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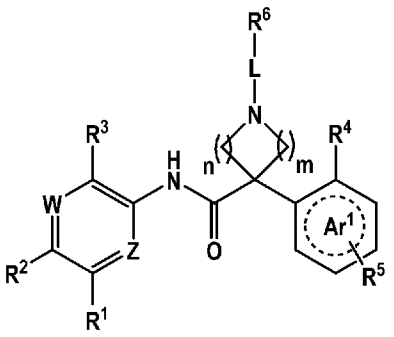


Formula (I)

(57) Abstract: The present invention relates to pyridinyl derivatives of Formula (I) Formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, Ar^1, L, W, Z, m and n are as described in the description, their preparation, to pharmaceutically acceptable salts thereof, and to their use as pharmaceuticals, to pharmaceutical compositions containing one or more compounds of Formula (I), and especially to their use as LPA1 receptor modulators.

WO 2019/234115 A1

ALKOXY-SUBSTITUTED PYRIDINYL DERIVATIVES AS LPA1 RECEPTOR ANTAGONISTS AND THEIR USE IN THE TREATMENT OF FIBROSIS

The present invention relates to LPA_1 receptor antagonists of Formula (I) and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing a compound of the Formula (I), and their use as medicaments inhibiting fibrotic processes or other disorders in which LPA_1 receptors play a role, either alone or in combination with other active compounds or therapies.

Lysophospholipids are membrane-derived bioactive lipid mediators, of which one of the most medically important is lysophosphatidic acid (LPA). LPA is not a single molecular entity but a collection of endogenous structural variants with fatty acids of varied lengths and degrees of saturation (Fujiwara et al., J. Biol. Chem. 2005, 280, 35038-35050). The structural backbone of the LPAs is derived from glycerol-based phospholipids such as phosphatidylcholine (PC) or phosphatidic acid (PA). The LPAs are bioactive lipids (signaling lipids) that regulate various cellular signaling pathways by binding to the same class of 7-transmembrane domain G protein-coupled (GPCR) receptors (Chun, J., Hla, T., Spiegel, S., Moolenaar, W., Editors, Lysophospholipid Receptors: Signaling and Biochemistry, 2013, Wiley; ISBN: 978-0- 470-56905-4; Zhao, Y. et al, Biochim. Biophys. Acta (BBA)-Mol. Cell Biol. Of Lipids, 2013, 1831, 86-92). The currently known LPA receptors are designated as LPA_1, LPA_2, LPA_3, LPA_4, LPA_5 and LPA_6 (Choi, J. W., Annu. Rev. Pharmacol. Toxicol. 2010, 50, 157-186). The nucleotide sequence and the amino acid sequence for the human LPA_1 receptor is known in the art and are published (Hecht et al 1996 *J. Cell. Biol.* 135:1071–83, An et al 1997 Biochem. Biophys. Res. Comm. 231:619-622).

The LPAs have long been known as precursors of phospholipid biosynthesis in both eukaryotic and prokaryotic cells, but the LPAs have emerged only recently as signaling molecules that are rapidly produced and released by activated cells, notably platelets, to influence target cells by acting on specific cell-surface receptors (see, e.g., Moolenaar et al., BioEssays, 2004, 26, 870-881, and van Leewen et al, Biochem. Soc. Trans., 2003, 31, 1209-1212). Besides being synthesized and processed to more complex phospholipids in the endoplasmic reticulum, LPAs can be generated through the hydrolysis of pre-existing phospholipids following cell activation; for example, the sn-2 position is commonly missing a fatty acid residue due to deacylation, leaving only the sn-1 hydroxyl esterified to a fatty acid. Moreover, a key enzyme in the production of LPA, autotaxin (lysoPLD/NPP2), may be the product of an oncogene, as many tumor types up- regulate autotaxin (Brindley, D., J. Cell Biochem. 2004, 92, 900-12). The concentrations of LPAs in human plasma & serum as well as human bronchoalveolar lavage fluid (BALF) have been reported, including determinations made using sensitive and specific LC/MS & LC/MS/MS procedures (Baker et al., Anal. Biochem. 2001, 292, 287-295; Onorato et al., J. Lipid Res., 2014, 55, 1784-1796).

LPA influences a wide range of biological responses, ranging from induction of cell proliferation, stimulation of cell migration and neurite retraction, gap junction closure, and even slime mold chemotaxis (Goetzl, et al,

Scientific World J., 2002, 2, 324- 338; Chun, J., Hla, T., Spiegel, S., Moolenaar, W., Editors, Lysophospholipid Receptors: Signaling and Biochemistry, 2013, Wiley; ISBN; 978-0-470-56905-4). The body of knowledge about the biology of LPA continues to grow as more and more cellular systems are tested for LPA responsiveness. For instance, it is now known that, in addition to stimulating cell growth and proliferation, LPAs promote cellular tension and cell-surface fibronectin binding, which are important events in wound repair and regeneration (Moolenaar et al., BioEssays, 2004, 26, 870-881). Recently, anti-apoptotic activity has also been ascribed to LPA, and it has recently been reported that PPARγ is a receptor/target for LPA (Simon et al., J. Biol. Chem., 2005, 280, 14656-14662).

Fibrosis is the result of an uncontrolled tissue healing process leading to excessive accumulation and insufficient resorption of extracellular matrix (ECM) which ultimately results in end-organ failure (Rockey et al., New Engl. J. Med., 2015, 372, 1138-1149). Recently it was reported that the LPA_1 receptor was over-expressed in idiopathic pulmonary fibrosis (IPF) patients. LPA_1 receptor knockout mice were also protected from bleomycin-induced lung fibrosis (Tager et al., Nature Med., 2008, 14, 45-54). Thus, antagonizing the LPA_1 receptor may be useful for the treatment of fibrosis (Stoddard et al., Biomol. Ther., 2015, 23 (1), 1-11; Rancoule et al., Expert. Opin. Inv. Drug 2011, 20 (85), 657-667 ; Yang et al., *IOVS* 2009, 50 (3) 1290-1298; Pradère et al., J. Am. Soc. Nephro. 2007, 18, 3110–3118; Abu El-Asrar et al., Acta Ophthalmol. 2012, 90, e84-e89) such as pulmonary fibrosis, hepatic fibrosis, renal fibrosis, arterial fibrosis and systemic sclerosis, and thus the diseases that result from fibrosis (pulmonary fibrosis-Idiopathic Pulmonary Fibrosis [IPF], hepatic fibrosis -Non-alcoholic Steatohepatitis [NASH], renal fibrosis-diabetic nephropathy, systemic sclerosis-scleroderma (Castellino et al., Arthritis Rheum. 2011, 63 (5), 1405–1415).

Corticosteroids in combination with immunosuppressant drugs, cytostatic drugs and antioxidants are used in the treatment of IPF. Corticosteroids may cause side effects when used in long term treatment. Pirefinidone is approved for treatment of IPF but the therapeutic mechanism of action is not known and also, side effects are associated with the use of pirfenidone. Therefore, orally active compounds which specifically target the fibrotic processes with reduced side effects would significantly improve current treatments of uncontrolled fibrotic diseases.

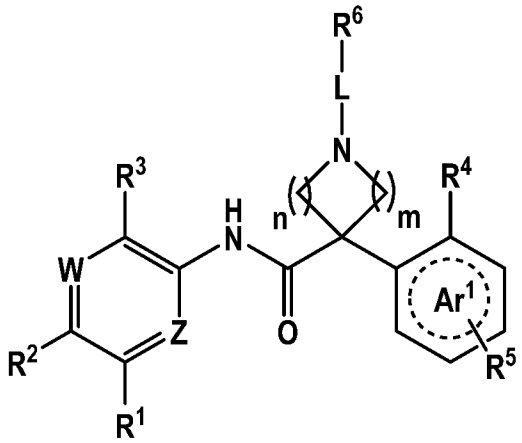
The use of LPA_1 receptor antagonists is not limited to fibrosis, and can apply to other disorders where LPA/LPA_1 receptor axis plays a role in the pathology; such as pain including acute pain, chronic pain, and neuropathic pain (Inoue et al, Nat. Med. 2004, 10 (7) 712-718; Kuner, Nat. Med. 2010, 16 (11), 1258-1266) including fibromyalgia stemming from the formation of fibrous scar tissue in contractile (voluntary) muscles, wherein fibrosis binds the tissue and inhibits blood flow, resulting in pain, and cancer pain; malignant and benign proliferative diseases including cancer (Stoddard et al., Biomol. Ther., 2015, 23 (1), 1-11; Komachi et al., Cancer Sci. 2012, 103 (6), 1099-1104; Zeng et al., The Prostate 2009, 69, 283-292), and the control of proliferation of tumor cells, invasion and metastasis of carcinomas, pleural mesothelioma (Yamada, Cancer Sci., 2008, 99 (8), 1603-1610), peritoneal mesothelioma, or bone metastases (Boucharaba et al, J. Clin. Invest., 2004, 1 14(12), 1714-1725; Boucharaba et al, Proc. Natl. acad. Sci., 2006, 103(25) 9643-9648);

inflammation (Li et al., Kidney International 2017, 91(6), 1362-1373; Lin et al., Am. J. Pathol. 2018, 188 (2), 353-366; Watanabe et al., J. Clin. Gastroenterol. 2007, 41 (6), 616-623; Watanabe et al., Life Sciences 2007, 81, 1009-1015); nervous system disorders (Stoddard et al., Biomol. Ther., 2015, 23 (1), 1-11; Choi et al., Biochim. Biophys. Acta 2013, 1831, 20–32; Nagai et al., Molecular Pain 2010, 6, 78); and respiratory diseases including allergic respiratory diseases, and hypoxia (Georas et al., Clin. Exp. Allergy 2007, 37 (3), 311-322). LPA has been shown to have contracting action on bladder smooth muscle cell isolated from bladder, and promotes growth of prostate-derived epithelial cell (J. Urology, 1999, 162, 1779-1784; J. Urology, 2000, 163, 1027-1032). LPA further has been shown to contract the urinary tract and prostate in vitro and increases intraurethral pressure in vivo (WO 02/062389). LPA has further been linked to obesity and insulin resistance (K. D'Souza et al., Nutrients 2018, 10, 399).

WO2013/096771 discloses a broad generic scope of TGR5 agonists, claimed to be active in the treatment of diabetes. US2007/0078120 (WO2005/037269) discloses a broad generic scope of piperidine derivatives claimed to be useful to lower the blood concentration of LDL cholesterol. WO2003/088908 discloses a broad generic scope of potassium channel inhibitors exemplifying some piperidine derivatives which, however, are different form the present compounds by at least the absence of present mandatory substituent R^4. WO2012/078805 and WO2009/135590 disclose structurally remote compounds that act as antagonists of the LPA_1 receptor and are claimed to show certain anti-fibrotic effects.

The present invention provides novel compounds of Formula (I) that are antagonists for the G protein-coupled receptor LPA_1 and may have a potent and long-lasting anti-fibrotic effect which may be mediated by inhibiting vascular leakage, inhibiting the conversion of fibroblasts to myofibroblasts, and/or inhibiting the subsequent release of pro-fibrotic cytokines by myofibroblasts. The present compounds may thus be useful to treat e.g. uncontrolled fibrotic diseases and other diseaes and disorders related to LPA_1 signalling.

1) A first aspect of the invention relates to compounds of the Formula (I),



Formula (I)

wherein

- **W** represents N, and **Z** represents CH; or
- **Z** represents N, and **W** represents CH;

R^1 is hydrogen or fluoro;

R^2 is hydrogen, halogen (especially chloro), methyl, ethyl, methoxy or ethoxy;

R^3 is C_{1-3}-alkoxy (especially methoxy, isopropoxy) or C_{1-3}-fluoroalkoxy (especially difluoromethoxy);

Ar^1 represents phenyl, or 6-membered heteroaryl containing one or two nitrogen atoms (especially pyridinyl); (notably, Ar^1 represents phenyl), wherein said group Ar^1 is substituted with R^4 and R^5, wherein

- R^4 is n-propyl, isopropyl, C_{3-6}-cycloalkyl optionally containing a ring oxygen atom (especially cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydro-2H-pyran-4-yl), or cyclopent-1-en-1-yl; [wherein it is understood that said substituent R^4 is attached in *ortho*-position with regard to the point of the attachment of the rest of the molecule] and
- R^5 represents one substituent independently selected from hydrogen, fluoro, methyl or methoxy [in a sub-embodiment, in case Ar^1 represents phenyl, R^5 especially represents hydrogen; fluoro in position 5 or 6; methyl in position 4, 5 or 6; or methoxy in position 5 of said phenyl group; in particular, in such case, R^5 represents one substituent independently selected from hydrogen, fluoro, methyl and methoxy in position 5 of said phenyl group];

m and **n** independently represent the integer 1 or 2; and

the group $-L^1-R^6$ represents

- hydrogen;
- $-C_{1-4}$-alkyl;
- $-C_{0-6}$-alkylene-C_{3-6}-cycloalkyl; wherein the C_{3-6}-cycloalkyl independently is unsubstituted or mono-substituted with halogen (especially fluoro);
- -CO-H;
- $-L^1-CO-R^{C11}$ wherein R^{C11} independently represents hydroxy; -O-benzyl; $-O-C_{1-6}$-alkyl; C_1-fluoroalkyl; or $-NR^{N11}R^{N12}$; wherein independently R^{N11} is hydrogen or C_{1-4}-alkyl, and R^{N12} is hydrogen, C_{1-4}-alkyl, $-SO_2-C_{1-6}$-alkyl, or $-O-R^{O11}$, wherein R^{O11} independently represents hydrogen, C_{1-6}-alkyl, or benzyl; and

  $-L^1-$ independently represents

  - $-C_{1-6}$-alkylene-, $-CO-C_{1-6}$-alkylene-, $-SO_2-C_{1-6}$-alkylene-, $-CO-O-C_{1-6}$-alkylene-, $-CO-NH-C_{1-6}$-alkylene-, or $-SO_2-NH-C_{1-6}$-alkylene-;
  - $-C_{1-6}$-alkylene-, $-CO-C_{1-6}$-alkylene-, or $-SO_2-C_{1-6}$-alkylene-; wherein in the above groups said C_{1-6}-alkylene independently is mono-substituted with hydroxy, C_{1-3}-alkoxy, $-O-CO-C_{1-4}$-alkyl, or $-NR^{N13}R^{N14}$; wherein independently R^{N13} is hydrogen or C_{1-4}-alkyl, and R^{N14} is hydrogen, C_{1-4}-alkyl or $-CO-O-C_{1-4}$-alkyl;
  - $-C_{2-6}$-alkylene-, $-CO-C_{2-6}$-alkylene-, or $-SO_2-C_{2-6}$-alkylene-; wherein in the above groups said C_{2-6}-alkylene independently is di-substituted wherein the substituents are independently selected from

hydroxy and -N$R^{N15}R^{N16}$; wherein independently R^{N15} is hydrogen or C_{1-4}-alkyl, and R^{N16} is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;

- -C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-NH-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, or -CO-O-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-;
- -C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, -CO-O-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, -CO-NH-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, or -SO_2-NH-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-; wherein **Cy**^{1} independently represents a C_{3-6}-heterocycloalkylene containing one ring oxygen atom, or one ring nitrogen atom, wherein said ring nitrogen, in case it has a free valency, independently is unsubstituted, or mono-substituted with C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
- -C_{2-4}-alkylene-O-C_{2-4}-alkylene-O-C_{1-4}-alkylene-, or -CO-C_{1-4}-alkylene-O-C_{2-4}-alkylene-O-C_{1-4}-alkylene-;
- -C_{2-4}-alkylene-**X**^{11}-C_{1-4}-alkylene-, -CO-O-C_{2-4}-alkylene-**X**^{11}-C_{1-4}-alkylene-, -CO-NH-C_{2-4}-alkylene-**X**^{11}-C_{1-4}-alkylene-, or -SO_2-NH-C_{2-4}-alkylene-**X**^{11}-C_{1-4}-alkylene-; wherein **X**^{11} independently represents oxygen, or a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, or -CO-O-C_{1-4}-alkyl;
- -CO-C_{1-4}-alkylene-**X**^{12}-C_{1-4}-alkylene-, -SO_2-C_{1-4}-alkylene-**X**^{12}-C_{1-4}-alkylene-, or -CO-C_{1-4}-alkylene-**X**^{12}-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-; wherein **X**^{12} independently represents oxygen, or a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, -CO-O-C_{1-4}-alkyl, or C_{1-3}-alkoxy-C_{2-4}-alkyl;
- -C_{2-4}-alkylene-**X**^{13}-C_{1-4}-alkylene-; wherein **X**^{13} represents -NH-CO-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy;
- -C_{1-4}-alkylene-**X**^{14}-C_{1-4}-alkylene-; wherein **X**^{14} represents -CO-NH-;
- -CO-C_{2-6}-alkenylene- or -SO_2-C_{2-6}-alkenylene-; or
- -CO-C_{2-6}-fluoroalkylene-;

- -**L**^{2}-hydroxy; wherein -**L**^{2}- represents
  - -CO-C_{1-6}-alkylene- or -SO_2-C_{1-6}-alkylene-; wherein in the above groups said C_{1-6}-alkylene independently is unsubstituted, or mono-substituted with hydroxy, C_1-fluoroalkyl, or -N$R^{N21}R^{N22}$ wherein independently R^{N21} is hydrogen or C_{1-4}-alkyl, and R^{N22} is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{2-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-, wherein in the above groups said C_{2-6}-alkylene independently is unsubstituted, or mono-substituted with hydroxy, C_1-fluoroalkyl, or -N$R^{N23}R^{N24}$ wherein independently R^{N23} is hydrogen or C_{1-4}-alkyl, and R^{N24} is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-;

- -C_{0-4}-alkylene-**Cy²**-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-**Cy²**-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-**Cy²**-C_{0-4}-alkylene-; wherein **Cy²** independently represents a C_{3-6}-heterocycloalkylene group containing one ring oxygen atom, or one ring nitrogen atom; wherein said ring nitrogen, in case it has a free valency, is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
- -C_{2-4}-alkylene-(O-C_{2-4}-alkylene)$_p$- or -CO-C_{1-4}-alkylene-(O-C_{2-4}-alkylene)$_p$-; wherein **p** independently represents the integer 1 or 2;
- -C_{2-4}-alkylene-**X²¹**-C_{2-4}-alkylene-; wherein **X²¹** represents a nitrogen atom which is unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, or -CO-O-C_{1-4}-alkyl;
- -CO-C_{1-4}-alkylene-**X²²**-C_{2-4}-alkylene-, -CO-C_{1-4}-alkylene-**X²²**-C_{1-4}-alkylene-C_{3-6}-cycloalkylene-, or -SO_2-C_{1-4}-alkylene-**X²²**-C_{2-4}-alkylene-; wherein **X²²** represents a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, or -CO-O-C_{1-4}-alkyl;
- -C_{2-4}-alkylene-**X²³**-C_{1-4}-alkylene-; wherein **X²³** represents -NH-CO-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy;
- -C_{1-4}-alkylene-**X²⁴**-C_{2-4}-alkylene-; wherein **X²⁴** represents -CO-NH-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy; or
- 3,4-dioxocyclobut-1-ene-1,2-diyl;

- **-L³**-O-**R^O31** wherein **R^O31** is -C_{1-4}-alkyl, -CO-C_{1-4}-alkyl or -CO-C_{2-4}-alkenyl; and

  -L³- independently represents
  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene- or -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-;
- **-L⁴-NR^N1R^N2** wherein independently **R^N1** is hydrogen or C_{1-4}-alkyl; and **R^N2** is hydrogen; C_{1-4}-alkyl; C_{1-3}-fluoroalkyl; C_{3-6}-cycloalkyl; C_{1-3}-alkoxy-C_{2-4}-alkylene; -CO-C_{1-4}-alkyl; -SO_2-C_{1-4}-alkyl; or -SO_2-C_1-fluoroalkyl; and

  -L⁴- independently represents
  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-; or
  - -C_{0-4}-alkylene-**Cy⁴**-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-**Cy⁴**-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-**Cy⁴**-C_{0-4}-alkylene-; wherein **Cy⁴** independently represents a C_{3-6}-heterocycloalkylene group containing one ring oxygen atom;
- **-L⁵-NR^N3R^N4** wherein **R^N3** is hydrogen, C_{1-4}-alkyl, or C_{1-3}-alkoxy-C_{2-4}-alkylene; and **R^N4** is -CO-O-C_{1-4}-alkyl; -CO-N**R^N51R^N52** wherein **R^N51** and **R^N52** are independently selected from hydrogen and C_{1-4}-alkyl; or -SO_2-**NR^N53R^N54** wherein independently **R^N53** is hydrogen or C_{1-4}-alkyl, and **R^N54** is hydrogen, C_{1-4}-alkyl, or -CO-C_{1-4}-alkyl;

  and **-L⁵-** independently represents
  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene- or -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-;

- **-L^{6}-N(R^{N61})-O-R^{O61}** wherein **R^{N61}** is hydrogen, -CO-C$_{1-4}$-alkyl, or -CO-O-C$_{1-4}$-alkyl; and **R^{O61}** independently represents hydrogen, C$_{1-6}$-alkyl, or benzyl;
  and **-L^{6}-** independently represents
  - -C$_{2-6}$-alkylene-, -CO-C$_{1-6}$-alkylene-, -SO$_2$-C$_{1-6}$-alkylene-, -CO-O-C$_{2-6}$-alkylene-, -CO-NH-C$_{2-6}$-alkylene-, or -SO$_2$-NH-C$_{2-6}$-alkylene-;
- **-L^{7}-NR^{N5}R^{N6}** wherein **R^{N5}** is hydrogen or C$_{1-4}$-alkyl (especially hydrogen); **R^{N6}** is hydrogen, C$_{1-4}$-alkyl, -CO-C$_{1-4}$-alkyl, C$_{1-3}$-fluoroalkyl, or C$_{3-6}$-cycloalkyl (especially hydrogen); and
  -L^{7}- independently represents
  - -CO-, or -SO$_2$-;
- **-L^{8}-SO$_2$-R^{S81}** wherein **R^{S81}** independently represents -C$_{1-6}$-alkyl; C$_1$-fluoroalkyl; hydroxy; **-NR^{N81}R^{N82}** wherein independently **R^{N81}** is hydrogen or C$_{1-4}$-alkyl, and **R^{N82}** is hydrogen, C$_{1-4}$-alkyl, -CO-C$_{1-6}$-alkyl; and
  -L^{8}- independently represents
  - -C$_{1-6}$-alkylene-, -CO-C$_{1-6}$-alkylene-, -SO$_2$-C$_{1-6}$-alkylene-, -CO-O-C$_{2-6}$-alkylene-, -CO-NH-C$_{1-6}$-alkylene-, or -SO$_2$-NH-C$_{1-6}$-alkylene-;
- **-L^{9}-HET^{1}**, wherein **HET^{1}** represents 5- or 6-membered heteroaryl (especially pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl),
  wherein said **HET^{1}** independently is unsubstituted or mono-, or di-substituted wherein the substituents are independently selected from C$_{1-4}$-alkyl (especially methyl); halogen; cyano; hydroxy; hydroxymethyl; -C$_{0-2}$-alkylene-**Cy^{91}**-COOR^{O91} wherein R^{O91} is hydrogen or C$_{1-4}$-alkyl, and wherein **Cy^{91}** represents a C$_{3-6}$-cycloalkylene group; or -C$_{0-2}$-alkylene-COOR^{O92} wherein R^{O92} is hydrogen or C$_{1-4}$-alkyl; and
  -L^{9}- independently represents
  - -C$_{0-6}$-alkylene-, -CO-C$_{0-6}$-alkylene-, -SO$_2$-C$_{0-6}$-alkylene-, -CO-O-C$_{1-6}$-alkylene-, -CO-NH-C$_{1-6}$-alkylene-, or -SO$_2$-NH-C$_{1-6}$-alkylene-;
- **-L^{10}-**C$_{4-6}$-heterocyclyl, wherein the C$_{4-6}$-heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said C$_{4-6}$-heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:
  - one or two oxo substituents each attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionaly adjacent, a carbamate group, or, in case second ring nitrogen is additionaly adjacent, a urea group); and / or
  - two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom or a ring oxygen atom (thus forming together with the nitrogen a -C(CH$_3$)$_2$-N- or with the oxygen a -C(CH$_3$)$_2$-O-group); and / or
  - two oxo substituents at a ring sulfur ring atom (thus forming a -SO$_2$- group); and / or

- C_{1-4}-alkyl, C_{1-3}-alkoxy-C_{2-4}-alkyl, C_{2-3}-fluoroalkyl, or -CO-C_{1-4}-alkyl attached to a ring nitrogen atom having a free valency; and

-L[10]- independently represents

- -C_{0-6}-alkylene-, -CO-C_{0-6}-alkylene-, -SO_2-C_{0-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;

- **-L[11]**-cyano; wherein **-L[11]-** represents -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene, or -C_{0-6}-alkylene-;
- **-L[12]**-NO_2; wherein **-L[12]-** represents -C_{2-6}-alkylene-; or
- **-L[13]**-C_{1-4}-alkyl; wherein **-L[13]-** represents -CO-, -CO-O-, or -SO_2-.

In a sub-embodiment, the present invention especially relates to compounds of Formula (I) as defined in embodiment 1), wherein the linker **L** in the group **-L-R[6]** is as defined hereinbefore (or, *mutatis mutandis*, in any one of embodiments below) wherein the length of such linker L (i.e. each of the particular linker groups **-L[1]-**, **-L[2]-**, **-L[3]-**, **-L[4]-**, **-L[5]-**, **-L[6]-**, **-L[7]-**, **-L[8]-**, **-L[9]-**, **-L[10]-**, **-L[11]-**, **-L[12]-**, and **-L[13]-**) is such that the group **R[6]** is distanced from the nitrogen atom to which **L** is attached by at maximum 9 atoms (preferably it is distanced by at maximum 5 atoms).

It is understood that the linker groups in group **-L-R[6]** (such as **-L[1]-**, **-L[2]-**, **-L[3]-**, **-L[4]-**, **-L[5]-**, **-L[6]-**, **-L[7]-**, **-L[8]-**, **-L[9]-**, **-L[10]-**, **-L[11]-**, **-L[12]-**, and **-L[13]-**) are to be read from left to right: for example a linker group -CO-C_{0-6}-alkylene- is attached to the rest of the molecule on the -CO- group part of said linker.

The compounds of formulae (I), (II) and (III) may contain one or more stereogenic or asymmetric centers, such as one or more asymmetric carbon atoms, which are allowed to be present in (R)- as well as (S)-configuration. The compounds of formulae (I), (II) and (III) may further encompass compounds with one or more double bonds which are allowed to be present in Z- as well as E-configuration and/or compounds with substituents at a ring system which are allowed to be present, relative to each other, in cis- as well as trans-configuration. The compounds of formulae (I), (II) and (III) may thus be present as mixtures of stereoisomers or preferably as pure stereoisomers. Mixtures of stereoisomers may be separated in a manner known to a person skilled in the art.

In case a particular compound (or generic structure) is designated as (R)- or (S)-enantiomer, such designation is to be understood as referring to the respective compound (or generic structure) in enriched, especially essentially pure, enantiomeric form. Likewise, in case a specific asymmetric center in a compound is designated as being in (R)- or (S)-configuration or as being in a certain relative configuration, such designation is to be understood as referring to the compound that is in enriched, especially essentially pure, form with regard to the respective configuration of said asymmetric center. In analogy, *cis*- or *trans*-designations are to be understood as referring to the respective stereoisomer of the respective relative configuration in enriched, especially essentially pure, form. Likewise, in case a particular compound (or generic structure) is designated as Z- or E-stereoisomer (or in case a specific double bond in a compound is designated as being in Z- or E-configuration), such designation is to be understood as referring to the respective compound (or generic

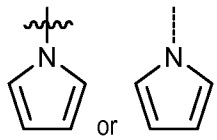
structure) in enriched, especially essentially pure, stereoisomeric form (or to the compound that is in enriched, especially essentially pure, form with regard to the respective configuration of the double bond).

The term "enriched", when used in the context of stereoisomers, is to be understood in the context of the present invention to mean that the respective stereoisomer is present in a ratio of at least 70:30, especially of at least 90:10 (i.e., in a purity of at least 70% by weight, especially of at least 90% by weight), with regard to the respective other stereoisomer / the entirety of the respective other stereoisomers.

The term “essentially pure”, when used in the context of stereoisomers, is to be understood in the context of the present invention to mean that the respective stereoisomer is present in a purity of at least 95% by weight, especially of at least 99% by weight, with regard to the respective other stereoisomer / the entirety of the respective other stereoisomers.

The present invention also includes isotopically labelled, especially ^{2}H (deuterium) labelled compounds of Formula (I) according to embodiments 1) to 36), which compounds are identical to the compounds of Formula (I) except that one or more atoms have each been replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Isotopically labelled, especially ^{2}H (deuterium) labelled compounds of formulae (I), (II) and (III) and salts thereof are within the scope of the present invention. Substitution of hydrogen with the heavier isotope ^{2}H (deuterium) may lead to greater metabolic stability, resulting e.g. in increased *in-vivo* half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of formulae (I), (II) and (III) are not isotopically labelled, or they are labelled only with one or more deuterium atoms. In a sub-embodiment, the compounds of formulae (I), (II) and (III) are not isotopically labelled at all. Isotopically labelled compounds of formulae (I), (II) and (III) may be prepared in analogy to the methods described hereinafter, but using the appropriate isotopic variation of suitable reagents or starting materials.

In this patent application, a bond drawn with a wavy line or with a dotted line shows the point of attachment of the radical drawn. For example, the radical



is a 1*H*-pyrrol-1-yl group.

Whenever a substituent R^5 is designated to be in a specific position of the phenyl moiety to which it is attached, it is understood that the point of attachment of the substituent R^4 is considered position 2 of said phenyl moiety.

In some instances, the compounds of formulae (I), (II) and (III) may contain tautomeric forms. Such tautomeric forms are encompassed in the scope of the present invention. In case tautomeric forms exist of a certain residue, and only one form of such residue is disclosed or defined, the other tautomeric form(s) are understood

to be encompassed in such disclosed residue. For example, the group 3-hydroxy-1H-pyrazol-4-yl is to be understood as also encompassing its tautomeric form 3-oxo-2,3-dihydro-1H-pyrazol-4-yl. Likewise, the group 3-hydroxy-1H-pyrazol-5-yl is to be understood as also encompassing its tautomeric form 3-oxo-2,3-dihydro-1H-pyrazol-5-yl; the group 3-hydroxy-1H-1,2,4-triazole-5-yl is to be understood as also encompassing its tautomeric forms 3-hydroxy-4H-1,2,4-triazol-5-yl, 3-hydroxy-3H-1,2,4-triazol-5-yl, as well as 3-oxo-2,5-dihydro-1H-1,2,4-triazol-5-yl and 3-oxo-4,5-dihydro-1H-1,2,4-triazol-5-yl; the group 3-hydroxyisoxazole-5-yl is to be understood as also encompassing its tautomeric form 3-oxo-2,3-dihydroisoxazole-5-yl; the group 5-hydroxy-[1,2,4]oxadiazol-3-yl is to be understood as also encompassing its tautomeric form 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl and the group 5-hydroxy-[1,3,4]oxadiazol-2-yl is to be understood as also encompassing its tautomeric form 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl; the group 4-oxo-4,5-dihydro-oxazole-2-yl is to be understood as also encompassing its tautomeric form 4-hydroxy-oxazole-2-yl; the group 2,4-dioxoimidazolidin-1-yl is to be understood as also encompassing its tautomeric form 2,4-dihydroxy-imidazol-1-yl; and the group 2,5-dioxoimidazolidin-1-yl is to be understood as also encompassing its tautomeric form 2,5-dihydroxy-imidazol-1-yl.

Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, salt, or the like.

Any reference to compounds of formulae (I), (II) and (III) according to embodiments 1) to 36) is to be understood as referring also to the salts (and especially the pharmaceutically acceptable salts) of such compounds, as appropriate and expedient.

The term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. Such salts include inorganic or organic acid and/or base addition salts depending on the presence of basic and/or acidic groups in the subject compound. For reference see for example “Handbook of Phramaceutical Salts. Properties, Selection and Use.”, P. Heinrich Stahl, Camille G. Wermuth (Eds.), Wiley-VCH, 2008; and “Pharmaceutical Salts and Co-crystals”, Johan Wouters and Luc Quéré (Eds.), RSC Publishing, 2012.

Definitions provided herein are intended to apply uniformly to the compounds of formulae (I), (II) and (III), as defined in any one of embodiments 1) to 33), and, *mutatis mutandis*, throughout the description and the claims unless an otherwise expressly set out definition provides a broader or narrower definition. It is well understood that a definition or preferred definition of a term defines and may replace the respective term independently of (and in combination with) any definition or preferred definition of any or all other terms as defined herein.

Whenever a substituent is denoted as optional, it is understood that such substituent may be absent (i.e. the respective residue is unsubstituted with regard to such optional substituent), in which case all positions having a free valency (to which such optional substituent could have been attached to; such as for example in an aromatic ring the ring carbon atoms and / or the ring nitrogen atoms having a free valency) are substituted with hydrogen where appropriate. Likewise, in case the term “optionally” is used in the context of (ring)

heteroatom(s), the term means that either the respective optional heteroatom(s), or the like, are absent (i.e. a certain moiety does not contain heteroatom(s) / is a carbocycle / or the like), or the respective optional heteroatom(s), or the like, are present as explicitly defined.

The term “halogen” means fluorine, chlorine, or bromine, preferably fluorine or chlorine.

The term “alkyl”, used alone or in combination, refers to a saturated straight or branched chain hydrocarbon group containing one to six carbon atoms. The term “C_{x-y}-alkyl” (x and y each being an integer), refers to an alkyl group as defined before, containing x to y carbon atoms. For example a C_{1-6}-alkyl group contains from one to six carbon atoms. Examples of alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, 3-methyl-butyl, 2,2-dimethyl-propyl and 3,3-dimethyl-butyl. For avoidance of any doubt, in case a group is referred to as e.g. propyl or butyl, it is meant to be n-propyl, respectively n-butyl. Preferred are methyl and ethyl. Most preferred is methyl.

The term “-C_{x-y}-alkylene-”, used alone or in combination, refers to bivalently bound alkyl group as defined before containing x to y carbon atoms. The term “-C_{0-y}-alkylene-“ refers to a direct bond, or to a -(C_{1-y})alkylene- as defined before. Preferably, the points of attachment of a -C_{1-y}-alkylene group are in 1,1-diyl, in 1,2-diyl, or in 1,3-diyl arrangement. Preferably, the points of attachment of a -C_{2-y}-alkylene group are in 1,2-diyl or in 1,3-diyl arrangement. In case a $C_{0\ y}$-alkylene group is used in combination with another substituent, the term means that either said substituent is linked through a $C_{1\ y}$-alkylene group to the rest of the molecule, or it is directly attached to the rest of the molecule (i.e. a C_0-alkylene group represents a direct bond linking said substituent to the rest of the molecule). The alkylene group -C_2H_4- refers to -CH_2-CH_2- if not explicitly indicated otherwise. Examples of -C_{0-4}-alkylene- groups are notably methylene, ethylene, and propane-1,3-diyl. Examples of -C_{0-6}-alkylene- groups are notably methylene, ethylene, propane-1,3-diyl, and 3-methylbutane-1,3-diyl (especially methylene, ethylene, and propane-1,3-diyl). Examples of -C_{1-6}-alkylene- groups are notably methylene, ethylene, ethane-1,1-diyl, propane-1,3-diyl, propane-1,2-diyl, propane-2,2-diyl, 2-methylpropane-1,2-diyl, 2-methylpropane-1,1-diyl, 2,2-dimethylpropane-1,3-diyl, butane-1,4-diyl, 3-methylbutane-1,3-diyl, and 4-methylpentane-1,4-diyl. Examples of -C_{1-4}-alkylene- groups are notably methylene, ethylene, propane-2,2-diyl, and 2-methylpropane-1,2-diyl (especially methylene). Examples of -C_{2-6}-alkylene- groups are notably ethylene, propane-1,3-diyl, propane-1,2-diyl, 2,2-dimethylpropane-1,3-diyl, 2-methylpropane-1,2-diyl, 3-methylbutane-1,3-diyl, and 4-methylpentane-1,4-diyl (most preferably ethylene, propane-1,3-diyl, propane-1,2-diyl, 2-methylpropane-1,2-diyl, 3-methylbutane-1,3-diyl, and 4-methylpentane-1,4-diyl). Examples of -C_{2-4}-alkylene- groups are notably ethylene, propane-1,2-diyl and propane-1,3-diyl.

An example of a group -$\mathbf{L^2}$-hydroxy wherein -$\mathbf{L^2}$- represents C_{2-6}-alkylene which is mono-substituted with hydroxy is 2,3-dihydroxypropyl.

The term "alkenyl", used alone or in combination, refers to a straight or branched hydrocarbon chain containing two to five carbon atoms and one carbon-carbon double bond. The term "C_{x-y}-alkenyl" (x and y each being an

integer), refers to an alkenyl group as defined before containing x to y carbon atoms. For example a C_{2-5}-alkenyl group contains from two to five carbon atoms. An example of alkenyl group is notably prop-1-en-2-yl.

The term "-C_{x-y}-alkenylene-", used alone or in combination, refers to bivalently bound alkenyl group as defined before containing x to y carbon atoms. Examples of -C_{2-6}-alkenylene- groups are notably ethen-1,2-diyl, prop-1-en-2,3-diyl, and prop-1-en-1,3-diyl.

The term "fluoroalkyl", used alone or in combination, refers to an alkyl group as defined before containing one to three carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. The term "C_{x-y}-fluoroalkyl" (x and y each being an integer) refers to a fluoroalkyl group as defined before containing x to y carbon atoms. For example a C_{1-3}-fluoroalkyl group contains from one to three carbon atoms in which one to seven hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkyl groups include trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl and 2,2,2-trifluoroethyl. Preferred are C_1-fluoroalkyl groups such as trifluoromethyl.

The term "fluoroalkoxy", used alone or in combination, refers to an alkoxy group as defined before containing one to three carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. The term "C_{x-y}-fluoroalkoxy" (x and y each being an integer) refers to a fluoroalkoxy group as defined before containing x to y carbon atoms. For example a C_{1-3}-fluoroalkoxy group contains from one to three carbon atoms in which one to seven hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkoxy groups include trifluoromethoxy, difluoromethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy and 2,2,2-trifluoroethoxy. Preferred are C_1-fluoroalkoxy groups such as trifluoromethoxy and difluoromethoxy, as well as 2,2,2-trifluoroethoxy.

The term "cycloalkyl", used alone or in combination, refers especially to a saturated monocyclic, or to a fused-, bridged-, or spiro-bicyclic hydrocarbon ring containing three to eight carbon atoms. The term "C_{x-y}-cycloalkyl" (x and y each being an integer), refers to a cycloalkyl group as defined before containing x to y carbon atoms. For example a C_{3-6}-cycloalkyl group contains from three to six carbon atoms. Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, as well as the bicyclic group bicyclo[1.1.1]pentane. Preferred are cyclopropyl, cyclobutyl, and cyclopentyl; especially cyclopropyl.

The term "C_{x-y}-cycloalkyl optionally containing a ring oxygen atom" refers to a cycloalkyl group as defined before containing x to y carbon atoms, wherein one ring carbon atom of said C_{x-y}-cycloalkyl may be replaced by an oxygen atom. Such groups are unsubstituted or substituted as explicitly defined. Examples are especially the C_{3-6}-cycloalkyl groups cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; as well as oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl. A particular "C_{3-6}-cycloalkyl, wherein said C_{3-6}-cycloalkyl contains one ring oxygen atom" is tetrahydro-2H-pyran-4-yl.

The term "-C_{x-y}-cycloalkylene-", used alone or in combination, refers to bivalently bound cycloalkyl group as defined before containing x to y carbon atoms. Preferably, the points of attachment of any bivalently bound cycloalkyl group are in 1,1-diyl, or in 1,2-diyl arrangement. An example of a -C_{3-6}-cycloalkylene- group is notably

cyclopropane-1,1-diyl. Examples of -C_{3-8}-cycloalkylene- groups are notably cyclopropane-1,1-diyl, cyclopropane-1,2-diyl, cyclobutane-1,1-diyl, bicyclo[1.1.1]pentane-1,3-diyl, cyclohexane-1,3-diyl, and cyclohexane-1,4-diyl (especially cyclopropane-1,1-diyl, cyclopropane-1,2-diyl, and cyclobutane-1,1-diyl).

The term “alkoxy”, used alone or in combination, refers to an alkyl-O- group wherein the alkyl group is as defined before. The term “C_{x-y}-alkoxy” (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms. For example a C_{1-4}-alkoxy group means a group of the formula C_{1-4}-alkyl-O- in which the term “C_{1-4}-alkyl” has the previously given significance. Examples of alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.-butoxy and tert.-butoxy. Preferred are ethoxy and especially methoxy.

The term "heterocyclyl”, used alone or in combination, and if not explicitly defined in a broader or more narrow way, refers to a saturated or unsaturated non-aromatic monocyclic hydrocarbon ring containing one or two ring heteroatoms independently selected from nitrogen, sulfur, and oxygen (especially one oxygen atom, one sulfur atom, one nitrogen atom, two nitrogen atoms, two oxygen atoms, one nitrogen atom and one oxygen atom). The term “C_{x-y}-heterocyclyl” refers to such a heterocycle containing x to y ring atoms. Examples of heterocyclyl groups as used in the group -$\mathbf{L^{10}}$-C_{4-6}-heterocyclyl are notably oxetan-3-yl, thietane-3-yl, imidazolidin-1-yl, 4,5-dihydrooxazol-2-yl, 1,3-dioxolan-4-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, morpholin-3-yl, morpholin-4-yl and morpholin-2-yl. Heterocyclyl group are unsubstituted or substituted as explicitly defined.

The term “-C_{x-y}-heterocycloalkylene-”, used alone or in combination, refers to bivalently bound heterocyclyl group as defined before containing x to y ring atoms. Examples of C_{3-6}-heterocycloalkylene containing one ring oxygen atom, or containing one ring nitrogen atom as used in the groups $\mathbf{Cy^1}$, $\mathbf{Cy^2}$, and, *mutatis mutandis*, $\mathbf{Cy^4}$ are notably the nitrogen conainting groups azetidin-1,3-diyl, azetidin-3,3-diyl, pyrrolidine-2,4-diyl, piperidin-1,4-diyl and piperidin-4,4-diyl; and the oxygen containing groups oxetan-3,3-diyl, tetrahydrofuran-3,3-diyl, and tetrahydro-2H-pyran-4,4-diyl.

The term "heteroaryl", used alone or in combination, means a 5- to 10-membered monocyclic or bicyclic aromatic ring containing one to a maximum of four heteroatoms, each independently selected from oxygen, nitrogen and sulfur. Examples of such heteroaryl groups are furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl, quinolinyl, isoquinolinyl, naphthyridinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyrrolopyridinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrrolopyrazinyl, imidazopyridinyl, imidazopyridazinyl, and imidazothiazolyl. The above-mentioned heteroaryl groups are unsubstituted or substituted as explicitly defined. For the substituent $\mathbf{Ar^1}$ representing "6-membered heteroaryl containing one or two nitrogen atoms", the term means the respective above-mentioned 6-membered groups; especially pyridinyl or pyrazinyl; in particular pyridin-2-yl, pyridin-4-yl, or pyrazin-2-yl. For the substituent $\mathbf{HET^1}$ representing "5- or

6-membered heteroaryl", the term means the above-mentioned 5- or 6-membered groups. Notably, the term refers to 5-membered heteroaryl containing one to four heteroatoms, such as especially furanyl, imidazolyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, or tetrazolyl; or to 6-membered heteroaryl containing one or two nitrogen atoms; such as especially pyrimidinyl, pyrazinyl, pyridazinyl, or pyridinyl. Particular examples of 5-membered heteroaryl as used for **HET^1** are furan-2-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, 1H-pyrrol-2-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, oxazol-2-yl, oxazol-4-yl, isoxazol-5-yl, 1,2,4-oxadiazol-3-yl, 2H-1,2,3-triazol-2-yl, 1H-1,2,3-triazol-4-yl, 4H-1,2,4-triazol-4-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, and 1H-tetrazol-5-yl; and in addition to the above-listed 1H-1,2,3-triazol-1-yl, and 2H-tetrazol-2-yl. Particular examples of 6-membered heteroaryl as used for **HET^1** are pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridin-2-yl, pyridin-4-yl, pyridin-3-yl, pyridazin-3-yl, and pyrazin-2-yl.

For avoidance of doubt, certain groups having tautomeric forms which may be considered predominantly aromatic (such as for example 3-hydroxy-isoxazolyl, 5-hydroxy-[1,2,4]oxadiazol-3-yl, 3-hydroxy-[1,2,4]oxadiazol-5-yl, 3-hydroxy-1H-pyrazol-4-yl, or 2-hydroxy-[1,3,4]oxadiazolyl groups) are defined herein as heteroaryl groups **HET^1**, even though their corresponding tautomeric forms (3-oxo-2,3-dihydro-2H-isoxazolyl, respectively, 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, 3-oxo-4,5-dihydro-[1,2,4]oxadiazol-5-yl, 3-oxo-2,3-dihydro-1H-pyrazol-4-yl, 2-oxo-2,3-dihydro-3H-[1,3,4]oxadiazolyl) could also be considered as a non-aromatic heterocyclyl group. Likewise, certain groups having tautomeric forms which may be considered predominantly non-aromatic (such as 2,4-dioxoimidazolidin-1-yl, 4-oxo-4,5-dihydro-oxazole-2-yl) as defined for the substituent **-L^{10}**-C_{4-6}-heterocyclyl, are defined herein as not being part of substituted heteroaryl groups as defined for **HET^1**, even though their corresponding tautomeric form (4-hydroxy-oxazole-2-yl, respectively, 2,4-dihydroxy-imidazol-1-yl), could also be considered as an heteroaryl group **HET^1**. It is understood that the corresponding tautomers are encompassed in the respective scope **-L^9-HET^1**, respectively, **-L^{10}**-C_{4-6}-heterocyclyl as defined.

The term "cyano" refers to a group -CN.

The term "oxo" refers to a group =O which is preferably attached to a chain or ring carbon or sulfur atom as for example in a carbonyl group -(CO)-, or a sulfonyl group -(SO_2)-.

Whenever the word “between” is used to describe a numerical range, it is to be understood that the end points of the indicated range are explicitly included in the range. For example: if a temperature range is described to be between 40 ºC and 80 ºC, this means that the end points 40 ºC and 80 ºC are included in the range; or if a variable is defined as being an integer between 1 and 4, this means that the variable is the integer 1, 2, 3, or 4.

Unless used regarding temperatures, the term “about” placed before a numerical value “X” refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term “about” placed before a temperature “Y” refers in the current application to an interval extending from the temperature Y minus 10ºC to Y plus 10ºC, and preferably to an interval extending from Y minus 5ºC to Y plus 5ºC. Besides, the term “room temperature” as used herein refers to a temperature of about 25°C.

Further embodiments of the invention are presented hereinafter:

2) A second embodiment relates to compounds according to embodiment 1), wherein **R**^{1} is hydrogen.

3) Another embodiment relates to compounds according to embodiment 1), wherein **R**^{1} is fluoro.

4) Another embodiment relates to compounds according to any one of embodiments 1) to 3), wherein **R**^{2} is hydrogen, chloro, methyl, ethyl, methoxy or ethoxy.

5) Another embodiment relates to compounds according to any one of embodiments 1) to 3), wherein

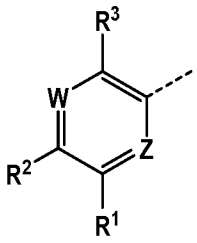
- **W** represents N, **Z** represents CH; and **R**^{2} is hydrogen, methyl, methoxy or ethoxy (especially methyl); or
- **Z** represents N, **W** represents CH; and **R**^{2} is chloro, bromo, methyl, or methoxy (especially chloro).

6) Another embodiment relates to compounds according to any one of embodiments 1) to 5), wherein **R**^{3} is methoxy, isopropoxy, or difluoromethoxy (especially methoxy or difluoromethoxy).

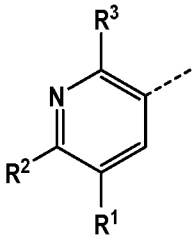
7) Another embodiment relates to compounds according to any one of embodiments 1) to 5), wherein **R**^{3} is C_{1-3}-alkoxy (notably methoxy, isopropoxy, especially methoxy).

8) Another embodiment relates to compounds according to any one of embodiments 1) to 5), wherein **R**^{3} is C_{1-3}-fluoroalkoxy (especially difluoromethoxy).

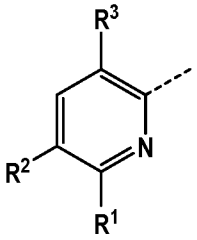
9) Another embodiment relates to compounds according to embodiment 1), wherein the fragment:



represents:

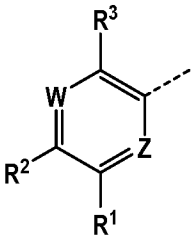
- 

wherein **R**^{1} is hydrogen or fluoro (especially hydrogen); **R**^{2} is hydrogen, chloro, methyl, ethyl, methoxy or ethoxy (especially methyl); and **R**^{3} is C_{1-3}-alkoxy (especially methoxy, isopropoxy) or C_{1-3}-fluoroalkoxy (especially difluoromethoxy); or

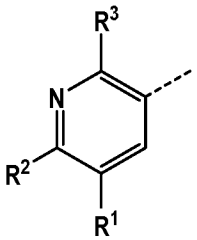
- 

wherein **R1** is hydrogen; **R2** is halogen (especially chloro), methyl, or methoxy; and **R3** is C_{1-3}-alkoxy (especially methoxy) or C_{1-3}-fluoroalkoxy (especially difluoromethoxy).

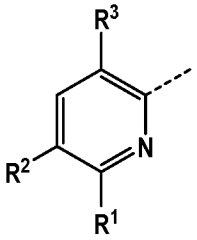
10) Another embodiment relates to compounds according to embodiment 1), wherein the fragment:



represents:

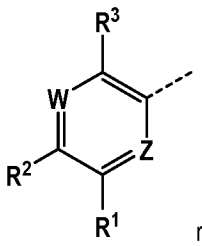
- 

wherein **R1** is hydrogen; **R2** is hydrogen, methyl, methoxy (especially methyl); and **R3** is C_{1-3}-alkoxy (especially methoxy) or C_{1-3}-fluoroalkoxy (especially difluoromethoxy); or

- 

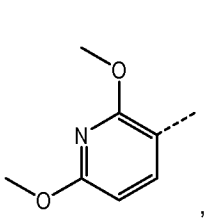
wherein **R1** is hydrogen; **R2** is halogen (especially chloro); and **R3** is methoxy, or difluoromethoxy.

11) Another embodiment relates to compounds according to embodiment 1), wherein the fragment:



represents a ring independently selected from the following groups A) or B):

A)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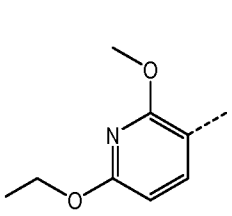
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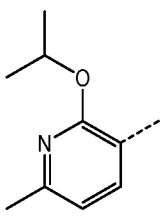
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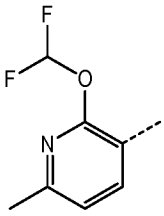
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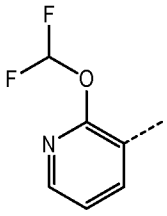
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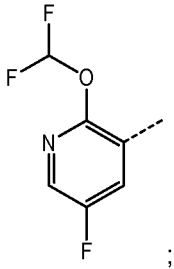
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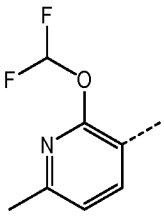
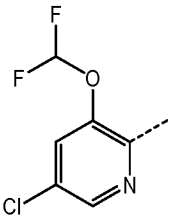

;

B)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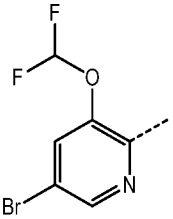
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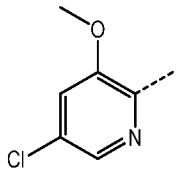
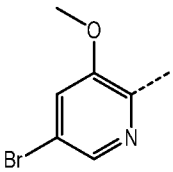
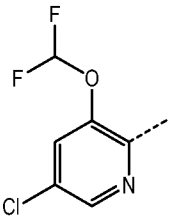

, or

; especially

;

wherein each of the above groups A) and B) form a particular sub-embodiment.

12) Another embodiment relates to compounds according to any one of embodiments 1) to 11), wherein **Ar**[1] represents phenyl [wherein it is understood that said phenyl is substituted with **R**[4] and **R**[5] as explicitly defined].

