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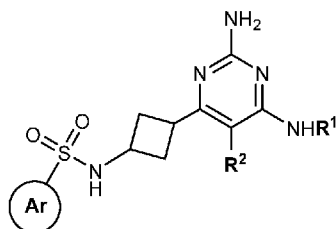
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(54) Title: ARYL- AND HETEROARYL-SULFONAMIDE DERIVATIVES AS CCR8 MODULATORS

(57) Abstract: The present invention relates to compounds of Formula (I), their synthesis and use as CCR8 receptor modulators in medicine.



(I)

ARYL- AND HETEROARYL-SULFONAMIDE DERIVATIVES AS CCR8 MODULATORS

The present invention relates to novel compounds represented by Formula (I), or pharmaceutically acceptable salts thereof, and their use as active ingredients in medicine. The invention further concerns a process for the preparation of said compounds, pharmaceutical compositions containing one or more of said compounds, and their use as C-C

5 chemokine receptor 8 (CCR8) modulators, either alone or in combination with other active compounds or therapies, in the prevention or treatment of diseases or disorders such as cancer, fibrotic diseases, atopic diseases, and neuropathic pain. Furthermore, the invention relates to certain isotopically labelled compounds, or pharmaceutically acceptable salts thereof, and their use in radiopharmaceutical therapy (RPT) or medical imaging such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT).

10 Chemokine receptors, such as CCR8, are a group of G-protein coupled receptors (GPCRs) that recognize and bind to peptide chemokine ligands with high affinity. The predominant functions of chemokine receptors and their ligands are to induce leukocyte trafficking to-and-from lymphoid organs and tissues in the steady state, as well as in the context of an infection or inflammation. Additionally, chemokine signaling events can induce the activation of integrin molecules on the surface of immune cells, allowing for adhesion to activated endothelium, facilitating migration from blood into

15 inflamed tissue (Montresor A, *Frontiers in Imm.*, 2012; Meissner A, *Blood*, 2003).

CCR8 (alias CKRL1, CMKBR8, CMKBRL2, CC-CKR-8, CCR-8, CDw198, CKRL1, CMKBR8, CMKBRL2, CY6, GPRCY6, or TER1) has four known chemokine ligands: CCL1 (alias I-309 or SCYA1), CCL8 (alias MCP2, SCYA10, or SCYA8), CCL16 (alias ILINCK, NCC4, or SCYA16), and CCL18 (alias AMAC1, DCCK1, MIP4, PARC, or SCYA18).

CCL1 was first identified as a cytokine secreted by activated human T lymphocytes. Human CCL1 is the best-

20 established natural ligand for CCR8, but other chemokine ligands such as CCL18 were reported to interact with hCCR8 as well. CCR8 is the only known receptor for CCL1, whereas the other CCR8 ligands bind several chemokine receptors, as well as decoy receptors. CCR8 positive cells respond to CCL1 stimulation with increased intracellular calcium, chemotaxis and enhanced survival. CCL1 is considered a Th2-related cytokine due to the expression of the CCR8 receptor on Th2 cells, but not on Th1 cells, suggesting that CCL1 plays an important role in allergies and asthma. The

25 CCL1-CCR8 axis also plays a role in the homing of lymphocytes to the healthy skin and contributes to the immune protection of the skin (Schaerli P et al.; *J. Exp. Med.* 2004, 199, 1265–1275 and Ebert L et al.; *J. Immunol.* 2006, 176, 4331–4336).

Tumors are comprised of abnormally proliferating malignant cancer cells but also of a functionally supportive microenvironment. This tumor microenvironment is comprised of a complex array of cells, extracellular matrix

30 components, and signaling molecules, and is established by the altered communication between stromal and tumor cells. As tumors expand in size, they elicit the production of diverse factors that can help the tumor grow such as angiogenic factors (promoting ingrowth of blood vessels) or that can help evade the attack of the host immune response. CCL1 is such an immuno-modulatory factor produced in tumors.

High expression of CCL1 in a cancer cell occurs in leukemia caused by viruses such as human T cell leukemia virus

35 type 1 (HTLV-1). Properties similar to the human CCL1 are shown by viral macrophage inflammatory protein-I (vMIP-

l), a viral protein homologous to CCL1 expressed in tumor cells transformed by the herpes virus. Another example is Kaposi sarcoma-related human herpes virus-8 (Haque, NS et al; Blood. 2001, 97, 39-45).

In hepatocellular carcinomas, the expression of CCL1 is elevated in 12 of 34 tumor stroma and peritumoral tissues. The expression of CCL1 has also been demonstrated in breast cancer stem cells, bladder cancer tumors, and renal cell carcinomas. (Korbecki, J et al. Int. J. Mol. Sci. 2020, 21, 7619).

