as a yellow oil, from methyl 2-(6-chloropyridin-3-yl)acetate (500 mg), according to general procedure (XIII) in THF with NaH (3.0 eq.) and MeI (3.0 eq).

M/Z (M[^{35}Cl]+H)$^+$: 214.1

Compound **210**: tert-butyl 4-(5-(1-methoxy-2-methyl-1-oxopropan-2-yl)pyridin-2-yl)-2,2-dimethylpiperazine-1-carboxylate

Compound **210** was prepared according to general procedure (Xb), starting from Compound **209** (330 mg) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (1.2 eq.). The crude Compound **210** (580 mg) was obtained as a yellow solid and engaged directly in the following step.

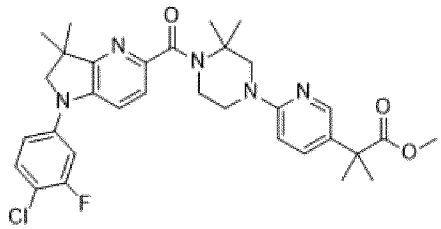
M/Z (M+H)$^+$: 392.3

Compound **211**: methyl 2-(6-(3,3-dimethylpiperazin-1-yl)pyridin-3-yl)-2-methylpropanoate hydrochloride

Compound **211** was prepared according to general procedure (XII) starting from Compound **210** (580 mg) in DCM using TFA. The reaction mixture was concentrated under reduced pressure then purified by Ion Exchange chromatography (Isolute SCX-2, load in DCM, elution with NH_3 1N in MeOH), and freeze dried with HCl (0.1N, aq.) to obtain Compound **211** (210 mg, 42% over 2 steps) as an orange solid.

M/Z (M+H)$^+$: 292.3

Example **174**: methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)-2-methylpropanoate

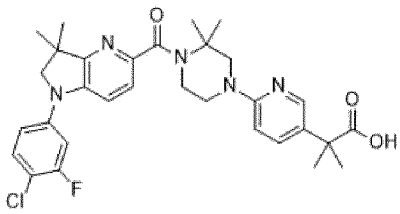


Example **174** was prepared according to general procedure (XIV) starting from Compound **71** (100 mg) and Compound **211** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **174** (120 mg, 63%) as a yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, 2 CH_3); 1.48 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 3.48-3.54 (m, 2H, N-CH_2); 3.58 (s, 3H, O-CH_3); 3.78-3.86 (m, 6H, 3 N-CH_2); 6.58-6.61 (m, 1H, Ar); 7.17-7.21 (m, 1 H, Ar); 7.30-7.37 (m, 2 H, Ar); 7.47-7.58 (m, 3H, 3 Ar); 8.05 (d, *J* 8.6 Hz, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^{+}$: 594.4

Example **175**: 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)-2-methylpropanoic acid



Example **175** was prepared according to general procedure (XI) starting from Example **174** (154 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 60:40 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **175** (98 mg, 39%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.36 (s, 6H, 2 CH_3); 1.51 (s, 6H, 2 CH_3); 1.56 (s, 6H, 2 CH_3); 3.70-3.76 (m, 2H, N-CH_2); 3.87 (bs, 2H, N-CH_2); 3.93-3.99 (m, 4H, 2 N-CH_2); 7.19 (dd, *J* 8.6 2.9 Hz, 1H, Ar); 7.31-7.36 (m, 2H, 2 Ar); 7.40 (d, *J* 8.6 Hz, 1H, Ar); 7.53-7.59 (m, 2H, 2 Ar); 7.75-7.79 (m, 1H, Ar); 8.01-8.08 (m, 1H, Ar); COOH was not observed.

M/Z (M[^{35}Cl]+H)$^{+}$: 580.4

Compound **212**: 4-methyl-N-(pyridin-3-yl)benzenesulfonamide

To a solution of 3-aminopyridine (10.0 g) in 60 ml of pyridine, was added p-tosyl chloride (24.3 g) and the solution was heated at 120 °C. After 2 hours the solution was poured in cold water (100 mL, 0°C), the white precipitate was collected by filtration and washed with water. The solid was dissolved in THF, washed with brine, and dried over $MgSO_4$ to afford Compound **212** (20.0 g, 75%) as a white solid.

M/Z (M+H)$^{+}$: 249.2

Compound **213**: 4-methyl-N-(3-methylbut-3-en-1-yl)-N-(pyridin-3-yl)benzenesulfonamide

To a solution of Compound **212** (5.00 g) in THF (150 mL) was added 3-methylbut-3-en-1-ol (1.73 g) and Triphenylphosphine (5.28 g). Then, Diisopropyl azodicarboxylate (407 mg) was added dropwise at 0°C. The reaction was stirred at 25°C for 4 hours. The reaction was quenched with water (150 mL), and then extracted with EtOAc (3*200 mL). The combined organic layers were washed with brine (300 mL) and dried over Na_2SO_4. The crude was purified by flash chromatography (Petroleum Ether/EtOAc, 80:20) to obtain Compound **213** (5.00 g, 78%) as a white solid.

M/Z (M+H)$^{+}$: 317.2

Compound **214**: 4,4-dimethyl-1-tosyl-1,2,3,4-tetrahydro-1,5-naphthyridine

To a solution of Compound **213** (5.00 g) in EtOH (100 mL) was added Iron tri(4-methoxypent-3-en-2-one) (5.58 g), 2-(tert-butylperoxy)-2-methylpropane (2.31 g) and silylbenzene (4.28 g). The reaction was heated at 60 °C for 16 hours then concentrated under reduced pressure. The residue was quenched with water (100 mL), and then extracted with EtOAc (3*200 mL). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4. The crude was purified by flash chromatography (Petroleum Ether/EtOAc, 75:25) to obtain Compound **214** (1.00 g, 20%) as a yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz,) δ: 1.08-1.10 (m, 6H, $C(CH_3)_2$); 1.40-1.46 (m, 2H, CH_2); 2.38 (s, 3H, $ArCH_3$); 3.78-3.84 (m, 2H, $N\text{-}CH_2$); 7.10-7.15 (m, 1H); 7.22 (d, *J* 7.4 Hz, 2H); 7.45 (d, *J* 7.4 Hz, 2H); 8.16 (d, *J* 8.4 Hz, 1H); 8.35-8.40 (m, 1H).

M/Z $(M+H)^+$: 317.2

Compound **215**: 4,4-dimethyl-1,2,3,4-tetrahydro-1,5-naphthyridine

A solution of Compound **214** (1.50 g) in HBr (aq. 40%wt, 50 mL) was heated at 70 °C for 12 hours. The solution was treated with $NaHCO_3$ (1M aq., to pH = 9) and extracted with EtOAc (3*100 mL). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4. The crude was purified by flash chromatography (Petroleum Ether/EtOAc, 75:25) to obtain Compound **215** (600 mg, 78%) as a yellow solid.

M/Z $(M+H)^+$: 163.2

Compound **216**: 1-(4-chloro-3-fluorophenyl)-4,4-dimethyl-1,2,3,4-tetrahydro-1,5-naphthyridine

To a solution of Compound **215** (160 mg) in Toluene (15 mL) was added 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (72 mg), 1-chloro-2-fluoro-4-iodobenzene (379 mg), 2-(Dicyclohexylphosphanyl)-2',4',6'-tris(isopropyl)biphenyl (47 mg) and sodium 2-methylpropan-2-olate (190 mg). The reaction was heated at 100 °C for 5 hours. The reaction was quenched with water (30 mL), and then extracted with EtOAc (3*50 mL). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4. The crude was purified by flash chromatography (Petroleum Ether/EtOAc, 75:25) to obtain Compound **216** (115 mg, 40%) as a yellow solid.

M/Z $(M[^{35}Cl]+H)^+$: 291.2

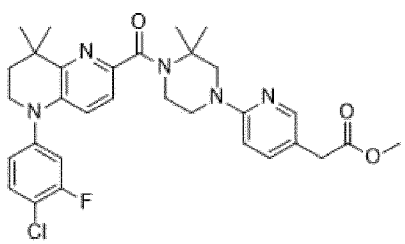
Compound **217**: 6-bromo-1-(4-chloro-3-fluorophenyl)-4,4-dimethyl-1,2,3,4-tetrahydro-1,5-naphthyridine

To a solution of Compound **216** (115 mg) in MeCN (15 mL) was added acetic acid (25 µL) and N-Bromosuccinimide (70 mg). The reaction was stirred at 25°C for 2 hours. The solution was treated with $NaHCO_3$ (1M aq., to pH = 9) and extracted with EtOAc (3*50 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The crude was purified by flash chromatography (Petroleum Ether/EtOAc, 90:10) to obtain Compound **217** (120 mg, 82%) as a yellow solid.

M/Z $(M[^{81}Br][^{35}Cl]+H)^+$: 369.0

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.26-1.30 (m, 6H, $C(CH_3)_2$); 1.84-1.89 (m, 2H, CH_2); 3.59-3.63 (m, 2H, $N\text{-}CH_2$); 7.05 (d, *J* 8.6 Hz, 1H, Ar); 7.13 (ddd, *J* 4.2, 3.5, 2.9 Hz, 2H, 2 Ar); 7.37 (dd, *J* = 11.3, 2.5 Hz, 1H, Ar);7.56 (t, *J* = 8.7 Hz, 1H, Ar).

Example **176**: methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-8,8-dimethyl-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

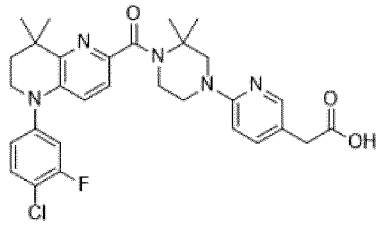


To a solution of Compound **217** (100 mg) in Dioxane (10 mL) was added Xantphos Pd G4 (26 mg),Triethylamine (60 µL) and Compound **111** (71 mg). The reaction was heated at 100 °C for 5 hours in CO atmosphere. The reaction diluted with water (100 mL), and then extracted with EtOAc (3*50 mL). The organic phase was washed with brine (100 mL) and dried with anhydrous sodium sulfate. The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The crude was purified by flash chromatography to obtain Example **176** (140 mg, 89%) as a yellow solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.30-1.36 (m, 6H, $C(CH_3)_2$); 1.49 (s, 6H, $C(CH_3)_2$); 1.86-1.89 (m, 2H, CH_2); 3.50-3.56 (m, 4H, $CH_2C(O)$ + N-CH_2); 3.61 (s, 3H, O-CH_3); 3.63-3.69 (m, 2H, N-CH_2); 3.80-3.87 (m, 2H, N-CH_2); 3.92-3.96 (m, 2H, N-CH_2); 6.58-6.61 (m, 1H, Ar); 7.10 (d, *J* 8.6 Hz, 1H, Ar); 7.16-7.20 (m, 1 H, Ar); 7.25 (d, *J* 8.6 Hz, 1H, Ar); 7.39-7.47 (m, 2H, 2 Ar); 7.60 (t, *J* = 8.7 Hz, 1H, Ar); 7.97 (d, *J* = 2.2 Hz, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 580.2

Example **177**: 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-8,8-dimethyl-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



To a solution of Example **176** (150 mg) in THF (2 mL) was added LiOH (124 mg) and H_2O (3 mL). The reaction mixture was stirred at 25°C for 1 hour, concentrated under reduced pressure and the residue was purified by preparative HPLC (MeCN/H_2O + 0.05% NH_3) to obtain Example **177** (33 mg, 22%) as a white solid.

^{1}HNMR (DMSO-d_6, 400 MHz) δ: 1.34 (s, 6H, $C(CH_3)_2$); 1.49 (s, 6H, $C(CH_3)_2$); 1.89-1.97 (m, 2H, CH_2); 3.41 (s, 2H, $CH_2C(O)$); 3.50-3.56 (m, 2H, N-CH_2); 3.64-3.69 (m, 2H, N-CH_2); 3.84 (s, 2H, N-CH_2); 3.91-3.95 (m, 2H, N-CH_2); 6.58-6.61 (m, 1H, Ar); 7.10 (d, *J* 8.6 Hz, 1H, Ar); 7.16-7.21 (m, 1 H, Ar); 7.25 (d, *J* 8.6 Hz, 1H, Ar); 7.40-7.46 (m, 2H, 2 Ar); 7.60 (t, *J* = 8.7 Hz, 1H, Ar); 7.95 (d, *J* = 2.2 Hz, 1H, Ar). COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 566.2

Compound **218**: 2-bromo-7,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-5(4H)-one

To a solution of 3-bromo-1H-pyrazol-5-amine (1.00 g) in 1,4-dioxane (15 mL) was added cesium carbonate (4.02 g) and 3-methylbut-2-enoyl chloride (805 mg). The reaction was subjected to microwave irradiation at 80 °C for 2 hours and 120 °C for 2 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether 100% to petroleum ether/EtOAc 70:30) to obtain Compound **218** (1.1 g) as a yellow solid.

M/Z (M[^{79}Br]+H)$^+$: 244.0.

Compound **219**: 2-bromo-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine

Compound **218** (3.40 g) was dissolved in BH_3-THF (1M, 139 mL) at 0°C. The reaction mixture was stirred at 25°C for 18 hours then MeOH (100 mL) was added and the mixture was refluxed for 1 hour, then concentrated under reduced pressure. The residue was treated with H_2O (100 mL), extracted with EtOAc (3*70 mL), the combined

organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain Compound **219** (3.26 g) as a white solid.

M/Z ($M[^{79}Br]+H)^+$: 230.0.

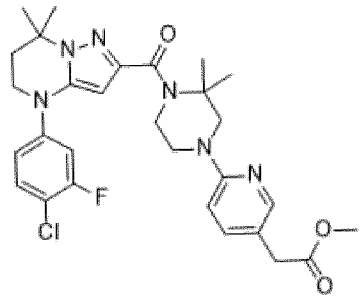
Compound **220**: 2-bromo-4-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine

To a solution of Compound **219** (1.50 g) in Toluene (100 mL) was added 1-chloro-2-fluoro-4-iodobenzene (2.51 g), $Pd(dppf)Cl_2$ (477 mg), 2-(Dicyclohexylphosphanyl)-2',4',6'-tris(isopropyl)biphenyl (311 mg) and sodium 2-methylpropan-2-olate (1.25 g). The reaction mixture was sparged with Nitrogen and heated at 100°C for 2 hours. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether 100% to petroleum ether/EtOAc 70:30) to obtain Compound **220** (1.24 g, 53%) as a brown solid.

^1H NMR (DMSO-d_6, 400 MHz) δ: 1.48(s, 6H, $C(CH_3)_2$); 2.07-2.18 (m, 2H, CH_2); 3.65-3.78 (m, 2H, N-CH_2); 5.75 (s, 1H, Ar); 7.14-7.21 (m, 1H, Ar); 7.29-7.39 (m, 1H, Ar); 7.50-7.54 (m, 1H, Ar).

M/Z ($M[^{79}Br][^{35}Cl]+H)^+$: 358.0.

Example **178**: methyl 2-(6-(4-(4-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

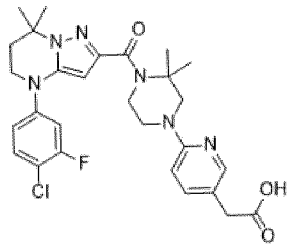


To a solution of Compound **220** (500 mg) in dioxane (50 mL) was added Compound **111** (734 mg), XantPhos Pd G4 (134 mg) and NEt_3 (282 mg). The reaction was heated at 110 °C for 32 hours under CO atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum ether 100% to petroleum ether/EtOAc 5:95) to obtain Example **178** (189 mg, 23%) as a brown solid.

^1H NMR (DMSO-d_6, 400 MHz) δ: 1.45 (s, 6H, $C(CH_3)_2$); 1.53 (s, 6H, $C(CH_3)_2$); 2.12-2.20 (m, 2H, CH_2); 3.47 (s, 2H, $CH_2C(O)$); 3.50-3.54 (m, 2H, N-CH_2); 3.60 (s, 3H, O-CH_3); 3.70-3.79 (m, 2H, N-CH_2); 3.83 (s, 2H, N-CH_2); 4.10-4.20 (m, 2H, N-CH_2); 5.89 (s, 1H, Ar); 6.55-6.61 (m, 1H, Ar); 7.16-7.25 (m, 1H, Ar); 7.30-7.47 (m, 2H, 2 Ar); 7.47-7.59 (m,1H, Ar); 7.92-7.97 (m, 1H).

M/Z ($M[^{35}Cl]+H)^+$: 569.2

Example **179**: 2-(6-(4-(4-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid

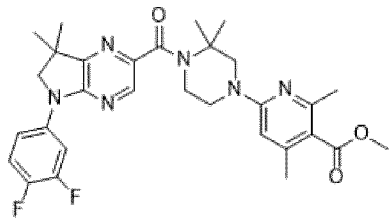


To a solution of Example **178** (189 mg) in THF (10 mL) was added LiOH (39.8 mg) dissolved in water (2.00 mL) at 0 °C. The reaction was stirred at 25°C for 3 hours. The mixture was adjusted pH to 5 with HCl (aq. 1M) and extracted with EtOAc (3*20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by Prep-HPLC (MeCN/H_2O with 0.05% HCOOH) to obtain Example **178** (73 mg, 39%) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.45 (s, 6H, $C(CH_3)_2$); 1.53 (s, 6H, $C(CH_3)_2$); 2.13-2.22 (m, 2H, CH_2); 3.41 (s, 2H, $CH_2C(O)$); 3.45-3.50 (m, 2H, N-CH_2); 3.70-3.77 (m, 2H, N-CH_2); 3.83 (s, 2H, N-CH_2); 4.10-4.19 (m, 2H, N-CH_2); 5.89 (s, 1H, Ar); 6.55-6.61 (m, 1H, Ar); 7.16-7.25 (m, 1H, Ar); 7.30-7.47 (m, 2H, 2 Ar); 7.47-7.59 (m,1H, Ar); 7.92-7.97 (m, 1H), 12.15 (bs, 1H, COOH).

M/Z ($M[^{35}Cl]+H)^+$: 555.2.

Example **180**: methyl 6-(4-(5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

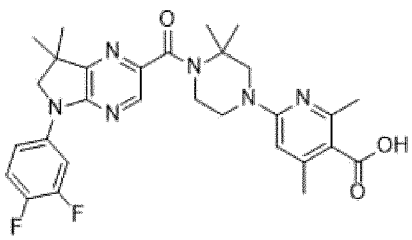


Example **180** was prepared according to general procedure (XIV) starting from Compound **208** (80 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **180** (116 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.39 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 2.23 (s, 3H, $ArCH_3$); 2.34 (s, 3H, $ArCH_3$); 3.49-3.53 (m, 2H, 2 N-CH_2); 3.68-3.85 (m, 5H, O-CH_3 + N-CH_2); 3.90-3.95 (m, 2H, N-CH_2); ; 3.98 (s, 2H, N-CH_2); 6.37 (s, 1H, Ar); 7.36-7.56 (m, 2H, 2 Ar); 7.61-7.69 (m, 1H, Ar); 8.11 (ddd, *J* 13.8, 7.4, 2.2 Hz, 1H, Ar); 8.19 (s, 1H, Ar);

M/Z $(M+H)^+$: 565.1.

Example **181**: 6-(4-(5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **181** was prepared according to general procedure (XI) starting from Example **180** (116 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **181** (33 mg, 24% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.38 (s, 6H, 2 x CH_3); 1.51 (s, 6H, 2 x CH_3); 2.30 (s, 3H, CH_3); 2.45 (s, 3H, CH_3); 3.58-3.65 (m, 2H, N-CH_2); 3.79-3.88 (m, 2H, N-CH_2); 3.92 (s, 2H, N-CH_2); ; 3.97 (s, 2H, N-CH_2); 6.46-6.73 (bs, 1H, Ar); 7.50 (dd, *J* 19.2, 9.4 Hz, 1H, Ar); 7.59-7.69 (m, 1H, Ar); 8.11 (ddd, *J* 13.8, 7.4, 2.2 Hz, 1H, Ar); 8.19 (s, 1H, Ar); COOH was not observed.

M/Z $(M+H)^+$: 551.4.

Compound **221**: 3-chloro-N-cyclopentylpyrazin-2-amine

A solution of 2,3-dichloropyrazine (500 mg) and cyclopentanamine (1.63 mL) in MeTHF (5 mL) was heated at 80°C for 16 hours. The reaction mixture was washed with HCl (aq. 0.1 N, 10 mL), with Brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure to obtain crude Compound **221** (560 mg).

M/Z $(M[^{35}Cl]+H)^+$: 198.2

Compound **222**: 3-chloro-N-cyclopentyl-N-(2-methylallyl)pyrazin-2-amine

To a solution of Compound **221** (560 mg) in THF (28 mL) was added potassium tert-butoxide (445 mg) at 0°C. After 10 minutes, 3-bromo-2-methylprop-1-ene (590 µL) was added and the reaction mixture was stirred at 25°C for 17 hours, then heated at 50 °C for 4 hours. Another protion of base (445 mg) and 3-bromo-2-methylprop-1-ene (590 µL) were added and the mixture was heated at 50°C gor another 17 hours. The reaction mixture was quenched with NH_4Cl (sat. aq. 150 mL), diluted with water (50 mL), and extracted with EtOAc (3*150 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 90:10) to obtain Compound **222** (382 mg, 45% over 2 steps) as a yellow oil.

M/Z $(M[^{35}Cl]+H)^+$: 252.1

Compound **223**: 5-cyclopentyl-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **223** was prepared according to general procedure (XVIII) starting from Compound **222** (381 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **223** (239 mg, 73%) as a yellow oil.

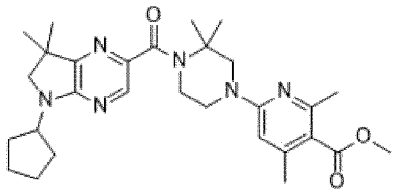
M/Z $(M[^{35}Cl]+H)^+$: 218.2

Compound **224**: 2-bromo-5-cyclopentyl-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **224** (320 mg, 98%) was obtained without further purification as a yellow solid following general procedure (XVI) in MeCN, starting from Compound **223** (239 mg).

M/Z $(M[^{35}Cl][^{81}Br]+H)^+$: 298.2

Example **182**: methyl 6-(4-(5-cyclopentyl-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

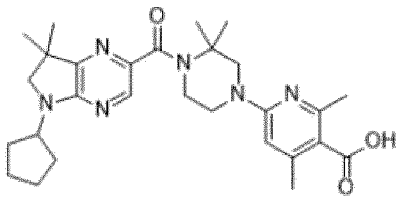


Example **182** was prepared according to general procedure (XIV) starting from Compound **224** (100 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Example **182** (90 mg, 51%) as a clear oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.28 (s, 6H, 2 CH_3); 1.46 (s, 6H, 2 CH_3); 1.57-1.72 (m, 6H, 3 CH_2); 1.79-1.86 (m, 2H, CH_2); 2.23 (s, 3H, CH_3); 2.40 (s, 3H, CH_3); 3.43 (s, 2H, N-CH_2); 3.52-3.55 (m, 2H, N-CH_2); 3.78 (s, 3H, O-CH_3); 3.78-3.90 (m, 4H, 2 N-CH_2); 4.39 (q, *J* 7.3 Hz, 1H, N-CH); 6.36 (s, 1H, Ar); 7.95 (s, 1H, Ar).

M/Z $(M+H)^+$: 521.5

Example **183**: 6-(4-(5-cyclopentyl-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **183** was prepared according to general procedure (XI) starting from Example **182** (90 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 95:05 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **183** (57 mg, 60%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.29 (s, 6H, 2 CH_3); 1.51 (s, 6H, 2 CH_3); 1.56-1.72 (m, 6H, 3 CH_2); 1.81-1.88 (m, 2H, CH_2); 2.36 (s, 3H, CH_3); 2.55 (s, 3H, CH_3); 3.46 (s, 2H, N-CH_2); 3.69-3.72 (m, 2H, N-CH_2); 3.89 (t, *J* 5.2 Hz, 2H, N-CH_2); 3.95 (s, 2H, N-CH_2); 4.41 (m, *J* 7.3 Hz, 1H, N-CH); 6.90 (bs, 1H, Ar); 7.95 (s, 1H, Ar); COOH was not observed.

M/Z $(M+H)^+$: 507.4.

Compound **225**: 3-chloro-N-(3-fluoro-4-methylphenyl)-N-(2-methylallyl)pyrazin-2-amine

Crude Compound **225** (1070 mg) was obtained as a brown oil according to general procedure (XVII) on a 500 mg scale, using 3-fluoro-4-methylaniline.

M/Z $(M[^{35}Cl]+H)^+$: 292.2.

Compound **226**: 5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **226** was prepared according to general procedure (XVIII) starting from crude Compound **225** (970 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **226** (385 mg, 45% over 2 steps) as an orange oil.

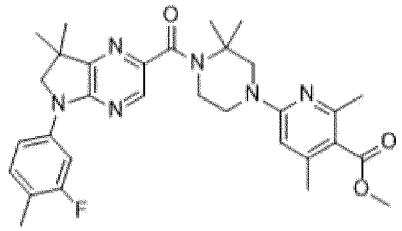
M/Z $(M+H)^+$: 258.2

Compound **227**: 2-bromo-5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **227** (394 mg, 86%) was obtained as a yellow solid following general procedure (XVI) in MeCN, after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30), starting from Compound **226** (350 mg).

M/Z ($M[^{79}Br]+H)^+$: 336.2.

Example **184**: methyl 6-(4-(5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

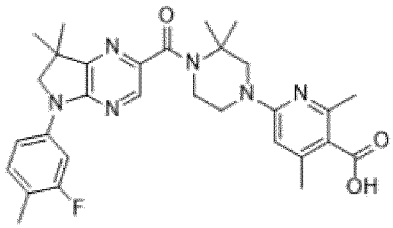


Example **184** was prepared according to general procedure (XIV) starting from Compound **227** (150 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Example **184** (150 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.39 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 2.22 (s, 3H, CH_3); 2.24 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 3.53-3.56 (m, 2H, N-CH_2); 3.78 (s, 3H, O-CH_3); 3.78-3.83 (m, 2H, N-CH_2); 3.86-3.89 (m, 2H, N-CH_2); 3.96 (s, 2H, N-CH_2); 6.35 (s, 1H, Ar); 7.28-7.34 (m, 1H, Ar); 7.45-7.54 (m, 1H, Ar); 7.85-7.90 (m, 1H, Ar); 8.18 (s, 1H, Ar).

M/Z $(M+H)^+$: 561.5

Example **185**: 6-(4-(5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **185** was prepared according to general procedure (XI) starting from Example **184** (150 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 90:10 to 50:50) and freeze dried with HCl (0.1 N in water) to obtain Example **185** (87 mg, 56% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.36 (s, 6H, $(CH_3)_2$); 1.52 (s, 6H, $(CH_3)_2$); 2.21 (s, 3H, CH_3); 2.33 (s, 3H, CH_3); 3.62-3.70 (m, 2H, N-CH_2); 3.83-3.90 (m, 2H, N-CH_2); 3.92-3.97 (m, 4H, N-CH_2); 6.75 (bs, 1H, Ar); 7.28-7.34 (m, 1H, Ar); 7.51-7.54 (m, 1H, Ar); 7.65-7.70 (m, 1H, Ar); 8.18 (s, 1H, Ar). One CH_3 and COOH were not observed.

M/Z $(M+H)^+$: 547.4.

Compound **228**: 3-chloro-N-(4-chloro-3,5-difluorophenyl)-N-(2-methylallyl)pyrazin-2-amine

Crude Compound **228** (856 mg) was obtained as a brown oil according to general procedure (XVII) on a 683 mg scale, using 4-chloro-3,5-difluoroaniline.

M/Z ($M[^{35}Cl]_2+H)^+$: 330.2

Compound **229**: 5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **229** was prepared according to general procedure (XVIII) starting from crude Compound **228** (856 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **229** (586 mg, 65% over 2 steps) as a white solid.

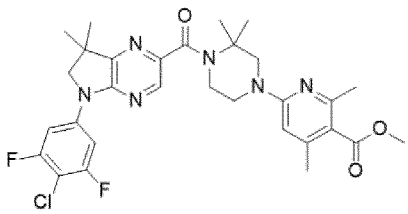
M/Z ($M[^{35}Cl]+H)^+$: 296.2

Compound **230**: 2-bromo-5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **230** (461 mg, 62%) was obtained as a white solid following general procedure (XVI) in MeCN, after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30), starting from Compound **229** (586 mg).

M/Z ($M[^{81}Br][^{35}Cl]+H)^+$: 376.2.

Example **186**: methyl 6-(4-(5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

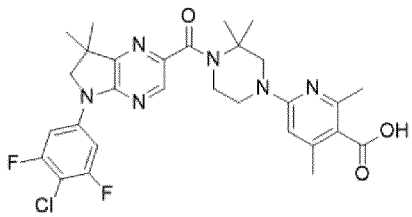


Example **186** was prepared according to general procedure (XIV) starting from Compound **230** (150 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **186** (166 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.40 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 2.23 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 3.51-3.58 (m, 2H, N-CH_2); 3.75-3.82 (m, 5H, O-CH_3 N-CH_2); 3.87-3.92 (m, 2H, N-CH_2); 4.00 (s, 2H, N-CH_2); 6.37 (s, 1H, Ar); 7.88-7.98 (m, 2H, 2 Ar); 8.26 (s, 1H, Ar).

M/Z ($M[^{35}Cl]+H)^+$: 599.4

Example **187**: 6-(4-(5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **187** was prepared according to general procedure (XI) starting from Example **186** (166 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **187** (45 mg, 18% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.40 (s, 6H, 2 CH_3); 1.53 (s, 6H, 2 CH_3); 2.32 (s, 3H, CH_3); 2.47 (s, 3H, CH_3); 3.59-3.69 (m, 2H, N-CH_2); 3.80-3.88 (m, 2H, N-CH_2); 3.87 (s, 2H, N-CH_2); 4.00 (s, 2H, N-CH_2); 6.50-6.82 (bs, 1H, Ar); 7.91-7.95 (m, 2H, 2 Ar); 8.27 (s, 1H, Ar); COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 585.4

Compound **231**: 3-chloro-N-(3-chloro-4-methylphenyl)-N-(2-methylallyl)pyrazin-2-amine

Crude Compound **231** (1010 mg) was obtained as a yellow oil according to general procedure (XVII) on a 500 mg scale, using 3-chloro-4-methylaniline.

M/Z (M[^{35}Cl]$_2$+H)$^+$: 308.1

Compound **232:** 5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **232** was prepared according to general procedure (XVIII) starting from crude Compound **231** (1010 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **232** (419 mg, 46% over 2 steps) as an off-white solid.

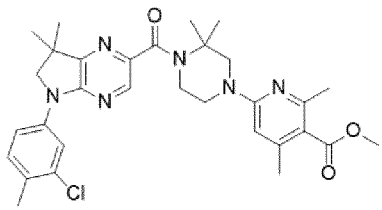
M/Z (M[^{35}Cl]+H)$^+$: 274.2

Compound **233**: 2-bromo-5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **233** (354 mg, 73%) was obtained as a yellow solid following general procedure (XVI) in MeCN, after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30), starting from Compound **232** (377 mg).

M/Z (M[^{81}Br][^{35}Cl] +H)$^+$: 354.2

Example **188**: methyl 6-(4-(5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

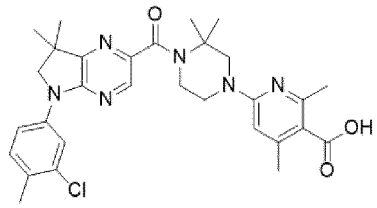


Example **188** was prepared according to general procedure (XIV) starting from Compound **233** (150 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **188** (189 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.39 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 2.23 (s, 3H, CH_3); 2.34 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 3.51-3.58 (m, 2H, N-CH_2); 3.78-3.85 (m, 5H, O-CH_3 N-CH_2); 3.85-3.89 (m, 2H, N-CH_2); 3.99 (s, 2H, N-CH_2); 6.37 (s, 1H, Ar); 7.36-7.53 (m, 2H, 2 Ar); 7.81-7.89 (m, 1H, Ar); 8.19-8.22 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 577.5

Example **189**: 6-(4-(5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **189** was prepared according to general procedure (XI) starting from Example **188** (189 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **189** (83 mg, 35% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.38 (s, 6H, 2 x CH_3); 1.52 (s, 6H, 2 x CH_3); 2.30 (s, 3H, CH_3); 2.33 (s, 3H, CH_3); 3.61-3.75 (m, 2H, N-CH_2); 3.82-3.88 (m, 2H, N-CH_2); 3.96 (s, 4H, 2 N-CH_2); 6.62-6.95 (bs, 1H, Ar); 7.38 (d, J 8.6 Hz; 1H, Ar); 7.68 (d, J 8.6, 2.5 Hz; 1H, Ar); 8.09 (d, J 2.5 Hz; 1H, Ar); 8.20 (s, 1H, Ar); one CH_3 and COOH were not observed.

M/Z (M[^{35}Cl]+H)$^+$: 563.4.

Compound **234**: 3-chloro-N-(3-chloro-4-fluorophenyl)-N-(2-methylallyl)pyrazin-2-amine

Crude Compound **234** (960 mg) was obtained as a yellow oil according to general procedure (XVII) on a 500 mg scale, using 3-chloro-4-fluoroaniline.