13) Another embodiment relates to compounds according to any one of embodiments 1) to 11), wherein **Ar**[1] represents a 6-membered heteroaryl containing one or two nitrogen atoms (especially pyridinyl, pyrimidinyl, or pyrazinyl; in particular pyridin-2-yl, pyridin-4-yl, or pyrazin-2-yl) [wherein it is understood that said heteroaryl is substituted with **R**[4] and **R**[5] as explicitly defined].

14) Another embodiment relates to compounds according to any one of embodiments 1) to 13) [especially according to embodiment 12)], wherein **R**[4] is n-propyl, isopropyl, or monocyclic C_{3-6}-cycloalkyl (especially cyclobutyl, or cyclopentyl).

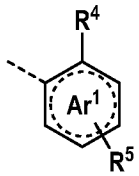
15) Another embodiment relates to compounds according to any one of embodiments 1) to 13) [especially according to embodiments 12) or 13]], wherein **R4** is n-propyl, isopropyl.

16) Another embodiment relates to compounds according to any one of embodiments 1) to 13) [especially according to embodiment 12)], wherein **R4** is monocyclic C_{3-6}-cycloalkyl (especially cyclobutyl, cyclopentyl).

17) Another embodiment relates to compounds according to any one of embodiments 1) to 16), wherein **R5** represents hydrogen, fluoro, or methyl (notably hydrogen, or fluoro in position 5 or 6 of the phenyl moiety, or methyl in position 5 of the phenyl moiety; especially hydrogen, or fluoro in position 5 or 6 of the phenyl moiety).

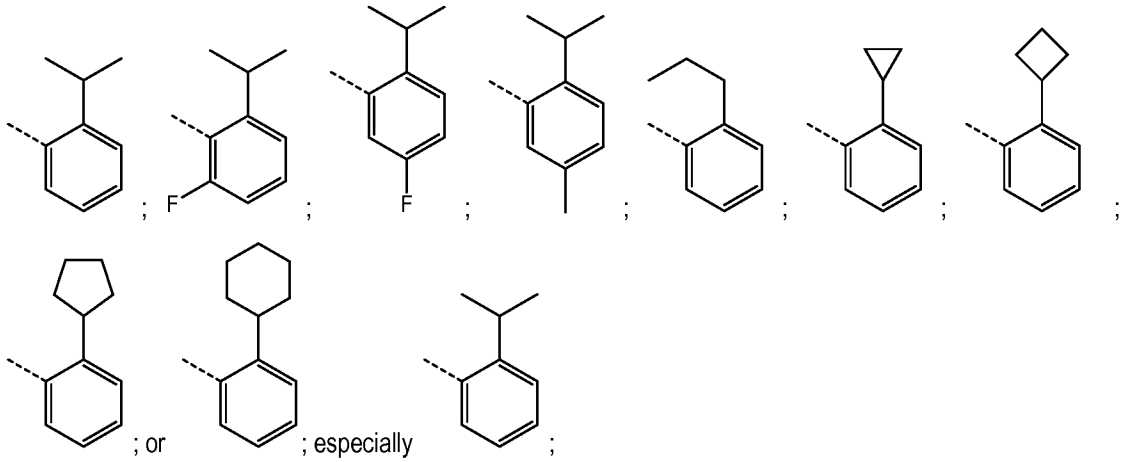
18) Another embodiment relates to compounds according to any one of embodiments 1) to 16), wherein **R5** represents hydrogen.

19) Another embodiment relates to compounds according to any one of embodiments 1) to 11), wherein the fragment:



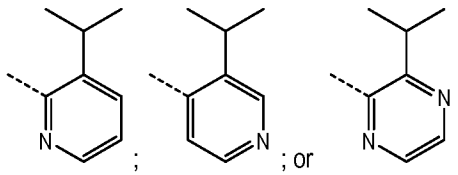
represents a ring independently selected from the following groups A) or B):

A)



; or ; especially ;

B)



; ; or ;

wherein each of the above groups A) and B) form a particular sub-embodiment.

20) Another embodiment relates to compounds according to any one of embodiments 1) to 19), wherein **m** and **n** both are 1, or **m** and **n** both are 2.

21) Another embodiment relates to compounds according to any one of embodiments 1) to 19), wherein **m** and **n** both are 1.

22) Another embodiment relates to compounds according to any one of embodiments 1) to 21), wherein the group **-L-R^{6}** represents

- hydrogen;
- **-L^{1}**-CO-**R^{C11}** wherein **R^{C11}** independently represents hydroxy; -O-benzyl; -O-C_{1-6}-alkyl; C_1-fluoroalkyl; or -N**R^{N11}R^{N12}**; wherein independently **R^{N11}** is hydrogen or C_{1-4}-alkyl, and **R^{N12}** is hydrogen, C_{1-4}-alkyl, -SO_2-C_{1-6}-alkyl, or -O-**R^{O11}**, wherein **R^{O11}** independently represents hydrogen, C_{1-6}-alkyl, or benzyl; and

  -L^{1}- independently represents

  - -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;
  - -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, or -SO_2-C_{1-6}-alkylene-; wherein in the above groups said C_{1-6}-alkylene independently is mono-substituted with hydroxy, C_{1-3}-alkoxy, -O-CO-C_{1-4}-alkyl, or -N**R^{N13}R^{N14}**; wherein independently **R^{N13}** is hydrogen or C_{1-4}-alkyl, and **R^{N14}** is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{2-6}-alkylene-, -CO-C_{2-6}-alkylene-, or -SO_2-C_{2-6}-alkylene-; wherein in the above groups said C_{2-6}-alkylene independently is di-substituted wherein the substituents are independently selected from hydroxy and -N**R^{N15}R^{N16}**; wherein independently **R^{N15}** is hydrogen or C_{1-4}-alkyl, and **R^{N16}** is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-NH-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, or -CO-O-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-;
  - -C_{0-4}-alkylene-**Cy^{1}**-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-**Cy^{1}**-C_{0-4}-alkylene-, -CO-O-C_{0-4}-alkylene-**Cy^{1}**-C_{0-4}-alkylene-, -CO-NH-C_{0-4}-alkylene-**Cy^{1}**-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-**Cy^{1}**-C_{0-4}-alkylene-, or -SO_2-NH-C_{0-4}-alkylene-**Cy^{1}**-C_{0-4}-alkylene-; wherein **Cy^{1}** independently represents a C_{3-6}-heterocycloalkylene containing one ring oxygen atom, or one ring nitrogen atom, wherein said ring nitrogen, in case it has a free valency, independently is unsubstituted, or mono-substituted with C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{2-4}-alkylene-O-C_{2-4}-alkylene-O-C_{1-4}-alkylene-, or -CO-C_{1-4}-alkylene-O-C_{2-4}-alkylene-O-C_{1-4}-alkylene-;
  - -C_{2-4}-alkylene-**X^{11}**-C_{1-4}-alkylene-, -CO-O-C_{2-4}-alkylene-**X^{11}**-C_{1-4}-alkylene-, -CO-NH-C_{2-4}-alkylene-**X^{11}**-C_{1-4}-alkylene-, or -SO_2-NH-C_{2-4}-alkylene-**X^{11}**-C_{1-4}-alkylene-; wherein **X^{11}** independently represents oxygen, or a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, or -CO-O-C_{1-4}-alkyl;
  - -CO-C_{1-4}-alkylene-**X^{12}**-C_{1-4}-alkylene-, -SO_2-C_{1-4}-alkylene-**X^{12}**-C_{1-4}-alkylene-, or -CO-C_{1-4}-alkylene-**X^{12}**-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-; wherein **X^{12}** independently represents oxygen, or a

nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, or -CO-O-C_{1-4}-alkyl;

- -C_{2-4}-alkylene-$\mathbf{X^{13}}$-C_{1-4}-alkylene-; wherein $\mathbf{X^{13}}$ represents -NH-CO-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy;
- -C_{1-4}-alkylene-$\mathbf{X^{14}}$-C_{1-4}-alkylene-; wherein $\mathbf{X^{14}}$ represents -CO-NH-;
- -CO-C_{2-6}-alkenylene- or -SO_2-C_{2-6}-alkenylene-; or
- -CO-C_{2-6}-fluoroalkylene-;

- $\mathbf{-L^2}$-hydroxy; wherein $\mathbf{-L^2-}$ represents
  - -CO-C_{1-6}-alkylene- or -SO_2-C_{1-6}-alkylene-; wherein in the above groups said C_{1-6}-alkylene independently is unsubstituted, or mono-substituted with hydroxy, C_1-fluoroalkyl, or -N$\mathbf{R^{N21}R^{N22}}$ wherein independently $\mathbf{R^{N21}}$ is hydrogen or C_{1-4}-alkyl, and $\mathbf{R^{N22}}$ is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{2-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-, wherein in the above groups said C_{2-6}-alkylene independently is unsubstituted, or mono-substituted with hydroxy, C_1-fluoroalkyl, or -N$\mathbf{R^{N23}R^{N24}}$ wherein independently $\mathbf{R^{N23}}$ is hydrogen or C_{1-4}-alkyl, and $\mathbf{R^{N24}}$ is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-;
  - -C_{0-4}-alkylene-$\mathbf{Cy^2}$-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-$\mathbf{Cy^2}$-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-$\mathbf{Cy^2}$-C_{0-4}-alkylene-; wherein $\mathbf{Cy^2}$ independently represents a C_{3-6}-heterocycloalkylene group containing one ring oxygen atom, or one ring nitrogen atom; wherein said ring nitrogen, in case it has a free valency, is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{2-4}-alkylene-(O-C_{2-4}-alkylene)$_p$- or -CO-C_{1-4}-alkylene-(O-C_{2-4}-alkylene)$_p$-; wherein $\mathbf{p}$ independently represents the integer 1 or 2;
  - -C_{2-4}-alkylene-$\mathbf{X^{21}}$-C_{2-4}-alkylene-; wherein $\mathbf{X^{21}}$ represents a nitrogen atom which is unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, or -CO-O-C_{1-4}-alkyl;
  - -CO-C_{1-4}-alkylene-$\mathbf{X^{22}}$-C_{2-4}-alkylene-, -CO-C_{1-4}-alkylene-$\mathbf{X^{22}}$-C_{1-4}-alkylene-C_{3-6}-cycloalkylene-, or -SO_2-C_{1-4}-alkylene-$\mathbf{X^{22}}$-C_{2-4}-alkylene-; wherein $\mathbf{X^{22}}$ represents a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, or -CO-O-C_{1-4}-alkyl;
  - -C_{2-4}-alkylene-$\mathbf{X^{23}}$-C_{1-4}-alkylene-; wherein $\mathbf{X^{23}}$ represents -NH-CO-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy;
  - -C_{1-4}-alkylene-$\mathbf{X^{24}}$-C_{2-4}-alkylene-; wherein $\mathbf{X^{24}}$ represents -CO-NH-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy;
- $\mathbf{-L^3}$-O-$\mathbf{R^{O31}}$ wherein $\mathbf{R^{O31}}$ is -CO-C_{1-4}-alkyl or -CO-C_{2-4}-alkenyl; and

$\mathbf{-L^3-}$ independently represents

- $-C_{2-6}$-alkylene-, $-CO-C_{1-6}$-alkylene- or $-SO_2-C_{1-6}$-alkylene-, $-CO-O-C_{2-6}$-alkylene-, $-CO-NH-C_{2-6}$-alkylene-, or $-SO_2-NH-C_{2-6}$-alkylene-;

- **$-L^4-NR^{N1}R^{N2}$** wherein independently **R^{N1}** is hydrogen or C_{1-4}-alkyl; and **R^{N2}** is hydrogen; C_{1-4}-alkyl; C_{1-3}-fluoroalkyl; C_{3-6}-cycloalkyl; C_{1-3}-alkoxy-C_{2-4}-alkylene; $-CO-C_{1-4}$-alkyl; $-SO_2-C_{1-4}$-alkyl; or $-SO_2-C_1$-fluoroalkyl;
  and
  $-L^4-$ independently represents
  - $-C_{2-6}$-alkylene-, $-CO-C_{1-6}$-alkylene-, $-SO_2-C_{1-6}$-alkylene-, $-CO-O-C_{2-6}$-alkylene-, $-CO-NH-C_{2-6}$-alkylene-, or $-SO_2-NH-C_{2-6}$-alkylene-; or
  - $-C_{0-4}$-alkylene-**Cy^4**-C_{0-4}-alkylene-, $-CO-C_{0-4}$-alkylene-**Cy^4**-C_{0-4}-alkylene-, or $-SO_2-C_{0-4}$-alkylene-**Cy^4**-C_{0-4}-alkylene-; wherein **Cy^4** independently represents a C_{3-6}-heterocycloalkylene group containing one ring oxygen atom;

- **$-L^5-NR^{N3}R^{N4}$** wherein **R^{N3}** is hydrogen, C_{1-4}-alkyl, or C_{1-3}-alkoxy-C_{2-4}-alkylene; and **R^{N4}** is $-CO-O-C_{1-4}$-alkyl; $-CO-NR^{N51}R^{N52}$ wherein **R^{N51}** and **R^{N52}** are independently selected from hydrogen and C_{1-4}-alkyl; or $-SO_2-NR^{N53}R^{N54}$ wherein independently **R^{N53}** is hydrogen or C_{1-4}-alkyl, and **R^{N54}** is hydrogen, C_{1-4}-alkyl, or $-CO-C_{1-4}$-alkyl;
  and **$-L^5-$** independently represents
  - $-C_{2-6}$-alkylene-, $-CO-C_{1-6}$-alkylene- or $-SO_2-C_{1-6}$-alkylene-, $-CO-O-C_{2-6}$-alkylene-, $-CO-NH-C_{2-6}$-alkylene-, or $-SO_2-NH-C_{2-6}$-alkylene-;

- **$-L^6-N(R^{N61})-O-R^{O61}$** wherein **$R^{N61}$** is hydrogen, $-CO-C_{1-4}$-alkyl, or $-CO-O-C_{1-4}$-alkyl; and **R^{O61}** independently represents hydrogen, C_{1-6}-alkyl, or benzyl;
  and **$-L^6-$** independently represents
  - $-C_{2-6}$-alkylene-, $-CO-C_{1-6}$-alkylene-, $-SO_2-C_{1-6}$-alkylene-, $-CO-O-C_{2-6}$-alkylene-, $-CO-NH-C_{2-6}$-alkylene-, or $-SO_2-NH-C_{2-6}$-alkylene-;

- **$-L^7-NR^{N5}R^{N6}$** wherein **R^{N5}** is hydrogen or C_{1-4}-alkyl (especially hydrogen); **R^{N6}** is hydrogen, C_{1-4}-alkyl, $-CO-C_{1-4}$-alkyl, C_{1-3}-fluoroalkyl, or C_{3-6}-cycloalkyl (especially hydrogen); and
  $-L^7-$ independently represents
  - $-CO-$, or $-SO_2-$;

- **$-L^8-SO_2-R^{S81}$** wherein **R^{S81}** independently represents $-C_{1-6}$-alkyl; C_1-fluoroalkyl; hydroxy; **$-NR^{N81}R^{N82}$** wherein independently **R^{N81}** is hydrogen or C_{1-4}-alkyl, and **R^{N82}** is hydrogen, C_{1-4}-alkyl, $-CO-C_{1-6}$-alkyl; and
  $-L^8-$ independently represents
  - $-C_{1-6}$-alkylene-, $-CO-C_{1-6}$-alkylene-, $-SO_2-C_{1-6}$-alkylene-, $-CO-O-C_{2-6}$-alkylene-, $-CO-NH-C_{1-6}$-alkylene-, or $-SO_2-NH-C_{1-6}$-alkylene-;

- **$-L^9-HET^1$**, wherein **HET^1** represents 5- or 6-membered heteroaryl (especially pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, oxazolyl, isoxazolyl; thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl),

wherein said **HET^1** independently is unsubstituted or mono-, or di-substituted wherein the substituents are independently selected from C_{1-4}-alkyl (especially methyl), halogen, cyano, hydroxy, -C_{0-2}-alkylene-**Cy^{91}**-$COOR^{O91}$ wherein R^{O91} is hydrogen or C_{1-4}-alkyl, and wherein **Cy^{91}** represents a C_{3-6}-cycloalkylene group; or -C_{0-2}-alkylene-$COOR^{O92}$ wherein R^{O92} is hydrogen or C_{1-4}-alkyl; and

-L^9- independently represents

- -C_{0-6}-alkylene-, -CO-C_{0-6}-alkylene-, -SO_2-C_{0-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;

- **-L^{10}**-C_{4-6}-heterocyclyl, wherein the C_{4-6}-heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said C_{4-6}-heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:
  - one or two oxo substituents each attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionaly adjacent, a carbamate group, or, in case second ring nitrogen is additionaly adjacent, a urea group); and / or
  - two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom or a ring oxygen atom (thus forming together with the nitrogen a -$C(CH_3)_2$-N- or with the oxygen a -$C(CH_3)_2$-O-group); and / or
  - two oxo substituents at a ring sulfur ring atom (thus forming a -SO_2- group); and / or
  - C_{1-4}-alkyl, C_{1-3}-alkoxy-C_{2-4}-alkyl, C_{2-3}-fluoroalkyl, or -CO-C_{1-4}-alkyl attached to a ring nitrogen atom having a free valency; and

  -L^{10}- independently represents
  - -C_{0-6}-alkylene-, -CO-C_{0-6}-alkylene-, -SO_2-C_{0-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;
- **-L^{11}**-cyano; wherein **-L^{11}-** represents -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene, or -C_{0-6}-alkylene-;
- **-L^{12}**-NO_2; wherein **-L^{12}-** represents -C_{2-6}-alkylene-; or
- **-L^{13}**-C_{1-4}-alkyl; wherein **-L^{13}-** represents -CO-, or -CO-O-.

23) Another embodiment relates to compounds according to any one of embodiments 1) to 21), wherein the group **-L-R^6** represents

- hydrogen;
- **-L^1**-CO-**R^{C11}** wherein **R^{C11}** independently represents hydroxy; -O-benzyl; -O-C_{1-6}-alkyl; C_1-fluoroalkyl; or -**N$R^{N11}R^{N12}$**; wherein independently **R^{N11}** is hydrogen or C_{1-4}-alkyl, and **R^{N12}** is hydrogen, C_{1-4}-alkyl, -SO_2-C_{1-6}-alkyl, or -O-**R^{O11}**, wherein **R^{O11}** independently represents hydrogen, C_{1-6}-alkyl, or benzyl; and

  -L^1- independently represents
  - -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;

- $-C_{1-6}$-alkylene-, $-CO-C_{1-6}$-alkylene-, or $-SO_2-C_{1-6}$-alkylene-; wherein in the above groups said C_{1-6}-alkylene independently is mono-substituted with hydroxy, C_{1-3}-alkoxy, $-O-CO-C_{1-4}$-alkyl, or $-NR^{N13}R^{N14}$; wherein independently R^{N13} is hydrogen or C_{1-4}-alkyl, and R^{N14} is hydrogen, C_{1-4}-alkyl or $-CO-O-C_{1-4}$-alkyl;
- $-C_{2-6}$-alkylene-, $-CO-C_{2-6}$-alkylene-, or $-SO_2-C_{2-6}$-alkylene-; wherein in the above groups said C_{2-6}-alkylene independently is di-substituted wherein the substituents are independently selected from hydroxy and $-NR^{N15}R^{N16}$; wherein independently R^{N15} is hydrogen or C_{1-4}-alkyl, and R^{N16} is hydrogen, C_{1-4}-alkyl or $-CO-O-C_{1-4}$-alkyl;
- $-C_{0-4}$-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, $-CO-C_{0-4}$-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, $-SO_2-C_{0-4}$-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, $-CO-NH-C_{0-4}$-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, or $-CO-O-C_{0-4}$-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-;
- $-C_{0-4}$-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, $-CO-C_{0-4}$-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, $-CO-O-C_{0-4}$-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, $-CO-NH-C_{0-4}$-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, $-SO_2-C_{0-4}$-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, or $-SO_2-NH-C_{0-4}$-alkylene-**Cy**^{1}-C_{0-4}-alkylene-; wherein **Cy**^{1} independently represents a C_{3-6}-heterocycloalkylene containing one ring oxygen atom, or one ring nitrogen atom, wherein said ring nitrogen, in case it has a free valency, independently is unsubstituted, or mono-substituted with C_{1-4}-alkyl or $-CO-O-C_{1-4}$-alkyl;
- $-CO-C_{1-4}$-alkylene-**X**^{12}-C_{1-4}-alkylene-, $-SO_2-C_{1-4}$-alkylene-**X**^{12}-C_{1-4}-alkylene-, or $-CO-C_{1-4}$-alkylene-**X**^{12}-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-; wherein **X**^{12} independently represents oxygen, or a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, $-CO-O-C_{1-4}$-alkyl, or C_{1-3}-alkoxy-C_{2-4}-alkyl;
- $-C_{2-4}$-alkylene-**X**^{13}-C_{1-4}-alkylene-; wherein **X**^{13} represents -NH-CO-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy;
- $-CO-C_{2-6}$-alkenylene- or $-SO_2-C_{2-6}$-alkenylene-; or
- $-CO-C_{2-6}$-fluoroalkylene-;

- -**L**^{2}-hydroxy; wherein -**L**^{2}- represents
  - $-CO-C_{1-6}$-alkylene- or $-SO_2-C_{1-6}$-alkylene-; wherein in the above groups said C_{1-6}-alkylene independently is unsubstituted, or mono-substituted with hydroxy, C_1-fluoroalkyl, or $-NR^{N21}R^{N22}$ wherein independently R^{N21} is hydrogen or C_{1-4}-alkyl, and R^{N22} is hydrogen, C_{1-4}-alkyl or $-CO-O-C_{1-4}$-alkyl;
  - $-C_{2-6}$-alkylene-, $-CO-O-C_{2-6}$-alkylene-, $-CO-NH-C_{2-6}$-alkylene-, or $-SO_2-NH-C_{2-6}$-alkylene-, wherein in the above groups said C_{2-6}-alkylene independently is unsubstituted, or mono-substituted with hydroxy, C_1-fluoroalkyl, or $-NR^{N23}R^{N24}$ wherein independently R^{N23} is hydrogen or C_{1-4}-alkyl, and R^{N24} is hydrogen, C_{1-4}-alkyl or $-CO-O-C_{1-4}$-alkyl;
  - $-C_{0-4}$-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, $-CO-C_{0-4}$-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, or $-SO_2-C_{0-4}$-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-;

- -C_{0-4}-alkylene-**Cy²**-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-**Cy²**-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-**Cy²**-C_{0-4}-alkylene-; wherein **Cy²** independently represents a C_{3-6}-heterocycloalkylene group containing one ring oxygen atom, or one ring nitrogen atom; wherein said ring nitrogen, in case it has a free valency, is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
- -CO-C_{1-4}-alkylene-**X²²**-C_{2-4}-alkylene-, -CO-C_{1-4}-alkylene-**X²²**-C_{1-4}-alkylene-C_{3-6}-cycloalkylene-, or -SO_2-C_{1-4}-alkylene-**X²²**-C_{2-4}-alkylene-; wherein **X²²** represents a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, or -CO-O-C_{1-4}-alkyl; or
- -C_{2-4}-alkylene-**X²³**-C_{1-4}-alkylene-; wherein **X²³** represents -NH-CO-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy;

- **-L⁴-NR^N1R^N2** wherein independently **R^N1** is hydrogen or C_{1-4}-alkyl; and **R^N2** is hydrogen; C_{1-4}-alkyl; C_{1-3}-fluoroalkyl; C_{3-6}-cycloalkyl; C_{1-3}-alkoxy-C_{2-4}-alkylene; -CO-C_{1-4}-alkyl; -SO_2-C_{1-4}-alkyl; or -SO_2-C_1-fluoroalkyl; and

  -L⁴- independently represents
  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-; or
  - -C_{0-4}-alkylene-**Cy⁴**-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-**Cy⁴**-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-**Cy⁴**-C_{0-4}-alkylene-; wherein **Cy⁴** independently represents a C_{3-6}-heterocycloalkylene group containing one ring oxygen atom;
- **-L⁵-NR^N3R^N4** wherein **R^N3** is hydrogen, C_{1-4}-alkyl, or C_{1-3}-alkoxy-C_{2-4}-alkylene; and **R^N4** is -CO-O-C_{1-4}-alkyl; -CO-N**R^N51R^N52** wherein **R^N51** and **R^N52** are independently selected from hydrogen and C_{1-4}-alkyl; or -SO_2-**NR^N53R^N54** wherein independently **R^N53** is hydrogen or C_{1-4}-alkyl, and **R^N54** is hydrogen, C_{1-4}-alkyl, or -CO-C_{1-4}-alkyl;

  and **-L⁵-** independently represents
  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene- or -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-;
- **-L⁶-N(R^N61)-O-R^O61** wherein **R^N61** is hydrogen, -CO-C_{1-4}-alkyl, or -CO-O-C_{1-4}-alkyl; and **R^O61** independently represents hydrogen, C_{1-6}-alkyl, or benzyl;

  and **-L⁶-** independently represents
  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-;
- **-L⁷-NR^N5R^N6** wherein **R^N5** is hydrogen or C_{1-4}-alkyl (especially hydrogen); **R^N6** is hydrogen, C_{1-4}-alkyl, -CO-C_{1-4}-alkyl, C_{1-3}-fluoroalkyl, or C_{3-6}-cycloalkyl (especially hydrogen); and

  -L⁷- independently represents
  - -CO-, or -SO_2-;
- **-L⁸-SO_2-R^S81** wherein **R^S81** independently represents -C_{1-6}-alkyl; C_1-fluoroalkyl; hydroxy; -**NR^N81R^N82** wherein independently **R^N81** is hydrogen or C_{1-4}-alkyl, and **R^N82** is hydrogen, C_{1-4}-alkyl, -CO-C_{1-6}-alkyl; and

-L^8- independently represents

- -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;

- -L^9-HET^1, wherein HET^1 represents 5- or 6-membered heteroaryl (especially pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, oxazolyl, isoxazolyl; thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl),

  wherein said HET^1 independently is unsubstituted or mono-, or di-substituted wherein the substituents are independently selected from C_{1-4}-alkyl (especially methyl); halogen; cyano; hydroxy; hydroxymethyl; -C_{0-2}-alkylene-Cy^{91}-$COOR^{O91}$ wherein R^{O91} is hydrogen or C_{1-4}-alkyl, and wherein Cy^{91} represents a C_{3-6}-cycloalkylene group; or -C_{0-2}-alkylene-$COOR^{O92}$ wherein R^{O92} is hydrogen or C_{1-4}-alkyl; and

  -L^9- independently represents

  - -C_{0-6}-alkylene-, -CO-C_{0-6}-alkylene-, -SO_2-C_{0-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;

- -L^{10}-C_{4-6}-heterocyclyl, wherein the C_{4-6}-heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said C_{4-6}-heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:

  - one or two oxo substituents each attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionaly adjacent, a carbamate group, or, in case second ring nitrogen is additionaly adjacent, a urea group); and / or
  - two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom or a ring oxygen atom (thus forming together with the nitrogen a -$C(CH_3)_2$-N- or with the oxygen a -$C(CH_3)_2$-O-group); and / or
  - two oxo substituents at a ring sulfur ring atom (thus forming a -SO_2- group); and / or
  - C_{1-4}-alkyl, C_{1-3}-alkoxy-C_{2-4}-alkyl, C_{2-3}-fluoroalkyl, or -CO-C_{1-4}-alkyl attached to a ring nitrogen atom having a free valency; and

  -L^{10}- independently represents

  - -C_{0-6}-alkylene-, or -CO-C_{0-6}-alkylene-;

- -L^{11}-cyano; wherein -L^{11}- represents -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene, or -C_{0-6}-alkylene-;or

- -L^{13}-C_{1-4}-alkyl; wherein -L^{13}- represents -CO-, -CO-O, or -SO_2.

24) Another embodiment relates to compounds according to any one of embodiments 1) to 21), wherein the group -L-R^6 represents

- hydrogen;

- -L^1-CO-R^{C11} wherein R^{C11} independently represents hydroxy; -O-C_{1-6}-alkyl; C_1-fluoroalkyl; or -$NR^{N11}R^{N12}$; wherein independently R^{N11} is hydrogen, and R^{N12} is -SO_2-C_{1-6}-alkyl; and

-L^1- independently represents

- -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;
- -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, or -SO_2-C_{1-6}-alkylene-; wherein in the above groups said C_{1-6}-alkylene independently is mono-substituted with hydroxy;
- -C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, or -CO-O-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-;
- -C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, -CO-O-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-; wherein **Cy**^{1} independently represents a C_{3-6}-heterocycloalkylene containing one ring oxygen atom;
- -CO-C_{1-4}-alkylene-**X**^{12}-C_{1-4}-alkylene-; wherein **X**^{12} independently represents oxygen, or a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl or C_{3-6}-cycloalkyl;
- -CO-C_{2-6}-alkenylene- or -SO_2-C_{2-6}-alkenylene-; or
- -CO-C_{2-6}-fluoroalkylene-;

- -L^2-hydroxy; wherein -L^2- represents
  - -CO-C_{1-6}-alkylene-; wherein the C_{1-6}-alkylene is unsubstituted, or mono-substituted with C_1-fluoroalkyl;
  - -C_{2-6}-alkylene-, wherein the C_{2-6}-alkylene is unsubstituted, or mono-substituted with hydroxy;
  - -C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, or -CO-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-;
  - -C_{0-4}-alkylene-**Cy**^{2}-C_{0-4}-alkylene-, or -CO-C_{0-4}-alkylene-**Cy**^{2}-C_{0-4}-alkylene-; wherein **Cy**^{2} independently represents a C_{3-6}-heterocycloalkylene group containing one ring oxygen atom;
  - -CO-C_{1-4}-alkylene-**X**^{22}-C_{2-4}-alkylene-; wherein **X**^{22} represents a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, or C_{3-6}-cycloalkyl; or
  - -C_{2-4}-alkylene-**X**^{23}-C_{1-4}-alkylene-; wherein **X**^{23} represents -NH-CO-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy;
- -L^4-N**R**^{N1}**R**^{N2} wherein independently **R**^{N1} is hydrogen or C_{1-4}-alkyl; and **R**^{N2} is hydrogen; C_{1-4}-alkyl; C_{1-3}-fluoroalkyl; C_{3-6}-cycloalkyl; C_{1-3}-alkoxy-C_{2-4}-alkylene; -CO-C_{1-4}-alkyl; -SO_2-C_{1-4}-alkyl; or -SO_2-C_1-fluoroalkyl; and

  -L^4- independently represents

- -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -L^5-**NR**^{N3}**R**^{N4} wherein **R**^{N3} is hydrogen or C_{1-4}-alkyl; and **R**^{N4} is -SO_2-**NR**^{N53}**R**^{N54} wherein independently **R**^{N53} is hydrogen or C_{1-4}-alkyl, and **R**^{N54} is hydrogen or C_{1-4}-alkyl;

  and -L^5- independently represents

  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene- or -SO_2-C_{1-6}-alkylene-;
- -L^6-N(**R**^{N61})-O-**R**^{O61} wherein **R**^{N61} is -CO-C_{1-4}-alkyl; and **R**^{O61} represents hydrogen;

  and -L^6- independently represents

- $-C_{2-6}$-alkylene-, $-CO-C_{1-6}$-alkylene-, $-SO_2-C_{1-6}$-alkylene-;

- **$-L^7-NR^{N5}R^{N6}$** wherein **R^{N5}** is hydrogen or C_{1-4}-alkyl (especially hydrogen); **R^{N6}** is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl; and

  $-L^7-$ independently represents

  - $-CO-$, or $-SO_2-$;

- **$-L^8-SO_2-R^{S71}$** wherein **R^{S81}** independently represents $-C_{1-6}$-alkyl; C_1-fluoroalkyl; hydroxy; **$-NR^{N81}R^{N82}$** wherein independently **R^{N81}** is hydrogen or C_{1-4}-alkyl, and **R^{N82}** is hydrogen, C_{1-4}-alkyl, $-CO-C_{1-6}$-alkyl; and

  $-L^8-$ independently represents

  - $-C_{1-6}$-alkylene-, $-CO-C_{1-6}$-alkylene-, or $-SO_2-C_{1-6}$-alkylene-;

- **$-L^9$-HET^1**, wherein **HET^1** represents 5- or 6-membered heteroaryl (especially pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, oxazolyl, isoxazolyl; thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl),

  wherein said **HET^1** independently is unsubstituted or mono-, or di-substituted wherein the substituents are independently selected from C_{1-4}-alkyl (especially methyl); halogen; cyano; hydroxy; hydroxymethyl; $-C_{0-2}$-alkylene-**Cy^{91}**-$COOR^{O91}$ wherein R^{O91} is hydrogen or C_{1-4}-alkyl, and wherein **Cy^{91}** represents a C_{3-6}-cycloalkylene group; or $-C_{0-2}$-alkylene-$COOR^{O92}$ wherein R^{O92} is hydrogen or C_{1-4}-alkyl; and

  $-L^9-$ independently represents

  - $-C_{0-6}$-alkylene-, $-CO-C_{0-6}$-alkylene-, $-SO_2-C_{0-6}$-alkylene-, or $-CO-NH-C_{1-6}$-alkylene-;

- **$-L^{10}-C_{4-6}$**-heterocyclyl, wherein the C_{4-6}-heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said C_{4-6}-heterocyclyl independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from:

  - one or two oxo substituents each attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionaly adjacent, a carbamate group, or, in case second ring nitrogen is additionaly adjacent, a urea group); and / or
  - two oxo substituents at a ring sulfur ring atom (thus forming a $-SO_2-$ group); and / or
  - C_{1-4}-alkyl attached to a ring nitrogen atom having a free valency; and

  $-L^{10}-$ independently represents

  - $-C_{0-6}$-alkylene-, or $-CO-C_{0-6}$-alkylene-;

- **$-L^{11}$**-cyano; wherein **$-L^{11}-$** represents $-C_{0-6}$-alkylene-; or

- **$-L^{13}-C_{1-4}$**-alkyl; wherein **$-L^{13}-$** represents -CO-.

25) Another embodiment relates to compounds according to any one of embodiments 1) to 21), wherein the group **-L-R^6** represents

- **$-L^1$**-COOH; wherein

  $-L^1-$ represents

- -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;
- -CO-C_{1-6}-alkylene-; wherein said C_{1-6}-alkylene is mono-substituted with hydroxy;
- -C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, or -CO-O-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-;
- -CO-C_{0-4}-alkylene-**Cy^1**-C_{0-4}-alkylene-; wherein **Cy^1** independently represents a C_{3-6}-heterocycloalkylene containing one ring oxygen atom;
- -CO-C_{1-4}-alkylene-**X^{12}**-C_{1-4}-alkylene-; wherein **X^{12}** independently represents a nitrogen atom which is unsubstituted, or mono-substituted with C_{1-4}-alkyl;
- -CO-C_{2-6}-alkenylene- or -SO_2-C_{2-6}-alkenylene-; or
- -CO-C_{2-6}-fluoroalkylene-;

- **-L^2-**hydroxy; wherein **-L^2-** represents
  - -C_{2-6}-alkylene-, wherein the C_{2-6}-alkylene is unsubstituted, or mono-substituted with hydroxy; or
  - -CO-C_{1-4}-alkylene-**X^{22}**-C_{2-4}-alkylene-; wherein **X^{22}** represents a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl or C_{3-6}-cycloalkyl;
- **-L^7-N$R^{N5}R^{N6}$** wherein both **R^{N5}** is hydrogen; **R^{N6}** is hydrogen, or C_{3-6}-cycloalkyl; and

  -L^7- independently represents
  - -CO-, or -SO_2-; or
- **-L^9-HET^1**, wherein **HET^1** represents 5- or 6-membered heteroaryl selected from pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, oxazolyl, isoxazolyl; thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl [especially pyrrolyl, triazolyl, tetrazolyl, furanyl, oxazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl],

  wherein said **HET^1** independently is unsubstituted or mono-, or di-substituted wherein the substituents are independently selected from C_{1-4}-alkyl (especially methyl); halogen; cyano; hydroxy; hydroxymethyl; -C_{0-2}-alkylene-**Cy^{91}**-$COOR^{O91}$ wherein R^{O91} is hydrogen or C_{1-4}-alkyl, and wherein **CY^{91}** represents a C_{3-6}-cycloalkylene group; or -C_{0-2}-alkylene-$COOR^{O92}$ wherein R^{O92} is hydrogen or C_{1-4}-alkyl; and

  -L^9- independently represents
  - -C_{0-6}-alkylene-, -CO-C_{0-6}-alkylene-.

26) Another embodiment relates to compounds according to any one of embodiments 1) to 21), wherein the group **-L-R^6** represents

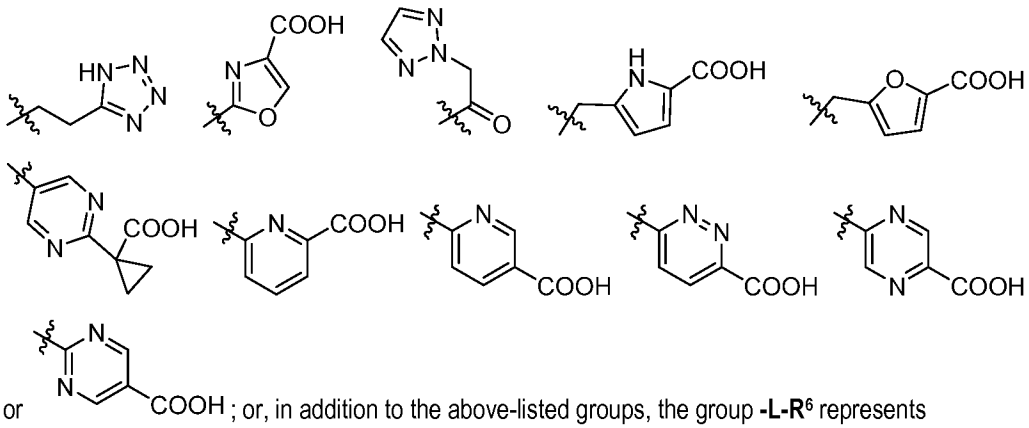
- **-L^1-**COOH; and

  -L^1- represents
  - -CH_2-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-$C(CH_3)_2$-CH_2-, *-CH_2-CH_2-$C(CH_3)_2$-, *-CH_2-CH_2-CH_2-$C(CH_3)_2$-, *-CO-CH_2-CH_2-, *-CO-$CH(CH_3)$-CH_2-, *-CO-CH_2-$C(OH)(CH_3)$-, *-CO-CH_2-CH_2-CH_2-, *-CO-CH_2-$C(CH_3)_2$-, *-CO-$C(CH_3)_2$-CH_2-, *-SO_2-CH_2-, *-SO_2-CH_2-CH_2-, *-SO_2-CH_2-CH_2-CH_2-, *-SO_2-CH_2-$C(CH_3)_2$-, *-CO-O-

CH_2-, *-CO-O-CH(CH_3)-, *-CO-O-CH_2-C(CH_3)$_2$-, *-CO-NH-C(CH_3)$_2$-CH_2-, *-CO-NH-CH_2-C(CH_3)$_2$-, *-CO-NH-CH_2-CH_2-C(CH_3)$_2$-, *-SO_2-NH-CH_2-; *-CH_2-CH_2-CH_2-cyclopropane-1,1-diyl-, *-CO-cyclopropane-1,2-yl-, *-CO-CH_2-cyclopropane-1,1-diyl-, *-CO-CH_2-cyclobutane-1,1-diyl-, *-SO_2-cyclopropane-1,1-diyl-CH_2-, *-CO-O-cyclopropane-1,1-diyl-, *-CO-O-CH_2-cyclopropane-1,1-diyl-;

- *-CO-CH_2-(tetrahydro-2H-pyran-4,4-diyl)-;
- *-CO-CH_2-N(n-butyl)-CH_2-;
- *-SO_2-CH=CH-, *-CO-C(CH_2)-CH_2-; or
- *-CO-CF_2-CH_2-;

- **-L^2**-hydroxy; wherein **-L^2-** represents
  - *-CH_2-CH(OH)-CH_2-; or
  - *-CO-CH_2-NH-CH_2-CH_2-, *-CO-CH_2-NH-CH(CH_3)-CH_2-, *-CO-CH_2-NH-CH_2-CH(CH_3)-;
- **-L^7**-NH_2; wherein

  -L^7- represents
  - -SO_2-; or
- **-L^9-HET^1**, wherein **-L^9-HET^1** represents
  - 

  or ; or, in addition to the above-listed groups, the group **-L-R^6** represents
- **-L^7**-NH-cyclopropyl; wherein

  -L^7- represents
  - -CO-;

wherein in the above groups the asterisks indicate the bond which is connected to the rest of the molecule.

27) The invention, thus, relates to compounds of the Formula (I) as defined in embodiment 1), or to such compounds further limited by the characteristics of any one of embodiments 2) to 26), under consideration of their respective dependencies; to pharmaceutically acceptable salts thereof; and to the use of such compounds as further described herein below. For avoidance of any doubt, especially the following embodiments relating to the compounds of Formula (I) are thus possible and intended and herewith specifically disclosed in individualized form:

1, 2+1, 5+1, 5+2+1, 6+1, 6+2+1, 6+5+1, 6+5+2+1, 8+1, 8+2+1, 8+5+1, 8+5+2+1, 9+1, 11+1, 12+1, 12+2+1, 12+5+1, 12+5+2+1, 12+6+1, 12+6+2+1, 12+6+5+1, 12+6+5+2+1, 12+8+1, 12+8+2+1, 12+8+5+1,

12+8+5+2+1, 12+9+1, 12+11+1, 14+1, 14+12+1, 14+12+2+1, 14+12+5+1, 14+12+5+2+1, 14+12+6+1, 14+12+6+2+1, 14+12+6+5+1, 14+12+6+5+2+1, 14+12+8+1, 14+12+8+2+1, 14+12+8+5+1, 14+12+8+5+2+1, 14+12+9+1, 14+12+11+1, 18+1, 18+12+1, 18+12+2+1, 18+12+5+1, 18+12+5+2+1, 18+12+6+1, 18+12+6+2+1, 18+12+6+5+1, 18+12+6+5+2+1, 18+12+8+1, 18+12+8+2+1, 18+12+8+5+1, 18+12+8+5+2+1, 18+12+9+1, 18+12+11+1, 18+14+1, 18+14+12+1, 18+14+12+2+1, 18+14+12+5+1, 18+14+12+5+2+1, 18+14+12+6+1, 18+14+12+6+2+1, 18+14+12+6+5+1, 18+14+12+6+5+2+1, 18+14+12+8+1, 18+14+12+8+2+1, 18+14+12+8+5+1, 18+14+12+8+5+2+1, 18+14+12+9+1, 18+14+12+11+1, 19+1, 19+2+1, 19+5+1, 19+5+2+1, 19+6+1, 19+6+2+1, 19+6+5+1, 19+6+5+2+1, 19+8+1, 19+8+2+1, 19+8+5+1, 19+8+5+2+1, 19+9+1, 19+11+1, 21+1, 21+2+1, 21+5+1, 21+5+2+1, 21+6+1, 21+6+2+1, 21+6+5+1, 21+6+5+2+1, 21+8+1, 21+8+2+1, 21+8+5+1, 21+8+5+2+1, 21+9+1, 21+11+1, 21+12+1, 21+12+2+1, 21+12+5+1, 21+12+5+2+1, 21+12+6+1, 21+12+6+2+1, 21+12+6+5+1, 21+12+6+5+2+1, 21+12+8+1, 21+12+8+2+1, 21+12+8+5+1, 21+12+8+5+2+1, 21+12+9+1, 21+12+11+1, 21+14+1, 21+14+12+1, 21+14+12+2+1, 21+14+12+5+1, 21+14+12+5+2+1, 21+14+12+6+1, 21+14+12+6+2+1, 21+14+12+6+5+1, 21+14+12+6+5+2+1, 21+14+12+8+1, 21+14+12+8+2+1, 21+14+12+8+5+1, 21+14+12+8+5+2+1, 21+14+12+9+1, 21+14+12+11+1, 21+18+1, 21+18+12+1, 21+18+12+2+1, 21+18+12+5+1, 21+18+12+5+2+1, 21+18+12+6+1, 21+18+12+6+2+1, 21+18+12+6+5+1, 21+18+12+6+5+2+1, 21+18+12+8+1, 21+18+12+8+2+1, 21+18+12+8+5+1, 21+18+12+8+5+2+1, 21+18+12+9+1, 21+18+12+11+1, 21+18+14+1, 21+18+14+12+1, 21+18+14+12+2+1, 21+18+14+12+5+1, 21+18+14+12+5+2+1, 21+18+14+12+6+1, 21+18+14+12+6+2+1, 21+18+14+12+6+5+1, 21+18+14+12+6+5+2+1, 21+18+14+12+8+1, 21+18+14+12+8+2+1, 21+18+14+12+8+5+1, 21+18+14+12+8+5+2+1, 21+18+14+12+9+1, 21+18+14+12+11+1, 21+19+1, 21+19+2+1, 21+19+5+1, 21+19+5+2+1, 21+19+6+1, 21+19+6+2+1, 21+19+6+5+1, 21+19+6+5+2+1, 21+19+8+1, 21+19+8+2+1, 21+19+8+5+1, 21+19+8+5+2+1, 21+19+9+1, 21+19+11+1, 25+1, 25+2+1, 25+5+1, 25+5+2+1, 25+6+1, 25+6+2+1, 25+6+5+1, 25+6+5+2+1, 25+8+1, 25+8+2+1, 25+8+5+1, 25+8+5+2+1, 25+9+1, 25+11+1, 25+12+1, 25+12+2+1, 25+12+5+1, 25+12+5+2+1, 25+12+6+1, 25+12+6+2+1, 25+12+6+5+1, 25+12+6+5+2+1, 25+12+8+1, 25+12+8+2+1, 25+12+8+5+1, 25+12+8+5+2+1, 25+12+9+1, 25+12+11+1, 25+14+1, 25+14+12+1, 25+14+12+2+1, 25+14+12+5+1, 25+14+12+5+2+1, 25+14+12+6+1, 25+14+12+6+2+1, 25+14+12+6+5+1, 25+14+12+6+5+2+1, 25+14+12+8+1, 25+14+12+8+2+1, 25+14+12+8+5+1, 25+14+12+8+5+2+1, 25+14+12+9+1, 25+14+12+11+1, 25+18+1, 25+18+12+1, 25+18+12+2+1, 25+18+12+5+1, 25+18+12+5+2+1, 25+18+12+6+1, 25+18+12+6+2+1, 25+18+12+6+5+1, 25+18+12+6+5+2+1, 25+18+12+8+1, 25+18+12+8+2+1, 25+18+12+8+5+1, 25+18+12+8+5+2+1, 25+18+12+9+1, 25+18+12+11+1, 25+18+14+1, 25+18+14+12+1, 25+18+14+12+2+1, 25+18+14+12+5+1, 25+18+14+12+5+2+1, 25+18+14+12+6+1, 25+18+14+12+6+2+1, 25+18+14+12+6+5+1, 25+18+14+12+6+5+2+1, 25+18+14+12+8+1, 25+18+14+12+8+2+1, 25+18+14+12+8+5+1, 25+18+14+12+8+5+2+1, 25+18+14+12+9+1, 25+18+14+12+11+1, 25+19+1, 25+19+2+1, 25+19+5+1, 25+19+5+2+1, 25+19+6+1, 25+19+6+2+1, 25+19+6+5+1, 25+19+6+5+2+1, 25+19+8+1, 25+19+8+2+1, 25+19+8+5+1, 25+19+8+5+2+1, 25+19+9+1, 25+19+11+1, 25+21+1, 25+21+2+1, 25+21+5+1, 25+21+5+2+1, 25+21+6+1, 25+21+6+2+1, 25+21+6+5+1, 25+21+6+5+2+1, 25+21+8+1,

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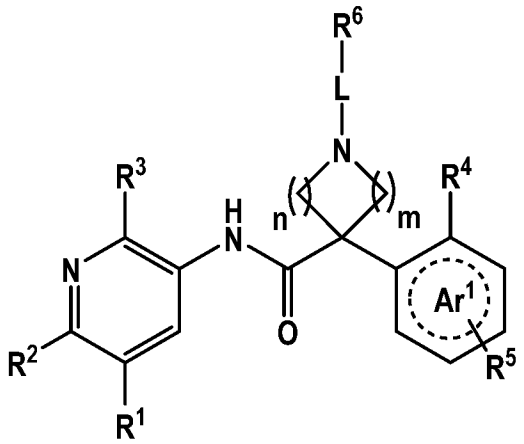
26+21+14+12+11+1, 26+21+18+1, 26+21+18+12+1, 26+21+18+12+2+1, 26+21+18+12+5+1, 26+21+18+12+5+2+1, 26+21+18+12+6+1, 26+21+18+12+6+2+1, 26+21+18+12+6+5+1, 26+21+18+12+6+5+2+1, 26+21+18+12+8+1, 26+21+18+12+8+2+1, 26+21+18+12+8+5+1, 26+21+18+12+8+5+2+1, 26+21+18+12+9+1, 26+21+18+12+11+1, 26+21+18+14+1, 26+21+18+14+12+1, 26+21+18+14+12+2+1, 26+21+18+14+12+5+1, 26+21+18+14+12+5+2+1, 26+21+18+14+12+6+1, 26+21+18+14+12+6+2+1, 26+21+18+14+12+6+5+1, 26+21+18+14+12+6+5+2+1, 26+21+18+14+12+8+1, 26+21+18+14+12+8+2+1, 26+21+18+14+12+8+5+1, 26+21+18+14+12+8+5+2+1, 26+21+18+14+12+9+1, 26+21+18+14+12+11+1, 26+21+19+1, 26+21+19+2+1, 26+21+19+5+1, 26+21+19+5+2+1, 26+21+19+6+1, 26+21+19+6+2+1, 26+21+19+6+5+1, 26+21+19+6+5+2+1, 26+21+19+8+1, 26+21+19+8+2+1, 26+21+19+8+5+1, 26+21+19+8+5+2+1, 26+21+19+9+1, 26+21+19+11+1.

In the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the dependency from another embodiment. The different individualized embodiments are separated by commas. In other words, "26+21+11+1" for example refers to embodiment 26) depending on embodiment 21), depending on embodiment 11), depending on embodiment 1), i.e. embodiment "26+21+11+1" corresponds to the compounds of Formula (I) as defined in embodiment 1), further limited by all the structural features of the embodiments 11), 21), and 26).