In solid tumors, CCL1 is produced by Cancer Associated Fibroblasts, Tumor Associated Macrophages, CCR8-CD11b+ myeloid cells, and Regulatory T-cells. The secretion of CCL1 by myeloid cells is involved in Treg cell infiltration. An increased expression of CCR8 is observed in Treg cells and NKT cells, particularly in cancer patients, and a low expression is observed in CD8+ T cells or Th1 cells. Interactions between CCL1 and CCR8 enhance the expression of FoxP3 and activated CCR8+ Treg cells strongly suppress antitumor immunity by promoting ATP-adenosine metabolism by CD39 and secretion of IL-10 and granzyme B. (Ohue,Y and Nishikawa, H, Cancer Sci, 2019, 110(7):2080-2089).

In cancer, CCL1 is involved in the recruitment of CCR8+ CD11b+ myeloid cells (Eruslanov, E et al, Clin Cancer Res. 2013, 19, 1670-1680) as well as Regulatory T cells (Kuehnemuth, B et al, BMC Cancer 2018, 18, 1278) to the tumor site. CCL1 can also participate in the conversion of CD4+ T cells into Treg (Hoelzinger, DB et al, J Immunol. 2010, 184, 6833-6842), in a process dependent on transforming growth factor- β , which increases the expression of CCL1 in CD4+ T cells. This is followed by an autocrine conversion of this cell to Treg, which also involves CCL1. In addition, CCL1 supports the immunosuppressive function of Treg in the tumor niche (Hoelzinger, DB et al, J Immunol. 2010, 184, 6833-6842), which is crucial for the interaction of cancer stem cells and CAF with the Tregs (Xu, Y et al, Stem cells 2017, 35, 2351-2365). CCL1 increases the expression of interleukin 6 in MDSC, which acts as a proinflammatory in the tumor microenvironment (Eruslanov, E et al, Clin Cancer Res. 2013, 19, 1670-1680). It was also reported that CCL1 causes angiogenesis on vascular endothelial cells via CCR8 (Haque, NS, et al, Blood, 2001, 97, 39-45).

In cancer, CCL1 has an antiapoptotic activity and induces chemoresistance to anticancer drugs due to the activation of the ERK MAPK cascade via CCR8 (Louahed, J et al, Eur J immunol. 2003, 33,494-501). CCL1 also stimulates proliferation (Cao, Q et al, Mol Med Rep. 2016, 13, 27-34) and causes the migration of bladder cancer cells (Yeh, CR, et al, Am J Cancer Res. 2018, 50, 894-907). At the same time, due to the expression of CCL1 in lymph nodes, this chemokine participates in metastasis to these peripheral lymphoid organs through the CCR8 receptor on cancer cells that have entered lymphatic vessels. This process is important in metastasis to lymph nodes in malignant melanoma, which often leads to increased CCR8 expression in the cancer cells of this tumor (Das, S et al, J Exp Med. 2013, 210, 1509-1528).

CCL18 is produced by dendritic cells, especially in germinal centers of regional lymph nodes. This chemokine then causes the chemoattraction of naïve T cells. This leads to the initiation of an immunological response. CCL18 also acts as an anti-inflammatory chemokine, a marker for the macrophage M2 subset (Schraufstatter, IU et al, Immunology, 2012, 135, 287-298). In a tumor, CCL18 is mainly produced by Tumor Associated Macrophages (Pettersen, JS et al; J. Investig. Dermatol. 2011, 131, 1322-1330) and causes cancer cell migration as well as Epithelial to Mesenchymal Transition by activating its receptors PITPNM3 and CCR8 (Hong, R et al; Asian Pac. J. Cancer Prev, 2012, 13, 1877-1880; Islam, SA et al; J. Exp. Med. 2013, 210, 1889-1898). CCL18 recruits immature dendritic cells to the tumor niche

and participates in the differentiation of immature dendritic cells into tumor-associated dendritic cells (TADC) (Azzaoui, I et al; Blood, 2011, 118, 3549-3558). CCL18 binds to glycosaminoglycans on extracellular vesicles, which allows them to be retained on cells with an expression of CCR8. CCL18 also increases the proliferation of cancer cells, but this depends on the tumor type. For example, CCL18 decreases the proliferation of acute lymphocytic leukemia B cells and cutaneous T-cell lymphoma (CTCL) (Catusse, J et al; J.Cell.Physiol. 2010, 225, 792-800; Gunther, C et al; Am J. Pathol. 2011, 179, 1434-1442). In addition, CCL18 increases the proliferation of glioma and oral squamous cell carcinoma cells. An increased expression of CCL18 in lesional skin and serum of patients with CTCL as well as in patients with diffuse large B cell lymphoma is associated with a worse prognosis.