M/Z (M[^{35}Cl]$_2$+H)$^+$: 312.2

Compound **235:** 5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **235** was prepared according to general procedure (XVIII) starting from crude Compound **234** (960 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **235** (511 mg, 55% over 2 steps) as an off-white solid.

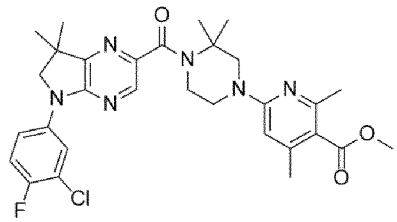
M/Z (M[^{35}Cl]+H)$^+$: 278.1

Compound **236**: 2-bromo-5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **236** (504 mg, 77%) was obtained as a yellow solid following general procedure (XVI) in MeCN, after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30), starting from Compound **235** (511 mg).

M/Z (M[^{81}Br][^{35}Cl] +H)$^+$: 358.1

Example **190**: methyl 6-(4-(5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

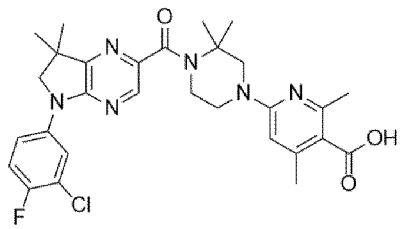


Example **190** was prepared according to general procedure (XIV) starting from Compound **236** (150 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **190** (122 mg) as a brown oil.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.40 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 2.24 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 3.51-3.58 (m, 2H, N-CH_2); 3.76-3.82 (m, 5H, O-CH_3 N-CH_2); 3.85-3.89 (m, 2H, N-CH_2); 3.99 (s, 2H, N-CH_2); 6.34-6.40 (bs, 1H, Ar); 7.42 (d, *J* 8.6 Hz, 1H, Ar); 7.68 (d, *J* 8.6, 2.5 Hz, 1H, Ar); 8.10 (d, *J* 2.5 Hz, 1H, Ar); 8.19 (s, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 581.4

Example **191**: 6-(4-(5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **191** was prepared according to general procedure (XI) starting from Example **190** (122 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **191** (43 mg, 18% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.40 (s, 6H, 2 CH_3); 1.53 (s, 6H, 2 CH_3); 2.34 (s, 3H, CH_3); 3.61-3.73 (m, 2H, N-**CH_2**); 3.82-3.91 (m, 2H, N-CH_2); 3.95 (s, 2H, N-CH_2); 4.00 (s, 2H, N-CH_2); 6.59-6.89 (bs, 1H, Ar); 7.44-7.56 (m, 1H, Ar); 7.80-7.88 (m; 1H, Ar); 8.18-8.24 (m; 1H, Ar); 8.22 (s, 1H, Ar); One CH_3 and COOH were not observed.

M/Z (M[^{35}Cl]+H)$^+$: 567.4.

Compound **237**: 3-chloro-N-(3-chloro-4-(trifluoromethyl)phenyl)-N-(2-methylallyl)pyrazin-2-amine

Crude Compound **237** (780 mg) was obtained as a yellow oil according to general procedure (XVII) on a 500 mg scale, using 3-chloro-4-(trifluoromethyl)aniline.

M/Z (M[^{35}Cl]$_2$+H)$^+$: 363.2

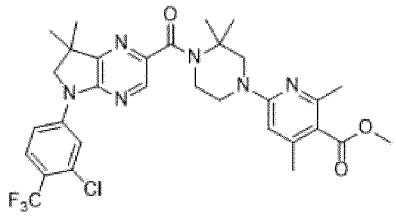
Compound **238:** 5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **238** was prepared according to general procedure (XVIII) starting from crude Compound **237** (780 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **238** (528 mg, 48% over 2 steps) as a white solid.

M/Z (M[^{35}Cl]+H)$^+$: 328.3

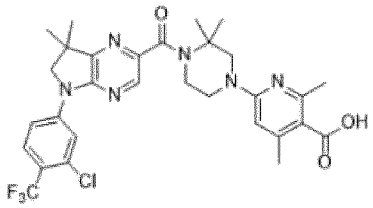
Compound **239**: 2-bromo-5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine
Compound **239** (503 mg, 78%) was obtained as a white solid following general procedure (XVI) in MeCN without further purification starting from Compound **238** (520 mg).
M/Z (M[^{81}Br][^{35}Cl] +H)$^+$: 408.0

Example **192**: methyl 6-(4-(5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



Example **192** was prepared according to general procedure (XIV) starting from Compound **239** (150 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 30:70) to obtain Example **192** (112 mg, 48%) as a white solid.
^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.40 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 2.24 (s, 3H, CH_3); 2.34 (s, 3H, CH_3); 3.52-3.58 (m, 2H, N-CH_2); 3.75-3.82 (m, 5H, O-CH_3 N-CH_2); 3.85-3.88 (m, 2H, N-CH_2); 3.99 (s, 2H, N-CH_2); 6.37 (s, 1H, Ar); 7.85-7.90 (m, 1H, Ar); 7.96-8.00 (m, 1H, Ar); 8.25 (s, 1H, Ar); 8.29-8.32 (m, 1H, Ar).
M/Z (M[^{35}Cl]+H)$^+$: 631.3

Example **193**: 6-(4-(5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **193** was prepared according to general procedure (XI) starting from Example **192** (122 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **193** (43 mg, 18% over 2 steps) as a yellow solid.
^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.40 (s, 6H, $(CH_3)_2$); 1.53 (s, 6H, $(CH_3)_2$); 2.33 (s, 3H, CH_3); 3.60-3.71 (m, 2H, CH_2); 3.81-3.88 (m, 2H, CH_2); 3.92-3.97 (m, 2H, CH_2); 4.05 (s, 2H, CH_2); 6.77 (bs, 1H, Ar); 7.86-7.89 (m, 1H, Ar); 7.96-7.99 (m, 1H, Ar); 8.29 (s, 1H, Ar); 8.30-8.32 (m, 1H, Ar), One CH_3 and COOH were not observed
M/Z (M[^{35}Cl]+H)$^+$: 617.3

Compound **240**: diethyl 1-(1-((tert-butoxycarbonyl)amino)-2-methylpropan-2-yl)-1H-pyrazole-3,5-dicarboxylate
To a solution of diethyl 1H-pyrazole-3,5-dicarboxylate (3.0 g) in THF (30 mL) was added tert-butyl (2-hydroxy-2-methylpropyl) carbamate (5.35 g), Ph_3P (6.67 g) and DIAD (5.15 g). The reaction was heated at 50 °C for 1 hour

under a nitrogen atmosphere. The mixture was quenched with H_2O (60 mL) and extracted with EtOAc (3*60 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 then concentrated. The crude was purified by flash chromatography (Petroleum ether 100% to Petroleum ether/EtOAc 80:20) to obtain Compound **240** (3.56 g, 65%) as a yellow oil.

M/Z $(M+H)^+$: 284.2.

Compound **241**: ethyl 7,7-dimethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylate

A solution of Compound **240** (3.56 g) and HCl (4M in dioxane, 46 mL) was stirred at 25°C for 4 hours. The reaction mixture was treated with Na_2CO_3 (sat. aq.) to pH = 10 and extracted with EtOAc (3*80 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain Compound 241 (2.12 g, 96%) as a yellow solid.

^1H NMR (DMSO-d_6, 400 MHz) δ 1.30 (t, *J* 7.1 Hz, 3H, CH_2-CH_3); 1.50 (s, 6H, $C(CH_3)_2$); 3.49-3.53 (m, 2H, N-CH_2); 4.26-4.33 (m, 2H, N-CH_2), 7.09 (s, 1H, Ar), 8.44 (s, 1H, C(O)NH).

M/Z $(M+H)^+$: 238.1.

Compound **242**: ethyl 7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylate

A solution of Compound **241** (1.0 g) and BH_3.THF (1M in THF, 63 mL) was stirred at 25°C for 16 hours, then quenched with 50 mL MeOH and refluxed for 1 hour. The mixture was then concentrated under reduced pressure, taken up in H_2O (50 mL), and extracted with EtOAc (3*50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether 100% to Petroleum ether/EtOAc 0:100) to obtain Compound **242** (0.45 g, 47%) as a white solid.

^1H NMR (DMSO-d_6, 400 MHz) δ 1.27 (t, *J* 7.1 Hz, 3H, CH_2-CH_3), 1.44 (s, 6H, $C(CH_3)_2$), 2.94 (s, 2H, N-CH_2); 3.88 (s, 2H, N-CH_2); 4.24 (q, *J* 7.1 Hz, 2H, CH_2-CH_3); 6.40 (s, 1H, Ar).

M/Z $(M+H)^+$: 224.1

Compound **243**: ethyl 5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylate

To a solution of Compound **242** (451 mg), in Dioxane (50 mL), was added 1-chloro-2-fluoro-4-iodobenzene (777 mg), RuPhos Pd G4 (172 mg) and cesium carbonate (1.32 g). The reaction was sparged with nitrogen then heated at 100°C for 2 hours, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum ether 100% to Petroleum ether/EtOAc 60:40) to obtain Compound **243** (548 mg, 77%) as an off-white solid.

^1H NMR (DMSO-d_6, 400 MHz) δ 1.29 (t, *J* 7.1 Hz, 3H, CH_2-CH_3); 1.52 (s, 6H, $C(CH_3)_2$); 3.65-3.71 (m, 2H, N-CH_2); 4.27 (q, *J* 7.1 Hz, 2H, CH_2-CH_3); 4.45-4.51 (m, 2H, N-CH_2); 6.56 (s, 1H, Ar); 6.82-6.98 (m, 1H, Ar) ; 7.06-7.18 (m, 1H, Ar); 7.35-7.47 (m, 1H, Ar).

M/Z $(M[^{35}Cl]+H)^+$: 352.1

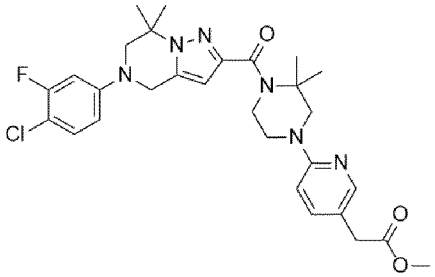
Compound **244**: 5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid

To a solution of Compound 243 (528 mg) in THF (25 mL) was added LiOH (359 mg) and H_2O (5 mL). The reaction mixture was stirred at 25°C for 48 hours, acidified with HCl (1M, aq.) to pH = 5, then extracted with EtOAc (3*30 mL).

The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain Compound **244** (488 mg) as a white solid.

M/Z ($M[^{35}Cl]+H)^+$: 324.1

Example **194**: methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

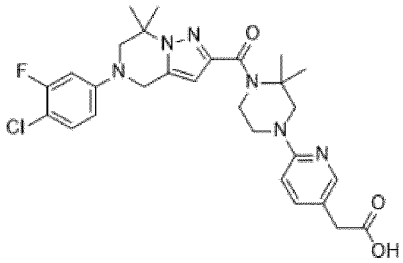


To a solution of Compound **244** (200 mg) in DMF (15 mL) was added HATU (352 mg) and DIPEA (240 mg) at 0°C. The mixture was stirred for 20 minutes before adding Compound **111** (195 mg). The reaction mixture was stirred at 25°C for 2 hours then diluted with H_2O (10 mL) and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum ether 100% to Petroleum ether/EtOAc 30:70) to obtain Example **194** (381 mg) as a yellow solid.

^1H NMR (DMSO-d_6, 400 MHz) δ 1.47 (s, 6H, $C(CH_3)_2$); 1.52 (s, 6H), $C(CH_3)_2$); 3.48 (t, *J* 5.4 Hz, 2H, N-CH_2); 3.54 (s, 2H, $CH_2C(O)$); 3.61 (s, 3H, O-CH_3); 3.68 (s, 2H, N-CH_2); 3.84 (s, 2H, N-CH_2); 4.11 (t, *J* 5.4 Hz, 2H, N-CH_2); 4.50 (s, 2H, N-CH_2); 6.31 (s, 1H, Ar); 6.59 (d, *J* 8.8 Hz, 1H, Ar); 6.87-6.94 (m, 1H, Ar); 7.06-7.15 (m, 1H, Ar); 7.36-7.47 (m, 2H); 7.96 (d, *J* = 2.1 Hz, 1H);

M/Z ($M[^{35}Cl]+H)^+$: 569.2.

Example **195**: 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



To a solution of Example **194** (189 mg) in THF (30 mL) was added LiOH (152 mg) dissolved in water (6 mL) at 0 °C. The reaction was stirred at 25°C for 3 hours. The mixture was adjusted pH to 5 with HCl (aq. 1M) and extracted with EtOAc (3*30 mL). The combined organic layer was washed with brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by Prep-HPLC (MeCN/H_2O with 0.05% HCOOH) to obtain Example **195** (163 mg, 46%) as a white solid.

^1H NMR (DMSO-d_6, 400 MHz) δ 1.48 (s, 6H, $C(CH_3)_2$); 1.53 (s, 6H), $C(CH_3)_2$); 3.43 (s, 2H, $CH_2C(O)$); 3.49 (t, *J* 5.4 Hz, 2H, N-CH_2); 3.69 (s, 2H, N-CH_2); 3.85 (s, 2H, N-CH_2); 4.11 (t, *J* 5.4 Hz, 2H, N-CH_2); 4.51 (s, 2H, N-CH_2); 6.32 (s,

1H, Ar); 6.59 (d, *J* 8.6 Hz, 1H, Ar); 6.89-6.96 (m, 1H, Ar); 7.08-7.16 (m, 1H, Ar); 7.36-7.50 (m, 2H, 2 Ar); 7.95 (d, *J* = 2.0 Hz, 1H, Ar); 12.26 (bs, 1H, COOH);
M/Z (M[^{35}Cl]+H)$^{+}$: 555.2.

Compound **245**: methyl 5-bromo-6-((4-methylphenyl)sulfonamido)picolinate
To a solution of methyl 6-amino-5-bromopicolinate (5.00 g) in Pyridine (100 mL) was added 4-methylbenzenesulfonyl chloride (4.95 g), and the reaction was stirred at 120 °C. After 6 hours, H_2O (300 mL) was added. The mixture was extracted with EtOAc (2*300 mL), the combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum ether/EtOAc 50:50) to obtain Compound **245** (3.00 g, 36%) as a yellow solid.
M/Z (M[^{79}Br]+H)$^{+}$: 385.0.

Compound **246**: methyl 5-bromo-6-((4-methyl-N-(2-methylallyl)phenyl)sulfonamido)picolinate
To a solution of Compound **245** (3.40 g) in THF (80 mL) was added triphenylphosphine (3.47 g) and 2-methylprop-2-en-1-ol (764 mg), followed by Diisopropyl azodicarboxylate (3.57 g), slowly mixture at 0 °C. The reaction was stirred at 25°C for 3 hours, then, H_2O (200 mL) was added. The mixture was extracted with EtOAc (2*200 mL), the combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure The residue was purified by flash chromatography (Petroleum ether/EtOAc 75:25) to obtain Compound **246** (2.20 g, 56%) as a yellow solid.
M/Z (M[^{79}Br]+H)$^{+}$: 439.0.

Compound **247**: methyl 3-(4-chloro-3-fluorobenzyl)-3-methyl-1-tosyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carboxylate
To a solution of Compound **246** (2.00 g) in DMF (30 mL) was added K_2CO_3 (2.52 g) and (4-chloro-3-fluorophenyl)boronic acid (1.59 g) and $Pd_2(dba)_3$ (2.08 g). The reaction was stirred at 100 °C for 3 hours, then H_2O (100 mL) was added, and the mixture was extracted with EtOAc (2*100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum ether/EtOAc 75:25) to obtain Compound **247** (2.00 g, 89%) as a white solid.
^{1}H NMR (DMSO-d_6, 400 MHz,) δ 1.33 (s, 3H, C(CH_3)); 2.33 (s, 3H, Ar-CH_3); 2.90-3.01 (m, 2H, Ar-CH_2); 3.67 (d, *J* = 10.1 Hz, 1H, N-CH_aH_b); 3.91 (s, 3H, O-CH_3); 4.09 (d, *J* = 10.1 Hz, 1H, N-CH_aH_b); 6.73 (dd, *J* = 8.2, 1.8 Hz, 1H, Ar); 6.98 (dd, *J* = 10.6, 1.8 Hz, 1H, Ar); 7.26-7.38 (m, 2H); 7.63-7.75 (m, 3H); 7.90 (d, *J* = 8.4 Hz, 2H);
M/Z (M[^{35}Cl]+H)$^{+}$: 489.1.

Compound **248**: methyl 3-(4-chloro-3-fluorobenzyl)-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carboxylate
To a solution of Compound **247** (1.60 g) in H_2SO_4 (20 mL) was heated at 100 °C for 3 hours, then the mixture was added slowly in ice water (200 mL) and extracted with EtOAc (2*200 mL), the combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum ether/EtOAc 50:50) to obtain Compound **248** (650 mg, 59%) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz,) δ 1.27 (s, 3H, C(CH_3)); 2.83-2.95 (m, 2H, Ar-CH_2); 3.14 (d, *J* = 9.1 Hz, 1H, N-CH_aH_b); 3.51 (d, *J* = 9.5 Hz, 1H, N-CH_aH_b); 3.78 (s, 3H, O-CH_3); 6.74 (s, 1H, Ar); 6.84-6.88 (m, 1H, Ar); 7.05-7.11 (m, 1H, Ar); 7.19-7.30 (m, 2H, 2 Ar); 7.40-7.46 (m, 1H, N-H);

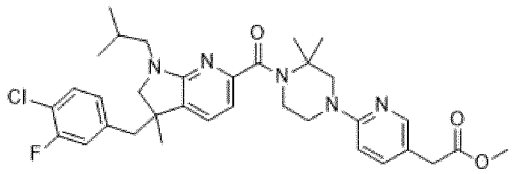
M/Z (M[^{35}Cl]+H)$^+$: 335.0.

Compound **249**: 3-(4-chloro-3-fluorobenzyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid

To a solution of Compound **248** (500 mg) in Toluene (10 mL) was added Potassium 2-methylpropan-2-olate (1.68 g) and 1-bromo-2-methylpropane (1.02 g). The mixture was purged with argon and heated at 60 °C for 3 hours then treated with H_2O (100 mL) and the mixture was extracted with EtOAc (2*100 mL), the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum ether/EtOAc 33:67) to obtain Compound **249** (300 mg, 54%) as a white solid.

M/Z (M[^{35}Cl]+H)$^+$: 377.1.

Example **196**: methyl 2-(6-(4-(3-(4-chloro-3-fluorobenzyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

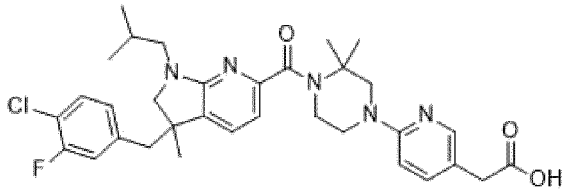


To a solution of Compound **249** (300 mg) in DMF (10 mL) was added HATU (454 mg) and DIPEA (309 mg) at 0°C. The mixture was stirred for 20 minutes before adding Compound **111** (252 mg). The reaction mixture was stirred at 25°C for 2 hours then diluted with H_2O (50 mL) and extracted with EtOAc (2*50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum ether/EtOAc 75:25) to obtain Example **196** (300 mg, 60%) as a yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79-0.90 (m, 6H, CH-(CH_3)$_2$); 1.32-1.36 (m, 3H, C-CH_3); 1.59-1.62 (m, 6H, C-(CH_3)$_2$); 1.81-1.89 (m, 1H, CH-(CH_3)$_2$); 2.74-2.91 (m, 3H, Ar-CH_2 N-CH_aH_b); 3.08-3.14 (m, 1H, N-CH_aH_b); 3.19-3.27 (m, 1H, N-CH_aH_b); 3.42-3.48 (m, 1H, N-CH_aH_b); 3.49 (s, 2H, CH_2C(O)); 3.52-3.56 (m, 2H, N-CH_2); 3.69 (s, 3H, O-CH_3); 3.80-3.87 (m, 4H, 2 N-CH_2); 6.42 (d, *J* = 8.6 Hz, 1H, Ar); 6.70-6.79 (m, 3H, 3 Ar); 6.99 (d, *J* = 7.2 Hz, 1H, Ar); 7.21-7.25 (m, 1H, Ar); 7.42 - 7.49 (m, 1H, Ar); 8.04 (d, *J* = 2.1 Hz, 1H, Ar);

M/Z (M[^{35}Cl]+H)$^+$: 622.3.

Example **197**: 2-(6-(4-(3-(4-chloro-3-fluorobenzyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



To a solution of Example **196** (300 mg) in THF (10 mL) was added LiOH (35 mg) dissolved in water (2 mL) at 0 °C. The reaction was stirred at 25°C for 3 hours. The mixture was adjusted pH to 6 with HCl (aq. 1M) and extracted with EtOAc (2*10 mL). The combined organic laye were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by Prep-HPLC (MeCN/H_2O with 0.05% HCOOH) to obtain Example **197** (200 mg, 68%) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.65-0.80 (m, 6H, CH-$(CH_3)_2$); 1.34 (s, 3H, C-CH_3); 1.42-1.50 (m, 6H, C-$(CH_3)_2$); 1.74-1.79 (m, 1H, CH-$(CH_3)_2$); 2.76-2.90 (m, 3H, Ar-CH_2 N-CH_aH_b); 3.03-3.14 (m, 2H, N-CH_aH_b); 3.40-3.44 (m, 4H, CH_2C(O) N-CH_2); 3.54-3.67 (m, 3H, N-CH_aH_b, N-CH_2); 3.79-3.85 (m, 2H, N-CH_2); 6.51 (d, *J* 8.7 Hz, 1H, Ar); 6.60 (d, *J* 7.1 Hz, 1H, Ar); 6.82-6.88 (m, 1H, Ar); 6.99-7.04 (m, 1H, Ar); 7.32 (d, *J* 7.2 Hz, 1H, Ar); 7.37 - 7.47 (m, 2H, 2 Ar); 7.94 (d, *J* 2.2 Hz, 1H, Ar); 12.26 (bs, 1H, COOH);

M/Z (M[^{35}Cl]+H)$^+$: 608.3

Compound **250**: 1-(3-chloropyridin-2-yl)-3-oxocyclobutane-1-carbonitrile

To a solution of Compound **181** (800 mg) and $RuCl_3$·H_2O (194 mg) in a MeCN/DCM/H_2O mixture (2:2:3, 14 mL) was added $NaIO_4$ at 0°C portionwise. The mixture was stirred at 25°C for 15 hours then diluted in H_2O (50 mL) and extracted with DCM (3*50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain Compound **250** (786 mg, 97%) as a black solid.

M/Z (M[^{35}Cl]+H)$^+$: 207.1

Compound **251**: 1-(3-chloropyridin-2-yl)-3-hydroxycyclobutane-1-carbonitrile

To a solution of Compound **250** (786 mg) in MeOH (10 mL) at 0°C was added $NaBH_4$ (216 mg) portionwise. The reaction mixture was stirred at 0°C for 30 minutes then quenched in NH_4Cl (sat. aq, 50 mL) and extracted with DCM (3*50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain Compound **251** (719 mg, 91%, 6:4 diastereoisomeric mixture) as a brown oil.

M/Z (M[^{35}Cl]+H)$^+$: 209.1

Compound **252**: 1-(3-chloropyridin-2-yl)-3-methoxycyclobutane-1-carbonitrile

Compound **252** was prepared according to general procedure (XIII) starting from Compound **251** (719 mg) and Iodomethane (2.0 eq), and using NaH (60% in mineral oil, 2.0 eq) in THF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 20:80) to obtain Compound **252** (654 mg, 85%, 6:4 diastereoisomeric mixture) as a clear oil.

M/Z (M[^{35}Cl]+H)$^+$: 223.1

Compound **253**: (1-(3-chloropyridin-2-yl)-3-methoxycyclobutyl)methanamine

Compound **253** (369 mg) was obtained as a clear oil following general procedure (XVa), starting from Compound **252** (719 mg).

M/Z (M[^{35}Cl]+H$^+$): 227.1

Compound **254**: (minor diastereoisomere) 1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

And Compound **255**: (major diastereoisomere) 1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **254** and Compound **255** were prepared according to general procedure (Xc) from Compound **253** (361 mg) and 4-bromo-1-chloro-2-fluorobenzene. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **254** (88 mg, 8% over 2 steps) as a white solid and Compound **255** (125 mg, 12% over 2 steps) as a white solid.

Compound **254**: M/Z (M[^{35}Cl]+H$^+$): 319.3.

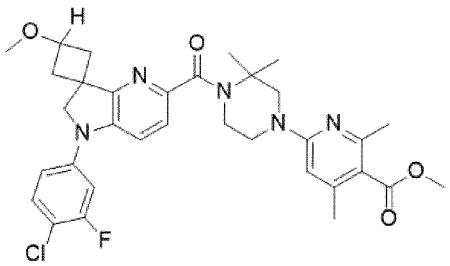
Compound **255**: M/Z (M[^{35}Cl]+H$^+$): 319.3.

Compound **256**: (major diastereoisomere) 5'-bromo-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **256** was prepared according to general procedure (XVI) in MeCN from Compound **255** (125 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **256** (123 mg, 79%) as a clear oil.

M/Z (M[^{35}Cl][^{81}Br]+H)$^+$: 399.1.

Example **198**: (major diastereoisomere) methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

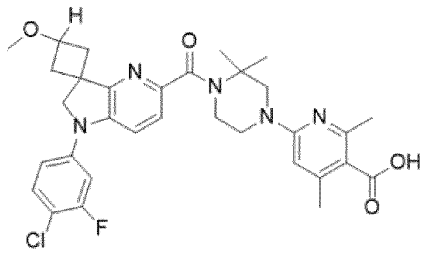


Example **198** was prepared according to general procedure (XIV) starting from Compound **256** (123 mg) and Compound **10** (1.5 eq), and using triethylamine (4.0 eq), $Mo(CO)_6$ (2.0 eq), XantPhos Pd G4 (0.13 eq), and DBU (5.8 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **198** (93 mg) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.51 (s, 6H, $C(CH_3)_2$); 2.25 (s, 3H, $ArCH_3$); 2.36 (s, 3H, $ArCH_3$); 2.37-2.45 (m, 2H, 2 CH_aH_b); 3.23 (s, 3H, O-CH_3); 3.59-3.65 (m, 2H, N-CH_2-CH_2); 3.79 (s, 3H, C(O)OCH_3); 3.85-3.89 (m, 2H, N-CH_2-CH_2); 3.93 (s, 2H, N-CH_2); 3.98-4.13 (m, 1H, OCH); 4.21 (s, 2H, N-CH_2); 6.35 (s, 1H, Ar); 7.19 (dd, *J* 8.9, 2.0 Hz, 1H, Ar); 7.32 (dd, *J* 11.8, 2.5 Hz, 1H, Ar); 7.38 (d, *J* 8.5 Hz, 1H, Ar); 7.53-7.60 (m, 2H, 2 Ar); 2 CH_aH_b were not observed.

M/Z (M[^{35}Cl]+H$^+$): 622.4.

Example **199**: (major diastereoisomere) 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **199** was prepared according to general procedure (XI) starting from Example **198** (93 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **199** (44 mg, 22% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.54 (s, 6H, $C(CH_3)_2$); 2.33 (s, 3H, $ArCH_3$); 2.36-2.45 (m, 2H, 2 CH_aH_b); 2.52-2.58 (m, 2H, 2 CH_aH_b); 3.22 (s, 3H, O-CH_3); 3.66-3.75 (m, 2H, N-CH_2-CH_2); 3.85-3.94 (m, 2H, N-CH_2-CH_2); 3.98 (s, 2H, N-CH_2); 3.95-4.11 (m, 1H, OCH); 4.20 (s, 2H, N-CH_2); 6.66 (s, 1H, Ar); 7.19 (dd, *J* 8.9, 2.0 Hz, 1H, Ar); 7.33 (dd, *J* 11.8, 2.5 Hz, 1H, Ar); 7.38 (d, *J* 8.5 Hz, 1H, Ar); 7.53-7.60 (m, 2H, 2 Ar); One $ArCH_3$ and COOH were not observed.

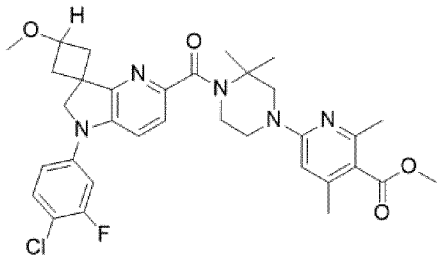
M/Z (M[^{35}Cl]+H$^+$): 608.4.

Compound **257**: (minor diastereoisomere) 5'-bromo-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **257** was prepared according to general procedure (XVI) in MeCN from Compound **254** (88 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **257** (64 mg, 58%) as a clear oil.

M/Z (M[^{35}Cl][^{81}Br]+H)$^+$: 399.1.

Example **200**: (minor diastereoisomere) methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

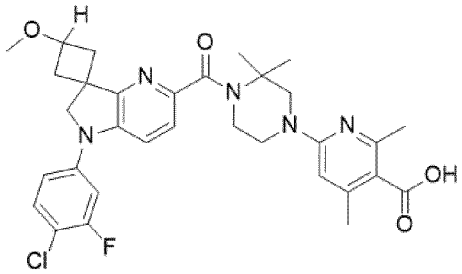


Example **200** was prepared according to general procedure (XIV) starting from Compound **257** (123 mg) and Compound **10** (1.5 eq), and using triethylamine (4.0 eq), $Mo(CO)_6$ (2.0 eq), XantPhos Pd G4 (0.13 eq), and DBU (5.8 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **200** (46 mg) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.51 (s, 6H, $C(CH_3)_2$); 2.25 (s, 3H, $ArCH_3$); 2.26-2.29 (m, 2H, 2 CH_aH_b); 2.34 (s, 3H, $ArCH_3$); 2.61-2.70 (m, 2H, 2 CH_aH_b); 3.24 (s, 3H, O-CH_3); 3.59-3.65 (m, 2H, N-CH_2-CH_2); 3.79 (s, 3H, C(O)OCH_3); 3.83-3.96 (m, 4H, N-CH_2-CH_2, N-CH_2); 4.17 (s, 2H, N-CH_2); 4.22-4.38 (m, 1H, OCH); 6.36 (s, 1H, Ar); 7.17 (dd, *J* 8.6, 2.0 Hz, 1H, Ar); 7.32 (dd, *J* 11.8, 2.6 Hz, 1H, Ar); 7.39 (d, *J* 8.5 Hz, 1H, Ar); 7.54-7.61 (m, 2H, 2 Ar);

M/Z (M[^{35}Cl]+H$^+$): 622.4.

Example **201**: (minor diastereoisomere) 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid

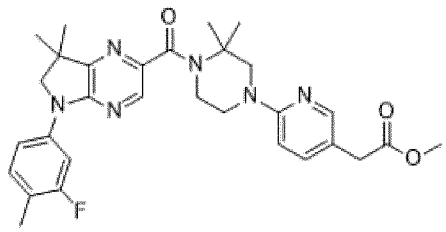


Example **201** was prepared according to general procedure (XI) starting from Example **200** (46 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **200** (20 mg, 19% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.55 (s, 6H, $C(CH_3)_2$); 2.20-2.30 (m, 2H, 2 CH_aH_b); 2.33 (s, 3H, $ArCH_3$); 2.61-2.71 (m, 2H, 2 CH_aH_b); 3.23 (s, 3H, $O\text{-}CH_3$); 3.68-3.78 (m, 2H, $N\text{-}CH_2\text{-}CH_2$); 3.91-3.97 (m, 4H, $N\text{-}CH_2$ $N\text{-}CH_2\text{-}CH_2$); 4.15 (s, 2H, $N\text{-}CH_2$); 4.23-4.36 (m, 1H, OCH); 6.71 (s, 1H, Ar); 7.23-7.33 (m, 1H, Ar); 7.36-7.43 (m, 1H, Ar); 7.48-7.58 (m, 2H, 2 Ar); One $ArCH_3$ and COOH were not observed.

M/Z (M[^{35}Cl]+H^+): 608.3.

Example **202**: methyl 2-(6-(4-(5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

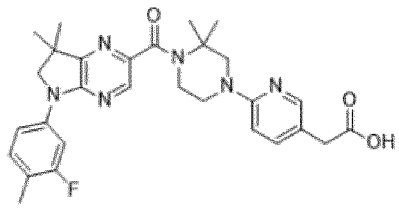


Example **202** was prepared according to general procedure (XIV) starting from Compound **227** (150 mg) and Compound **111** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Example **202** (164 mg) as a yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.38 (s, 6H, $(CH_3)_2$); 1.50 (s, 6H, $(CH_3)_2$); 2.21 (s, 3H, $ArCH_3$); 3.48-3.53 (m, 4H, $CH_2C(O)$ $N\text{-}CH_2$); 3.59-3.66 (m, 4H, 2 $N\text{-}CH_2$); 3.78-3.88 (m, 3H, $O\text{-}CH_3$); 3.96 (s, 2H, $N\text{-}CH_2$); 7.29-7.32 (m, 1H, Ar); 7.35-7.43 (m, 1H, Ar); 7.49-7.53 (m, 1H, Ar); 7.52-7.55 (m, 1H, Ar); 7.96-8.01 (m, 2H, 2 Ar); 8.18 (s, 1H, Ar);

M/Z $(M+H)^+$: 547.4

Example **203**: 2-(6-(4-(5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid

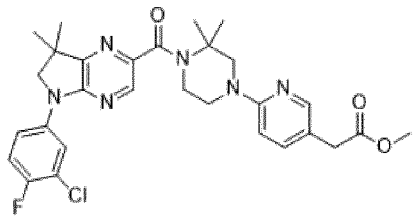


Example **203** was prepared according to general procedure (VII) starting from Example **202** (142 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **203** (90 mg, 35% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.36 (s, 6H, $(CH_3)_2$); 1.55 (s, 6H, $(CH_3)_2$); 2.20 (s, 3H, $ArCH_3$); 3.66 (s, 2H, $C(O)CH_2$); 3.71-3.77 (m, 2H, N-CH_2); 3.88-3.91 (m, 2H, N-CH_2); 3.92 (s, 2H, N-CH_2); 4.04 (s, 2H, N-CH_2); 7.27-7.33 (m, 1H, Ar); 7.38-7.42 (m, 1H, Ar); 7.49-7.53 (m, 1H, Ar); 7.64-7.69 (m, 1H, Ar); 7.96-8.01 (m, 2H, 2 Ar); 8.20 (s, 1H, Ar). One COOH was not observed.