28) A second aspect of the invention relates to compounds of the Formula (I) which are compounds of Formula (II),



Formula (II)

wherein **R**^{1}, **R**^{2}, **R**^{3}, **Ar**^{1}, **R**^{4}, **R**^{5}, **m**, **n**, and the group **-L-R**^{6} are as defined in embodiment 1);

wherein the characteristics disclosed in embodiments 2) to 27) are intended to apply *mutatis mutandis* also to the compounds formula (II) according to embodiment 28); wherein in particular the following embodiments are thus possible and intended and herewith specifically disclosed in individualized form:

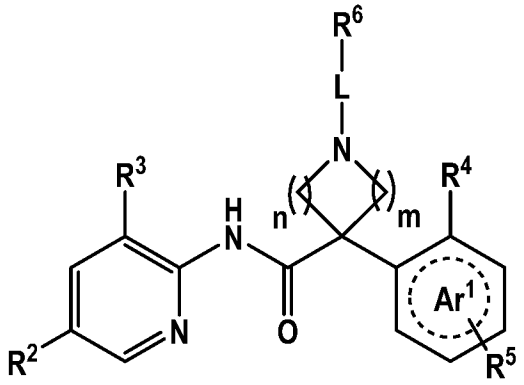
28+2, 28+5+2, 28+5, 28+6+2, 28+6+5+2, 28+6+5, 28+6, 28+8+2, 28+8+5+2, 28+8+5, 28+8, 28+12+2, 28+12+5+2, 28+12+5, 28+12+6+2, 28+12+6+5+2, 28+12+6+5, 28+12+6, 28+12+8+2, 28+12+8+5+2,

28+12+8+5, 28+12+8, 28+12, 28+14+12+2, 28+14+12+5+2, 28+14+12+5, 28+14+12+6+2, 28+14+12+6+5+2, 28+14+12+6+5, 28+14+12+6, 28+14+12+8+2, 28+14+12+8+5+2, 28+14+12+8+5, 28+14+12+8, 28+14+12, 28+14, 28+18+12+2, 28+18+12+5+2, 28+18+12+5, 28+18+12+6+2, 28+18+12+6+5+2, 28+18+12+6+5, 28+18+12+6, 28+18+12+8+2, 28+18+12+8+5+2, 28+18+12+8+5, 28+18+12+8, 28+18+12, 28+18+14+12+2, 28+18+14+12+5+2, 28+18+14+12+5, 28+18+14+12+6+2, 28+18+14+12+6+5+2, 28+18+14+12+6+5, 28+18+14+12+6, 28+18+14+12+8+2, 28+18+14+12+8+5+2, 28+18+14+12+8+5, 28+18+14+12+8, 28+18+14+12, 28+18+14, 28+18, 28+21+2, 28+21+5+2, 28+21+5, 28+21+6+2, 28+21+6+5+2, 28+21+6+5, 28+21+6, 28+21+8+2, 28+21+8+5+2, 28+21+8+5, 28+21+8, 28+21+12+2, 28+21+12+5+2, 28+21+12+5, 28+21+12+6+2, 28+21+12+6+5+2, 28+21+12+6+5, 28+21+12+6, 28+21+12+8+2, 28+21+12+8+5+2, 28+21+12+8+5, 28+21+12+8, 28+21+12, 28+21+14+12+2, 28+21+14+12+5+2, 28+21+14+12+5, 28+21+14+12+6+2, 28+21+14+12+6+5+2, 28+21+14+12+6+5, 28+21+14+12+6, 28+21+14+12+8+2, 28+21+14+12+8+5+2, 28+21+14+12+8+5, 28+21+14+12+8, 28+21+14+12, 28+21+14, 28+21+18+12+2, 28+21+18+12+5+2, 28+21+18+12+5, 28+21+18+12+6+2, 28+21+18+12+6+5+2, 28+21+18+12+6+5, 28+21+18+12+6, 28+21+18+12+8+2, 28+21+18+12+8+5+2, 28+21+18+12+8+5, 28+21+18+12+8, 28+21+18+12, 28+21+18+14+12+2, 28+21+18+14+12+5+2, 28+21+18+14+12+5, 28+21+18+14+12+6+2, 28+21+18+14+12+6+5+2, 28+21+18+14+12+6+5, 28+21+18+14+12+6, 28+21+18+14+12+8+2, 28+21+18+14+12+8+5+2, 28+21+18+14+12+8+5, 28+21+18+14+12+8, 28+21+18+14+12, 28+21+18+14, 28+21+18, 28+21, 28+22+2, 28+22+5+2, 28+22+5, 28+22+6+2, 28+22+6+5+2, 28+22+6+5, 28+22+6, 28+22+8+2, 28+22+8+5+2, 28+22+8+5, 28+22+8, 28+22+12+2, 28+22+12+5+2, 28+22+12+5, 28+22+12+6+2, 28+22+12+6+5+2, 28+22+12+6+5, 28+22+12+6, 28+22+12+8+2, 28+22+12+8+5+2, 28+22+12+8+5, 28+22+12+8, 28+22+12, 28+22+14+12+2, 28+22+14+12+5+2, 28+22+14+12+5, 28+22+14+12+6+2, 28+22+14+12+6+5+2, 28+22+14+12+6+5, 28+22+14+12+6, 28+22+14+12+8+2, 28+22+14+12+8+5+2, 28+22+14+12+8+5, 28+22+14+12+8, 28+22+14+12, 28+22+14, 28+22+18+12+2, 28+22+18+12+5+2, 28+22+18+12+5, 28+22+18+12+6+2, 28+22+18+12+6+5+2, 28+22+18+12+6+5, 28+22+18+12+6, 28+22+18+12+8+2, 28+22+18+12+8+5+2, 28+22+18+12+8+5, 28+22+18+12+8, 28+22+18+12, 28+22+18+14+12+2, 28+22+18+14+12+5+2, 28+22+18+14+12+5, 28+22+18+14+12+6+2, 28+22+18+14+12+6+5+2, 28+22+18+14+12+6+5, 28+22+18+14+12+6, 28+22+18+14+12+8+2, 28+22+18+14+12+8+5+2, 28+22+18+14+12+8+5, 28+22+18+14+12+8, 28+22+18+14+12, 28+22+18+14, 28+22+18, 28+22+21+2, 28+22+21+5+2, 28+22+21+5, 28+22+21+6+2, 28+22+21+6+5+2, 28+22+21+6+5, 28+22+21+6, 28+22+21+8+2, 28+22+21+8+5+2, 28+22+21+8+5, 28+22+21+8, 28+22+21+12+2, 28+22+21+12+5+2, 28+22+21+12+5, 28+22+21+12+6+2, 28+22+21+12+6+5+2, 28+22+21+12+6+5, 28+22+21+12+6, 28+22+21+12+8+2, 28+22+21+12+8+5+2, 28+22+21+12+8+5, 28+22+21+12+8, 28+22+21+12, 28+22+21+14+12+2, 28+22+21+14+12+5+2, 28+22+21+14+12+5, 28+22+21+14+12+6+2, 28+22+21+14+12+6+5+2, 28+22+21+14+12+6+5, 28+22+21+14+12+6, 28+22+21+14+12+8+2, 28+22+21+14+12+8+5+2, 28+22+21+14+12+8+5, 28+22+21+14+12+8, 28+22+21+14+12, 28+22+21+14, 28+22+21+18+12+2, 28+22+21+18+12+5+2, 28+22+21+18+12+5, 28+22+21+18+12+6+2, 28+22+21+18+12+6+5+2, 28+22+21+18+12+6+5, 28+22+21+18+12+6, 28+22+21+18+12+8+2,

28+22+21+18+12+8+5+2, 28+22+21+18+12+8+5, 28+22+21+18+12+8, 28+22+21+18+12, 28+22+21+18+14+12+2, 28+22+21+18+14+12+5+2, 28+22+21+18+14+12+5, 28+22+21+18+14+12+6+2, 28+22+21+18+14+12+6+5+2, 28+22+21+18+14+12+6+5, 28+22+21+18+14+12+6, 28+22+21+18+14+12+8+2, 28+22+21+18+14+12+8+5+2, 28+22+21+18+14+12+8+5, 28+22+21+18+14+12+8, 28+22+21+18+14+12, 28+22+21+18+14, 28+22+21+18, 28+22+21, 28+22, 28+26+2, 28+26+5+2, 28+26+5, 28+26+6+2, 28+26+6+5+2, 28+26+6+5, 28+26+6, 28+26+8+2, 28+26+8+5+2, 28+26+8+5, 28+26+8, 28+26+12+2, 28+26+12+5+2, 28+26+12+5, 28+26+12+6+2, 28+26+12+6+5+2, 28+26+12+6+5, 28+26+12+6, 28+26+12+8+2, 28+26+12+8+5+2, 28+26+12+8+5, 28+26+12+8, 28+26+12, 28+26+14+12+2, 28+26+14+12+5+2, 28+26+14+12+5, 28+26+14+12+6+2, 28+26+14+12+6+5+2, 28+26+14+12+6+5, 28+26+14+12+6, 28+26+14+12+8+2, 28+26+14+12+8+5+2, 28+26+14+12+8+5, 28+26+14+12+8, 28+26+14+12, 28+26+14, 28+26+18+12+2, 28+26+18+12+5+2, 28+26+18+12+5, 28+26+18+12+6+2, 28+26+18+12+6+5+2, 28+26+18+12+6+5, 28+26+18+12+6, 28+26+18+12+8+2, 28+26+18+12+8+5+2, 28+26+18+12+8+5, 28+26+18+12+8, 28+26+18+12, 28+26+18+14+12+2, 28+26+18+14+12+5+2, 28+26+18+14+12+5, 28+26+18+14+12+6+2, 28+26+18+14+12+6+5+2, 28+26+18+14+12+6+5, 28+26+18+14+12+6, 28+26+18+14+12+8+2, 28+26+18+14+12+8+5+2, 28+26+18+14+12+8+5, 28+26+18+14+12+8, 28+26+18+14+12, 28+26+18+14, 28+26+18, 28+26+21+2, 28+26+21+5+2, 28+26+21+5, 28+26+21+6+2, 28+26+21+6+5+2, 28+26+21+6+5, 28+26+21+6, 28+26+21+8+2, 28+26+21+8+5+2, 28+26+21+8+5, 28+26+21+8, 28+26+21+12+2, 28+26+21+12+5+2, 28+26+21+12+5, 28+26+21+12+6+2, 28+26+21+12+6+5+2, 28+26+21+12+6+5, 28+26+21+12+6, 28+26+21+12+8+2, 28+26+21+12+8+5+2, 28+26+21+12+8+5, 28+26+21+12+8, 28+26+21+12, 28+26+21+14+12+2, 28+26+21+14+12+5+2, 28+26+21+14+12+5, 28+26+21+14+12+6+2, 28+26+21+14+12+6+5+2, 28+26+21+14+12+6+5, 28+26+21+14+12+6, 28+26+21+14+12+8+2, 28+26+21+14+12+8+5+2, 28+26+21+14+12+8+5, 28+26+21+14+12+8, 28+26+21+14+12, 28+26+21+14, 28+26+21+18+12+2, 28+26+21+18+12+5+2, 28+26+21+18+12+5, 28+26+21+18+12+6+2, 28+26+21+18+12+6+5+2, 28+26+21+18+12+6+5, 28+26+21+18+12+6, 28+26+21+18+12+8+2, 28+26+21+18+12+8+5+2, 28+26+21+18+12+8+5, 28+26+21+18+12+8, 28+26+21+18+12, 28+26+21+18+14+12+2, 28+26+21+18+14+12+5+2, 28+26+21+18+14+12+5, 28+26+21+18+14+12+6+2, 28+26+21+18+14+12+6+5+2, 28+26+21+18+14+12+6+5, 28+26+21+18+14+12+6, 28+26+21+18+14+12+8+2, 28+26+21+18+14+12+8+5+2, 28+26+21+18+14+12+8+5, 28+26+21+18+14+12+8, 28+26+21+18+14+12, 28+26+21+18+14, 28+26+21+18, 28+26+21, 28+26.

In the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the limitations as outlined above.

29) A third aspect of the invention relates to compounds of the Formula (I) which are compounds of Formula (III),



Formula (III)

wherein R^2, R^3, Ar^1, R^4, R^5, **m**, **n**, and the group **-L-**R^6 are as defined in embodiment 1);

wherein the characteristics disclosed in embodiments 2) to 27) are intended to apply *mutatis mutandis* also to the compounds formula (III) according to embodiment 29); wherein in particular the following embodiments are thus possible and intended and herewith specifically disclosed in individualized form:

29+8, 29+11, 29+12+8, 29+12+11, 29+12, 29+15+8, 29+15+11, 29+15+12+8, 29+15+12+11, 29+15+12, 29+15, 29+18+8, 29+18+11, 29+18+12+8, 29+18+12+11, 29+18+12, 29+18+15+8, 29+18+15+11, 29+18+15+12+8, 29+18+15+12+11, 29+18+15+12, 29+18+15, 29+18, 29+21+8, 29+21+11, 29+21+12+8, 29+21+12+11, 29+21+12, 29+21+15+8, 29+21+15+11, 29+21+15+12+8, 29+21+15+12+11, 29+21+15+12, 29+21+15, 29+21+18+8, 29+21+18+11, 29+21+18+12+8, 29+21+18+12+11, 29+21+18+12, 29+21+18+15+8, 29+21+18+15+11, 29+21+18+15+12+8, 29+21+18+15+12+11, 29+21+18+15+12, 29+21+18+15, 29+21+18, 29+21, 29+26+8, 29+26+11, 29+26+12+8, 29+26+12+11, 29+26+12, 29+26+15+8, 29+26+15+11, 29+26+15+12+8, 29+26+15+12+11, 29+26+15+12, 29+26+15, 29+26+18+8, 29+26+18+11, 29+26+18+12+8, 29+26+18+12+11, 29+26+18+12, 29+26+18+15+8, 29+26+18+15+11, 29+26+18+15+12+8, 29+26+18+15+12+11, 29+26+18+15+12, 29+26+18+15, 29+26+18, 29+26+21+8, 29+26+21+11, 29+26+21+12+8, 29+26+21+12+11, 29+26+21+12, 29+26+21+15+8, 29+26+21+15+11, 29+26+21+15+12+8, 29+26+21+15+12+11, 29+26+21+15+12, 29+26+21+15, 29+26+21+18+8, 29+26+21+18+11, 29+26+21+18+12+8, 29+26+21+18+12+11, 29+26+21+18+12, 29+26+21+18+15+8, 29+26+21+18+15+11, 29+26+21+18+15+12+8, 29+26+21+18+15+12+11, 29+26+21+18+15+12, 29+26+21+18+15, 29+26+21+18, 29+26+21, 29+26, 29.

In the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the limitations as outlined above.

30) Another embodiment relates to compounds of formula (III) according to embodiment 29), wherein

R^2 is halogen (especially chloro), methyl, ethyl, methoxy or ethoxy;

R^3 is C_{1-3}-alkoxy (especially methoxy) or C_{1-3}-fluoroalkoxy (especially difluoromethoxy);

Ar^{1} represents phenyl, or 6-membered heteroaryl containing one or two nitrogen atoms (especially pyridinyl); (notably, **Ar**^{1} represents phenyl), wherein said group **Ar**^{1} is substituted with **R**^{4} and **R**^{5}, wherein

- **R**^{4} is n-propyl, isopropyl, or C_{3-6}-cycloalkyl optionally containing a ring oxygen atom (especially cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydro-2H-pyran-4-yl); [wherein it is understood that said substituent **R**^{4} is attached in *ortho*-position with regard to the point of the attachment of the rest of the molecule] (wherein **R**^{4} is in particular isopropyl) and
- **R**^{5} represents hydrogen or fluoro (wherein **R**^{5} is in particular hydrogen);

m and **n** independently represent the integer 1 or 2 (especially both **m** and **n** represent the integer 1); and

the group **-L-R**^{6} represents

- hydrogen;
- **-L**^{1}-CO-**R**^{C11} wherein **R**^{C11} independently represents hydroxy; -O-benzyl; -O-C_{1-6}-alkyl; C_{1}-fluoroalkyl; or -N**R**^{N11}**R**^{N12}; wherein independently **R**^{N11} is hydrogen or C_{1-4}-alkyl, and **R**^{N12} is hydrogen, C_{1-4}-alkyl, -SO_2-C_{1-6}-alkyl, or -O-**R**^{O11}, wherein **R**^{O11} independently represents hydrogen, C_{1-6}-alkyl, or benzyl; and
  -L^{1}- independently represents
  - -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;
  - -C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-NH-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, or -CO-O-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-;
- **-L**^{2}-hydroxy; wherein **-L**^{2}- represents
  - -CO-C_{1-6}-alkylene- or -SO_2-C_{1-6}-alkylene-; wherein in the above groups said C_{1-6}-alkylene independently is unsubstituted, or mono-substituted with hydroxy, C_{1}-fluoroalkyl, or -N**R**^{N21}**R**^{N22} wherein independently **R**^{N21} is hydrogen or C_{1-4}-alkyl, and **R**^{N22} is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{2-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-, wherein in the above groups said C_{2-6}-alkylene independently is unsubstituted, or mono-substituted with hydroxy, C_{1}-fluoroalkyl, or -N**R**^{N23}**R**^{N24} wherein independently **R**^{N23} is hydrogen or C_{1-4}-alkyl, and **R**^{N24} is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-;
- **-L**^{7}-N**R**^{N5}**R**^{N6} wherein **R**^{N5} is hydrogen or C_{1-4}-alkyl (especially hydrogen); **R**^{N6} is hydrogen, C_{1-4}-alkyl, -CO-C_{1-4}-alkyl, C_{1-3}-fluoroalkyl, or C_{3-6}-cycloalkyl (especially hydrogen); and
  -L^{7}- independently represents
  - -CO-, or -SO_2-;

- **-L^{9}-HET^{1}**, wherein **HET^{1}** represents 5- or 6-membered heteroaryl (especially pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, oxazolyl, isoxazolyl; thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl),

  wherein said **HET^{1}** independently is unsubstituted or mono-, or di-substituted wherein the substituents are independently selected from C_{1-4}-alkyl (especially methyl), halogen, cyano, hydroxy, hydroxymethyl, and -C_{0-2}-alkylene-**Cy^{91}**-$COOR^{O91}$ wherein R^{O91} is hydrogen or C_{1-4}-alkyl, and wherein **Cy^{91}** represents a C_{3-6}-cycloalkylene group; or -C_{0-2}-alkylene-$COOR^{O92}$ wherein R^{O92} is hydrogen or C_{1-4}-alkyl; and

  -L^{9}- independently represents

  - -C_{0-6}-alkylene-, -CO-C_{0-6}-alkylene-, -SO_2-C_{0-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-; or

- **-L^{10}-**C_{4-6}-heterocyclyl, wherein the C_{4-6}-heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said C_{4-6}-heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:
  - one or two oxo substituents each attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionaly adjacent, a carbamate group, or, in case second ring nitrogen is additionaly adjacent, a urea group); and / or
  - two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom or a ring oxygen atom (thus forming together with the nitrogen a -$C(CH_3)_2$-N- or with the oxygen a -$C(CH_3)_2$-O-group); and / or
  - two oxo substituents at a ring sulfur ring atom (thus forming a -SO_2- group); and / or
  - C_{1-4}-alkyl, C_{1-3}-alkoxy-C_{2-4}-alkyl, C_{2-3}-fluoroalkyl, or -CO-C_{1-4}-alkyl attached to a ring nitrogen atom having a free valency; and

  -L^{10}- independently represents

  - -C_{0-6}-alkylene-, -CO-C_{0-6}-alkylene-, -SO_2-C_{0-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-.

31) Another embodiment relates to compounds of formula (III) according to embodiment 29) or 30), wherein **R^{2}** is halogen (especially chloro), methyl, or methoxy.

32) Another embodiment relates to compounds of formula (III) according to any one of embodiments 29) to 31), wherein **R^{4}** is isopropyl.

33) Another embodiment relates to compounds of formula (III) according to any one of embodiments 29) to 32), wherein the group **-L-R^{6}** represents:

- hydrogen;
- **-L^{1}-CO-R^{C11}** wherein **R^{C11}** independently represents hydroxy; -O-benzyl; or -O-C_{1-6}-alkyl; and

-L^1- independently represents

- -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;
- -C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-NH-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, or -CO-O-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-;

- -L^7-N$R^{N5}R^{N6}$ wherein R^{N5} is hydrogen or C_{1-4}-alkyl (especially hydrogen); R^{N6} is hydrogen, C_{1-4}-alkyl, -CO-C_{1-4}-alkyl, C_{1-3}-fluoroalkyl, or C_{3-6}-cycloalkyl (especially hydrogen); and

  -L^7- independently represents
  - -CO-, or -SO_2-; or
- -L^{10}-C_{4-6}-heterocyclyl, wherein the C_{4-6}-heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said C_{4-6}-heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:
  - one or two oxo substituents each attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionaly adjacent, a carbamate group, or, in case second ring nitrogen is additionaly adjacent, a urea group); and

  -L^{10}- independently represents
  - -C_{0-6}-alkylene-, -CO-C_{0-6}-alkylene-, -SO_2-C_{0-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-.

34) Another embodiment relates to compounds of Formula (I) according to embodiment 1), which are selected from the following compounds:

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)pyrrolidine-3-carboxamide;

1-(2-aminoethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-hydroxypropyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-cyano-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(3-(1H-tetrazol-5-yl)propyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-hydroxy-3-methylbutyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(1-hydroxycyclopropyl)ethyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(2-aminopropyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)propanoic acid;

1-(2-cyanoethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2,3-dihydroxypropyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2,3-dihydroxypropyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(oxetan-3-yl)azetidine-3-carboxamide;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)butanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3,3-dimethylbutanoic acid;

5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-1H-pyrrole-2-carboxylic acid;

5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)furan-2-carboxylic acid;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(4-hydroxy-4-methylpentyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylpentanoic acid;

1-(3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)propyl)cyclopropane-1-carboxylic acid;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(methylsulfonamido)ethyl)azetidine-3-carboxamide;

(S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-hydroxy-3-(2-hydroxyacetamido)propyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(cyanomethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(2-(1H-tetrazol-5-yl)ethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(4-cyanobutanoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-acetyl-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(3-sulfamoylpropanoyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(N-methylsulfamoyl)acetyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-((methylsulfonyl)glycyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(N-methyl-N-sulfamoylglycyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(5,5,5-trifluoro-4-oxopentanoyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)-1-(5,5,5-trifluoro-4-oxopentanoyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxyoxetan-3-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-hydroxyisoxazole-5-carbonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide [tautomeric form: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-oxo-2,3-dihydroisoxazole-5-carbonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide];

1-(2-(1H-tetrazol-1-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

1-(2-(2H-1,2,3-triazol-2-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(2-(2H-1,2,3-triazol-2-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxy-1H-pyrazol-5-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide [and tautomeric forms thereof, such as N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-oxo-2,3-dihydro-1H-pyrazol-5-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide];

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxy-1H-pyrazol-4-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide [and tautomeric forms thereof, such as N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-oxo-2,3-dihydro-1H-pyrazol-4-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide];

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxy-1H-pyrazol-4-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide [and tautomeric forms thereof, such as N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-oxo-2,3-dihydro-1H-pyrazol-4-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide];

1-(L-alanyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)-1-((2-methoxyethyl)glycyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((2-hydroxyethyl)glycyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((2-hydroxyethyl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-((2-methoxyethyl)glycyl)azetidine-3-carboxamide;

(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((R)-(2-hydroxypropyl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

(S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((S)-(2-hydroxypropyl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((R)-(1-hydroxypropan-2-yl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

(S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((R)-(1-hydroxypropan-2-yl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-oxopropanoic acid;

3-(4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)-3-oxopropanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobutanoic acid;

4-(4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)-4-oxobutanoic acid;

(S)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-methyl-4-oxobutanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

1-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)cyclopropane-1-carboxylic acid;

1-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)cyclobutane-1-carboxylic acid;

(R)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-methyl-4-oxobutanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3,3-dimethyl-4-oxobutanoic acid;

3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)but-3-enoic acid;

(1S,2R)-2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)cyclopropane-1-carboxylic acid;
(1R,2S)-2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)cyclopropane-1-carboxylic acid;
5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-5-oxopentanoic acid;
4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3,3-difluoro-4-oxobutanoic acid;
(S)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-hydroxy-2-methyl-4-oxobutanoic acid;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(5,5,5-trifluoro-4-hydroxypentanoyl)azetidine-3-carboxamide;
4-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)tetrahydro-2H-pyran-4-carboxylic acid;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(sulfamoylglycyl)azetidine-3-carboxamide;
1-(N-acetyl-N-hydroxyglycyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)acetic acid;
2-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)sulfonyl)acetic acid;
3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propanoic acid;
3-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)sulfonyl)propanoic acid;
3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)-2,2-dimethylpropanoic acid;
2-(1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)cyclopropyl)acetic acid;
4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)butanoic acid;
(E)-3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)acrylic acid;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((3-(hydroxyamino)-3-oxopropyl)sulfonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)acetic acid;

2-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidine-1-carbonyl)oxy)acetic acid;

(R)-2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)propanoic acid;

1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)cyclopropane-1-carboxylic acid;

3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)-2,2-dimethylpropanoic acid;

1-(((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)methyl)cyclopropane-1-carboxylic acid;

((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropyl phenyl)azetidin-1-yl)sulfonyl)glycine;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(2-(difluoromethoxy)pyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(2,6-dimethoxypyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(6-ethoxy-2-methoxypyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(N-methylsulfamoyl)azetidine-3-carboxamide;

1-(N-cyclopropylsulfamoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(sulfamoylamino)ethyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-5-fluoropyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-3-methylbutanoic acid;

N1-((1H-imidazol-4-yl)methyl)-N4-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-1,4-carboxamide;

3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-2,2-dimethylpropanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-2,2-dimethylbutanoic acid;

N4-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-1,4-dicarboxamide;

N4-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-N1-(2-hydroxyethyl)-4-(2-isopropylphenyl)piperidine-1,4-dicarboxamide;

6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)nicotinic acid;

6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)picolinic acid;

2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidine-5-carboxylic acid;

6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyridazine-3-carboxylic acid;

5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrazine-2-carboxylic acid;

1-(5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidin-2-yl)cyclopropane-1-carboxylic acid;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(4-fluoropyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-fluoropyridin-4-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(5-fluoropyrimidin-4-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)pyridin-3-yl)-1-(5-fluoropyrimidin-4-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(5-cyanopyridin-2-yl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(5-cyanopyridin-2-yl)-N-(2-(difluoromethoxy)pyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(5-cyanopyrimidin-2-yl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(5-cyanopyrimidin-2-yl)-N-(2-(difluoromethoxy)pyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)oxazole-4-carboxylic acid;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(5-fluoropyrimidin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-methylpyrimidin-4-yl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(4-oxo-4,5-dihydrooxazol-2-yl)azetidine-3-carboxamide [tautomeric form: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(4-hydroxy-oxazol-2-yl)azetidine-3-carboxamide];

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(5-hydroxy-1,2,4-oxadiazol-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide [tautomeric form: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)azetidine-3-carboxamide];

3-(2-cyclopentylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide;

3-(2-cyclohexylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide;

4-(3-(2-cyclobutylphenyl)-3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

4-(3-(2-cyclopentylphenyl)-3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

4-(3-(2-cyclohexylphenyl)-3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-propylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-fluoro-6-isopropylphenyl)azetidine-3-carboxamide;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropyl-5-methylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-fluoro-6-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(5-fluoro-2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid; and

N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-propylglycine.

35) In addition to the compounds listed in embodiment 33), further compounds of Formula (I) according to embodiment 1), are selected from the following compounds:

Methyl N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-(2-methoxyethyl)glycinate;

N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-(2-methoxyethyl)glycine;

Methyl (2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)glycinate;

(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)glycine;

N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-ethylglycine;

3-(2-isopropylphenyl)-N-(6-methyl-2-propoxypyridin-3-yl)-1-sulfamoylazetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(3-isopropylpyridin-2-yl)azetidin-1-yl)-4-oxobutanoic acid;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-2-yl)-1-sulfamoylazetidine-3-carboxamide;

N1-cyclopropyl-N3-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-2-yl)azetidine-1,3-dicarboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(5-fluoro-2-methylpyrimidin-4-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-fluoro-6-methylpyridin-2-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-4-yl)azetidine-3-carboxamide;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-4-yl)-1-sulfamoylazetidine-3-carboxamide;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyrazin-2-yl)azetidine-3-carboxamide; and
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyrazin-2-yl)-1-sulfamoylazetidine-3-carboxamide.

36) In addition to the compounds listed in embodiments 33) and 34, further compounds of Formula (I) according to embodiment 1), are selected from the following compounds:

N-(5-chloro-3-methoxypyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(5-bromo-3-methoxypyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(5-bromo-3-(difluoromethoxy)pyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(3-(difluoromethoxy)-5-methylpyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(3,5-dimethoxypyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(2-cyclopentylphenyl)azetidine-3-carboxamide;
N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide;
Methyl 4-(3-((5-chloro-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoate;
4-(3-((5-chloro-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoic acid;
4-(3-((5-bromo-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoic acid;
Methyl 4-(3-((5-bromo-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoate;
Methyl 4-(3-((5-bromo-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoate;
4-(3-((5-chloro-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;
4-(3-((5-chloro-3-methoxypyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;
4-(3-((5-bromo-3-methoxypyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;
4-(3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;
1-(2-(3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)cyclobutane-1-carboxylic acid;
Benzyl 3-((3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propanoate;

3-((3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propanoic acid;

N-(5-chloro-3-methoxypyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(5-bromo-3-methoxypyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(5-bromo-3-(difluoromethoxy)pyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(3,5-dimethoxypyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(2-cyclopentylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(3-isopropylpyridin-2-yl)-1-sulfamoylazetidine-3-carboxamide;

N^3-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-N^1-cyclopropyl-3-(2-isopropylphenyl)azetidine-1,3-dicarboxamide;

N^3-(5-bromo-3-(difluoromethoxy)pyridin-2-yl)-N^1-cyclopropyl-3-(2-isopropylphenyl)azetidine-1,3-dicarboxamide;

2-methoxy-2-oxoethyl 3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate;

2-((3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)acetic acid;

1-((3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)cyclopropane-1-carboxylic acid; and

N-(3-(difluoromethoxy)-5-methylpyridin-2-yl)-3-(2-isopropylphenyl)-1-(4-oxo-4,5-dihydrooxazol-2-yl)azetidine-3-carboxamide.

The compounds of formulae (I), (II) and (III) according to embodiments 1) to 36) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral (such especially oral e.g. in form of a tablet or a capsule) or parenteral administration (including topical application or inhalation).

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds of Formula (I) or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

The present invention also relates to a method for the prevention / prophylaxis or treatment of a disease or disorder mentioned herein comprising administering to a subject a pharmaceutically active amount of a compound of formulae (I), (II) or (III) according to embodiments 1) to 36).

For avoidance of any doubt, if compounds are described as useful for the prevention / prophylaxis or treatment of certain diseases, such compounds are likewise suitable for use in the preparation of a medicament for the prevention / prophylaxis or treatment of said diseases. Likewise, such compounds are also suitable in a method

for the prevention / prophylaxis or treatment of such diseases, comprising administering to a subject (mammal, especially human) in need thereof, an effective amount of such compound.

The compounds of formulae (I), (II), and (III) according to embodiments 1) to 36) are useful for the prevention and/or treatment of fibrosis (and diseases or disorders associated with fibrosis), or of other disorders mediated by LPA_1 receptor signalling.

The terms "fibrosis" refers to conditions that are associated with the abnormal accumulation of cells and/or fibronectin and/or collagen and/or increased fibroblast recruitment in an organ; including fibrosis of individual organs or tissues such as the heart, kidney, liver, joints, lung, pleural tissue, peritoneal tissue, skin, cornea, retina, musculoskeletal and digestive tract.

The term fibrosis may in particular be defined as comprising

- all forms of pulmonary fibrosis including lung diseases associated with fibrosis, including idiopathic pulmonary fibrosis; pulmonary fibrosis secondary to systemic inflammatory disease such as rheumatoid arthritis, scleroderma, lupus; cryptogenic fibrosing alveolitis; pulmonary fibrosis secondary to sarcoidosis; iatrogenic pulmonary fibrosis including radiation induced fibrosis; silicosis; asbestos induced pulmonary; and pleural fibrosis;
- renal fibrosis; including renal fibrosis associated with CKD, chronic renal failure, tubulointerstitial nephritis, and/orchronic nephropathies such as (primary) glomerulonephritis and glomerulonephritis secondary to systemic inflammatory diseases such as lupus and scleroderma, diabetes, focal segmental glomerular sclerosis, IgA nephropathy, hypertension, renal allograft, and Alport syndrome;
- gut fibrosis, including gut fibrosis secondary to scleroderma, and radiation induced gut fibrosis;
- all forms of liver fibrosis, including cirrhosis, alcohol induced liver fibrosis, nonalcoholic steatohepatitis, biliary duct injury, primary biliary cirrhosis (also known as primary biliary cholangitis), infection or viral induced liver fibrosis (e.g. chronic HCV infection), and autoimmune hepatitis;
- head and neck fibrosis, including radiation induced head and neck fibrosis;
- corneal scarring, including sequelae of LASIK (laser-assisted in situ keratomileusis), corneal transplant, and trabeculectomy;
- hypertrophic scarring and keloids, including burn induced or surgical hypertrophic scarring and keloids;
- and other fibrotic diseases, e.g. endometriosis, spinal cord fibrosis, myelofibrosis, cardiac fibrosis, perivascular fibrosis; as well as formation of scar tissue, Peyronie's disease, abdominal or bowel adhesions, bladder fibrosis, fibrosis of the nasal passages, and fibrosis mediated by fibroblasts.

The term “prevention /prophylaxis of fibrosis” includes the prevention of fibrosis in a subject that has been exposed to one or more environmental conditions that are known to increase the risk of fibrosis of an organ or tissue, especially the risk of lung, liver or kidney fibrosis; or in a subject that has a genetic predisposition of developing fibrosis of an organ or tissue; as well as the prevention or minimization of scarring following injury including surgery.

Other disorders mediated by LPA_1 receptor signalling notably comprise dermatological disorders, pain, malignant and benign proliferative diseases, respiratory diseases, nervous system disorders, cardiovascular diseases, and inflammatory disorders, obesity, and insulin resistance.

The term "dermatological disorder," refers to a skin disorder. Such dermatological disorders include proliferative or inflammatory disorders of the skin such as systemic sclerosis, atopic dermatitis, bullous disorders, collagenosis, psoriasis, scleroderma, psoriatic lesions, dermatitis, contact dermatitis, eczema, urticaria, rosacea, wound healing, scarring, hypertrophic scarring, keloids, Kawasaki Disease, rosacea, Sjogren-Larsso syndrome, urticaria; especially systemic sclerosis.

The term "pain" refers to acute pain, chronic pain, and neuropathic pain. A particular example is fibromyalgia, especially fibromyalgia that stems from the formation of fibrous scar tissue in contractile muscles, and cancer pain.

The term "malignant and benign proliferative disease" especially refers to cancer, and the control of proliferation of tumor cells, invasion and/or metastasis of carcinomas.

The term "cancer," refers to all sorts of cancers such as carcinomas; adenocarcinomas; leukemias; sarcomas; lymphomas; myelomas; metastatic cancers; brain tumors; neuroblastomas; pancreatic cancers; gastro-intestinal cancers; lung cancers; breast cancers; prostate cancers; endometrial cancers; skin cancers; bladder cancers; head and neck cancers; neuroendocrine tumors; ovarian cancers; cervical cancers; oral tumors; nasopharyngeal tumors; thoracic cancers; and virally induced tumors. Notably the term refers to pleural mesothelioma, peritoneal mesothelioma, and bone metastases, as well as brain tumors including brain metastases, malignant gliomas, glioblastoma multiforme, medulloblastoma, meningiomas; neuroblastoma; pancreatic cancer including pancreatic adenocarcinoma/pancreatic ductal adenocarcinoma; gastro-intestinal cancers including colon carcinoma, colorectal adenoma, colorectal adenocarcinoma, metastatic colorectal cancer, familial adenomatous polyposis (FAP), gastric cancer, gallbladder cancer, cholangiocarcinoma, hepatocellular carcinoma; Kaposi's sarcoma; leukemias including acute myeloid leukemia, adult T-cell leukemia; lymphomas including Burkitt's lymphoma, Hodgkin's lymphoma, MALT lymphoma, and primary intra-ocular B-Cell lymphoma; lung cancer including non-small cell lung cancer; breast cancer including triple negative breast carcinoma; rhabdomyosarcoma; prostate cancer including castrate-resistant prostate cancer; esophageal squamous cancer; (oral) squamous cell carcinoma; endometrial cancer; thyroid carcinoma including papillary thyroid carcinoma; metastatic cancers; lung metastasis; skin cancer including melanoma and metastatic melanoma; bladder cancer including urinary bladder cancer, urothelial cell carcinoma; multiple myelomas; osteosarcoma; head and neck cancer; and renal carcinomas including renal cell carcinoma renal clear cell carcinoma, metastatic renal cell carcinoma, metastatic renal clear cell carcinoma; as well as neuroendocrine tumors; ovarian cancer; cervical cancer; oral tumors; nasopharyngeal tumors; thoracic cancer; choriocarcinoma; Ewing's sarcoma; and virally induced tumors.

The term "respiratory disease," refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, eustachian tubes, trachea, bronchi, lungs, related muscles (e.g. diaphragm and intercostals), and nerves. Respiratory diseases include interstitial pneumonia, asthma refering to any disorder of the lungs characterized by variations in pulmonary gas flow associated with airway constriction of whatever cause (intrinsic, extrinsic, or both; allergic or non-allergic) including adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma; rhinitis including seasonal allergic rhinitis, perennial allergic rhinitis; chronic obstructive pulmonary disease (COPD) including chronic bronchitis or emphysema; airway inflammation, sarcoidosis, cystic fibrosis, hypoxia, and acute lung injury and acute respiratory distress (including bacterial pneumonia induced, trauma induced, viral pneumonia induced, ventilator induced, non-pulmonary sepsis induced, and aspiration induced).

The term "nervous system disorder" refers to conditions that alter the structure or function of the brain, spinal cord or peripheral nervous system, including but not limited to Alzheimer's Disease, cerebral edema, multiple sclerosis, neuropathies, Parkinson's Disease, nervous system disorders resulting from blunt or surgical trauma (including post-surgical cognitive dysfunction and spinal cord or brain stem injury, and head injury), cerebral edema, migraine, as well as the neurological aspects of disorders such as degenerative disk disease and sciatica.

The term "cardiovascular disease," as used herein refers to diseases affecting the heart or blood vessels or both, including but not limited to: arrhythmia (atrial or ventricular or both); atherosclerosis and its sequelae; cerebral ischemia, stroke, angina; cardiac rhythm disturbances; myocardial ischemia; myocardial infarction; cardiac or vascular aneurysm including aortic aneurysm; retinal ischemia; reperfusion injury following ischemia of the brain, heart or other organ or tissue; restenosis; peripheral obstructive arteriopathy of a limb, an organ, or a tissue; endotoxic, surgical, or traumatic shock; hypertension, valvular heart disease, heart failure, abnormal blood pressure; shock; vasoconstriction (including that associated with migraines); vascular abnormality, thrombosis, insufficiency limited to a single organ or tissue.

The term "inflammatory disorder" include psoriasis, rheumatoid arthritis, vasculitis, inflammatory bowel disease, dermatitis, osteoarthritis, inflammatory muscle disease, vaginitis, interstitial cystitis, scleroderma, eczema, allogeneic or xenogeneic transplantation (organ, bone marrow, stem cells and other cells and tissues) graft rejection, graft-versus-host disease, mixed connective tissue disease, lupus erythematosus, type I diabetes, dermatomyositis, phlebitis, Sjogren's syndrome, granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), thyroiditis (e.g., Hashimoto's and autoimmune thyroiditis), myasthenia gravis, autoimmune hemolytic anemia, chronic relapsing hepatitis, allergic conjunctivitis, atopic dermatitis, sinusitis, and inflammation mediated by neutrophils.

Further disorders in which LPA_1 receptor plays a role notably comprise prostate and bladder disorders such as benign prostatic hyperplasia, diseases linked to eosinophil and/or basophil and/or dendritic cell and/or neutrophil and/or monocyte and/or T-cell recruitment, cardiomyopathy, myocardial remodeling, vascular remodeling, vascular permeability disorders, renal diseases, renal papillary necrosis, renal failure, tumor growth, metabolic diseases, pruritus, ocular diseases, macular degeneration, endocrine disorders, hyperthyroidism, osteoporosis, diabetes-related disease (nephropathy, retinopathy).

The present invention further relates to the compounds of the formulae (I), (II) and (III) for use in the treatment of the diseases and disorders mentioned herein (especially for the treatment of fibrosis) wherein the compound of formulae (I), (II), and (III) is intended to be used in combination (whether in a single pharmaceutical composition, or in separate treatment) with one or several antifibrotic agents. Examples of such antifibrotic agents include corticosteroids, immunosuppressants, B-cell antagonists, and uteroglobin.

Preparation of compounds of formulae (I), (II), and (III):

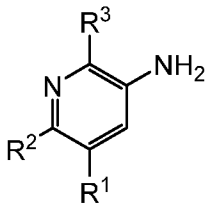
The compounds of formulae (I), (II) and (III) can be prepared by well-known literature methods, by the methods given below, by the methods given in the experimental part below or by analogous methods. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by a person skilled in the art by routine optimisation procedures. In some cases the order of carrying out the following reaction schemes, and/or reaction steps, may be varied to facilitate the reaction or to avoid unwanted reaction products. In the general sequence of reactions outlined below, the generic groups R^1, R^2, R^3, R^4, R^5, R^6, and L are as defined for Formula (I). Other abbreviations used herein are explicitly defined, or are as defined in the experimental section. In some instances the generic groups R^1, R^2, R^3, R^4, R^5, R^6, and L might be incompatible with the assembly illustrated in the schemes below and so will require the use of protecting groups (PG). The use of protecting groups is well known in the art (see for example “Protective Groups in Organic Synthesis", T.W. Greene, P.G.M. Wuts, Wiley-Interscience, 1999; P. J. Kocienski, Protecting Groups, Thieme Stuttgart, 1994). For the purposes of this discussion, it will be assumed that such protecting groups as necessary are in place. In some cases the final product may be further modified, for example, by manipulation of substituents to give a new final product. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, hydrolysis and transition-metal catalysed cross-coupling reactions which are commonly known to those skilled in the art. The compounds obtained may also be converted into salts, especially pharmaceutically acceptable salts, in a manner known per se.

The compounds of formulae (I), (II) and (III) can be manufactured by the methods given below, by the methods given in the experimental part or by analogous methods. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by a person skilled in the art by routine optimisation procedures.

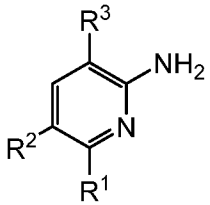
Compounds of the formulae (I), (II) and (III) of the present invention can be prepared according to the general sequence of reactions outlined below. Only a few of the synthetic possibilities leading to compounds of formulae (I), (II) and (III) are described.

Compounds of Formula (I) are prepared by reacting a compound of Structure 1a or Structure 1b with a compound of Structure 2 in a solvent such as DMF, THF, DCM, EtOAc etc. in the presence of one or more carboxylate activating agents such as $SOCl_2$, $(COCl)_2$, $POCl_3$, EDC, HOBt, HBTU, TBTU, DCC, CDI, T3P etc. and in the presence or absence of a base such as TEA, DIPEA, NaH, K_2CO_3, etc. (Montalbetti CA., Falque V. *Tetrahedron* 2005 (46) 10827-10852; Valeur E., Bradley M. *Chem. Soc. Rev.* 2009 (389) 606-31). Residue R^4 can be present at coupling stage or introduced at a later stage by replacing Br by an alkyl group under Negishi conditions or via a Suzuki/Hydrogenation sequence known to a person skilled in the art. (Matsushita LH., Negishi E. *J. Org. Chem.* 1982 (47) 4161-4165; Kerins, F. et al. *J. Org. Chem.* 2002 (67) 4968-4971).

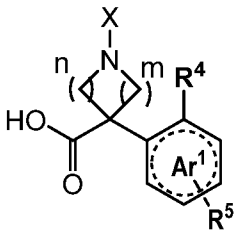
In compound of Formula I, the couplings of Structure 1a and Structure 1b with Structure 2 may be carried out with side chain L-R^6 = X already present or with a Structure 2 wherein N bears a protecting group = X. Functionality R^6 is then introduced, after deprotection, by the formation of an amine, amide, sulfonamide, carbamate, urea or sulfamide linker (L), for example, in a manner known to a person skilled in the art.



Structure 1a

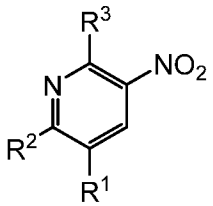


Structure 1b

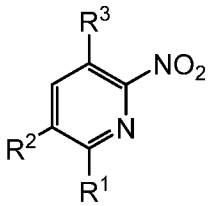


Structure 2

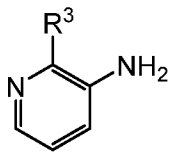
Compounds of Structure 1a and Structure 1b may be commercially available or may be prepared by reducing a compound of Structure 3a or Structure 3b in a solvent such as THF, MeOH, EtOH, iPrOH etc. in the presence of H_2/Pd/C or H_2 / Pt+V/C or Fe etc. (Dolle V. *et al*. Tetrahedron 1997 (53) 12505-12524; Möbus K. *et al*. Top. Catal. 2010 (53),1126–1131; WO2012/055995). If R^1 = H and R^2= Cl or Br, Structure 1a and Structure 1b may also be prepared by chlorinating or brominating a compound of Structure 3c and Structure 3d with N-chlorosuccinimide or N-bromosuccinimide in a manner known to a person skilled in the art.



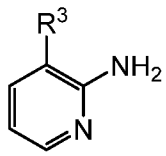
Structure 3a



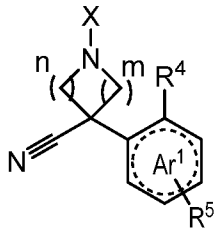
Structure 3b



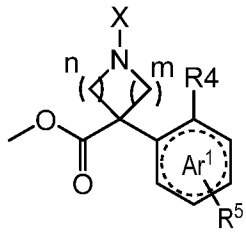
Structure 3c



Structure 3d

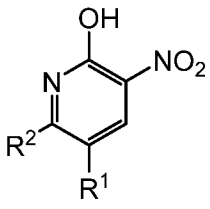


Structure 4

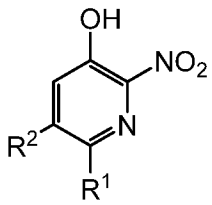


Structure 5

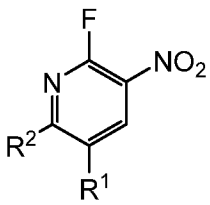
Compounds of Structure 2 may be prepared by reacting a compound of Structure 4 with 25% NaOH or concentrated H_2SO_4/AcOH or concentrated HCl at elevated temperature in a solvent such as water, EtOH etc (US20120232026; WO2005/049605; US20080319188). Compounds of Structure 2 may also be prepared by hydrolyzing a compound of Structure 5 with aqueous solution of NaOH, or LiOH etc. in a solvent such as water, MeOH, EtOH, THF etc.



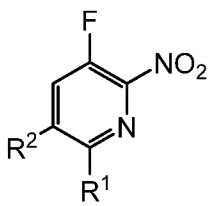
Structure 6a



Structure 6b

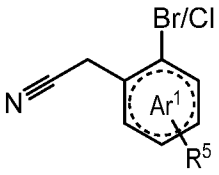


Structure 7a

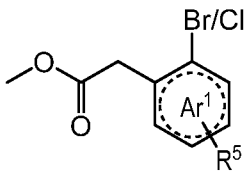


Structure 7b

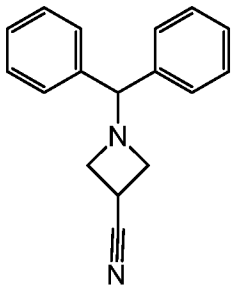
Compounds of Structure 3a, Structure 3b, Structure 3c and Structure 3d may be commercially available or may be prepared by reacting Structure 6a or Structure 6b (where R^1 represents H or F and R^2 represents H, halogen, $C_{1\text{-}2}$-alkyl, OMe or OEt) with sodium chlorodifluoroacetate or 2,2-difluoro-2-(fluorosulfonyl)acetic acid at 60°C or more in a solvent such as DMF, MeCN, etc. and in the presence of Na_2SO_4 or a base such as Cs_2CO_3, K_2CO_3 etc. (Thomoson C.S. *et al. J.Fluorine.Chem.* 2014 (168) 34-39; Sperry J. B. *et al. Org.ProcessRes.Dev.* 2011 (15) 721-725; WO2012/055995). Compounds of Structure 3a, Structure 3b, Structure 3c and Structure 3d may also be prepared by reacting compounds of Structure 7a or Structure 7b with alcoholate such as NaOMe, NaOiPr in a solvent such as THF, DMF etc (WO2010/023181). For Structure 3c and Structure 3d the nitro group is reduced in a following step using H_2 and Pd/C for example. Residue R^3 can also be introduced at a later stage, after the amide coupling.



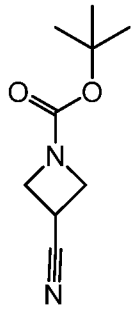
Structure 8



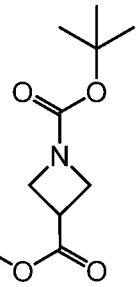
Structure 9



Structure 10



Structure 11



Structure 12

Compounds of Structure 4 and Structure 5 may be commercially available or may be prepared (for n and/or m > 1) by reacting 2-(2-haloaryl)acetonitrile (Structure 8) or methyl 2-(2-haloaryl)acetate (Structure 9), respectively, with *N*-benzyl-*N*,*N*-bis(2-chloroethyl)amine or *N*-boc-*N*,*N*-bis(2-chloroethyl)amine at 60°C or more in a solvent such as THF and in the presence of a base such as NaOH, NaH etc. Compounds of Structure 4 and Structure 5 may also be prepared by reacting 2-(2-bromophenyl)acetonitrile with paraformaldehyde in a solvent such as DMF in the presence of a base such as K_2CO_3 followed by a TFA-catalyzed 1,3-dipolar cycloaddition with commercially available N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine in DCM (Lit: JP2008110971). For n = m = 1, compounds of Structure 4 may be synthesized by reacting a compound of Structure 10, 11 or 12 with a 1,2-dihaloaryl, such as 1-bromo-2-fluorobenzene in a solvent such as THF in the presence of a base such as KHMDS (WO2012/017359). Alternatively, the bromo substituent can be replaced by R^4 = alkyl in a following step under Negishi conditions or via a Suzuki - hydrogenation sequence known to a person skilled in the art.

Depending on the nature of the functionalities present in residue R^6 in formulae (I), (II) and (III), these functionalities may require temporary protection. Appropriate protecting groups are known to a person skilled in the art and include e.g. a benzyl, an acetyl, or a trialkylsilyl group to protect an alcohol, a ketal to protect a diol, an ester to protect an acid etc. These protecting groups may be employed according to standard methodology.

Whenever the compounds of formulae (I), (II) or (III) are obtained in the form of mixtures of stereoisomers such as especially enantiomers, the stereoisomers can be separated using methods known to one skilled in the art: e.g. by formation and separation of diastereomeric salts or by HPLC over a chiral stationary phase such as a Daicel ChiralPak AD-H (5 μm) column, a Daicel ChiralCel OD-H (5 μm) column, a Daicel ChiralCel OD (10 μm) column, a Daicel ChiralPak IA or IB or IC or ID or IE (5 μm) column, Daicel ChiralPak AS-H (5 μm) column or a (R,R)-Whelk-01 (5 μm) column. Typical conditions of chiral HPLC are an isocratic mixture of eluent A (EtOH, in presence or absence of a base like TEA and/or diethylamine or of an acid like TFA) and eluent B (heptane). In Supercritical Fluid Chromatography (SFC) conditions, eluent A is CO_2 and eluent B is isopropanol.

Experimental Part

The following examples illustrate the invention but do not at all limit the scope thereof.

All temperatures are stated in °C. Commercially available starting materials were used as received without further purification. Unless otherwise specified, all reactions were carried out under an atmosphere of nitrogen or argon. Compounds were purified by flash chromatography on silica gel (Biotage), by prep TLC (TLC-plates from Merck, Silica gel 60 F_{254}) or by preparative HPLC. Compounds described in the invention are characterized by ^{1}H-NMR (400 MHz or 500 MHz Bruker; chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, hex = hexet, hept = heptet, m = multiplet, br = broad, coupling constants are given in Hz) and/or by LCMS (retention time t_R is given in min; molecular weight obtained for the mass spectrum is given in g/mol) using the conditions listed below.

LCMS with acidic conditions

LCMS-1: Waters Acquity Binary, Solvent Manager, MS: Waters SQ Detector, DAD: Acquity UPLC PDA Detector, ELSD: Acquity UPLC ELSD. Columns: Acquity UPLC CSH C18 1.7 um 2.1x50 mm from Waters, thermostated in the Acquity UPLC Column Manager at 60°C. Eluents: A: H2O + 0.05% formic acid; B: AcCN + 0.045% FA. Method: Gradient: 2% B 98% B over 2.0 min. Flow: 1.0 mL/min. Detection: UV 214 nm and ELSD.