CCR8 is a chemokine receptor preferentially, but not exclusively, expressed by FOXP3+ Tregs. CCR8+ Tregs were recently identified as master drivers of the immune regulation. The relative number of CCR8+ Tregs which is very low in the periphery increases along with the development of experimental autoimmune encephalomyelitis (EAE), a T cell-mediated autoimmune disease of the central nervous system. It was also observed that within the central nervous system, CCR8+ Tregs are potentiated by CCL1, possibly in an autocrine manner, which makes them "driver" regulatory cells that restrain the progression of the disease (Barsheshet, Y. et al; Proc. Natl. Acad. Sci. 2017, 114, 6086-6091).

Advances in staining reagents enabled to report CCR8 expression in human blood Th2 as well as Tregs (Iellem, A et al.; J. Exp. Med. 2001, 194, 847-853, Sebastiani, S. et al.; J. Immunol. 2001, 166, 996-1002). Along with this observation, in vivo studies revealed a clear role for CCR8 in type-2 inflammatory diseases including atopic dermatitis (Islam, S.A. et al; Nat. Immunol. 2011, 12, 167-177, Gombert, M. et al; J. Immunol. 2005, 174, 5082-5091), allergic enteritis (Blanco-Perez, F. et al; Sci. Rep. 2019, 9, 9608), and allergic asthma (Nguyen KD. et al.; J Allergy Clin Immunol. 2009;123(4):933-9.e10.) such as fungal-allergic asthma (Buckland KF. et al, J Allergy Clin Immunol. 2007 Apr;119(4):997-1004).

Owing to their chemotactic effects on inflammatory fibroblasts and various immune cells, such as monocytes and T cells, the interactions of CCR8 with its ligands CCL1, CCL8, and CCL18 have been implicated in exacerbating human fibrotic diseases and pathology in animal models of fibrotic disease (Liu, S. et al., Biomolecules 2023, 13, 333). Indeed, in murine models CCL1 interaction with CCR8 exacerbates bleomycin-driven lung fibrosis (Shan-shan Liu. et al., Immunity, 54, 9, 2021, 2042-2056.e8; and Suosi Liu., International Immunopharmacology, 120, 2023, 110343), carbon tetrachloride induced liver fibrosis (Heymann F. et al., Hepatology, 2012 Mar;55(3):898-909), salivary gland fibrosis modeling human immunoglobulin G4-related disease (Honda, F. et al., Arthritis Res Ther 23, 214, 2021), and skin and pulmonary fibrosis modeling human chronic graft-versus-host disease (Stem Cell Res Ther., 2020 Jun 26;11(1):254. doi: 10.1186/s13287-020-01768-7). In patients, CCL18 and CCR8 are elevated in idiopathic pulmonary fibrosis (Unterman A. et al., medRxiv, 2023, doi:10.1101/2023.04.29.23289296) and high serum CCL18 predicts poor patient outcome (Prasse A. et al., Am J Respir Crit Care Med, 2009 Apr 15;179(8):717-23). Furthermore, CCL1-CCR8 interaction is associated with more severe human IgG4-related sclerosing cholangitis (Yoh Zen et al., Journal of Hepatology, 59, 5, 2013, 1059-1064). An association of CCR8 being a part of a gene locus related to systemic sclerosis in a chicken model of scleroderma/systemic sclerosis has been disclosed by Weronica Ek. et. al., Developmental & Comparative Immunology, 38, 2, 2012, 352-359. Moreover, CCR8 mediates immune cell infiltration and resultant fibrosis in a murine model of allogeneic kidney transplant (Dangi A, et al., J Am Soc Nephrol. 2022 Oct;33(10):1876-

1890). In animal models of postsurgical and post-inflammatory formation of peritoneal adhesions, CCR8 was determined to promote adhesion formation in part via an autocrine CCL1-CCR8 signaling loop in peritoneal macrophages that regulated their recruitment and aggregation (Akiyoshi Hoshino et al., *J Immunol.*, 2007 Apr 15;178(8):5296-304). CCR8 signaling in myeloid cells may sensitize individuals to bacterial infection. In a model of polymicrobial septic peritonitis, Matsukawa and colleagues observed that CCR8 skews macrophage polarization and limits clearance of microbes following cecal ligation and puncture in mice, ultimately increasing risk of death (Matsukawa, A., et al., 2006, *FASEB J*, 20: 302-304). Moreover, Asai and colleagues demonstrated that inhibition of CCL1 enhances resistance of mice to *Staphylococcus aureus* infection in a model of burn-related immune dysregulation (Akira Asai et al., *Journal of Leukocyte Biology*, 92, 4, 2012, 859–867, <https://doi.org/10.1096/fj.04-1728fje>). CCL1-CCR8 signaling may play a deleterious role in chronic obstructive pulmonary disease (COPD) and allergic type exacerbations: CCR8 expression is pronounced in lung myeloid cells of patients with Global Initiative for Obstructive Lung Disease (GOLD) stage IV COPD (Martina Kvist Reimer et al. *Clinical and Vaccine Immunology*, 2011, 18, 12, doi: 10.1128/CVI.05275-11), and COPD exacerbation risk is associated with certain single nucleotide polymorphism profiles in the CCL1 gene (Takabatake N. et al., *Am J Respir Crit Care Med*. 2006 Oct 15;174(8):875-85, doi:10.1164/rccm.200603-443OC).