M/Z $(M+H)^+$: 533.4

Example **204**: methyl 2-(6-(4-(5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

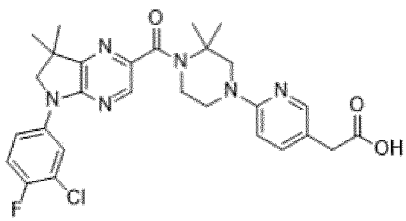


Example **204** was prepared according to general procedure (XIV) starting from Compound **236** (150 mg) and Compound **111** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **204** (144 mg) as a yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.39 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 3.50-3.60 (m, 4H, N-CH_2 $CH_2C(O)$); 3.64 (s, 3H, O-CH_3); 3.77-3.85 (m, 4H, 2 N-CH_2); 3.98 (s, 2H, N-CH_2); 7.41-7.51 (m, 3H, 3 Ar); 7.82-7.85 (m, 1H, Ar); 7.94-7.96 (m, 1H, Ar); 8.17-8.20 (m, 2H, 2 Ar).

M/Z $(M[^{35}Cl]+H)^+$: 567.3

Example **205**: 2-(6-(4-(5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **205** was prepared according to general procedure (VII) starting from Example **204** (148 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **205** (96 mg, 39% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.40 (s, 6H, 2 CH_3); 1.56 (s, 6H, 2 CH_3); 3.67 (s, 2H, $CH_2C(O)$); 3.70-3.79 (m, 2H, N-CH_2); 3.87-3.96 (m, 2H, N-CH_2); 3.99 (s, 2H, N-CH_2); 4.01 (s, 2H, N-CH_2); 7.34-7.45 (m, 1H, Ar); 7.47-7.53 (m, 1H, Ar); 7.82-7.87 (m, 1H, Ar); 7.95-8.02 (m, 1H, Ar); 8.17-8.26 (m, 2H, 2 Ar); One COOH was not observed.
M/Z (M[^{35}Cl]+H)$^+$: 553.3

Compound **258**: methyl 1-(3-chloropyrazin-2-yl)cyclopentane-1-carboxylate
Compound **258** was prepared according to general procedure (Ib) from dichloropyrazine (1.85 g) and methyl cyclopentanecarboxylate. The crude Compound **258** (3.40 g) obtained as an orange oil was directly engaged in the following step.
M/Z (M[^{35}Cl]+H)$^+$: 241.0.

Compound **259**: (1-(3-chloropyrazin-2-yl)cyclopentyl)methanol
Compound **259** was prepared according to general procedure (XX) from Compound **258** (1.00 g). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **259** (0.24 g, 32% over 2 steps) as a clear oil.
M/Z (M[^{35}Cl]+H)$^+$: 213.1.

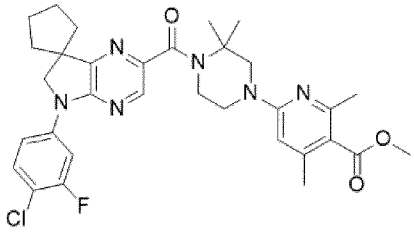
Compound **260**: 1-(3-chloropyrazin-2-yl)cyclopentane-1-carbaldehyde
Compound **260** was prepared according to general procedure (XXI) from Compound **259** (260 mg). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **260** (169 mg, 66%) as a clear oil.
M/Z (M[^{35}Cl]+H)$^+$: 211.1.

Compound **261**: 4-chloro-N-((1-(3-chloropyrazin-2-yl)cyclopentyl)methyl)-3-fluoroaniline
Compound **261** was prepared according to general procedure (XXII) from Compound **260** (165 mg) and 4-chloro-3-fluoroaniline. The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **261** (147 mg, 55%) as a clear oil.
M/Z (M[^{35}Cl]$_2$+H)$^+$: 340.2.

Compound **262**: 5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]
Compound **262** was prepared according to general procedure (XXIII) from Compound **261** (145 mg). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **262** (100 mg, 77%) as a white solid.
M/Z (M[^{35}Cl]+H)$^+$: 304.2.

Compound **263**: 2'-bromo-5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]
Compound **263** (137 mg, 64%) was obtained as a beige solid following general procedure (XVI) in EtOAc, after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30), starting from Compound **262** (170 mg).
M/Z (M[^{81}Br][^{35}Cl] +H)$^+$: 384.1

Example **206**: methyl 6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

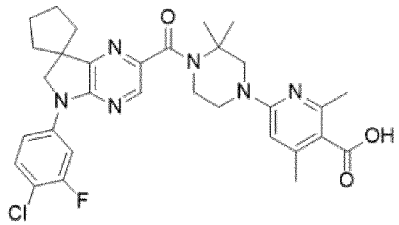


Example **206** was prepared according to general procedure (XIV) starting from Compound **263** (137 mg) and Compound **10** (1.5 eq), and using triethyl amine (5.0 eq), $Mo(CO)_6$ (1.95 eq), XantPhos Pd G4 (0.13 eq), and DBU (6 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **206** (110 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.50 (s, 6H, 2 CH_3); 1.79-2.03 (m, 8H, 4 CH_2); 2.23 (s, 3H, $ArCH_3$); 2.34 (s, 3H, $ArCH_3$); 3.52-3.60 (m, 2H, N-CH_2); 3.76-3.83 (m, 5H, N-CH_2 O-CH_3); 3.89 (s, 2H, N-CH_2); 4.08 (s, 2H, N-CH_2); 6.36 (m, 1H, Ar); 7.58-7.66 (m, 1H, Ar); 7.76-7.78 (m, 1H, Ar); 8.05-8.07 (m, 1H, Ar); 8.21 (s, 1H, Ar);

M/Z (M[^{35}Cl]+H)$^+$: 607.4.

Example **207**: 6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **207** was prepared according to general procedure (XI) starting from Example **206** (110 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **207** (35 mg, 16% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.49 (s, 6H, 2 CH_3); 1.77-2.00 (m, 8H, 4 CH_2); 2.27 (s, 3H, $ArCH_3$); 2.38 (s, 3H, $ArCH_3$); 3.53-3.60 (m, 2H, N-CH_2); 3.78-3.84 (m, 2H, N-CH_2); 3.88 (s, 2H, N-CH_2); 4.08 (s, 2H, N-CH_2); 6.36 (s, 1H, Ar); 7.62 (t, *J* 9.0 Hz, 1H, Ar); 7.76 (dd, *J* 9.0, 2.5 Hz,1H, Ar); 8.09 (dd, *J* 12.7, 2.5 Hz, 1H, Ar); 8.22 (s, 1H, Ar); 12.73 (bs, 1H, COOH).

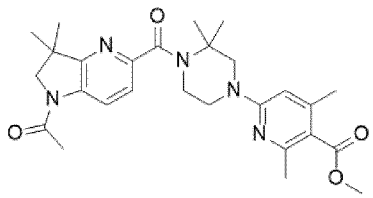
M/Z (M[^{35}Cl]+H)$^+$: 593.5.

Compound **264**: 1-(5-chloro-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)ethan-1-one

To a solution of Compound **70** (500 mg) in DCM (13 mL) was added triethylamine (575 µL) and acetyl chloride (292 µL). The reaction mixture was stirred at 25°C for 1 hour, then diluted in DCM (20 mL) and washed with K_2CO_3 (sat. aq. 2*10 mL), brine (10 mL) and dried over $MgSO_4$ to obtain Compound **264** (608 mg, 99%) as a brown solid.

M/Z (M[^{35}Cl]+H)$^+$: 225.1.

Example **208**: methyl 6-(4-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



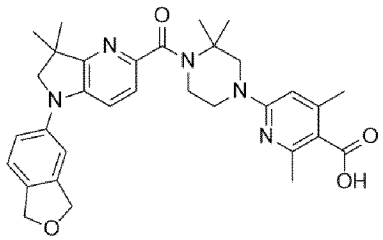
Example **208** was prepared according to general procedure (XIV) starting from Compound **264** (200 mg) and Compound **10** (1.5 eq), and using triethyl amine (5.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, DCM 100% to DCM/MeOH 97:03) to obtain Example **208** (453 mg) as a yellow oil.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.34 (s, 6H, 2 CH_3); 1.49 (s, 6H, 2 CH_3); 2.20 (s, 3H, CH_3-C(O)); 2.23 (s, 3H, $ArCH_3$); 2.34 (s, 3H, $ArCH_3$); 3.50-3.55 (m, 2H, N-CH_2); 3.65-3.70 (m, 2H, N-CH_2); 3.75 (s, 3H, O-CH_3); 3.89 (s, 2H, N-CH_2); 3.98 (s, 2H, N-CH_2); 6.36 (m, 1H, Ar); 7.39 (d, *J* 8.4 Hz, 1H, Ar); 8.27 (d, *J* 8.4 Hz, 1H, Ar);
M/Z $(M+H)^+$: 494.4.

Compound **265**: methyl 6-(4-(3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

To a solution of Example **208** (439 mg) in MeOH (20 mL) was added HCl (6N, aq. 15 mL). The reaction mixture was heated at 100 °C for 30 minutes then quenched with NaOH (6N, aq. to pH > 7) and extracted with EtOAc (2*50 mL). The combined organic layers were washed with brine, dried over MgSO4 and concentrated under reduced pressure to obtain Compound **265** (249 mg, 62% over 2 steps) as an orange oil.
M/Z $(M+H)^+$: 452.4.

Example **209**: 6-(4-(1-(1,3-dihydroisobenzofuran-5-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



To a solution of Compound **265** (83 mg) in ^{t}BuOH (2.0 mL) was added Sodium ^{t}Butoxide (177 mg) and the reaction mixture was heated at 60°C for 24 hours. 5-Bromo-1,3-dihydro-isobenzofuran (73 mg) was added at 25°C, the reaction mixture was sparged with Argon for 10 minutes, RuPhos Pd G4 (8 mg) was added and the reaction mixture was heated at 80°C for 18 hours. The reaction mixture was cooled at 40°C and MeOH (1.0 mL) was added, the mixture was filtered, formic acid (104 µL) and DMSO (0.5 mL) were added and the mixture was fitlered. The filtrate was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 75:25 to 35:65) and freeze dried with HCl (0.1 N in water) to obtain Example **209** (10 mg, 9%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.36 (s, 6H, 2 CH_3); 1.52 (s, 6H, 2 CH_3); 2.33 (s, 3H, $ArCH_3$); 3.63-3.70 (m, 2H, N-CH_2); 3.84 (s, 2H, N-CH_2); 3.88-3.94 (m, 4H, 2 N-CH_2); 4.98-5.00 (m, 4H, 2 O-CH_2); 6.52-6.93 (m, 1H, Ar); 7.19

(dd, *J* 8.4, 2.0 Hz, 1H, Ar); 7.27 (s, 1H, Ar); 7.31-7.35 (m, 2H, 2 Ar); 7.42 (d, *J* 8.4 Hz, 1H, Ar); One CH_3 and COOH were not observed.

M/Z $(M+H)^+$: 556.4

Compound **266** 3-chloro-N-(4-fluorophenethyl)pyrazin-2-amine

A solution of 2,3-dichloropyrazine (500 mg) and 4-Fluorophenethylamine (1.05 g) in MeTHF (5 mL) was heated at 110°C for 16 hours. The reaction mixture was washed with HCl (aq. 0.1 N, 50 mL), and extracted with EtOAc (2*50 mL). The combined organic layers were washed with Brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure to obtain crude Compound **266** (857 mg).

M/Z $(M[^{35}Cl]+H)^+$: 252.1.

Compound **267**: 3-chloro-N-(4-fluorophenethyl)-N-(2-methylallyl)pyrazin-2-amine

To a solution of Compound **266** (857 mg) in THF (34 mL) was added potassium tert-butoxide (535 mg) at 0°C. After 10 minutes, 3-bromo-2-methylprop-1-ene (708 µL) was added and the reaction mixture was stirred at 25°C for 48 hours, then heated at 50 °C for 4 hours. Another portion of base (535 mg) and 3-bromo-2-methylprop-1-ene (708 µL) were added and the mixture was heated at 50°C for another 17 hours. The reaction mixture was quenched with NH_4Cl (sat. aq. 150 mL), diluted with water (50 mL), and extracted with EtOAc (3*150 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 90:10) to obtain Compound **222** (660 mg, 54% over 2 steps) as an orange oil.

M/Z $(M[^{35}Cl]+H)^+$: 306.2.

Compound **268**: 5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **268** was prepared according to general procedure (XVIII) starting from Compound **267** (660 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **268** (417 mg, 71%) as a yellow oil.

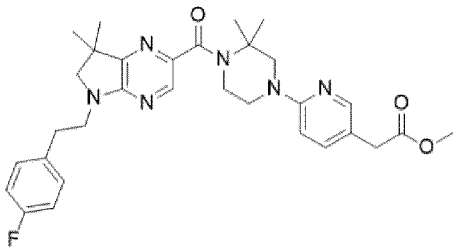
M/Z $(M[^{35}Cl]+H)^+$: 272.2.

Compound **269**: 2-bromo-5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **269** (531 mg, 99%) was obtained without further purification as a yellow oil following general procedure (XVI) in EtOAc, starting from Compound **268** (417 mg).

M/Z $(M[^{35}Cl][^{81}Br]+H)^+$: 350.2.

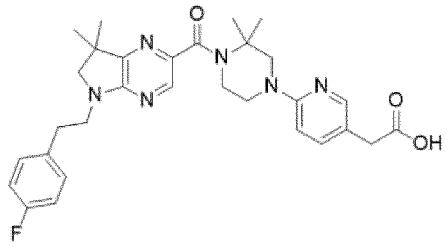
Example **210**: methyl 2-(6-(4-(5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



Example **210** was prepared according to general procedure (XIV) starting from Compound **269** (150 mg) and Compound **111** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.1 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 00:100) to obtain Example **210** (54 mg, 23%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.20 (s, 6H, 2 CH_3); 1.46 (s, 6H, 2 CH_3); 2.91 (t, *J* 7.2 Hz, 2H, Ar-CH_2); 3.39 (s, 2H, N-CH_2); 3.46-3.55 (m, 4H, N-CH_2 N-CH_2); 3.60-3.64 (m, 5H, N-CH_2 O-CH_3); 3.76-3.81 (m, 4H, 2 N-CH_2); 6.58 (d, *J* 8.7 Hz, 1H, Ar); 7.08-7.14 (m, 2H, 2 Ar); 7.25-7.31 (m, 2H, 2 Ar); 7.41-7.45 (m, 1H, Ar); 7.93-8.00 (m, 2H, 2 Ar);
M/Z $(M+H)^+$: 561.5

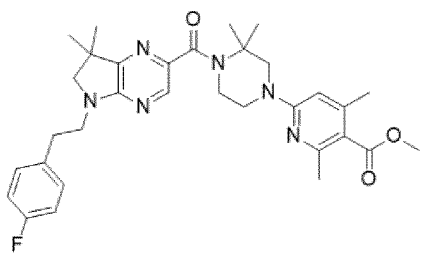
Example **211**: 2-(6-(4-(5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **211** was prepared according to general procedure (VII) starting from Example **210** (54 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 40:60) and freeze dried with HCl (0.1 N in water) to obtain Example **211** (35 mg, 62%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.23 (s, 6H, 2 CH_3); 1.52 (s, 6H, 2 CH_3); 2.91 (t, *J* 7.2 Hz, 2H, Ar-CH_2); 3.39 (s, 2H, $CH_2C(O)$); 3.62-3.70 (m, 4H, N-CH_2 N-CH_2); 3.72 (t, *J* 5.3 Hz, 2H, N-CH_2); 3.90 (t, *J* 5.3 Hz, 2H, N-CH_2); 3.98 (s, 2H, N-CH_2); 7.08-7.14 (m, 2H, 2 Ar); 7.28-7.34 (m, 2H, 2 Ar); 7.37-7.41 (m, 1H, Ar); 7.95-8.00 (m, 3H, 3 Ar); COOH was not observed.
M/Z $(M+H)^+$: 547.4.

Example **212**: methyl 6-(4-(5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

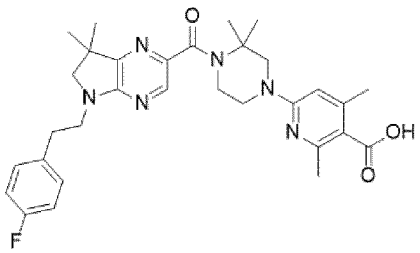


Example **212** was prepared according to general procedure (XIV) starting from Compound **269** (150 mg) and Compound **10** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.1 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **212** (144 mg, 59%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.20 (s, 6H, 2 CH_3); 1.46 (s, 6H, 2 CH_3); 2.23 (s, 3H, $ArCH_3$); 2.34 (s, 3H, $ArCH_3$); 2.90 (t, *J* 7.2 Hz, 2H, Ar-CH_2); 3.37 (s, 2H, N-CH_2); 3.52-3.55 (m, 2H, N-CH_2); 3.62 (t, *J* 7.2 Hz, 2H, N-CH_2); 3.76-3.86 (m, 5H, N-CH_2 O-CH_3); 3.99 (s, 2H, N-CH_2); 6.35 (s, 1H, Ar); 7.07-7.14 (m, 2H, 2 Ar); 7.27-7.31 (m, 2H, 2 Ar); 7.93 (s, 1H, Ar);

M/Z $(M+H)^+$: 575.5

Example **213**: 2-(6-(4-(5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **213** was prepared according to general procedure (XI) starting from Example **212** (144 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 95:05 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **213** (97 mg, 65%) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.23 (s, 6H, 2 CH_3); 1.51 (s, 6H, 2 CH_3); 2.36 (s, 3H, $ArCH_3$); 2.55 (s, 3H, $ArCH_3$); 2.91 (t, *J* 6.8 Hz, 2H, Ar-CH_2); 3.39 (s, 2H, N-CH_2); 3.64 (t, *J* 6.8 Hz, 2H, N-CH_2); 3.71-3.74 (m, 2H, N-CH_2); 3.86-3.89 (m, 2H, N-CH_2); 3.96 (s, 2H, N-CH_2); 6.91 (s, 1H, Ar); 7.07-7.13 (m, 2H, 2 Ar); 7.28-7.33 (m, 2H, 2 Ar); 7.95 (s, 1H, Ar); COOH was not observed.

M/Z $(M+H)^+$: 561.5.

Compound **270**: 1-(3-chloropyridin-2-yl)-3,3-dimethylcyclobutane-1-carbonitrile

Compound **270** was prepared according to general procedure (I) from 3-chloro-2-fluoropyridine (820 mg) and 3,3-dimethylcyclobutane-1-carbonitrile. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 85:15) to obtain Compound **270** (886 mg, 64%) as a yellow oil.

M/Z $(M[^{35}Cl]+H^+)$: 221.6

Compound **271**: (1-(3-chloropyridin-2-yl)-3,3-dimethylcyclobutyl)methanamine

Compound **271** (440 mg, 49%) was obtained as a white solid following general procedure (XVa), starting from Compound **270** (886 mg).

M/Z $(M[^{35}Cl]+H^+)$: 225.2.

Compound **272**: 1'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **272** was prepared according to general procedure (Xc) from Compound **271** (440 mg) and 4-bromo-1-chloro-2-fluorobenzene. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 90:10) to obtain Compound **272** (197 mg, 32%) as a white solid.

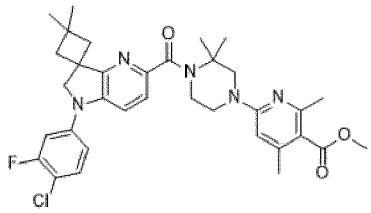
M/Z (M[^{35}Cl]+H$^+$): 317.3.

Compound **273**: 5'-bromo-1'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **273** (230 mg, 97%) was obtained as a beige solid according to general procedure (XVI) in EtOAc from Compound **272** (197 mg) without further purification.

M/Z (M[^{35}Cl][^{81}Br]+H)$^+$: 397.1.

Example **214**: methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

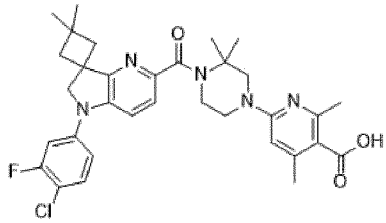


Example **214** was prepared according to general procedure (XIV) starting from Compound **273** (230 mg) and Compound **10** (2.5 eq), and using triethyl amine (6.1 eq), $Mo(CO)_6$ (2.6 eq), XantPhos Pd G4 (0.18 eq), and DBU (6.9 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 85:15) to obtain Example **214** (140 mg, 39%) as a white solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.28-1.30 (m, 6H, 2 CH_3); 1.51 (s, 6H, 2 CH_3); 2.05-2.10 (m, 2H, cyclobutyl); 2.23 (s, 3H, $ArCH_3$); 2.25-2.29 (m, 1H, cyclobutyl); 2.34 (s, 3H, $ArCH_3$); 2.37-2.39 (m, 1H, cyclobutyl); 3.67-3.70 (m, 2H, N-CH_2); 3.78 (s, 3H, O-CH_3); 3.87-3.94 (m, 4H, 2 N-CH_2); 4.29 (s, 2H, N-CH_2); 6.35 (s, 1H, Ar); 7.22 (dd, *J* 9.0, 2.1 Hz, 1H, Ar); 7.34-7.41 (m, 2H, 2 Ar); 7.51-7.58 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]+H)$^+$: 620.4

Example **215**: 6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **215** was prepared according to general procedure (XI) starting from Example **214** (140 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **215** (49 mg, 34% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.28-1.29 (m, 6H, 2 CH_3); 1.55 (s, 6H, 2 CH_3); 2.07 (d, *J* 12.1 Hz, 2H, cyclobutyl); 2.34-2.38 (m, 5H, cyclobutyl $ArCH_3$); 2.54 (bs, 3H, $ArCH_3$); 3.76-3.80 (m, 2H, N-CH_2); 3.98-4.02 (m, 4H, 2 N-CH_2);

4.28 (s, 2H, N-CH_2); 6.73 (s, 1H, Ar); 7.22 (dd, *J* 9.0, 2.1 Hz, 1H, Ar); 7.34-7.42 (m, 2H, 2 Ar); 7.51-7.57(m, 2H, 2 Ar); COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 606.3.

Compound **274**: 3-chloro-N-(2-methylallyl)-N-(3,4,5-trifluorophenyl)pyrazin-2-amine

Crude Compound **274** (1220 mg) was obtained as a brown oil according to general procedure (XVII) on a 500 mg scale, using 3,4,5-trifluoroaniline.

M/Z (M[^{35}Cl]+H)$^+$: 314.2.

Compound **275**: 7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **275** was prepared according to general procedure (XVIII) starting from crude Compound **274** (970 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **275** (461 mg, 49% over 2 steps) as a yellow oil.

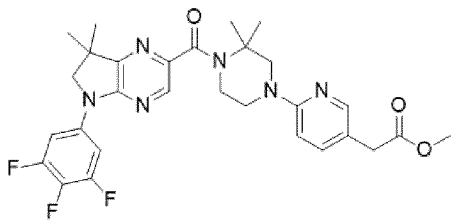
M/Z (M+H)$^+$: 280.1

Compound **276**: 2-bromo-7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **276** (566 mg, 96%) was obtained as a brown solid following general procedure (XVI) in EtOAc without further purification, starting from Compound **275** (461 mg).

M/Z (M[^{79}Br]+H)$^+$: 358.1.

Example **216**: methyl 2-(6-(4-(7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

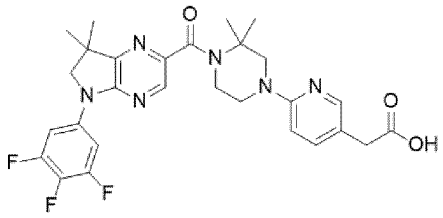


Example **216** was prepared according to general procedure (XIV) starting from Compound **276** (150 mg) and Compound **111** (1.5 eq), and using triethyl amine (3.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **216** (160 mg, 67%) as a green oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.39 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 3.33-3.54 (m, 4H, N-CH_2 + CH_2C(O)); 3.60 (s, 3H, O-CH_3); 3.77-3.86 (m, 4H, 2 N-CH_2); 3.97 (s, 2H, N-CH_2); 6.58-6.61 (m, 1H, Ar); 7.42-7.46 (m, 1 H, Ar); 7.87-7.93 (m, 2H, 2 Ar); 7.95-7.97 (m, 1H, Ar); 8.23 (s, 1H, Ar).

M/Z (M+H)$^+$: 569.4

Example **217**: 2-(6-(4-(7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid

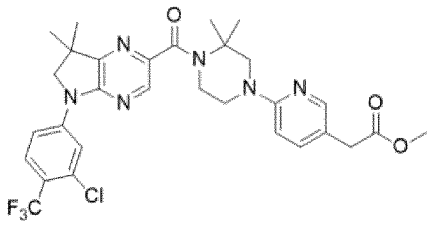


Example **217** was prepared according to general procedure (VII) starting from Example **216** (60 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **217** (28 mg, 22% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.40 (s, 6H, 2 CH_3); 1.56 (s, 6H, 2 CH_3); 3.65 (s, 2H, N-CH_2); 3.72 (t, *J* 5.2 Hz, 2H, N-CH_2); 3.91 (t, *J* 5.2 Hz, 2H, N-CH_2); 3.97-3.98 (m, 4H, Ar-CH_2 + N-CH_2); 7.33-7.36 (m, 1H, Ar); 7.88-7.97 (m, 4H, 4 Ar); 8.26 (s, 1H, Ar); COOH

M/Z $(M+H)^+$: 555.4.

Example **218**: methyl 2-(6-(4-(5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

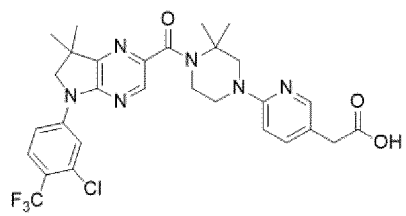


Example **218** was prepared according to general procedure (XIV) starting from Compound **239** (150 mg) and Compound **111** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **218** (157 mg, 67%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.40 (s, 6H, 2 CH_3); 1.50 (s, 6H, 2 CH_3); 3.46-3.54 (m, 4H, N-CH_2 + CH_2C(O)); 3.60 (s, 3H, O-CH_3); 3.77-3.85 (m, 4H, 2 N-CH_2); 3.99 (s, 2H, N-CH_2); 6.59 (d, *J* 9 Hz, 1H, Ar); 7.42-7.46 (m, 1 H, Ar); 7.86-7.89 (m, 1H, Ar); 7.95-7.97 (m, 2H, 2 Ar); 8.27 (s, 1H, Ar); 8.30-8.31 (m,, 1H, Ar); .

M/Z $(M[^{35}Cl]+H)^+$: 617.4

Example **219**: 2-(6-(4-(5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **219** was prepared according to general procedure (VII) starting from Example **216** (140 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 60:40) and freeze dried with HCl (0.1 N in water) to obtain Example **217** (20 mg, 8% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.41 (s, 6H, $(CH_3)_2$); 1.55 (s, 6H, $(CH_3)_2$); 3.57-3.61 (m, 2H, N-CH_2); 3.64-3.68 (m, 2H, N-CH_2); 3.85-3.89 (m, 2H, N-CH_2); 3.92 (s, 2H, $CH_2C(O)$); 4.05 (s, 2H, N-CH_2); 7.22 (bs, 1H, Ar); 7.79-7.89 (m, 2H, 2 Ar); 7.94-7.99 (m, 2H, 2 Ar); 8.30-8.32 (m, 2H, 2 Ar); 12.53 (bs, 1H, COOH).

M/Z $(M[^{35}Cl]+H)^+$: 617.4

Compound **277**: 3-chloro-N-(3,4-dichlorophenyl)-N-(2-methylallyl)pyrazin-2-amine

Crude Compound **277** (1110 mg) was obtained as a yellow oil according to general procedure (XVII) on a 500 mg scale, using 3,4-dichloroaniline.

M/Z $(M[^{35}Cl_3]+H)^+$: 330.2

Compound **278**: 5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **278** was prepared according to general procedure (XVIII) starting from crude Compound **277** (1110 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **278** (505 mg, 52% over 2 steps) as a white solid.

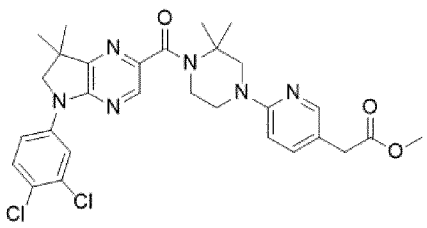
M/Z $(M[^{35}Cl_2]+H)^+$: 294.1

Compound **279**: 2-bromo-5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine

Compound **279** (457 mg, 71%) was obtained as a yellow solid following general procedure (XVI) in EtOAc after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30), starting from Compound **278** (505 mg).

M/Z $(M[^{35}Cl_2][^{79}Br]+H)^+$: 372.1

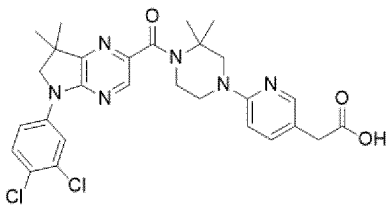
Example **220**: methyl 2-(6-(4-(5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



Example **220** was prepared according to general procedure (XIV) starting from Compound **279** (150 mg) and Compound **111** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **220** (100 mg) as a yellow solid

M/Z $(M[^{35}Cl]_2+H)^+$: 583.3

Example **221**: 2-(6-(4-(5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **221** was prepared according to general procedure (VII) starting from Example **220** (100 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 60:40) and freeze dried with HCl (0.1 N in water) to obtain Example **221** (8 mg, 4% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.39 (s, 6H, $(CH_3)_2$); 1.54 (s, 6H, $(CH_3)_2$); 3.58-3.62 (m, 2H, N-CH_2); 3.64-3.68 (m, 2H, N-CH_2); 3.87-3.91 (m, 4H, CH_2C(O) N-CH_2); 4.00 (s, 2H, N-CH_2); 7.25 (bs, 1H, Ar); 7.67 (d, *J* 9.0 Hz, 1H, Ar); 7.85-7.89 (m, 2H, 2 Ar); 7.94 (s, 1H, Ar); 8.24 (s, 2H, 2 Ar); 12.58 (bs, 1H, COOH)

M/Z (M[^{35}Cl]$_2$+H)$^+$: 569.3

Compound **280**: N-((1-(3-chloropyrazin-2-yl)cyclopentyl)methyl)-3,4-difluoroaniline

Compound **280** was prepared according to general procedure (XXII) from Compound **260** (380 mg) and 3,4-difluoroaniline. The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **280** (469 mg) as a clear oil.

M/Z (M[^{35}Cl]+H)$^+$: 324.2

Compound **281**: 5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]

Compound **281** was prepared according to general procedure (XXIII) from Compound **280** (460 mg). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **281** (301 mg, 58% over 2 steps) as a white solid.

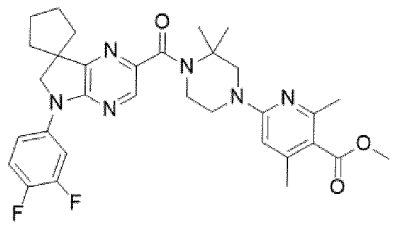
M/Z (M+H)$^+$: 288.3

Compound **282**: 2'-bromo-5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]

Compound **282** (264 mg, 69%) was obtained as a beige solid following general procedure (XVI) in EtOAc, after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30), starting from Compound **281** (302 mg).

M/Z (M[^{81}Br]+H)$^+$: 366.1

Example **222**: methyl 6-(4-(5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



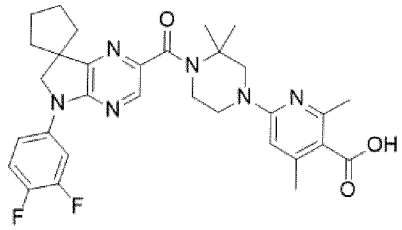
Example **222** was prepared according to general procedure (XIV) starting from Compound **282** (150 mg) and Compound **10** (1.5 eq), and using triethyl amine (5.2 eq), $Mo(CO)_6$ (1.95 eq), XantPhos Pd G4 (0.13 eq), and DBU (6

eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **222** (178 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.50 (s, 6H, 2 CH_3); 1.79-2.08 (m, 8H, 4 CH_2); 2.24 (s, 3H, $ArCH_3$); 2.35 (s, 3H, $ArCH_3$); 3.52-3.59 (m, 2H, N-CH_2); 3.76-3.87 (m, 5H, N-CH_2 O-CH_3); 3.89 (s, 2H, N-CH_2); 4.08 (s, 2H, N-CH_2); 6.37 (m, 1H, Ar); 7.37-7.59 (m, 1H, Ar); 7.65-7.78 (m, 1H, Ar); 8.05-8.17 (m, 1H, Ar); 8.25 (s, 1H, Ar);

M/Z $(M+H)^+$: 591.5.