LCMS-2: Aligent 1100 series with mass spectrometry detection (MS: Finnigan single quadrupole). Column: Zorbax RRHD SB-Aq (1.8 um, 3.0 x 50 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient:95% B → 5% B over 5 min (flow: 4.5 mL/min)

Preparative HPLC with acidic conditions

Prep-HPLC-1: Column: Waters XBridge C18 (10 um, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% formic acid [eluent B]. Gradient:95% B → 5% B over 5 min (flow: 75 mL/min). Detection: UV/Vis + MS

Prep-HPLC-2: Column: Waters Zorbax SB-Aq (5 um, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% formic acid [eluent B]. Gradient:95% B → 5% B over 5 min (flow: 75 mL/min). Detection: UV/Vis + MS

Preparative HPLC with basic conditions

Prep-HPLC-3: Column: Waters XBridge C18 (10 um, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% NH_4OH [eluent B]. Gradient:90% B → 5% B over 6.5 min (flow: 75 mL/min). Detection: UV/Vis + MS

Racemates can be separated into their enantiomers e.g. by preparative HPLC (column: ChiralPaK AS-H 30x250 mm, 5 um, 20% iPrOH in supercritical CO_2)

Abbreviations (as used herein):

Ac	acetyl
AcOH	acetic acid
aq.	aqueous

BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
Boc-D-Glu-OtBu	Boc-L-glutamic acid 1-*tert*-butyl ester
Bn	benzyl
BSA	bovine serum albumin
Bu	butyl such as in tert.-Bu (= tertiary butyl)
CDI	carbonyl diimidazole
Cs_2CO_3	cesium carbonate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DCM	dichloromethane
DIPEA	diisopropyl-ethylamine, Hünig's base, ethyl-diisopropylamine
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDC	N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide
eq.	equivalent(s)
Et	ethyl (such as in OEt: ethoxy)
EtOAc	ethyl acetate
EtOH	ethanol
Ex.	example(s)
h	hour(s)
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HCl	hydrochloric acid
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
H_2SO_4	sulfuric acid
iPr	isopropyl
KHMDS	potassium bis(trimethylsilyl)amide
K_2CO_3	potassium carbonate
LCMS	liquid chromatography – mass spectrometry
Lit.	Literature
LPA	lysophosphatidic acid
$LPAR_1$	lysophosphatidic receptor 1

Me	methyl (such as in OMe: methoxy)
MeCN	acetonitrile
MeOH	methanol
$NaBH_4$	sodium borohydride
NaH	sodium hydride
NaOtBu	sodium tert-butoxide
Na_2SO_4	sodium sulfate
NMM	N-methylmorpholine
$POCl_3$	phosphoryl chloride
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(OH)_2/C$	palladium hydroxide in charcoal
$Pd(OAc)_2$	palladium acetate
prep.	preparative
r.t.	room temperature
sat.	saturated
TBME	*tert*-butyl methyl ether
TBTU	2-(1H-benzotriazole-1-yl)-1,2,3,3-tetramethyluronium tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
T3P	propylphosphonic anhydride
t_R	retention time

Preparation of Intermediates

Intermediate 1.A: 2-Methoxy-6-methylpyridin-3-amine

Step 1. Methanol (256 uL, 6.39 mmol) is added drop wise into a stirred suspension of NaH (60% dispersion in oil, 256 mg, 6.39 mmol) in anhydrous THF (10 mL) at 0 °C and the resulting solution is stirred for 0.5 h. To this solution is added drop wise a solution of 2-fluoro-6-methyl-3-nitropyridine (1.0 g, 6.09 mmol) in anhydrous THF (5 mL). After complete addition the solution is stirred at 0 °C for 0.5 h, before being allowed to warm to ambient temperature. The reaction is stirred at ambient temperature for 18 h, quenched with water (30 mL) and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organic extracts are washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. 2-Methoxy-6-methyl-3-nitropyridine is obtained as a yellow oil (539 mg, 53 % yield) after purification by prep-HPLC (Prep-HPLC-3). ^{1}H NMR (400 MHz, DMSO D6) δ: 8.34 (d, J = 8.1 Hz, 1 H), 7.09 (d, J = 8.1 Hz, 1 H), 4.01 (s, 3 H), 2.51 (s, 3 H).

Step 2. To a degassed solution of 2-methoxy-6-methyl-3-nitropyridine (539 mg, 3.21 mmol) in methanol (10 mL) is added $Pd(OH)_2/C$ (255 mg) followed by ammonium formate. The reaction mixture is stirred at 50°C for 20 h and is then filtered over a Whatmann-Filter and evaporated. The residue is dissolved in EtOAc (30 mL) and the organic solution is washed with sat. $NaHCO_3$ sol. (15 mL) followed by brine (15 mL). The organic phase is dried over $MgSO_4$, filtered and evaporated to give 2-methoxy-6-methylpyridin-3-amine **I-1.A** as a yellow oil (199 mg, 45% yield). LCMS-2: t_R = 0.38 min, $[M+1]^+$ 139.13; ^1H NMR (400 MHz, DMSO D6) δ: 6.78 (d, J = 7.5 Hz, 1 H), 6.54 (d, J = 7.5 Hz, 1 H), 4.65 (s, 2 H), 3.82 (s, 3 H), 2.23 (s, 3 H).

Intermediate 1.B: 2-Isopropoxy-6-methylpyridin-3-amine

2-Isopropoxy-6-methylpyridin-3-amine **I-1.B** is synthesized using the methodology described for **I-1.A** starting from commercially available 2-fluoro-6-methyl-3-nitropyridine and isopropanol. ^1H NMR (400 MHz, DMSO D6) δ: 6.77 (d, J = 7.5 Hz, 1 H), 6.49 (d, J = 7.5 Hz, 1 H), 5.22 (m, 1 H), 4.53 (s, 2 H), 2.21 (s, 3 H), 1.27 (d, J = 6.2 Hz, 6 H).

Intermediate 1.C: 2-(Difluoromethoxy)-6-methylpyridin-3-amine

Step 1. A suspension of 6-methyl-3-nitropyridin-2-ol (10 g, 61.6 mmol) and Na_2SO_4 (21.89 g, 15.4 mmol) in MeCN (250 mL) is heated up to 60°C and 2,2-difluoro-2-(fluorosulfonyl)acetic acid (8.8 mL, 80 mmol) is added drop wise over 10 min. The reaction mixture is stirred for another hour and is then quenched with NaOH 3M (250 mL) and the acetonitrile is removed in vacuo. The remaining aqueous component is extracted with EtOAc (3 x 200 mL). The combined organic extracts are washed with water (50 mL) followed by brine (100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The yellow oil is purified by column chromatography (Biotage, Heptane: EtOAc 1:0 to 1:1) to give 2-(difluoromethoxy)-6-methyl-3-nitropyridine as a yellow oil that crystallized upon standing (10.9 g, 85 % yield). ^1H NMR (400 MHz, DMSO D6) δ: 8.51 (d, J = 8.2 Hz, 1 H), 7.82 (t, J = 71.3 Hz, 1 H), 7.39 (d, J = 8.2 Hz, 1 H), 3.37 (s), 2.55 (s, 3 H).

Step 2. To 2-(difluoromethoxy)-6-methyl-3-nitropyridine (4.65 g, 22.8 mmol) in degassed methanol (100 mL) is added 10% palladium on carbon-50% wet (350 mg) and the reaction is hydrogenated at atmospheric pressure for 18 h. The mixture is filtered through Celite pad. The pad is rinsed with THF (3 x 10 mL) and the organic solution is concentrated in vacuo to afford 2-(difluoromethoxy)-6-methylpyridin-3-amine **I-1.C** as a pale yellow oil that crystallized upon standing (4.1 g, 92 % yield). LCMS-2: t_R = 0.75 min, no mass; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.52 (t, J = 73.5 Hz, 1 H), 6.96 (d, J = 7.8 Hz, 1 H), 6.77 (d, J = 7.8 Hz, 1 H), 2.36 (s, 3 H).

Intermediate 2 : 1-Benzhydryl-3-(2-bromophenyl)azetidine-3-carboxylic acid

Step 1. To a solution of commercially available 1-bromo-2-fluorobenzene (5 g, 28.6 mmol) in THF (60 mL) is added 1-benzhydrylazetidine-3-carbonitrile (10.6 g, 42.9 mmol) and KHMDS 95% (10.3 mL, 42.9 mmol). The reaction mixture is left stirring at room temperature overnight. The reaction mixture is then concentrated to an oil under vacuum, diluted with EtOAc (100 mL) and washed with water (2 x 50 mL). The organic phase is dried over $MgSO_4$ and concentrated under vacuum. The crude material is purified by prep. HPLC (Prep-HPLC-2

conditions) to afford 1-benzhydryl-3-(2-bromophenyl)azetidine-3-carbonitrile as a beige solid (7.64 g, 66% yield). ^{1}H NMR (400 MHz, DMSO D6) δ: 7.70 (d, J = 7.9 Hz, 1 H), 7.47-7.42 (m, 6 H), 7.36-7.31 (m, 5 H), 7.25-7.21 (m, 2 H), 4.56 (s, 1 H), 3.98 (d, J = 8.0 Hz, 2 H), 3.49-3.42 (m, 2 H).

Step 2. To a solution of 1-benzhydryl-3-(2-bromophenyl)azetidine-3-carbonitrile (7.2 g, 17.9 mmol) in ethanol (80 mL) is added NaOH 25% (40 mL). The reaction mixture is stirred at 80°C for 3-4 days (reaction monitored by LCMS) and is then cooled down to 0°C and acidified by aq. 2M HCl. The mixture is extracted with EtOAc (2 x 200 mL), dried over MgSO4, filtered and evaporated. The crude material is purified by column chromatography (eluent: DCM/MeOH 9:1) to give 1-benzhydryl-3-(2-bromophenyl)azetidine-3-carboxylic acid **I-2** as yellow foam (6.37 g, 84% yield). LCMS-2: t_R = 0.83 min, $[M+1]^+$ 423.99; ^{1}H NMR (400 MHz, DMSO D6) δ: 7.54 (d, J = 7.8 Hz, 1 H), 7.43-7.41 (m, 4 H), 7.37 (d, J = 4.2 Hz, 2 H), 7.29 (t, J = 7.3 Hz, 4 H), 7.21-7.17 (m, 3 H), 4.47 (s, 1 H), 3.88 (d, J = 7.8 Hz, 2 H), 3.36 (d, J = 7.7 Hz, 2 H).

Intermediate 3: 1-Benzhydryl-3-(2-bromophenyl)azetidine-3-carbonyl chloride

1-Benzhydryl-3-(2-bromophenyl)azetidine-3-carboxylic acid **I-3** (538 mg, 1.38mmol) is dissolved in DCM (10 mL). Three drops of DMF are added followed by thionyl chloride (0.5 mL, 6.9 mmol) and the reaction is stirred at 50°C for 1h (monitored by LCMS). The reaction mixture is then evaporated to give crude 1-benzhydryl-3-(2-bromophenyl)azetidine-3-carbonyl chloride **I-3** as a wax (620 mg) that is used a such.

Intermediate 4: 1-(*tert*-butoxycarbonyl)-4-(2-isopropylphenyl)piperidine-4-carboxylic acid

Step 1. A mixture of commercially available 2-bromophenylacetonitrile (10 g, 51 mmol) and tetrabutylammonium hydrogen sulfate (1.77 g, 5.1 mmol) in 60 mL of THF and 90 mL of 50% aqueous NaOH solution is heated at reflux for 10 min. Thereafter N-benzyl-N,N-bis(2-chloroethyl)amine hydrochloride (15 g, 56.1 mmol) are added at r.t. and the mixture is refluxed overnight. Cooling to r.t. is followed by dilution with water (120 mL) and extraction with EtOAc (2 x 200 mL). The combined organic extracts are washed with brine (100mL), dried with $MgSO_4$, and concentrated in vacuo. The crude compound is crystallized in acetonitrile to give 1-benzyl-4-(2-bromophenyl)piperidine-4-carbonitrile (12.6 g, 69% yield) as white crystalline solid. ^{1}H NMR (500 MHz, DMSO D6) δ: 7.75 (dd, J_1 = 1.3 Hz, J_2 = 7.9 Hz, 1 H), 7.55 (dd, J_1 = 1.6 Hz, J_2 = 8.1 Hz, 1 H), 7.48 (td, J_1 = 1.3 Hz, J_2 = 7.4 Hz, 1 H), 7.35-7.32 (m, 5 H), 7.30-7.25 (m, 1 H), 3.58 (s, 2 H), 3.01-2.98 (m, 1 H), 2.98-2.95 (m, 1 H), 2.54-2.52 (m, 2H), 2.43-2.39 (m, 2 H), 2.00 (td, J_1 = 3.4 Hz, J_2 = 12.8 Hz, 2 H).

Step 2. A mixture of 1-benzyl-4-(2-bromophenyl)piperidine-4-carbonitrile (29.4 g, 82.9 mmol), acetic acid (75 mL) and concentrated sulfuric acid (75 mL) in water (75 mL) is stirred at reflux for 4 days (reaction monitored by LCMS). The reaction mixture is then diluted with water (50 mL) and 25% aqueous solution HCl (50 mL) and is stirred for 15 min. TBME (100 mL) is added. The mixture for sirred for another 15 min and is stored at 4°C overnight. The white precipitate is filtered, rinsed with TBME and dried in vacuo to give 1-benzyl-4-(2-bromophenyl)piperidine-4-carboxylic acid (22.1 g, 71% yield) as a white powder. LCMS-2: t_R = 0.72 min, $[M+1]^+$ 374.17 and 376.18.

Step 3. 1-Benzyl-4-(2-bromophenyl)piperidine-4-carboxylic acid (10 g, 26.7 mmol) and isopropenyl boronic acid pinacolester (15.1 mL, 80.2 mmol) are dissolved in dioxane (120 mL) and water (60 mL). Tripotassium phosphate (29.9 g, 134 mmol) is then added followed by palladium acetate (300 mg, 1.34 mmol) and di(1-adamantyl)-n-butylphosphine (969 mg, 2.67 mmol). The degassed reaction mixture is heated at 100°C overnight (reaction monitored by LCMS) The reaction is diluted with EtOAc (200 mL) and extracted with 2N HCl (20 mL). The acidic aqueous phase is extracted with EtOAc (3 x 150 mL). All organic phases are combined (650 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated to give the crude compound that is purified by prep. HPLC (Prep-HPLC-3 conditions) to give 1-benzyl-4-(2-(prop-1-en-2-yl)phenyl)piperidine-4-carboxylic acid **I-4** as a beige solid (8.4 g, 93 % yield). ^{1}H NMR (400 MHz, DMSO D6) δ: 12.70 (s, 1 H), 7.44 (d, J = 7.9 Hz, 1 H), 7.33-7.18 (m, 7 H), 7.01 (dd, J_1 = 1.2 Hz, J_2 = 7.3 Hz, 1 H), 5.10 (s, 1 H), 4.71 (s, 1 H), 2.43-2.38 (m, 4 H), 2.34-2.31 (m, 2 H), 2.13-2.11 (m, 2 H), 2.01 (s, 3 H).

Step 4. A degassed mixture of 1-benzyl-4-(2-(prop-1-en-2-yl)phenyl)piperidine-4-carboxylic acid (8.4 g, 24.8 mmol) and Pd/C 10%-50% water (2g) in MeOH/THF 1:1 (200 mL) is hydrogenated at r.t. for 4 days (reaction monitored by LCMS). The mixture is degassed with argon, filtered on Celite pad, rinsed with THF, dried over $MgSO_4$ and evaporated to give 4-(2-isopropylphenyl)piperidine-4-carboxylic acid (5.6 g, 92% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO) δ: 9.06 (s br, 1 H), 7.38 (dd, J_1 = 1.4 Hz, J_2 = 7.8 Hz, 1 H), 7.31-7.27 (m, 2 H), 7.24-7.16 (m, 1 H), 3.44 (s br, 1 H), 3.27-3.12 (m, 5 H), 2.38 (m, 2 H), 2.20-2.12 (m, 2 H), 1.14 (d, J = 6.7 Hz, 6 H).

Step 5. A mixture of 4-(2-isopropylphenyl)piperidine-4-carboxylic acid (5.65 g, 23.2 mmol) , DIPEA (13.6 mL, 79.7 mmol) and Boc_2O (4.8 g, 21.9 mmol) is stirred at r.t. for 24 h. Water is then added followed by 1N HCl in order to adjust the pH to 1. The reaction mixture is extracted four times with DCM (4 x 200 mL). The combined extracts are dried over MgSO4, dried, filtered an evaporated to give 1-(*tert*-butoxycarbonyl)-4-(2-isopropylphenyl)piperidine-4-carboxylic acid **I-4** (9 g, quantitative) as a yellow oil. ^{1}H NMR (400 MHz, DMSO D6) δ: 12.73 (s, 1 H), 7.36-7.31 (m, 2 H), 7.26-7.23 (m, 1 H), 7.18-7.14 (m, 1 H), 3.75-3.65 (m, 2 H), 3.32-3.25 (m, 3 H), 2.28-2.20 (m, 2 H), 1.89-1.77 (m, 2 H), 1.41 (s, 9 H), 1.14 (d, J = 6.6 Hz, 6 H).

Alternatively, **I-4** can be prepared from commercial available 4-(2-bromophenyl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid:

Step 1. 1-(*tert*-Butoxycarbonyl)-4-(2-(prop-1-en-2-yl)phenyl)piperidine-4-carboxylic acid is prepared from commercial available 4-(2-bromophenyl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid following the methodology described for **I-4** in step 3 (59% yield). ^{1}H NMR (400 MHz, DMSO D6) δ: 7.44 (dd, J_1 = 1.5 Hz, J_2 = 8.0 Hz, 1 H), 7.30-7.22 (m, 2 H), 7.05 (dd, J_1 = 1.8 Hz, J_2 = 7.2 Hz, 1 H), 5.14 (t, J = 1.6 Hz, 1 H), 4.75 (d, J = 1.0 Hz, 1 H), 3.54-3.48 (m, 2 H), 3.32-3.15 (m, 2 H), 2.27-2.23 (m, 2 H), 2.06-2.00 (m, 5 H).

Step 2. A degassed mixture of 1-(*tert*-butoxycarbonyl)-4-(2-(prop-1-en-2-yl)phenyl)piperidine-4-carboxylic acid (986 mg, 2.85 mmol) and Pd/C 10%-50% water (100 mg) in MeOH/THF 1:1 (60 mL) is hydrogenated at r.t. for

1 h (reaction monitored by LCMS). The mixture is degassed with argon, filtered on Celite pad, rinsed with THF, dried over $MgSO_4$ and evaporated to give 1-(*tert*-butoxycarbonyl)-4-(2-isopropylphenyl)piperidine-4-carboxylic acid **I-4** as a white foam (923 mg, 93% yield).

Intermediate 5: 1-benzyl-3-(2-bromophenyl)pyrrolidine-3-carboxylic acid

Step 1. Paraformaldehyde (2.17 ml, 14.8 mmol) and K_2CO_3 (1.37 g, 9.9 mmol) are added to a solution of commercially available 2-bromophenylacetonitrile (1.32 mL, 9.9 mmol) in DMF (60 mL). The reaction is stirred at 80°C for 1 night. After cooling to r.t., water (100 mL) is added and the aqueous layer is extracted with EtOAc (150 mL, 50 mL). The combined organic extracts are washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude compound is purified by prep. HPLC (Prep-HPLC-3 conditions) to give 2-(2-bromophenyl)acrylonitrile (561 mg, 27% yield) as an orange oil. ^{1}H NMR (400 MHz, DMSO) δ: 7.77-7.74 (m, 1 H), 7.53-7.48 (m, 2 H), 7.42 (ddd, J_1 = 2.9 Hz, J_2 = 6.3 Hz, J_3 = 8.0 Hz, 1 H), 6.61 (s, 1 H), 6.36 (s, 1 H).

Step 2. 2-(2-Bromophenyl)acrylonitrile (461 mg, 2.22 mmol) and N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine (1.18 mL, 4.43 mmol) are dissolved in DCM (10mL). To this solution TFA (208 uL, 2.66 mmol) is added under ice-cooling. After returning to rt, the reaction is stirred for overnight. The reaction mixture is then poured into water (25 mL) and extracted with DCM (2x50mL). The combined organic extracts are washed with $NaHCO_3$, followed with brine, is dried over $MgSO_4$, filtered and evaporated. The crude compound is purified by prep HPLC (Prep-HPLC-3 conditions) to give 1-benzyl-3-(2-bromophenyl)pyrrolidine-3-carbonitrile (495 mg, 65% yield) as a yellow oil. LCMS-2: t_R = 0.74 min, $[M+1]^+$ 341.22 and 343.20.

Step 3. 1-Benzyl-3-(2-bromophenyl)pyrrolidine-3-carbonitrile (495 mg, 1.45 mmol) is subjected to the hydrolysis conditions described for **I-4** to give 1-benzyl-3-(2-bromophenyl)pyrrolidine-3-carboxylic acid **I-5** as a beige solid (293 mg, 56% yield). LCMS-2: t_R = 0.64 min, $[M+1]^+$ 360.16 and 362.16.

Intermediate 6: 1-(*tert*-butoxycarbonyl)-4-(2-isopropylphenyl)piperidine-4-carboxylic acid

Step 1. To a solution of **I-2** (5.0 g, 11.8 mmol) in MeOH (30 mL) is added conc. sulfuric acid (10mL). The reaction mixture is stirred at 75°C for 24 h and is then evaporated. The residue is dissolved in EtOAc (100 mL) and washed with sat. $NaHCO_3$. The phases are separated and the organic phase is washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated. The crude compound is purified by Chromatography (CombiFlash Hept /EtOAc 9:1) to methyl 1-benzhydryl-3-(2-bromophenyl)azetidine-3-carboxylate as yellow oil (4.12 g, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (dd, J_1 = 1.1 Hz, J_2 = 8.0 Hz, 1 H), 7.49-7.41 (m, 4 H), 7.38-7.32 (m, 1 H), 7.32-7.26 (m, 5 H), 7.24-7.19 (m, 2 H), 7.17 (td, J_1 = 1.9 Hz, J_2 = 7.9 Hz, 1 H), 4.43 (s, 1 H), 4.08 (d, J = 8.3 Hz, 2 H), 3.74 (s, 3 H), 3.51 (d, J = 8.2 Hz, 2 H).

Step 2. Methyl 1-benzhydryl-3-(2-bromophenyl)azetidine-3-carboxylate (4.12 g, 9.44 mmol) is subjected to the Suzuki conditions described for intermediate 3 to give methyl 1-benzhydryl-3-(2-(prop-1-en-2-yl)phenyl)azetidine-3-carboxylate as a yellow oil (3.64 g, 97% yield). ^{1}H NMR (400 MHz, DMSO D6) δ: 7.40-

7.38 (m, 4 H), 7.30-7.23 (m, 7 H), 7.21-7.17 (m, 2 H), 7.12-7.10 (m, 1 H), 5.06 (s, 1 H), 4.59 (s, 1 H), 4.42 (s, 1 H), 3.82 (d, *J* = 7.7 Hz, 2 H), 3.66 (s, 3 H), 3.21 (d, *J* = 7.7 Hz, 2 H), 1.92 (s, 3 H).

Step 3. Methyl 1-benzhydryl-3-(2-(prop-1-en-2-yl)phenyl)azetidine-3-carboxylate (3.64 g, 9.16 mmol) is subjected to the saponification conditions described for I-3 to give 1-benzhydryl-3-(2-(prop-1-en-2-yl)phenyl)azetidine-3-carboxylic acid as a beige solid (3.35 g, 95% yield). ^{1}H NMR (400 MHz, DMSO D6) *δ*: 7.39 (d, *J* = 7.3 Hz, 4 H), 7.28 (t, *J* = 7.4 Hz, 4 H), 7.23-7.17 (m, 5 H), 7.11-7.09 (m, 1 H), 5.06 (s, 1 H), 4.71 (s, 1 H), 4.39 (s, 1 H), 3.82 (d, *J* = 7.6 Hz, 2 H), 3.14 (d, *J* = 7.5 Hz, 2 H), 1.95 (s, 3 H).

Step 4. A mixture of 1-benzhydryl-3-(2-(prop-1-en-2-yl)phenyl)azetidine-3-carboxylic acid (3.35 g, 8.74 mmol), 25% HCl solution (18 mL) and $Pd(OH)_2$/C 20% (1.6 g) in MeOH (100 mL) is degassed and is then hydrogenated at 1 bar for 18 h (reaction monitored by LCMS). The reaction mixture is then degassed with argon and is filtered on Celite pad which is rinsed with MeOH. Volatiles are evaporated and the residue is crystallized in MeCN to give hydrochloride of 3-(2-isopropylphenyl)azetidine-3-carboxylic acid as a white solid (1.17 g, 61% yield). ^{1}H NMR (400 MHz, DMSO D6) *δ*: 13.55 (s br, 1 H), 9.40 (s br, 1 H), 9.15 (s br, 1 H), 7.39 (d, *J* = 6.9 Hz, 1 H), 7.34 (t, *J* = 7.2 Hz, 1 H), 7.24 (t, *J* = 7.0 Hz, 1 H), 7.18 (d, *J* = 7.6 Hz, 1 H), 4.57-4.54 (m, 2 H), 4.39-4.35 (m, 2 H), 1.13 (d, *J* = 6.7 Hz, 6 H).

Step 5. To a suspension of 3-(2-isopropylphenyl)azetidine-3-carboxylic acid hydrochloride (1.17 g, 4.57 mmol) in DCM (25 ml) is added DIPEA (5.9 mL, 34.4 mmol) followed by Boc_2O (1.1 g, 5.02 mmol). The mixture stirred at room temperature for 24 h. 1N HCl is added in order to adjust the pH to 1, and the reaction mixture is extracted with DCM (4 times). The combined organic extracts are dried over $MgSO_4$, filtered and evaporated. The residue is purified by chromatography (CombiFlash Hept/EtOAc 1.5:1) to give 1-(*tert*-butoxycarbonyl)-4-(2-isopropylphenyl)piperidine-4-carboxylic acid **I-6** as a white solid (0.85 g, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.36-7.31 (m, 2 H), 7.26-7.21 (m, 1 H), 7.18 (d, *J* = 7.0 Hz, 1 H), 4.64 (d, *J* = 8.5 Hz, 2 H), 4.37 (d, *J* = 8.5 Hz, 2 H), 2.61 (m, 1 H), 1.46 (s, 9 H), 1.19 (d, *J* = 6.7 Hz, 6 H).

Intermediate 7: 1-benzhydryl-3-(2-bromo-6-methylphenyl)azetidine-3-carboxylic acid

Intermediate **I-7** is prepared from 3-bromo-2-fluorotoluene according to the method described for **I-2**. For a cleaner hydrolysis of the nitrile group to the corresponding carboxylic acid a two step sequence is preformed, using first basic conditions (KOH) to form the intermediate amide followed by an acidic hydrolysis of the amide as described for **I-4**. LCMS-2: t_R = 0.84 min, $[M+1]^+$ 435.86.

Intermediate 8: 1-benzhydryl-3-(2-bromo-5-methylphenyl)azetidine-3-carboxylic acid

Intermediate **I-8** is prepared from 4-bromo-3-fluorotoluene according to the method described for **I-2**. LCMS-2: t_R = 0.85 min, $[M+1]^+$ 435.75.

Intermediate 9: 1-benzhydryl-3-(2-bromo-4-methylphenyl)azetidine-3-carboxylic acid

Intermediate **I-9** is prepared from 3-bromo-4-fluorotoluene according to the method described for **I-2**. For a cleaner hydrolysis of the nitrile group to the corresponding carboxylic acid a two step sequence is preformed,

using first basic conditions (KOH) to form the intermediate amide followed by an acidic hydrolysis of the amide as described for **I-4**. LCMS-2: t_R = 0.86 min, $[M+1]^+$ 435.93.

Intermediate 10: 1-benzhydryl-3-(2-bromo-6-fluorophenyl)azetidine-3-carboxylic acid

Intermediate **I-10** is prepared from 1-bromo-2,3-difluoro-benzene according to the method described for **I-2**. LCMS-2: t_R = 0.83 min, $[M+1]^+$ 440.24.

Intermediate 11: 1-benzhydryl-3-(2-bromo-5-fluorophenyl)azetidine-3-carboxylic acid

Intermediate **I-11** is prepared from 1-bromo-2,4-difluoro-benzene according to the method described for **I-2**. LCMS-2: t_R = = 0.83 min, $[M+1]^+$ 440.21.

Intermediate 12: 1-benzhydryl-3-(2-bromo-5-methoxyphenyl)azetidine-3-carboxylic acid

Intermediate **I-12** is prepared from 4-bromo-3-fluoroanisole according to the method described for **I-2**. LCMS-2: t_R = 0.84 min, $[M+1]^+$ 451.97.

Intermediate 13: 3-(carboxymethyl)oxetane-3-carboxylic acid

The title compound **I-13** is prepared from commercially available ethyl-2-(3-cyanooxetan-2-yl)acetate according to the method described in US20080207573.

Intermediate 14: 3-(2-(benzyloxy)-2-oxoethoxy)propanoic acid

To a solution of benzyl-glycolate (1.0 g, 6.02 mmol) in DMF (60 mL) is added a suspension of NaH (60% dispersion in oil, 433 mg, 10.8 mmol). After 1 h a solution of 2-(3-brom-propoxy)-tetrahydro-2-H-pyran (1.07 g, 4.81 mmol) in DMF (2 mL) is added and the reaction mixture is stirred at 80°C for 2 h. Water (23 mL) is then added and the mixture is extracted with EtOAc (100 mL). The extract is washed with brine, dried over $MgSO_4$, filtered and evaporated. The yellow residue is purified by prep. HPLC (Prep-HPLC-3 conditions) to give benzyl 2-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)acetate (192 mg) as a yellow oil. Next, a solution of benzyl 2-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)acetate (138 mg, 0.46 mmol) and p--toluenesulfonic acid monohydrate (8.8 mg, 0.05 mmol) in MeOH (10 mL) is stirred at r.t. for 2 h (reaction monitored by LCMS). The reaction is diluted with Et_2O (60 mL) and washed with $NaHCO_3$ (10 mL). The organic phase is dried over $MgSO_4$, filtered and evaporated to give crude benzyl 2-(3-hydroxypropoxy)acetate that is dissolved in MeCN (5 mL). Sequentially a buffer solution of NaH_2PO_4 (0.1mol/L, 0.5 mL), 2,2,6,6-tetramethylpiperidin-1-oxyl radical (TEMPO, 7.3 mg, 0.05 mmol), aq. solution of sodium chlorite (80 g/L, 1.1 mL) and sodium hypochlorite (50 uL) are added and the reaction mixture is stirred at 50 °C overnight. The mixture is then quenched with saturated sodium sulphite (2 mL) and volatiles are evaporated. The residue is dissolved in 3 mL of DMF/MeCN (1:1) and is purified by prep. HPLC (Prep-HPLC-3 conditions) to give the title compound **I-14** as a beige wax (11 mg). LCMS-2: t_R = 0.76 min, $[M+1]^+$ 239.18; ^{1}H NMR (500 MHz, MeOD) δ: 7.38 (m), 7.42-7.30 (m, 5 H), 5.20 (s, 2 H), 4.19 (s, 2 H), 3.81 (t, J = 6.4 Hz, 2 H), 2.58 (t, J = 6.4 Hz, 2 H).

Intermediate 15: 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid

The title compound **I-15** is prepared from commercially available dimethyl bicyclo[1.1.1]pentane-1,3-dicarboxylate according to the method described in *J.Med.Chem.* 2012, 55(7), 3414-3424 (Stepan, A. F. *et al.*).

Intermediate 16: 3-(methylsulfonamido)-3-oxopropanoic acid

The title compound **I-16** is prepared from commercially available methylpropiolate and methansulfonylazide according to the method described in X. Wang *et al.Tetrahedron* 2011, 67, 6294-6299.

Intermediate 17: 4-ethoxy-3,3-difluoro-4-oxobutanoic acid

To a solution of 2,2-difluorosuccinic acid (100 mg, 0.649 mmol) in isopropylacetate (2 mL) trifluoroacetic anhydride (108 uL, 0.78 mmol) is added. The solution is stirred at 50 °C for 1 h to yield 2,2-difluorosuccinic anhydride that is opened with ethanol (200 uL) to afford crude 3,3-difluoro-4-methoxy-4-oxobutanoic acid **I-17** (160 mg) as a yellow oil. ^{1}H NMR (400 MHz, DMSO) δ: 13.20 (s br, 1 H), 4.30 (q, J = 7.2 Hz, 1 H), 3.36 (t, J_{H-F}= 14.9 Hz, 2 H), 1.25 (t, J = 7.2 Hz, 3 H).

Intermediate 18: (*S*)-(+)-Citramalic acid

Intermediate **I-18** is prepared from commercially available (R)-(+)-4-methyl-4-(trichloromethyl)-2-oxetanone according to the method described in M. Gill *et al.*, *Aust. J. Chem.* **2000**, *53*, 245-256.

Examples

Example 1: 3-(2-isopropylphenyl)-N-(2-methoxy-6-methylpyridin-3-yl)azetidine-3-carboxamide

Step 1. To a solution of 2-methoxy-6-methylpyridin-3-amine **I-1.A** (191 mg, 1.38 mmol) in THF (10 mL) is added a suspension of NaH (60% dispersion in oil, 120 mg, 2.76 mmol). After stirring the mixture for 30 min, a suspension of benzhydryl-3-(2-bromophenyl)azetidine-3-carbonyl chloride **I-3** (608 mg, 1.38 mmol) in THF (10 mL) is added drop wise and stirring is continued for 2 h (reaction monitored by LCMS). The reaction mixture is then diluted with DCM (50 mL) and is washed with water (20 mL). The organic phase is dried over $MgSO_4$, filtered and evaporated. The crude compound is crystallized in MeCN to give 1-benzhydryl-3-(2-bromophenyl)-N-(2-methoxy-6-methylpyridin-3-yl)azetidine-3-carboxamide as an off-white solid (278 mg, 37% yield). ^{1}H NMR (400 MHz, DMSO D6) δ: 11.10 (s, 1H), 8.42 (d, J = 7.9 Hz, 1 H), 7.62-7.57 (m, 5 H), 7.40-7.34 (m, 5 H), 7.28-7.18 (m, 4 H), 6.88 (d, J = 7.9 Hz, 1 H), 4.73 (s, 1 H), 4.17 (s, 3 H), 4.01 (d, J = 7.0 Hz, 2 H), 3.52 (d, J = 7.3 Hz, 2 H), 2.42 (s, 3 H).

Step 2. 1-Benzhydryl-N-(2-methoxy-6-methylpyridin-3-yl)-3-(2-(prop-1-en-2-yl)phenyl)azetidine-3-carboxamide is prepared from 1-benzhydryl-3-(2-bromophenyl)-N-(2-methoxy-6-methylpyridin-3-yl)azetidine-3-carboxamide following the methodology described for **I-6** - step 3 (216 mg, 84% yield). ^{1}H NMR (400 MHz, DMSO D6) δ: 11.24 (s, 1 H), 8.44 (d, J = 7.9 Hz, 1 H), 7.57 (d, J = 7.5 Hz, 4 H), 7.36 (t, J = 7.5 Hz, 4 H), 7.26-7.15 (m, 5 H),

7.00 (d, *J* = 7.3 Hz, 1 H), 6.88 (d, *J* = 7.9 Hz, 1 H), 4.98 (s, 1 H), 4.74 (s, 1 H), 4.68 (s, 1 H), 4.16 (s, 3 H), 3.87 (d, *J* = 7.4 Hz, 2 H), 3.33 (d, *J* = 7.4 Hz, 2 H), 2.42 (s, 3 H), 1.94 (s, 3 H).

Step 3. A mixture of 1-benzhydryl-N-(2-methoxy-6-methylpyridin-3-yl)-3-(2-(prop-1-en-2-yl)phenyl)azetidine-3-carboxamide (216 mg, 0.43 mmol), 25% HCl solution (4.5 mL) and $Pd(OH)_2$/C 20% wt. % (300 mg) in MeOH (25 mL) is degassed and is then hydrogenated at 1 bar for 18 h (reaction monitored by LCMS). The reaction mixture is then degassed with argon and is filtered on Celite pad which is rinsed with MeOH (10 mL). Volatiles are evaporated and the residue is dissolved in EtOAc (60 mL). The organic solution is washed with a solution of NaOH 5N aq. (30 mL), is dried over $MgSO_4$, filtered and evaporated. The crude material is purified by prep-TLC (eluent: DCM/MeOH: 9/1) to give 3-(2-isopropylphenyl)-N-(2-methoxy-6-methylpyridin-3-yl)azetidine-3-carboxamide **Ex 1** as a white solid (32 mg, 22% yield). LCMS-1: t_R = 0.68 min, $[M+1]^+$ 340.43; ^{1}H NMR (400 MHz, CD_3OD) δ: 8.34 (d, *J* = 7.9 Hz, 1 H), 7.46-7.35 (m, 4 H), 6.78 (d, *J* = 7.9 Hz, 1 H), 4.31 (d, *J* = 8.5 Hz, 2 H), 4.17 (d, *J* = 8.5 Hz, 2 H), 3.72 (s, 3 H), 2.49 (m, 1 H), 2.36 (s, 3 H), 1.13 (d, *J* = 6.7 Hz, 6 H).

Example 2: N-(2-isopropoxy-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

N-(2-isopropoxy-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide is prepared from 2-isopropoxy-6-methylpyridin-3-amine **I-1.B** (1.8 g) and benzhydryl-3-(2-bromophenyl)azetidine-3-carbonyl chloride **I-3** (4.36 g) following the methodology described for **Ex 1** (1.29 g, white solid). LCMS-1: t_R = 0.80 min, $[M+1]^+$ 368.34;^{1}H NMR (400 MHz, CD_3OD) δ: 8.45 (d, *J* = 7.9 Hz, 1 H), 7.49-7.47 (m, 2 H), 7.43-7.40 (m, 2 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 5.51 (s, 1 H), 5.18-5.11 (m, 1 H), 4.38 (d, *J* = 8.2 Hz, 2 H), 4.21 (d, *J* = 8.0 Hz, 2 H), 2.37-2.44 (m, 1 H), 2.33 (s, 3 H), 1.13 (d, *J* = 6.7 Hz, 7 H), 1.02 (d, *J* = 6.2 Hz, 6 H).

Example 3: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide is prepared from 2-(difluoromethoxy)-6-methylpyridin-3-amine **I-1.C** (229 mg) and benzhydryl-3-(2-bromophenyl)azetidine-3-carbonyl chloride **I-3** (608 mg) following the methodology described for **Ex 1** (110 mg, yellow oil). LCMS-1: t_R = 0.71 min, $[M+1]^+$ 376.22; ^{1}H NMR (500 MHz, DMSO D6) δ: 9.90 (s, 1 H), 8.24 (d, *J* = 8.0 Hz, 1 H), 7.63 (t, *J* = 72.6 Hz, 1 H), 7.33 (dd, J_1 = 1.3 Hz, J_2 = 7.8 Hz, 1 H), 7.28 (td, J_1 = 1.2 Hz, J_2 = 7.3 Hz, 1 H), 7.19 (m, J_1 = 1.4 Hz, J_2 = 7.7 Hz, 1 H), 7.14 (dd, J_1 = 1.1 Hz, J_2 = 7.7 Hz, 1 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 4.07 (m, 2 H), 4.01 (m, 2 H), 2.38 (s, 3 H), 1.09 (d, *J* = 6.7 Hz, 6 H).

Example 4: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-4-carboxamide and Example 4.1: *tert*-butyl 4-((2-hydroxy-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidine-1-carboxylate

Step 1. To a solution of 1-(*tert*-butoxycarbonyl)-4-(2-isopropylphenyl)piperidine-4-carboxylic acid **I-4** (2 g, 5.76 mmol) and DMF (1 mL) in pyridine (20 mL) is added $POCl_3$ (0.79 mL, 8.63 mmol) drop wise over 35 min (complete conversion into its acyl chloride is monitored by LCMS with MeOH quench). Next, the reaction mixture is evaporated to remove the volatiles. The crude material is suspended in pyridine (20 mL) and added

drop wise to a solution of 3-amino-6-methylpyridin-2-ol (14.4 mmol, 1.79 g) in pyridine (10 mL). The reaction mixture is stirred at r.t. for 2 h and is then evaporated. The residue is dissolved in EtOAc (50 mL), is washed with water (20 mL) followed by sat. $NaHCO_3$ solution (50 mL) and brine (50 mL). The organic phase is then dried over $MgSO_4$, filtered and evaporated. The crude product is purified by prep. HPLC (Prep-HPLC-3 conditions) to give *tert*-butyl 4-((2-hydroxy-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidine-1-carboxylate (850 mg, 33% yield) as a yellow oil. LCMS-1: t_R = 1.24 min, $[M+1]^+$ 454.07; ^1H NMR (400 MHz, DMSO D6) δ: 11.88 (s, 1 H), 8.12 (d, J = 7.4 Hz, 1 H), 7.81 (s, 1 H), 7.52 (d, J = 7.5 Hz, 1 H), 7.41 (dd, J_1 = 1.4 Hz, J_2 = 7.8 Hz, 1 H), 7.35 (t, J = 7.0 Hz, 1 H), 7.29 (td, J_1 = 1.4 Hz, J_2 = 7.8 Hz, 1 H), 5.99 (d, J = 7.5 Hz, 1 H), 3.49 (s br, 4 H), 3.11-3.04 (m, 1 H), 2.28-2.24 (m, 2 H), 2.10 (s, 3 H), 1.99-1.95 (m, 2 H), 1.40 (s, 9 H), 1.02 (d, J = 6.6 Hz, 6 H).

Step 2. To a solution of 4-((2-hydroxy-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidine-1-carboxylate (850 mg, 1.87 mmol) in DMF (20 mL) is added Cs_2CO_3 (916 mg, 2.81 mmol) followed by sodium chlorodifluoroacetate (429 mg, 2.81 mmol). The reaction mixture is stirred at 60°C for 18 h. Next the mixture is diluted with EtOAc (50 mL) and is washed with sat. $NaHCO_3$ solution (25 mL) followed by brine (25 mL). The organic phase is dried over $MgSO_4$, filtered and evaporated. The residue is purified by prep. HPLC (Prep-HPLC-3 conditions) to give *tert*-butyl 4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidine-1-carboxylate as a beige powder (709 mg) **Ex 4-1** that contained about 15% of a regioisomer. LCMS-1 : t_R = 1.48 min, $[M+1]^+$ 504.17. ^1H NMR (400 MHz, DMSO D6) δ: 8.23 (s, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 7.53 (t, J = 72.6 Hz, 1 H), 7.50-7.48 (m, 1 H), 7.41 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1 H), 7.34 (d, J = 6.1 Hz, 1 H), 7.27 (m, 1 H), 7.09 (d, J = 8.0 Hz, 1 H), 3.67-3.60 (m, 2 H), 3.53-3.42 (m, 2 H), 3.28-3.20 (m, 1 H), 2.41-2.37 (m, 5 H), 1.98-1.90 (m, 2 H), 1.41 (s, 9 H), 1.09 (d, J = 6.6 Hz, 6 H).

Step 3. To a solution of 4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidine-1-carboxylate (709 mg, 1.41mmol) in DCM (20 mL) is added TFA (1.1 mL, 14.1mmol) at 10°C. The reaction mixture is stirred at r.t. for 2 h (monitored by LCMS) and is then evaporated. The residue is purified by prep. HPLC (Prep-HPLC-3 conditions) to give N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropyl-phenyl)piperidine-4-carboxamide **Ex 4** (416 mg, 73% yield) as a white solid. LCMS-1 : t_R = 0.74 min, $[M+1]^+$ 404.06. ^1H NMR (400 MHz, DMSO D6) δ: 7.97 (d, J = 8.0 Hz, 1 H), 7.91 (s, 1 H), 7.53-7.51 (m, 1 H), 7.50 (t, J = 72.5 Hz, 1 H), 7.39 (dd, J_1 = 1.5 Hz, J_2 = 7.7 Hz, 1 H), 7.33-7.25 (m, 2 H), 7.09 (d, J = 8.0 Hz, 1 H), 3.26-3.17 (m, 1 H), 3.01-2.96 (m, 2 H), 2.75-2.71 (m, 2 H), 2.36 (s, 3 H), 2.34-2.27 (m, 2 H), 1.95-1.89 (m, 2 H), 1.06 (d, J = 6.6 Hz, 6 H).

Example 5: N-(6-chloro-2-methoxypyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

Step 1. To a solution of **I-6** (40 mg, 0.125 mmol), commercial 6-chloro-2-methoxypyridin-3-amine (25 mg, 0.15 mmol) and pyridine (70 uL, 0.07 mmol) in EtOAc (1 mL) is added T3P 50% sol. in EtOAc (300 uL, 0.5 mmol). The reaction mixture is stirred at 65°C overnight. Water (5 mL) is then added and the reaction mixture is extracted with EtOAc (3 x 10 mL). The combined organic extracts are dried over $MgSO_4$, filtered and

evaporated. The residue is purified by prep. HPLC (Prep-HPLC-1 conditions) to afford tert-butyl 3-((6-chloro-2-methoxypyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate as a yellow oil (54 mg, 62% yield). LCMS-2: t_R = 1.22 min, $[M+1]^+$ 460.37. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (d, J = 8.2 Hz, 1 H), 7.48-7.41 (m, 2 H), 7.39-7.32 (m, 3 H), 6.92 (d, J = 8.2 Hz, 1 H), 4.80-4.54 (m, 2 H), 4.52-4.28 (m, 2 H), 3.75 (s, 3 H), 2.43 (m, 1 H), 1.48 (s, 9 H), 1.14 (d, J = 6.6 Hz, 6 H).

Step 2. tert-Butyl 3-((6-chloro-2-methoxypyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate is subjected to the Boc deprotection conditions described for **Ex 4** to give **Ex 5** as colorless oil (30 mg, 75% yield). LCMS-1: t_R = 0.72 min, $[M+1]^+$ 360.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (d, J = 8.2 Hz, 1 H), 8.38 (s, 1 H), 7.41-7.36 (m, 2 H), 7.34-7.29 (m, 1 H), 7.17 (d, J = 7.7 Hz, 1 H), 6.92 (d, J = 8.2 Hz, 1 H), 4.27 (s br, 4 H), 3.85 (s, 3 H), 2.51-2.41 (m, 1 H), 1.14 (d, J = 6.7 Hz, 6 H).

Example 6: N-(2,6-dimethoxypyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide hydrochloride and Example 6-1: tert-butyl 3-((2,6-dimethoxypyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate

N-(2,6-dimethoxypyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide hydrochloride **Ex 6** and tert-butyl 3-((2,6-dimethoxypyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate **Ex 6-1** are prepared from commercially available 3-amino-2,6-dimethoxypyridine hydrochloride (35 mg) and **I-6** (46 mg) following the methodology described for **Ex 5.**

Ex 6 (65 mg, yellow wax). LCMS-1: t_R = 0.70 min, $[M+1]^+$ 356.02.

Ex 6-1 (72 mg, white solid). LCMS-1: t_R = 1.44 min, $[M+1]^+$ 456.24.

Example 7: N-(2-(difluoromethoxy)pyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide hydrochloride

N-(2-(difluoromethoxy)pyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide hydrochloride **Ex 7** is prepared from commercially available 2-(difluoromethoxy)pyridin-3-amine hydrochloride (32 mg) and **I-6** (40 mg) following the methodology described for **Ex 5** (31 mg, white solid). LCMS-1: t_R = 0.68 min, $[M+1]^+$ 362.33; ^{1}H NMR (500 MHz, DMSO D6) δ: 8.63 (s, 1 H), 8.13 (d, J = 7.8 Hz, 1 H), 8.05 (d, J = 4.6 Hz, 1 H), 7.58 (t, J = 72.2 Hz, 1 H), 7.51 (d, J = 7.7 Hz, 1 H), 7.48-7.40 (m, 2 H), 7.39-7.29 (m, 2 H), 4.74-4.61 (m, 2 H), 4.48-4.42 (m, 2 H), 2.46-2.40 (m, 1 H), 1.12 (d, J = 6.6 Hz, 6 H).

Example 8: N-(2-(difluoromethoxy)-5-fluoropyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-5-fluoropyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 8** is prepared from commercially available 3-amino-5-fluoropyridin-2-ol (89 mg) and **I-6** (86 mg) following the methodology described for **Ex 4** (13.5 mg, colorless oil). LCMS-1: t_R = 0.72 min, $[M+1]^+$ 380.13.

Example 9: N-(6-ethoxy-2-methoxypyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

N-(6-ethoxy-2-methoxypyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 9** is prepared from commercially available 6-ethoxy-2-methoxypyrdin-3-amine (77 mg) and **I-6** (70 mg) using the $POCl_3$ methodology described for **Ex 4** (88 mg, yellow oil). LCMS-1: t_R = 0.76 min, $[M+1]^+$ 470.10.

Example 10: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)pyrrolidine-3-carboxamide

Step 1. 1-Benzyl-3-(2-bromophenyl)pyrrolidine-3-carboxylic acid **I-5** (273 mg, 0.76 mmol) is coupled to 2-(difluoromethoxy)-6-methylpyridin-3-amine hydrochloride **I-1.C** (319, 1.52 mmol) following the methodology described for **Ex 1** in step 1 to give 1-benzyl-3-(2-bromophenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)pyrrolidine-3-carboxamide (317 mg, 81% yield) as a pale yellow oil. LCMS-2: t_R = 0.89 min, $[M+1]^+$ 516.17 and 518.16.

Step 2. Following the methodology described for **I-4** - step 3, 1-benzyl-3-(2-bromophenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)pyrrolidine-3-carboxamide (307 mg, 0.60 mmol) is reacted with isopropenyl boronic acid pinacolester (0.56 mL, 2.97 mmol) to give

1-benzyl-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-(prop-1-en-2-yl)phenyl)pyrrolidine-3-carboxamide (228 mg, 80% yield) as a colorless oil. LCMS-2: t_R = 0.94 min, $[M+1]^+$ 478.30.

Step 3. To a solution of 1-benzyl-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-(prop-1-en-2-yl)phenyl)pyrrolidine-3-carboxamide (228 mg, 0.48 mmol) in 10 mL of methanol/THF 1:1 is added Pd/C 10% (100 mg, 0.03 mmol). The reaction mixture is degassed, hydrogenated at 1 bar and stirred for 2 h (reaction progress monitored by LCMS). The mixture is filtered on Celite and is evaporated to dryness to give the title compound **Ex 10** (138 mg, 74% yield) as a colorless oil. LCMS-1: t_R = 0.83 min, $[M+1]^+$ 390.29. ^{1}H NMR (400 MHz, CDCl3) δ: 8.49 (d, J = 8.1 Hz, 1 H), 7.60 (s, 1 H), 7.45-7.37 (m, 2 H), 7.29 (m, J = 76.8 Hz, 1 H), 7.32-7.26 (m, 2 H), 6.92 (d, J = 8.0 Hz, 1 H), 3.81-3.68 (m, 1 H), 3.47-3.25 (m, 2 H), 3.15-2.94 (m, 2 H), 2.90-2.75 (m, 1 H), 2.39 (s, 3 H), 2.31-2.18 (m, 1 H), 1.17 (d, J = 6.6 Hz, 3 H), 1.13 (d, J = 6.6 Hz, 3 H).

Example 11-1: 1-(2-aminoethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

Step 1. To a solution of N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 3** (200 mg, 0.53 mmol) and TEA (222 uL, 1.60 mmol) in DCM (5 mL) is added N-Boc-bromoethylamine (239 mg, 1.07 mmol). The reaction mixture is stirred overnight. Another portion of N-Boc-bromoethylamine (239 mg, 1.07 mmol) is then added and stirring is continued for 24h. The reaction mixture is diluted with DCM (20 mL) and is washed with water (15 mL) followed by brine (10 mL). The organic phase is dried over $MgSO_4$, filtered and evaporated. The residue is purified by prep. HPLC (Prep-HPLC-3 conditions) to

give *tert*-butyl (2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethyl)carbamate (180 mg, 0.35 mmol, 66% yield). LCMS-2: t_R = 0.99 min, $[M+1]^+$ 519.19.

Step 2. *tert*-Butyl (2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethyl)carbamate is dissolved in DCM (10 mL) and TFA (250 uL, 3.27 mmol) is added. The reaction mixture is stirred overnight and is then quenched with sat. $NaHCO_3$ (5 mL). The organic phase is collected and the aqueous phase is extracted with DCM (2 x 10 mL). The combined organic phases are dried over $MgSO_4$, filtered and evaporated to give 1-(2-aminoethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 11-1** (90 mg, 62% yield) as a wax. LCMS-1: t_R = 0.64 min, $[M+1]^+$ 419.4.

Table 1: Examples 11-2 to 11-11

Examples **11-2** to **11-11** are synthesized by nucleophilic substitution using the methodology described for example **Ex 11-1** starting from **Ex 3** or **Ex 4** and various haloalkanes. In step 1 other bases than TEA can be used such as NaOAc or Cs_2CO_3. In step 1, DCM can be replaced by DMF, MeCN or MeOH.

Example	Name	Analytics LCMS-1
Ex 11-2	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$420.36 t_R 0.71
Ex 11-3	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-hydroxyethyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide	$[M+1]^+$448.38 t_R 0.73
Ex 11-4	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-hydroxypropyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$434.17 t_R 0.73
Ex 11-5	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(oxetan-3-ylmethyl)azetidine-3-carboxamide	$[M+1]^+$446.39 t_R 0.74
Ex 11-6	1-cyano-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$401.43 t_R 1.26
Ex 11-7	1-(3-(1H-tetrazol-5-yl)propyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$486.44 t_R 0.80
Ex 11-8	1-((1H-tetrazol-5-yl)methyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$458.10 t_R 0.92
Ex 11-9	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-hydroxy-3-methylbutyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$462.03 t_R 0.84
Ex 11-10	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(1-hydroxycyclopropyl)ethyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$460.04 t_R 0.83

Ex 11-11	1-(2-aminopropyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$433.36 t_R 0.75

Example 11-12: 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)acetic acid

Step 1. Cesium carbonate (87 mg, 0.27 mmol) and benzyl bromoacetate (33 uL, 0.2 mmol) are added to a solution of N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 3** (50 mg, 0.13 mmol,) in DMF (2 mL). The reaction mixture is stirred at r.t. overnight (reaction monitored by LCMS). The mixture is then diluted with water (10 mL) and extracted with EtOAc (2 x 15 mL). The combined extracts are dried over $MgSO_4$, filtered and evaporated to give benzyl 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)acetate (16 mg, 23% yield) as a colorless oil that is used as such in the next step. LCMS-2: t_R = 1.01 min, $[M+H]^+$ = 524.17.