CCL1/CCR8 neuronal signaling plays an important role in the development of neuropathic pain (Zychowska, M. et al.; *International Immunopharmacology*, 52, 2017, 261-271; and Akimoto, N., et al.; *Cell Death Dis* 4, e679 (2013)). The interaction of CCL1 and CCR8 has been implicated in neuropathic pain exacerbation (Pawlik K., *Molecules* 2023, 28(15), 5766). Specifically, animal and ex vivo models suggest CCL1 enhances allodynia and neuropathy via CCR8 signaling in neurons, microglia, and astrocytes in the spinal cord (Akimoto N. et al, *Biochem Biophys Res Commun*, 2013, Jul 5;436(3):455-61; Zychowska M. et al., *Int Immunopharmacol.* 2017 Nov;52:261-271; Noda M. et al., *Neurochem Int.*, 2018 Oct;119:184-189; Wang C. et al., *Neurosci Res.* 2020 May;154:20-26; and Ruff M. et al., *Life Sci.* 2022 Oct 1; 306: 120788). Moreover, neutralization of CCL1 and CCR8 signaling ameliorates pain in animal models of diabetic neuropathy and potentiates the analgesic effects of opioids, representing a potential human therapeutic application (Zychowska M. et al., *Int Immunopharmacol.* 2017 Nov;52:261-271; and Ruff M. et al., *Life Sci.* 2022 Oct 1; 306: 120788).

Healthy human skin was then reported as the primary residence site of CCR8+ cells with 50% of all skin $\alpha\beta$ T cells expressing CCR8 (Ebert, L.M. et al; *J. Immunol.* 2006, 176, 4331–4336, McCully, M.L et al.; *Blood* 2012, 120, 4591–4598). Similarly, CCR8 was also identified in CD16-expressing NK cells that reside mainly in human skin but not in peripheral blood (Ebert, L.M. et al; *J. Immunol.* 2006, 176, 4331–4336, Schaerli, P. et al; *J. Exp. Med.* 2004, 199, 1265–1275).

Recently, CCR8 has been identified as a potential specific marker for tumor-infiltrating Tregs. CCR8 expression is selectively upregulated in these Tregs in multiple cancers, including lung, colorectal, breast (Plitas, G et al.; *Immunity* 2016, 45, 1122–1134, De Simone, M. et al.; *Immunity* 2016, 45, 1135–1147, Wang, L. et al.; *Nat. Immunol.* 2019, 20, 1220–1230). These CCR8+ Tregs represent a highly suppressive subpopulation of Tregs and the high number of CCR8+ Tregs in the tumor microenvironment correlates with poor prognosis in various breast cancer types (Plitas, G et al.; *Immunity* 2016, 45, 1122–1134, De Simone, M. et al.; *Immunity* 2016, 45, 1135–1147, Zheng, C. et al.; *Cell*

2017, 169, 1342–1356, Magnuson, A.M. et al.; Proc. Natl. Acad. Sci. USA 2018, 115, E10672–E10681). Because CCR8 is rarely expressed on Tregs and T effector cells in peripheral blood or healthy tissues, targeting CCR8+ tumor Tregs is expected to cause minimal toxicity risks making CCR8 a promising therapeutic target to inhibit the immunosuppressive functions of tumor-resident Tregs and increase the anti-tumor immune response.

- 5 CCR8 is a seven-transmembrane G-protein-coupled chemokine receptor (GPCR) expressed primarily on intratumoral FOXP3hi Tregs (Plitas, G et al.; Immunity 2016, 45, 1122–1134, De Simone, M. et al.; Immunity 2016, 45, 1135–1147, Wang, L. et al.; Nat. Immunol. 2019, 20, 1220–1230). In addition to affecting the migration of Tregs to the Tumor microenvironment, the CCL1-CCR8 axis also potentiates the immunosuppressive capacity of Tregs through upregulation of CCR8, FOXP3, IL-10 and other suppressive factors (Vila-Caballer M et al.; J Mol Cell Cardiol.
- 10 2019;132:154–1).