Example **223**: 6-(4-(5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **223** was prepared according to general procedure (XI) starting from Example **222** (178 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **223** (49 mg, 25% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.54 (s, 6H, 2 CH_3); 1.77-2.04 (m, 8H, 4 CH_2); 2.36 (s, 3H, $ArCH_3$); 2.54 (s, 3H, $ArCH_3$); 3.64-3.77 (m, 2H, N-CH_2); 3.85-3.93 (m, 2H, N-CH_2); 3.98 (s, 2H, N-CH_2); 4.07 (s, 2H, N-CH_2); 6.68-7.00 (m, 1H, Ar); 7.45-7.57 (m, 1H, Ar); 7.64-7.74 (m, 1H, Ar); 8.07-8.15 (m, 1H, Ar); 8.20 (s, 1H, Ar); COOH was not observed.

M/Z $(M+H)^+$: 577.5.

Compound **282**: (1-(3-chloropyridin-2-yl)-3-methylenecyclobutyl)methanamine

To a solution of Compound **181** (1.35 g) in THF (40 mL) at 0°C was added a dropwise DIBAL (1N in THF, 29 mL). The reaction mixture was stirred at 0°C for 2 hours then at 25°C for 48 hours, and quenched by slow addition in Potassium tartrate (sat. aq. 200 mL). The mixture was extracted with EtOAc (2*100 mL), the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by Ion Exchange chromatography (Isolute SCX-2, load in DCM, elution with NH_3 1N in MeOH), to obtain Compound **282** (1.19 g) as an orange oil.

M/Z $(M[^{35}Cl]+H^+)$: 209.5.

Compound **283**: 1'-(4-chloro-3-fluorophenyl)-3-methylene-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]

Compound **283** was prepared according to general procedure (Xc) from Compound **282** (480 mg) and 4-bromo-1-chloro-2-fluorobenzene. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **283** (314 mg, 459%) as a white solid.

M/Z $(M[^{35}Cl]+H^+)$: 301.1.

Compound **284**: (1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridin]-3-yl)methanol

To a solution of Compound **283** (403 mg) in THF (16 mL) at 0°C was added BH_3·DMS (0.51 mL). The reaction mixture was stirred at 0°C for 1 hour, NaOH (2N aq., 16 mL) was added dropwise at 0°C followed by H_2O_2 (30% in H_2O, 11 mL) and the mixture was stirred for 18 hours at 25°C. The reaction mixture was diluted in water (50 mL) and extracted with EtOAc (3*100 mL), the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in MeOH (50 mL) treated with HCl (2M in Et_2O, 10 mL) and distilled at 60°C, the distillation was repeated 3 times to recover Compound **284** (472 mg, as a diastereoisomers mixture 80:20), a yellow solid, as the residue,

M/Z ($M[^{35}Cl]+H^+$): 319.3.

Compound **285**: 1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine] major isomer

Compound **286**: 1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine] minor isomer

Compound **285** and Compound **286** was prepared according to general procedure (XIII) starting from Compound **284** (472 mg) and Iodomethane (4.0 eq), and using NaH (60% in mineral oil, 4.0 eq) in THF. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **285** (207 mg, 46% over 2 steps) as a white solid and Compound **286** (51 mg, 11% over 2 steps) as a yellow oil.

Compound **285**: M/Z ($M[^{35}Cl]+H)^+$: 333.3 .

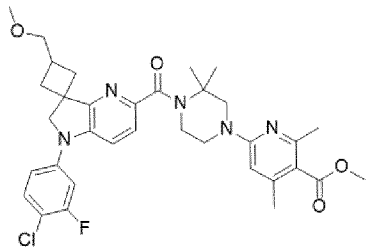
Compound **286**: M/Z ($M[^{35}Cl]+H)^+$: 333.3 .

Compound **287**: 5'-bromo-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine] major isomer

Compound **287** (247 mg, 63%) was obtained as a clear oil following general procedure (XVI) in EtOAc, after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30), starting from Compound **285** (317 mg).

M/Z ($M[^{35}Cl][^{81}Br]+H)^+$: 413.1.

Example **224**: methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate major isomer

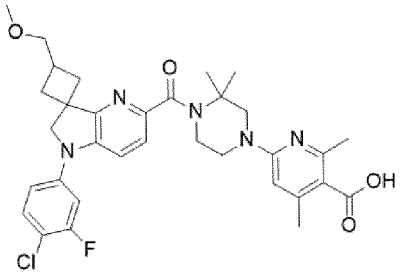


Example **224** was prepared according to general procedure (XIV) starting from Compound **287** (150 mg) and Compound **10** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **224** (134 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.51 (s, 6H, 2 x CH_3); 2.17-2.33 (m, 7H, 2 CH_2 $ArCH_3$); 2.36 (s, 3H, $ArCH_3$); 2.60-2.69 (m, 1H, CH); 3.26 (s, 3H, OCH_3), 3.52 (d, J 6.8 Hz, 2H, CH_2-OCH_3); 3.60-3.71 (m, 2H, N-CH_2); 3.79 (s, 3H, $C(O)OCH_3$); 3.83-3.91 (m,4H, 2 N-CH_2); 4.26 (s, 2H, N-CH_2); 6.37 (s, 1H, Ar); 7.19 (dd, J 8.6, 2.6 Hz, 1H, Ar); 7.34 (dd, J 12.0, 2.6 Hz, 1H, Ar); 7.39 (d, J 8.6 Hz, 1H, Ar); 7.52-7.61 (m, 2H, 2 Ar);

(M[^{35}Cl]+H)$^+$: 636.3.

Example **225**: 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid major isomer



Example **225** was prepared according to general procedure (XI) starting from Example **224** (134 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **225** (76 mg, 32% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.55 (s, 6H, 2 CH_3); 2.17-2.33 (m, 4H, 2 CH_2); 2.34 (s, 3H, $ArCH_3$); 2.58-2.69 (m, 1H, CH); 3.26 (s, 3H, OCH_3), 3.51 (d, J 6.8 Hz, 2H, CH_2-OCH_3); 3.69-3.80 (m, 2H, N-CH_2); 3.90-4.04 (m, 2H, N-CH_2); 3.97 (s, 2H, N-CH_2); 4.26 (s, 2H, N-CH_2); 6.61 (s, 1H, Ar); 7.19 (dd, J 8.6, 2.6 Hz, 1H, Ar); 7.34 (dd, J 12.0, 2.6 Hz, 1H, Ar); 7.39 (d, J 8.6 Hz, 1H, Ar); 7.48-7.61 (m, 2H, 2 Ar); One CH_3 and COOH were not observed

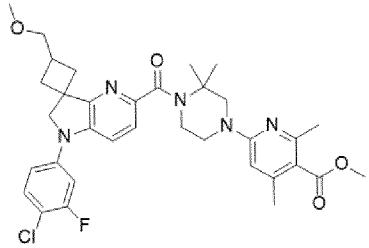
M/Z (M[^{35}Cl]+H)$^+$: 622.4

Compound **288**: 5'-bromo-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine] minor isomer

Compound **288** (89 mg, 80%) was obtained as a beige oil following general procedure (XVI) in EtOAc, after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30), starting from Compound **286** (90 mg).

M/Z (M[^{35}Cl][^{81}Br]+H)$^+$: 413.1.

Example **226**: methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate minor isomer



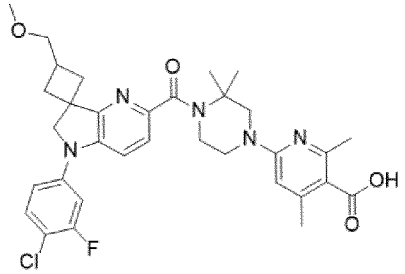
Example **226** was prepared according to general procedure (XIV) starting from Compound **288** (68 mg) and Compound **10** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5

eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **226** (68 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.50 (s, 6H, 2 CH_3); 2.06-2.17 (m, 2H, 2 CH_aH_b), 2.19-2.27 (m, 4H, CH_aH_b $ArCH_3$); 2.35 (s, 3H, $ArCH_3$); 2.37-2.45 (m, 1H, CH_aH_b); 2.80-2.92 (m, 1H, CH); 3.29 (s, 3H, OCH_3), 3.42 (d, J 6.3 Hz, 2H, CH_2-OCH_3); 3.60-3.68 (m, 2H, N-CH_2); 3.78 (s, 3H, C(O)OCH_3); 3.84-3.91 (m, 4H, 2 N-CH_2); 4.11 (s, 2H, N-CH_2); 6.34 (s, 1H, Ar); 7.18 (dd, J 8.7, 1.5 Hz, 1H, Ar); 7.34 (dd, J 11.7, 2.7 Hz, 1H, Ar); 7.39-7.44 (m, 2H, 2 Ar); 7.51-7.58 (m, 2H, 2 Ar);

(M[^{35}Cl]+H)$^+$: 636.3.

Example **227**: 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid minor isomer

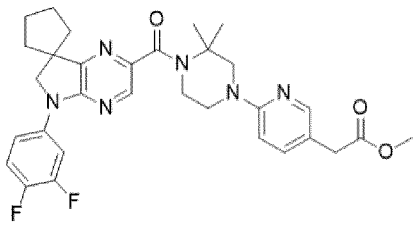


Example **227** was prepared according to general procedure (XI) starting from Example **226** (68 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **227** (22 mg, 15% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6 , 300 MHz) δ: 1.52 (s, 6H, 2 CH_3); 2.05-2.16 (m, 2H, 2 CH_aH_b); 2.29 (s, 3H, $ArCH_3$); 2.42 (s, 3H, $ArCH_3$); 2.80-2.91 (m, 1H, CH); 3.29 (s, 3H, OCH_3), 3.43 (d, J 6.5 Hz, 2H, CH_2O); 3.61-3.70 (m, 2H, N-CH_2); 3.86-3.97 (m, 4H, 2 N-CH_2); 4.12 (s, 2H, N-CH_2); 6.27-6.60 (m, 1H, Ar); 7.18 (dd, J 9.0, 2.5 Hz, 1H, Ar); 7.32 (dd, J 11.8, 2.5 Hz, 1H, Ar); 7.40 (d, J 8.4 Hz, 1H, Ar); 7.49-7.60 (m, 2H, 2 Ar)

M/Z (M[^{35}Cl]+H)$^+$: 622.3

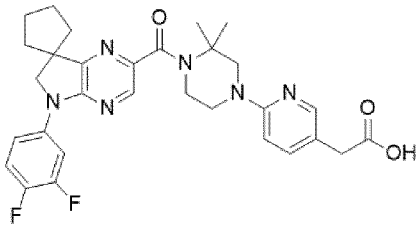
Example **228**: methyl 2-(6-(4-(5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



Example **228** was prepared according to general procedure (XIV) starting from Compound **282** (100 mg) and Compound **111** (1.3 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 20:80) to obtain Example **228** (112 mg) as a yellow solid

M/Z (M+H)$^+$: 577.4

Example **229**: 2-(6-(4-(5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **229** was prepared according to general procedure (VII) starting from Example **228** (110 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 95:05 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **229** (70 mg, 44% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.54 (s, 6H, $(CH_3)_2$); 1.79-1.91 (m, 8H $(CH_2)_4$); 3.66 (s, 2H, $CH_2C(O)$); 3.70-3.73 (m, 2H, N-CH_2); 3.89-3.93(m, 2H, N-CH_2); 4.00 (s, 2H, N-CH_2); 4.05 (s, 2H, N-CH_2); 7.34-3.37 (m, 1H, Ar); 7.45-7.54 (m, 1H, Ar); 7.66-7.70 (m, 1H, Ar); 7.96-8.00 (m, 2H, 2 Ar); 8.06-8.14 (m, 1H, Ar); 8.20 (s, 1H, Ar); 13.97 (bs, 1H, CO_2H).

M/Z $(M+H)^+$: 563.4

Compound **289**: methyl 1-(3-chloropyrazin-2-yl)cyclobutane-1-carboxylate

Compound **289** was prepared according to general procedure (Ib) from dichloropyrazine (1.80 g) and methyl cyclobutanecarboxylate. The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **289** (1.40 g) as a yellow solid.

M/Z $(M[^{35}Cl]+H)^+$: 227.1

Compound **290**: (1-(3-chloropyrazin-2-yl)cyclobutyl)methanol

Compound **290** was prepared according to general procedure (XX) from Compound **289** (1.36 g). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **290** (0.51 g, 22% over 2 steps) as a yellow solid.

M/Z $(M[^{35}Cl]+H)^+$: 199.2

Compound **291**: 1-(3-chloropyrazin-2-yl)cyclobutane-1-carbaldehyde

Compound **291** was prepared according to general procedure (XXI) from Compound **290** (505 mg). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **291** (473 mg) as a clear oil.

M/Z $(M[^{35}Cl]+H)^+$: 197.1.

Compound **292**: 4-chloro-N-((1-(3-chloropyrazin-2-yl)cyclobutyl)methyl)-3-fluoroaniline

Compound **292** was prepared according to general procedure (XXII) from Compound **291** (450 mg) and 4-chloro-3-fluoroaniline. The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **292** (428 mg, 52% over 2 steps) as a white solid.

M/Z $(M[^{35}Cl]_2+H)^+$: 326.2.

Compound **293**: 5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]

Compound **293** was prepared according to general procedure (XXIII) from Compound **292** (425 mg). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **293** (344 mg, 91%) as a white solid.

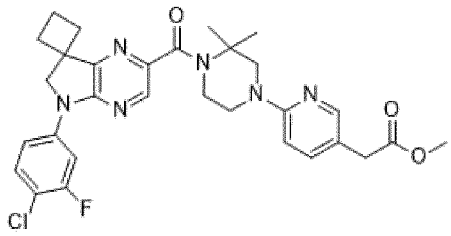
M/Z (M[^{35}Cl]+H)$^{+}$: 290.2.

Compound **294**: 2'-bromo-5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]

Compound **294** (303 mg, 69%) was obtained as a beige solid following general procedure (XVI) in EtOAc, after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30), starting from Compound **293** (344 mg).

M/Z (M[^{81}Br][^{35}Cl] +H)$^{+}$: 380.2.

Example **230**: methyl 2-(6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

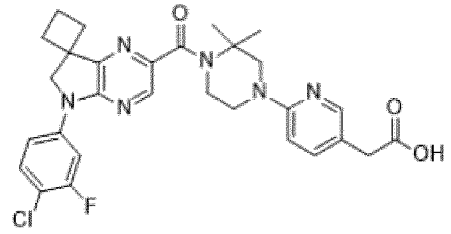


Example **230** was prepared according to general procedure (XIV) starting from Compound **294** (150 mg) and Compound **111** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **230** (180 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.51 (s, 6H, 2 CH_3); 2.00-2.23 (m, 2H, CH_2); 2.24-2.47 (m, 4H, 2 $C(CH_2)$; 3.50-3.57 (m, 4H, $CH_2C(O)$ N-CH_2); 3.57-3.66 (m, 5H, O-CH_3 N-CH_2); 3.80-3.83 (m, 4H, 2 N-CH_2); 4.30 (s, 2H, N-CH_2); 6.53-6.61 (m, 1H, Ar); 7.36-7.48 (m, 1H, 1 Ar); 7.58-7.64 (m, 1H, Ar); 7.69-7.73 (m, 1H, Ar); 7.92-7.98 (m, 1H, Ar); 8.04-8.09 (m, 1H, Ar); 8.22 (s, 1H, Ar);

M/Z (M[^{35}Cl]+H)$^{+}$: 579.4.

Example **231**: 2-(6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **231** was prepared according to general procedure (VII) starting from Example **230** (180 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **230** (78 mg, 32% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.58 (s, 6H, 2 CH_3); 1.97-2.25 (m, 2H, CH_2); 2.25-2.40 (m, 2H, $C(CH_2)$); 3.63 (s, 2H, $CH_2C(O)$); 3.66-3.77 (m, 2H,N-CH_2); 3.93-4.04 (m, 4H, 2 N-CH_2); 4.32 (s, 2H, N-CH_2); 7.24 (bs, 1H, Ar); 7.63 (m, 1H, Ar); 7.73 (dd, *J* 9.0, 2.5 Hz, 1H, Ar); 7.82-8.00 (m, 2H, 2 Ar); 8.08 (dd, 12.5, 2.5 Hz, 1H, Ar); 8.25 (s, 1H, Ar); one $C(CH_2)$ and COOH were not observed.

M/Z (M[^{35}Cl]+H)$^+$: 565.4

Compound **295**: methyl 1-(3-chloropyrazin-2-yl)-3,3-dimethylcyclobutane-1-carboxylate

Compound **295** was prepared according to general procedure (Ib) from dichloropyrazine (1.85 g) and methyl 3,3-dimethylcyclobutane-1-carboxylate. The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 85:15) to obtain Compound **295** (1.40 g, 44%) as a yellow oil.

M/Z (M[^{35}Cl]+H)$^+$: 255.1

Compound **296**: (1-(3-chloropyrazin-2-yl)-3,3-dimethylcyclobutyl)methanol

Compound **296** was prepared according to general procedure (XX) from Compound **295** (1.73 g). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **296** (1.00 g, 65%) as a yellow oil.

M/Z (M[^{35}Cl]+H)$^+$: 227.1

Compound **297**: 1-(3-chloropyrazin-2-yl)-3,3-dimethylcyclobutane-1-carbaldehyde

Compound **297** was prepared according to general procedure (XXI) from Compound **296** (1000 mg). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **297** (873 mg, 88%) as a yellow oil.

M/Z (M[^{35}Cl]+H)$^+$: 225.1

Compound **298**: N-((1-(3-chloropyrazin-2-yl)-3,3-dimethylcyclobutyl)methyl)-3,4-difluoroaniline

Compound **298** was prepared according to general procedure (XXII) from Compound **297** (290 mg) and 3,4-difluoroaniline. The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **298** (217 mg, 50%) as a white solid.

M/Z (M[^{35}Cl]+H)$^+$: 338.2.

Compound **299**: 5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]

Compound **299** was prepared according to general procedure (XXIII) from Compound **298** (215 mg). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **299** (157 mg, 82%) as a white solid.

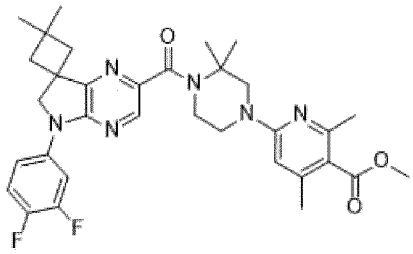
M/Z (M+H)$^+$: 302.3

Compound **300**: 2'-bromo-5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]

Compound **300** (163 mg, 82%) was obtained as a beige solid following general procedure (XVI) in EtOAc, after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30), starting from Compound **299** (157 mg).

M/Z (M[^{81}Br] +H)$^+$: 382.2.

Example **232**: methyl 6-(4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

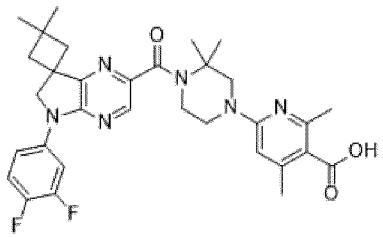


Example **232** was prepared according to general procedure (XIV) starting from Compound **300** (157 mg) and Compound **10** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **232** (131 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.29 (s, 6H, 2 C(CH_3)); 1.51 (s, 6H, C(CH_3)$_2$); 2.11-2.15 (m, 2H, 2 CH_aH_b); 2.23 (s, 3H, ArCH_3); 2.34-2.38 (m, 5H, 2 CH_aH_b ArCH_3); 3.66-3.69 (m, 2H, N-CH_2); 3.78 (s, 3H, OCH_3); 3.86-3.90 (m, 4H, 2 N-CH_2); 4.40 (s, 2H, N-CH_2); 6.36 (s, 1H, Ar); 7.45-7.55 (m, 1H, Ar); 7.73-7.75 (m, 1H, Ar); 8.08-8.20 (m, 1H, Ar); 8.53 (s, 1H, Ar).

M/Z (M+H)$^+$: 605.4

Example **233**: 6-(4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **233** was prepared according to general procedure (XI) starting from Example **232** (138 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 60:40 to 20:80) and freeze dried with HCl (0.1 N in water) to obtain Example **233** (54 mg, 21% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.31 (s, 6H, 2 C(CH_3)); 1.51 (s, 6H, C(CH_3)$_2$); 2.11-2.16 (m, 2H, 2 CH_aH_b); 2.26 (s, 3H, ArCH_3); 2.34-2.38 (m, 5H, 2 CH_aH_b ArCH_3); 3.65-3.68 (m, 2H, N-CH_2); 3.86-3.89 (m, 4H, 2 N-CH_2); 4.41 (s, 2H, N-CH_2); 6.33 (s, 1H, Ar); 7.45-7.55 (m, 1H, Ar); 7.71-7.74 (m, 1H, Ar); 8.08-8.16 (m, 1H, Ar); 8.20 (s, 1H, Ar); 12.69 (bs, 1H, COOH).

M/Z (M+H)$^+$: 591.5

Compound **301**: N-((1-(3-chloropyrazin-2-yl)-3,3-dimethylcyclobutyl)methyl)-3,4,5-trifluoroaniline

Compound **301** was prepared according to general procedure (XXII) from Compound **297** (290 mg) and 3,4,5-trifluoroaniline. The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **301** (154 mg, 34%) as a clear oil.

M/Z (M[^{35}Cl]+H)$^+$: 356.2.

Compound **302**: 3,3-dimethyl-5'-(3,4,5-trifluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]

Compound **302** was prepared according to general procedure (XXIII) from Compound **301** (150 mg). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 80:20) to obtain Compound **302** (128 mg, 95%) as a white solid.

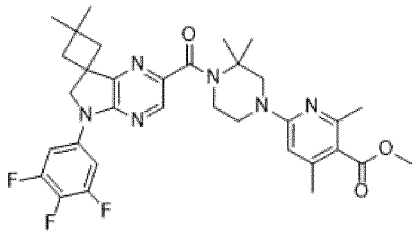
M/Z (M+H)$^+$: 320.3

Compound **303**: 2'-bromo-3,3-dimethyl-5'-(3,4,5-trifluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]

Compound **303** (138 mg, 87%) was obtained as a white solid following general procedure (XVI) in EtOAc, after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30), starting from Compound **302** (128 mg).

M/Z (M[^{81}Br] +H)$^+$: 400.2.

Example **234**: methyl 6-(4-(3,3-dimethyl-5'-(3,4,5-trifluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

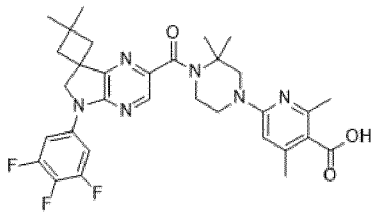


Example **234** was prepared according to general procedure (XIV) starting from Compound **303** (138 mg) and Compound **10** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **234** (111 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.29-1.31 (m, 6H, 2 C(CH_3)); 1.51 (s, 6H, C(CH_3)$_2$); 2.11-2.15 (m, 2H, 2 CH_aH_b); 2.23 (s, 3H, ArCH_3); 2.34-2.38 (m, 5H, 2 CH_aH_b ArCH_3); 3.65-3.69 (m, 2H, N-CH_2); 3.78 (s, 3H, OCH_3); 3.86-3.90 (m, 4H, 2 N-CH_2); 4.40 (s, 2H, N-CH_2); 6.36 (s, 1H, Ar); 7.92-8.01 (m, 2H, 2 Ar); 8.53 (s, 1H, Ar).

M/Z (M+H)$^+$: 623.4.

Example **235**: 6-(4-(3,3-dimethyl-5'-(3,4,5-trifluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid

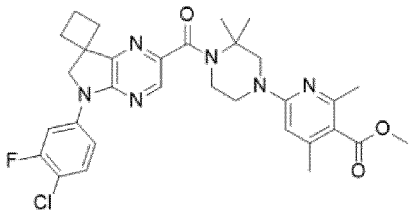


Example **235** was prepared according to general procedure (XI) starting from Example **234** (111 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 50:50 to 10:90) and freeze dried with HCl (0.1 N in water) to obtain Example **235** (48 mg, 21% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.29-1.31 (m, 6H, 2 $C(CH_3)$); 1.52 (s, 6H, $C(CH_3)_2$); 2.11-2.17 (m, 2H, 2 CH_aH_b); 2.28 (s, 3H, $ArCH_3$); 2.34-2.38 (m, 3H, 2 CH_aH_b); 2.42 (s, 3H, $ArCH_3$); 3.65-3.75 (m, 2H, N-CH_2); 3.92-3.97 (m, 4H, 2 N-CH_2); 4.40 (s, 2H, N-CH_2); 6.51 (s, 1H, Ar); 7.92-7.98 (m, 2H, 2 Ar); 8.08-8.16 (m, 1H, Ar); 8.24 (s, 1H, Ar); COOH was not observed.

M/Z $(M+H)^+$: 609.4

Example **236**: methyl 6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

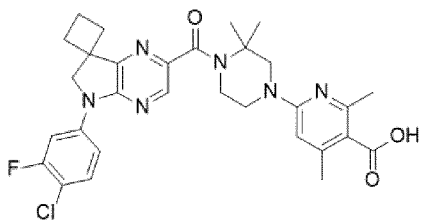


Example **236** was prepared according to general procedure (XIV) starting from Compound **294** (150 mg) and Compound **10** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **236** (178 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.51 (s, 6H, $C(CH_3)_2$); 1.99-2.21 (m, 2H, 2 CH_aH_b); 2.23 (s, 3H, $ArCH_3$); 2.26-2.36 (m, 5H, 2 CH_aH_b $ArCH_3$); 3.58-3.68 (m, 2H, CH_2 N-CH_2); 3.78 (s, 3H, O-CH_3); 3.82-3.91 (m, 4H, 2 N-CH_2); 4.31 (s, 2H, N-CH_2); 6.38 (s, 1H, Ar); 7.59-7.65 (m, 1H, Ar); 7.71-7.74 (m, 1H, Ar); 8.05-8.10 (m, 1H, Ar); 8.23 (s, 1H, Ar);

M/Z $(M[^{35}Cl]+H)^+$: 593.5

Example **237**: 6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid

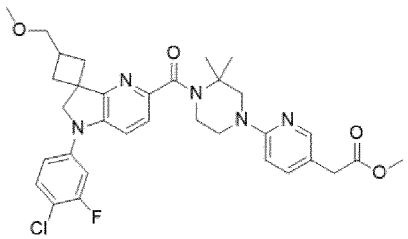


Example **237** was prepared according to general procedure (XI) starting from Example **236** (178 mg). The crude was purified by preparative HPLC (Column 1, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 0:100) and freeze dried with HCl (0.1 N in water) to obtain Example **237** (15 mg, 6% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.52 (s, 6H, $C(CH_3)_2$); 1.96-2.20 (m, 2H, 2 CH_aH_b); 2.29 (s, 3H, $ArCH_3$); 2.32-2.49 (m, 5H, 2 CH_aH_b $ArCH_3$); 3.58-3.64 (m, 4H, CH_2 N-CH_2); 3.83-3.99 (m, 4H, 2 N-CH_2); 4.30 (s, 2H, N-CH_2); 6.52 (s, 1H, Ar); 7.57-7.72 (m, 2H, 2 Ar); 8.02-8.13 (m, 1H, Ar); 8.22 (s, 1H, Ar); COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 579.4.

Example **238**: methyl 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate major isomer

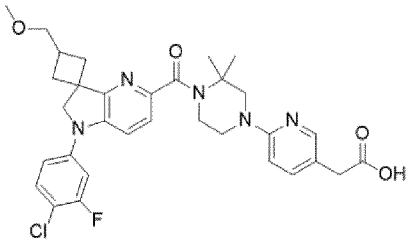


Example **238** was prepared according to general procedure (XIV) starting from Compound **287** (92 mg) and Compound **111** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **238** (101 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.51 (s, 6H, $C(CH_3)_2$); 2.18-2.38 (m, 4H, 4 CH_aH_b); 2.56-2.68 (m, 1H, CH); 3.26 (s, 3H, OCH_3); 3.48-3.57 (m, 4H, N-CH_2 CH_2OMe); 3.58-3.64 (m, 5H, $C(O)OCH_3$ N-CH_2); 3.80-3.93 (m, 4H, $CH_2C(O)$ N-CH_2); 4.25 (s, 2H, N-CH_2); 6.60 (d, *J* 8.7 Hz, 1H, Ar); 7.19 (dd, J 9.0, 1.8 Hz, 1H, Ar); 7.30-7.46 (m, 3H, 3 Ar); 7.50-7.60 (m, 2H, 2 Ar); 7.95-7.97 (m, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 622.4

Example **239**: 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid major isomer

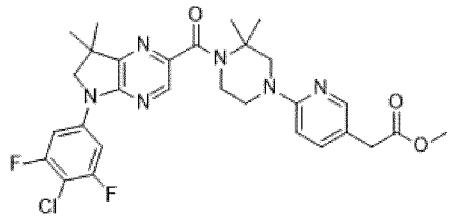


Example **239** was prepared according to general procedure (VII) starting from Example **238** (101 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 35:65) and freeze dried with HCl (0.1 N in water) to obtain Example **239** (70 mg, 49% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.57 (s, 6H, $C(CH_3)_2$); 2.16-2.37 (m, 4H, 4 CH_aH_b); 2.56-2.68 (m, 1H, CH); 3.22 (s, 3H, OCH_3); 3.49 (d, J 7.5 Hz, 2H, CH_2OMe); 3.65 (s, 2H, $CH_2C(O)$); 3.71-3.79 (m, 2H, N-CH_2); 3.93-4.04 (m, 4H, 2 N-CH_2); 4.25 (s, 2H, N-CH_2); 7.19 (dd, J 8.9, 2.6 Hz, 1H, Ar); 7.25-7.40 (m, 3H, 3 Ar); 7.52-7.59 (m, 2H, 2 Ar); 7.91-8.01 (m, 2H, 2 Ar); COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 608.4

Example **240**: methyl 2-(6-(4-(5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

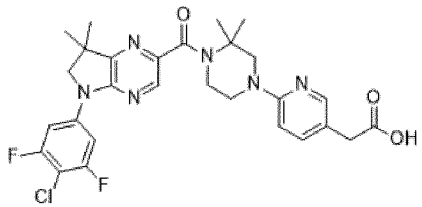


Example **240** was prepared according to general procedure (XIV) starting from Compound **230** (150 mg) and Compound **111** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **240** (150 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.40 (s, 6H, $C(CH_3)_2$); 1.50 (s, 6H, $C(CH_3)_2$); 3.46-3.54 (m, 4H, N-CH_2 CH_2-C(O)); 3.60 (s, 3H, OCH_3); 3.75-3.82 (m, 2H, N-CH_2); 3.85-3.93 (m, 2H, N-CH_2); 3.99 (s, 2H, N-CH_2); 4.00 (s, 2H, N-CH_2); 6.59 (d, *J* 8.4 Hz, 1H, Ar); 7.35-7.52 (m, 1H, 1 Ar); 7.87-7.99 (m, 3H, 3 Ar); 8.26 (s, 1H, Ar).

M/Z ($M[^{35}Cl]+H)^+$: 585.4

Example **241**: 2-(6-(4-(5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **241** was prepared according to general procedure (VII) starting from Example **240** (150 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) and freeze dried with HCl (0.1 N in water) to obtain Example **241** (90 mg, 37% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.40 (s, 6H, $C(CH_3)_2$); 1.55 (s, 6H, $C(CH_3)_2$); 3.63 (s, 2H, CH_2-C(O)); 3.66-3.74 (m, 2H, N-CH_2); 3.85-3.93 (m, 2H, N-CH_2); 3.97 (s, 2H, N-CH_2); 4.00 (s, 2H, N-CH_2); 7.28 (bs, 1H, Ar); 7.83-8.03 (m, 4H, 4 Ar); 8.29 (s, 1H, Ar); COOH was not observed.