Step 2. To a solution of benzyl 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)acetate (16 mg, 0.03 mmol) 1 mL of ethanol/THF 1:1 is added Pd/C (4 mg, 0.03 mmol). The reaction mixture is degassed, hydrogenated at 1 bar and stirred overnight. The mixture is filtered on Celite and is evaporated to dryness to give the title compound **Ex 11-12** (11 mg, 83% yield) as a white solid. LCMS-1: t_R = 0.86 min, $[M+1]^+$ 434.30.

Example 11-13: ethyl 3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)propanoate and Example 11-14: 3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)propanoic acid

Step 1. A mixture of **Ex 3** hydrochloride (60 mg, 0.15 mmol), methyl acrylate (20 uL, 0.19 mmol) and Cs_2CO_3 (71 mg, 0.22 mmol) in DMF (15 mL) is stirred at r.t. for 18 h. The reaction mixture is evaporated and the residue is purified by prep-HPLC (Prep-HPLC-3 conditions) to give **Ex 11-13** as a white solid (51 mg, 73% yield). LCMS-1: t_R = 0.82 min, $[M+1]^+$ 476.33; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.89 (s, 1 H), 8.60 (d, J = 8.1 Hz, 1 H), 7.46 (t, J = 73.0 Hz, 1 H), 7.35-7.33 (m, 2 H), 7.26-7.21 (m, 1 H), 7.03 (d, J = 7.4 Hz, 1 H), 6.92 (d, J = 8.1 Hz, 1 H), 4.22-4.11 (m, 4 H), 3.70-3.55 (m, 2 H), 2.88 (t, J = 7.4 Hz, 2 H), 2.58-2.46 (m, 3 H), 2.41 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.18 (d, J = 6.8 Hz, 6 H).

Step 2. Ethyl 3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)propanoate **Ex 11-13** (45 mg, 0.09 mmol) is dissolved in MeOH/THF 1:1 (5 mL) and is treated with 2M LiOH (1 mL, 2.0 mmol). The solution is stirred at r.t. for 2 h (reaction progress monitored by LCMS). The reaction mixture is filtered through a syringue filterand is evaporated. The residue is purified by prep-HPLC (Prep-HPLC-3 conditions) to give **Ex 11-14** as a white solid (11 mg, 25% yield). LCMS-1: t_R = 0.77 min, $[M+1]^+$ 447.99; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.58 (d, J = 8.1 Hz, 1 H), 7.56 (s, 1 H), 7.46-7.42 (m, 2 H), 7.38-7.34 (m, 1 H), 7.30

(t, *J* = 72.8 Hz, 1 H), 7.23 (d, *J* = 7.5 Hz, 1 H), 6.94 (d, *J* = 8.1 Hz, 1 H), 4.48-4.28 (m, 2 H), 3.99-3.75 (m, 2 H), 3.00 (t, *J* = 6.1 Hz, 2 H), 2.50-2.40 (m, 3 H), 2.39 (s, 3 H), 1.15 (d, *J* = 6.5 Hz, 6 H).

Example 11-15: 1-(2-amino-2-oxoethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

To a solution of 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)acetic acid **Ex 11-12** (11 mg, 0.025 mmol) in DCM (0.5 mL) at 0°C under nitrogen is added isobutyl chloroformate (8 mg, 0.06 mmol) followed by TEA (8 uL, 0.06 mmol). The reaction mixture is stirred at 0°C for 30 min then ammonium hydroxide (8 uL, 0.05 mmol) is added. The mixture is allowed to warm up to r.t. and is stirred for 30 min. The volatiles are evaporated in vacuo and the residue is purified by prep. HPLC (Prep-HPLC-3 conditions) to give 1-(2-amino-2-oxoethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine -3-carboxamide **Ex 11-15** (10 mg, 80% yield) as a colorless oil. LCMS-1: t_R = 0.72 min, $[M+H]^+$ = 433.33.

Example 11-16: 1-(2-cyanoethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

1-(2-Cyanoethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 11-16** is prepared from **Ex 3** and acrylonitrile following the methodology described for **Ex 11-13** to give the title compound as a beige solid. LCMS-1: t_R = 0.93 min, $[M+H]^+$ = 529.14.

Example 11-17: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-hydroxy-2,2-dimethylpropyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

To a solution of N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carbox-amide **Ex 3** (68 mg, 0.18 mmol) and 3-hydroxy-2,2-dimethyl-propanal (25 mg, 0.245 mmol) in MeOH (2 mL) under inert atmosphere is added sodium cyanoborohydride (18 mg, 0.29 mmol). The reaction mixture is stirred at 50°C for 2 h (reaction monitored by LCMS) and is then quenched with water (2 mL). The mixture is diluted with MeCN (2 mL) and is then purified by prep. HPLC (Prep-HPLC-3 conditions) to give the title compound **Ex 11-17** (46 mg, 55% yield) as a colorless glass. LCMS-1: t_R = 0.79 min, $[M+1]^+$ 462.41; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.61 (d, *J* = 8.1 Hz, 1 H), 8.07 (s, 1 H), 7.42-7.35 (m, 3 H), 7.33-7.29 (m, 1 H), 7.19 (d, *J* = 7.7 Hz, 1 H), 6.92 (d, *J* = 8.1 Hz, 1 H), 4.25 (s br, 2 H), 3.70 (s br, 2 H), 3.50 (s, 2 H), 2.60 (s, 2 H), 2.53-2.45 (m, 1 H), 2.39 (s, 3 H), 1.14 (d, *J* = 6.7 Hz, 6 H), 0.94 (s, 6 H).

Table 2: Examples 11-18 to 11-66

Examples **11-18** to **11-66** are synthesized using the methodology described for example **Ex 11-17** starting from **Ex 3** or **Ex 4** and various aldehydes by using sodium cyanoborohydride or other reducing agents. Functional groups, such as alcohol or acid, may be protected with an appropriate protecting group. For example esters are saponified by 2N LiOH after the reductive amination step.

Example	Name	Analytics LCMS-1
Ex 11-18	(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2,3-dihydroxypropyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$450.22 t_R 0.71
Ex 11-19	(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2,3-dihydroxypropyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide	$[M+1]^+$478.39 t_R 0.72
Ex 11-20	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(oxetan-3-yl)azetidine-3-carboxamide	$[M+1]^+$432.35 t_R 0.84
Ex 11-21	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-((2-methyloxazol-4-yl)methyl)azetidine-3-carboxamide	$[M+1]^+$471.37 t_R 0.81
Ex 11-22	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-((1-methyl-1H-pyrazol-5-yl)methyl)azetidine-3-carboxamide	$[M+1]^+$470.37 t_R 0.86
Ex 11-23	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-((1-methyl-1H-pyrazol-4-yl)methyl)azetidine-3-carboxamide	$[M+1]^+$470.38 t_R 0.74
Ex 11-24	methyl 3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylpropanoate	$[M+1]^+$490.04 t_R 0.96
Ex 11-25	3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylpropanoic acid	$[M+1]^+$476.05 t_R 0.93
Ex 11-26	methyl 1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)cyclopropane-1-carboxylate	$[M+1]^+$488.29 t_R 0.82
Ex 11-27	1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)cyclopropane-1-carboxylic acid	$[M+1]^+$474.02 t_R 0.85
Ex 11-28	methyl 4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)butanoate	$[M+1]^+$476.48 t_R 0.82
Ex 11-29	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)butanoic acid	$[M+1]^+$462.35 t_R 0.74
Ex 11-30	methyl 4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoate	$[M+1]^+$504.35 t_R 0.86
Ex 11-31	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoic acid	$[M+1]^+$490.01 t_R 0.78
Ex 11-32	ethyl 4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3,3-dimethylbutanoate	$[M+1]^+$518.02 t_R 0.99
Ex 11-33	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3,3-dimethylbutanoic acid	$[M+1]^+$490.33 t_R 0.91
Ex 11-34	ethyl 5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)isoxazole-3-carboxylate	$[M+1]^+$529.24 t_R 1.24

Ex 11-35	5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)isoxazole-3-carboxylic acid	$[M+1]^+$501.02 t_R 0.95
Ex 11-36	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(isoxazol-5-ylmethyl)azetidine-3-carboxamide	$[M+1]^+$457.00 t_R 0.88
Ex 11-37	methyl 4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-1H-pyrazole-3-carboxylate	$[M+1]^+$514.38 t_R 0.88
Ex 11-38	4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-1H-pyrazole-3-carboxylic acid	$[M+1]^+$500.22 t_R 0.88
Ex 11-39	ethyl 3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-1H-pyrazole-4-carboxylate	$[M+1]^+$528.10 t_R 0.84
Ex 11-40	3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-1H-pyrazole-4-carboxylic acid	$[M+1]^+$500.37 t_R 0.87
Ex 11-41	methyl 2-(2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-1H-pyrrol-1-yl)acetate	$[M+1]^+$527.41 t_R 0.87
Ex 11-42	2-(2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-1H-pyrrol-1-yl)acetic acid	$[M+1]^+$513.03 t_R 0.97
Ex 11-43	methyl 5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-1H-pyrrole-2-carboxylate	$[M+1]^+$513.14 t_R 0.84
Ex 11-44	5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-1H-pyrrole-2-carboxylic acid	$[M+1]^+$499.38 t_R 0.77
Ex 11-45	methyl 6-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)picolinate	$[M+1]^+$525.31 t_R 0.84
Ex 11-46	6-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)picolinic acid	$[M+1]^+$511.05 t_R 0.84
Ex 11-47	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(oxazol-2-ylmethyl)azetidine-3-carboxamide	$[M+1]^+$457.24 t_R 0.96
Ex 11-48	methyl 2-(4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetate	$[M+1]^+$529.02 t_R 0.78
Ex 11-49	2-(4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetic acid	$[M+1]^+$515.09 t_R 0.82
Ex 11-50	methyl 4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)picolinate	$[M+1]^+$525.04 t_R 0.97
Ex 11-51	4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)picolinic acid	M+1]$^+$511.03 t_R 0.88

Ex 11-52	methyl 5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)picolinate	$[M+1]^+$525.08 t_R 0.92
Ex 11-53	5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)picolinic acid	$[M+1]^+$511.05 t_R 0.85
Ex 11-54	methyl 5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)pyrazine-2-carboxylate	$[M+1]^+$526.47 t_R 0.89
Ex 11-55	5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)-carbamoyl)3-(2-isopropylphenyl)azetidin-1-yl)methyl)pyrazine-2-carboxylic acid	$[M+1]^+$512.08 t_R 0.84
Ex 11-56	methyl 5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)furan-2-carboxylate	$[M+1]^+$514.42 t_R 0.97
Ex 11-57	5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)furan-2-carboxylic acid	$[M+1]^+$500.27 t_R 0.87
Ex 11-58	ethyl 2-(2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)oxazol-4-yl)acetate	$[M+1]^+$543.24 t_R 1.07
Ex 11-59	2-(2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)oxazol-4-yl)acetic acid	$[M+1]^+$515.27 t_R 0.90
Ex 11-60	1-(4-cyano-4-methylpentyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$471.46 t_R 0.90
Ex 11-61	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(4-methyl-4-nitropentyl)azetidine-3-carboxamide	$[M+1]^+$505.50 t_R 0.94
Ex 11-62	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(methylamino)ethyl)azetidine-3-carboxamide	$[M+1]^+$433.05 t_R 0.74
Ex 11-63	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(ethylamino)ethyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$447.31 t_R 0.77
Ex 11-64	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-methyl-2-(methylamino)propyl)azetidine-3-carboxamide	$[M+1]^+$461.20 t_R 0.91
Ex 11-65	5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-methylpentan-2-yl acetate	$[M+1]^+$510.08 t_R 0.95
Ex 11-66	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(4-hydroxy-4-methylpentyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$476.50 t_R 0.85

Example 11-67: Methyl 2-(1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)cyclopropyl)acetate and Example 11-68: 2-(1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)cyclopropyl)acetic acid

Step 1. A mixture of **Ex 3** hydrochloride (50 mg, 0.115 mmol), methyl 2-[1-(bromomethyl)cyclopropyl]acetate (37.5 mg, 0.172 mmol) and Cs_2CO_3 (150 mg, 0.46 mmol) in MeCN (1 mL) is stirred at 50°C for 18 h. The reaction mixture is evaporated and the residue is purified by prep-HPLC (Prep-HPLC-3 conditions) to give **Ex 11-67** as a colorless oil (32 mg, 56% yield). LCMS-1: t_R = 0.85 min, $[M+1]^+$ 502.06.

Step 2. methyl 2-(1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)cyclopropyl)acetate **Ex 11-67** (30 mg, 0.06 mmol) is dissolved in MeOH (2 mL) and is treated with 2M LiOH (1 mL, 2.0 mmol). The solution is stirred at r.t. overnight (reaction progress monitored by LCMS). The reaction mixture is cooled down to 0°C and slowly acidified to pH 4 with a solution of 2N HCl. The aqueous solution is then extracted with EtOAc twice. The combined organic extracts are dried over $MgSO_4$, filtered and evaporated to give the hydrochloride salt of **Ex 11-68** as a white solid (20 mg, 69% yield). LCMS-1: t_R = 0.84 min, $[M+1]^+$ 488.04.

Table 3: Examples 11-69 to 11-76

Examples **11-69** to **11-76** are synthesized using the methodology described for example **Ex 11-68** starting from **Ex 3** that is reacted with funtionalized haloalkanes.

Example	Name	Analytics LCMS-1
Ex 11-69	5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylpentanoic acid	$[M+1]^+$504.42 t_R 0.81
Ex 11-70	methyl 1-(3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)propyl)cyclopropane-1-carboxylate	$[M+1]^+$516.07 t_R 0.87
Ex 11-71	1-(3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)propyl)cyclopropane-1-carboxylic acid	$[M+1]^+$502.07 t_R 0.81
Ex 11-72	1-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethyl)cyclopropane-1-carboxylic acid	$[M+1]^+$488.08 t_R 1.14
Ex 11-73	1-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethyl)cyclobutane-1-carboxylic acid	$[M+1]^+$502.09 t_R 1.20
Ex 11-74	ethyl 2-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethoxy)acetate	$[M+1]^+$506.48 t_R 0.84
Ex 11-75	2-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethoxy)acetic acid	$[M+1]^+$478.04 t_R 0.80

Ex 11-76	3-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethyl)tetrahydrofuran-3-carboxylic acid	$[M+1]^+$518.12 t_R 1.22

Example 11-77: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(methylsulfonamido)ethyl)azetidine-3-carboxamide

To a solution of 1-(2-aminoethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 11-1** (73 mg , 0.18 mmol) in DCM (10 mL) is added triethylamine (98 uL, 0.78 mmol) followed by methanesulfonylchloride (27 uL, 0.35 mmol). The reaction mixture is stirred at r.t. overnight. The volatiles are evaporated and the residue is purified by prep. HPLC (Prep-HPLC-1 conditions) to give the title compound **Ex 11-77** (18 mg, 21% yield) as a foam. LCMS-1: t_R = 0.73 min, $[M+1]^+$ 497.06.

Example 11-78: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(dimethylamino)ethyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethyl methanesulfonate is synthesized from **Ex 11-2** following the methodology described for the preparation of **Ex 11-76**. The mesylate (40 mg, 0.08 mmol) is then reacted with 1M dimetlyamine in THF (5 mL) and stirred at 60°C. The reaction mixture is evaporated and the residue is purified by purified by prep. HPLC (Prep-HPLC-1 conditions) to give the title compound **Ex 11-78** (8 mg, 22% yield) as a foam. LCMS-1: t_R = 0.80 min, $[M+1]^+$ 447.03.

Example 11-79: Ethyl (2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethyl)glycinate and Example 11-80: (2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethyl)glycine

Step 1. methyl (2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethyl)glycinate **Ex 11-79** is synthesized from **Ex 11-1** and ethyl chloroacetate according to the protocol described for the preparation of **Ex 11-67.** LCMS-1: t_R = 0.87 min, $[M+1]^+$ 505.11.

Step 2. (2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethyl)glycine **Ex 11-80** is synthesized according to the protocol described for the preparation of **Ex 11-14**. LCMS-1: t_R = 0.76 min, $[M+1]^+$ 477.07.

Example 11-81: Ethyl N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethyl)-N-methylglycinate and Example 11-82: N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethyl)-N-methylglycine

Examples **11-81** and **11-82** are prepared from **Ex 11-62** in a similar manner to **Ex 11-79** and **Ex 11-80.**

Ex 11-81 LCMS-1: t_R = 0.94 min, $[M+1]^+$ 519.06. Ex 11-82 LCMS-1: t_R = 0.77 min, $[M+1]^+$ 491.12

Example 11-83: (S)-1-(3-amino-2-hydroxypropyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

Step 1. To a solution of N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 3** (450 mg, 1.2 mmol) in isopropanol (5 mL) is added an aqueous solution of 3M NaOH (1.5 mL) followed by R-epichlorhydrin (282 uL, 3.6 mmol). The reaction mixture is stirred at r.t. overnight, is diluted with EtOAc (15 mL) and is washed with water (10 mL). The organic phase is dried over $MgSO_4$, filtered and evaporated. The residue is purified by prep. TLC (eluent: heptane/ethylacetate 4:1) to give (R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(oxiran-2-ylmethyl)azetidine-3-carboxamide (245 mg, 47% yield) as an oil. LCMS-2: t_R = 0.89 min, $[M+H]^+$ = 432.10.

Step 2. To a solution of (R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(oxiran-2-ylmethyl)azetidine-3-carboxamide (50 mg, 0.12 mmol) in MeOH (1 mL) is added 7M NH_3 in MeOH (10 uL, 0.35 mmol). The reaction mixture is stirred at 60°C for 6 h. The volatiles are then evaporated and the residue is purified by prep. HPLC (Prep-HPLC-3 conditions) to give the title compound **Ex 11-83** (53 mg, 100% yield) as a glass. LCMS-1: t_R = 0.53 min, $[M+1]^+$ 449.07.

Table 4: Examples 11-84 and 11-85

Examples **11-84** and **11-85** are synthesized using the methodology described for example **Ex 11-83** using methyl- or dimethylamine as nucleophile.

Example	Name	Analytics LCMS-1
Ex 11-84	(S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-hydroxy-3-(methylamino)propyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$463.08 t_R 0.54
Ex 11-85	(S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-(dimethylamino)-2-hydroxypropyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$477.17 t_R 0.55

Example 11-86: (S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-hydroxy-3-(2-hydroxyacetamido)propyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

(S)-1-(3-amino-2-hydroxypropyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 11-83** (52 mg, 0.12 mmol) is added to a solution of glycolic acid (0.14 mmol, 11 mg), EDC (33 mg, 0.17 mmol), HOBt (23.5 mg, 0.17 mmol) and DIPEA (40 uL, 0.23 mmol) in DMF (5 mL). The reaction mixture is stirred at r.t. for 1 h, is then evaporated to dryness and purified by prep. HPLC (Prep-HPLC-2 conditions) to give the title compound **Ex 11-86** (22 mg, 37% yield) as an oil. LCMS-1: t_R = 0.68 min, $[M+1]^+$ 507.35; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.50 (d, J = 8.1 Hz, 1 H), 7.62-7.57 (m, 1 H), 7.49-7.43 (m, 3 H), 7.39-7.35 (m, 1 H), 7.26 (t, J = 83.8 Hz,1 H), 7.21 (d, J = 7.7 Hz, 1 H), 6.93 (d, J = 8.2 Hz, 1 H), 5.70-5.01 (m, 4H),

4.19-4.05 (m, 3 H), 3.48-3.42 (m, 1 H), 3.42-3.33 (m, 2 H), 3.29-3.20 (m, 1 H), 2.38 (s, 3 H), 2.29-2.18 (m, 1 H), 1.19 (d, *J* = 6.1 Hz, 6 H).

Example 11-87: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(2-hydroxyacetamido)ethyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(2-hydroxyacetamido)ethyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 11-87** (35 mg, solid) is prepared from -(2-aminoethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl) azetidine-3-carboxamide **Ex 11-1** (73 mg, 0.17 mmol) following the methodology described for **Ex 11-86**. LCMS-1: t_R = 0.69 min, $[M+1]^+$ 477.36; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.56 (d, *J* = 8.1 Hz, 1 H), 8.48 (s, 1 H), 7.24-7.43 (m, 5 H), 7.16 (m, 1 H), 6.94 (d, *J* = 8.1 Hz, 1 H), 4.32-3.14 (m, 2 H), 4.11 (s, 2 H), 3.79-3.57 (m, 2 H), 3.44-3.42 (m, 2 H), 2.79 (t, *J* = 5.6 Hz, 2 H), 2.50-2.43 (m, 1 H), 2.40 (s, 3 H), 1.16 (d, *J* = 6.6 Hz, 6 H).

Example 11-88: 1-(cyanomethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

To a solution of **Ex 3** hydrochloride (100 mg, 0.24 mmol) and bromoacetonitrile (19 uL, 0.27 mmol) in DMF (2 mL) is added Cs_2CO_3 (158 mg, 0.49 mmol). The reaction mixture is stirred at r.t. for 1 h (reaction monitored by LCMS), is then extracted with DCM (2 x 20 mL). The organic extracts are washed with water (10 mL), followed by brine (10mL) and are then dried over $MgSO_4$, filtered and evaporated. The residue is purified by prep. HPLC (Prep-HPLC-1 conditions) to give the title compound **Ex 11-88** (50 mg, 50% yield) as a beige solid. LCMS-1: t_R = 1.25 min, $[M+1]^+$ 415.37; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.60 (d, *J* = 8.1 Hz, 1 H), 8.17 (s, 1 H), 7.42-7.38 (m, 2 H), 7.32 (t, *J* = 72.8 Hz, 1 H), 7.34-7.30 (m, 1 H), 7.17 (d, *J* = 6.6 Hz, 1 H), 6.94 (d, *J* = 8.1 Hz, 1 H), 4.30-4.21 (m, 2 H), 3.96-3.85 (m, 2 H), 3.65 (s, 2 H), 2.56-2.47 (m, 1 H), 2.40 (s, 3 H), 1.16 (d, *J* = 6.7 Hz, 6 H).

Example 11-89: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((3-(hydroxymethyl)oxetan-3-yl)methyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

To a solution of **Ex 3** hydrochloride (200 mg, 0.49 mmol) and (3-(bromo-methyl)oxetanyl-3-yl)methanol (88 uL, 0.49 mmol) in MeCN (10 mL) is added Cs_2CO_3 (316 mg, 0.97 mmol). The reaction mixture is stirred at 85°C for 2 h (reaction monitored by LCMS). Water is added (20 mL) and the mixture is then extracted with EtOAc (2 x 50 mL). The organic extracts are washed with brine (10 mL), are dried over $MgSO_4$, filtered and evaporated. The residue is purified by prep. HPLC (Prep-HPLC-1 conditions) to give the title compound **Ex 11-89** (157 mg, 68% yield) as a beige solid. LCMS-1: t_R = 0.75 min, $[M+1]^+$ 476.37.

Example 11-90: methyl 3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)oxetane-3-carboxylate and Example 11-91: 3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)oxetane-3-carboxylic acid

Methyl 3-(bromomethyl)oxetane-3-carboxylate (172 mg, 0.82 mmol), prepared from commercially available 3-(bromomethyl)oxetane-3-carboxylic acid and trimethylsilyldiazomethane, is reacted with **Ex 3** hydrochloride (150 mg, 0.36 mmol) following the methodology described for **Ex 11-89** to give methyl 3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)oxetane-3-carboxylate **Ex 11-90.** LCMS-1: t_R = 1.02 min, $[M+1]^+$ 504.03. The methylester is then saponified with LiOH following the methodology described for **Ex 11-14** to afford **Ex 11-91** (17 mg, 9% yield) as a beige wax. LCMS-1: t_R = 0.90 min, $[M+1]^+$ 490.29.

Example 11-92: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3,3-dimethyl-4-(methylamino)-4-oxobutyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3,3-dimethyl-4-(methylamino)-4-oxobutyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 11-92** is prepared from 4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoic acid **Ex 11-31** and 2N methylamine in THF following the methodology described for **Ex 11-86**. Colorless oil. LCMS-1: t_R = 0.79 min, $[M+1]^+$ 503.52.

Example 11-93: 1-(4-amino-3,3-dimethyl-4-oxobutyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

Ex 11-31 (60 mg, 0.114 mmol) is reacted with allylamine (10 uL, 0.125 mmol) according to the methodology descibed for **Ex 11-86**. The obtained allylamide is purified by prep HPLC (Prep-HPLC-2 conditions) and is then introduced (48 mg, 0.09 mmol) into a sealed tube containing tetrachlorobis(2,7-dimethyl-2,6-octadienylene)diruthenium (1.7 mg, 0.002 mmol), KIO_4 (21 mg, 0.09 mmol) and water (1 mL). The reaction mixture is heated at 100°C for 2 h under argon atmosphere. Water is added and the mixture is extracted with EtOAc. The organic extract is dried over $MgSO_4$, dried, filtered and evaporated. Crude compound is purified by prep. HPLC (Prep-HPLC-2 conditions) to give the title compound **Ex 11-93** as a colorless oil (8 mg, 18%). LCMS-1: t_R = 0.82 min, $[M+1]^+$ 489.12.

Example 11-94: 1-(4-amino-4-methylpentyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

To a solution of **Ex 11-61** (82 mg, 0.16 mmol) in AcOH (5 mL) is added ZnBr (2.5 eq, 114 mg) and the mixture is stirred at 100°C for 2 h in a microwave oven. Another portion of ZnBr (1.1 eq., 50 mg) is added and the reaction mixture is stirred at 100°C for 2 h. Purification by prep. HPLC (Prep-HPLC-1 conditions) afforded the title compound **Ex 11-94** as a beige wax (16 mg, 17% yield). LCMS-1: t_R = 0.61 min, $[M+1]^+$ 475.15.

Example 11-95: 1-(2-(1H-tetrazol-5-yl)ethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

1-(2-(1H-tetrazol-5-yl)ethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 11-95** was prepared from 3-(2-isopropylphenyl)-N-(2-methoxy-6-methylpyridin-3-yl)azetidine-3-carboxamide **Ex 3** and 5-(2-bromoethyl)-1H-1,2,3,4-tetrazole following the methodology described for **Ex 11-1** to **11-11**. Colorless oil. LCMS-1: t_R = 0.80 min, $[M+1]^+$ 472.06.

Example 12-1: 1-(4-cyanobutanoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

To a solution of 3-(2-isopropylphenyl)-N-(2-methoxy-6-methylpyridin-3-yl)azetidine-3-carboxamide **Ex 3** (72 mg, 0.19 mmol) and 4-cyanobutanoic acid (21.6 mg, 0.19 mmol) in DMF (2 mL), EDC (55 mg, 0.29 mmol), HOBt (39 mg, 0.29 mmol) and DIPEA (65 uL, 0.49 mmol) are added. The mixture is stirred at r.t. for 1 h (reaction progress monitored by LCMS) before it is diluted with sat. aq. $NaHCO_3$ and extracted twice with EtOAc. The combined org. extracts are dried over $MgSO_4$, filtered and concentrated. The crude product is purified by prep. HPLC (Prep-HPLC-3 conditions) to give 1-(4-cyanobutanoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 12-1** (52 mg, 58% yield) as a yellow oil; LCMS-1: t_R = 1.17 min, $[M+1]^+$ 471.07.

Table 5: Examples 12-2 to 12-31

Examples **12-2** to **12-31** are synthesized using the methodology described for **Ex 12-1** above starting from **Ex 3** or **Ex 4**. Standard coupling reagents can be used such as EDC/HOBt, TBTU, HATU, T3P. Carboxylic acid reagents are commercially available or prepared according to literature protocols.

Example	Name	Analytics LCMS-1
Ex 12-2	1-acetyl-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 418.06 t_R 1.14
Ex 12-3	2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethane-1-sulfonic acid	$[M+1]^+$ 498.10 t_R 1.33
Ex 12-4	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-sulfamoylacetyl)azetidine-3-carboxamide	$[M+1]^+$497.10 t_R 1.07
Ex 12-5	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(3-sulfamoylpropanoyl)azetidine-3-carboxamide	$[M+1]^+$511.17 t_R 1.07
Ex 12-6	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(N-methylsulfamoyl)acetyl)azetidine-3-carboxamide	$[M+1]^+$511.30 t_R 1.12
Ex 12-7	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-((methylsulfonyl)glycyl)azetidine-3-carboxamide	$[M+1]^+$ 511.15 t_R 1.10

Ex 12-8	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(N-methyl-N-sulfamoylglycyl)azetidine-3-carboxamide	$[M+1]^+$ 526.18 t_R 1.11
Ex 12-9	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(3-(methylsulfonamido)-3-oxopropanoyl)azetidine-3-carboxamide	$[M+1]^+$ 539.20 t_R 1.11
Ex 12-10	1-(carbamoylglycyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 476.44 t_R 0.99
Ex 12-11	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(5,5,5-trifluoro-4-oxopentanoyl)azetidine-3-carboxamide	$[M+1]^+$ 528.43 t_R 1.21
Ex 12-12	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)-1-(5,5,5-trifluoro-4-oxopentanoyl)piperidine-4-carboxamide	$[M+1]^+$ 556.28 t_R 1.28
Ex 12-13	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxyoxetan-3-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 490.02 t_R 1.08
Ex 12-14	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxyoxetan-3-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide	$[M+1]^+$ 518.36 t_R 1.15
Ex 12-15	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(1H-pyrazole-4-carbonyl)azetidine-3-carboxamide	$[M+1]^+$ 470.09 t_R 1.08
Ex 12-16	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-hydroxyisoxazole-5-carbonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide [tautomeric form: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-oxo-2,3-dihydroisoxazole-5-carbonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide]	$[M+1]^+$ 487.24 t_R 1.16
Ex 12-17	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-hydroxy-1H-1,2,4-triazole-5-carbonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide [and tautomeric forms thereof, such as N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-oxo-4,5-dihydro-1H-1,2,4-triazol-5-carbonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide]	$[M+1]^+$ 486.96 t_R 1.05
Ex 12-18	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(1H-tetrazole-5-carbonyl)azetidine-3-carboxamide	$[M+1]^+$ 472.09 t_R 1.30
Ex 12-19	1-(2-(1H-tetrazol-5-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 486.06 t_R 1.07
Ex 12-20	1-(2-(1H-tetrazol-1-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-4-carboxamide	$[M+1]^+$ 514.37 t_R 1.16
Ex 12-21	1-(2-(2H-1,2,3-triazol-2-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 484.99 t_R 1.16
Ex 12-22	1-(2-(2H-1,2,3-triazol-2-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-4-carboxamide	$[M+1]^+$ 513.06 t_R 1.21

Ex 12-23	1-(2-(4H-1,2,4-triazol-4-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 485.33 t_R 1.01
Ex 12-24	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxy-1H-pyrazol-5-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide [and tautomeric forms thereof, such as N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-oxo-2,3-dihydro-1H-pyrazol-5-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide]	$[M+1]^+$ 500.11 t_R 1.01
Ex 12-25	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxy-1H-pyrazol-5-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide [and tautomeric forms thereof, such as N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-oxo-2,3-dihydro-1H-pyrazol-5-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide]	$[M+1]^+$ 528.01 t_R 1.06
Ex 12-26	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxy-1H-pyrazol-4-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide [and tautomeric forms thereof, such as N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-oxo-2,3-dihydro-1H-pyrazol-4-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide]	$[M+1]^+$ 500.32 t_R 1.03
Ex 12-27	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxy-1H-pyrazol-4-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide [and tautomeric forms thereof, such as N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-oxo-2,3-dihydro-1H-pyrazol-4-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide]	$[M+1]^+$ 528.21 t_R 1.08
Ex 12-28	1-(3-(4H-1,2,4-triazol-4-yl)propanoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 499.36 t_R 1.00
Ex 12-29	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-(3-hydroxyisoxazol-5-yl)propanoyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide [tautomeric form: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-(3-oxo-2,3-dihydroisoxazole-5-yl)propanoyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide]	$[M+1]^+$ 514.99 t_R 1.12
Ex 12-30	1-(4-(1H-tetrazol-5-yl)butanoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 514.17 t_R 1.08
Ex 12-31	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(1-methylpiperidin-4-yl)acetyl)azetidine-3-carboxamide	$[M+1]^+$ 515.18 t_R 0.77

Example 12-32: tert-butyl (1-(4-(2-isopropylphenyl)-4-((2-methoxy-4-methylphenyl)carbamoyl) piperidine-1-carbonyl)cyclopropyl)carbamate and Example 12-33: 1-(L-alanyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

Step 1. tert-butyl (S)-(1-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-1-oxopropan-2-yl)carbamate **Ex 12-32** is prepared from **Ex 3** (69 mg, 0.183 mmol) and commercially available Boc-alanine (35 mg, 0.183 mmol) following the method described for **Ex 12-1**. White solid (81 mg, 81% yield). LCMS-1: t_R = 1.30 min, $[M+1]^+$ 547.02.

Step 2. 1-(L-alanyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 12-33** is prepared from **Ex 12-32** (75 mg, 0.137 mmol) following the reaction conditions of step 2 described for **Ex 11-1**: 44 mg, 72% yield after prep. HPLC (Prep-HPLC-3 conditions). LCMS-1: t_R = 0.74 min, $[M+1]^+$ 446.99 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (d, *J* = 8.1 Hz, 1 H), 7.48-7.45 (m, 2 H), 7.42-7.37 (m, 1 H), 7.35-7.31 (m, 1 H), 7.26 (d, *J* = 72.8 Hz, 1 H), 7.24 (s, 1 H), 6.94 (d, *J* = 8.1 Hz, 1 H), 5.17-4.94 (m, 1 H), 4.78-4.40 (m, 3 H), 3.70-3.50 (m, 1 H), 2.46-2.39 (m, 4 H), 1.40 (d, *J* = 6.8 Hz, 1.5 H), 1.27 (d, *J* = 6.8 Hz, 1.5 H), 1.23-1.09 (m, 6 H).

Table 6: Examples 12-34 to 12-51

Examples **12-34** to **12-51** are synthesized using the methodology described for **Ex 12-33** starting from **Ex 3** or **Ex 4**. Standard coupling reagents can be used such as EDC/HOBt, TBTU, HATU, T3P for example.

Example	Name	Analytics LCMS-1
Ex 12-34	(S)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-hydroxy-4-oxobutanoic acid	$[M+1]^+$ 492.14 t_R 1.05
Ex 12-35	(R)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-hydroxy-4-oxobutanoic acid	$[M+1]^+$ 492.17 t_R 1.05
Ex 12-36	(S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide	$[M+1]^+$ 560.02 t_R 1.31
Ex 12-37	(S)-4-(4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)-2-hydroxy-4-oxobutanoic acid	$[M+1]^+$ 520.35 t_R 1.11
Ex 12-38	1-(2-(3-aminooxetan-3-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 489.36 t_R 0.75
Ex 12-39	tert-butyl (S)-(1-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-hydroxy-1-oxopropan-2-yl)carbamate	$[M+1]^+$ 563.20 t_R 1.21
Ex 12-40	1-(L-seryl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 463.36 t_R 0.72
Ex 12-41	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((4S)-4-hydroxypyrrolidine-2-	$[M+1]^+$ 489.37

	carbonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	t_R 0.73
Ex 12-42	(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(morpholine-2-carbonyl)azetidine-3-carboxamide	$[M+1]^+$ 489.38 t_R 0.76
Ex 12-43	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(morpholine-3-carbonyl)azetidine-3-carboxamide	$[M+1]^+$ 489.20 t_R 0.76
Ex 12-44	(S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(morpholin-3-yl)acetyl)azetidine-3-carboxamide	$[M+1]^+$ 503.37 t_R 0.76
Ex 12-45	(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(morpholin-3-yl)acetyl)azetidine-3-carboxamide	$[M+1]^+$ 503.16 t_R 0.76
Ex 12-46	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(3-oxopiperazin-2-yl)acetyl)azetidine-3-carboxamide	$[M+1]^+$ 516.17 t_R 0.73
Ex 12-47	tert-butyl (2-(4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)-2-oxoethyl)(2-methoxyethyl)carbamate	$[M+1]^+$ 619.29 t_R 1.37
Ex 12-48	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)-1-((2-methoxyethyl)glycyl)piperidine-4-carboxamide	$[M+1]^+$ 519.40 t_R 0.80
Ex 12-49	tert-butyl (2-(4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)-2-oxoethyl)(2-hydroxyethyl)carbamate	$[M+1]^+$ 605.18 t_R 1.29
Ex 12-50	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((2-hydroxyethyl)glycyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide	$[M+1]^+$ 505.34 t_R 0.78
Ex 12-51	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-(2-(2-hydroxyethoxy)ethoxy)propanoyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 536.14 t_R 1.08

Example 12-52: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((2-hydroxyethyl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

Step 1. To an ice-cold solution of **Ex 3** (150 mg, 0.4 mmol) and DIPEA (205 uL, 1.2 mmol) in THF (10 mL) is added chloroacetyl chloride (48 uL, 0.6 mmol). The reaction mixture is stirred at r.t. for 18 h and is then diluted with EtOAc. The organic solution is washed with water, dried over $MgSO_4$, filtered and evaporated to give crude chloroacetamide intermediate that is used as such in the next step.

Step 2. Chloroacetamide intermediate is dissolved in MeCN (10 mL). Ethanolamine (49 uL, 0.80 mmol) and K_2CO_3 (221 mg, 1.6 mmol) are added and the reaction mixture is then stirred at 65°C for 18 h (reaction progress monitored by LCMS). The mixture is diluted with DCM (20 mL), washed with water (10 mL) dried over $MgSO_4$, filtered and evaporated. The residue is then purified by prep-TLC (DCM/MeOH 9:1) to give **Ex 12-52** as pale yellow foam (60 mg, 32% yield). LCMS-1: t_R = 0.73 min, $[M+1]^+$ 477.15.

Table 7: Examples 12-53 to 12-60

Examples **12-53** to **12-60** are synthesized using the methodology described above for **Ex 12-52** starting from **Ex 3**.

Example	Name	Analytics LCMS-1
Ex 12-53	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxyazetidin-1-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 489.29 t_R 0.77
Ex 12-54	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-((2-methoxyethyl)glycyl)azetidine-3-carboxamide	$[M+1]^+$ 491.41 t_R 0.76
Ex 12-55	(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((R)-(2-hydroxypropyl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 491.38 t_R 0.75
Ex 12-56	(S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((S)-(2-hydroxypropyl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 491.07 t_R 0.75
Ex 12-57	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(((1-hydroxycyclopropyl)methyl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 503.38 t_R 0.76
Ex 12-58	(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((R)-(1-hydroxypropan-2-yl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 491.40 t_R 0.75
Ex 12-59	(S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((R)-(1-hydroxypropan-2-yl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 491.40 t_R 0.75
Ex 12-60	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-((2-hydroxyethyl)amino)propanoyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 491.39 t_R 0.74

Example 12-61: Methyl 4-(3-(2-isopropylphenyl)-3-((2-methoxy-6-methylpyridin-3-yl)carbamoyl) azetidin-1-yl)-4-oxobutanoate and Example 12-62: 4-(3-(2-isopropylphenyl)-3-((2-methoxy-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-4-oxobutanoic acid

Step 1. To a solution of 3-(2-isopropylphenyl)-N-(2-methoxy-6-methylpyridin-3-yl)azetidine-3-carboxamide **Ex 1** (30 mg, 0.088 mmol) and 4-methoxy-4-oxobutanoic acid (14.7 mg, 0.11 mmol), HATU (40.3 mg, 0.11 mmol), and DIPEA (45 uL, 0.26 mmol) are added. The mixture is stirred at r.t. for 1 h (reaction progress monitored by LCMS) before it is diluted with sat. aq. $NaHCO_3$ and extracted twice with EtOAc. The combined org. extracts are dried over $MgSO_4$, filtered and concentrated. The crude product is purified by prep. HPLC (Prep-HPLC-3 conditions) to give methyl 4-(3-(2-isopropylphenyl)-3-((2-methoxy-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-4-oxobutanoate **Ex 12-61** (20 mg, 50% yield) as a yellow oil. LCMS-1: t_R = 1.18 min, $[M+1]^+$ 454.39; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.41 (d, J = 7.8 Hz, 1 H), 7.49-7.44 (m, 2 H), 7.40-7. 34 (m, 3 H), 6.72 (d, J = 8.0 Hz, 1 H),

5.08-4.96 (m, 1 H), 4.72-4.62 (m, 1 H), 4.58-4.45 (m, 2 H), 3.70 (s, 3 H), 3.69 (s, 3 H), 2.79-2.73 (m, 1 H), 2.69-2.61 (m, 1 H), 2.51-2.41 (m, 3 H), 2.38 (s, 3 H), 1.18 (d, J_1 = 6.7 Hz, 3 H), 1.12 (d, J_1 = 6.7 Hz, 3 H).

Step 2. 4-(3-(2-Isopropylphenyl)-3-((2-methoxy-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-4-oxobutanoate (20 mg, 0.044 mmol) is dissolved in MeOH/THF 1:1 (1 mL) and is treated with 2M LiOH (45 uL, 18.4 mmol). The solution is stirred at r.t. for 2 h (reaction progress monitored by LCMS). The reaction mixture is then diluted with water, acidified to pH 1 with 6N HCl and extracted twice with EtOAc. The combined organic extracts are dried over $MgSO_4$, filtered and evaporated to give 4-(3-(2-isopropylphenyl)-3-((2-methoxy-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-4-oxobutanoic acid **Ex 12-62** as a pale yellow oil (13 mg, 67% yield). LCMS-1: t_R = 1.07 min, $[M+1]^+$ 440.36; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.40 (d, J = 7.9 Hz, 1 H), 7.51-7.43 (m, 2 H), 7.41-7.30 (m, 3 H), 6.73 (d, J = 7.9 Hz, 1 H), 5.12-4.95 (m, 1 H), 4.69 (d, J = 8.5 Hz, 1 H), 4.62-4.44 (m, 2 H), 3.71 (s, 3 H), 2.82-2.64 (m, 2 H), 2.60-2.48 (m, 2 H), 2.45-2.41 (m, 1 H), 2.38 (s, 3 H), 1.19 (d, J = 6.6 Hz, 3 H), 1.12 (d, J = 6.6 Hz, 3 H).

Table 8: Examples 12-63 to 12-114

Examples **12-63** to **12-114** are synthesized using the methodology described for **Ex 12-62** starting from **Ex 2**, **Ex 3**, **Ex 4**, **Ex 5**, **Ex 6, Ex7, Ex 8,** or **Ex 10**. Standard coupling reagents can be used such as EDC/HOBt, TBTU, HATU, T3P for example. Carboxylic acid reagents are commercially available or prepared according to literature protocols. If another functional group is present, an additional deprotection step is required such as Boc cleavage of amine under acidic conditions.

Example	Name	Analytics LCMS-1
Ex 12-63	3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-oxopropanoic acid	$[M+1]^+$462.01 t_R 1.09
Ex 12-64	1-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)cyclopropane-1-carboxylic acid	$[M+1]^+$488.13 t_R 1.12
Ex 12-65	ethyl-3-(4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)-3-oxopropanoate	$[M+1]^+$518.21 t_R 1.27
Ex 12-66	3-(4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)-3-oxopropanoic acid	$[M+1]^+$490.21 t_R 1.15
Ex 12-67	methyl 4-(3-((2-isopropoxy-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobutanoate	$[M+1]^+$482.42 t_R 1.33
Ex 12-68	4-(3-((2-isopropoxy-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobutanoic acid	$[M+1]^+$468.38 t_R 1.23
Ex 12-69	methyl 4-(3-((6-chloro-2-methoxypyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobutanoate	$[M+1]^+$474.13 t_R 1.23

Ex 12-70	4-(3-((6-chloro-2-methoxypyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobutanoic acid	$[M+1]^+$460.41 t_R 1.12
Ex 12-71	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobutanoic acid	$[M+1]^+$475.97 t_R 1.09
Ex 12-72	methyl 4-(4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)-4-oxobutanoate	$[M+1]^+$518.05 t_R 1.25
Ex 12-73	4-(4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)-4-oxobutanoic acid	$[M+1]^+$504.20 t_R 1.15
Ex 12-74	ethyl (E)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobut-2-enoate	M+1]$^+$501.99 t_R 1.29
Ex 12-75	(E)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobut-2-enoic acid	$[M+1]^+$474.13 t_R 1.13
Ex 12-76	ethyl (Z)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobut-2-enoate	$[M+1]^+$502.09 t_R 1.24
Ex 12-77	(Z)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobut-2-enoic acid	$[M+1]^+$474.10 t_R 1.17
Ex 12-78	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-methyl-4-oxobutanoic acid	$[M+1]^+$490.05 t_R 1.13
Ex 12-79	(S)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-methyl-4-oxobutanoic acid	$[M+1]^+$490.00 t_R 1.13
Ex 12-80	(R)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-methyl-4-oxobutanoic acid	$[M+1]^+$490.08 t_R 1.13
Ex 12-81	methyl 4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoate	$[M+1]^+$518.01 t_R 1.30
Ex 12-82	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$504.19 t_R 1.20
Ex 12-83	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)pyrrolidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$518.02 t_R 1.21
Ex 12-84	4-(3-((2-(difluoromethoxy)pyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$490.14 t_R 1.14
Ex 12-85	methyl 4-(3-((2,6-dimethoxypyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoate	$[M+1]^+$498.15 t_R 1.28
Ex 12-86	4-(3-((2,6-dimethoxypyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$484.03 t_R 1.17

Ex 12-87	4-(3-((2-(difluoromethoxy)-5-fluoropyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$508.02 t_R 1.19
Ex 12-88	1-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)cyclopropane-1-carboxylic acid	$[M+1]^+$502.32 t_R 1.15
Ex 12-89	1-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)cyclobutane-1-carboxylic acid	$[M+1]^+$516.00 t_R 1.22
Ex 12-90	(R)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-methyl-4-oxobutanoic acid	$[M+1]^+$490.35 t_R 1.13
Ex 12-91	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3,3-dimethyl-4-oxobutanoic acid	$[M+1]^+$504.32 t_R 1.18
Ex 12-92	methyl 3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)but-3-enoate	$[M+1]^+$502.07 t_R 1.24
Ex 12-93	3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)but-3-enoic acid	$[M+1]^+$488.11 t_R 1.15
Ex 12-94	methyl (1S,2R)-2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)cyclopropane-1-carboxylate	$[M+1]^+$502.34 t_R 1.18
Ex 12-95	(1S,2R)-2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)cyclopropane-1-carboxylic acid	$[M+1]^+$488.08 t_R 1.10
Ex 12-96	methyl (1R,2S)-2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)cyclopropane-1-carboxylate	$[M+1]^+$502.17 t_R 1.18
Ex 12-97	(1R,2S)-2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)cyclopropane-1-carboxylic acid	$[M+1]^+$488.02 t_R 1.10
Ex 12-98	3-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)oxetane-3-carboxylic acid	$[M+1]^+$518.08 t_R 1.09
Ex 12-99	2-(3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxetan-3-yl)acetic acid	$[M+1]^+$518.02 t_R 1.09
Ex 12-100	ethyl (S)-3-amino-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobutanoate	$[M+1]^+$ 505.19 t_R 0.75
Ex 12-101	(S)-3-amino-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobutanoic acid	$[M+1]^+$ 491.06 t_R 1.19
Ex 12-102	5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-5-oxopentanoic acid	$[M+1]^+$490.05 t_R 1.10
Ex 12-103	5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-5-oxopentanoic acid	$[M+1]^+$518.07 t_R 1.18

Ex 12-104	ethyl (R)-3-acetoxy-5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-5-oxopentanoate	$[M+1]^+$576.38 t_R 1.26
Ex 12-105	(R)-5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-hydroxy-5-oxopentanoic acid	$[M+1]^+$506.09 t_R 1.05
Ex 12-106	benzyl 2-(2-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethoxy)ethoxy)acetate	$[M+1]^+$626.09 t_R 1.32
Ex 12-107	2-(2-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethoxy)ethoxy)acetic acid	$[M+1]^+$536.00 t_R 1.08
Ex 12-108	2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid	$[M+1]^+$514.19 t_R 1.13
Ex 12-109	benzyl 2-(3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-oxopropoxy)acetate	$[M+1]^+$596.01 t_R 1.33
Ex 12-110	2-(3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-oxopropoxy)acetic acid	$[M+1]^+$506.35 t_R 1.11
Ex 12-111	ethyl 4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-difluoro-4-oxobutanoate	$[M+1]^+$539.98 t_R 1.32
Ex 12-112	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-difluoro-4-oxobutanoic acid	$[M+1]^+$512.05 t_R 1.30
Ex 12-113	ethyl 3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)azetidine-3-carboxylate	$[M+1]^+$531.11 t_R 0.81
Ex 12-114	3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)azetidine-3-carboxylic acid	$[M+1]^+$503.16 t_R 0.83

Example 12-115: 4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3,3-difluoro-4-oxobutanoic acid

4-(3-((2-(Difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3,3-difluoro-4-oxobutanoic acid **Ex 12-115** is prepared from **Ex 3** hydrochloride (50 mg, 0.12 mmol) and 2,2-difluorosuccinic acid (23 mg, 0.15 mmol) following the amide coupling methodology described in Step 1 for **Ex 12-1**: white solid, 31 mg, 50% yield. LCMS-1: t_R = 1.21 min, $[M+1]^+$ 511.97. ^{1}H NMR (500 MHz, DMSO-D6) δ: 12.97 (s br, 1 H), 8.36 (s, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 7.4 Hz, 1 H), 7.52 (t, *J* = 72.5 Hz, 1 H), 7.44 (m, 1 H), 7.42-7.39 (m, 1 H), 7.33-7.30 (m, 1 H), 7.12 (d, *J* = 8.0 Hz, 1 H), 5.11 (d, *J* = 9.3 Hz, 1 H), 4.84 (d, *J* = 9.4 Hz, 1 H), 4.72 (d, *J* = 10.2 Hz, 1 H), 4.39 (d, *J* = 10.2 Hz, 1 H), 3.32-3.18 (m, 2 H), 2.38 (s, 3 H), 1.12 (t, *J* = 6.4 Hz, 6 H).

Example 12-116: (R)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-hydroxy-2-methyl-4-oxobutanoic acid

(R)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-hydroxy-2-methyl-4-oxobutanoic acid **Ex 12-116** is prepared from **Ex 3** hydrochloride (50 mg, 0.12 mmol) and (R)-(-)-citramalic acid (22 mg, 0.15 mmol) following the amide coupling methodology described in Step 1 for **Ex 12-1**: white solid, 15 mg, 24% yield. LCMS-1: t_R = 1.10 min, $[M+1]^+$ 506.03.

Example 12-117: (S)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-hydroxy-2-methyl-4-oxobutanoic acid

(S)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-hydroxy-2-methyl-4-oxobutanoic acid **Ex 12-117** is prepared from **Ex 3** hydrochloride (50 mg, 0.12 mmol) and (S)-(-)-citramalic acid (22 mg, 0.15 mmol) following the amide coupling methodology described in Step 1 for **Ex 12-1**: colorless oil, 18 mg, 29% yield. LCMS-1: t_R = 1.11 min, $[M+1]^+$ 506.38.

Example 12-118: (2R,3R)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,3-dihydroxy-4-oxobutanoic acid

To a solution of **Ex 3** (20 mg, 0.05 mmol) in DCM (2 mL) is added diacetyl-L-tartaric anhydride (13 mg, 0.06 mmol) followed by DIPEA (18 uL, 0.10 mmol). The reaction mixture is stirred at r.t. for 15 min and is then concentrated. The residue is dissolved in MeCN (1 mL) and treated with NaOMe. The reaction mixture is stirred for 30 min (reaction monitored by LCMS) and is then quenched with ammonium chloride, is concentrated and purified by prep. HPLC (Prep-HPLC-1 conditions) to give the title compound **Ex 12-118** as an oil (15 mg, 56% yield). LCMS-1: t_R = 1.03 min, $[M+1]^+$ 508.11.

Example 12-119: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(4-(methylsulfonamido)-4-oxobutanoyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(4-(methylsulfonamido)-4-oxobutanoyl)azetidine-3-carboxamide **Ex 12-119** is prepared from **Ex 12-71** (90 mg, 0.189 mmol) and methansulfonamide (18 mg, 0.189 mmol) following the amide coupling methodology described in Step 1 for **Ex 12-1**: 4 mg, 4% yield. LCMS-1: t_R = 1.11 min, $[M+1]^+$ 553.09.

Example 12-120: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(5,5,5-trifluoro-4-hydroxypentanoyl)azetidine-3-carboxamide

To a solution of **Ex 12-11** (10 mg, 0.02 mmol) in MeOH (0.5 mL) is added $NaBH_4$ (10 mg, 0.26 mmol). The reaction mixture is stirred for 2 h, is then quenched with water and extracted with DCM (2 x 10 mL). The combined extracts are dried over $MgSO_4$, filtered and evaporated. The residue is then purified by prep. HPLC (Prep-HPLC-2 conditions) to give **Ex 12-120** (1.5 mg, 15% yield). LCMS-1: t_R = 1.22 min, $[M+1]^+$ 530.21.