Various groups have recently reported the generation of humanized anti-CCR8 antibodies for use in depleting tumor associated Tregs and treating cancer. Preclinical data indicates that treatment with mCCR8 depleting antibodies provides therapeutic benefit alone or in combination with immune checkpoint inhibitors such as anti-PD1 treatment in several mouse models including the colorectal cancer models CT26 and MC38, the melanoma model B16-F10, the

15 bladder cancer model MB49, the breast cancer model 4T1 and the lung cancer model LLC-OVA (Villarreal, D.O et al.; Cancer Res. 2018, 78, 5340–5348, Bhatt, D. et al.; J. Exp. Med. 2021, 218, e20201329, Campbell, J.R. et al.; Cancer Res. 2021, 81, 2983–2994, Van Damme, H. et al.; J. Immunother. Cancer 2021, 9, e001749). In addition, neutralization of the CCR8 natural ligand CCL1 inhibits the Treg suppressive functions and enhances anti-tumor immunity (Hoelzinger D.B et al.; J. Immunol. 2010, 184:6833–6842).

- 20 One of the major reasons for which the success of immune checkpoint inhibitors can be limited is that therapy is given on cancer types that are designated as “cold tumors” either lacking infiltration of effector CD8+ T cells, or including massive accumulation of Tregs that suppress their activities. Targeting CCR8, mostly with depleting antibodies, are currently under preclinical development by several lead companies.

Small molecule CCR8 antagonists, such as the compounds of the present invention, may be useful to inhibit the

25 recruitment of CCR8+ Tregs to the tumor site and/or to decrease the suppressive functions of intratumoral CCR8+ Tregs resulting in a favorable environment for a positive response to immune-check point inhibitors or others current therapies.

The compounds of the present invention may be useful, alone, or in combination with one or more therapeutic agents or therapies, for the prevention / prophylaxis or treatment of cancer, especially cancer types infiltrated with intratumoral

30 Tregs expressing CCR8. Such cancer types are *inter alia* oral squamous cell carcinoma (Fraga M. et al.; Front. Immunol. 2021, 12:643298), head and neck squamous cell carcinoma (Sun et al; Transl Cancer Res 2020;9(10):5882-5892, Meng et al; Front. Oncol. 2021, 11:618187), liver cancer (Zheng, C. et al.; Cell 2017, 169, 1342-1356.e1316, Wiedemann G.M. et al; Pathology, 2019 51(6), 586–659), hepatocellular carcinoma (Nieto P. et al., Genome Res. 2021,10:1913-1926), extrahepatic cholangiosarcoma (Xu L. et al, J Transl Med. 2022 20(1):210), gastrointestinal

35 stromal tumors (Li HL. et al; World J Gastroenterol. 2020; 26(31):4656-4668. Fujimoto et al; J Immunol. 2018 ; 200(9):3291-3303), colorectal cancer (De Simone, M. et al.; Immunity 2016, 45, 1135–1147, Nieto P. et al., Genome Res. 2021,10:1913-1926), lung cancer (Liu F. et al; J Inflamm Res. 2021; 14:267-285, Yu L. et al; Int

Immunopharmacol. 2021 107734, Pastor M.D. et al; J Thorac Oncol. 2016 12:2183-2192, Campbell, J.R. et al.; Cancer Res. 2021, 81, 2983–2994), non- small cell lung cancer (De Simone, M. et al.; Immunity 2016, 45, 1135–1147, Van Damme, H. et al.; J. Immunother. Cancer 2021, 9, e001749, Haruna M. et al; Sci Rep. 2022, 12(1):5377, Nieto P. et al., Genome Res. 2021,10:1913-1926), bladder cancer, kidney cancer (Eruslanov, E et al.; Clin. Cancer Res. 2013, 19, 1670–1680, Wang, T. et al.;Cancer Immunol. Immunother. 2020, 69, 1855–1867, Kidani Y. et al; Proc Natl Acad Sci U S A. 2022, 119(7):e2114282119, Campbell, J.R. et al.; Cancer Res. 2021, 81, 2983–2994), melanoma (Das S. et al., J Exp Med. 2013, 210(8):1509-1528; Nieto P. et al., Genome Res. 2021,10:1913-1926; Sade Feldman M. et al, Cell. 2018, 175(4): 998–1013), breast cancer (Plitas, G et al.; Immunity 2016, 45, 1122–1134, Wang, L. et al.; Nat. Immunol. 2019, 20, 1220–1230, Kuehnemuth, B et al, BMC Cancer 2018, 18, 1278, Ding S. et al; Int Immunopharmacol. 2021, 100:108122), lymphoma (Xing X. et al, Appl Immunohistochem Mol Morphol. 2015 (8):580-589) cutaneous T cell lymphoma (Giustinani J. et al Blood Adv. 2022, 6(11):3507-3512), endometrial tumors (Campbell, J.R. et al.; Cancer Res. 2021, 81, 2983–2994, Nieto P. et al., Genome Res. 2021,10:1913-1926), Kaposi sarcoma (Haque, N.S. et al; Blood 2001, 97, 39–45), and basal cell carcinoma (Nieto P. et al., Genome Res. 2021,10:1913-1926).