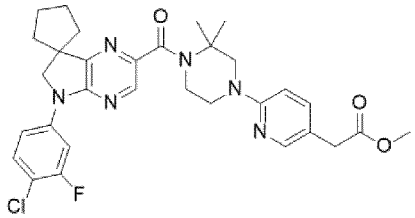
M/Z ($M[^{35}Cl]+H)^+$: 571.4

Compound **304**: 5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carboxylic acid

In the first chamber of a two-chamber reactor (2*20 mL) was prepared a solution of Compound **263** (1.05 g) and triethyl amine (0.77 mL) in a dioxane/water mixture (1:1, 12 mL). In the second chamber a suspension of $Mo(CO)_6$ (445 mg) in dioxane (12 mL) was prepared. Both chambers were sparged with argon for 10 minutes then XantPhos Pd G4 (53 mg) was added in the first chamber, and DBU (0.74 mL) was added in the second chamber. The set up was crimped and heated at 85°C for 16 hours. The mixture in the first chamber was filtered over a Celite pad, rinsed with EtOAc (40 mL) and water (10 mL), the filtrate was washed with water (2*30 mL). The aqueous washing were acidified with HCl (1N aq.) to pH = 6, the solid was recovered by filtration, dried under high vacuum, taken up in DCM

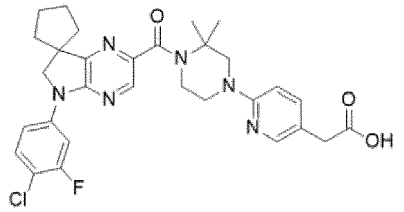
(10 mL) and combined with the organic layer. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to obtain Compound **304** (542 mg, 57%) as an orange solid.
M/Z $(M[^{35}Cl]+H)^+$: 348.2

Example **242**: methyl 2-(6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



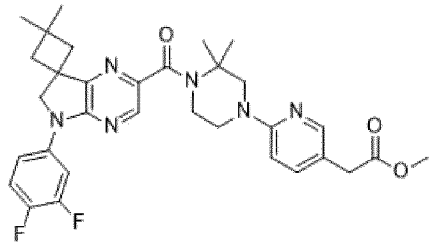
Example **242** was prepared according to general procedure (VIIIa) starting from Compound **304** (117 mg), Compound **111** (101 mg) and N,N-diisopropylethylamine (4.0 eq.) in DCM. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **242** (103 mg, 52%) as a yellow solid.
M/Z $(M[^{35}Cl]+H)^+$: 593.4.

Example **243**: 2-(6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



To a solution of Example **242** (450 mg) in THF (2 mL) was added $LiOH{\cdot}H_2O$ (64 mg) in water (2 mL). The mixture was stirred at 20°C for 45 minutes then diluted with EtOAc (10 mL) and treated with K_2CO_3 (sat. aq. 20 mL). The phases were separated and the aqueous layer was washed with Et_2O (10 mL) then acidified with HCl (1N, aq.) to pH = 6.5 and extracted with DCM (3*15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in HCl (1N, aq. 10 mL), washed with MTBE (2*10 mL), then treated with K_2CO_3 (sat.aq.) to pH = 6.5 and extracted with DCM (3*20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain Example **243** (272 mg, 62%) as a yellow solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.50 (s, 6H, $C(CH_3)_2$); 1.81-2.00 (m, 8H, $(CH_2)_4$); 3.42 (s, 2H, CH_2-C(O)); 3.46-3.51 (m, 2H, N-CH_2); 3.78-3.85 (m, 4H, 2 N-CH_2); 4.08 (s, 2H, N-CH_2); 6.57 (d, *J* 8.7 Hz, 1H, Ar); 7.44 (dd, *J* 8.7, 2.4 Hz, 1H, Ar); 7.62 (t, *J* 8.8 Hz, 1H, Ar); 7.76 (dd, *J* 8.8, 2.5 Hz, 1H, Ar); 7.94 (d, *J* 2.3 Hz, 1H, Ar); 8.08 (dd, *J* 8.8, 2.3 Hz, 1H, Ar); 8.21 (s, 1H, Ar); 12.39 (bs, 1H, COOH).
M/Z $(M[^{35}Cl]+H)^+$: 579.4

Example **244**: methyl 2-(6-(4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

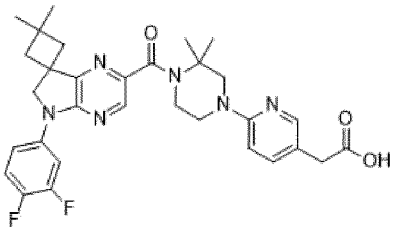


Example **244** was prepared according to general procedure (XIV) starting from Compound **300** (733 mg) and Compound **111** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30 then DCM/MeOH 80:20) to obtain Example **244** (835 mg) as a red solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.28 (s, 3H, $C(CH_3)$); 1.30 (s, 3H, $C(CH_3)$); 1.55 (s, 6H, $C(CH_3)_2$); 2.11-2.16 (m, 2H, 2 CH_aH_b); 2.34-2.38 (m, 2H, 2 CH_aH_b); 3.63-3.66 (m, 5H, N-CH_2 OCH_3); 3.90-4.01 (m, 4H, 2 N-CH_2 $CH_2C(O)$); 4.40 (s, 2H, N-CH_2); 7.00 (bs, 1H, Ar); 7.46-7.56 (m, 1H, Ar); 7.70-7.75 (m, 2H, 2 Ar); 7.95-7.97 (m, 1H, Ar); 8.08-8.16 (m, 1H, Ar); 8.20 (s, 1H, Ar); One N-CH_2 was not observed.

M/Z $(M+H)^+$: 591.4

Example **245**: 2-(6-(4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



To a solution of Example **244** (835 mg) in THF (4 mL) was added $LiOH{\cdot}H_2O$ (119 mg) in water (4 mL).The reaction mixture was stirred at 20°C for 45 minutes then treated with HCl (1N, aq.) to pH = 2 and diluted with MTBE (10 mL).. The solid was recovered by filtration and dried under high vacuum to obtain Example **245** (364 mg, 33%) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.29 (s, 6H, $C(CH_3)_2$); 1.51 (s, 6H, $C(CH_3)_2$); 2.11-2.16 (m, 2H, 2 CH_aH_b); 2.34-2.38 (m, 2H, 2 CH_aH_b); 3.43 (s, 2H, $CH_2C(O)$); 3.55-3.62 (m, 2H, N-CH_2); 3.79-3.92 (m, 4H, 2 N-CH_2); 4.40 (s, 2H, N-CH_2); 6.56 (dd, *J* 8.7Hz, 1H, Ar); 7.42-7.55 (m, 2H, 2 Ar); 7.68-7.75 (m, 1H, Ar); 7.95 (m, 1H, Ar); 8.08-8.16 (m, 1H, Ar); 8.20 (s, 1H, Ar); 12.29 (bs, 1H, COOH).

M/Z $(M+H)^+$: 577.5

Compound **305**: 4-chloro-N-((1-(3-chloropyrazin-2-yl)-3,3-dimethylcyclobutyl)methyl)-3-fluoroaniline

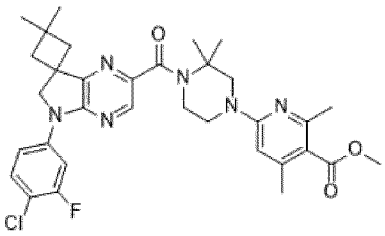
To a solution of Compound **297** (4.49 g), 4-chloro-3-fluoroaniline (3.49 g) and TFA (3.08 mL) in iPrOAc (200 mL) at 25°C was added sodium triacetoxyhydroborate (5.09 g) portionwise over 10 minutes.The reaction mixture was stirred for 1 hour at 25°C, then diluted with EtOAc (100 mL), treated with NaOH (5N, aq.) to pH = 9 and extracted with EtOAc (2*100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain Compound **305** (8.52 g) as brown oil.

M/Z $(M[^{35}Cl]_2+H)^+$: 354.2.

Compound **306**: 5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]
Compound **306** was prepared according to general procedure (XXIII) from Compound **305** (8.52 g). The crude was purified by trituration in CyHex (30 mL) to obtain Compound **306** (3.44 g, 48%) as a beige solid.
M/Z ($M[^{35}Cl]+H)^+$: 318.2

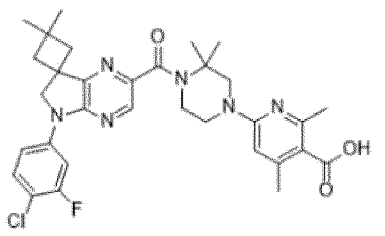
Compound **307**: 2'-bromo-5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]
Compound **307** (3.67 g, 87%) was obtained as a beige solid following general procedure (XVI) in EtOAc, after purification by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 90:10), starting from Compound **306** (3.40 g).
M/Z ($M[^{35}Cl][^{81}Br]+H)^+$: 398.1.

Example **246**: methyl 6-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



Example **246** was prepared according to general procedure (XIV) starting from Compound **307** (1000 mg) and Compound **10** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Example **246** (944 mg) as a red solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.30 (s, 6H, $C(CH_3)_2$); 1.51 (s, 6H, $C(CH_3)_2$); 2.12-2.16 (m, 2H, CH_aH_b); 2.23 (s, 3H, $ArCH_3$); 2.34-2.39 (m, 5H, 2 CH_aH_b $ArCH_3$); 3.65-3.68 (m, 2H, N-CH_2); 3.78 (s, 3H, OCH_3); 3.85-3.90 (m, 4H, 2 N-CH_2); 4.42 (s, 2H, N-CH_2); 6.35 (s, 1H, Ar); 7.58-7.64 (m, 1H, Ar); 7.78-7.82 (m, 1H, Ar); 8.08-8.13 (m, 1H, Ar); 8.23 (s, 1H, Ar).
M/Z ($M[^{35}Cl]+H)^+$: 621.4.

Example **247**: 6-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid

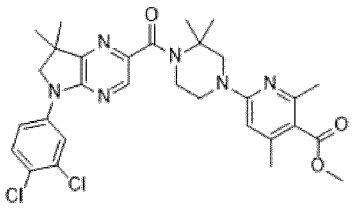


Example **247** was prepared according to general procedure (XI) starting from Example **246** (944 mg). The crude was purified by trituration in hot EtOH (5 mL) to obtain Example **247** (324 mg, 30% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.29 (s, 3H, C(CH_3)); 1.31 (s, 3H, C(CH_3)); 1.53 (s, 6H, C(CH_3)$_2$); 2.12-2.16 (m, 2H, CH_aH_b); 2.30 (s, 3H, ArCH_3); 2.35-2.39 (m, 2H, 2 CH_aH_b); 2.45 (s, 3H, ArCH_3); 3.70-3.73 (m, 2H, N-CH_2); 3.89-3.93 (m, 4H, 2 N-CH_2); 4.42 (s, 2H, N-CH_2); 6.58 (bs, 1H, Ar); 7.59-7.65 (m, 1H, Ar); 7.78-7.81 (m, 1H, Ar); 8.08-8.13 (m, 1H, Ar); 8.24 (s, 1H, Ar); COOH was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 607.4.

Example **248**: methyl 6-(4-(5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

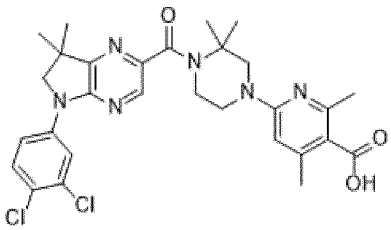


Example **248** was prepared according to general procedure (XIV) starting from Compound **279** (150 mg) and Compound **10** (1.5 eq), and using triethyl amine (4.0 eq), Mo(CO)$_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 30:70) to obtain Example **248** (174 mg) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.39 (m, 6H, C(CH_3)$_2$); 1.51 (s, 6H, C(CH_3)$_2$); 2.23 (s, 3H, ArCH_3); 2.34 (m, 3H,ArCH_3); 3.54-3.57 (m, 2H, N-CH_2); 3.75-3.81 (m, 5H, N-CH_2 OCH_3); 3.86-3.90 (m, 2H, N-CH_2); 4.00 (s, 2H, N-CH_2); 6.37 (s, 1H, Ar); 7.63-7.69 (m, 1H, Ar); 7.85-7.90 (m, 1H, Ar); 8.20-8.26 (m, 2H, 2 Ar).

M/Z (M[^{35}Cl]$_2$+H)$^+$: 623.4.

Example **249**: 6-(4-(5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **249** was prepared according to general procedure (XI) starting from Example **248** (157 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 00:100) and freeze dried with HCl (0.1 N in water) to obtain Example **248** (88 mg, 35% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.39 (s, 6H, C(CH_3)$_2$); 1.51 (s, 6H, C(CH_3)$_2$); 2.31 (s, 3H, ArCH_3); 2.44 (s, 3H, ArCH_3); 3.60-3.64 (m, 2H, N-CH_2); 3.80-3.84 (m, 2H, N-CH_2); 3.91 (s, 2H, N-CH_2); 3.99 (s, 2H, N-CH_2); 6.62 (bs, 1H, Ar); 7.67 (d, *J* 9.0 Hz, 1H, Ar); 7.87 (dd, *J* 9.0; 2.4 Hz, 1H, Ar); 8.23 (s, 1H, Ar); 8.25 (d, *J* 2.4 Hz, 1H, Ar); COOH was not observed.

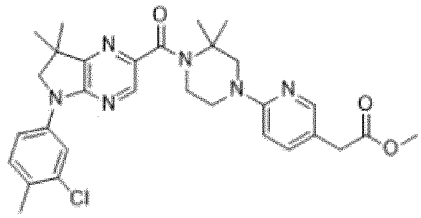
M/Z (M[^{35}Cl]$_2$+H)$^+$: 583.3.

Compound **308**: 5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carboxylic acid

Compound **308** was prepared according to general procedure (XIV) starting from Compound **233** (150 mg) and Compound **111** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). In this case the filtrate was extracted with K_2CO_3 (2M, aq., 2*5 mL) and the combined aqueous layers were freeze-dried to obtain crude Compound **308** (120 mg) as a white solid which was directly engaged in the following step.

M/Z $(M[^{35}Cl]+H)^+$: 318.2

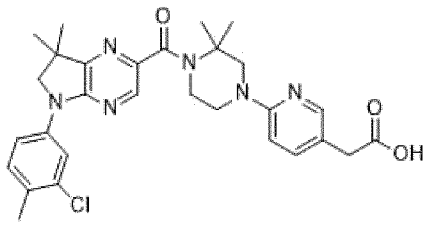
Example **250**: methyl 2-(6-(4-(5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



Example **250** was prepared according to general procedure (VIIIa) starting from Compound **308** (117 mg), Compound **111** (101 mg) and N,N-diisopropylethylamine (4.0 eq.) in DCM. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **250** (103 mg, 52%) as a yellow solid.

M/Z $(M[^{35}Cl]+H)^+$: 593.4.

Example **251**: 2-(6-(4-(5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **251** was prepared according to general procedure (VII) starting from Example **250** (101 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 35:65) and freeze dried with HCl (0.1 N in water) to obtain Example **251** (70 mg, 49% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.29 (s, 6H, $C(CH_3)_2$); 1.51 (s, 6H, $C(CH_3)_2$); 2.11-2.16 (m, 2H, 2 CH_aH_b); 2.34-2.38 (m, 2H, 2 CH_aH_b); 3.43 (s, 2H, $CH_2C(O)$); 3.55-3.62 (m, 2H, N-CH_2); 3.79-3.92 (m, 4H, 2 N-CH_2); 4.40 (s, 2H, N-CH_2); 6.56 (dd, *J* 8.7Hz, 1H, Ar); 7.42-7.55 (m, 2H, 2 Ar); 7.68-7.75 (m, 1H, Ar); 7.95 (m, 1H, Ar); 8.08-8.16 (m, 1H, Ar); 8.20 (s, 1H, Ar); 12.29 (bs, 1H, COOH).

M/Z $(M+H)^+$: 577.5

Compound **309**: N-(2-bromopyridin-3-yl)-4-methylbenzenesulfonamide

To a solution of 2-bromopyridin-3-amine (10.00 g) in Pyridine (150 mL), was added 4-methylbenzenesulfonyl chloride (13.22 g) and the solution was heated at 40 °C for 6 hours. The mixture was diluted with water (300 mL) and extracted with EtOAc (2*300 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 and

concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 50:50) to obtain Compound **309** (10.0 g, 52%) as a yellow solid.
M/Z ($M[^{79}Br]+H)^+$: 327.0.

Compound **310**: methyl 3-((N-(2-bromopyridin-3-yl)-4-methylphenyl)sulfonamido)-2,2-dimethylpropanoate
To a solution of Compound **309** (9.00 g) in THF (150 mL) was added PPh_3 (10.82 g) and methyl 3-hydroxy-2,2-dimethylpropanoate (4.36 g), then diisopropyl azodicarboxylate (11.12 g) was added portionwise at 0°C and the mixture was stirred at 25°C for 3 hours. The reaction mixture was diluted in water (300 mL) and extracted with EtOAc (2*300 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 75:25) to obtain Compound **310** (9.00 g, 74%) as a yellow solid.
M/Z ($M[^{79}Br]+H)^+$: 441.0.

Compound **311**: 3,3-dimethyl-1-tosyl-2,3-dihydro-1,5-naphthyridin-4(1H)-one
To a solution of Compound 310 (9.00 g) in THF (200 mL) at -78°C under inert atmosphere was added slowly n-butyllithium (16.3 mL, 2.5 M in hexane). The mixture was stirred at -78°C for 3 hours, then quenched in cooled water (200 mL, 0°C) and extracted wih EtOAc (2*200 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 80:20) to obtain Compound **311** (4.50 g, 66%) as a white solid.
^1H NMR (DMSO-d_6, 400 MHz) δ: 1.17 (s, 6H, $C(CH_3)_2$); 2.40 (s, 3H, $ArCH_3$); 4.07 (s, 2H, $N-CH_2$); 7.48 (d, *J* 8.2 Hz, 2H, 2 Ar); 7.53 (dd, *J* 8.6, 4.2 Hz, 1H, Ar); 7.94 (d, *J* 8.2 Hz, 2H, 2 Ar); 8.02 (dd, *J* 8.6, 1.2 Hz, 1H); 8.44 (dd, *J* 4.2, 1.2 Hz, 1H).
M/Z $(M+H)^+$: 331.1.

Compound **312**: 3,3-dimethyl-1-tosyl-1,2,3,4-tetrahydro-1,5-naphthyridin-4-ol
To a solution of Compound **311** (4.00 g) in THF (100 mL) was added portionwise $NaBH_4$ (0.92 g) at 25°C and the mixture was stirred at 25°C for 3 hours then quenched in cooled water (200 mL, 0°C) and extracted with EtOAc (2* 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 75:25) to obtain Compound **312** (3.00 g, 74%) as a white solid.
M/Z $(M+H)^+$: 333.1.

Compound **313**: 4-methoxy-3,3-dimethyl-1-tosyl-1,2,3,4-tetrahydro-1,5-naphthyridine
To a solution of Compound **312** (3.00 g) in THF (50 mL) was added NaH (0.72 g, 60% in mineral oil) at 0°C portionwise under inert atmosphere. The mixture was stirred at 0°C for 30 minutes then iodomethane (2.56 g) was added and the mixture was stirred for 3 hours at 25°C then quenched in cooled water (100 mL, 0°C) and extracted with EtOAc (2*100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 84:16) to obtain Compound **313** (2.70 g, 86%) as a white solid.
M/Z $(M+H)^+$: 346.1.

Compound **314**: 4-methoxy-3,3-dimethyl-1,2,3,4-tetrahydro-1,5-naphthyridine

To a solution of Compound **313** (2.50 g) in MeOH (50 mL) was added Magnesium (1.75 g) and the mixture was refluxed for 6 hours, then filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with water (50 mL) and extracted with EtOAc (2*50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 50:50) to obtain Compound **314** (1.30 g, 93%) as a white solid.

M/Z $(M+H)^+$: 193.1.

Compound **315**: 1-(4-chloro-3-fluorophenyl)-4-methoxy-3,3-dimethyl-1,2,3,4-tetrahydro-1,5-naphthyridine

To a solution of Compound **314** (1.20 g) in Toluene (20 mL) was added 1-chloro-2-fluoro-4-iodobenzene (8.00 g), $Pd(PPh_3)_4$ (1.44 g) and Sodium tert-butoxide (1.80 g), the mixture was sparged with Argon for 2 minutes then refluxed for 6 hours. The mixture was diluted with water (50 mL) and extracted with EtOAc (2*50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 75:25) to obtain Compound **315** (0.60 g, 30%) as a white solid.

^1H NMR ($CDCl_3$, 400 MHz) δ: 0.89-0.93 (m, 3H, $C(CH_3)_a(CH_3)_b$); 1.12-1.16 (m, 3H, $C(CH_3)_a(CH_3)_b$); 2.98-3.02 (m, 1H, CH_aH_b); 3.51 (s, 3H, OCH_3); 3.65-3.68 (m, 1H, CH_aH_b); 3.78 (s, 1H, $CH\text{-}OCH_3$); 6.95-7.07 (m, 4H, 4 Ar); 7.35-7.42 (m, 1H, Ar); 7.99-8.03 (m, 1H, Ar).

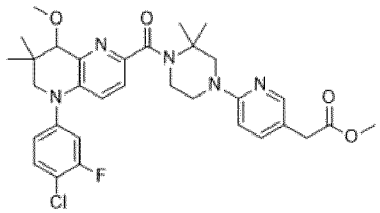
M/Z $(M[^{35}Cl]+H)^+$: 321.1.

Compound **316**: 6-bromo-1-(4-chloro-3-fluorophenyl)-4-methoxy-3,3-dimethyl-1,2,3,4-tetrahydro-1,5-naphthyridine

To a solution of Compound **315** (600 mg) in THF (10 mL) was added N-bromo-succinimide (128 mg) and Acetic acid (112 mg), the mixture was stirred at 25°C for 3 hours then diluted with water (20 mL) and extracted with EtOAc (2*20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 75:25) to obtain Compound **316** (550 mg, 73%) as a white solid.

M/Z $(M[^{79}Br][^{35}Cl]+H)^+$: 399.0.

Example **252**: methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-8-methoxy-7,7-dimethyl-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



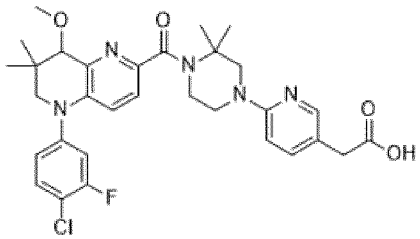
To a solution of Compound **316** (550 mg) in dioxane (10 mL) was added Compound **111** (435 mg), XantPhos Pd G4 (1100 mg) and NEt_3 (418 mg). The reaction was heated at 110 °C for 6 hours under CO atmosphere, then diluted with water (20 mL) and extracted with EtOAc (2*20 mL). The combined organic layers were washed with brine (50

mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 50:50) to obtain Example **252** (430 mg, 51%) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.83-0.91 (m, 3H, $C(CH_3)_a(CH_3)_b$); 1.07-1.13 (m, 3H, $C(CH_3)_a(CH_3)_b$); 1.47-1.52 (m, 6H, $C(CH_3)_2$); 3.13-3.19 (m, 1H, CH_aH_b); 3.40-3.46 (m, 5H, OCH_3 N-CH_2); 3.46-3.58 (m, 2H, N-CH_2); 3.59-3.64 (m, 4H, CH_2-C(O) N-CH_2); 3.74-3.81 (m, 1H, CH_aH_b); 3.83 (s, 3H, C(O)OCH_3); 3.93-4.03 (m, 1H, CH-OCH_3); 6.58-6.62 (m, 1H, Ar); 7.11-7.15 (m, 1H, Ar); 7.18-7.24 (m, 1H, Ar); 7.34-7.39 (m, 1H, Ar); 7.42-7.50 (m, 2H, 2 Ar); 7.60-7.66 (m, 1H, Ar); 7.96 (d, J 2.4 Hz, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 610.2.

Example **253**: 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-8-methoxy-7,7-dimethyl-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



To a solution of Example **252** (400 mg) in THF (10 mL) was added a solution of LiOH (314 mg) in water (4 mL) and the mixture was stirred at 25°C for 3 hours, then the mixure was acidified to pH = 6 with HCl (0.5 M aq.) and extracted with EtOAc (2*10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by preparative HPLC (H_2O/MeCN + 0.05% HCOOH) to obtain Example **253** (145 mg, 37%) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.83-0.91 (m, 3H, $C(CH_3)_a(CH_3)_b$); 1.07-1.13 (m, 3H, $C(CH_3)_a(CH_3)_b$); 1.47-1.52 (m, 6H, $C(CH_3)_2$); 3.13-3.19 (m, 1H, CH_aH_b); 3.40-3.46 (m, 5H, OCH_3 N-CH_2); 3.46-3.58 (m, 2H, N-CH_2); 3.58-3.64 (m, 1H, CH_aH_b); 3.75-3.78 (m, 1H, CH-OCH_3); 3.79-4.03 (m, 4H, CH_2-C(O) N-CH_2); 6.58-6.62 (m, 1H, Ar); 7.11-7.15 (m, 1H, Ar); 7.18-7.24 (m, 1H, Ar); 7.34-7.39 (m, 1H, Ar); 7.42-7.50 (m, 2H, 2 Ar); 7.60-7.66 (m, 1H, Ar); 7.95 (d, J 2.4 Hz, 1H, Ar); 12.27 (bs, 1H, COOH).

M/Z (M[^{35}Cl]+H)$^+$: 596.2.

Compound **317**: 2-(5-chloro-3-fluoropyridin-2-yl)-2-methylpropanenitrile

To a solution of 5-chloro-2,3-difluoropyridine (25.00 g) and isobutyronitrile (23.17 g) in Toluene (500 mL) was added slowly at 0°C NaHMDS (1M in THF, 167 mL) under inert atmosphere. The reaction was stirred for 16 hours at 25°C then quenched with cooled water (300 mL, 0°C) and extracted with EtOAc (2*300 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 90:10) to obtain Compound **317** (27.20 g, 82%) as a white solid.

M/Z (M[^{35}Cl]+H)$^+$: 199.2.

Compound **318**: 2-(5-chloro-3-fluoropyridin-2-yl)-2-methylpropan-1-amine

To Compound **317** (26.20 g) was added BH_3·THF (1M in THF, 265 mL) at 0°C under inert atmosphere. The mixture was heated at 60°C for 4 hours then quenched by slow addition in cooled water (300 mL, 0°C). The mixture was freeze dried to obtain crude Compound **318** (n.d.) directly used in the following step.

Compound **319**: 6-chloro-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

To a solution of crude Compound **318** (7.00 g) in NMP (70 mL) was added K_2CO_3 (24.00 g), the mixture was heated at 150°C for 3 hours then diluted with water (300 mL) and extracted with EtOAc (2*300 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 80:20) to obtain Compound **319** (0.83 g, 13%) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.21 (s, 6H, $C(CH_3)_2$); 3.31 (d, *J* 1.8 Hz, 2H, N-CH_2); 6.07 (d, *J* 2.0 Hz, 1H, Ar); 6.74 (d, *J* 1.8 Hz, 1H, NH); 7.60 (d, *J* 2.0 Hz, 1H, Ar).

M/Z ($M[^{35}Cl]+H)^+$: 183.2.

Compound **320**: tert-butyl 6-chloro-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate

To a solution of Compound **319** (3.30 g) in THF (30 mL) was added NEt_3 (7.40 g) and Boc_2O (15.80 g). The mixture was heated at 60°C for 16 hours then diluted with water (100 mL) and extracted with EtOAc (2*100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 90:10) to obtain Compound **320** (1.50 g, 29%) as a white solid.

M/Z ($M[^{35}Cl]+H)^+$: 283.2.

Compound **321**: tert-butyl 6-methoxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate

To a solution of Compound **320** (1.10 g) in Dioxane (10 mL) was added Sodium tert-butoxide (0.53 g), MeOH (0.63 g), and tBuBrettPhos Pd G3 (0.33 g). The mixture was sparged with Argon for 1 minute then irradiated at 50°C in a microwave reactor. The mixture was filtered over celite, the solids were rinsed with EtOAc (30 mL) and the combined filtrates were concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 80:20) to obtain Compound **321** (0.65 g, 60%) as a white solid.

M/Z $(M+H)^+$: 279.2.

Compound **322**: tert-butyl 5-bromo-6-methoxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate

To a solution of Compound **321** (650 mg) in DMF (5 mL) was added N-bromosuccinimide (525 mg) and the reaction was stirred at 25°C for 2 hours then diluted with water (30 mL) and extracted with EtOAc (2*30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether/EtOAc 80:20) to obtain Compound **322** (800 mg, 96%) as a yellow solid.

M/Z ($M[^{79}Br]+H)^+$: 357.2.

Compound **323**: 1-(tert-butyl) 5-methyl 6-methoxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-1,5-dicarboxylate

To a solution of Compound **322** (500 mg) in MeOH (5 mL) was added Xphos (200 mg), $Pd(OAc)_2$ (200 mg) and NEt_3 (568 mg). The reaction was heated at 70 °C for 48 hours under CO atmosphere, then filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum ether 100% to Petroleum ether/EtOAc 50:50) to obtain Compound **323** (300 mg, 60%) as a white solid.

M/Z $(M+H)^+$: 337.2.

Compound **334**: methyl 6-methoxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylate

To a solution of Compound **323** (400 mg) in DCM (4 mL) was added TFA (2.0 mL). The mixture was stirred at 25 °C for 2 hours then concentrated under reduced pressure. The residue was quenched in $NaHCO_3$ (sat. aq. 10 mL) and extracted with EtOAc (2*20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude Compound **334** (290 mg) as a yellow oil.

M/Z $(M+H)^+$: 237.2.

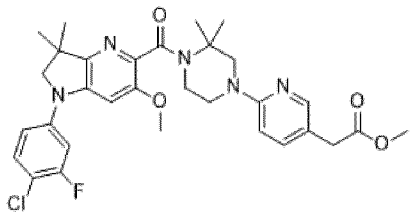
Compound **335**: 1-(4-chloro-3-fluorophenyl)-6-methoxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxylic acid

To a solution of Compound **334** (290 mg) and 1-chloro-2-fluoro-4-iodobenzene (1.57 g) in Toluene (10 mL) was added Sodium tert-butoxide (354 mg), XPhos (59 mg) and $Pd(dppf)Cl_2$·DCM (90 mg). The mixture was sparged with argon for 3 minutes then heated at 100°C for 16 hours. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography (C18 as stationary phase, MeOH/water 40:60) to obtain Compound **335** (270 mg, 63% over 2 steps) as a brown solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.26 (s, 6H, $C(CH_3)_2$); 3.72 (s, 3H, OCH_3); 3.74 (s, 2H, $N\text{-}CH_2$); 7.02 (s, 1H, Ar); 7.10-7.15 (m, 1H, Ar); 7.18-7.25 (m, 1H, Ar); 7.46-7.50 (m, 1H, Ar); COOH was not observed.

M/Z $(M+H)^+$: 351.2.

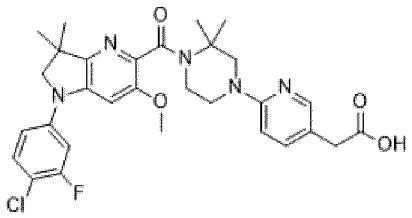
Example **254**: methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-6-methoxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



To a solution of Compound **335** (270 mg) and Compound **111** (243 mg) in DMF (10 mL) was added HATU (439 mg) and $NEt(iPr)_2$ (300 mg), the mixture was stirred at 25°C for 2 hours then diluted with water (50 mL) and extracted with EtOAc (2*30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (DCM/MeOH 90:10) to obtain Example **254** (270 mg, 59%) as a yellow solid.

M/Z $(M[^{35}Cl]+H)^+$: 596.2.

Example **255**: 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-6-methoxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



To a solution of Example **254** (60 mg) in THF (2 mL) was added LiOH (2M in water, 2 mL), the mixture was stirred at 70°C for 2 hours then filtered and concentrated. The residue was purified by preparative HPLC (H_2O/MeCN + 0.05% HCOOH) to obtain Example **255** (25 mg, 43%) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.31 (s, 6H, $C(CH_3)_2$); 1.50 (s, 6H, $C(CH_3)_2$); 3.29-3.31 (m, 2H, N-CH_2); 3.35-3.40 (m, 2H, N-CH_2); 3.41 (s, 2H, N-CH_2); 3.50 (s, 2H, N-CH_2); 3.83 (s, 3H, OCH_3); 3.84 (s, 2H, $CH_2C(O)$); 6.53-6.59 (m, 1H, Ar); 7.15 (s, 1H, Ar); 7.19-7.26 (m, 1H, Ar); 7.34-7.39 (m, 1H, Ar); 7.42-7.49 (m, 1H, Ar); 7.52-7.58 (m, 1H, Ar); 7.94 (d, J 2.2 Hz, 1H, Ar); 12.30 (bs, 1H, COOH).

M/Z ($M[^{35}Cl]+H)^+$: 582.2

Compound **336**: 4-(3-bromoprop-1-en-2-yl)-1-chloro-2-fluorobenzene

To a solution of 1-chloro-2-fluoro-4-(prop-1-en-2-yl)benzene (7.50 g) in THF (150 mL) was added N-bromosuccinimide (11.74 g) and Acetic acid (2.64 g), the mixture was stirred at 25°C for 3 hours then diluted with water (200 mL) and extracted with EtOAc (2*200 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum Ether/EtOAc 91:9) to obtain Compound **336** (6.00 g, 54%) as a yellow solid.

M/Z ($M[^{79}Br][^{35}Cl]+H)^+$: 248.9.

Compound **337**: 6-chloro-N-(2-(4-chloro-3-fluorophenyl)allyl)-3-iodopyridin-2-amine

To a solution of Compound **336** (6.00 g) and 6-chloro-3-iodopyridin-2-amine (7.34 g) in THF (100 mL) was added Potassium tert-butoxide (5.40 g), the mixture wat stirred at 25°C for 3 hours under inert atmosphere then quenched with water (200 mL) and extracted with EtOAc (2*200 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum Ether/EtOAc 67:33) to obtain Compound **337** (3.50 g, 34%) as a white solid.