Example 12-121: 2-(2-(3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-oxopropoxy)ethoxy)acetic acid

To a solution of **Ex 12-51** (32 mg, 0.06 mmol) in MeCN (5 mL) is sequentially added a buffer solution of NaH_2PO_4 (0.1mol/L, 0.5 mL), 2,2,6,6-tetramethylpiperidin-1-oxyl radical (TEMPO, 1 mg, 0.006 mmol), aq. solution of sodium chlorite (80 g/L, 0.5 mL) and sodium hypochlorite (50 uL). The reaction mixture is stirred at 50 °C overnight. The mixture is then quenched with saturated sodium sulphite (2 mL) and volatiles are evaporated. The residue is dissolved in 3 mL of DMF/MeCN (1:1) and is purified by prep. HPLC (Prep-HPLC-3 conditions) to give the title compound **Ex 12-121** as a beige wax (14.7 mg, 45% yield). LCMS-1: t_R = 1.08 min, $[M+1]^+$ 550.09.

Example 12-122: 4-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)tetrahydro-2H-pyran-4-carboxylic acid

To a solution of **Ex 3** hydrochloride (50 mg, 0.121 mmol) in DCM (2 mL), TEA (34 uL, 0.243 mmol) is added, followed by commercially available 2,8-dioxaspiro[4.5]decane-1,3-dione dissolved in DCM (1 mL). The reaction mixture is stirred at r.t. for 1 h and is then evaporated. Crude compound is purified by prep. HPLC (Prep-HPLC 2 conditions) to give the title compound **Ex 12-122** as a white solid (41 mg, 62% yield). LCMS-1: t_R = 1.13 min, $[M+1]^+$ 546.00.

Example 12-123: 3-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)tetrahydrofuran-3-carboxylic acid

3-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)tetrahydrofuran-3-carboxylic acid **Ex 12-123** (12 mg, white solid) is prepared from **Ex 3** and commercially available 2,7-dioxaspiro[4.4]nonane-1,3-dione following the methodology described for **Ex 12-122**. LCMS-1: t_R = 1.10 min, $[M+1]^+$ 531.97.

Example 12-124: 4-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-1-methylpiperidine-4-carboxylic acid

4-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-1-methylpiperidine-4-carboxylic acid **Ex 12-124** (43 mg, white solid) is prepared from **Ex 3** and commercially available 8-methyl-2-oxa-8-azaspiro[4.5]decane-1,3-dione hydrochloride following the methodology described for **Ex 12-122**. LCMS-1: t_R = 0.77 min, $[M+1]^+$ 559.10.

Example 12-125: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(3-(methoxyamino)-3-oxopropanoyl)azetidine-3-carboxamide

To a solution of **Ex 12-63** (60 mg, 0.13 mmol) in DCM (4 mL), O-methylhydroxylamine (16 mg, 0.19 mmol), DIPEA (67 uL, 0.39 mmol) and T3P in DCM (50%, 0.16 mmol) are added. The mixture is stirred at r.t. for 18 h, is concentrated in vacuo. The residue is purified by prep. HPLC (Prep-HPLC-1 conditions) to give the title compound **Ex 12-125** (48 mg, 75% yield) as a white solid; LCMS-1: t_R = 1.05 min, $[M+1]^+$ 491.13.

Example 12-126: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(2,4-dioxoimidazolidin-1-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(2,4-dioxoimidazolidin-1-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 12-126** (7 mg, white solid) is prepared from **Ex 3** and 2-(2,4-dioxoimidazolidin-1-yl)acetic acid following the methodology described for **Ex 12-61**. LCMS-1: t_R = 1.06 min, $[M+1]^+$ 515.99; ^{1}H NMR (500 MHz, DMSO) δ: 10.92 (s, 1 H), 8.32 (s, 1 H), 8.00 (d, J = 8.0 Hz, 1 H), 7.55 (d, J = 7.4 Hz, 1 H), 7.52 (t, J = 72.5 Hz, 1 H), 7.44 (dd, J_1 = 1.3 Hz, J_2 = 7.8 Hz, 1 H), 7.40 (t, J = 7.5 Hz, 1 _H), 7.32 (m, 1 H), 7.12 (d, J = 8.1 Hz, 1 H), 4.89 (d, J = 8.5 Hz, 1 H), 4.65 (d, J = 8.5 Hz, 1 H), 4.58 (d, J = 9.6 Hz, 1 H), 4.36 (d, J = 10.1 Hz, 1 H), 4.05 (d, J = 17.1 Hz, 1 H), 4.02 (d, J = 17.1 Hz, 1 H), 3.90 (s, 2 H), 2.38 (s, 3 H), 1.13 (d, J = 6.7 Hz, 3 H), 1.10 (d, J = 6.7 Hz, 3 H).

Example 12-127: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(2,5-dioxoimidazolidin-1-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(2,5-dioxoimidazolidin-1-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 12-127** (22.5 mg, white solid) is prepared from **Ex 3** and (2,5-dioxoimidazolidin-1-yl)acetic acid following the methodology described for **Ex 5** with T3P as coupling reagent. LCMS-1: t_R = 1.07 min, $[M+1]^+$ 515.96; ^{1}H NMR (500 MHz, CDCl3) δ: 8.57 (d, J = 8.1 Hz, 1 H), 7.51-7.46 (m, 2 H), 7.42-7.39 (m, 1 H), 7.34 (dd, J_1 = 0.9 Hz, J_2 = 7.9 Hz, 1 H), 7.27 (t, J = 72.5 Hz, 1 H), 7.24 (s, 1 H), 6.96 (d, J = 8.2 Hz, 1 H), 5.46 (s, 1 H), 5.08 (s br, 1 H), 4.70 (s br, 1 H), 4.61 (s br, 2 H), 4.30 (d, J = 16.2 Hz, 1 H), 4.13-4.09 (m, 3 H), 2.42-2.37 (m, 4 H), 1.20 (d, J = 6.6 Hz, 3 H), 1.13 (d, J = 6.5 Hz, 3 H).

Example 12-128: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(sulfamoylglycyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(sulfamoylglycyl)azetidine-3-carboxamide **Ex 12-128** (25 mg, white solid) is prepared from **Ex 3** and 2-(sulfamoylamino)acetic acid following the methodology described for **Ex 5** with T3P as coupling reagent. LCMS-1: t_R = 1.07 min, $[M+1]^+$ 512.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (d, J = 8.1 Hz, 1 H), 7.56-7.46 (m, 2 H), 7.41 (td, J = 2.0 Hz and J = 7.7 Hz, 1 H), 7.33-7.28 (m, 2 H), 7.26 (t, J = 72.8 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1 H), 5.11-4.99 (s br, 1 H), 4.84-4.67 (s br, 1 H), 4.67-4.46 (s br, 2 H), 3.97 (d, J = 16.4 Hz, 1 H), 3.75 (d, J = 16.4 Hz, 1 H), 2.40 (s, 3 H), 2.38-2.33 (m, 1 H), 1.20 (d, J = 6.5 Hz, 3 H), 1.14 (d, J = 6.5 Hz, 3 H).

Example 12-129: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(1,1-dioxidothietane-3-carbonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(1,1-dioxidothietane-3-carbonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 12-129** (21 mg, white solid) is prepared from **Ex 3** and thietane-3-carboxylic acid 1,1-dioxide following the methodology described for **Ex 5** with EDC/HOBt as coupling reagents. LCMS-1: t_R = 1.15 min, $[M+1]^+$ 508.32.

Example 12-130: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-(N-hydroxyacetamido)propanoyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

Step 1. To a solution of **Ex 3** hydrochloride (300 mg, 0.73 mmol) and DIPEA (822 uL, 4.79 mmol) in THF (30 mL) at 0°C is added acryloyl chloride (89 uL, 1.09 mmol) dropwise. The reaction mixture is stirred at 0°C for 30 min (reaction monitored by LCMS), is then diluted with Et_2O, washed with $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and evaporated to give the crude acrylamide intermediate that is purified by prep. HPLC (Prep-HPLC-1 conditions) to afford a colorless glassy compound (259 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.55 (d, J = 8.1 Hz, 1 H), 7.50-7.44 (m, 2 H), 7.40-7.38 (m, 1 H), 7.37-7.34 (m, 1 H), 7.28 (t, J = 72.6 Hz), 7.25 (s, 1 H), 6.94 (d, J = 8.2 Hz, 1 H), 6.38 (dd, J_1 = 1.8 Hz, J_2 = 17.0 Hz, 1 H), 6.28 (dd, J_1 = 10.3 Hz, J_2 = 17.0 Hz, 1 H), 5.74 (dd, J_1 = 1.8 Hz, J_2 = 10.3 Hz, 1 H), 5.13-5.04 (s br, 1 H), 4.97-4.85 (br s, 1 H), 4.79-4.75 (s br, 1 H), 4.59-4.48 (s br, 1 H), 2.46-2.40 (m, 1 H), 2.38 (s, 3 H), 1.19 (d, J = 6.6 Hz, 3 H), 1.14 (d, J = 6.5 Hz, 3 H).

Step 2. To a solution of acrylamide intermediate (250 mg, 0.58 mmol) and tert-butyl N-(benzyloxy)carbamate (569 mg, 1.16 mmol) in DMF is added Cs_2CO_3 (569 mg, 1.75 mmol). The reaction mixture is stirred at 65°C for 4 h (reaction monitored by LCMS), is then diluted with EtOAc (50 mL), is washed with water (20 mL) followed by brine (20 mL) and is dried over $MgSO_4$. The organic solution is filtered, evaporated and purified by prep. HPLC (Prep-HPLC-1 conditions) to give tert-butyl (benzyloxy)(3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-oxopropyl)carbamate as a colorless wax (289 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.54 (d, J = 8.1 Hz, 1 H), 7.49-7.43 (m, 2 H), 7.42-7.36 (m, 3 H), 7.34-7.30 (m, 3 H), 7.28 (s, 1 H), 7.26 (t, J = 72.6 Hz, 1 H), 7.22 (s, 1 H), 6.94 (d, J = 8.2 Hz, 1 H), 4.95-4.79 (m, 3 H), 4.71-4.60 (m, 1 H), 4.54-4.30 (m, 2 H), 3.80 (t, J = 7.3 Hz, 2 H), 2.47-2.42 (m, 2 H), 2.40-2.34 (m, 4 H), 1.50 (s, 9 H), 1.15 (d, J = 6.6 Hz, 3 H), 1.12 (d, J = 6.6 Hz, 3 H).

Step 3. tert-butyl (benzyloxy)(3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-oxopropyl)carbamate (285 mg, 0.44 mmol) is subjected to the Boc deprotection conditions described for **Ex 4** to give after prep. HPLC (Prep-HPLC-3 conditions) **Ex 12-130** as a white solid (231 mg, 96% yield). LCMS-1: t_R = 1.30 min, $[M+1]^+$ 553.40. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.55 (d, J = 8.1 Hz, 1 H), 7.50-7.45 (m, 2 H), 7.39 (td, $J_1 = 1.9$ Hz, J_2 = 7.8 Hz, 1 H), 7.36-7.28 (m, 6 H), 7.27 (t, J = 72.9 Hz, 1H), 7.24 (s, 1 H), 6.94 (d, J = 8.2 Hz, 1 H), 5.98 (s br, 1 H), 5.03-4.88 (m, 1 H), 4.74-4.61 (m, 3 H), 4.58-4.40 (m, 2 H), 3.31-3.23 (m, 2 H), 2.50-2.41 (m, 2 H), 2.40-2.37 (m, 4 H), 1.17 (d, J = 6.6 Hz, 3 H), 1.14 (d, J = 6.6 Hz, 3 H).

Example 12-131: 1-(3-(N-(benzyloxy)acetamido)propanoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide and Example 12-132: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-(N-hydroxyacetamido)propanoyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

Step 1. To a solution of N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-(N-hydroxyacetamido)propanoyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 12-130** (225 mg, 0.41 mmol) in DCM (7 mL), DIPEA (105 uL, 0.61 mmol) and Ac_2O (58 uL, 0.61 mmol) are added successively. The solution is stirred at r.t. for 1.5 h

(reaction monitored by LCMS), is then concentrated and purified by prep. HPLC (Prep-HPLC-1 conditions) to afford 1-(3-(N-(benzyloxy)acetamido)propanoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 12-131** as a white solid (228 mg, 94% yield). LCMS-1: t_R = 1.29 min, $[M+1]^+$ 595.26.

Step 2. 1-(3-(N-(benzyloxy)acetamido)propanoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide (220 mg, 0.37 mmol) is subjected to the hydrogenation conditions described for **I-1.A** to give the title compound **Ex 12-132** as a white solid (114 mg, 60% yield). LCMS-1: t_R = 1.08 min, $[M+1]^+$ 505.39; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.54 (d, *J* = 8.1 Hz, 1 H), 7.52-7.47 (m, 2 H), 7.43-7.39 (m, 1 H), 7.32 (d, *J* = 7.7 Hz, 1 H), 7.28 (m, 1 H), 7.27 (t, *J* = 72.5 Hz, 1 H), 6.95 (d, *J* = 8.1 Hz, 1 H), 5-05-4.85 (s br, 1 H), 4.83-4.65 (s br, 1 H), 4.63-4.44 (s br, 2 H), 4.04-3.96 (m, 1 H), 3.94-3.88 (m, 1 H), 2.71-2.64 (m, 1 H), 2.61-2.54 (m, 1 H), 2.42-2.34 (m, 4 H), 2.15 (s, 3 H), 1.19 (d, *J* = 6.5 Hz, 3 H), 1.15 (d, *J* = 6.1 Hz, 3 H).

Example 12-133: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-(hydroxyamino)propanoyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

To a stirred solution of tert-butyl N-(benzyloxy)carbamate (45 mg, 0.20 mmol) in anhydrous DMF (5 mL), NaH (60 wt%, 9 mg, 0.22 mol) is added and the resulting mixture is stirred at r.t. for 30 min. 1-(2-Bromoacetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-azetidine-3-carboxamide (100 mg, 0.20 mmol), prepared from **Ex 3** and 2-bromoacetyl bromide according to Step 1 of **Ex 12-52**, is added and the reaction mixture is stirred at r.t. for 18 h. The reaction is then quenched with water (10 mL) and is extracted with hexane (50 mL and 2 x 10 mL). The combined extracts are dried over $MgSO_4$, filtered and evaporated. The residue is purified by prep. HPLC (Prep-HPLC-1 conditions) to give the title compound **Ex 12-133** as beige solid (65 mg, 51 % yield). LCMS-1: t_R = 1.45 min, $[M+1]^+$ 639.05.

Example 12-134: 1-((benzyloxy)glycyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

Ex 12-133 (60 mg, 0.09 mmol) is subjected to the Boc deprotection conditions described for **Ex 4** to give after prep. HPLC (Prep-HPLC-3 conditions) **Ex 12-134** as a beige solid (30 mg, 59% yield). LCMS-1: t_R = 1.31 min, $[M+1]^+$ 539.49.

Example 12-135: 1-(N-acetyl-N-(benzyloxy)glycyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide and Example 12-136: 1-(N-acetyl-N-hydroxyglycyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

Examples **Ex 12-135** and **Ex 12-136** are prepared from **Ex 12-134** according to the methodology described for **Ex 12-131** and **Ex 12-132**.

Ex 12-135: beige solid. LCMS-1: t_R = 1.29 min, $[M+1]^+$ 581.58.

Ex 12-136: white solid. LCMS-1: t_R = 1.07 min, $[M+1]^+$ 491.42 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (d, *J* = 8.1 Hz, 1 H), 8.44-8.05 (s br, 1 H), 7.50-7.45 (m, 2 H), 7.40 (m, 1 H), 7.31 (d, *J* = 7.7 Hz, 1 H), 7.28 (t, *J* = 65.3 Hz,

1 H), 7.26 (s, 1 H), 6.95 (d, *J* = 8.2 Hz, 1 H), 4.98 (s br, 1 H), 4.73 (s br, 1 H), 4.58-4.48 (m, 3 H), 4.36 (d, *J* = 16.7 Hz, 1 H), 2.39 (s, 3 H), 2.36 (m, 1 H), 2.23 (s, 3 H), 1.19 (d, *J* = 6.6 Hz, 3 H), 1.14 (d, *J* = 6.6 Hz, 3 H).

Example 12-137: 1-(2-(1-acetylpiperidin-4-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

1-(2-(1-acetylpiperidin-4-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 12-137** (11 mg, colorless oil) is prepared from **Ex 3** and commercially available 1-acetyl-4-piperdine acetic acidfollowing the methodology described for **Ex 5** with EDC/HOBt as coupling reagents. LCMS-1: t_R = 1.15 min, $[M+1]^+$ 543.06.

Example 12-138: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(piperidin-4-yl)acetyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(piperidin-4-yl)acetyl)azetidine-3-carboxamide **Ex 12-138** (36 mg, colorless oil) is prepared from **Ex 3** and commercially available 2-(1-(t-butoxycarbonyl)piperidin-4-yl)acetic acid following the coupling methodology described for **Ex 5** and a Boc deprotection with HCl in dioxane. LCMS-1: t_R = 0.82 min, $[M+1]^+$ 501.49.

Example 12-139: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(1-(2-methoxyethyl)piperidin-4-yl)acetyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(1-(2-hydroxyethyl)piperidin-4-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 12-139** (16 mg, colorless oil) is prepared from **Ex 3** and commercially available 2-bromoethyl methyl ether following the coupling methodology described for **Ex 11-67.** LCMS-1: t_R = 0.84 min, $[M+1]^+$ 559.12.

Example 12-140: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(1-(2-hydroxyethyl)piperidin-4-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(1-(2-hydroxyethyl)piperidin-4-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 12-140** (16 mg, colorless oil) is prepared from **Ex 3** and commercially available 2-bromoethanol following the coupling methodology described for **Ex 11-67** LCMS-1: t_R = 0.81 min, $[M+1]^+$ 454.29

Example 12-141: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(1-(2-fluoroethyl)piperidin-4-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

To a suspension of N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(piperidin-4-yl)acetyl)azetidine-3-carboxamide **Ex 12-138** (34 mg, 0.06 mmol), 1-fluoro-2-iodomethane (22 mg, 0.13 mmol) and Bu_4NF (4 mg, 0.01 mmol) in acetone (1 mL) is added K_2CO_3 (43.7 mg, 0.32 mmol), The reaction mixture is stirred at rt under nitrogen atmosphere for 16h. Two other portions of 1-fluoro-2-iodomethane (22 mg, 0.13 mmol) are added after 2 h and 4 h to get full conversion. The mixture is evaporated and the residue is partitioned between EtOAc and water. The organic phase is collected, dried over $MgSO_4$, filtered, and

concentrated. The crude product is purified by prep-HPLC (Prep-HPLC-2 conditions) to afford N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(1-(2-fluoroethyl)piperidin-4-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 12-141** as a colorless oil (29 g, 84% yield). LCMS-1: t_R = 0.83 min, $[M+1]^+$ 547.03.

Example 12-142: N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-methylglycine

Example 12-142 is prepared according to the methodology described for **Ex 12-52** using bromoacetyl bromide, an amino carboxylic ester (sacrosine methyl ester) and **Ex 3**. Yellow oil. LCMS-1: t_R = 0.93 min, $[M+1]^+$ 505.30.

Example 13-1: 2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)acetic acid

Step 1. To a solution **Ex 3** (90 mg, 0.239 mmol) and TEA (100 uL, 0.73 mmol, 3 eq.) in DCM (5 mL) is added chlorosulfonyl acetic acid ethyl ester (44.6 mg, 0.239 mmol) dropwise. The reaction mixture is stirred at r.t. overnight and is then concentrated. The residue is purified by prep. HPLC (Prep-HPLC-2 conditions) to give ethyl 2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)acetate (43 mg, 34% yield). LCMS-2: t_R = 1.16 min, $[M+1]^+$ 526.20.

Step 2. A solution of ethyl 2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)acetate (43 mg, 0.082 mmol) in EtOH/THF (1:1, 1 mL) is treated with 2N LiOH aq. (85 mL, 170 mmol). The reaction mixture is stirred at r.t. for 2 h and are then concentrated. The residue is dissolved in water. The resulting solution is acidified to pH 1 with 1N HCl aq. solution and is then extracted with EtOAc (2x 10 mL). The combined extracts are dried over $MgSO_4$, filtered and evaporated to give **Ex 13-1** (41 mg, 100% yield). LCMS-1: t_R = 1.19 min, $[M+1]^+$ 498.16; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (d, *J* = 8.1 Hz, 1 H), 7.53-7.43 (m, 2 H), 7.42-7.37 (m, 1 H), 7.36 (s, 1 H), 7.30-7.23 (m, 2 H), 6.95 (d, *J* = 8.1 Hz, 1 H), 5.32 (s, 2 H), 4.81-4.58 (m, 2 H), 4.25 (s, 2 H), 2.40 (s, 3 H), 2.38-2.31 (m, 1 H), 1.16 (d, *J* = 6.6 Hz, 6 H).

Table 9: Examples 13-2 to 13-27

Examples **13-2** to **13-27** are synthesized using the methodology described for **Ex 13-1** starting from **Ex 3, Ex 4** or **Ex 7**. In case of benzylester, hydrogenation is performed as second step to obtain the corresponding carboxylic acid.

Example	Name	Analytics LCMS-1
Ex 13-2	methyl 2-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)sulfonyl)acetate	$[M+1]^+$539.93 t_R 1.27
Ex 13-3	2-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)sulfonyl)acetic acid	$[M+1]^+$526.10 t_R 1.22

Ex 13-4	Benzyl 3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propanoate	$[M+1]^+$602.12 t_R 1.39
Ex 13-5	3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propanoic acid	$[M+1]^+$512.20 t_R 1.16
Ex 13-6	methyl 3-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)sulfonyl)propanoate	$[M+1]^+$554.03 t_R 1.30
Ex 13-7	benzyl 3-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)sulfonyl)propanoate	$[M+1]^+$630.04 t_R 1.43
Ex 13-8	3-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)sulfonyl)propanoic acid	$[M+1]^+$540.13 t_R 1.20
Ex 13-9	benzyl 3-((3-((2-(difluoromethoxy)pyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propanoate	$[M+1]^+$588.02 t_R 1.35
Ex 13-10	3-((3-((2-(difluoromethoxy)pyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propanoic acid	$[M+1]^+$498.23 t_R 1.10
Ex 13-11	methyl 3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)-2,2-dimethylpropanoate	$[M+1]^+$554.00 t_R 1.33
Ex13-12	3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)-2,2-dimethylpropanoic acid	$[M+1]^+$539.98 t_R 1.23
Ex 13-13	ethyl 2-(1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)cyclopropyl)acetate	$[M+1]^+$566.58 t_R 1.38
Ex 13-14	2-(1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)cyclopropyl)acetic acid	$[M+1]^+$538.09 t_R 1.21
Ex 13-15	methyl 3-(((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)methyl)oxetane-3-carboxylate	$[M+1]^+$568.07 t_R 1.25
Ex 13-16	3-(((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)methyl)oxetane-3-carboxylic acid	$[M+1]^+$554.00 t_R 1.16
Ex 13-17	4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)butanoic acid	$[M+1]^+$526.18 t_R 1.16
Ex 13-18	methyl 5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)pentanoate	$[M+1]^+$554.02 t_R 1.30
Ex 13-19	5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)pentanoic acid	$[M+1]^+$540.01 t_R 1.19
Ex13-20	methyl (E)-3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)acrylate	$[M+1]^+$524.44 t_R 1.32
Ex 12-21	(E)-3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)acrylic acid	$[M+1]^+$509.96 t_R 1.25

Ex 13-22	methyl 4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)-1H-pyrazole-5-carboxylate	$[M+1]^+$564.16 t_R 1.17
Ex 13-23	4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)-1H-pyrazole-5-carboxylic acid	$[M+1]^+$550.22 t_R 1.13
Ex 13-24	ethyl 5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)-1H-pyrazole-4-carboxylate	$[M+1]^+$578.13 t_R 1.22
Ex 13-25	5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)-1H-pyrazole-4-carboxylic acid	$[M+1]^+$550.10 t_R 1.07
Ex 13-26	methyl 5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)isoxazole-3-carboxylate	$[M+1]^+$565.04 t_R 1.34
Ex 13-27	3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)-3-methoxypropanoic acid	$[M+1]^+$542.00 t_R 1.20

Example 13-28: 1-((3-((benzyloxy)amino)-3-oxopropyl)sulfonyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide and Example 13-29: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((3-(hydroxyamino)-3-oxopropyl)sulfonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

Step 1. To a solution of 3-chlorosulfonylpropionyl chloride (prepared from 1,2-oxathiolane-5-one 2-dioxide: lit. US6734184, Novartis AG) (28 mg, 0.15 mmol) and TEA (39 uL, 0.67 mmol) in DMF is added O-benzylhydroxylamine (18.6 mg, 0.15 mmol). The reaction mixture is stirred at r.t. for 5 min and **Ex 3** hydrochloride (55 mg, 0.13 mmol) is then added and stirring is continued for 18 h. Water is added and the reaction mixture is purified by prep. HPLC (Prep-HPLC-3 conditions) to give **Ex 13-28** as a white solid (12.5 mg, 15% yield). LCMS-1: t_R = 1.28 min, $[M+1]^+$ 618.10.

Step 2. **Ex 13-28** (12 mg, 0.02 mmol) is hydrogenated according to the method described for **Ex 11-12** to give **Ex 13-29** as a pale yellow oil (8 mg, 76% yield). LCMS-1: t_R = 1.08 min, $[M+1]^+$ 527.01;^{1}H NMR (400 MHz, MeOD) δ: 8.29 (d, J = 8.1 Hz, 1 H), 7.57 (s, 0.25 H), 7.49-7.46 (m, 3 H), 7.43-7.37 (m, 2 H), 7.21 (s, 0.25 H), 7.06 (d, J = 8.1 Hz, 1 H), 4.64 (d, J = 8.0 Hz, 2 H), 4.47 (d, J = 8.0 Hz, 2 H), 3.45 (t, J = 7.4 Hz, 2 H), 2.61 (t, J = 7.4 Hz, 2 H), 2.52-2.44 (m, 1 H), 2.41 (s, 3 H), 1.17 (d, J = 6.7 Hz, 6 H).

Example 13-30: 3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propane-1-sulfonic acid

Ex 3 hydrochloride (50 mg) is reacted with commercially available 3-(chlorosulfonyl)propane-1-sulfonyl fluoride (32 mg) following the same conditions as step 1 of **Ex 13-1**. The fluorosulfonyl product (32 mg, 0.057 mmol) is then hydrolyzed with NaOH 32% aq. (1 mL) at 50°C for 18 h to give the title compound **Ex 13-30** that is isolated according to step 2 of **Ex 13-1** (19 mg, 28% yield over 2 steps, oil). LCMS-1: t_R = 1.35 min, $[M+1]^+$ 562.10; ^{1}H NMR (400 MHz, CD_3OD) δ: 8.31 (d, J = 8.0 Hz, 1 H), 7.51-7.42 (m, 3 H), 7.39 (dd, J_1 = 2.3 Hz, J_2 =

14.1 Hz, 1 H), 7.38 (t, *J* = 72.8 Hz, 1 H), 7.06 (d, *J* = 8.1 Hz, 1 H), 4.66 (d, *J* = 7.9 Hz, 2 H), 4.46 (d, *J* = 7.9 Hz, 2 H), 3.40-3.34 (m, 2 H), 3.06-2.98 (m, 2 H), 2.54-2.48 (m, 1 H), 2.41 (s, 3 H), 2.31 (m, 2 H), 1.16 (d, *J* = 6.7 Hz, 6 H).

Example 14-1: 2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropyl phenyl)azetidine-1-carbonyl)oxy)acetic acid

Step 1. To a solution of methylglycolate (500 mg, 1.18 mmol) and TEA (2.34 mL, 16.7 mmol) in MeCN (20 mL), is added *N,N*-disuccinimidylcarbonate (1.56 g, 6.11 mmol). The reaction mixture is stirred overnight, is then diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to give methyl 2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)acetate (940 mg, 73% yield). The former compound is added to a solution of **Ex 3** (50 mg, 0.133 mmol) and DIPEA (57 uL, 0.33 mmol) in DMF (5 mL). The reaction mixture is stirred for 18h, concentrated and purified by prep HPLC (Prep-HPLC-2 conditions) to give 2-methoxy-2-oxoethyl 3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate: 48 mg, 73% yield.

Step 2. 2-Methoxy-2-oxoethyl 3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate (48 mg,0.098 mmol) is dissolved in THF (3 mL) and is treated with 2M LiOH (130 uL). The solution is stirred at r.t. for 2 h (reaction progress monitored by LCMS). The reaction mixture is then diluted with water, acidified to pH 1 with 6N HCl and extracted twice with EtOAc. The combined organic extracts are dried over $MgSO_4$, filtered and evaporated. The residue is purified by prep. HPLC (Prep-HPLC-2 conditions) to give **Ex 14-1** as a white solid (24 mg, 51% yield). LCMS-1: t_R = 1.18 min, $[M+1]^+$ 478.45.

Table 10: Examples 14-2 to 14-14

Examples **14-2** to **14-14** are synthesized using the methodology described for **Ex 14-1** starting from **Ex 3** or **Ex 4**.

Example	Name	Analytics LCMS-1
Ex 14-2	2-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidine-1-carbonyl)oxy)acetic acid	$[M+1]^+$ 520.12 t_R 1.32
Ex 14-3	2-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidine-1-carbonyl)oxy)acetic acid	$[M+1]^+$ 506.07 t_R 1.23
Ex 14-4	(S)-2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)propanoic acid	$[M+1]^+$ 492.08 t_R 1.22
Ex 14-5	(R)-2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)propanoic acid	$[M+1]^+$ 492.00 t_R 1.22
Ex 14-6	1-methoxy-2-methyl-1-oxopropan-2-yl 3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate	$[M+1]^+$ 520.08 t_R 1.42

Ex 14-7	1-(methoxycarbonyl)cyclopropyl 3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate	$[M+1]^+$ 534.26 t_R 1.32
Ex 14-8	1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)cyclopropane-1-carboxylic acid	$[M+1]^+$ 504.06 t_R 1.22
Ex 14-9	3-methoxy-2,2-dimethyl-3-oxopropyl 3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate	$[M+1]^+$ 534.26 t_R 1.37
Ex 14-10	3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)-2,2-dimethylpropanoic acid	$[M+1]^+$ 520.17 t_R 1.25
Ex 14-11	(1-(methoxycarbonyl)cyclopropyl)methyl 3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate	$[M+1]^+$ 532.13 t_R 1.33
Ex 14-12	1-(((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)methyl)cyclopropane-1-carboxylic acid	$[M+1]^+$ 518.02 t_R 1.22
Ex 14-13	(3-(methoxycarbonyl)oxetan-3-yl)methyl 3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate	$[M+1]^+$ 548.09 t_R 1.27
Ex 14-14	3-(((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)methyl)oxetane-3-carboxylic acid	$[M+1]^+$ 534.10 t_R 1.17

Example 15-1: Ethyl ((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)glycinate and Example 15-2: ((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropyl phenyl)azetidin-1-yl)sulfonyl)glycine

Step 1. A solution of chlorosulfonyl isocyanate (42 uL, 0.48 mmol) in DCM (1 mL) is cooled down to 0°C and 2-bromoethanol (35 uL, 0.48 mmol) in DCM (1 mL) is added. The reaction mixture stirred for 1 h at 0°C, then ethyl 2-aminoacetate (52 mg, 0.48 mmol) in DCM (1 mL) is added followed by TEA (200 uL,1.43 mmol, 3 eq.). The reaction is stirred at 35°C for 14 h and is then concentrated under reduced pressure. The residue is dissolved in DMF (1 mL) and is added to a solution of **Ex 3** (51 mg, 0.14 mmol) and TEA (285 uL, 2.05 mmol) in DMF (1.5 mL). The reaction mixture is stirred at 95°C overnight. The reaction mixture is then concentrated and the residue is purified by prep. HPLC (Prep-HPLC-3 conditions) yielding **Ex 15-1** as an off-white solid (32 mg, 43% yield). LCMS-1: t_R = 1.24 min, $[M+1]^+$ 541.23; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.55 (d, J = 8.1 Hz, 1 H), 7.47-7.40 (m, 2 H), 7.39-7.35 (m, 1 H), 7.33 (s, 1 H), 7.28 (t, J_{HF} = 72.5 Hz, 1 H), 7.27 (dd, J_1 = 0.9 Hz, J_2 = 7.8 Hz, 1 H), 6.94 (d, J = 8.1 Hz, 1 H), 4.96 (s, 1 H), 4.67-4.52 (m, 2 H), 4.51-4.36 (m, 2 H), 4.25 (q, J = 7.2 Hz, 2 H), 3.93 (s, 2 H), 2.44-2.36 (m, 4 H), 1.31 (s, 3 H), 1.14 (d, J = 6.7 Hz, 6 H).

Step 2. A solution of **Ex 15-1** (28 mg, 0.052 mmol) in MeOH/THF (1:1, 1mL) is treated with 2N LiOH aq. (104 uL, 0.10 mmol). The reaction mixture is stirred at r.t. for 18 h and organic solvents are then evaporated. The residue is dissolved in water. The resulting solution is acidified to pH 1 with 1N HCl aq solution and is then extracted with EtOAc (3x 10 mL). The combined extracts are dried over $MgSO_4$, filtered and evaporated to give

Ex 15-2 as a yellow oil (26 mg, 98% yield). LCMS-1: t_R = 1.13 min, $[M+1]^+$ 513.10; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.56 (d, J = 8.1 Hz, 1 H), 7.48-7.42 (m, 3 H), 7.39-7.35 (m, 1 H), 7.27 (t, J_{HF} = 72.5 Hz, 1 H), 7.25 (d, J = 7.7 Hz, 1 H), 6.98 (d, J = 8.2 Hz, 1 H), 4.63-4.52 (m, 2 H), 4.51-4.40 (m, 2 H), 4.01 (s, 2 H), 2.45-2.34 (m, 4 H), 1.15 (d, J = 6.6 Hz, 6 H).

Example 15-3: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(N-(2-hydroxyethyl)sulfamoyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

Step 1. A solution of chlorosulfonyl isocyanate (12 uL, 0.14 mmol) in DCM (1 mL) is cooled down to 0°C and 2-bromoethanol (10 uL, 0.13 mmol) in DCM (1 mL) is added. The reaction mixture stirred for 1 h at 0°C, then **Ex 3** (57 mg, 0.14 mmol) in DCM (2 mL) is added followed by TEA (78 uL, 0.55 mmol, 4 eq.). The reaction is stirred at r.t. for 1.5 h and is then concentrated under reduced pressure to give crude N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-((2-oxooxazolidin-3-yl)sulfonyl)azetidine-3-carboxamide. LCMS-2: t_R = 1.12 min, $[M+1]^+$ 525.14.

Step 2. N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-((2-oxooxazolidin-3-yl)sulfonyl)azetidine-3-carboxamide (70 mg, 0.13 mmol) is dissolved in EtOH (1 mL) and NaOH 6N (0.4 mL, 2.4 mmol) is added. The reaction mixture is stirred for 2 h and is then diluted with water (5 ml) and extracted with DCM (3 x 20 mL). The oraginc extracts are dired over $MgSO_4$, filtered and evaporated. The residue is purified by prep. HPLC (Prep-HPLC-1 conditions) yielding **Ex 15-3** as a beige solid (32 mg, 44% yield over 2 steps). LCMS-1: t_R = 1.12 min, $[M+1]^+$ 499.10. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.55 (d, J = 8.1 Hz, 1 H), 7.50-7.43 (m, 2 H), 7.40-7.34 (s, 2 H), 7.26 (t, J = 71.8 Hz, 1 H), 7.25 (d, J = 7.7 Hz, 1 H), 6.94 (d, J = 8.1 Hz, 1 H), 4.55 (s, 2 H), 4.46 (s, 2 H), 3.84 (t, J = 4.8 Hz, 2 H), 3.37 (t, J = 4.8 Hz, 2 H), 2.39 (m, 4 H), 1.15 (d, J = 6.6 Hz, 6 H).

Example 15-4: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(N-(2-fluoroethyl)sulfamoyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(N-(2-fluoroethyl)sulfamoyl)-3-(2-isopropyl-phenyl)azetidine-3-carboxamide **Ex 15-4** (3.5 mg, yellow solid) is prepared from **Ex 3** and commercially available 2-fluoroethylamine following the methodology described for **Ex 15-3**. LCMS-1: t_R = 1.10 min, $[M+1]^+$ 501.00.

Example 15-5: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide

To a solution of **Ex 3** (50 mg, 0.12 mmol) and TEA (51 uL, 0.36 mmol) in dioxane (2 mL) is added sulfamide (12 mg, 0.12 mmol). The reaction mixture is stirred at 100°C for 18 h and is then evaporated. The crude compound is purified by prep. HPLC (Prep HPLC 2) to give the title compound **Ex 15-5** as a white solid (35 mg, 63% yield). LCMS-1: t_R = 1.14 min, $[M+1]^+$ 455.39; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.55 (d, J = 8.1 Hz, 1 H), 7.50-7.44 (m, 2 H), 7.41-7.39 (m, 1 H), 7.37-7.34 (m, 1 H), 7.31-7.27 (m, 2 H), 6.95 (d, J = 8.1 Hz, 1 H), 4.78 (s, 2 H), 4.72-4.59 (m, 2 H), 4.53-4.37 (m, 2 H), 2.44-2.33 (m, 4 H), 1.15 (d, J = 6.7 Hz, 6 H).

Table 11: Examples 15-6 to 15-18

Examples **15-6** to **15-18** are synthesized using the methodology described for **Ex 15-5** starting from **Ex 1**, **Ex 2**, **Ex 3**, **Ex 6**, **Ex 7, Ex 8** or **Ex 9** that are reacted with sulfamide or mono-alkyl sulfamides.

Example	Name	Analytics LCMS-1
Ex 15-6	N-(2-(difluoromethoxy)pyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 441.13 t_R 1.06
Ex 15-7	N-(2,6-dimethoxypyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 434.99 t_R 1.10
Ex15-8	N-(6-ethoxy-2-methoxypyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 449.15 t_R 1.17
Ex 15-9	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(N-methylsulfamoyl)azetidine-3-carboxamide	$[M+1]^+$ 469.21 t_R 1.21
Ex 15-10	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(N-ethylsulfamoyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 483.11 t_R 1.25
Ex 15-11	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(N-propylsulfamoyl)azetidine-3-carboxamide	$[M+1]^+$ 496.99 t_R 1.30
Ex 15-12	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(N-isopropylsulfamoyl)azetidine-3-carboxamide	$[M+1]^+$ 497.00 t_R 1.29
Ex 15-13	1-(N-cyclopropylsulfamoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 495.00 t_R 1.26
Ex 15-14	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(sulfamoylamino)ethyl)azetidine-3-carboxamide	$[M+1]^+$ 498.29 t_R 0.72
Ex 15-15	N-(2-(difluoromethoxy)-5-fluoropyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 459.13 t_R 1.13
Ex 15-16	3-(2-isopropylphenyl)-N-(2-methoxy-6-methylpyridin-3-yl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 419.05 t_R 1.13
Ex 15- 17	N-(2-ethoxy-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 433.34 t_R 1.21
Ex 15- 18	N-(2-isopropoxy-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 447.14 t_R 1.28

Example 16-1: 1-(N-acetylsulfamoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

A mixture of **Ex 15-5** (35 mg, 0.08 mmol) NMM (85 uL, 0.08 mmol) and DMAP (1 mg, 0.008 mmol) in DCM (2 mL) is chilled in ice and acetic anhydride (5 drops) is added. The reaction is stirred for 3 h and quenched with MeOH. The mixture is evaporated to dryness and purified by prep. HPLC (Prep-HPLC-2 conditions) to give the title compound **Ex 16-1** as a white solid (18 mg, 47% yield). LCMS-1: t_R = 1.17 min, $[M+1]^+$ 497.01; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.60 (s br, 1 H), 8.53 (d, *J* = 8.1 Hz, 1 H), 7.52-7.46 (m, 2 H), 7.43-7.38 (m, 1 H), 7.31-7.27 (m, 2 H), 7.26 (t, *J* = 72.5 Hz, 1 H), 6.95 (d, *J* = 8.1 Hz, 1 H), 5.02-4.84 (m, 2 H), 4.76-4.54 (m, 2 H), 2.40 (s, 3 H), 2.35-2.28 (m, 1 H), 2.25 (s, 3 H), 1.16 (d, *J* = 6.5 Hz, 6 H).

Table 12: Examples 16-2 to 16-5

Examples **16-2** to **16-5** are synthesized using the methodology described for **Ex 16-1** starting from **Ex 12-4, Ex 12-5, Ex 12-8** or **Ex 15-6**.

Example	Name	Analytics LCMS-1
Ex 16-2	1-(N-acetylsulfamoyl)-N-(2-(difluoromethoxy)pyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 483.00 t_R 1.11
Ex 16-3	1-(2-(N-acetylsulfamoyl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 539.41 t_R 1.12
Ex 16-4	1-(3-(N-acetylsulfamoyl)propanoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 553.48 t_R 1.12
Ex 16-5	1-(N-(N-acetylsulfamoyl)-N-methylglycyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 568.03 t_R 1.14

Example 17-1: Methyl 3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-3-methylbutanoate and Example 17-2: 3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-3-methylbutanoic acid

Method A

Step 1. To a solution **Ex 3** hydrochloride (35 mg, 0.085 mmol) and TEA (24 uL, 0.17 mmol, 2 eq.) in DCM (5 mL) is added methyl 3-isocyanato-3-methylbutanoate (15 mg, 0.085 mmol) dropwise. The reaction mixture is stirred at r.t. for 1 h (reaction progress monitored by LCMS) and is then concentrated. The residue is purified by prep. HPLC (Prep-HPLC-3 conditions) to give **Ex 17-1** as a white solid (37.5 mg, 83% yield); LCMS-1: t_R = 1.30 min, $[M+1]^+$ 533.44; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (d, *J* = 8.1 Hz, 1 H), 7.48-7.40 (m, 2 H), 7.39-7.33 (m, 2 H), 7.30 (t, J_{H-F}= 72.6 Hz, 1 H), 7.28 (d, *J* = 5.3 Hz, 1 H), 6.93 (d, *J* = 8.1 Hz, 1 H), 4.93 (s, 1 H), 4.72-4.56 (m,

2 H), 4.48-4.29 (m, 2 H), 3.67 (s, 3 H), 2.69 (s, 2 H), 2.42-2.50 (m, 1 H), 2.38 (s, 3 H), 1.45 (s, 6 H), 1.15 (d, *J* = 6.7 Hz, 6 H).

Step 2. A solution of **Ex 16-1** (33 mg, 0.063 mmol) in MeOH/THF (1:3, 4 mL) is treated with 2N LiOH aq. (1 mL, 1.0 mmol). The reaction mixture is stirred at r.t. for 5 h and are then concentrated. The residue is purified by prep HPLC (Prep-HPLC-2 conditions) yielding **Ex 17-2** as a white solid (23 mg, 71% yield). LCMS-1: t_R = 1.16 min, $[M+1]^+$ 519.40; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.52 (d, *J* = 8.1 Hz, 1 H), 7.44-7.39 (m, 2 H), 7.34-7.31 (m, 3 H), 7.24 (t,J_{H-F}= 72.6 Hz, 1 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 5.98-5.78 (m, 1 H), 4.74-4.50 (m, 2 H), 4.50-4.27 (m, 2 H), 2.54 (s, 2 H), 2.39 (qt, *J* = 6.1 Hz, 1 H), 2.34 (s, 3 H), 1.36 (s, 6 H), 1.12 (d, *J* = 6.1 Hz, 6 H).

Example 17-3: N1-((1H-imidazol-4-yl)methyl)-N4-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-1,4-carboxamide

Method B

To a solution of C-(1H-imidazol-4(5)-yl)-methylamine.2HCl (46 mg, 0.34 mmol, 2.5 eq) in MeCN (2 mL), are added bis(2,2,2-trifluoroethyl) carbonate (52 uL, 0.34 mmol 2.5 eq) and DIPEA (142 uL, 0.82 mmol, 6 eq). The resulting mixture is heated at 75°C for 2 h and then is allowed to cool to r.t. A solution of Ex 4 (55 mg, 0.14 mmol) and DBU (6 uL, 0.04 mmol, 0.3 eq) in MeCN (1 mL) is added and the mixture is heated at 75°C overnight. DCM (20 mL) is then added and the organic solution is washed with water (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Crude product is purified by prep HPLC (Prep-HPLC-3 conditions) to give **Ex 17-3** as an off white solid (17.6 mg, 25% yield). LCMS-1: t_R = 0.79 min, $[M+1]^+$ 527.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46 (d, *J* = 8.1 Hz, 1 H), 7.61 (s, 1 H), 7.46-7.39 (m, 3 H), 7.33-7.30 (m, 1 H), 7.27 (t, J_{H-F} = 72.5 Hz, 1 H), 7.11 (s, 1 H), 6.92 (d, *J* = 8.2 Hz, 1 H), 6.89 (s, 1 H), 5.60-6.32 (s br, 1 H), 5.51 (t, *J* = 5.0 Hz, 1 H), 4.34 (d, *J* = 5.1 Hz, 2 H), 3.73-3.60 (m, 4 H), 3.16-3.10 (m, 1 H), 2.52-2.47 (m, 2 H), 2.38 (s, 3 H), 2.20-2.14 (m, 2 H), 1.10 (d, *J* = 6.6 Hz, 6 H).

Table 13: Examples 17-4 to 17-24

Examples **17-4** to **17-24** are synthesized using either Method A or B described for **Ex 17-2** and **Ex 17-3** respectively starting from **Ex 3** or **Ex 4**. For Method B, bis(2,2,2-trifluoroethyl) carbonate can be replaced by CDI.

Example	Name	method	Analytics LCMS-1
Ex 17-4	(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)glycine	A	$[M+1]^+$ 477.00 t_R 1.05
Ex 17-5	3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)propanoic acid	A	$[M+1]^+$ 491.17 t_R 1.05

Ex 17-6	methyl (3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)-L-valinate	B	$[M+1]^+$ 533.02 t_R 1.29
Ex 17-7	(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)-L-valine	B	$[M+1]^+$ 519.12 t_R 1.19
Ex 17-8	methyl (3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)-L-alaninate	B	$[M+1]^+$ 505.02 t_R 1.18
Ex 17-9	(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)-L-alanine	B	$[M+1]^+$ 491.06 t_R 1.10
Ex 17-10	ethyl 1-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)cyclopropane-1-carboxylate	B	$[M+1]^+$ 531.10 t_R 1.21
Ex 17-11	1-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)cyclopropane-1-carboxylic acid	B	$[M+1]^+$ 503.47 t_R 1.10
Ex 17-12	ethyl 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-2-methylpropanoate	B	$[M+1]^+$ 533.15 t_R 1.27
Ex 17-13	2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-2-methylpropanoic acid	B	$[M+1]^+$ 505.48 t_R 1.15
Ex 17-14	methyl 1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)methyl)cyclopropane-1-carboxylate	B	$[M+1]^+$ 531.09 t_R 1.23
Ex 17-15	1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)methyl)cyclopropane-1-carboxylic acid	B	$[M+1]^+$ 517.09 t_R 1.13
Ex 17-16	methyl 3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-2,2-dimethylpropanoate	B	$[M+1]^+$ 533.13 t_R 1.25
Ex 17-17	3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-2,2-dimethylpropanoic acid	B	$[M+1]^+$ 519.03 t_R 1.14
Ex 17-18	methyl 4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-2,2-dimethylbutanoate	B	$[M+1]^+$ 547.24 t_R 1.27
Ex 17-19	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-2,2-dimethylbutanoic acid	B	$[M+1]^+$ 533.06 t_R 1.17
Ex 17-20	N4-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-1,4-dicarboxamide	A	$[M+1]^+$ 447.00 t_R 1.10

Ex 17-21	2-(4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidine-1-carboxamido)ethyl methacrylate	A	$[M+1]^+$ 559.27 t_R 1.29
Ex 17-22	N4-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-N1-(2-hydroxyethyl)-4-(2-isopropylphenyl)piperidine-1,4-dicarboxamide	A	$[M+1]^+$ 491.21 t_R 1.09
Ex 17-23	methyl (3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)-D-alaninate	B	$[M+1]^+$ 505.01 t_R 1.18
Ex 17-24	(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)-D-alanine	B	$[M+1]^+$ 491.03 t_R 1.10

Example 17-25: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(piperazine-1-carbonyl)azetidine-3-carboxamide

A solution of **Ex 3** hydrochloride (30 mg, 0.07 mmol) and TEA (30 uL, 0.22 mmol) in DMF (1 mL) under argon is cooled down to 0°C before addition of a solution of tert-butyl 4-(carbonochloridoyl)piperazine-1-carboxylate (24.8 mg, 0.09 mmol) in 1mL DMF. The reaction mixture is stirred at r.t. for 1 h (reaction monitored by LCMS) and is then quenched with water (0.5 mL). Purification by prep. HPLC (Prep-HPLC-3 conditions) afforded tert-butyl-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)piperazine-1-carboxylate as a white solid (42 mg, 98 5 yield). LCMS-1: t_R = 1.37 min, $[M+1]^+$ 588.02. tert-Butyl-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)piperazine-1-carboxylate (40 mg) is then treated with TFA as described for **Ex 4** to afford the title compound **Ex 17-25** as yellow solid (27 mg, 80%). LCMS-1: t_R = 0.76 min, $[M+1]^+$ 488.40.

Example 17-26: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(4-methylpiperazine-1-carbonyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(4-methylpiperazine-1-carbonyl)azetidine-3-carboxamide **Ex 17-26** is prepared from 4-methyl-1-piperazincarbonylchloride according to the metholology described for **Ex 17-25**. White solid. LCMS-1: t_R = 0.77 min, $[M+1]^+$ 502.18.

Example 17-27: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(morpholine-4-carbonyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(morpholine-4-carbonyl)azetidine-3-carboxamide **Ex 16-27** is prepared from 4-morpholincarbonylchloride according to the metholology described for **Ex 16-25**. White solid. LCMS-1: t_R = 1.19 min, $[M+1]^+$ 489.10

Example 18-1: Methyl 6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)nicotinate and Example 18-2: 6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)nicotinic acid

Method C

Step 1. **Ex 3** hydrochloride (30 mg, 0.073 mmol), methyl 6-chloropyridine-3-carboxylate (28.7 mg, 0.164 mmol, 2.2 eq.) and Cs_2CO_3 (53 mg, 0.164 mmol, 2.2 eq.) are suspended in DMA and the mixture is stirred at 90°C for 18 h (reaction monitored by LCMS). The mixture is cooled down to r.t., diluted with EtOAc (50 mL) and washed sequentially with water and brine. The organic phase is dried over $MgSO_4$, filtered and evaporated. The crude product is purified by prep HPLC (Prep-HPLC-3 conditions) to give **Ex 17-1** as a white solid (18 mg, 50% yield). LCMS-1: t_R = 1.36 min, $[M+1]^+$ 511.31; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.83-8.82 (m, 1 H), 8.58 (d, J = 8.1 Hz, 1 H), 8.06 (dd, J_1 = 2.2 Hz, J_2 = 8.8 Hz, 1 H), 7.50-7.45 (m, 2 H), 7.43-7.36 (m, 3 H), 7.28 (t, J_{H-F}= 72.5 Hz, 1 H), 6.94 (d, J = 8.2 Hz, 1 H), 6.37 (d, J = 8.8 Hz, 1 H), 4.97-4.85 (m, 2 H), 4.67-4.51 (m, 2 H), 3.89 (s, 3 H), 2.59-2.49 (m, 1 H), 2.39 (s, 3 H), 1.19 (d, J = 6.7 Hz, 6 H).

Step 2. A solution of **Ex 18-1** (18 mg, 0.035 mmol) in MeOH/THF (1:1, 1mL) is treated with 2N LiOH (0.088mL). The reaction mixture is stirred at r.t. for 18 h and organic solvents are then evaporated. The residue is dissolved in water. The resulting solution is acidified to pH 1 with 1N HCl aq solution and is then extracted with EtOAc (3x 10 mL). The combined extracts are dried over $MgSO_4$, filtered and evaporated to give **Ex 18-2** as a colorless oil (14 mg, 80% yield). LCMS-1: t_R = 1.21 min, $[M+1]^+$ 497.35; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.86 (d, J = 1.6 Hz, 1 H), 8.56 (d, J = 8.1 Hz, 1 H), 8.14 (dd, J_1 = 1.6 Hz, J_2 = 8.9 Hz, 1 H), 7.52-7.38 (m, 4 H), 7.36 (s, 1 H), 7.21 (t, J_{H-F}= 72.6 Hz, 1 H), 6.94 (d, J = 8.1 Hz, 1 H), 6.45 (d, J = 8.9 Hz, 1 H), 5.14-4.93 (s br, 2 H), 4.85-4.57 (m, 2 H), 2.53-2.43 (m, 1 H), 2.39 (s, 3 H), 1.20 (d, J = 6.5 Hz, 6H).