Specifically, the potential role of CCR8 in oral squamous cell carcinoma (OSCC) is known from the literature. Fraga et al. reported that 40% of the tumor infiltrated Tregs were CCR8 positive in OSCC and that CCL1 as well as CCL18 were involved in their recruitment. The OSCC secretome contributes to the upregulation of CCR8 expression on Tregs and Teff (Fraga M. et al.; Front. Immunol. 2021, 12:643298).

Specifically, the role of CCR8 in head and neck squamous cell carcinoma (HNSCC) has been suggested in the literature using two independent data set analysis. A correlation has been established between the CCR8 high expression and a worse prognosis for patients with HNSCC (Sun et al; Transl Cancer Res 2020;9(10):5882-5892) while another study reported a significant higher level of CCR8 in tumor tissues than in normal tissues (Meng et al; Front. Oncol. 2021, 11:618187).

A specific expression of CCR8 in tumor associated Tregs in liver cancer has been described in the literature. A landscape of infiltrating T cells in hepatocellular carcinoma revealed a particular gene signature among which CCR8 was reported to be specifically expressed in tumor Tregs but not in peripheral Tregs or in others T cells than Tregs Zheng, C. et al.; Cell 2017, 169, 1342-1356.e1316). In addition, CCL1 expression was also reported in peripheral and extratumoral stromal compartment in hepatocellular carcinomas suggesting an involvement in the CCR8+ Tregs recruitment (Wiedemann G.M. et al; Pathology, 2019 51(6), 586–659).

Furthermore, a specific expression of CCR8 in tumor associated Tregs in extrahepatic cholangiosarcoma was reported. Single-cell landscape of immunocytes in patients with extrahepatic cholangiosarcoma revealed that CCR8 was only expressed in tumor-infiltrating Tregs but not in peripheral Tregs or conventional T cells (Xu L. et al, J Transl Med. 2022 20(1):210).

Specifically, a role of CCR8 in gastrointestinal stromal tumors (GIST) has been reported in the literature. A correlation between CCR8 expression and a worse prognosis for patients with GIST was described (Li HL. et al; World J Gastroenterol. 2020; 26(31):4656-4668). Furthermore, a gene signature of colorectal adenocarcinoma-associated

Tregs identified a specific CCR8 overexpression compared to normal intestinal samples (Fujimoto et al; J Immunol. 2018 ; 200(9):3291-3303).

De Simone et al. reported a transcriptional landscape of tumor-infiltrating Tregs from human colorectal tumor tissues and identified CCR8 as one of the top 5 genes overexpressed in tumor associated Tregs compared to peripheral blood Tregs. The specific expression of CCR8 in tumor-infiltrating Tregs was then confirmed at the protein level by FACS analysis (De Simone, M. et al.; Immunity 2016, 45, 1135–1147).

In addition, a role of CCR8 in lung cancer was reported in several studies. De Simone et al. also did a similar transcriptional landscape of tumor-infiltrating Tregs from human non-small cell lung cancer (NSCLC) and CCR8 was highly expressed compared to peripheral blood Tregs. FACS analysis also confirmed the specific expression of CCR8 in tumor Tregs (De Simone, M. et al.; Immunity 2016, 45, 1135–1147). In lung adenocarcinoma, a high expression of CCR8 mRNA was found in various data sets (Liu F. et al; J Inflamm Res. 2021; 14:267-285) and CCL1 was particularly overexpressed in bronchoalveolar lavage fluid from patients with adenocarcinoma (Yu L. et al; Int Immunopharmacol. 2021 107734) suggesting CCL1 as an interesting biomarker in this indication (Pastor M.D.et al; J Thorac Oncol. 2016 12:2183-2192). Interestingly, it was also reported in NSCLC that intratumoral CCR8+ Tregs are more immunosuppressive than CCR8- Tregs in mouse and human tumor tissues. No major CCR8 positivity was found on peripheral Tregs (Van Damme, H. et al.; J. Immunother. Cancer 2021, 9, e001749,). Another study was also able to show the impact of CCR8+ Tregs on the cytotoxic CD8+ T cells in human lung cancer. The Cancer Genome Atlas analysis revealed that CD8 T cell activities were suppressed in highly CCR8 expressing tumors. The depletion of CCR8+ cells in an ex vivo assay with lung tumor infiltrating cells, was able to enhance CD8+ T cell function. Furthermore, CCR8+ Tregs but not CCR8- Tregs markedly prevent CD8+ T cells cytotoxic activity. The therapeutic effect of targeting CCR8 was ultimately demonstrated in a murine model of lung cancer (LLC mouse model) (Haruna M. et al; Sci Rep. 2022, 12(1):5377).