M/Z ($M[^{35}Cl]_2+H)^+$: 422.9

Compound **338**: 6-chloro-3-(4-chloro-3-fluorophenyl)-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine

To a solution of Compound **337** (1.50 g), tetrabutylammonium bromide (1.37 g), NEt_3 (1.08 g), and Potassium formate (597 mg) in DMF (30 mL) was added $Pd(OAc)_2$ (398 mg). The mixture was sparged with Argon for 2 minutes, heated at 110°C for 3 hours under inert atmosphere, then diluted with water (50 mL) and extracted with EtOAc (2*50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum Ether/EtOAc 50:50) to obtain Compound **338** (200 mg, 19%) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.68 (s, 3H, $C(CH_3)$); 3.65-3.69 (m, 1H, N-CH_aH_b); 3.73-3.77 (m, 1H, N-CH_aH_b); 5.34 (bs, 1H, NH); 6.55-6.59 (m, 1H, Ar); 7.00-7.05 (m, 2H, 2 Ar); 7.07-7.13 (m, 1H, Ar); 7.30-7.35 (m, 1H, Ar).

M/Z ($M[^{35}Cl]_2+H)^+$: 297.0

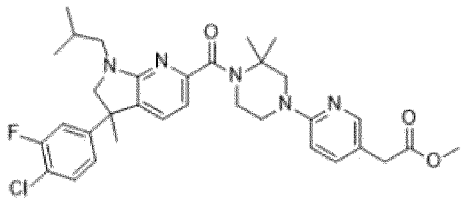
Compound **339**: 6-chloro-3-(4-chloro-3-fluorophenyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine

To a solution of Compound **338** (200 mg) in THF (5 mL) was added 1-bromo-2-methylpropane (185 mg) and Potassium tert-butoxide (151 mg). The mixture was heated at 60°C for 3 hours under inert atmosphere then quenched with water (10 mL) and extracted with EtOAc (2*10 mL). The combined organic layers were concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum Ether/EtOAc 75:25) to obtain Compound **339** (90 mg, 37%) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90-0.96 (m, 6H, $C(CH_3)_2$); 1.65 (s, *3*H, $C(CH_3)$); 1.86-2.00 (m, 1H, CH); 3.16-3.26 (m, 2H, CH_2-CH); 3.48-3.54 (m, 1H, N-CH_aH_b); 3.55-3.61 (m, 1H, N-CH_aH_b); 6.44-6.48 (m, 1H, Ar); 6.88-6.93 (m, 1H, Ar); 6.98-7.02 (m, 1H, Ar); 7.05-7.11 (m, 1H, Ar); 7.30-7.35 (m, 1H, Ar).

M/Z ($M[^{35}Cl]_2$+H)$^+$: 353.0

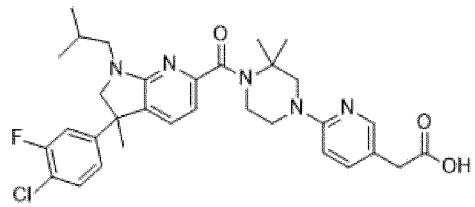
Example **256**: methyl 2-(6-(4-(3-(4-chloro-3-fluorophenyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



To a solution of Compound **339** (80 mg) in Dioxane (3 mL) was added Compound **111** (72 mg), NEt_3 (69 mg), and XantPhos Pd G4 (367 mg). The mixture was heated at 110°C for 16 hours under CO atmosphere then diluted with water (50 mL) and extracted with EtOAc (2*50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum Ether/EtOAc 50:50) to obtain Example **256** (70 mg, 50%) as a white solid.

M/Z ($M[^{35}Cl]$+H)$^+$: 608.3

Example **257**: 2-(6-(4-(3-(4-chloro-3-fluorophenyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



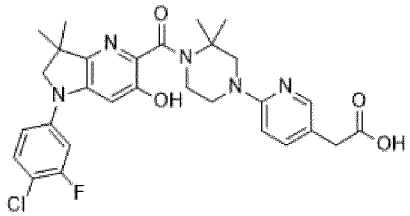
To a solution of Example **256** (70 mg) in THF (3 mL) was added LiOH (28 mg) in water (1 mL). The mixture was stirred at 25°C for 3 hours then acidified to pH = 6 with HCl (aq. 0.5 M) and extracted with EtOAc (2*10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative HPLC (H_2O/MeCN + 0.05% HCOOH) to obtain Example **257** (26 mg, 38%) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.87-0.93 (m, 6H, $CH(CH_3)_2$); 1.47 (s, 6H, $C(CH_3)_2$); 1.66 (s, *3*H, $C(CH_3)$); 1.93-2.02 (m, 1H, CH); 3.08-3.14 (m, 1H, CH_aH_b-CH); 3.17-3.24 (m, 1H, CH_aH_b-CH); 3.41 (s, 2H, N-CH_2); 3.46-3.48 (m, 2H, N-CH_2); 3.55 (d, J 9.6 Hz, 1H, N-CH_aH_b); 3.68-3.77 (m, 3H, N-CH_aH_b N-CH_2); 3.84 (s, 2H, $CH_2C(O)$); 6.53-6.57 (m, 1H,

Ar); 6.63-6.67 (m, 1H, Ar); 7.15-7.19 (m, 1H, Ar); 7.29-7.33 (m, 1H, Ar); 7.38-7.44 (m, 2H, 2 Ar); 7.52-7.58 (m, 1H, Ar); 7.94 (s, 1H, Ar); 12.25 (bs, 1H, COOH).

M/Z ($M[^{35}Cl]+H)^+$: 594.3

Example **258**: 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-6-hydroxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



A solution of Example **255** (120 mg) in DCM (5 mL) was sparged with Argon for 3 minutes then BBr_3 (1M in DCM, 3.1 mL) was added at 0°C and the reaction mixture was stirred at 25°C for 3 days then quenched with water (10 mL) and extracted with EtOAc (2*20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative HPLC (H_2O/MeCN + 0.05% HCOOH) to obtain Example **258** (6 mg, 5%) as a yellow solid.

^1H NMR (DMSO-d_6, 400 MHz) δ: 1.32 (s, 6H, $C(CH_3)_2$); 1.51 (s, 6H, $C(CH_3)_2$); 3.46 (bs, 2H, N-CH_2); 3.56 (bs, 2H, N-CH_2); 3.85 (bs, 2H, N-CH_2); 3.86 (s, 2H, $CH_2C(O)$); 4.06 (bs, 2H, N-CH_2); 6.63 (bs, 1H, Ar); 6.97 (bs, 1H, Ar); 7.16-7.20 (m, 1H, Ar); 7.28-7.36 (m, 1H, Ar); 7.44 (bs, 1H, Ar); 7.55-7.61 (m, 1H, Ar); 7.95 (d, J 2.0 Hz, 1H, Ar); 11.33 (bs, 1H, OH); 12.31 (bs, 1H, COOH).

M/Z ($M[^{35}Cl]+H)^+$: 568.2

Compound **340**: tert-butyl 4-(8-methoxy-8-oxooctanoyl)-2,2-dimethylpiperazine-1-carboxylate

To a solution of 8-methoxy-8-oxooctanoic acid (439 mg), HATU (1240 mg) and $NEt(iPr)_2$ (1.2 mL) in DCM (7.8 mL) was added tert-butyl 2,2-dimethylpiperazine-1-carboxylate (500 mg). The mixture was stirred at 25°C for 18 hours then washed with HCl (1N aq. 20 mL), with $NaHCO_3$ (sat. aq. 20 mL), and with brine (20 mL), the combined organic layer were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 60:40) to obtain Compound **340** (649 mg, 72%) as a clear oil.

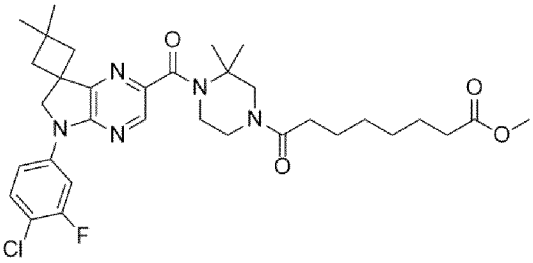
M/Z $(M+H)^+$: 385.4.

Compound **341**: methyl 8-(3,3-dimethylpiperazin-1-yl)-8-oxooctanoate hydrochloride

To a solution of Compound 340 (645 mg) in DCM (8.3 mL) was added HCl (2M in Et_2O, 8.3 mL) and the mixture was stirred at 25°C for 18 hours then concentrated under reduced pressure to obtain Compound 341 (522 mg, 97%) as a clear oil.

M/Z $(M+H)^+$: 285.4.

Example **259**: methyl 8-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-8-oxooctanoate

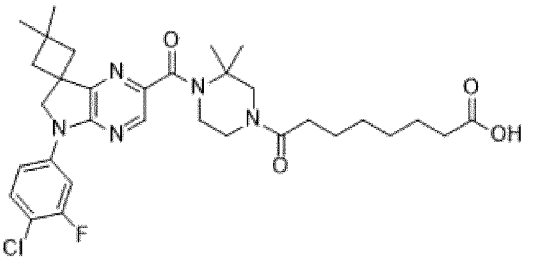


Example **259** was prepared according to general procedure (XIV) starting from Compound **307** (150 mg) and Compound **341** (1.5 eq), and using triethyl amine (3.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 00:100) to obtain Example **259** (363 mg, 55%) as an orange solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.20-1.34 (m, 10H, 2 $CH_2CH_2CH_2C(O)$ $C(CH_3)_2$); 1.45-1.53 (m, 10H, 2 $CH_2CH_2C(O)$ $C(CH_3)_2$); 2.08-2.17 (m, 2H, 2 CH_aH_b); 2.23-2.39 (m, 6H, 2 CH_aH_b 2 $CH_2C(O)$); 3.48-3.66 (m, 6H, N-CH_2 N-CH_aH_b OCH_3); 3.68-3.81 (m, 3H, N-CH_2 N-CH_aH_b); 4.37-4.45 (m, 2H, N-CH_2); 7.58-7.65 (m, 1H, Ar); 7.76-7.83 (m, 1H, Ar); 8.05-8.14 (m, 1H, Ar); 8.20-8.23 (m, 1H, Ar).

M/Z $(M[^{35}Cl]+H)^+$: 628.5.

Example **260**: 8-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-8-oxooctanoic acid

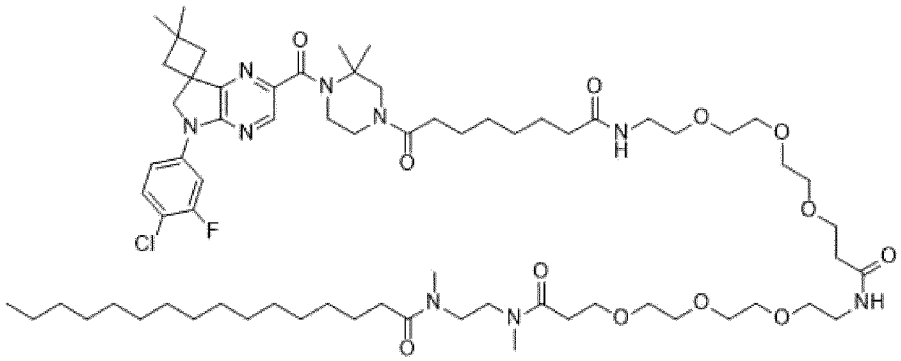


To a solution of Example **259** (310 mg) in THF (4 mL) was added LiOH (62 mg) in water (2 mL). The mixture was stirred at 25°C for 18 hours then concentrated under reduced pressure. The residue was diluted in water (20 mL), treated with HCl (1M, aq) to pH = 3 and extracted with EtOAc (2*30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was freeze dried with water to obtain Example **260** (298 mg, 98%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.22-1.34 (m, 10H, 2 $CH_2CH_2CH_2C(O)$ $C(CH_3)_2$); 1.47-1.51 (m, 10H, 2 $CH_2CH_2C(O)$ $C(CH_3)_2$); 2.08-2.39 (m, 8H, 4 CH_aH_b 2 $CH_2C(O)$); 3.48-3.81 (m, 6H, 2 N-CH_2 N-CH_aH_b); 4.37-4.45 (m, 2H, N-CH_2); 7.59-7.65 (m, 1H, Ar); 7.76-7.81 (m, 1H, Ar); 8.01-8.12 (m, 1H, Ar); 8.20-8.23 (m, 1H, Ar); 11.98 (bs, 1H, COOH).

M/Z $(M[^{35}Cl]+H)^+$: 614.5.

Example **261**: N-(37-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-3-methyl-4,17,30,37-tetraoxo-7,10,13,20,23,26-hexaoxa-3,16,29-triazaheptatriacontyl)-N-methylpalmitamide



To a solution of Example **260** (100 mg) in THF (4 mL) was added HATU (108 mg) and $NEt(iPr)_2$ (113 µL), after 5 minutes of stirring, N-(1-amino-26-methyl-12,25-dioxo-3,6,9,16,19,22-hexaoxa-13,26-diazaoctacosan-28-yl)-N-methylpalmitamide (163 mg) was added and the mixture stirred for 2 hours at 25°C. The mixture was treated with HCl (1M, aq, 20 mL) and extracted with EtOAc (2*30 mL). The combined organic layers were washed with $NaHCO_3$ (sat. aq. 20 mL), with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Interchim® 20 µm, DCM 100% to DCM/MeOH 90:10) then freeze-dried with water to obtain Example **261** (186 mg, 86%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 0.84 (t, = 6.6 Hz, 3H, $CH_2C\mathbf{H}_3$); 1.17-1.33 (m, 36H); 1.38-1.56 (m, 12H); 2.00-2.38 (m, 12H); 2.78-2.83 (m, 2H); 2.90-2.97 (m, 4H); 3.13-3.22 (m, 4H); 3.35-3.42 (m, 8H); 3.43-3.53 (m, 16H); 3.54-3.65 (m, 7H); 3.68-3.82 (m, 3H); 4.38-4.44 (m, 2H); 7.58-7.64 (m, 2H, Ar C(O)NH); 7.88-7.92 (m, 1H, NH); 8.06-8.15 (m, 1H, Ar); 8.20-8.24 (m, 1H, Ar).

M/Z $(M+2H)^{2+}$: 665.3. Mp: ND.

Compound **342**: methyl 4-chloro-2,6-dimethylnicotinate

A solution of methyl 3-aminocrotonate (3.55 g) in $POCl_3$ (11 mL) was heated at 110°C for 1 hour, then the reaction mixture was quenched in ice (100 mL), treated by slow addition of NaOH (15% aq. 100 mL) at 0°C, then extracted with EtOAc (2*100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **342** (1.15 g, 34%) as a yellow oil.

^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.42 (s, 3H, $ArCH_3$); 2.46 (s, 3H, $ArCH_3$); 3.90 (s, 3H, OCH_3); 7.41 (s, 1H, Ar).

M/Z $(M[^{35}Cl]+H)^+$: 200.2.

Compound **343**: methyl 4-(3,3-dimethylpiperazin-1-yl)-2,6-dimethylnicotinate

To a solution of Compound **342** (400 mg) in MeTHF (4 mL) was added Sodium tert-butoxide (385 mg) and 2,2-dimethylpiperazine (275 mg). The mixture was sparged with Argon for 10 minutes then RuPhos Pd G4 (85 mg) was added and the mixture was stirred at 25°C for 18 hours then HCl (1N aq., 10 mL) and EtOAc (10 mL) were added. The mixture was filtered over a pad of Celite, the pad was rinsed with EtOAc (10 mL) and water (10 mL). The aqueous layer was washed with EtOAc (2*50 mL) then treated with NaOH (1N aq.) to pH = 3, washed with DCM (2*50 mL) then further treated with NaOH (1N aq.) to pH = 12.and extracted with DCM (2*60 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain Compound **343** (73 mg, 13%) as a yellow oil.

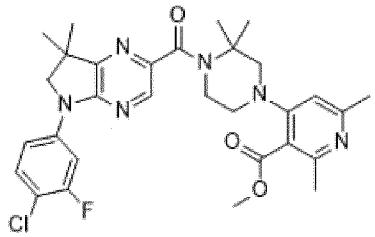
M/Z $(M+H)^+$: 278.3.

Compound **344**: 5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carboxylic acid

In the first chamber of a two-chamber reactor (2*5 mL) was prepared a solution of Compound **128** (203 mg) and triethyl amine (159 µL) in a dioxane/water mixture (1:1, 3 mL). In the second chamber a suspension of $Mo(CO)_6$ (75 mg) in dioxane (3 mL) was prepared. Both chambers were sparged with argon for 10 minutes then XantPhos Pd G4 (11 mg) was added in the first chamber, and DBU (127 µL) was added in the second chamber. The set up was crimped and heated at 85°C for 20 hours. The mixture in the first chamber was filtered over a Celite pad, rinsed with EtOAc (50 mL) and water (20 mL), the filtrate was washed with water (2*30 mL). The aqueous washing were acidified with HCl (1N aq.) to pH = 6, the solid was recovered by filtration and dried under high vacuum, to obtain Compound **344** (100 mg, 55%) as a beige solid.

M/Z $(M[^{35}Cl]+H)^+$: 322.2.

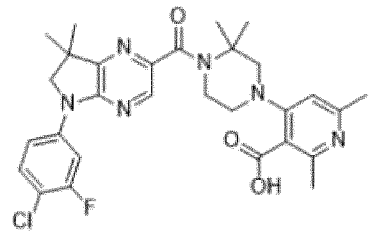
Example **262**: methyl 4-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,6-dimethylnicotinate



Example **262** was prepared according to general procedure (VIIIa) starting from Compound **344** (75 mg), Compound **343** (1.1 eq.) and N,N-diisopropylethylamine (3.0 eq.) in DCM. The crude Example **262** (256 mg) was directly engaged in the following step.

M/Z $(M[^{35}Cl]+H)^+$: 581.4.

Example **263**: 4-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,6-dimethylnicotinic acid



Example **263** was prepared according to general procedure (VII) starting from crude Example **262** (246 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 00:100) and freeze dried with water to obtain Example **263** (6 mg, 5% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.38 (s, 6H, $C(CH_3)_2$); 1.50 (s, 6H, $C(CH_3)_2$); 2.36-2.48 (m, 6H, 2 $ArCH_3$); 3.65-3.78 (m, 6H, 3 N-CH_2); 3.98 (s, 2H, N-CH_2); 6.67 (m, 1H, Ar); 7.58-7.64 (m, 1H, Ar); 7.70-7.74 (m, 1H, Ar); 8.06-8.11 (m, 1H, Ar); 8.22 (s, 1H, Ar), 13.01 (bs, 1H, COOH).

M/Z $(M[^{35}Cl]+H)^+$: 567.4.

Compound **345**: 2,6-dichloro-N-(4-chloro-3-fluorophenyl)pyridin-3-amine

A solution of 3-bromo-2,6-dichloropyridine (200 mg), 4-chloro-3-fluoroaniline (128 mg), and Sodium tert-butoxide (102 mg) in Toluene (4.5 mL) was sparged with Argon for 10 minutes, then $P(t\text{-}Bu)_3$ Pd G4 (26 mg) was added and the mixture was heated at 80°C for 4 hours. The mixture was filtered over a pad of Celite, the pad was rinsed with EtOAc (10 mL) and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (30 mL), washed with water (2*20 mL), with brine (20 mL) and dried over $MgSO_4$ and concentrated under reduced pressure to obtain crude Compound **345** (298 mg) as a brown oil which was directely engaged in the following step.

M/Z $(M[^{35}Cl]_2[^{37}Cl]+H)^+$: 293.1.

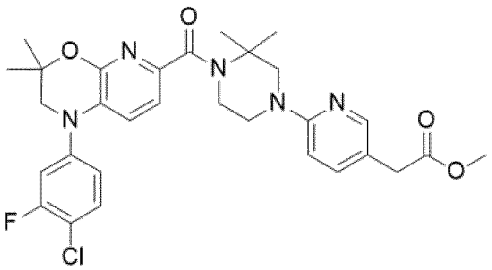
Compound **346**: 6-chloro-1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine

To a solution of crude Compound **345** (257 mg) and Sodium tert-butoxide (102 mg) in THF (4 mL) at 50°C were added 11 portions of 1,2-Epoxy-2-methylpropane (11*94 µL) over 7 days. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2*10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 70:30) to obtain Compound **346** (119 mg, 41% over 2 steps) as a brown oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.32 (s, 6H, $C(CH_3)_2$); 3.55 (s, 2H, $N\text{-}CH_2$); 6.91 (d, *J* 8.4 Hz, 1H, Ar); 7.14-7.18 (m, 1H, Ar); 7.37-7.41 (m, 1H, Ar); 7.43 (d, *J* 8.4 Hz, 1H, Ar), 7.52-7.58 (m, 1H, Ar).

M/Z $(M[^{35}Cl]_2+H)^+$: 327.2.

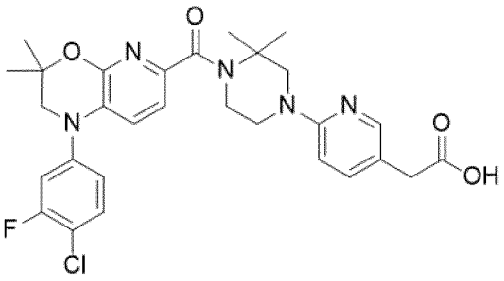
Example **264**: methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



Example **264** was prepared according to general procedure (XIV) starting from Compound **346** (119 mg) and Compound **111** (1.5 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude Example **264** (142 mg) was directly engaged in the following step.

M/Z $(M[^{35}Cl]+H)^+$: 582.3.

Example **265**: 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



Example **265** was prepared according to general procedure (VII) starting from Example **264** (142 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 0:100) and freeze dried to obtain Example **265** (25 mg, 12% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.35 (s, 6H, $C(CH_3)_2$); 1.47 (s, 6H, $C(CH_3)_2$); 3.40-3.47 (m, 4H, N-CH_2); 3.58 (s, 2H, N-CH_2); 3.75-3.86 (m, 4H, N-CH_2, $CH_2C(O)$); 6.57 (d, *J* 8.7 Hz, 1H, Ar); 7.06 (d, *J* 8.2 Hz, 1H, Ar); 7.22 (dd, *J* 8.7, 1.9 Hz, 1H, Ar); 7.34-7.47 (m, 3H, 3 Ar); 7.55-7.63 (m, 1H, Ar); 7.94 (d, *J* 1.9 Hz, 1H, Ar); COOH signal was not observed.
M/Z ($M[^{35}Cl]+H)^+$: 568.4

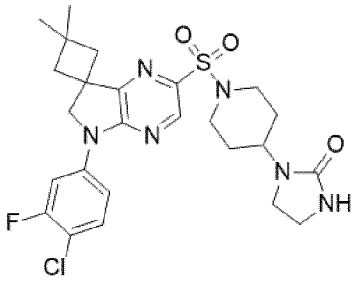
Compound **347**: 2'-(benzylthio)-5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]

A solution of Compound **307** (300 mg), phenylmethanethiol (98 µL) and $Net(iPr)_2$ (260 µL) in Dioxane (7.5 mL) was sparged with Argon for 5 minutes then XantPhos Pd G4 (73 mg) was added and the mixture was heated at 95°C for 18 hours. The mixture was filtered over a pad of Celite, the pad was rinsed with EtOAc (10 mL) and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 90:10) to obtain Compound **347** (297 mg, 89%) as a yellow solid.
M/Z ($M[^{37}Cl]+H)^+$: 442.1.

Compound **348**: 5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-sulfonyl chloride

To a solution of Compound **347** (150 mg) in a water/acetic acid mixture (4.8 mL 1:11), N-chlorosuccinimide (137 mg) was added. The mixture was stirred at 25°C for 2 hours then diluted with water (10 mL), and extracted with EtOAc (2*10 mL). The combined organic layers were concentrated under reduced pressure and the residue was co-evaporated with CyHex (3*10 mL) to obtain crude Compound **348** (193 mg) as a yellow solid which was directly engaged in the following step.
M/Z $(M+H)^+$: Not observed.
Derivation with piperidine was used to monitor the reaction.

Example **266**: 1-(1-((5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazin]-2'-yl)sulfonyl)piperidin-4-yl)imidazolidin-2-one



To a solution of crude Compound **348** (97 mg) in DCM (2.3 mL) was added 1-(Piperidin-4-yl)imidazolidine-2-one (118 mg) and the mixture was stirred at 25°C for 20 hours. The residue was purified by flash chromatography (Interchim® 20 µm, DCM 100% to DCM/MeOH 90:10), then by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 50:50 to 10:90) and freeze dried to obtain Example **266** (12 mg, 6% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.26 (s, 3H, C(CH_3)); 1.28 (s, 3H, C(CH_3)); 1.59-1.67 (m, 4H, CH_2); 2.14-2.18 (m, 2H, CH_aH_b); 2.34-2.38 (m, 2H, CH_aH_b); 2.73-2.82 (m, 2H, N-CH_2); 3.18-3.25 (m, 4H, N-CH_2); 3.47-3.57 (m, 1H, N-CH); 3.79-3.83 (m, 2H, N-CH_2); 4.44 (s, 2H, N-CH_2); 6.28 (s, 1H, NH); 7.65 (t, *J* 8.8 Hz, 1H, Ar); 7.79-7.83 (m, 1H, Ar); 8.12 (dd, *J* 12.4, 2.5 Hz, 1H, Ar); 8.38 (s, 1H, Ar).

Compound **349**: 4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrazino[2,3-b][1,4]oxazine

To a solution of crude 2,3-dichloropyrazine (500 mg) and 4-Chloro-3-fluoroaniline (489 mg) in THF (15 mL) was added Sodium tert-butoxide (968 mg) at 0°C. The mixture was stirred at 20°C for 18 hours then at 50°C were added 9 portions of 1,2-Epoxy-2-methylpropane (9*358 µL) over 5 days. The reaction mixture was diluted with EtOAc (50 mL), washed with water (2*25 mL), with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Compound **349** (600 mg, 61%) as a yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.38 (s, 6H, C(CH_3)$_2$); 3.76 (s, 2H, N-CH_2); 7.26-7.33 (m, 1H, Ar); 7.52-7.61 (m, 2H, 2 Ar); 7.63 (d, *J* 3.0 Hz, 1H, Ar); 7.69 (d, *J* 3.0 Hz, 1H, Ar).

M/Z (M[^{35}Cl]+H)$^+$: 294.2.

Compound **350**: 7-bromo-4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrazino[2,3-b][1,4]oxazine

Compound **350** (800 mg, 64%) was obtained as a brown oil following general procedure (XVI) in EtOAc without further purification, starting from Compound **349** (600 mg).

M/Z (M[^{37}Cl][^{81}Br]+H)$^+$: 376.1.

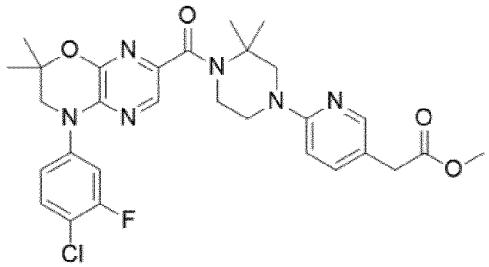
Compound **351**: 4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrazino[2,3-b][1,4]oxazine-7-carboxylic acid

In the first chamber of a two-chamber reactor (2*5 mL) was prepared a solution of Compound **350** (300 mg) and triethyl amine (224 µL) in a dioxane/water mixture (1:1, 3 mL). In the second chamber a suspension of $Mo(CO)_6$ (212 mg) in dioxane (3 mL) was prepared. Both chambers were sparged with argon for 10 minutes then XantPhos Pd G4 (16 mg) was added in the first chamber, and DBU (180 µL) was added in the second chamber. The set up was crimped and heated at 85°C for 18 hours. The mixture in the first chamber was filtered over a Celite pad, rinsed with

MeOH (20 mL), the filtrate was concentrated under reduced pressure then dissolved in water (30 mL). The solution was washed with EtOAc (2*25 mL), treated with HCl (1M aq., to pH = 3) and extracted with MTBE (3*20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain Compound **351** (216 mg) as a brown oil.

M/Z (M[^{35}Cl]+H)$^+$: 338.2.

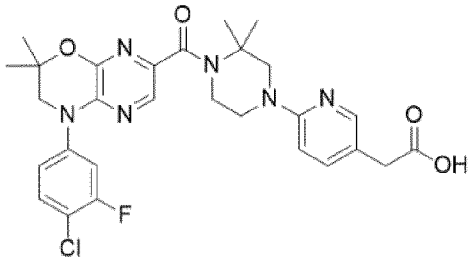
Example **267**: methyl 2-(6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrazino[2,3-b][1,4]oxazine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)266yridine-3-yl)acetate



Example **267** was prepared according to general procedure (VIIIb) starting from Compound **351** (100 mg), Compound **111** (1.2 eq.) and DIPEA (3 eq.) in MeTHF. Example **267** (208 mg) was obtained without further purification as a brown oil.

M/Z (M[^{35}Cl]+H)$^+$: 583.3

Example **268**: 2-(6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrazino[2,3-b][1,4]oxazine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)266yridine-3-yl)acetic acid



Example **268** was prepared according to general procedure (VII) starting from Example **267** (208 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 80:20 to 40:60) and freeze dried with HCl (0.1 N, aq.) to obtain Example **268** (108 mg, 47% over 3 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.41 (s, 6H, $(CH_3)_2$); 1.52 (s, 6H, $(CH_3)_2$); 3.64-3.71 (m, 4H, 2 N-CH_2); 3.83 (s, 2H, $CH_2C(O)$); 3.90-3.94 (m, 2H, N-CH_2); 3.98 (s, 2H, N-CH_2); 7.32-7.39 (m, 2H, 2 Ar); 7.57-7.64 (m, 2H, 2 Ar); 7.94-8.00 (m, 3H, 3 Ar); COOH signal was not observed.

M/Z (M[^{35}Cl]+H)$^+$: 569..4

Compound **352**: 5-(tert-butyl) 2-methyl 7,7-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridine-2,5(4H)-dicarboxylate

To a solution of tert-butyl 2-bromo-7,7-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (754 mg) in MeOH (30 mL) was added $Pd(OAc)_2$ (108 mg), X-Phos (310 mg), and NEt_3 (1.20 mL). The mixture was heated at 60°C for 5 hours under CO atmosphere then filtered and the filtrate was concentrated under reduced pressure. The

residue was purified by flash chromatography (Petroleum Ether 100% to Petroleum Ether/EtOAc 75:25) to obtain Compound **352** (283 mg, 39%) as a brown oil.

M/Z $(M+H)^+$: 327.2.

Compound **353**: methyl 7,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate

To a solution of Compound **352** (253 mg) in DCM (3 mL) was added TFA (1.0 mL) at 0°C. The mixture was stirred at 25°C for 2 hours then diluted with EtOAc (50 mL) and washed with $NaHCO_3$ (sat. aq. 3*20 mL). Combined aqueous washes were adjusted to pH = 11 and extracted with EtOAc (3*30 mL). All organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude Compound **353** (181 mg) as a brown solid.

M/Z $(M+H)^+$: 227.2.

Compound **354**: methyl 5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate

To a solution of Compound **353** (151 mg) in Dioxane (15 mL) was added Cs_2CO_3 (437 mg) and 1-chloro-2-fluoro-4-iodobenzene (256 mg) was added RuPhos Pd G4 (57 mg). The mixture was heated at 100°C for 4 hours under inert atmosphere then filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum Ether 100% to Petroleum Ether/EtOAc 80:20) to obtain Compound **354** (151 mg, 64%) as a yellow solid.

M/Z $(M[^{35}Cl]+H)^+$: 355.2.

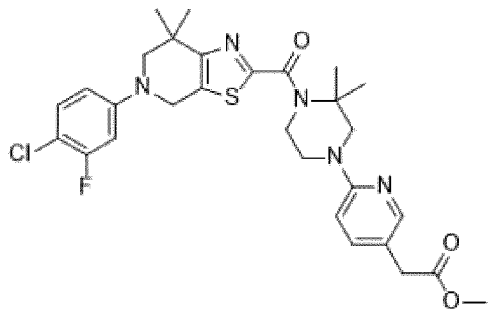
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.31 (s, 6H, $C(CH_3)_2$); 3.46 (s, 2H, N-CH_2); 3.90 (s, 3H, OCH_3); 4.59 (s, 2H, N-CH_2); 6.86-6.91 (m, 1H, Ar); 7.02-7.09 (m, 1H, Ar); 7.35-7.41 (m, 1H, Ar).

Compound **355**: 5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid

To a solution of Compound **354** (152 mg) in THF (15 mL) was added LiOH (103 mg) in water (2 mL) at 0°C. The mixture was heated at 60°C for 3 hours then treated with HCl (2M, aq.) to pH = 3 and extracted with EtOAc (3*30 mL). The combined organic layers were washed with brine (40 mL) dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude Compound **355** (174 mg) as a brown oil.

M/Z $(M[^{35}Cl]+H)^+$: 341.0.

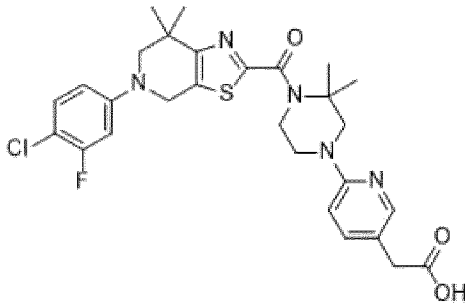
Example **269**: methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



To a solution of Compound **355** (119 mg) in DMF (8 mL) was added diethyl (4-oxobenzo[d][1,2,3]triazin-3(4H)-yl) phosphate (209 mg) and $NEt(iPr)_2$ (0.30 mL) and the mixture was stirred at 0°C for 30 minutes then Compound **111** (110 mg) was added. The mixture was stirred at 25°C for 5 hours then diluted with water (20 mL) and extracted with EtOAc (3*30 mL). The combined organic layers were washed with brine (30 mL) dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum Ether 100% to Petroleum Ether/EtOAc 60:40) to obtain Example **269** (75 mg, 37%) as a yellow solid.