Example 18-3: 6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)picolinic acid

Method D

To a solution of **Ex 3** hydrochloride (52 mg, 0.126 mmol) in toluene (2 mL), are added ethyl-6-bromopicolinate (43.6 mg, 0.189 mmol, 1.5 eq), NaOtBu (36 mg, 0.379 mmol, 3 eq.), $Pd_2(dba)_3$ (11.6 mg, 0.013mmol, 0.1 eq.) and BINAP (16.2 mg, 0.025 mmol, 0.2 eq.). The resulting mixture is degassed and is heated at 110°C overnight. The reaction is quenched with 2N HCl aq. (10 mL) and the mixture is diluted with EtOAc. The phases are separated. The organic phase is dried over $MgSO_4$, filtered and evaporated. The crude product is purified by prep TLC (eluent: DCM/MeOH: 9/1) to give **Ex 18-3** as a yellow solid (10 mg, 17% yield). LCMS-1: t_R = 1.22 min, $[M+1]^+$ 497.34; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.57 (d, J = 8.0 Hz, 1 H), 7.76-7.66 (m, 1 H), 7.58 (d, J = 7.0 Hz, 1 H), 7.47 (s, 2 H), 7.46-7.33 (m, 3 H), 7.27 (t, J = 70.5 Hz, 1 H), 6.94 (d, J = 8.1 Hz, 1 H), 6.67 (d, J = 7.9 Hz, 1 H), 5-03-4.78 (m, 2 H), 4.69-4.40 (m, 2 H), 2.59-2.47 (m, 1 H), 2.39 (s, 3 H), 1.20 (d, J = 6.4 Hz, 6 H).

Table 14: Examples 18-4 to 18-33

Examples **18-4** to **18-33** are synthesized according to Method C or Method D described for **Ex 18-2** and **Ex 18-3** respectively, starting from **Ex 3** or **Ex 7**.

Example	Name	Method	Analytics LCMS-1
Ex 18-4	methyl 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidine-5-carboxylate	C	$[M+1]^+$ 512.18 t_R 1.36
Ex 18-5	2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidine-5-carboxylic acid	C	$[M+1]^+$ 498.09 t_R 1.24
Ex 18-6	methyl 6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyridazine-3-carboxylate	C	$[M+1]^+$ 512.38 t_R 1.22
Ex 18-7	6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyridazine-3-carboxylic acid	C	$[M+1]^+$ 498.35 t_R 1.14
Ex 18-8	methyl 5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrazine-2-carboxylate	C	$[M+1]^+$ 512.21 t_R 1.29
Ex 18-9	5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrazine-2-carboxylic acid	C	$[M+1]^+$ 498.48 t_R 1.20
Ex 18-10	ethyl 4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidine-2-carboxylate	C	$[M+1]^+$ 526.28 t_R 1.23
Ex 18-11	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidine-2-carboxylic acid	C	$[M+1]^+$ 498.08 t_R 0.95
Ex 18-12	methyl 6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidine-4-carboxylate	C	$[M+1]^+$ 512.37 t_R 1.21
Ex 18-13	6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidine-4-carboxylic acid	C	$[M+1]^+$ 498.35 t_R 1.00
Ex 18-14	ethyl 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidine-4-carboxylate	C	$[M+1]^+$ 526.38 t_R 1.38
Ex 18-15	2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidine-4-carboxylic acid	C	$[M+1]^+$ 498.34 t_R 1.25
Ex 18-16	methyl 1-(5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidin-2-yl)cyclopropane-1-carboxylate	D	$[M+1]^+$ 552.23 t_R 1.31
Ex 18-17	1-(5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidin-2-yl)cyclopropane-1-carboxylic acid	D	$[M+1]^+$ 538.31 t_R 1.32

Ex 18-18	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(4-fluoropyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	C	$[M+1]^+$ 471.40 t_R 1.34
Ex 18-19	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-fluoropyridin-4-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	C	$[M+1]^+$ 471.01 t_R 0.84
Ex 18-20	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(5-fluoropyrimidin-4-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	C	$[M+1]^+$ 472.40 t_R 1.25
Ex 18-21	N-(2-(difluoromethoxy)pyridin-3-yl)-1-(5-fluoropyrimidin-4-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	C	$[M+1]^+$ 457.98 t_R 1.19
Ex 18-22	1-(5-cyanopyridin-2-yl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	C	$[M+1]^+$ 478.38 t_R 1.35
Ex 18-23	1-(5-cyanopyridin-2-yl)-N-(2-(difluoromethoxy)pyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	C	$[M+1]^+$ 464.30 t_R 1.29
Ex 18-24	1-(5-cyanopyrimidin-2-yl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	C	$[M+1]^+$ 479.16 t_R 1.33
Ex 17-25	1-(5-cyanopyrimidin-2-yl)-N-(2-(difluoromethoxy)pyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	C	$[M+1]^+$ 465.00 t_R 1.27
Ex 18-26	1-(4-chloro-6-methylpyrimidin-2-yl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	C	$[M+1]^+$ 502.00 t_R 1.39
Ex 18-27	ethyl 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)oxazole-4-carboxylate	C	$[M+1]^+$ 515.46 t_R 1.36
Ex 18-28	2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)oxazole-4-carboxylic acid	C	$[M+1]^+$ 487.08 t_R 1.21
Ex 18-29	ethyl 2-(3-((2-(difluoromethoxy)pyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)oxazole-4-carboxylate	C	$[M+1]^+$ 500.98 t_R 1.29
Ex 18-30	2-(3-((2-(difluoromethoxy)pyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)oxazole-4-carboxylic acid	C	$[M+1]^+$ 473.21 t_R 1.13
Ex 18-31	ethyl 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)oxazole-5-carboxylate	C	$[M+1]^+$ 515.13 t_R 1.36
Ex 18-32	2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)oxazole-5-carboxylic acid	C	$[M+1]^+$ 487.01 t_R 1.20
Ex 18-33	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(5-fluoropyrimidin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	C	$[M+1]^+$ 471.99 t_R 1.40

Example 18-34: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-methylpyrimidin-4-yl)azetidine-3-carboxamide

Ex 18-26 (65 mg, 0.129 mmol) is subjected to the hydrogenation conditions described for **I-1.A** to give N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-methylpyrimidin-4-yl)azetidine-3-carboxamide **Ex 18-34** as a white solid (53 mg, 83% yield). LCMS-1: t_R = 0.84 min, $[M+1]^+$ 468.38; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.56 (d, J = 8.1 Hz, 1 H), 8.16 (d, J = 5.9 Hz, 1 H), 7.47 (d, J = 1.3 Hz, 2 H), 7.43-7.39 (m, 2 H), 7.32 (s, 1 H), 7.26 (t, J_{HF} = 73.5 Hz 1 H), 6.93 (d, J = 8.2 Hz, 1 H), 6.15 (d, J = 5.9 Hz, 1 H), 5.00-4.76 (m, 2 H), 4.64-4.45 (m, 2 H), 2.55 (s, 3 H), 2.54-2.48 (m, 1 H), 2.39 (s, 3 H), 1.19 (d, J = 6.7 Hz, 6 H).

Example 18-35: methyl 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-1-methyl-1H-imidazole-5-carboxylate and Example 18-36: 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-1-methyl-1H-imidazole-5-carboxylic acid

Step 1. To a mixture of the **Ex 3** hydrochloride (100 mg, 0.243 mol), 2-bromo-3-methyl-3H-imidazole-4-carboxylic acid methyl ester (56 mg, 0.243 mmol), DIPEA (83 uL, 0.486 mmol), 18-crown-6 (1.29 g, 4.86 mmol) and CsF (38 mg, 0.243 mmol) is heated to 120°C overnight. The mixture is then evaporated and the residue is purified by prep. HPLC (Prep-HPLC-3 conditions) to give methyl 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-1-methyl-1H-imidazole-5-carboxylate **Ex 18-35** (20 mg, 16%) as a yellow oil. LCMS-1: t_R = 1.16 min, $[M+1]^+$ 514.19.

Step 2. **Ex 18-35** (20 mg, 0.039 mmol) is saponified according to the methodology described for **Ex 12-62** to give **Ex 18-36** (13 mg, 68%) as white solid. LCMS-1: t_R = 0.98 min, $[M+1]^+$ 500.00.

Example 19: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(4-oxo-4,5-dihydrooxazol-2-yl)azetidine-3-carboxamide [tautomeric form: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(4-hydroxy-oxazol-2-yl)azetidine-3-carboxamide]

To a solution of **Ex 3** (80 mg, 0.21 mmol) in DCM (3 mL), chloroacetyl isocyanate (19 uL, 0.21 mmol) is added. The reaction mixture is stirred for 1 h at r.t. (The reaction progress is monitored by LCMS). The mixture is poured into water and is extracted with DCM (2 x 15 mL). The combined extracts are dried over $MgSO_4$, filtered and concentrated. The residue is dissolved in THF (4 mL) and DBU (72 uL, 0.48 mmol, 2 eq.) is added. The reaction mixture is stirred at r.t. for 1 h, is then poured into aq. 1N HCl and is extracted with EtOAc (2 x 20 mL). The combined extracts are dried over $MgSO_4$, filtered and concentrated. The crude product is then purified by prep. HPLC (Prep-HPLC-1 conditions) to give **Ex 19** as a colorless oil (72 mg, 65% yield). LCMS-1: t_R = 1.11 min, $[M+1]^+$ 459.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (d, J = 8.1 Hz, 1 H), 7.57-7.48 (m, 2 H), 7.44-7.39 (m, 1 H), 7.32 (d, J = 7.8 Hz, 1 H), 7.27 (m, 2 H), 6.96 (d, J = 8.1 Hz, 1 H), 5.10-4.89 (m, 2 H), 4.86-4.72 (m, 1 H), 4.67-4.53 (m, 3 H), 2.39 (s, 3 H), 2.34 (m, 1 H), 1.17 (dd, J_1 = 6.7 Hz, J_2 = 11.7 Hz, 6 H).

Example 20: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(1H-tetrazol-5-yl)azetidine-3-carboxamide

To a solution of **Ex 11-6** (32 mg, 0.08 mmol) in DMF (2.5 mL) is added ammonium chloride (6.4 mg, 0.12 mmol) and sodium azide (7.8 mg, 0.12mmol) at r.t. The mixture is then heated to 100°C for 2 h. The reaction mixture is injected in prep. HPLC (Prep-HPLC-1 conditions) to afford the title compound **Ex 20** as a white solid (24 mg, 68% yield). LCMS-1: t_R = 1.12 min, $[M+1]^+$ 444.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.42 (d, J = 8.1 Hz, 1 H), 7.40-7.27 (m, 4 H), 7.21-7.11 (m, 3 H), 6.77 (d, J = 8.2 Hz, 1 H), 4.91-4.65 (m, 2 H), 4.58-4.35 (m, 2 H), 2.35-2.27 (m, 1 H), 2.26 (s, 3 H), 1.00 (d, J = 6.4 Hz, 6 H).

Example 21: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(5-hydroxy-1,2,4-oxadiazol-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide [tautomeric form: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)azetidine-3-carboxamide]

To an ethanolic solution (1mL) of **Ex 11-6** (41 mg, 0.102 mmol) is added hydroxylamine hydrochloride (11 mg, 0.158 mmol) and TEA (36 uL, 0.258 mmol). The reaction mixture is heated to 80 °C for 2 h. It is then cooled, concentrated in vacuo, dissolved in EtOAc, washed with water, dried over $MgSO_4$ and concentrated in vacuo again. The crude material is redissolved in MeCN (2 mL), and CDI (21 mg, 0.129 mmol) is added. The reaction mixture is heated to 60 °C for 2 h and is then cooled and concentrated. Purification by prep. HPLC (Prep-HPLC-3 conditions) afforded the title compound **Ex 21** as a white solid (37 mg, 79% yield). LCMS-1: t_R = 1.16 min, $[M+1]^+$ 460.04; ^{1}H NMR (400 MHz, DMSO) δ: 12.19 (s, 1 H), 8.56 (s, 1 H), 7.92 (d, J = 7.9 Hz, 1 H), 7.53 (d, J_{H-F} = 72.5 Hz, 1 H), 7.48 (d, J = 7.7 Hz, 1 H), 7.39-7.44 (m, 1 H), 7.34-7.38 (m, 1 H), 7.27-7.32 (m, 1 H), 7.12 (d, J = 8.1 Hz, 1 H), 4.64 (d, J = 8.0 Hz, 2 H), 4.40 (d, J = 8.0 Hz, 2 H), 2.62-2.54 (m, 1 H), 2.38 (s, 3 H), 1.11 (d, J = 6.7 Hz, 6 H).

Example 22: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((5-hydroxy-1,2,4-oxadiazol-3-yl)methyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide [tautomeric form: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-((5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)methyl)azetidine-3-carboxamide]

The title compound **Ex 22** is prepared from **Ex 10-48** according to the method described for **Ex 21**. Yellow solid. LCMS-1: t_R = 1.11 min, $[M+1]^+$ 474.34. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.53 (d, J = 8.1 Hz, 1 H), 8.06 (s, 1 H), 7.40 (m, 2 H), 7.34 (t, J = 72.6 Hz, 1 H), 7.30-7.34 (m, 1 H), 7.15 (d, J = 7.6 Hz, 1 H), 6.94 (d, J = 8.2 Hz, 1 H), 4.34-4.23 (m, 2 H), 3.87-3.70 (m, 2 H), 3.65 (s, 2 H), 2.52-2.44 (m, 1 H), 2.40 (s, 3 H), 1.15 (d, J = 6.5 Hz, 6 H).

Example 23: 3-(2-cyclopropylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide

3-(2-cyclopropylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide **Ex 23** is prepared from 1-benzhydryl-3-(2-bromophenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide and cyclopropylboronic acid pinacol ester according to the method described for **Ex 1**. Colorless oil. LCMS-1: t_R = 0.71 min, $[M+1]^+$ 374.23. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.62 (d, J = 8.1 Hz, 1 H), 8.57 (s, 1 H), 7.37 (t, J = 72.9

Hz, 1 H), 7.31-7.29 (m, 2 H), 7.18 (dd, J_1 = 3.5 Hz, J_2 = 5.6 Hz, 1 H), 6.99 (dd, J_1 = 3.5 Hz, J_2 = 5.6 Hz, 1 H), 6.94 (d, J = 8.1 Hz, 1 H), 4.37 (d, J = 8.0 Hz, 2 H), 4.29 (d, J = 8.0 Hz, 2 H), 2.40 (s, 3 H), 1.46 (m, 1 H), 0.89-0.86 (m, 2 H), 0.73-0.68 (m, 2 H)

Example 24: 3-(2-cyclobutylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide

Step 1. To a solution of 1-benzhydryl-3-(2-bromophenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide (200 mg, 0.09 mmol) in THF (2 mL) degassed with argon is added (dppp)$NiCl_2$ (5.6 mg, 0.01 mmol). Cyclobutylzinc bromide 0.5M in THF (2.7 mL, 1.38 mmol) is then added dropwise at room temperature. The mixture is warmed up to 80°C and stirred overnight. The mixture is then quenched with water and $NaHCO_3$ is added. The aqueous solution is extracted with EtOAc (2 x 60 mL). The organic extracts are dried over $MgSO_4$, filtered and evaporated. The residue is purified by prep. HPLC (Prep-HPLC-1 conditions) afforded 1-benzhydryl-3-(2-cyclobutylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide as a colorless oil (115 mg, 60% yield). LCMS-2: t_R = 1.09 min, $[M+1]^+$ 554.36.

Step 2. 3-(2-cyclobutylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide **Ex 24** is prepared from 1-benzhydryl-3-(2-cyclobutylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide according to the hydrogenation conditions described for **Ex 1**. Beige solid (10 mg, 73% yield). LCMS-1: t_R = 0.74 min, $[M+1]^+$ 388.31.

Example 25: 3-(2-cyclopentylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide

1-Benzhydryl-3-(2-(cyclopent-1-en-1-yl)phenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide **Ex 25** is prepared from 1-benzhydryl-3-(2-bromophenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide and cyclopenten-1-yl boronic acid according to the method described for **Ex 1**, Colorless oil. LCMS-1: t_R = 0.78 min, $[M+1]^+$ 402.37.

Example 26: 3-(2-(cyclopent-1-en-1-yl)phenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide

1-benzhydryl-3-(2-(cyclopent-1-en-1-yl)phenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide (50 mg, 0.09 mmol), prepared according to the synthetical route described for **Ex 1**, is dissolved in 1,2-dichloroethane (2 mL). 1-Chloroethyl chloroformate (14 uL, 0.133 mmol) is added and the reaction mixture is stirred in a microwave (175 Watt) at 80°C for 8 h (formation of 1-chloroethyl 3-(2-(cyclopent-1-en-1-yl)phenyl)-3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)azetidine-1-carboxylate intermediate monitored by LCMS). Then MeOH (1 mL) is added. The reaction mixture is stirred at 45°C for 30 min and is then concentrated. The residue is purified by prep. HPLC (Prep-HPLC-1 conditions) to afford **Ex 26** as a pale yellow oil (36 mg, 100% yield). LCMS-1: t_R = 0.76 min, $[M+1]^+$ 400.35.

Example 27: 3-(2-cyclohexylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide

3-(2-Cyclohexylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide **Ex 27** is prepared prepared from 1-benzhydryl-3-(2-bromophenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide and cyclohexeny-1-yl boronic acid according to the method described for **Ex 1**. Colorless oil. LCMS-1: t_R = 0.82 min, $[M+1]^+$ 416.27. ^{1}H NMR (400 MHz, CDCl3) δ: 8.59 (d, *J* = 8.1 Hz, 1 H), 8.14 (s, 1 H), 7.34 (t, *J* = 72.8 Hz, 1 H), 7.41-7.35 (m, 2 H), 7.33-7.29 (m, 1 H), 7.17 (m, 1 H), 6.93 (d, *J* = 8.1 Hz, 1 H), 4.32 (br s, 4 H), 2.40 (s, 3 H), 2.07-1.98 (m, 1 H), 1.78-1.71 (m, 2 H), 1.65-1.61 (m, 2 H), 1.47-1.38 (m, 2 H), 1.25-1.29 (m, 4 H).

Example 28: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-(tetrahydro-2H-pyran-4-yl)phenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-(tetrahydro-2H-pyran-4-yl)phenyl)azetidine-3-carboxamide **Ex 28** can be prepared from 1-benzhydryl-3-(2-bromophenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide and 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester according to the method described for **Ex 1**. LCMS-1: t_R = 0.62 min, $[M+1]^+$ 418.22.

Example 29: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-propylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-propylphenyl)azetidine-3-carboxamide **Ex 29** is prepared from the hydrogenation of **Ex 23** according to the method described for **Ex 1**. LCMS-1: t_R = 0.72 min, $[M+1]^+$ 376.10.

Example 30: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-sulfamoyl-3-(2-(tetrahydro-2H-pyran-4-yl)phenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-sulfamoyl-3-(2-(tetrahydro-2H-pyran-4-yl)phenyl)azetidine-3-carboxamide **Ex 30** is prepared from **Ex 28** according to the method described for **Ex 15-5**. LCMS-1: t_R = 1.00 min, $[M+1]^+$ 497.13.

Table 15: Examples 31-1 to 31-7

Examples **31-1** to **31-7** are synthesized using the methodology described for **Ex 12-61 and Ex 12-62** starting from **Ex 23**, **Ex 24**, **Ex 25**, **Ex 27**, **Ex 28**, or **Ex-29**.

Example	Name	Analytics LCMS-1
Ex 31-1	4-(3-(2-cyclopropylphenyl)-3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 502.04 t_R 1.16
Ex 31-2	4-(3-(2-cyclobutylphenyl)-3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 516.00 t_R 1.23

Ex 31-3	4-(3-(2-cyclopentylphenyl)-3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 530.03 t_R 1.28
Ex 31-4	4-(3-(2-(cyclopent-1-en-1-yl)phenyl)-3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 528.00 t_R 1.25
Ex 31-5	4-(3-(2-cyclohexylphenyl)-3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 544.39 t_R 1.32
Ex 31-6	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-(tetrahydro-2H-pyran-4-yl)phenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 546.12 t_R 1.06
Ex 31-7	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-propylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 504.13 t_R 1.21

Example 32: 2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-(tetrahydro-2H-pyran-4-yl)phenyl)azetidin-1-yl)oxazole-4-carboxylic acid

2-(3-((2-(Difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-(tetrahydro-2H-pyran-4-yl)phenyl)azetidin-1-yl)oxazole-4-carboxylic acid **Ex 32** is prepared from **Ex 28** following the methodology described for **Ex 18-28** (beige solid). LCMS-1: t_R = 1.06 min, $[M+1]^+$ 528.98.

Example 33: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropyl-6-methylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropyl-6-methylphenyl)azetidine-3-carboxamide **Ex 33** is prepared from 2-(difluoromethoxy)-6-methylpyridin-3-amine **I-1.C** and intermediate **I-7** following the methodology described for **Ex 1** (colorless oil). LCMS-1: t_R = 0.73 min, $[M+1]^+$ 390.35.

Example 34: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropyl-5-methylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropyl-5-methylphenyl)azetidine-3-carboxamide **Ex 34** is prepared from 2-(difluoromethoxy)-6-methylpyridin-3-amine **I-1.C** and intermediate **I-8** following the methodology described for **Ex 1** (colorless oil). LCMS-1: t_R = 0.77 min, $[M+1]^+$ 390.02; ^{1}H NMR (500 MHz, CDCl3) δ: 8.60 (d, J = 8.1 Hz, 1 H), 8.12 (s, 1 H), 7.33 (t, J = 72.8 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.22 (d, J = 8.1 Hz, 1 H), 6.96 (s, 1 H), 6.93 (d, J = 8.1 Hz, 1 H), 4.34 (m, 4 H), 2.45-2.33 (m, 7 H), 1.13 (d, J = 6.6 Hz, 6 H).

Example 35: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropyl-4-methylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropyl-4-methylphenyl)azetidine-3-carboxamide **Ex 35** is prepared from 2-(difluoromethoxy)-6-methylpyridin-3-amine **I-1.C** and intermediate **I-9** following the methodology described for **Ex 1** (colorless oil). LCMS-1: t_R = 0.77 min, $[M+1]^+$ 389.97.

Example 36: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-fluoro-6-isopropylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-fluoro-6-isopropylphenyl)azetidine-3-carboxamide **Ex 36** is prepared from 2-(difluoromethoxy)-6-methylpyridin-3-amine **I-1.C** and intermediate **I-10** following the methodology described for **Ex 1** (white solid). LCMS-1: t_R = 0.71 min, $[M+1]^+$ 394.14.

Example 37: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(5-fluoro-2-isopropylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(5-fluoro-2-isopropylphenyl)azetidine-3-carboxamide **Ex 37** is prepared from 2-(difluoromethoxy)-6-methylpyridin-3-amine **I-1.C** and intermediate **I-11** following the methodology described for **Ex 1**. LCMS-1: t_R = 0.73 min, $[M+1]^+$ 394.32.

Example 38: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropyl-5-methoxyphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropyl-5-methoxyphenyl)azetidine-3-carboxamide **Ex 38** is prepared from 2-(difluoromethoxy)-6-methylpyridin-3-amine **I-1.C** and intermediate **I-12** following the methodology described for **Ex 1**. LCMS-1: t_R = 0.74 min, $[M+1]^+$ 406.35.

Table 16: Examples 39-1 to 39-6

Examples **39-1** to **39-6** are synthesized using the methodology described for **Ex 12-61** and **Ex 12-62** starting from **Ex 33, Ex 34**, **Ex 35**, **Ex 36**, **Ex 37,** or **Ex 38**.

Example	Name	Analytics LCMS-1
Ex 39-1	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropyl-6-methylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 518.05 t_R 1.26
Ex 39-2	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropyl-5-methylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 518.06 t_R 1.26
Ex 39-3	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropyl-4-methylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 518.23 t_R 1.23
Ex 39-4	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-fluoro-6-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 522.18 t_R 1.20
Ex 39-5	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(5-fluoro-2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 522.00 t_R 1.20
Ex 39-6	4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropyl-5-methoxyphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 534.01 t_R 1.21

Example 40: 2-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethoxy)-2-methylpropanoic acid

2-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)ethoxy)-2-methylpropanoic acid **Ex 40** is prepared from **Ex 3** and methyl 2-methyl-2-2(2-oxoethoxy)propanoate (preparation in WO2017177004), according to a reductive amination as described for **Ex 11-17**. The methyl ester group is then hydrolyzed under basic conditions using LiOH 2N. LCMS-1: t_R = 0.84 min, $[M+1]^+$ 516.12.

Example 41: 4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)cyclohexane-1-carboxylic acid

4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-cyclohexane-1-carboxylic acid **Ex 41** is prepared from **Ex 3** and commercially available 4-formyl-cylohexanecarboxylic acid ethyl ester, according to a reductive amination as described for **Ex 11-17**. The ethyl ester group is then hydrolyzed under basic conditions using LiOH 2N. LCMS-1: t_R = 0.82 min, $[M+1]^+$ 516.30.

Examples 42 to **48** are synthesized using the methodology described for **Ex 12-142**.

Example	Name	Analytics LCMS-1
Ex 42	N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-propylglycine	$[M+1]^+$ 533.33 t_R 0.99
Ex 43	N-cyclopropyl-N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)glycine	$[M+1]^+$ 531.31 t_R 1.15
Ex 44	3-((2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)amino)propanoic acid	$[M+1]^+$ 505.31 t_R 0.80
Ex 45	3-((2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)amino)-2,2-dimethylpropanoic acid	$[M+1]^+$ 533.07 t_R 0.88
Ex 46	1-(((2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)amino)methyl)cyclopropane-1-carboxylic acid	$[M+1]^+$ 530.96 t_R 0.83
Ex 47	3-((2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)amino)-3-methylbutanoic acid	$[M+1]^+$ 533.33 t_R 0.89
Ex 48	1-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)piperidine-4-carboxylic acid	$[M+1]^+$ 545.32 t_R 0.80

Example 49: (R)-2-amino-5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-5-oxopentanoic acid

(R)-2-amino-5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-5-oxopentanoic acid **Ex 49** (51 mg, beige solid) is prepared from **Ex 3** and commercially available Boc-D-Glu-OtBu following the methodology described for **Ex 12-63 to 12-114**. LCMS-1: t_R = 0.89 min, $[M+1]^+$ 487.08.

Examples 50 to 52:

Examples **50-52** are synthesized using the methodology described for **Ex 12-62** starting from **Ex 3.**

Example	Name	Analytics LCMS-1
Ex 50	(1s,4s)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)cyclohexane-1-carboxylic acid	$[M+1]^+$ 530.11 t_R 1.22
Ex 51	(1S,3R)-3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)cyclohexane-1-carboxylic acid	$[M+1]^+$ 529.97 t_R 1.19
Ex 52	4-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)cyclohexane-1-carboxylic acid	$[M+1]^+$ 543.97 t_R 1.20

Example 53: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3,3-dimethyl-4-(methylsulfonamido)-4-oxobutyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3,3-dimethyl-4-(methylsulfonamido)-4-oxobutyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide **Ex 53** is prepared by reacting **Ex 11-31** (20 mg, 0.038 mmol) with DCC (10 mg, 0.049 mmol) and methanesulfonamide (14 mg, 0.15 mmol) in DCM (5 mL), in the presence of DMAP (6.5 mg, 0.053 mmol). White solid (10 mg, 45 % yield). LCMS-1: t_R = 0.84 min, $[M+1]^+$ 567.08.

Table 17: Examples 54 to 58

Examples 54 to 58 are prepared according to the methodology described for **Ex 12-142** using bromoacetyl bromide, an amino carboxylic ester and **Ex 3.** Alternatively this type of derivatives can be prepared from [(t-butoxycarbonyl)amino]acetic acid and **Ex 3**, followed by Boc deprotection and nucleophilic substitution on methyl bromoacetate. The complete side chain could also be assembled before coupling with **Ex 3**. For example, N-ethyl-N-(2-methoxy-2-oxoethyl)glycine is prepared from commercially available N-(tert-butoxycarbonyl)-N-ethylglycine which is reacted with benzyl bromide, followed by nucleophilic substitution on methyl bromoacetate and hydrogenation: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.43-9.02 (s br, 1 H), 3.79 (s, 3 H), 3.67 (s, 2 H), 3.51 (s, 2 H), 2.95 (q, J = 7.2 Hz, 2 H), 1.19 (t, J = 7.2 Hz, 3 H).

Example	Name	Analytics LCMS-1
Ex 54	methyl N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-(2-methoxyethyl)glycinate	$[M+1]^+$ 563.43 t_R 1.14

Ex 55	(N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-(2-methoxyethyl)glycine	$[M+1]^+$ 549.37 t_R 0.97
Ex 56	methyl (2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)glycinate	$[M+1]^+$ 505,34 t_R 0.82
Ex 57	(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)glycine	$[M+1]^+$ 491.33 t_R 0.89
Ex 58	N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-ethylglycine	$[M+1]^+$ 519.38 t_R 0.94

Example 59: 3-(2-isopropylphenyl)-N-(6-methyl-2-propoxypyridin-3-yl)-1-sulfamoylazetidine-3-carboxamide

1) 3-(2-isopropylphenyl)-N-(6-methyl-2-propoxypyridin-3-yl)azetidine-3-carboxamide is prepared from commercially available 6-methyl-2-propoxypyridin-3-amine **I-1.D** (73 mg) and **I-6** (70 mg) using the $POCl_3$ methodology described for **Ex 4** (36 mg, yellow oil). LCMS-1: t_R =1.29 min, $[M+1]^+$ 447.33. 6-Methyl-2-propoxypyridin-3-amine **I-1.D** is synthesized using the methodology described for **I-1.A** starting from commercially available 2-fluoro-6-methyl-3-nitropyridine and n-propanol. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.87 (d, J = 7.5 Hz, 1 H), 6.56 (d, J = 7.5 Hz, 1 H), 4.34 (s, 2 H), 2.38 (s, 3 H), 1.84 (d, J = 7.2 Hz, 2 H), 1.06 (s, 3 H).

2) 3-(2-isopropylphenyl)-N-(6-methyl-2-propoxypyridin-3-yl)-1-sulfamoylazetidine-3-carboxamide **Ex 59** is prepared from 3-(2-isopropylphenyl)-N-(6-methyl-2-propoxypyridin-3-yl)azetidine-3-carboxamide according to the method described for **Ex 15-5**. LCMS-1: t_R = 1.29 min, $[M+1]^+$ 447.33.

Intermediate I-19: 5-chloro-3-(difluoromethoxy)pyridin-2-amine

3-(Difluoromethoxy)pyridin-2-amine (500 mg, 2.97 mmol) is dissolved in DMF (8 mL). N-Chlorosuccinimide (485 mg, 3.56 mmol) is added and the mixture is stirred at 80°C for 2 h (reaction monitored by LCMS). Water is added, and the compound is extracted with EtOAc. The organic phase is dried over $MgSO_4$, filtered and evaporated. The residue is purified by Prep-HPLC-2. The HPLC fractions are extracted with DCM (3 x 50 mL) and the collected organic layers are dried over $MgSO_4$, filtrered and evaporated to give the title compound **I-19** as a brown solid (424 mg, 73% yield). ^{1}H NMR (400 MHz, DMSO d6) δ: 7.85 (s, 1 H), 7.45 (s, 1 H), 7.17 (t, J = 73.4 Hz, 1 H), 6.34 (s br, 2 H).

Intermediate I-20: 1-(tert-butoxycarbonyl)-3-(2-cyclopentylphenyl)azetidine-3-carboxylic acid

1-Boc-3-(2-cyclopentylphenyl)azetidine-3-carboxylic acid **I-20** is prepared in analogy to **I-6** starting from 1-benzhydryl-3-(2-bromophenyl)azetidine-3-carbonitrile and cyclopenten-1-ylboronic acid. ^{1}H NMR (400 MHz, DMSO d6) δ: 13.15-12.90 (s br, 1 H), 7.33 (d, J = 7.6 Hz, 1 H), 7.30-7.24 (m, 1 H), 7.22 (d, J = 7.6 Hz, 1 H), 7.20-7.14 (m, 1 H), 4.42 (d, J = 7.9 Hz, 2 H), 4.21 (d, J = 7.9 Hz, 2 H), 2.63-2.53 (m, 1 H), 1.98-1.89 (m, 2 H), 1.83-1.74 (m, 2 H), 1.65-1.59 (m, 2 H), 1.52-1.45 (m, 2 H), 1.39 (s, 9 H).

Intermediate I-21: 3-(3-bromopyridin-2-yl)-1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid

3-(3-bromopyridin-2-yl)-1-Boc-azetidine-3-carboxylic acid **I-21** is prepared in analogy to the procedure described for **I-6** starting from ethyl 1-Boc-3-cyanoazetidine and 3-bromo-2-fluoropyridine. ^{1}H NMR (400 MHz, DMSO d6) δ: 8.45 (dd, J_1 = 1.4 Hz, J_2 = 4.7 Hz, 1 H), 7.91 (dd, J_1 = 1.4 Hz, J_2 = 7.9 Hz, 1 H), 7.14 (dd, J_1 = 4.7 Hz, J_2 = 7.9 Hz, 1 H), 4.31-4.16 (m, 4 H), 1.37 (s, 9 H).

Intermediate I-22: 1-(tert-butoxycarbonyl)-3-(6-fluoro-3-isopropylpyridin-2-yl)azetidine-3-carboxylic acid

1-Boc-3-(6-fluoro-3-isopropylpyridin-2-yl)azetidine-3-carboxylic acid **I-22** is prepared in analogy to **I-6** starting from ethyl 1-Boc-azetidine-3-carboxylate and 3-bromo-2,6-difluoropyridine. ^{1}H NMR (400 MHz, DMSO d6) δ: 8.02 (t, J = 8.3 Hz, 1 H), 7.15 (dd, J_1 = 2.5 Hz, J_2 = 8.8 Hz, 1H), 4.42-4.27 (m, 4 H), 2.48-2.42 (m, 1 H), 1.39 (s, 9 H), 1.14 (d, J = 6.6 Hz, 6 H).

Intermediate I-23: 3-(3-bromopyridin-2-yl)-1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid

3-(3-Bromopyridin-2-yl)-1-Boc-azetidine-3-carboxylic acid **I-23** is prepared in analogy to the procedure described for **I-6** starting from ethyl 1-Boc-3-cyanoazetidine and 3-chloro-4-cyanopyridine. ^{1}H NMR (400 MHz, DMSO d6) δ: 8.42 (s, 1 H), 8.38 (d, J = 4.9 Hz, 1 H), 7.33 (d, J = 4.9 Hz, 1 H), 4.44-4.19 (m, 4 H), 1.37 (s, 9 H).

Intermediate I-24: 1-benzyl-4-(2-bromopyridin-3-yl)piperidine-4-carboxylic acid

1-benzyl-4-(2-bromopyridin-3-yl)piperidine-4-carboxylic acid**I-24** was prepared according to the procedure described for intermediate **I-4**. LCMS-2: t_R = 0.55 min, $[M+1]^+$ 374.99 and 377.06.

Intermediate I-25: 1-(tert-butoxycarbonyl)-4-(4-chloropyridin-3-yl)piperidine-4-carboxylic acid

1-Boc-4-(4-chloropyridin-3-yl)piperidine-4-carboxylic acid **I-25** is prepared according to the procedure described in WO2009051715 starting from tert-butyl bis(2-chloroethyl)carbamate and 2-(4-chloropyridin-3-yl)acetonitrile (Synthesis 1992, 6, 528-30).

Intermediate I-26: 1-(tert-butoxycarbonyl)-3-(3-chloropyrazin-2-yl)azetidine-3-carboxylic acid

1-Boc-3-(3-chloropyrazin-2-yl)azetidine-3-carboxylic acid **I-26** is prepared in analogy to procedure described for **I-6** starting from ethyl 1-Boc-3-cyanoazetidine and 2,3-dichloropyrazine. ^{1}H NMR (400 MHz, DMSO d6) δ: 8.70 (d, J = 2.5 Hz, 1 H), 8.52 (d, J = 2.5 Hz, 1 H), 4.49 (d, J = 8.6 Hz, 2 H), 4.41-4.25 (m, 2 H), 1.37 (s, 9 H).

Intermediate I-27: 4-(5-bromopyrimidin-4-yl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid

4-(5-Bromopyrimidin-4-yl)-1-Boc-piperidine-4-carboxylic acid **I-27** is prepared in analogy to the procedure described in WO2009051715 starting from tert-butyl bis(2-chloroethyl)carbamate and 2-(5-chloropyrimidin-4-yl)acetonitrile.

Intermediate I-28 : 4-(4-bromopyrimidin-5-yl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid

4-(4-Bromopyrimidin-5-yl)-1-Boc-piperidine-4-carboxylic acid **I-28** is prepared in analogy to the procedure described in WO2009051715 starting from tert-butyl bis(2-chloroethyl)carbamate and 2-(4-bromopyrimidin-5-yl)acetonitrile. 2-(4-Bromopyrimidin-5-yl)acetonitrile is synthesized by nucleophilic substitution of sodium cyanide on 4-bromo-5-(bromomethyl)pyrimidine.

Example 60: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide

N-(2-(Difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide **Ex 60** is prepared from **I-1.C** and **I-21** under $POCl_3$/Pyr/DMF conditions followed by Suzuki coupling of isopropenyl boronic acid pinacolester, hydrogenation and finally Boc deprotection with TFA. LCMS-1: t_R = 0.67 min, $[M+1]^+$ 377.27.

Example 61: 4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(3-isopropylpyridin-2-yl)azetidin-1-yl)-4-oxobutanoic acid

4-(3-((2-(Difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(3-isopropylpyridin-2-yl)azetidin-1-yl)-4-oxobutanoic acid **Ex 61** is prepared from **Ex 60** according to the method described for **Ex 12-62**. LCMS-1: t_R = 1.02 min, $[M+1]^+$ 477.34.

Example 62: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-2-yl)-1-sulfamoylazetidine-3-carboxamide

N-(2-(Difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-2-yl)-1-sulfamoylazetidine-3-carboxamide **Ex 62** is prepared from **Ex 60** according to the method described for **Ex 15-5**. LCMS-1: t_R = 1.08 min, $[M+1]^+$ 456.28.

Example 63: N1-cyclopropyl-N3-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-2-yl)azetidine-1,3-dicarboxamide

N1-Cyclopropyl-N3-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-2-yl)azetidine-1,3-dicarboxamide **Ex 63** is prepared from **Ex 60** according to the method described for **Ex 17-2**. LCMS-1: t_R = 1.09 min, $[M+1]^+$ 460.36.

Table 18: Examples 64 and 65

Examples 64 and **65** are prepared from **Ex 60** and 4-chloro-5-fluoro-2-methylpyrimidine or 2-chloro-3-fluoro-6-picoline according to the methodology C described for **Ex 18-2**.

Example	Name	Analytics LCMS-1
Ex 64	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(5-fluoro-2-methylpyrimidin-4-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide	$[M+1]^+$ 487.33 t_R 1.00
Ex 65	N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-fluoro-6-methylpyridin-2-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide	$[M+1]^+$ 486,32 t_R 1.42

Example 66: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-4-yl)azetidine-3-carboxamide

N-(2-(Difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-4-yl)azetidine-3-carboxamide **Ex 66** is prepared from **I-1.C** and **I-24** under $POCl_3$/Pyr/DMF conditions followed by Suzuki coupling of isopropenyl

boronic acid pinacolester, hydrogenation and finally Boc deprotection with TFA. LCMS-1: t_R = 0.50 min, $[M+1]^+$ 377.28.

Example 67: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-4-yl)-1-sulfamoylazetidine-3-carboxamide

N-(2-(Difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-4-yl)-1-sulfamoylazetidine-3-carboxamide **Ex 67** is prepared from **Ex 66** according to the method described for **Ex 15-5**. LCMS-1: t_R = 0.73 min, $[M+1]^+$ 456.27.

Example 68: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyrazin-2-yl)azetidine-3-carboxamide

N-(2-(Difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyrazin-2-yl)azetidine-3-carboxamide **Ex 68** is prepared from **I-1.C** and **I-26** under $POCl_3$/Pyr/DMF conditions followed by Suzuki coupling of isopropenyl boronic acid pinacolester, hydrogenation and finally Boc deprotection with TFA. LCMS-1: t_R = 0.60 min, $[M+1]^+$ 378.29.

Example 69: N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyrazin-2-yl)-1-sulfamoylazetidine-3-carboxamide

N-(2-(Difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyrazin-2-yl)-1-sulfamoylazetidine-3-carboxamide **Ex 69** is prepared from **Ex 68** according to the method described for **Ex 15-5**. LCMS-1: t_R = 1.00 min, $[M+1]^+$ 457.27.

Table 19: Examples 70 to 77:

Examples 70 to 77 are prepared from commercially available or synthesized 3-alkoxy-pyridin-2-amines and intermediates **I-6**, **I-20 or I-21** using the $POCl_3$ methodology described for **Ex 4**. In case **I-21** is used, the Suzuki/Hydrogenation sequence is performed to introduce the *i*Pr unit after the amide coupling.

Example	Name	Analytics LCMS-1
Ex 70	N-(5-chloro-3-methoxypyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 361.23 t_R 0.63
Ex 71	N-(5-bromo-3-methoxypyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 404.25 and 406.23 t_R 0.65
Ex 72	N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 396.25 t_R 0.68
Ex 73	N-(5-bromo-3-(difluoromethoxy)pyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 440.21 and 442.21 t_R 0.69
Ex 74	N-(3-(difluoromethoxy)-5-methylpyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 376.29 t_R 0.64

Ex 75	N-(3,5-dimethoxypyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 356.27 t_R 0.64
Ex 76	N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(2-cyclopentylphenyl)azetidine-3-carboxamide	$[M+1]^+$ 422.27 t_R 0.76
Ex 77	N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide	$[M+1]^+$ 397.23 t_R 0.62

Table 20: Examples 78-1 to 78-3:

Examples 78-1 to 78-3 are synthesized by reductive amination as described for example **Ex 11-17** starting from **Ex 72** or **Ex 73**. Functional groups, such as acid or alcohol, may be protected with an appropriate protecting group. For example, esters are saponified by 2N LiOH after the reductive amination step.

Example	Name	Analytics LCMS-1
Ex 78-1	methyl 4-(3-((5-chloro-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoate	$[M+1]^+$ 524.32 t_R 0.82
Ex 78-2	4-(3-((5-chloro-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoic acid	$[M+1]^+$ 510.30 t_R 0.76
Ex 78-3	4-(3-((5-bromo-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoic acid	$[M+1]^+$ 554.28 and 556.28 t_R 0.78

Table 21: Examples 79-1 to 79-7

Examples 79-1 to 79-7 are synthesized by amide coupling from **Ex 70**, **Ex 71**, **Ex 72**, **Ex 73** or **Ex 74** and an acylchloride or a carboxylic acid in the presence of EDC/HOBt, or T3P and an organic base (DIPEA, pyridine for ex.). Functional groups, such as acid or alcohol, may be protected with an appropriate protecting group. For exemple esters are saponified by 2N LiOH after the reductive amination step.

Example	Name	Analytics LCMS-1
Ex 79-1	methyl 4-(3-((5-bromo-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoate	$[M+1]^+$ 582.28 and 584.28 t_R 1.24
Ex 79-2	4-(3-((5-bromo-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 568.24 and 570.24 t_R 1.14
Ex 79-3	4-(3-((5-chloro-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 524.28 t_R 1.12
Ex 79-4	4-(3-((5-chloro-3-methoxypyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 488.30 t_R 1.06

Ex 79-5	4-(3-((5-bromo-3-methoxypyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 532.26 and 534.26 t_R 1.08
Ex 79-6	4-(3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid	$[M+1]^+$ 504.30 t_R 1.06
Ex 79-7	1-(2-(3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)cyclobutane-1-carboxylic acid	$[M+1]^+$ 516.40 t_R 1.08

Table 22: Examples 80-1 and 80-2

Examples **80-1** and **80-2** are synthesized using the methodology described for **Ex 13-1** to **13-27** starting from **Ex 74.**

Example	Name	Analytics LCMS-1
Ex 80-1	benzyl 3-((3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propanoate	$[M+1]^+$ 602.36 t_R 1.30
Ex 80-2	3-((3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propanoic acid	$[M+1]^+$ 512.27 t_R 1.05

5

Table 23: Examples 81-1 to 81-5:

Examples 81-1 to 81-5 are synthesized according to the methodology described for **Ex 15-5** starting from **Ex 70**, **Ex 71**, **Ex 72, Ex 73, Ex 75**, **Ex 76** or **Ex 77**.

Example	Name	Analytics LCMS-1
Ex 81-1	N-(5-chloro-3-methoxypyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 439.27 t_R 0.99
Ex 81-2	N-(5-bromo-3-methoxypyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 483.10 and 485.10 t_R 1.00
Ex 81-3	N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 475.22 t_R 1.06
Ex 81-4	N-(5-bromo-3-(difluoromethoxy)pyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 521.20 t_R 1.2
Ex 81-5	N-(3,5-dimethoxypyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 435.31 t_R 0.90
Ex 81-6	N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(2-cyclopentylphenyl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 501.23 t_R 1.15

Ex 81-7	N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(3-isopropylpyridin-2-yl)-1-sulfamoylazetidine-3-carboxamide	$[M+1]^+$ 476.14 t_R 0.98

Table 24: Examples 82-1 and 82-2

Examples **82-1** and **82-2** are synthesized from isocyanatocyclopropane and **Ex 72** or **Ex 73** using Method A described for **Ex 17-2**.

Example	Name	method	Analytics LCMS-1
Ex 82-1	N3-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-N1-cyclopropyl-3-(2-isopropylphenyl)azetidine-1,3-dicarboxamide	A	$[M+1]^+$ 479.29 t_R 1.09
Ex 82-2	N3-(5-bromo-3-(difluoromethoxy)pyridin-2-yl)-N1-cyclopropyl-3-(2-isopropylphenyl)azetidine-1,3-dicarboxamide	A	$[M+1]^+$ 523.24 and 525.24 t_R 1.10

Table 25: Examples 83-1 to 83-3

Examples **83-1** to **83-3** are synthesized from **Ex 74** using the methodology described for **Ex 14-1**.

Example	Name	Analytics LCMS-1
Ex 83-1	2-methoxy-2-oxoethyl 3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate	$[M+1]^+$ 492.30 t_R 1.13
Ex 83-2	2-((3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)acetic acid	$[M+1]^+$ 478.30 t_R 1.04
Ex 83-3	1-((3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)cyclopropane-1-carboxylic acid	$[M+1]^+$ 518.32 t_R 1.09

Example 84: N-(3-(difluoromethoxy)-5-methylpyridin-2-yl)-3-(2-isopropylphenyl)-1-(4-oxo-4,5-dihydrooxazol-2-yl)azetidine-3-carboxamide

N-(3-(Difluoromethoxy)-5-methylpyridin-2-yl)-3-(2-isopropylphenyl)-1-(4-oxo-4,5-dihydrooxazol-2-yl)azetidine-3-carboxamide **Ex 84** is synthesized from **Ex 74** using the methodology described for **Ex 19**. LCMS-1: t_R = 0.97 min, $[M+1]^+$ 459.31.

Reference Example 85: N-(2-methoxypyridin-3-yl)-3-phenylazetidine-3-carboxamide

1) A solution of intermediate **I-2 (**678 mg, 1.61 mmol) in THF (30 mL) and MeOH (60 mL) is degassed with argon. Palladium hydroxide (210 mg) is then added and the reaction is hydrogenated at atmospheric pressure for 2 h. The mixture is filtered through Celite pad. The pad is rinsed with THF/MeOH (1:1) and the

organic solution is concentrated in vacuo to afford 3-phenylazetidine-3-carboxylic acid (271 mg, 95%). The latter (271 mg, 1.53 mmol) is dissolved in THF/water (60/10 mL), and DIPEA (1.05 mL) is added followed by Boc_2O (334 mg, 1.53 mmol). After 2h, the volatives are evaporated and the remaining aqueous solution is extracted with DCM (20 mL, then 3x10 mL). The organic extracts are combined and evaporated. The residue is purified by prep-HPLC (Prep-HPLC-1 conditions) to give 1-(tert-butoxycarbonyl)-3-phenylazetidine-3-carboxylic acid as a white solid (340 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43-7.37 (m, 2 H), 7.36-7.30 (m, 3 H), 4.63 (d, J = 8.7 Hz, 2 H), 4.34 (d, J = 8.7 Hz, 2 H).

2) 1-Boc-3-phenylazetidine-3-carboxylic acid is coupled to commercially available 2-methoxy-pyridin-3-amine under $POCl_3$/Pyr/DMF conditions followed by Boc deprotection with TFA to give the title compound **Ex 85** as a white solid. LCMS-1: t_R = 0.49 min, $[M+1]^+$ 284.18.

Reference Example 86: 1-(N-(2-methoxyethyl)sulfamoyl)-N-(2-methoxypyridin-3-yl)-3-phenylazetidine-3-carboxamide

1-(N-(2-Methoxyethyl)sulfamoyl)-N-(2-methoxypyridin-3-yl)-3-phenylazetidine-3-carboxamide **Ex 86** is prepared from **Ex 85** in analogy to **Ex 15-1**. LCMS-1: 0.97 min, $[M+1]^+$ 421.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (d, J = 7.8 Hz, 1 H), 7.85 (d, J = 4.8 Hz, 1 H), 7.61 (s, 1 H), 7.55-7.47 (m, 2 H), 7.47-7.40 (m, 1 H), 7.35 (d, J = 7.7 Hz, 2 H), 6.90 (dd, J_1 = 5.1 Hz, J_2 = 7.7 Hz, 1 H), 4.67 (t, J = 5.8 Hz, 1 H), 4.63 (d, J = 7.6 Hz, 2 H), 4.37 (d, J = 7.6 Hz, 2 H), 3.85 (s, 3 H), 3.53 (t, J = 4.9 Hz, 2 H), 3.40-3.31 (m, 5 H).

Biological Assays

Beta-arrestin recruitment assay to determine IC_{50} values for human $LPAR_1$

The Tango™ EDG2-*bla* U2OS cells are obtained from Invitrogen. These cells contain the human LPA_1 receptor cDNA linked to a TEV protease site and a Gal4-VP16 transcription factor integrated into the Tango™ GPCR-*bla* U2OS parental cell line. This parental cell line stably expresses a beta-arrestin / TEV protease fusion protein and the beta-lactamase (*bla*) reporter gene under the control of a UAS response element. Upon LPA (agonist) binding, LPA_1 receptor gets activated, leading to arrestin-protease recruitment and proteolytic release of the transcription factor: The transcription factor then regulates transcription of a beta-lactamase reporter construct, which is measured upon addition of the live-cell substrate.

10'000 Tango™ EDG2-bla U2OS cells are seeded in a 384-well black with clear bottom plate in 30µl Freestyle 293 Expression Medium (Invitrogen) and incubated for 20 h at 37°C, 5% CO_2. For antagonist assays, 5 µl of test compound (dilution series in DMSO / Freestyle 293 Expression medium / 0.1% fatty acid free BSA (Sigma)) or buffer control are added per well and incubated for 30 min at 37°C, 5% CO_2. 5 µl of LPA 18:1 (500nM final) (solution in Freestyle 293 Expression medium / 0.1% fatty acid free BSA (Sigma)) are added per well and the plate incubated for 16 h at 37°C, 5% CO_2. Cells are then loaded with LiveBLAzer-FRET™ B/G Substrate (Invitrogen) for 2 h in the dark and the fluorescence emission at 460nm and 530nm is measured

using the SynergyMx reader (BioTek). Following the background subtraction from both channels, the 460/530nm emission ratio for each well is calculated, then plotted and fitted to a 4-parameter logistic function to obtain IC50 values. IC50 is the concentration of antagonist inhibiting 50% of the maximal response.

Antagonistic activities (IC_{50} values) of exemplified compounds have been measured and antagonistic activities are displayed in Table 26.