Specifically, a role of CCR8 has been described in bladder and kidney cancer. Myeloid cells (CD33+ CD11b+) are CCR8+ in those indications and contribute to a strong immunosuppressive environment. An elevated level of CCL1 was found in primary human urothelial and renal cancer tissues (Eruslanov, E et al.; Clin. Cancer Res. 2013, 19, 1670–1680). Furthermore, it was also reported that CCR8 blockade could destabilize intratumoral Tregs into a fragile phenotype accompanied with reactivation of antitumor immunity and augment of anti-PD-1 therapeutic benefits in muscle invasive bladder cancer (MIBC) patients. It was also found that CCR8 expression by intratumoral Tregs maintains their stability and potentiated their suppressive function (Wang, T. et al.; Cancer Immunol. Immunother. 2020, 69, 1855–1867). Another study has shown that tumor infiltrating Tregs from human renal cancer tissue samples were 30 to 40% CCR8+ confirming the high specificity of CCR8 expression in human cancers (Kidani Y. et al; Proc Natl Acad Sci U S A. 2022, 119(7):e2114282119).

Specifically, the role of CCR8 was also described as strongly expressed in human malignant melanoma. CCL1 was detected in lymph node lymphatic sinuses but not in the peripheral lymphatics. This study suggests that the CCL1/CCR8 axis is involved in the metastasis invasion process in melanoma patients (Das S. et al., J Exp Med. 2013, 210(8):1509-1528). Single cell RNA sequencing data analysis found in Nieto et al. or Sade Feldman et al. identified a

specific expression of CCR8 in tumor infiltrated Tregs ((Nieto P. et al., Genome Res. 2021,10:1913-1926; Sade Feldman M. et al, Cell. 2018, 175(4): 998–1013).

Specifically, there is a body of evidence that CCR8 plays a role in breast cancer development. Plitas et al. identified that tumor Tregs were CCR8+ whereas peripheral blood Tregs were not. They also reported a correlation between a high CCR8+ FoxP3+ Tregs content with a bad prognosis for the patients (Plitas, G et al.; Immunity 2016, 45, 1122–1134). Furthermore, another study has shown that 50% of intratumoral Tregs are CCR8+ (Wang, L. et al.; Nat. Immunol. 2019, 20, 1220–1230). CCR8+ Tregs have been found to migrate towards CCL1 and to be immunosuppressive (Kuehnemuth, B et al, BMC Cancer 2018, 18, 1278, Ding S. et al; Int Immunopharmacol. 2021, 100:108122).

Furthermore, a role of CCR8 has been proposed in lymphoma. Overexpression of CCR8 has been reported in systemic ALK negative anaplastic large cell lymphomas (ALCL). Quantitative real-time PCR in frozen tissue and RNA in situ hybridization (ISH) in paraffin tissue showed higher CCR8 expression in ALCLs with *DUSP22* rearrangements than in non-rearranged cases (Xing X. et al, Appl Immunohistochem Mol Morphol. 2015 (8):580-589).

Furthermore, CCR8 was also shown to play a role in T cell lymphoma and specifically cutaneous T cell lymphoma (CTCL). The expression of CCR8 in lesional skin of CTCL patients is associated with high risks of disease progression. CCR8 is expressed by peripheral blood Sezary cells and is reported expressed at cell surface of other T cell lymphoma (Giustinani J. et al Blood Adv. 2022, 6(11):3507-3512).

Specifically, the role of CCR8 was reported in Kaposi sarcoma. Immunohistochemical studies identified CCR8 and CCL-1 on the endothelium of human atherosclerotic plaques and in endothelial-derived spindle cells of Kaposi sarcoma. In addition, the viral monocyte inflammatory protein-1 (vMIP-1), a human homologue of CCL1 is induced by the Kaposi sarcoma-related human herpesvirus-8 (Haque, N.S. et al; Blood 2001, 97, 39–45).

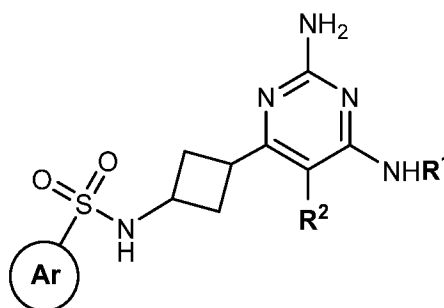
Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are common imaging techniques in nuclear medicine. The techniques use a radiopharmaceutical — a radioactive isotope attached to a ligand/drug, which is injected into the human body as a tracer. When the radiopharmaceutical undergoes beta plus decay, a positron is emitted, and when the positron interacts with an ordinary electron in the human body, the two particles annihilate and gamma rays are emitted, which are then detected and form a three-dimensional image. Radiopharmaceuticals are widely used e.g. in cardiology, neurology, and oncology. Examples of radioactive tracers used in oncology imaging include glucose uptake tracer [¹⁸F]fluorodeoxyglucose, tumor specific tracer [¹⁸F]fluorothymidine, and [¹⁸F]fluciclovine - a PET diagnostic agent in men with suspected prostate cancer recurrence.