M/Z $(M[^{35}Cl]+H)^+$: 586.2.

Example **270**: 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid

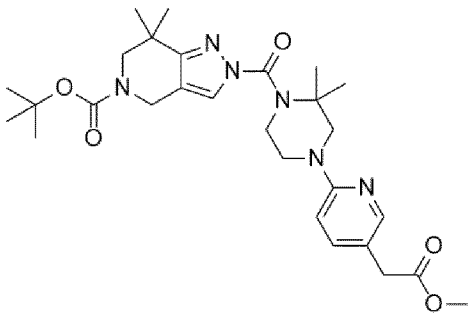


To a solution of Example **269** (103 mg) in THF (10 mL) was added LiOH (43 mg) in water (2 mL) at 0°C. The mixture was stirred at 25°C for 3 hours then treated with HCl (2M aq.) to pH = 2 and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (40 mL) dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative HPLC (H_2O/MeCN + 0.05% HCOOH) and further purified by flash chromatography (C18 as stationary phase, water 100% to MeOH/water 25:75) to obtain Example **270** (28 mg, 28%) as a yellow solid.

^1H NMR (DMSO-d_6, 400 MHz) δ: 1.31 (s, 6H, $C(CH_3)_2$); 1.47 (s, 6H, $C(CH_3)_2$); 3.22 (s, 2H, $N\text{-}CH_2$); 3.44 (s, 2H, $N\text{-}CH_2$); 3.50-3.56 (m, 2H, $N\text{-}CH_2$); 3.88 (s, 2H, $CH_2C(O)$); 4.52-4.54 (m, 4H, $N\text{-}CH_2$); 6.52-6.56 (m, 1H, Ar); 6.85-6.89 (m, 1H, Ar); 7.02-7.08 (m, 1H, Ar); 7.41-7.45 (m, 1H, Ar); 7.93 (d, *J* 1.6 Hz, 1H, Ar); COOH was not observed.

M/Z $(M[^{35}Cl]+H)^+$: 572.2.

Example **271**: tert-butyl 2-(4-(5-(2-methoxy-2-oxoethyl)pyridin-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-7,7-dimethyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate



To a solution of tert-butyl 7,7-dimethyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (100 mg) in DCM (10 mL) was added triphosgene (59 mg), and the mixture was stirred at 25°C for 5 minutes then $NEt(iPr)_2$ (0.43 mL)

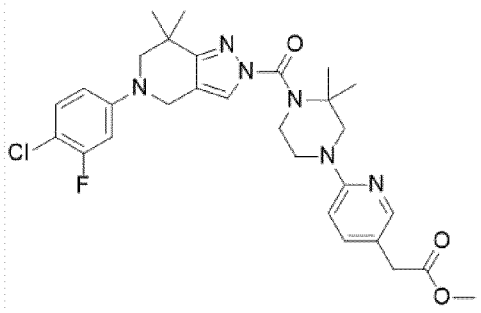
was added dropwise at 0°C. The mixture was stirred at 25°C for 2 hours then diluted with DCM (20 mL), quenched with water (20 mL) and extracted with DCM (3*20 mL). The combined organic layers were washed with brine (30 mL) dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum Ether 100% to Petroleum Ether/EtOAc 65:35) to obtain Example **271** (106 mg, 49%) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.22 (s, 6H, $C(CH_3)_2$); 1.43 (s, 9H, $C(CH_3)_3$); 1.45 (s, 6H, $C(CH_3)_2$); 3.39 (s, 2H, N-CH_2); 3.53-3.54 (m, 4H, 2 N-CH_2); 3.61 (s, 3H, OCH_3); 3.86 (s, 2H, $CH_2C(O)$); 3.87-3.94 (m, 2H, N-CH_2); 4.45 (s, 2H, N-CH_2); 6.63 (d, *J* 8.8 Hz, 1H, Ar); 7.45 (d, *J* 8.8 2.0 Hz, 1H, Ar); 7.97 (d, *J* 2.0 Hz, 1H, Ar);
M/Z $(M+H)^+$: 541.4.

Compound **356**: methyl 2-(6-(4-(7,7-dimethyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

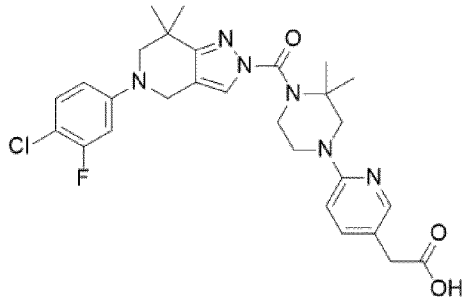
To a solution of Example **271** (182 mg) in DCM (3 mL) was added TFA (1.0 mL) at 0°C and the mixture was stirred at 25°C for 3 hours. The mixture was concentrated under reduced pressure, the residue was diluted with $NaHCO_3$ (sat. aq. 30 mL) and extracted with EtOAc (5*30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. To obtain crude Compound **356** (131 mg) as a yellow solid.
M/Z $(M+H)^+$: 441.4.

Example **272**: methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



To a solution of Compound **356** (123 mg) in Dioxane (10 mL) was added Cs_2CO_3 (183 mg) and 1-chloro-2-fluoro-4-iodobenzene (108 mg) was added RuPhos Pd G4 (24 mg). The mixture was heated at 100°C for 4 hours under inert atmosphere then filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum Ether 100% to Petroleum Ether/EtOAc 60:40) to obtain Example **272** (104 mg, 65%) as a yellow solid.
M/Z $(M[^{35}Cl]+H)^+$: 569.2.

Example **273**: 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



To a solution of Example **272** (110 mg) in THF (10 mL) was added LiOH (47 mg) in water (2 mL) at 0°C. The mixture was stirred at 25°C for 3 hours then treated with HCl (2M aq.) to pH = 3 and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (40 mL) dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative HPLC (H_2O/MeCN + 0.05% HCOOH) to obtain Example **273** (44 mg, 41%) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.31 (s, 6H, $C(CH_3)_2$); 1.46 (s, 6H, $C(CH_3)_2$); 3.37 (s, 2H, N-CH_2); 3.42 (s, 2H, N-CH_2); 3.50-3.59 (m, 2H, N-CH_2); 3.85 (s, 2H, $CH_2C(O)$); 3.88-3.99 (m, 2H, N-CH_2); 4.27 (s, 2H, N-CH_2); 6.60-6.64 (m, 1H, Ar); 6.81-6.85 (m, 1H, Ar); 6.97-7.03 (m, 1H, Ar); 7.34-7.36 (m, 1H, Ar); 7.42-7.46 (m, 1H, Ar); 7.92 (s, 1H, Ar); 7.95 (d, *J* 2.0 Hz, 1H, Ar); 12.35 (bs, 1H, COOH).

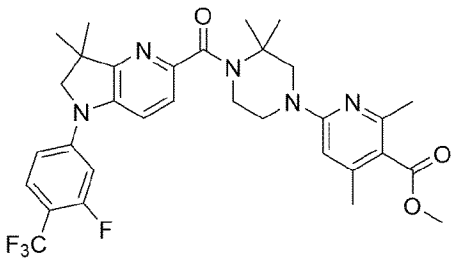
M/Z ($M[^{35}Cl]+H)^+$: 555.2.

Compound **357**: 5-chloro-1-(3-fluoro-4-(trifluoromethyl)phenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

Compound **357** was prepared according to general procedure (X) starting from Compound **70** (300 mg) and 4-bromo-2-fluoro-1-(trifluoromethyl)benzene (2.0 eq) with ^{t}BuONa (3.0 eq) at 100°C for 16 hours. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Compound **357** (110 mg, 19%) as a white solid.

M/Z ($M[^{35}Cl]+H)^+$: 345.2

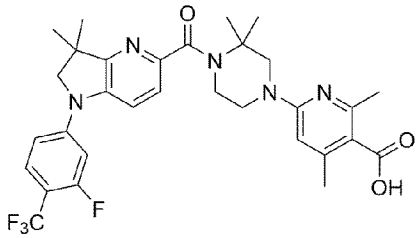
Example **274**: methyl 6-(4-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate



Example **274** was prepared according to general procedure (XIV) starting from Compound **357** (110 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 20 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Example **274** (55 mg) as a beige solid.

M/Z $(M+H)^+$: 615.1.

Example **275**: 6-(4-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid

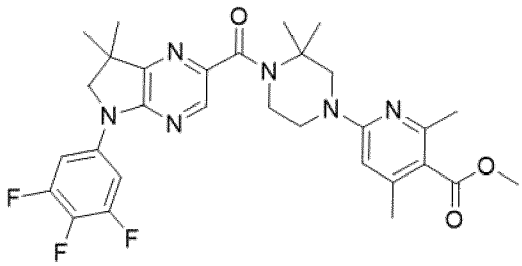


Example **275** was prepared according to general procedure (XI) starting from Example **274** (55 mg). The crude was purified by preparative HPLC (Column B, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 65:35 to 00:100) and freeze dried with HCl (0.1 N in water) to obtain Example **275** (9 mg, 16% over 2 steps) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.37 (s, 6H, $C(CH_3)_2$); 1.53 (s, 6H, $C(CH_3)_2$); 2.34 (s, 3H, $ArCH_3$); 2.54 (s, 3H, $ArCH_3$); 3.62-3.71 (m, 2H, N-CH_2); 3.86-3.91 (m, 2H, N-CH_2); 3.92-3.97 (m, 4H, 2 N-CH_2); 6.72 (bs, 1H, Ar); 7.27-7.36 (m, 2H, 2 Ar); 7.41 (d, *J* 8.7 Hz, 1H, Ar); 7.69-7.76 (m, 2H, 2 Ar); COOH was not observed.

M/Z $(M+H)^+$: 601.0.

Example **276**: methyl 6-(4-(7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

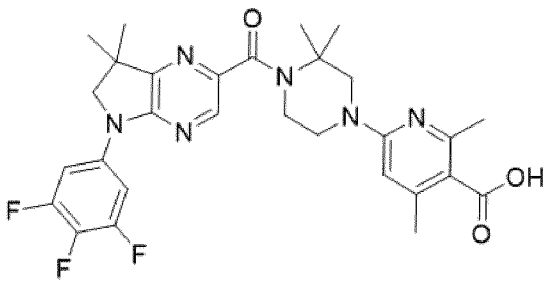


Example **276** was prepared according to general procedure (XIV) starting from Compound **276** (150 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **276** (147 mg, 60%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.40 (s, 6H, $C(CH_3)_2$); 1.50 (s, 6H, $C(CH_3)_2$); 2.23 (s, 3H, $ArCH_3$); 2.34 (s, 3H, $ArCH_3$); 3.53-3.56 (m, 2H, N-CH_2); 3.75-3.80 (m, 5H, OCH_3 N-CH_2); 3.88-3.90 (m, 2H, N-CH_2); 3.97 (s, 2H, N-CH_2); 6.37 (s, 1H, Ar); 7.87-7.93 (m, 2H, 2 Ar); 8.23 (s, 1H, Ar).

M/Z $(M+H)^+$: 583.5

Example **277**: 6-(4-(7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **277** was prepared according to general procedure (XI) starting from Example **276** (147 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) and freeze dried with HCl (0.1 N in water) to obtain Example **277** (52 mg, 34%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.39 (s, 6H, $C(CH_3)_2$); 1.53 (s, 6H, $C(CH_3)_2$); 2.33 (s, 3H, $ArCH_3$); 3.62-3.71 (m, 2H, N-CH_2); 3.83-3.88 (m, 2H, N-CH_2); 3.94-3.97 (m, 4H, 2 N-CH_2); 6.72 (bs, 1H, Ar); 7.88-7.93 (m, 2H, 2 Ar); 8.25 (s, 1H, Ar); One $ArCH_3$ and COOH were not observed.

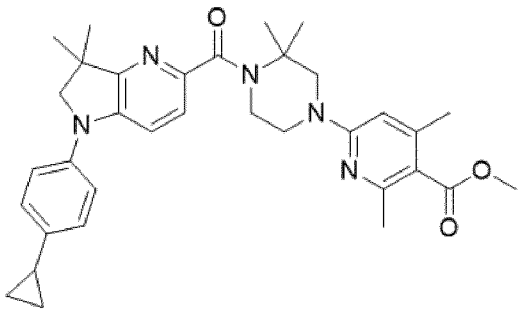
M/Z $(M+H)^+$: 569.4

Compound **358**: 5-chloro-1-(4-cyclopropylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

Compound **358** was prepared according to general procedure (X) starting from Compound **70** (150 mg) and 1-bromo-4-cyclopropylbenzene (2.0 eq) with ^{t}BuONa (3.0 eq) at 100°C for 16 hours. The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 40:60) to obtain Compound **357** (159 mg, 65%) as a beige solid.

M/Z $(M[^{35}Cl]+H)^+$: 299.6

Example **278**: methyl 6-(4-(1-(4-cyclopropylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate

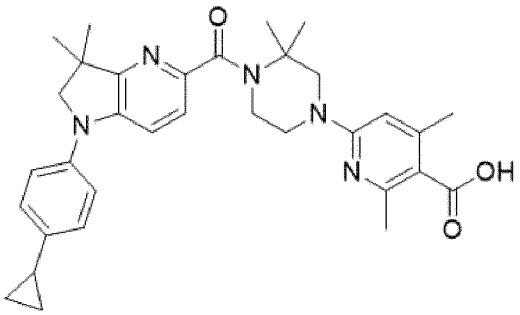


Example **278** was prepared according to general procedure (XIV) starting from Compound **358** (110 mg) and Compound **10** (2.0 eq), and using triethyl amine (4.0 eq), $Mo(CO)_6$ (1.5 eq), XantPhos Pd G4 (0.10 eq), and DBU (4.5 eq). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 50:50) to obtain Example **278** (170 mg) as a beige solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 0.60-0.65 (m, 2H, CH-CH_2); 0.89-0.95 (m, 2H, CH-CH_2); 1.35 (s, 6H, $C(CH_3)_2$); 1.50 (s, 6H, $C(CH_3)_2$); 1.85-1.98 (m, 1H, CH-CH_2); 2.24 (s, 3H, $ArCH_3$); 2.34 (s, 3H, $ArCH_3$); 3.52-3.61 (m, 2H, N-CH_2); 3.78 (s, 3H, OCH_3); 3.80-3.88 (m, 6H, 3 N-CH_2); 6.36 (s, 1H, Ar); 7.11 (d, *J* 8.7 Hz, 2H, 2 Ar); 7.19 (d, *J* 8.7 Hz, 2H, 2 Ar); 7.29-7.36 (m, 2H, 2 Ar).

M/Z $(M+H)^+$: 569.0

Example **279**: 6-(4-(1-(4-cyclopropylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid



Example **279** was prepared according to general procedure (XI) starting from Example **278** (85 mg). The crude was purified by preparative HPLC (Column A, H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH 70:30 to 30:70) and freeze dried with HCl (0.1 N in water) to obtain Example **279** (45 mg, 54% over 2 steps) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 0.61-0.66 (m, 2H, CH-CH_2); 0.89-0.96 (m, 2H, CH-CH_2); 1.35 (s, 6H, $C(CH_3)_2$); 1.49 (s, 6H, $C(CH_3)_2$); 1.86-1.95 (m, 1H, CH-CH_2); 2.28 (s, 3H, $ArCH_3$); 2.40 (s, 3H, $ArCH_3$); 3.54-3.60 (m, 2H, N-CH_2); 3.81 (s, 2H, N-CH_2); 3.84-3.93 (m, 4H, 2 N-CH_2); 6.40 (s, 1H, Ar); 7.11 (d, *J* 8.7 Hz, 2H, 2 Ar); 7.19 (d, *J* 8.7 Hz, 2H, 2 Ar); 7.32-7.35 (m, 2H, 2 Ar); COOH was not observed.

M/Z $(M+H)^+$: 555.0.

Compound **359:** tert-butyl 5-bromo-3,3-dimethyl-4-oxopiperidine-1-carboxylate

To a solution of tert-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (20.0 g) in DCM (400 mL) was added Phenyltrimethylammonium tribromide (36.4 g) at 0 °C and stirred at 0 °C for 4 hours . After completion of the reaction, the mixture was diluted with water (500 mL), extracted with DCM (2*400 mL) .The organic layers were washed with brine (500 mL), dried over Na_2SO_4 then concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum Ether/EtOAc 90:10) to obtain Compound **359** (9.0 g, 33%) as a brown solid.

M/Z $(M[^{79}Br]+H\text{-}tBu)^+$: 250.2.

Compound **360**: tert-butyl 7,7-dimethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate

To a solution of Compound **359** (2.0 g) in EtOH (20 mL) was added formamidine acetate (6.8 g). The mixture was stirred at 100 °C for 4 hours in microwave reactor. After completion of the reaction, the mixture was concentrated. The crude was diluted with water (20 mL), extracted with EtOAc (2*20 mL). The organic layers were washed with brine (20 mL), dried over Na_2SO_4 then concentrated under reduced pressure. The crude was purified by flash chromatography (DCM/MeOH 90:10) to obtain Compound **360** (1.0 g, 61%) as a brown solid.

M/Z $(M+H)^+$: 252.2.

Compound **361**: mixture of tert-butyl 3,7,7-trimethyl-3,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate and tert-butyl 1,7,7-trimethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate

To a solution of Compound **360** (1.0 g) in DMF (15 mL) was added NaH (60%, 0.95 g) at 0°C under nitrogen atmosphere. The reaction was stirred to 0°C for 30 minutes, Iodomethane (1.13 g) was added to the mixture. The

reaction was stirred to 0°C for 2 hours. then poured into cooled water (50 mL, 0°C) and extracted with EtOAc (2*40 mL). The organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate then concentrated. The crude was purified by flash chromatography (DCM/MeOH 90:10) to obtain Compound **361** (0.5 g, 47%) as a brown solid.

M/Z $(M+H)^+$: 266.2.

Compound **362**: mixture of 3,7,7-trimethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine and 1,7,7-trimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine

To a solution of Compound **361** (2.30 g) in DCM (20 mL) was added TFA (10 mL). The reaction was stirred at 25°C for 2 hours then concentrated under reduced pressure. The residue was treated with $NaHCO_3$ (sat. aq., 25 mL) and extracted with EtOAc (2*30 mL). The organic layers were dried over Na_2SO_4 then concentrated to obtain the crude Compound **362** (0.51 g, 35%) as a brown oil.

M/Z $(M+H)^+$: 166.2.

Compound **363**: 5-(4-chloro-3-fluorophenyl)-3,7,7-trimethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine

To a solution of Compound **362** (510 mg) and 4-Chloro-3-fluoroiodobenzene (2.37 g) in dioxane (10 mL) was added cesium carbonate (3.02 g) and RuPhos Pd G4 (263 mg). The reaction was purged with nitrogen for 3 minutes and stirred at 100 °C for 3 hours. The mixture was filtered, diluted with water (50 mL), extracted with EtOAc (2*30 mL). The organic layers were washed with brine (50 mL), dried over Na_2SO_4 then concentrated under reduced pressure. The crude was purified to obtain Compound **363** (130 mg, 14%) as a yellow solid.

M/Z $(M[^{35}Cl]+H)^+$: 294.2.

Compound **364**: 2-bromo-5-(4-chloro-3-fluorophenyl)-3,7,7-trimethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine

To a solution of Compound **363** (130 mg) in MeCN (3 mL) was added N-Bromosuccinimide (54 mg). The reaction was stirred at 25°C for 2 hours. The mixture was concentrated under reduced pressure and the residue was diluted with water (10 mL), extracted with EtOAc (2*10 mL). The organic layers were washed with brine (10 mL), dried over Na_2SO_4 then concentrated. The crude was purified by flash chromatography (DCM/MeOH 95:05) to obtain Compound **364** (150 mg, 91%) as a yellow solid.

M/Z $(M[^{79}Br][^{35}Cl]+H)^+$: 372.2.

Compound **365**: methyl 5-(4-chloro-3-fluorophenyl)-3,7,7-trimethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-2-carboxylate

To a solution of Compound **364** (120 mg) in MeOH (5 mL) was added XPhos (23 mg), triethylamine (66 mg) and Palladium (II) Acetate (11 mg). The reaction was stirred at 70 °C for 3 days under CO atmosphere. The mixture was filtered and concentrated and the residue was purified by flash chromatography (Petroleum Ether /EtOAc, 100:0 to 60:40) to obtain Compound **365** (30 mg, 26%) as a yellow solid.

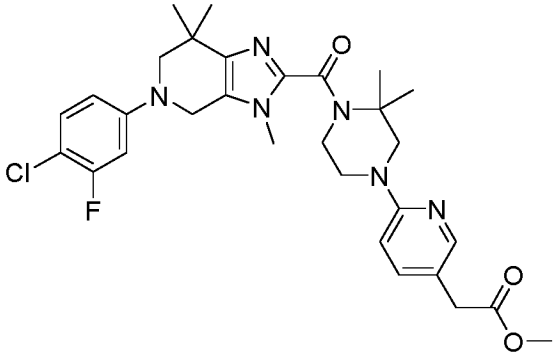
M/Z $(M[^{35}Cl]+H)^+$: 352.2.

Compound **366**: 5-(4-chloro-3-fluorophenyl)-3,7,7-trimethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-2-carboxylic acid

To a solution of Compound **365** (30 mg) in THF (2 mL) was added lithium hydroxide aqueous solution (2 M in H_2O, 2 mL). Then the reaction was stirred at 70 °C for 2 hours. After completion of the reaction, the mixture was filtered and concentrated to get the crude Compound **366** (17 mg) as a yellow oil.

M/Z ($M[^{35}Cl]+H)^+$: 338.2.

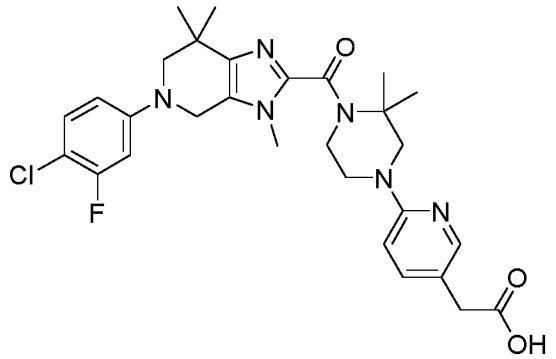
Example **280**: methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-3,7,7-trimethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate



To a solution of Compound **366** (17 mg) and Compound **111** (15.6 mg) in DMF (2 mL) was added HATU (27 mg) and N,N-Diisopropylethylamine (15.3 mg, 0.12 mmol). The reaction was stirred at 25°C for 2 hours. After completion of the reaction, the mixture was diluted with water (10 mL), extracted with EtOAc (2*10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 then concentrated. The crude was purified by flash chromatography (DCM/MeOH 98:2) to obtain Example **280** (15 mg, 51%) as a yellow solid.

M/Z ($M[^{35}Cl]+H)^+$: 583.2.

Example **281**: 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-3,7,7-trimethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid



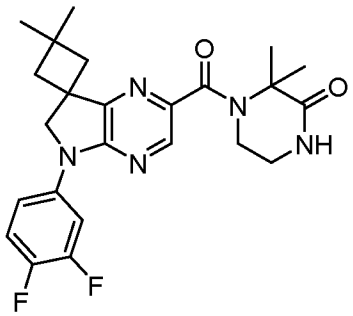
To a solution of Example **280** (15 mg) in THF (1 mL) was added lithium hydroxide aqueous solution (2 M in H_2O, 1 mL). The reaction was stirred at 70 °C for 2 hours. After completion of the reaction, the mixture was filtered and concentrated. The crude was purified by preparative HPLC (H_2O/MeCN + 0.05% HCOOH) to obtain Example **281** (1 mg, 7%) as a white solid.

M/Z ($M[^{35}Cl]+H)^+$: 569.2.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.22 (s, 6H, CH_3); 1.48 (s, 6H, CH_3); 3.17-3.21 (m, 2H, N-CH_2); 3.32-3.36 (m, 2H N-CH_2); 3.46-3.50 (m, 2H, N-CH_2); 3.60 (s, 3H, N-CH_3); 3.86 (s, 2H, $CH_2C(O)$); 4.05-4.08 (m, 2H, N-CH_2); 4.28 (s,

2H, N-CH_2); 6.52-6.57 (m, 1H, Ar); 6.87-6.93 (m, 1H, Ar), 7.03-7.11 (m, 1H, Ar), 7.35 (d, *J* 8.8 Hz, 1H); 7.41-7.45 (m, 1H, Ar); 7.91-7.93 (m, 1H, Ar); COOH was not observed.

Example **282:** 4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-2-one



Example **282** was prepared according to general procedure (XIV) starting from Compound **299** (250 mg) and 3,3-dimethylpiperazin-2-one (84 mg). The crude was purified by flash chromatography (Interchim® 50 µm, CyHex 100% to CyHex/EtOAc 0:100) to obtain Example **282** (18 mg, 6%) as a beige solid.

M/Z $(M+H)^+$: 456.3.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.23 (s, 3H, CH_3); 1.29 (s, 3H, CH_3); 1.68 (s, 6H, CH_3); 2.09-2.14 (m, 2H, CH_2); 2.30-2.34 (m, 2H, CH_2); 3.37-3.43 (m, 2H, N-CH_2); 3.58-3.65 (m, 2H, N-CH_2); 4.40 (s, 2H, N-CH_2); 7.45-7.55 (m, 1H, Ar); 7.69-7.76 (m, 1H, Ar); 8.06-8.15 (m, 2H, Ar + NH); 8.23 (s, 1H, Ar).

Biological examples

Example 283: *In vitro* human PAR-2 functional antagonist activity using calcium assays

Examples of the present invention were tested successively for their agonist and antagonist activities on human PAR-2 (hPAR-2) receptor expressed in HEK-293 cells in an endogenous manner. Compounds exert agonist activity if, by themselves in absence of the 2-Furoyl-LIGRLO-NH_2 peptide (selective hPAR-2 agonist), they activate PAR-2; they exert antagonist activity if they decrease the action of the 2-Furoyl-LIGRLO-NH_2 peptide on the receptor. The assay used to determine compound activity is based on calcium measurement.

Cell Culture: HEK-293 cells were maintained in Dulbecco's Modified Eagle's Medium supplemented with 10% Foetal Calf Serum, 1% Penicillin/Streptomycin at 37°C/5% CO_2. Flasks for tests (F75) are seeded with 6e+06 cells 24h before the experiment at 37°C/5% CO_2.

Calcium assay: Receptor activity was detected by changes in intracellular calcium measured using the fluorescent Ca^{2+} sensitive dye, Fluo4AM (Molecular Probes).

The day of the assay, medium was replaced by assay buffer (HBSS 1X (Gibco 14175-053), Hepes 20mM, $MgSO_4$-$7H_2O$ 1mM, Na_2CO_3 3.3mM, $CaCl_2$-$2H_2O$ 2.6mM, 0.5% bovine serum albumin (BSA), Probenecid 2.5mM, 0.1mg/mL Pluronic Acid) and complemented with 1µM Fluo4AM and cells were incubated during 1:30 h at 37°C.

Cells were then detached, resuspended in assay buffer and seeded in 384 wells, transparent-flat bottom black walled plates (2e+04 cells per well). Plates were incubated at +22°C for 20 min. Compounds stock solutions were prepared in 100% DMSO and dilutions in test buffer were carried out in polypropylene plates with a digital dispenser (D300e, Tecan). Compounds were added to the cells and intracellular Ca^{2+} measurements were collected at the same time on FLIPR Tetra® (Molecular Devices) with specific filters (Exc: 470-495 nm / Em: 515-575 nm).

Agonist and antagonist activities of compounds were consecutively evaluated on the same cell plate. Agonist activity was first measured after 10 min incubation with the compound alone. Then, cells were stimulated by an EC_{80} of the 2-Furoyl-LIGRLO-NH_2 peptide and fluorescence was recorded for an additional 5 min. EC_{80} of the 2-Furoyl-LIGRLO-NH_2 peptide was the concentration giving 80% of the maximal 2-Furoyl-LIGRLO-NH_2 response. Agonist activities are evaluated in comparison to basal signals evoked by assay buffer or maximal 2-Furoyl-LIGRLO-NH_2 response. None of the compounds tested were found to exhibit PAR-2 agonist activity. Antagonist activities are evaluated in comparison to basal signals evoked by assay buffer or EC_{80} of 2-Furoyl-LIGRLO-NH_2 alone.

For IC_{50} determination, a concentration-response test was performed using 20 or 8 concentrations (ranging over 4.5 logs) of each compound. Dose-response curves were fitted using a sigmoïdal dose-response 4 parameters (variable slope) analysis in XLfit Excel addon (IDBS) and IC_{50} of antagonist activity was calculated. Concentration-response experiments were performed in duplicate, in two independent experiments. IC_{50} values are categorized as following: A: $IC_{50} < 500$ nM; B: 500 nM $\leq IC_{50} \leq$ 10 µM; C: $IC_{50} >$ 10 µM

(A) – $IC_{50} < 500$ nM: Examples 3, 4, 8, 9, 12, 14, 15, 17, 18, 19, 20, 21, 27, 31, 39, 41, 43, 45, 53, 55, 56, 57, 58, 60, 61, 62, 65, 67, 69, 71, 73, 74, 79, 80, 81, 82, 83, 85, 89, 90, 96, 100, 101, 103, 105, 113, 115, 117, 119, 126, 128, 134, 140, 142, 144, 146, 148, 151, 154, 156, 158, 160, 164, 171, 173, 175, 177, 181, 185, 187, 189, 191, 193, 199, 201, 203, 205, 207, 209, 215, 217, 219, 221, 223, 225, 227 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 259, 260, 275, 277, 279, 282.

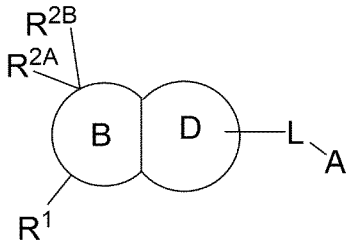
(B) – IC_{50} between 500 nM and 10 µM: Examples 1, 2, 6, 10, 11, 22, 23, 24, 26, 28, 29, 33, 35, 37, 47, 48, 50, 51, 54, 63, 75, 76, 77, 92, 94, 98, 107, 111, 121, 125, 130, 135, 137, 138, 162, 165, 167, 169, 195, 211, 213, 253, 257, 258, 261, 270, 273.

(C) – $IC_{50} >$ 10 µM: Examples 52, 87, 109, 120, 123, 133, 152, 179, 183, 197, 255, 263, 265, 266, 268.

It has thus been demonstrated that the compounds of formula (I), including in particular the above-described examples, are potent antagonists of PAR-2.