Table 26: IC_{50}

Example	IC_{50} $LPAR_1$ [nM]	Example	IC_{50} $LPAR_1$ [nM]	Example	IC_{50} $LPAR_1$ [nM]
1	421	12-36	21	14-6	143
2	320	12-37	22	14-7	79
3	10	12-38	25	14-8	14
4	8	12-39	481	14-9	42
4-1	19	12-40	60	14-10	4
5	594	12-41	69	14-11	127
6	84	12-42	71	14-12	5
6-1	605	12-43	106	14-13	29
7	413	12-44	79	14-14	30
8	338	12-45	61	15-1	5
9	163	12-46	556	15-2	7
10	7	12-47	59	15-3	11
11-1	6	12-48	9	15-4	15
11-2	5	12-49	30	15-5	1.3
11-3	32	12-50	9	15-6	10
11-4	5	12-51	360	15-7	4
11-5	29	12-52	9	15-8	4
11-6	11	12-53	17	15-9	10
11-7	13	12-54	10	15-10	10
11-8	55	12-55	3	15-11	6
11-9	14	12-56	7	15-12	25
11-10	12	12-57	17	15-13	11
11-11	5	12-58	10	15-14	2
11-12	22	12-59	10	15-15	10
11-13	16	12-60	58	15-16	50
11-14	14	12-61	276	15-17	31
11-15	22	12-62	65	15-18	7

11-16	4	12-63	10	16-1	69
11-17	48	12-64	19	16-2	158
11-18	8	12-65	3	16-3	83
11-19	14	12-66	12	16-4	120
11-20	6	12-67	75	16-5	47
11-21	60	12-68	33	17-1	18
11-22	108	12-69	230	17-2	12
11-23	775	12-70	60	17-3	8
11-24	280	12-71	10	17-4	34
11-25	20	12-72	4	17-5	41
11-26	400	12-73	7	17-6	9
11-27	38	12-74	97	17-7	26
11-28	12	12-75	50	17-8	4
11-29	11	12-76	7	17-9	48
11-30	98	12-77	31	17-10	13
11-31	7	12-78	27	17-11	46
11-32	805	12-79	15	17-12	11
11-33	8	12-80	18	17-13	25
11-34	79	12-81	34	17-14	7
11-35	43	12-82	6	17-15	16
11-36	9	12-83	24	17-16	9
11-37	6	12-84	51	17-17	12
11-38	270	12-85	140	17-18	6
11-39	10	12-86	27	17-19	7
11-40	270	12-87	41	17-20	11
11-41	67	12-88	5	17-21	5
11-42	43	12-89	2	17-22	9
11-43	310	12-90	14	17-23	5
11-44	5	12-91	5	17-24	86
11-45	64	12-92	110	17-25	270
11-46	17	12-93	7	17-26	240
11-47	41	12-94	51	17-27	210
11-48	304	12-95	14	18-1	16
11-49	547	12-96	34	18-2	6
11-50	47	12-97	13	18-3	7

11-51	41	12-98	26	18-4	31
11-52	79	12-99	16	18-5	11
11-53	115	12-100	23	18-6	10
11-54	95	12-101	83	18-7	12
11-55	142	12-102	12	18-8	10
11-56	64	12-103	19	18-9	11
11-57	12	12-104	41	18-10	120
11-58	68	12-105	54	18-11	34
11-59	38	12-106	59	18-12	11
11-60	47	12-107	150	18-13	17
11-61	39	12-108	28	18-14	560
11-62	48	12-109	20	18-15	47
11-63	92	12-110	66	18-16	2
11-64	63	12-111	18	18-17	8
11-65	315	12-112	39	18-18	1
11-66	14	12-113	53	18-19	2
11-67	326	12-114	2675	18-20	2
11-68	23	12-115	7	18-21	10
11-69	15	12-116	63	18-22	1
11-70	69	12-117	7	18-23	4
11-71	7	12-118	30	18-24	2
11-72	52	12-119	35	18-25	5
11-73	46	12-120	11	18-26	48
11-74	28	12-121	310	18-27	10
11-75	29	12-122	15	18-28	6
11-76	18	12-123	41	18-29	71
11-77	4.6	12-124	56	18-30	41
11-78	191	12-125	35	18-31	20
11-79	19	12-126	46	18-32	34
11-80	297	12-127	43	18-33	3
11-81	88	12-128	10	18-34	3
11-82	193	12-129	58	18-35	30
11-83	20	12-130	48	18-36	16
11-84	45	12-131	640	19	4
11-85	191	12-132	35	20	37

11-86	10	12-133	140	21	12
11-87	26	12-134	6	22	21
11-88	6	12-135	8	23	664
11-89	73	12-136	9	24	31
11-90	45	12-137	225	25	8.6
11-91	46	12-138	43	26	235
11-92	44	12-139	165	27	13
11-93	65	12-140	122	28	23
11-94	64	12-141	204	29	420
11-95	15	12-142	18	30	33
12-1	15	13-1	7	31-1	19
12-2	10	13-2	7	31-2	6
12-3	16	13-3	14	31-3	5
12-4	20	13-4	10	31-4	89
12-5	14	13-5	4	31-5	14
12-6	13	13-6	26	31-6	185
12-7	13	13-7	17	31-7	8
12-8	10	13-8	7	32	447
12-9	27	13-9	37	33	33
12-10	155	13-10	20	34	142
12-11	7	13-11	366	35	75
12-12	7	13-12	4	36	8
12-13	17	13-13	1755	37	112
12-14	7	13-14	10	38	287
12-15	36	13-15	280	39-1	51
12-16	9	13-16	16	39-2	15
12-17	25	13-17	7.0	39-3	40
12-18	25	13-18	72	39-4	5
12-19	17	13-19	55	39-5	10
12-20	2	13-20	18	39-6	56
12-21	5.6	13-21	14	40	29
12-22	7	13-22	270	41	96
12-23	21	13-23	100	42	7
12-24	19	13-24	750	43	14
12-25	15	13-25	400	44	155

12-26	7	13-26	25	45	63
12-27	4	13-27	28	46	100
12-28	222	13-28	110	47	95
12-29	32	13-29	10	48	103
12-30	25	13-30	49	49	44
12-31	337	14-1	12	50	68
12-32	1715	14-2	4.3	51	80
12-33	10	14-3	6	52	51
12-34	33	14-4	16	53	17
12-35	41	14-5	9		
54	69	71	564	80-1	55
55	44	72	15	80-2	110
56	8	73	10	81-1	15
57	54	74	486	81-2	13
58	48	75	4380	81-3	2
59	270	76	19	81-4	2
60	333	77	1030	81-5	63
61	70	78-1	457	81-6	22
62	3	78-2	17	81-7	5
63	8	78-3	13	82-1	3
64	15	79-1	65	82-2	3
65	37	79-2	11	83-1	74
66	1660	79-3	17	83-2	88
67	82	79-4	123	83-3	76
68	7620	79-5	104	84	310
69	27	79-6	200		
70	866	79-7	61		
Ref. example 85	>10 000	Ref. example 86	>10 000		

Assessment of *in vivo* Potency

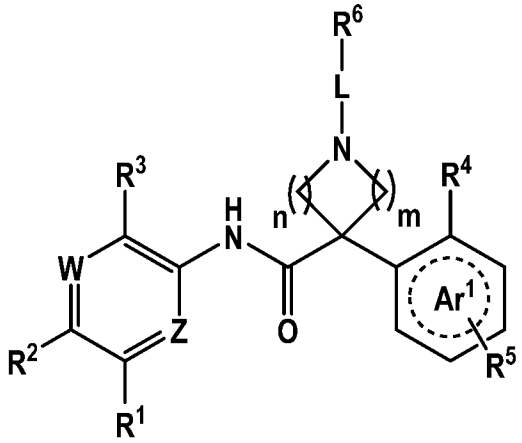
The *in vivo* potency of the compounds of formulae (I), (II) and (III) can be determined using a mouse LPA-induced skin vascular leakage model. Female Balb/c mice are treated with either vehicle or test compound (p.o.) for at least 1 h prior to administration of the albumin marker Evans blue (50 mg/kg, i.v., 0.9% NaCl) and subsequent challenge with LPA (5 µg, i.d.). After 30 minutes, mice are sacrificed by CO_2 inhalation. Discs of skin from the injection sites are removed, digested in formamide (500 µl, 37°C, 24 hrs) and the content of

Evans blue quantified by colorimetric assay. Results are expressed as extravasated Evans blue per skin disc (µg/disc).

As an example, the compound of **Ex 12-21** is able to effectively reduce LPA-induced vascular leakage after oral administration of 100mg/kg to mice as compared to a group of animals treated with vehicle only. Reduction of vascular leakage compared to vehicle group was ≥ 60%.

Claims

1. A compound of Formula (I),



Formula (I)

wherein

- **W** represents N, and **Z** represents CH; or
- **Z** represents N, and **W** represents CH;

R^1 is hydrogen or fluoro;

R^2 is hydrogen, halogen, methyl, ethyl, methoxy or ethoxy;

R^3 is C_{1-3}-alkoxy or C_{1-3}-fluoroalkoxy;

Ar^1 represents phenyl, or 6-membered heteroaryl containing one or two nitrogen atoms, wherein said group Ar^1 is substituted with R^4 and R^5, wherein

- R^4 is n-propyl, isopropyl, C_{3-6}-cycloalkyl optionally containing a ring oxygen atom, or cyclopent-1-en-1-yl; and
- R^5 represents one substituent independently selected from hydrogen, fluoro, methyl or methoxy;

m and **n** independently represent the integer 1 or 2; and

the group **-L-R^6** represents

- hydrogen;
- -C_{1-4}-alkyl;
- -C_{0-6}-alkylene-C_{3-6}-cycloalkyl; wherein the C_{3-6}-cycloalkyl independently is unsubstituted or mono-substituted with halogen;
- -CO-H;

- -L^1-CO-R^{C11} wherein R^{C11} independently represents hydroxy; -O-benzyl; -O-C_{1-6}-alkyl; C_1-fluoroalkyl; or -$NR^{N11}R^{N12}$; wherein independently R^{N11} is hydrogen or C_{1-4}-alkyl, and R^{N12} is hydrogen, C_{1-4}-alkyl, -SO_2-C_{1-6}-alkyl, or -O-R^{O11}, wherein R^{O11} independently represents hydrogen, C_{1-6}-alkyl, or benzyl; and

  -L^1- independently represents

  - -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;
  - -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, or -SO_2-C_{1-6}-alkylene-; wherein in the above groups said C_{1-6}-alkylene independently is mono-substituted with hydroxy, C_{1-3}-alkoxy, -O-CO-C_{1-4}-alkyl, or -$NR^{N13}R^{N14}$; wherein independently R^{N13} is hydrogen or C_{1-4}-alkyl, and R^{N14} is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{2-6}-alkylene-, -CO-C_{2-6}-alkylene-, or -SO_2-C_{2-6}-alkylene-; wherein in the above groups said C_{2-6}-alkylene independently is di-substituted wherein the substituents are independently selected from hydroxy and -$NR^{N15}R^{N16}$; wherein independently R^{N15} is hydrogen or C_{1-4}-alkyl, and R^{N16} is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-NH-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, or -CO-O-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-;
  - -C_{0-4}-alkylene-Cy^1-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-Cy^1-C_{0-4}-alkylene-, -CO-O-C_{0-4}-alkylene-Cy^1-C_{0-4}-alkylene-, -CO-NH-C_{0-4}-alkylene-Cy^1-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-Cy^1-C_{0-4}-alkylene-, or -SO_2-NH-C_{0-4}-alkylene-Cy^1-C_{0-4}-alkylene-; wherein Cy^1 independently represents a C_{3-6}-heterocycloalkylene containing one ring oxygen atom, or one ring nitrogen atom, wherein said ring nitrogen, in case it has a free valency, independently is unsubstituted, or mono-substituted with C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{2-4}-alkylene-O-C_{2-4}-alkylene-O-C_{1-4}-alkylene-, or -CO-C_{1-4}-alkylene-O-C_{2-4}-alkylene-O-C_{1-4}-alkylene-;
  - -C_{2-4}-alkylene-X^{11}-C_{1-4}-alkylene-, -CO-O-C_{2-4}-alkylene-X^{11}-C_{1-4}-alkylene-, -CO-NH-C_{2-4}-alkylene-X^{11}-C_{1-4}-alkylene-, or -SO_2-NH-C_{2-4}-alkylene-X^{11}-C_{1-4}-alkylene-; wherein X^{11} independently represents oxygen, or a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, or -CO-O-C_{1-4}-alkyl;
  - -CO-C_{1-4}-alkylene-X^{12}-C_{1-4}-alkylene-, -SO_2-C_{1-4}-alkylene-X^{12}-C_{1-4}-alkylene-, or -CO-C_{1-4}-alkylene-X^{12}-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-; wherein X^{12} independently represents oxygen, or a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, -CO-O-C_{1-4}-alkyl, or C_{1-3}-alkoxy-C_{2-4}-alkyl;
  - -C_{2-4}-alkylene-X^{13}-C_{1-4}-alkylene-; wherein X^{13} represents -NH-CO-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy;
  - -C_{1-4}-alkylene-X^{14}-C_{1-4}-alkylene-; wherein X^{14} represents -CO-NH-;
  - -CO-C_{2-6}-alkenylene- or -SO_2-C_{2-6}-alkenylene-; or
  - -CO-C_{2-6}-fluoroalkylene-;

- -L^2-hydroxy; wherein -L^2- represents
  - -CO-C_{1-6}-alkylene- or -SO_2-C_{1-6}-alkylene-; wherein in the above groups said C_{1-6}-alkylene independently is unsubstituted, or mono-substituted with hydroxy, C_1-fluoroalkyl, or -N$R^{N21}R^{N22}$ wherein independently R^{N21} is hydrogen or C_{1-4}-alkyl, and R^{N22} is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{2-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-, wherein in the above groups said C_{2-6}-alkylene independently is unsubstituted, or mono-substituted with hydroxy, C_1-fluoroalkyl, or -N$R^{N23}R^{N24}$ wherein independently R^{N23} is hydrogen or C_{1-4}-alkyl, and R^{N24} is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-;
  - -C_{0-4}-alkylene-Cy^2-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-Cy^2-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-Cy^2-C_{0-4}-alkylene-; wherein Cy^2 independently represents a C_{3-6}-heterocycloalkylene group containing one ring oxygen atom, or one ring nitrogen atom; wherein said ring nitrogen, in case it has a free valency, is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{2-4}-alkylene-(O-C_{2-4}-alkylene)$_p$- or -CO-C_{1-4}-alkylene-(O-C_{2-4}-alkylene)$_p$-; wherein **p** independently represents the integer 1 or 2;
  - -C_{2-4}-alkylene-X^{21}-C_{2-4}-alkylene-; wherein X^{21} represents a nitrogen atom which is unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, or -CO-O-C_{1-4}-alkyl;
  - -CO-C_{1-4}-alkylene-X^{22}-C_{2-4}-alkylene-, -CO-C_{1-4}-alkylene-X^{22}-C_{1-4}-alkylene-C_{3-6}-cycloalkylene-, or -SO_2-C_{1-4}-alkylene-X^{22}-C_{2-4}-alkylene-; wherein X^{22} represents a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, or -CO-O-C_{1-4}-alkyl;
  - -C_{2-4}-alkylene-X^{23}-C_{1-4}-alkylene-; wherein X^{23} represents -NH-CO-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy;
  - -C_{1-4}-alkylene-X^{24}-C_{2-4}-alkylene-; wherein X^{24} represents -CO-NH-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy; or
  - 3,4-dioxocyclobut-1-ene-1,2-diyl;
- -L^3-O-R^{O31} wherein R^{O31} is -C_{1-4}-alkyl, -CO-C_{1-4}-alkyl or -CO-C_{2-4}-alkenyl; and
  -L^3- independently represents
  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene- or -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-;
- -L^4-N$R^{N1}R^{N2}$ wherein independently R^{N1} is hydrogen or C_{1-4}-alkyl; and R^{N2} is hydrogen; C_{1-4}-alkyl; C_{1-3}-fluoroalkyl; C_{3-6}-cycloalkyl; C_{1-3}-alkoxy-C_{2-4}-alkylene; -CO-C_{1-4}-alkyl; -SO_2-C_{1-4}-alkyl; or -SO_2-C_1-fluoroalkyl; and
  -L^4- independently represents

- -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-; or
- -C_{0-4}-alkylene-**Cy^4**-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-**Cy^4**-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-**Cy^4**-C_{0-4}-alkylene-; wherein **Cy^4** independently represents a C_{3-6}-heterocycloalkylene group containing one ring oxygen atom;

- **-L^5-NR^{N3}R^{N4}** wherein **R^{N3}** is hydrogen, C_{1-4}-alkyl, or C_{1-3}-alkoxy-C_{2-4}-alkylene; and **R^{N4}** is -CO-O-C_{1-4}-alkyl; -CO-N**R^{N51}R^{N52}** wherein **R^{N51}** and **R^{N52}** are independently selected from hydrogen and C_{1-4}-alkyl; or -SO_2-**NR^{N53}R^{N54}** wherein independently **R^{N53}** is hydrogen or C_{1-4}-alkyl, and **R^{N54}** is hydrogen, C_{1-4}-alkyl, or -CO-C_{1-4}-alkyl;

  and **-L^5-** independently represents
  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene- or -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-;
- **-L^6-**N(**R^{N61}**)-O-**R^{O61}** wherein **R^{N61}** is hydrogen, -CO-C_{1-4}-alkyl, or -CO-O-C_{1-4}-alkyl; and **R^{O61}** independently represents hydrogen, C_{1-6}-alkyl, or benzyl;

  and **-L^6-** independently represents
  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-;
- **-L^7-NR^{N5}R^{N6}** wherein **R^{N5}** is hydrogen or C_{1-4}-alkyl; **R^{N6}** is hydrogen, C_{1-4}-alkyl, -CO-C_{1-4}-alkyl, C_{1-3}-fluoroalkyl, or C_{3-6}-cycloalkyl; and

  -L^7- independently represents
  - -CO-, or -SO_2-;
- **-L^8-**SO_2-**R^{S81}** wherein **R^{S81}** independently represents -C_{1-6}-alkyl; C_1-fluoroalkyl; hydroxy; -N**R^{N81}R^{N82}** wherein independently **R^{N81}** is hydrogen or C_{1-4}-alkyl, and **R^{N82}** is hydrogen, C_{1-4}-alkyl, -CO-C_{1-6}-alkyl; and

  -L^8- independently represents
  - -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;
- **-L^9-HET^1**, wherein **HET^1** represents 5- or 6-membered heteroaryl, wherein said **HET^1** independently is unsubstituted or mono-, or di-substituted wherein the substituents are independently selected from C_{1-4}-alkyl; halogen; cyano; hydroxy; hydroxymethyl; -C_{0-2}-alkylene-**Cy^{91}**-COOR^{O91} wherein R^{O91} is hydrogen or C_{1-4}-alkyl, and wherein **Cy^{91}** represents a C_{3-6}-cycloalkylene group; or -C_{0-2}-alkylene-COOR^{O92} wherein R^{O92} is hydrogen or C_{1-4}-alkyl; and

  -L^9- independently represents
  - -C_{0-6}-alkylene-, -CO-C_{0-6}-alkylene-, -SO_2-C_{0-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;
- **-L^{10}-**C_{4-6}-heterocyclyl, wherein the C_{4-6}-heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said C_{4-6}-

heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:

- one or two oxo substituents each attached to a ring carbon atom in alpha position to a ring nitrogen atom; and / or
- two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom or a ring oxygen atom; and / or
- two oxo substituents at a ring sulfur ring atom; and / or
- C_{1-4}-alkyl, C_{1-3}-alkoxy-C_{2-4}-alkyl, C_{2-3}-fluoroalkyl, or -CO-C_{1-4}-alkyl attached to a ring nitrogen atom having a free valency; and

-L^{10}- independently represents

- -C_{0-6}-alkylene-, -CO-C_{0-6}-alkylene-, -SO_2-C_{0-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;

- -L^{11}-cyano; wherein -L^{11}- represents -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene, or -C_{0-6}-alkylene-;
- -L^{12}-NO_2; wherein -L^{12}- represents -C_{2-6}-alkylene-;
- -L^{13}-C_{1-4}-alkyl; wherein -L^{13}- represents -CO-, -CO-O-, or -SO_2-;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

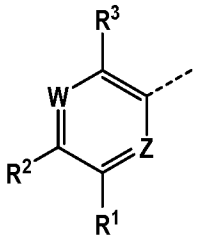
- **W** represents N, **Z** represents CH; and R^2 is hydrogen, methyl, methoxy or ethoxy; or
- **Z** represents N, **W** represents CH; and R^2 is chloro, bromo, methyl, or methoxy;

or a pharmaceutically acceptable salt thereof.

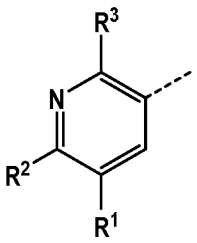
3. A compound according to claim 1 or 2, wherein R^3 represents methoxy, or difluoromethoxy;

or a pharmaceutically acceptable salt thereof.

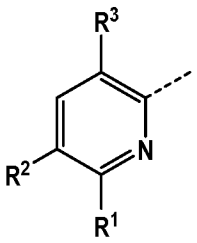
4. A compound according to claim 1, wherein the fragment:



represents:

- 

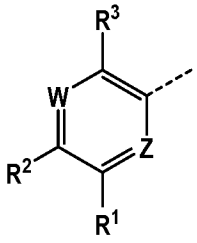
wherein **R1** is hydrogen or fluoro; **R2** is hydrogen, chloro, methyl, ethyl, methoxy or ethoxy; and **R3** is C_{1-3}-alkoxy or C_{1-3}-fluoroalkoxy; or

- 

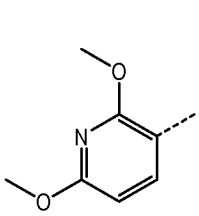
wherein **R1** is hydrogen; **R2** is halogen, methyl, or methoxy; and **R3** is C_{1-3}-alkoxy or C_{1-3}-fluoroalkoxy;

or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 1, wherein the fragment:

 represents a ring independently selected from the following groups A) or B):

A)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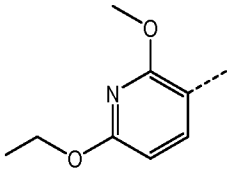
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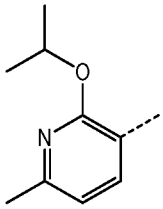
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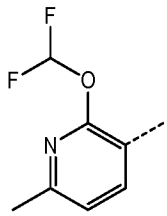
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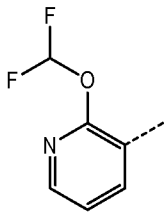
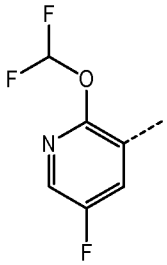
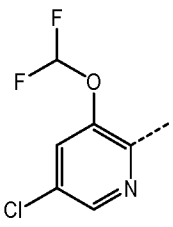

, or

;

B)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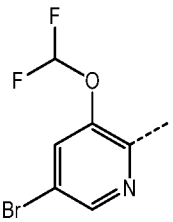
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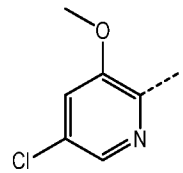
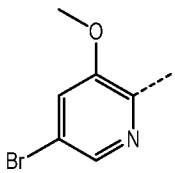

, or

;

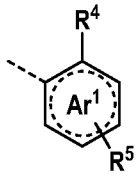
or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 5, wherein **Ar^1** represents phenyl; wherein said phenyl group is substituted with **R^4** and **R^5**, wherein

- **R^4** represents n-propyl, isopropyl, or monocyclic C_{3-6}-cycloalkyl; and
- **R^5** represents hydrogen, fluoro, or methyl;

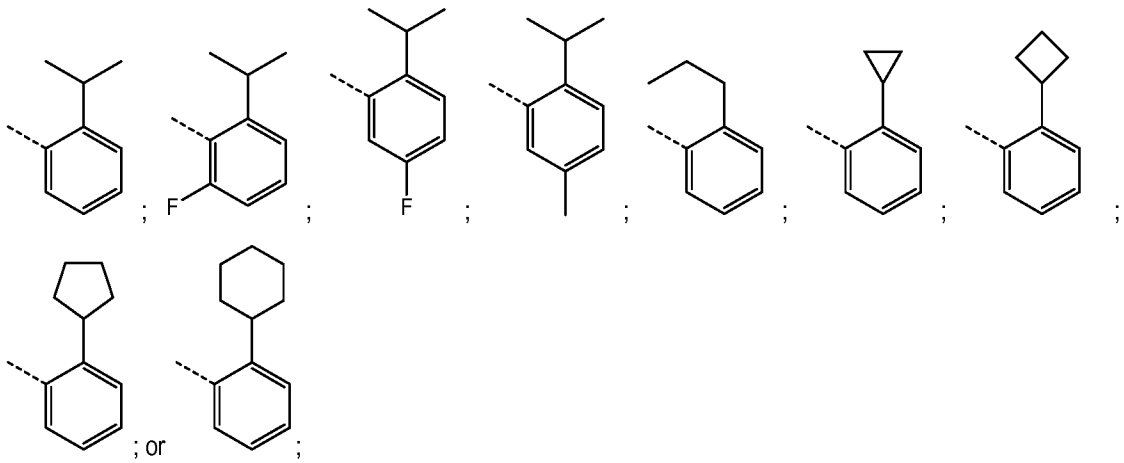
or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 5, wherein the fragment:

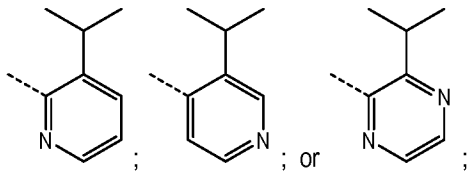


represents a ring independently selected from the following groups A) or B):

A)



B)



or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 7, wherein **m** and **n** both are 1;

or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 8, wherein the group **-L-R^6** represents

- hydrogen;
- **-L^1**-CO-**R^{C11}** wherein **R^{C11}** independently represents hydroxy; -O-benzyl; -O-C_{1-6}-alkyl; C_1-fluoroalkyl; or -N**R^{N11}R^{N12}**; wherein independently **R^{N11}** is hydrogen or C_{1-4}-alkyl, and **R^{N12}** is hydrogen, C_{1-4}-alkyl, -SO_2-C_{1-6}-alkyl, or -O-**R^{O11}**, wherein **R^{O11}** independently represents hydrogen, C_{1-6}-alkyl, or benzyl; and

  -L^1- independently represents

  - -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;
  - -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, or -SO_2-C_{1-6}-alkylene-; wherein in the above groups said C_{1-6}-alkylene independently is mono-substituted with hydroxy, C_{1-3}-alkoxy, -O-CO-C_{1-4}-alkyl, or -N**R^{N13}R^{N14}**; wherein independently **R^{N13}** is hydrogen or C_{1-4}-alkyl, and **R^{N14}** is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{2-6}-alkylene-, -CO-C_{2-6}-alkylene-, or -SO_2-C_{2-6}-alkylene-; wherein in the above groups said C_{2-6}-alkylene independently is di-substituted wherein the substituents are independently selected from

hydroxy and -N$R^{N15}R^{N16}$; wherein independently R^{N15} is hydrogen or C_{1-4}-alkyl, and R^{N16} is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;

- -C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-NH-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, or -CO-O-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-;
- -C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, -CO-O-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, -CO-NH-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-, or -SO_2-NH-C_{0-4}-alkylene-**Cy**^{1}-C_{0-4}-alkylene-; wherein **Cy**^{1} independently represents a C_{3-6}-heterocycloalkylene containing one ring oxygen atom, or one ring nitrogen atom, wherein said ring nitrogen, in case it has a free valency, independently is unsubstituted, or mono-substituted with C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
- -CO-C_{1-4}-alkylene-**X**^{12}-C_{1-4}-alkylene-, -SO_2-C_{1-4}-alkylene-**X**^{12}-C_{1-4}-alkylene-, or -CO-C_{1-4}-alkylene-**X**^{12}-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-; wherein **X**^{12} independently represents oxygen, or a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, -CO-O-C_{1-4}-alkyl, or C_{1-3}-alkoxy-C_{2-4}-alkyl;
- -C_{2-4}-alkylene-**X**^{13}-C_{1-4}-alkylene-; wherein **X**^{13} represents -NH-CO-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy;
- -CO-C_{2-6}-alkenylene- or -SO_2-C_{2-6}-alkenylene-; or
- -CO-C_{2-6}-fluoroalkylene-;

- -**L**^{2}-hydroxy; wherein -**L**^{2}- represents
  - -CO-C_{1-6}-alkylene- or -SO_2-C_{1-6}-alkylene-; wherein in the above groups said C_{1-6}-alkylene independently is unsubstituted, or mono-substituted with hydroxy, C_1-fluoroalkyl, or -N$R^{N21}R^{N22}$ wherein independently R^{N21} is hydrogen or C_{1-4}-alkyl, and R^{N22} is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{2-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-, wherein in the above groups said C_{2-6}-alkylene independently is unsubstituted, or mono-substituted with hydroxy, C_1-fluoroalkyl, or -N$R^{N23}R^{N24}$ wherein independently R^{N23} is hydrogen or C_{1-4}-alkyl, and R^{N24} is hydrogen, C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-C_{3-6}-cycloalkylene-C_{0-4}-alkylene-;
  - -C_{0-4}-alkylene-**Cy**^{2}-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-**Cy**^{2}-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-**Cy**^{2}-C_{0-4}-alkylene-; wherein **Cy**^{2} independently represents a C_{3-6}-heterocycloalkylene group containing one ring oxygen atom, or one ring nitrogen atom; wherein said ring nitrogen, in case it has a free valency, is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl or -CO-O-C_{1-4}-alkyl;
  - -CO-C_{1-4}-alkylene-**X**^{22}-C_{2-4}-alkylene-, -CO-C_{1-4}-alkylene-**X**^{22}-C_{1-4}-alkylene-C_{3-6}-cycloalkylene-, or -SO_2-C_{1-4}-alkylene-**X**^{22}-C_{2-4}-alkylene-; wherein **X**^{22} represents a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{3-6}-cycloalkyl, or -CO-O-C_{1-4}-alkyl; or

- -C_{2-4}-alkylene-X^{23}-C_{1-4}-alkylene-; wherein X^{23} represents -NH-CO-, and wherein said C_{2-4}-alkylene independently is unsubstituted, or mono-substituted with hydroxy;

- -L^4-$NR^{N1}R^{N2}$ wherein independently R^{N1} is hydrogen or C_{1-4}-alkyl; and R^{N2} is hydrogen; C_{1-4}-alkyl; C_{1-3}-fluoroalkyl; C_{3-6}-cycloalkyl; C_{1-3}-alkoxy-C_{2-4}-alkylene; -CO-C_{1-4}-alkyl; -SO_2-C_{1-4}-alkyl; or -SO_2-C_1-fluoroalkyl;
  and
  -L^4- independently represents
  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-; or
  - -C_{0-4}-alkylene-Cy^4-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-Cy^4-C_{0-4}-alkylene-, or -SO_2-C_{0-4}-alkylene-Cy^4-C_{0-4}-alkylene-; wherein Cy^4 independently represents a C_{3-6}-heterocycloalkylene group containing one ring oxygen atom;

- -L^5-$NR^{N3}R^{N4}$ wherein R^{N3} is hydrogen, C_{1-4}-alkyl, or C_{1-3}-alkoxy-C_{2-4}-alkylene; and R^{N4} is -CO-O-C_{1-4}-alkyl; -CO-$NR^{N51}R^{N52}$ wherein R^{N51} and R^{N52} are independently selected from hydrogen and C_{1-4}-alkyl; or -SO_2-$NR^{N53}R^{N54}$ wherein independently R^{N53} is hydrogen or C_{1-4}-alkyl, and R^{N54} is hydrogen, C_{1-4}-alkyl, or -CO-C_{1-4}-alkyl;
  and -L^5- independently represents
  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene- or -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-;

- -L^6-N(R^{N61})-O-R^{O61} wherein R^{N61} is hydrogen, -CO-C_{1-4}-alkyl, or -CO-O-C_{1-4}-alkyl; and R^{O61} independently represents hydrogen, C_{1-6}-alkyl, or benzyl;
  and -L^6- independently represents
  - -C_{2-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{2-6}-alkylene-, or -SO_2-NH-C_{2-6}-alkylene-;

- -L^7-$NR^{N5}R^{N6}$ wherein R^{N5} is hydrogen or C_{1-4}-alkyl; R^{N6} is hydrogen, C_{1-4}-alkyl, -CO-C_{1-4}-alkyl, C_{1-3}-fluoroalkyl, or C_{3-6}-cycloalkyl; and
  -L^7- independently represents
  - -CO-, or -SO_2-;

- -L^8-SO_2-R^{S81} wherein R^{S81} independently represents -C_{1-6}-alkyl; C_1-fluoroalkyl; hydroxy; -$NR^{N81}R^{N82}$ wherein independently R^{N81} is hydrogen or C_{1-4}-alkyl, and R^{N82} is hydrogen, C_{1-4}-alkyl, -CO-C_{1-6}-alkyl; and
  -L^8- independently represents
  - -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{2-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;

- -L^9-HET^1, wherein HET^1 represents 5- or 6-membered heteroaryl,
  wherein said HET^1 independently is unsubstituted or mono-, or di-substituted wherein the substituents are independently selected from C_{1-4}-alkyl; halogen; cyano; hydroxy; hydroxymethyl; -C_{0-2}-alkylene-Cy^{91}-

$COOR^{O91}$ wherein R^{O91} is hydrogen or C_{1-4}-alkyl, and wherein **Cy^{91}** represents a C_{3-6}-cycloalkylene group; or -C_{0-2}-alkylene-$COOR^{O92}$ wherein R^{O92} is hydrogen or C_{1-4}-alkyl; and

-L^{9}- independently represents

- -C_{0-6}-alkylene-, -CO-C_{0-6}-alkylene-, -SO_2-C_{0-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;

- **-L^{10}-**C_{4-6}-heterocyclyl, wherein the C_{4-6}-heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said C_{4-6}-heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:
  - one or two oxo substituents each attached to a ring carbon atom in alpha position to a ring nitrogen atom; and / or
  - two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom or a ring oxygen atom; and / or
  - two oxo substituents at a ring sulfur ring atom; and / or
  - C_{1-4}-alkyl, C_{1-3}-alkoxy-C_{2-4}-alkyl, C_{2-3}-fluoroalkyl, or -CO-C_{1-4}-alkyl attached to a ring nitrogen atom having a free valency; and

  -L^{10}- independently represents
  - -C_{0-6}-alkylene-, or -CO-C_{0-6}-alkylene-;
- **-L^{11}-**cyano; wherein **-L^{11}-** represents -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene, or -C_{0-6}-alkylene-;or
- **-L^{13}-**C_{1-4}-alkyl; wherein **-L^{13}-** represents -CO-, -CO-O, or -SO_2;

or a pharmaceutically acceptable salt thereof.

10. A compound according to any one of claims 1 to 8, wherein the group **-L-R^{6}** represents

- **-L^{1}-**COOH; wherein

  -L^{1}- represents
  - -C_{1-6}-alkylene-, -CO-C_{1-6}-alkylene-, -SO_2-C_{1-6}-alkylene-, -CO-O-C_{1-6}-alkylene-, -CO-NH-C_{1-6}-alkylene-, or -SO_2-NH-C_{1-6}-alkylene-;
  - -CO-C_{1-6}-alkylene-; wherein said C_{1-6}-alkylene is mono-substituted with hydroxy;
  - -C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -CO-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, -SO_2-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-, or -CO-O-C_{0-4}-alkylene-C_{3-8}-cycloalkylene-C_{0-4}-alkylene-;
  - -CO-C_{0-4}-alkylene-**Cy^{1}**-C_{0-4}-alkylene-; wherein **Cy^{1}** independently represents a C_{3-6}-heterocycloalkylene containing one ring oxygen atom;
  - -CO-C_{1-4}-alkylene-**X^{12}**-C_{1-4}-alkylene-; wherein **X^{12}** independently represents a nitrogen atom which is unsubstituted, or mono-substituted with C_{1-4}-alkyl;

- -CO-C_{2-6}-alkenylene- or -SO_2-C_{2-6}-alkenylene-; or
- -CO-C_{2-6}-fluoroalkylene-;

- **-L^2**-hydroxy; wherein **-L^2-** represents
  - -C_{2-6}-alkylene-, wherein the C_{2-6}-alkylene is unsubstituted, or mono-substituted with hydroxy; or
  - -CO-C_{1-4}-alkylene-**X^{22}**-C_{2-4}-alkylene-; wherein **X^{22}** represents a nitrogen atom which is independently unsubstituted, or mono-substituted with C_{1-4}-alkyl or C_{3-6}-cycloalkyl;
- **-L^7**-N**$R^{N5}R^{N6}$** wherein both **R^{N5}** is hydrogen; **R^{N6}** is hydrogen, or C_{3-6}-cycloalkyl; and

  -L^7- independently represents
  - -CO-, or -SO_2-;
- **-L^9-HET^1**, wherein **HET^1** represents 5- or 6-membered heteroaryl selected from pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl; wherein said **HET^1** independently is unsubstituted or mono-, or di-substituted wherein the substituents are independently selected from C_{1-4}-alkyl; halogen; cyano; hydroxy; hydroxymethyl; -C_{0-2}-alkylene-**Cy^{91}**-$COOR^{O91}$ wherein R^{O91} is hydrogen or C_{1-4}-alkyl, and wherein **CY^{91}** represents a C_{3-6}-cycloalkylene group; or -C_{0-2}-alkylene-$COOR^{O92}$ wherein R^{O92} is hydrogen or C_{1-4}-alkyl; and

  -L^9- independently represents
  - -C_{0-6}-alkylene-, -CO-C_{0-6}-alkylene-;

or a pharmaceutically acceptable salt thereof.

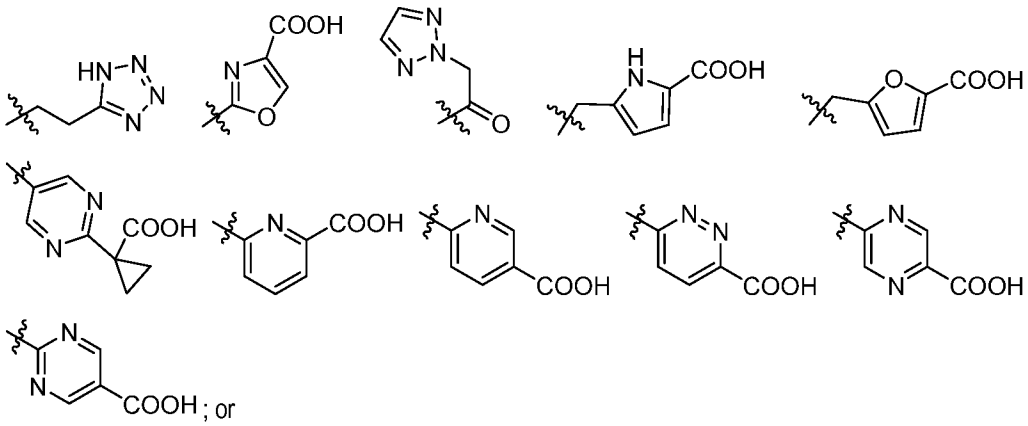
11. A compound according to any one of claims 1 to 8, wherein the group **-L-R^6** represents

- **-L^1**-COOH; and

  -L^1- represents
  - -CH_2-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-$C(CH_3)_2$-CH_2-, *-CH_2-CH_2-$C(CH_3)_2$-, *-CH_2-CH_2-CH_2-$C(CH_3)_2$-, *-CO-CH_2-CH_2-, *-CO-CH(CH_3)-CH_2-, *-CO-CH_2-C(OH)(CH_3)-, *-CO-CH_2-CH_2-CH_2-, *-CO-CH_2-$C(CH_3)_2$-, *-CO-$C(CH_3)_2$-CH_2-, *-SO_2-CH_2-, *-SO_2-CH_2-CH_2-, *-SO_2-CH_2-CH_2-CH_2-, *-SO_2-CH_2-$C(CH_3)_2$-, *-CO-O-CH_2-, *-CO-O-CH(CH_3)-, *-CO-O-CH_2-$C(CH_3)_2$-, *-CO-NH-$C(CH_3)_2$-CH_2-, *-CO-NH-CH_2-$C(CH_3)_2$-, *-CO-NH-CH_2-CH_2-$C(CH_3)_2$-, *-SO_2-NH-CH_2-; *-CH_2-CH_2-CH_2--cyclopropane-1,1-diyl-, *-CO-cyclopropane-1,2-yl-, *-CO-CH_2-cyclopropane-1,1-diyl-, *-CO-CH_2-cyclobutane-1,1-diyl-, *-SO_2-cyclopropane-1,1-diyl-CH_2-, *-CO-O-cyclopropane-1,1-diyl-, *-CO-O-CH_2-cyclopropane-1,1-diyl-;
  - *-CO-CH_2-(tetrahydro-2H-pyran-4,4-diyl)-;
  - *-CO-CH_2-N(n-butyl)-CH_2-;
  - *-SO_2-CH=CH-, *-CO-C(CH_2)-CH_2-; or
  - *-CO-CF_2-CH_2-;
- **-L^2**-hydroxy; wherein **-L^2-** represents

- *-CH_2-CH(OH)-CH_2-; or
- *-CO-CH_2-NH-CH_2-CH_2-, *-CO-CH_2-NH-CH(CH_3)-CH_2-, *-CO-CH_2-NH-CH_2-CH(CH_3)-;

- -**L**^{7}-NH_2; wherein

  -**L**^{7}- represents
  - -SO_2-;
- -**L**^{9}-**HET**^{1}, wherein -**L**^{9}-**HET**^{1} represents
  - 
- -**L**^{7}-NH-cyclopropyl; wherein

  -**L**^{7}- represents
  - -CO-;

wherein in the above groups the asterisks indicate the bond which is connected to the rest of the molecule;

or a pharmaceutically acceptable salt thereof.

12. A compound according to claim 1 wherein said compound is:

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)pyrrolidine-3-carboxamide;
1-(2-aminoethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-hydroxypropyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
1-cyano-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
1-(3-(1H-tetrazol-5-yl)propyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-hydroxy-3-methylbutyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(1-hydroxycyclopropyl)ethyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(2-aminopropyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)propanoic acid;

1-(2-cyanoethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2,3-dihydroxypropyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2,3-dihydroxypropyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(oxetan-3-yl)azetidine-3-carboxamide;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)butanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3,3-dimethylbutanoic acid;

5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)-1H-pyrrole-2-carboxylic acid;

5-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)methyl)furan-2-carboxylic acid;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(4-hydroxy-4-methylpentyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylpentanoic acid;

1-(3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)propyl)cyclopropane-1-carboxylic acid;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(methylsulfonamido)ethyl)azetidine-3-carboxamide;

(S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-hydroxy-3-(2-hydroxyacetamido)propyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(cyanomethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(2-(1H-tetrazol-5-yl)ethyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(4-cyanobutanoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-acetyl-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(3-sulfamoylpropanoyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(N-methylsulfamoyl)acetyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-((methylsulfonyl)glycyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(N-methyl-N-sulfamoylglycyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(5,5,5-trifluoro-4-oxopentanoyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)-1-(5,5,5-trifluoro-4-oxopentanoyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxyoxetan-3-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-hydroxyisoxazole-5-carbonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-oxo-2,3-dihydroisoxazole-5-carbonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(2-(1H-tetrazol-1-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

1-(2-(2H-1,2,3-triazol-2-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(2-(2H-1,2,3-triazol-2-yl)acetyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxy-1H-pyrazol-5-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-oxo-2,3-dihydro-1H-pyrazol-5-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxy-1H-pyrazol-4-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-oxo-2,3-dihydro-1H-pyrazol-4-yl)acetyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-hydroxy-1H-pyrazol-4-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(2-(3-oxo-2,3-dihydro-1H-pyrazol-4-yl)acetyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

1-(L-alanyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)-1-((2-methoxyethyl)glycyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((2-hydroxyethyl)glycyl)-4-(2-isopropylphenyl)piperidine-4-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((2-hydroxyethyl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-((2-methoxyethyl)glycyl)azetidine-3-carboxamide;

(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((R)-(2-hydroxypropyl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

(S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((S)-(2-hydroxypropyl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

(R)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((R)-(1-hydroxypropan-2-yl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

(S)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((R)-(1-hydroxypropan-2-yl)glycyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-oxopropanoic acid;

3-(4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)-3-oxopropanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-4-oxobutanoic acid;

4-(4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)-4-oxobutanoic acid;

(S)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-methyl-4-oxobutanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

1-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)cyclopropane-1-carboxylic acid;

1-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)cyclobutane-1-carboxylic acid;

(R)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3-methyl-4-oxobutanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3,3-dimethyl-4-oxobutanoic acid;

3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)but-3-enoic acid;

(1S,2R)-2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)cyclopropane-1-carboxylic acid;
(1R,2S)-2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)cyclopropane-1-carboxylic acid;
5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-5-oxopentanoic acid;
4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-3,3-difluoro-4-oxobutanoic acid;
(S)-4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-hydroxy-2-methyl-4-oxobutanoic acid;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(5,5,5-trifluoro-4-hydroxypentanoyl)azetidine-3-carboxamide;
4-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)tetrahydro-2H-pyran-4-carboxylic acid;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(sulfamoylglycyl)azetidine-3-carboxamide;
1-(N-acetyl-N-hydroxyglycyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)acetic acid;
2-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)sulfonyl)acetic acid;
3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propanoic acid;
3-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidin-1-yl)sulfonyl)propanoic acid;
3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)-2,2-dimethylpropanoic acid;
2-(1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)cyclopropyl)acetic acid;
4-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)butanoic acid;
(E)-3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)acrylic acid;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-((3-(hydroxyamino)-3-oxopropyl)sulfonyl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)acetic acid;

2-((4-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-4-(2-isopropylphenyl)piperidine-1-carbonyl)oxy)acetic acid;

(R)-2-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)propanoic acid;

1-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)cyclopropane-1-carboxylic acid;

3-((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)-2,2-dimethylpropanoic acid;

1-(((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)methyl)cyclopropane-1-carboxylic acid;

((3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropyl phenyl)azetidin-1-yl)sulfonyl)glycine;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(2-(difluoromethoxy)pyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(2,6-dimethoxypyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(6-ethoxy-2-methoxypyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(N-methylsulfamoyl)azetidine-3-carboxamide;

1-(N-cyclopropylsulfamoyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-(sulfamoylamino)ethyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-5-fluoropyridin-3-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;

3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-3-methylbutanoic acid;

N1-((1H-imidazol-4-yl)methyl)-N4-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-1,4-carboxamide;

3-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-2,2-dimethylpropanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxamido)-2,2-dimethylbutanoic acid;

N4-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-4-(2-isopropylphenyl)piperidine-1,4-dicarboxamide;

N4-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-N1-(2-hydroxyethyl)-4-(2-isopropylphenyl)piperidine-1,4-dicarboxamide;

6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)nicotinic acid;

6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)picolinic acid;

2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidine-5-carboxylic acid;

6-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyridazine-3-carboxylic acid;

5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrazine-2-carboxylic acid;

1-(5-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)pyrimidin-2-yl)cyclopropane-1-carboxylic acid;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(4-fluoropyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-fluoropyridin-4-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(5-fluoropyrimidin-4-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)pyridin-3-yl)-1-(5-fluoropyrimidin-4-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(5-cyanopyridin-2-yl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(5-cyanopyridin-2-yl)-N-(2-(difluoromethoxy)pyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(5-cyanopyrimidin-2-yl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

1-(5-cyanopyrimidin-2-yl)-N-(2-(difluoromethoxy)pyridin-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)oxazole-4-carboxylic acid;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(5-fluoropyrimidin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(2-methylpyrimidin-4-yl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(4-oxo-4,5-dihydrooxazol-2-yl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(4-hydroxy-oxazol-2-yl)azetidine-3-carboxamide];

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(5-hydroxy-1,2,4-oxadiazol-3-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-isopropylphenyl)-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)azetidine-3-carboxamide];

3-(2-cyclopentylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide;

3-(2-cyclohexylphenyl)-N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)azetidine-3-carboxamide;

4-(3-(2-cyclobutylphenyl)-3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

4-(3-(2-cyclopentylphenyl)-3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

4-(3-(2-cyclohexylphenyl)-3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-propylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(2-fluoro-6-isopropylphenyl)azetidine-3-carboxamide;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropyl-5-methylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-fluoro-6-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(5-fluoro-2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;

N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-propylglycine;

Methyl N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-(2-methoxyethyl)glycinate;

N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-(2-methoxyethyl)glycine;

Methyl (2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)glycinate;

(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)glycine;

N-(2-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)-N-ethylglycine;

3-(2-isopropylphenyl)-N-(6-methyl-2-propoxypyridin-3-yl)-1-sulfamoylazetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide;

4-(3-((2-(difluoromethoxy)-6-methylpyridin-3-yl)carbamoyl)-3-(3-isopropylpyridin-2-yl)azetidin-1-yl)-4-oxobutanoic acid;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-2-yl)-1-sulfamoylazetidine-3-carboxamide;

N1-cyclopropyl-N3-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-2-yl)azetidine-1,3-dicarboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(5-fluoro-2-methylpyrimidin-4-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-1-(3-fluoro-6-methylpyridin-2-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide;

N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-4-yl)azetidine-3-carboxamide;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyridin-4-yl)-1-sulfamoylazetidine-3-carboxamide;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyrazin-2-yl)azetidine-3-carboxamide;
N-(2-(difluoromethoxy)-6-methylpyridin-3-yl)-3-(3-isopropylpyrazin-2-yl)-1-sulfamoylazetidine-3-carboxamide;

N-(5-chloro-3-methoxypyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(5-bromo-3-methoxypyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(5-bromo-3-(difluoromethoxy)pyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(3-(difluoromethoxy)-5-methylpyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(3,5-dimethoxypyridin-2-yl)-3-(2-isopropylphenyl)azetidine-3-carboxamide;
N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(2-cyclopentylphenyl)azetidine-3-carboxamide;
N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(3-isopropylpyridin-2-yl)azetidine-3-carboxamide;
Methyl 4-(3-((5-chloro-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoate;
4-(3-((5-chloro-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoic acid;
4-(3-((5-bromo-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethylbutanoic acid;
Methyl 4-(3-((5-bromo-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoate;
Methyl 4-(3-((5-bromo-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoate;
4-(3-((5-chloro-3-(difluoromethoxy)pyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;
4-(3-((5-chloro-3-methoxypyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;
4-(3-((5-bromo-3-methoxypyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;
4-(3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2,2-dimethyl-4-oxobutanoic acid;
1-(2-(3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)-2-oxoethyl)cyclobutane-1-carboxylic acid;
Benzyl 3-((3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propanoate;
3-((3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidin-1-yl)sulfonyl)propanoic acid;

N-(5-chloro-3-methoxypyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;
N-(5-bromo-3-methoxypyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;
N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;
N-(5-bromo-3-(difluoromethoxy)pyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;
N-(3,5-dimethoxypyridin-2-yl)-3-(2-isopropylphenyl)-1-sulfamoylazetidine-3-carboxamide;
N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(2-cyclopentylphenyl)-1-sulfamoylazetidine-3-carboxamide;
N-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-3-(3-isopropylpyridin-2-yl)-1-sulfamoylazetidine-3-carboxamide;
N^3-(5-chloro-3-(difluoromethoxy)pyridin-2-yl)-N^1-cyclopropyl-3-(2-isopropylphenyl)azetidine-1,3-dicarboxamide;
N^3-(5-bromo-3-(difluoromethoxy)pyridin-2-yl)-N^1-cyclopropyl-3-(2-isopropylphenyl)azetidine-1,3-dicarboxamide;
2-methoxy-2-oxoethyl 3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carboxylate;
2-((3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)acetic acid;
1-((3-((3-(difluoromethoxy)-5-methylpyridin-2-yl)carbamoyl)-3-(2-isopropylphenyl)azetidine-1-carbonyl)oxy)cyclopropane-1-carboxylic acid; or
N-(3-(difluoromethoxy)-5-methylpyridin-2-yl)-3-(2-isopropylphenyl)-1-(4-oxo-4,5-dihydrooxazol-2-yl)azetidine-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

14. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use as a medicament.

15. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in the prevention or treatment of fibrosis, dermatological disorders, pain, malignant, benign proliferative diseases, respiratory diseases, nervous system disorders, cardiovascular diseases, inflammatory disorders, obesity, or insulin resistance.

16. Use of a compound according to any one of claims 1 to 12, or of a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the prevention or treatment of fibrosis, dermatological disorders, pain, malignant, benign proliferative diseases, respiratory diseases, nervous system disorders, cardiovascular diseases, inflammatory disorders, obesity, or insulin resistance.

17. A method for the prophylaxis or treatment of fibrosis, dermatological disorders, pain, malignant, benign proliferative diseases, respiratory diseases, nervous system disorders, cardiovascular diseases, inflammatory disorders, obesity, or insulin resistance; comprising administering to a subject in need thereof an effective amount of a compound as defined in any one of claims 1 to 12, or of a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/064690

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D405/14 C07D413/14 C07D401/12 A61P11/00
A61P9/00 A61P29/00 A61K31/4439 A61K31/444
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.
A	EP 2 481 725 A1 (ASTELLAS PHARMA INC [JP]) 1 August 2012 (2012-08-01) claims 1-29; examples 208-211, 234-237, 298-303; table 3 -----	1-17
A	WO 03/088908 A2 (SQUIBB BRISTOL MYERS CO [US]; LLOYD JOHN [US] ET AL.) 30 October 2003 (2003-10-30) cited in the application example 269 -----	1-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"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
15 July 2019	06/08/2019

Name and mailing address of the ISA/	Authorized officer
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1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/064690

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