CLAIMS

1. A compound of the following formula (I)



(I)

wherein:

ring B is a non-aromatic C_{4-8} carbocyclic ring or a non-aromatic 4- to 8-membered heterocyclic ring, which is fused to ring D,
wherein said carbocyclic ring or said heterocyclic ring is: (i) substituted with a group R^1; (ii) substituted with the groups R^{2A} and R^{2B} which are attached to the same ring carbon atom of said carbocyclic ring or said heterocyclic ring; and (iii) optionally substituted with one or more groups R^Y;

ring D is a 5- or 6-membered heteroaromatic ring, which is fused to ring B, wherein said heteroaromatic ring comprises at least one nitrogen ring atom, wherein said heteroaromatic ring is substituted with a group -L-A, and wherein said heteroaromatic ring is optionally substituted with one or more groups R^X;

R^1 is selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-5} alkylene)-carbocyclyl, and -(C_{0-5} alkylene)-heterocyclyl,
wherein said alkyl, said alkenyl, said alkynyl, the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, and the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{12}, wherein one or more -CH_2- units comprised in said alkyl, said alkenyl, said alkynyl, in the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, or in the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally replaced by a group independently selected from -$C(R^{L1})(R^{L1})$-, -O-, -S-, -SO-, -SO_2-, -CO-, and -$N(R^{L1})$-, wherein each R^{L1} is independently hydrogen or C_{1-5} alkyl, wherein two groups R^{L1} which are attached to the same carbon atom may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or a heterocycloalkyl,
and wherein the carbocyclyl group in said -(C_{0-5} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{11};

each R^{11} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc};

each R^{12} is independently selected from -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), carbocyclyl, heterocyclyl, and -L^Z-R^Z, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more groups R^{Cyc};

R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, wherein said cycloalkyl, said cycloalkenyl, said heterocycloalkyl or said heterocycloalkenyl is optionally substituted with one or more groups R^{21};

or R^{2A} and R^{2B} are each independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-5} alkylene)-carbocyclyl, and -(C_{0-5} alkylene)-heterocyclyl, wherein said alkyl, said alkenyl, said alkynyl, the alkylene group in said -(C_{0-5} alkylene)-carbocyclyl, and the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{22}, wherein one or more -CH_2- units comprised in said alkyl, said alkenyl, said alkynyl, in the alkylene group in

said -(C_{0-5} alkylene)-carbocyclyl, or in the alkylene group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-, and further wherein the carbocyclyl group in said -(C_{0-5} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-5} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc},

wherein R^{2A} and a group R^{Y} may also be mutually joined to form, together with the ring atoms that they are attached to, a carbocyclyl or heterocyclyl, wherein said carbocyclyl or said heterocyclyl is optionally substituted with one or more groups R^{Cyc};

each R^{21} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc};

each R^{22} is independently selected from -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-O-(C_{1-5} alkyl), -O-CO-(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), carbocyclyl, heterocyclyl, and -L^Z-R^Z, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more groups R^{Cyc};

each R^X is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc};

each R^Y is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc};

wherein any two groups R^Y which are attached to the same ring carbon atom (i) may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or a heterocycloalkyl, wherein said cycloalkyl or said heterocycloalkyl is optionally substituted with one or more groups R^{Cyc}, or (ii) may mutually form a group =O;

L is selected from -CO-, -SO- and -SO_2-;

group A is -N(-R^N)-R^N or heterocyclyl, wherein said heterocyclyl is attached via a ring nitrogen atom to group L, and wherein said heterocyclyl is optionally substituted with one or more groups R^A;

each R^N is independently selected from hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, -(C_{0-8} alkylene)-OH, -(C_{0-8} alkylene)-O(C_{1-5} alkyl), -(C_{0-8} alkylene)-SH, -(C_{0-8} alkylene)-S(C_{1-5} alkyl), -(C_{1-8} alkylene)-NH_2, -(C_{1-8} alkylene)-NH(C_{1-5} alkyl), -(C_{1-8} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-8} alkylene)-halogen, -(C_{1-8} alkylene)-C_{1-5} haloalkyl, -(C_{0-8} alkylene)-O-(C_{1-8} haloalkyl), -(C_{0-8} alkylene)-CN, -(C_{0-8} alkylene)-CHO, -(C_{0-8} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-8} alkylene)-COOH, -(C_{0-8} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-8} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-8} alkylene)-CO-NH_2, -(C_{0-8} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-8} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-8} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{1-8} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{1-8} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{1-8} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-8} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-8} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-8} alkylene)-SO_2-NH_2, -(C_{0-8} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-8} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{1-8} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{1-8} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-8} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-8} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-8} alkylene)-carbocyclyl, and -(C_{0-8} alkylene)-heterocyclyl, wherein one or more -CH_2- units comprised in said C_{1-8} alkyl, said C_{2-8} alkenyl, said C_{2-8} alkynyl, and in any of the aforementioned C_{0-8} alkylene and C_{1-8} alkylene groups are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-, wherein the carbocyclyl group in said -(C_{0-8} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-8} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc}, and wherein at least one group R^N is not hydrogen;

each R^A is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5}

alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, -(C_{0-3} alkylene)-heterocyclyl, and -L^Z-R^Z, wherein the carbocyclyl group in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl group in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups R^{Cyc}; and further wherein any two groups R^A, which are attached to the same carbon atom of group A, may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or a heterocycloalkyl, wherein said cycloalkyl or said heterocycloalkyl is optionally substituted with one or more groups R^{Cyc};

each R^{Cyc} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO(C_{1-5} alkyl), -COOH, -COO(C_{1-5} alkyl), -O-CO(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-NH(C_{1-5} alkyl), -SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-SO_2-(C_{1-5} alkyl), -N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -SO_2-(C_{1-5} alkyl), -SO-(C_{1-5} alkyl), -P(=O)(-OH)(-OH), -P(=O)(-OH)(-O-C_{1-5} alkyl), -P(=O)(-O-C_{1-5} alkyl)(-O-C_{1-5} alkyl), -(C_{0-3} alkylene)-cycloalkyl, -(C_{0-3} alkylene)-heterocycloalkyl, and -L^Z-R^Z;

each L^Z is independently selected from a covalent bond, C_{1-7} alkylene, C_{2-7} alkenylene, and C_{2-7} alkynylene, wherein said alkylene, said alkenylene and said alkynylene are each optionally substituted with one or more groups independently selected from halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), and -N(C_{1-5} alkyl)(C_{1-5} alkyl), and further wherein one or more -CH_2- units comprised in said alkylene, said alkenylene or said alkynylene are each optionally replaced by a group independently selected from -O-, -NH-, -N(C_{1-5} alkyl)-, -CO-, -S-, -SO-, and -SO_2-; and

each R^Z is independently selected from -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), -CN, -CHO, -CO(C_{1-5} alkyl), -COOH, -COO(C_{1-5} alkyl), -O-CO(C_{1-5} alkyl), -CO-NH_2, -CO-NH(C_{1-5} alkyl), -CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-CO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-CO(C_{1-5} alkyl), -NH-COO(C_{1-5} alkyl), -N(C_{1-5} alkyl)-COO(C_{1-5} alkyl), -O-CO-NH(C_{1-5} alkyl), -O-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -SO_2-NH_2, -SO_2-

$NH(C_{1-5}$ alkyl), $-SO_2-N(C_{1-5}$ alkyl)(C_{1-5} alkyl), $-NH-SO_2-(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl)$-SO_2-(C_{1-5}$ alkyl), $-SO_2-(C_{1-5}$ alkyl), $-SO-(C_{1-5}$ alkyl), aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, wherein said aryl, said heteroaryl, said cycloalkyl, and said heterocycloalkyl are each optionally substituted with one or more groups independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, halogen, C_{1-5} haloalkyl, $-O-(C_{1-5}$ haloalkyl), -CN, -OH, $-O(C_{1-5}$ alkyl), -SH, $-S(C_{1-5}$ alkyl), $-NH_2$, $-NH(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl)(C_{1-5} alkyl), -CHO, $-CO-(C_{1-5}$ alkyl), -COOH, $-CO-O-(C_{1-5}$ alkyl), $-O-CO-(C_{1-5}$ alkyl), $-CO-NH_2$, $-CO-NH(C_{1-5}$ alkyl), $-CO-N(C_{1-5}$ alkyl)(C_{1-5} alkyl), $-NH-CO-(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl$)-CO-(C_{1-5}$ alkyl), $-NH-COO(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl$)-COO(C_{1-5}$ alkyl), $-O-CO-NH(C_{1-5}$ alkyl), $-O-CO-N(C_{1-5}$ alkyl)(C_{1-5} alkyl), $-SO_2-NH_2$, $-SO_2-NH(C_{1-5}$ alkyl), $-SO_2-N(C_{1-5}$ alkyl)(C_{1-5} alkyl), $-NH-SO_2-(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl$)-SO_2-(C_{1-5}$ alkyl), $-SO-(C_{1-5}$ alkyl), $-SO_2-(C_{1-5}$ alkyl), carbocyclyl, and heterocyclyl, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more groups independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, halogen, C_{1-5} haloalkyl, $-O-(C_{1-5}$ haloalkyl), -CN, -OH, $-O(C_{1-5}$ alkyl), -SH, $-S(C_{1-5}$ alkyl), $-NH_2$, $-NH(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl)(C_{1-5} alkyl), -CHO, $-CO-(C_{1-5}$ alkyl), -COOH, $-CO-O-(C_{1-5}$ alkyl), $-O-CO-(C_{1-5}$ alkyl), $-CO-NH_2$, $-CO-NH(C_{1-5}$ alkyl), $-CO-N(C_{1-5}$ alkyl)(C_{1-5} alkyl), $-NH-CO-(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl$)-CO-(C_{1-5}$ alkyl), $-NH-COO(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl$)-COO(C_{1-5}$ alkyl), $-O-CO-NH(C_{1-5}$ alkyl), $-O-CO-N(C_{1-5}$ alkyl)(C_{1-5} alkyl), $-SO_2-NH_2$, $-SO_2-NH(C_{1-5}$ alkyl), $-SO_2-N(C_{1-5}$ alkyl)(C_{1-5} alkyl), $-NH-SO_2-(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl$)-SO_2-(C_{1-5}$ alkyl), $-SO-(C_{1-5}$ alkyl), and $-SO_2-(C_{1-5}$ alkyl);

with the proviso that:

– if ring B is a pyrrolidinyl ring, ring D is a pyridinyl ring, R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a cyclopropyl, L is -CO-, and group A is morpholin-4-yl, then R^1 is not 5-R^{11}-pyrimidin-2-yl or acetyl;

– if ring B and ring D together are a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-c]pyridinyl ring or a 6-oxo-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazinyl ring, R^{2A} and R^{2B} are each methyl, R^1 is phenyl which is optionally substituted with one or more groups R^{11}, L is -CO-, and group A is -NH-R^N, then R^N is not a heterocycloalkyl which comprises one oxidized sulfur ring atom, in which all other ring atoms are carbon atoms, and which is substituted with a methyl group;

– if ring B and ring D together are a 3-R^X-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazinyl ring, R^X is -OH, one of R^{2A} and R^{2B} is methyl, the other one of R^{2A} and R^{2B} is $-CON(-CH_3)_2$, R^1 is methyl, L is -CO-, and group A is -NH-R^N, then R^N is not 4-fluorobenzyl; and

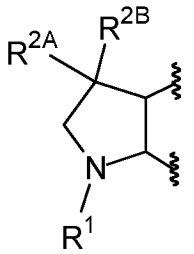
– if ring B and ring D together are a 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine ring, a 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine ring or a 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine, L is -CO-, group A is -NH-R^N, and R^1 is $-CH_2$-phenyl or $-CH_2$-pyridinyl, wherein the phenyl in said $-CH_2$-phenyl and the pyridinyl in said $-CH_2$-pyridinyl are each optionally substituted with one or more groups R^{11}, then R^{2A} and R^{2B} are not methyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, wherein ring B is a non-aromatic 4- to 8-membered heterocyclic ring which is optionally substituted with one or more groups R^Y.

3. The compound of claim 1 or 2, wherein ring B is a pyrrolidinyl ring or a piperidinyl ring, wherein said pyrrolidinyl ring or said piperidinyl ring is optionally substituted with one or more groups R^Y, and wherein the group R^1 is attached to the nitrogen ring atom of said pyrrolidinyl ring or said piperidinyl ring.

4. The compound of any one of claims 1 to 3, wherein ring B is a group of the following formula:



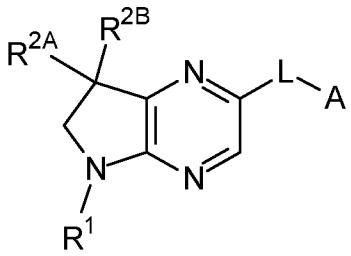
which is optionally substituted with one or two groups R^Y.

5. The compound of any one of claims 1 to 4, wherein ring D is a 6-membered heteroaromatic ring which comprises one or two nitrogen ring atoms while all remaining ring atoms are carbon atoms, and wherein said heteroaromatic ring is optionally substituted with one or more groups R^X.

6. The compound of any one of claims 1 to 5, wherein ring D is a pyridinyl ring or a pyrazinyl ring, wherein said pyridinyl ring or said pyrazinyl ring is optionally substituted with one or more groups R^X.

7. The compound of any one of claims 1 to 6, wherein ring D is a pyrazinyl ring which is optionally substituted with one or more groups R^X, wherein said pyrazinyl ring is fused via its ring carbon atoms 2 and 3 to ring B.

8. The compound of any one of claims 1 to 7, wherein the compound of formula (I) has the following structure:



9. The compound of any one of claims 1 to 8, wherein R^1 is -L^1-carbocyclyl or -L^1-heterocyclyl, wherein the carbocyclyl in said -L^1-carbocyclyl or the heterocyclyl in said -L^1-heterocyclyl is optionally substituted with one or more groups R^{11}, wherein each L^1 is independently selected from a bond, -C(R^{L1})(R^{L1})-, -O-, -S-, -SO-, -SO_2-, -CO-, and -N(R^{L1})-, wherein each R^{L1} is independently hydrogen or C_{1-5} alkyl, and further wherein two groups R^{L1} which are attached to the same carbon atom may also be mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or a heterocycloalkyl.

10. The compound of any one of claims 1 to 9, wherein R^1 is phenyl which is optionally substituted with one or more groups R^{11}.

11. The compound of any one of claims 1 to 10, wherein R^1 is 3-R^{11}-4-R^{11}-phenyl or 3-R^{11}-4-R^{11}-5-R^{11}-phenyl, wherein each R^{11} is independently selected from halogen, C_{1-5} haloalkyl, and C_{1-5} alkyl;
preferably wherein R^1 is selected from 4-chloro-3-fluoro-phenyl, 3,4-dichloro-phenyl, 3,4-difluoro-phenyl, 3-chloro-4-fluoro-phenyl, 3-fluoro-4-trifluoromethyl-phenyl, 3-chloro-4-trifluoromethyl-phenyl, 3-fluoro-4-methyl-phenyl, 3-chloro-4-methyl-phenyl, 3,4,5-trifluoro-phenyl, and 4-chloro-3,5-difluoro-phenyl.

12. The compound of any one of claims 1 to 11, wherein R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a cycloalkyl or heterocycloalkyl, wherein said cycloalkyl or said heterocycloalkyl is optionally substituted with one or more groups R^{21}.

13. The compound of any one of claims 1 to 12, wherein R^{2A} and R^{2B} are mutually joined to form, together with the carbon atom that they are attached to, a cyclopentyl or a tetrahydrofuranyl, wherein said cyclopentyl or said tetrahydrofuranyl is optionally substituted with one or more groups R^{21}.

14. The compound of any one of claims 1 to 11, wherein R^{2A} and R^{2B} are each independently selected from C_{1-5} alkyl, -(C_{0-5} alkylene)-cycloalkyl, -(C_{0-5} alkylene)-aryl, -(C_{0-5} alkylene)-heterocycloalkyl, and -(C_{0-5} alkylene)-heteroaryl, wherein said alkyl or the alkylene group in any of said -(C_{0-5} alkylene)-cycloalkyl, said -(C_{0-5} alkylene)-aryl, said -(C_{0-5} alkylene)-heterocycloalkyl, or said -(C_{0-5} alkylene)-heteroaryl is optionally substituted with one or more groups independently selected from -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN, and further wherein the cycloalkyl group in said -(C_{0-5} alkylene)-cycloalkyl, the aryl group in said -(C_{0-5} alkylene)-aryl, the heterocycloalkyl group in said -(C_{0-5} alkylene)-heterocycloalkyl, and the heteroaryl group in said -(C_{0-5} alkylene)-heteroaryl are each optionally substituted with one or more groups independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -O-(C_{1-5} haloalkyl), and -CN.

15. The compound of any one of claims 1 to 11 or 14, wherein R^{2A} and R^{2B} are each independently C_{1-5} alkyl;
preferably wherein R^{2A} and R^{2B} are each methyl.

16. The compound of any one of claims 1 to 15, wherein L is -CO-.

17. The compound of any one of claims 1 to 16, wherein group A is heterocycloalkyl which is attached via a ring nitrogen atom to group L, wherein said heterocycloalkyl is optionally substituted with one or more groups R^A.

18. The compound of any one of claims 1 to 17, wherein group A is 2,2-dimethyl-piperazin-1-yl, wherein the piperazinyl group in said 2,2-dimethyl-piperazin-1-yl is optionally substituted with one or more groups R^A;

preferably wherein group A is 2,2-dimethyl-4-(5-carboxy-4,6-dimethyl-pyridin-2-yl)piperazin-1-yl.

19. The compound of claim 1, wherein said compound is selected from:
1'-(4-chloro-3-fluorophenyl)-5'-(2,2-dimethyl-3-oxopiperazine-1-carbonyl)-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridin]-2'(1'H)-one;
1'-(4-chloro-3-fluorophenyl)-5'-(2,2-dimethyl-3-oxopiperazine-1-carbonyl)spiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridin]-2'(1'H)-one;
4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;
8-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-1,3,8-triazaspiro[4.5]decane-2,4-dione;
methyl 1-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperidine-4-carboxylate;
1-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperidine-4-carboxylic acid;
methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;
6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;
4-(1'-(3-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;
4-(1'-(2-chlorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;
4-(3,3-dimethyl-1-(thiophen-3-yl)-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;
4-(1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;
methyl 6-(4-(1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;
6-(4-(1-(3,4-difluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;
4-(1-(4-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;
methyl 6-(4-(1-(3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;
6-(4-(1-(3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;
4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;

4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-1-ethyl-3,3-dimethylpiperazin-2-one;

(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(3,3-dimethylmorpholino)methanone;

tert-butyl 4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate;

(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(2,2-dimethylpiperazin-1-yl)methanone;

(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(4-ethyl-2,2-dimethylpiperazin-1-yl)methanone;

1-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)ethan-1-one;

ethyl 4-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-oxobutanoate;

4-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-oxobutanoic acid;

ethyl 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-5-oxopentanoate;

5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-5-oxopentanoic acid;

8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-1-methyl-1,3,8-triazaspiro[4.5]decan-4-one;

2-(3-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-azabicyclo[3.1.0]hexan-6-yl)acetic acid;

methyl 2-(3-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-azabicyclo[3.1.0]hexan-6-yl)acetate;

methyl 2-((1R,5S,6S)-3-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-azabicyclo[3.1.0]hexan-6-yl)acetate;

2-((1R,5S,6S)-3-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-azabicyclo[3.1.0]hexan-6-yl)acetic acid;

ethyl 1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidine-4-carboxylate;

1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidine-4-carboxylic acid;

methyl 2-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-4-yl)acetate;

2-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-4-yl)acetic acid;

2-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid;

methyl 2-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate;

methyl 2-((3R,4S)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate;

2-((3R,4S)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid;

ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylpyrimidine-5-carboxylate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylpyrimidine-5-carboxylic acid;

ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyrimidine-5-carboxylate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-pyrimidine-5-carboxylic acid;

ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carboxylate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carboxylic acid;

methyl 6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

3-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)butanoic acid;

methyl 3-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)butanoate;

methyl (R)-3-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)butanoate;

(R)-3-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)butanoic acid;

N-(1-carbamoylcyclopropyl)-1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide;

methyl 6-((2-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)ethyl)(methyl)amino)-2,4-dimethylnicotinate;

6-((2-(1-(4-chloro-3-fluorophenyl)-N,3,3-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamido)ethyl)(methyl)amino)-2,4-dimethylnicotinic acid;

1-(4-chloro-3-fluorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide;

1-(4-chloro-3-fluorophenyl)-N-(2-hydroxy-2-methylpropyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide;

4-(1-(4-chloro-3-fluorophenyl)-3-ethyl-3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;

N-(1-carbamoylcyclopropyl)-1-(4-chloro-3-fluorophenyl)-3-ethyl-3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carboxamide;

4-(1'-(4-chloro-3-fluorophenyl)-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;

6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2,2',3,5,6-hexahydrospiro[pyran-4,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;

4-(1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;

methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2',4,5-tetrahydro-2H-spiro[furan-3,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

4-(8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;

cis-4-(8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;

4-((3aR,8aR)-8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;

4-((3aS,8aS)-8-(4-chloro-3-fluorophenyl)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3',2':4,5]pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-2-one;

methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

ethyl 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-1,3,4-thiadiazole-2-carboxylate;

(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(2,2-dimethyl-4-(1,3,4-thiadiazol-2-yl)piperazin-1-yl)methanone;

ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazole-5-carboxylate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazole-5-carboxylic acid;

ethyl 2-(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazol-5-yl)acetate;

2-(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-methylthiazol-5-yl)acetic acid;

methyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-5-methylthiazole-4-carboxylate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-5-methylthiazole-4-carboxylic acid;

1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-7,7-dimethyl-1,4-diazepan-5-one;

8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-2,8-diazaspiro[4.5]decan-1-one;

8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-2,8-diazaspiro[4.5]decan-3-one;

1-(1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-4-yl)imidazolidin-2-one;

ethyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-(trifluoromethyl)thiazole-5-carboxylate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-4-(trifluoromethyl)thiazole-5-carboxylic acid;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N,N-dimethylthiazole-4-carboxamide;

(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(4-(4-(4-hydroxypiperidine-1-carbonyl)thiazol-2-yl)-2,2-dimethylpiperazin-1-yl)methanone;

(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(2,2-dimethyl-4-(4-(morpholine-4-carbonyl)thiazol-2-yl)piperazin-1-yl)methanone;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carboxamide;

methyl 6-(4-(1-(3-fluoro-4-methylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(3-fluoro-4-methylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

methyl 6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-difluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-(1'-(4-chloro-3-fluorophenyl)-3-fluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridin]-2-en-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-((3S,4S)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate;

2-((3S,4S)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid;

methyl 2-((3R,4R)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate;

2-((3R,4R)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid;

ethyl (2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carbonyl)glycinate;

(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)thiazole-4-carbonyl)glycine;

methyl 2-((3S,4R)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetate;

2-((3S,4R)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3-methoxypiperidin-4-yl)acetic acid;

methyl 6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-5-yl)(2,2-dimethyl-4-(4-(4-methylpiperazine-1-carbonyl)thiazol-2-yl)piperazin-1-yl)methanone;

methyl 6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)isonicotinate;

2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)isonicotinic acid;

ethyl 3-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)isonicotinate;

3-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)isonicotinic acid;

ethyl 6-((1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-3-yl)amino)nicotinate;

6-((1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-3-yl)amino)nicotinic acid;

ethyl 6-((1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-3-yl)(methyl)amino)nicotinate;

6-((1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)piperidin-3-yl)(methyl)amino)nicotinic acid hydrochloride;

methyl 6-(4-(1'-(3,4-difluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(3,4-difluorophenyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-4-yl)acetate;

2-(2-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-4-yl)acetic acid;

ethyl 2-(5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-2-yl)acetate;

2-(5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-2-yl)acetic acid;

methyl 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

1'-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)spiro[indoline-3,3'-pyrrolidin]-2-one;

8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one;

ethyl 6-(6-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-2,6-diazaspiro[3.3]heptan-2-yl)nicotinate;

6-(6-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-2,6-diazaspiro[3.3]heptan-2-yl)nicotinic acid;

methyl 2-(1-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)piperidin-4-yl)acetate;

2-(1-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)piperidin-4-yl)acetic acid;

4-(1'-(4-chloro-3-fluorophenyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-2-one;

methyl 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-difluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-difluoro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

ethyl 2-((1R,5S)-8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)acetate;

2-((1R,5S)-8-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)acetic acid;

methyl 6-(4-(6-(5-(4-(5-(methoxycarbonyl)-4,6-dimethylpyridin-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)nicotinoyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

methyl 6-(4-(1-(5-chloropyridin-2-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(6-(5-(4-(5-carboxy-4,6-dimethylpyridin-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)nicotinoyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-(1-(5-chloropyridin-2-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(3,3-dimethyl-1-(pyridin-2-yl)-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

ethyl 1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-4-(pyridin-2-yl)piperidine-3-carboxylate;

(cis)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-4-(pyridin-2-yl)piperidine-3-carboxylic acid;

(trans)-1-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-4-(pyridin-2-yl)piperidine-3-carboxylic acid;

methyl 6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-3-methylpicolinate;

6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-3-methylpicolinic acid;

methyl 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2-methoxynicotinate;

5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2-methoxynicotinic acid;

methyl 6-(4-((1S,3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

methyl 6-(4-((1R,3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

methyl 6-(4-((3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1S,3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-((1R,3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-((3R)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-((1S,3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

methyl 6-(4-((1R,3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

methyl 6-(4-((3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1S,3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-((1R,3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

6-(4-((3S)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-diethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)nicotinate;

methyl 5-(4-(1-(3-fluoro-4-(4-(5-(methoxycarbonyl)pyridin-3-yl)-2,2-dimethylpiperazine-1-carbonyl)phenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)nicotinate;

5-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)nicotinic acid;

5-(4-(4-(5-(4-(5-carboxypyridin-3-yl)-2,2-dimethylpiperazine-1-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-2-fluorobenzoyl)-3,3-dimethylpiperazin-1-yl)nicotinic acid;

methyl 2-(6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)propanoate;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)propanoic acid;

methyl 6-(4-(1-(4-cyanocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(4-carbamoylcyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(1-(4,4-difluorocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-(4,4-difluorocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

4-(5-(4-(4,6-dimethylpyridin-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)cyclohexane-1-carbonitrile;

methyl 2-(6-(4-(1-cyclopentyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-cyclopentyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(1-(4-cyanocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-(4-cyanocyclohexyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)-2-methylpropanoate;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)-2-methylpropanoic acid;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-8,8-dimethyl-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-8,8-dimethyl-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(4-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(4-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(3,4-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-cyclopentyl-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-cyclopentyl-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(3-(4-chloro-3-fluorobenzyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(3-(4-chloro-3-fluorobenzyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(4-chloro-3-fluorophenyl)-3-methoxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(3-fluoro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(3-chloro-4-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(1,3-dihydroisobenzofuran-5-yl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

2-(6-(4-(5-(4-fluorophenethyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(3-chloro-4-(trifluoromethyl)phenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5'-(3,4-difluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(3,3-dimethyl-5'-(3,4,5-trifluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(3,3-dimethyl-5'-(3,4,5-trifluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-((1s,3s)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-((1r,3r)-1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1'-(4-chloro-3-fluorophenyl)-3-(methoxymethyl)-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[3,2-b]pyridine]-5'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3,5-difluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5'-(4-chloro-3-fluorophenyl)-5',6'-dihydrospiro[cyclopentane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(5-(3,4-dichlorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate

2-(6-(4-(5-(3-chloro-4-methylphenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-8-methoxy-7,7-dimethyl-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-8-methoxy-7,7-dimethyl-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-6-methoxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-6-methoxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(3-(4-chloro-3-fluorophenyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(3-(4-chloro-3-fluorophenyl)-1-isobutyl-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-6-hydroxy-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 8-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-8-oxooctanoate;

8-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-8-oxooctanoic acid;;

N-(37-(4-(5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-1-yl)-3-methyl-4,17,30,37-tetraoxo-7,10,13,20,23,26-hexaoxa-3,16,29-triazaheptatriacontyl)-N-methylpalmitamide;

methyl 4-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,6-dimethylnicotinate;

4-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,6-dimethylnicotinic acid;

methyl 2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(1-(4-chloro-3-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

1-(1-((5'-(4-chloro-3-fluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazin]-2'-yl)sulfonyl)piperidin-4-yl)imidazolidin-2-one;

methyl 2-(6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrazino[2,3-b][1,4]oxazine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(4-(4-chloro-3-fluorophenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrazino[2,3-b][1,4]oxazine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

tert-butyl 2-(4-(5-(2-methoxy-2-oxoethyl)pyridin-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-7,7-dimethyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-7,7-dimethyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

methyl 6-(4-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(7,7-dimethyl-5-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-b]pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 6-(4-(1-(4-cyclopropylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinate;

6-(4-(1-(4-cyclopropylphenyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-2,4-dimethylnicotinic acid;

methyl 2-(6-(4-(5-(4-chloro-3-fluorophenyl)-3,7,7-trimethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetate;

2-(6-(4-(5-(4-chloro-3-fluorophenyl)-3,7,7-trimethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)pyridin-3-yl)acetic acid;

4-(5'-(3,4-difluorophenyl)-3,3-dimethyl-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[2,3-b]pyrazine]-2'-carbonyl)-3,3-dimethylpiperazin-2-one;

or a pharmaceutically acceptable salt or solvate of any of the aforementioned compounds.

20. A compound as defined in any one of claims 1 to 19, wherein said compound is conjugated via a linker to a membrane anchor.

21. A pharmaceutical composition comprising the compound of any one of claims 1 to 20 and a pharmaceutically acceptable excipient.

22. The compound of any one of claims 1 to 20 or the pharmaceutical composition of claim 21 for use in the treatment or prevention of pain, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a central nervous system disorder, spinal cord injury, a metabolic disorder, a gastrointestinal disorder, a cardiovascular disorder, a fibrotic disorder, a respiratory disorder, a skin disorder, an allergic disorder, or cancer.

23. The compound of any one of claims 1 to 20 or the pharmaceutical composition of claim 21 for use in the treatment or prevention of neuropathic pain, inflammatory pain, cancer pain, post-operative incision pain, fracture pain, osteoporotic fracture pain, gout joint pain, chronic pain, spinal cord injury, atopic dermatitis, contact dermatitis, dry skin dermatitis, seborrhoeic dermatitis, arthritis, rheumatoid arthritis, osteoarthritis, psoriasis, psoriatic arthritis, multiple sclerosis, non-alcoholic steatohepatitis, obesity, diabetes, adipose inflammation, pancreatitis, metabolic syndrome, PAR-2 associated metabolic dysfunction, periodontitis, gingivitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, peptic ulcer disease, infectious enteritis, irritable bowel syndrome, atherosclerosis, asthma, interstitial lung disease, pulmonary fibrosis, rheumatoid arthritis-associated interstitial lung disease, liver fibrosis, cystic fibrosis, renal fibrosis, peritoneal fibrosis, pancreatic fibrosis, intestinal fibrosis, cardiac fibrosis, skin fibrosis, systemic lupus erythematosus, scleroderma, skin eczema, acne, rosacea, post-inflammatory hyperpigmentation, lichen planus, pruritus, polymyositis, vasculitis, Wegener's granulomatosis, Netherton syndrome, dermatomyositis, uveitis, liver cirrhosis, Alzheimer's disease, Parkinson's disease, dust mite allergy, cockroach allergy, or allergic asthma.

24. The compound of any one of claims 1 to 20 or the pharmaceutical composition of claim 21 for use in the treatment or prevention of cancer.

25. The compound for use according to claim 24 or the pharmaceutical composition for use according to claim 24, wherein said cancer is selected from colorectal cancer, colon cancer, gastric cancer, rectal cancer, liver cancer, breast cancer, pancreatic cancer, cervical cancer, prostate cancer, ovarian cancer, endometrial cancer, uterine sarcoma, germ cell cancer, esophageal cancer, leukemia, lung cancer, adrenal gland cancer, bile duct cancer, bladder cancer, head and neck cancer, kidney cancer, lymphoma, mesothelioma, sarcoma, melanoma, thyroid carcinoma, thymus cancer, and glioblastoma.

26. The compound for use according to claim 24 or 25 or the pharmaceutical composition for use according to claim 24 or 25, wherein said compound or said pharmaceutical composition is to be administered in combination with one or more anticancer drugs.

27. An anticancer drug for use in the treatment or prevention of cancer, wherein said anticancer drug is to be administered in combination with the compound of any one of claims 1 to 20 or the pharmaceutical composition of claim 21.

28. The compound for use according to claim 26 or the pharmaceutical composition for use according to claim 26 or the anticancer drug for use according to claim 27, wherein said anticancer drug(s) is/are selected from immune checkpoint inhibitors.

29. The compound for use according to claim 28 or the pharmaceutical composition for use according to claim 28 or the anticancer drug for use according to claim 28, wherein said immune checkpoint inhibitors are selected from anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-TIGIT antibodies, and anti-LAG3 antibodies.

30. The compound for use according to claim 28 or 29 or the pharmaceutical composition for use according to claim 28 or 29 or the anticancer drug for use according to claim 28 or 29, wherein said immune checkpoint inhibitors are selected from ipilimumab, tremelimumab, nivolumab, pembrolizumab, pidilizumab, cemiplimab, dostarlimab, spartalizumab, camrelizumab, sintilimab, tislelizumab, toripalimab, zimberelimab, AMP-224, AMP-514, JTX-4014, INCMGA00012, APE02058, atezolizumab, avelumab, durvalumab, KN035, CK-301, BMS-936559, MEDI4736, MPDL3280A, MDX-1105, MEDI6469, bintrafusp alfa, tiragolumab, vibostolimab, domvanalimab, etigilimab, BMS-986207, EOS-448, COM902, ASP8374, SEA-TGT, BGB-A1217, IBI-939, M6223, relatlimab, ieramilimab, encelimab, tebotelimab, REGN3767, FS118, IMP701, and IMP731.

31. *In vitro* use of a compound as defined in any one of claims 1 to 20 as a PAR-2 inhibitor.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2023/064898

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/064898

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D471/10 C07D491/14 C07D491/20 A61P29/00
A61K31/437 A61P35/00 A61P3/00 A61P9/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2022/076496 A1 (MERCK SHARP & DOHME [US]; LIM YEON HEE [US] ET AL.) 14 April 2022 (2022-04-14) page 89 - page 116; compounds 12,16,27a-b,36,37,45-49,59-61,93,130a-d,131 claim 1	1-18,21
X	EP 3 480 198 A1 (RIKEN [JP]; JAPANESE FOUND FOR CANCER RES [JP]) 8 May 2019 (2019-05-08) page 74 - page 85; compounds 106, 107, 114-117, 171 claim 1	1-18,21

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[X] Further documents are listed in the continuation of Box C.
[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 August 2023	22/08/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bissmire, Stewart

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/064898

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2006/090261 A1 (PFIZER PROD INC [US]; KAUFFMAN GOSS STRYKER [US] ET AL.) 31 August 2006 (2006-08-31) page 68; example 9 claim 1	1-18,21
X	US 2016/016937 A1 (NARDI ANTONIO [DE] ET AL) 21 January 2016 (2016-01-21) page 41 - page 44; compounds 131-171 claim 1	1-18,21
A	WO 2016/154075 A1 (VERTEX PHARMA [US]) 29 September 2016 (2016-09-29) cited in the application abstract claim 1	1-31
A	WO 2015/048245 A1 (VERTEX PHARMA [US]) 2 April 2015 (2015-04-02) cited in the application abstract claim 1	1-31
A	WO 2018/057588 A1 (VERTEX PHARMA [US]) 29 March 2018 (2018-03-29) cited in the application abstract	1-31
A	MEI-KWAN YAU ET AL: EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 26, no. 4, 3 March 2016 (2016-03-03), pages 471-483, XP055665770, GB ISSN: 1354-3776, DOI: 10.1517/13543776.2016.1154540 the whole document	1-31

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/064898

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