Radiopharmaceuticals can also be used as therapeutic agents in radiopharmaceutical therapy (RPT). A category of RPT involves the use of tumor-targeting agents that concentrate in tumors through natural physiological mechanisms occurring predominantly in neoplastic cells. A widely implemented example of this category of RPT is the radioiodine therapy of thyroid cancer, where radioactive iodine is injected in the body and it is absorbed and concentrated in the thyroid gland. The radiation can then destroy the gland and any other thyroid cells including cancer thyroid cells that take up iodine, with little effect on the rest of the body. In the context of the present invention, the compounds of Formula (I) comprising one or more radioactive isotopes of iodine may be used to associate with certain cells in the human/animal body and thereby destroy cancer cells by targeted delivery of radioactive iodine.

Certain small molecules targeting CCR8 have been disclosed in the art. For example, WO2004032856, WO2003037271, WO2005040167, WO2006107252, WO2006107253, WO2006107254, WO2008099165, and WO2007030061 relate to certain heterocyclic derivatives; WO2013131010 concerns a method of administration of diverse CCR8 antagonists on the surface of tumor cells; certain biphenyl ether derivatives are disclosed by Ghosh S et al. J. Med. Chem. 2006, 49, 9, 2669-2672; Jenkins TJ et al. J. Med. Chem. 2007, 50, 3, 566-584 teaches naphthalene-sulfonamide derivatives; Marro ML et al. Biochem. Biophys. Res. Commun. 2006, 349, 270-276 discloses RNA aptamers that block CCL1 chemokine function; Jin J et al. Bioorg. Med. Chem. Lett. 2007, 17, 6, 1722-1725 relates to certain aryl-oxazolidinones; Shamovsky I et al. J. Med. Chem. 2009, 52, 23, 7706-7723 discusses the metabolic stability and selectivity of a series of CCR8 related compounds; Karlsson AKC et al. Biochem. Biophys. Res. Commun. 2011, 407, 4, 764-771 and Connolly S et al. Biochemical Pharmacology 2012, 83, 778-787 disclose derivatives comprising a diazaspirodecane scaffold; Yong Wu et al. J. Med. Chem. 2023, 66, 7, 4548-4564 and WO2022000443 disclose IPG7236, a small molecule CCR8 antagonists in clinical stage of development (NCT05142592 and NCT05288543), and Petersen TP et al. Chem. Eur. J. 2013, 19, 9343 describes a multistep continuous-flow synthesis of certain biphenyl ethers. Furthermore, WO2004058736, WO2004058709, WO2004073619, and WO2004074438 disclose certain aryl- and heteroaryl-sulfonamides. The database CAS REGISTRYSM contains the structural formulas of certain aryl- and heteroaryl-sulfonamides (CAS RN 2068756-64-7, 2068741-89-7, 2068738-85-0, 2068733-03-7, 2068727-35-3, 2068732-71-6, 2068712-87-6, 2068699-30-7, 1783256-82-5, 1783305-08-7, 1783155-99-6, 1783110-79-1, 1783211-08-4, 1783040-48-1, 1783125-47-2, and 1783136-48-0), however, neither a synthesis nor a medical use thereof is disclosed.

The present invention provides novel aryl- and heteroaryl-sulfonamides of Formula (I) which are modulators, especially antagonists of the CCR8 receptor.

1) One aspect of the present invention relates to compounds of Formula (I)



Formula (I),

wherein

Ar represents

- phenyl;
- 5-membered heteroaryl containing from one to three ring heteroatoms independently selected from nitrogen, sulfur, and oxygen (notably such 5-membered heteroaryl is selected from thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, and triazolyl; especially selected from thiophen-2-yl, thiophen-3-

yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, [1,3,4]thiadiazol-2-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, isothiazol-5-yl, isoxazol-4-yl, oxazol-5-yl, 1H-[1,2,3]triazol-4-yl, and 2H-[1,2,3]triazol-4-yl; in particular selected from thiophen-2-yl and thiophen-3-yl); or

- 6-membered heteroaryl containing from one to three ring nitrogen atoms (notably such 6-membered heteroaryl is selected from pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; especially selected from pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, and pyridazin-3-yl; in particular selected from pyridin-3-yl);

wherein said phenyl, 5-membered heteroaryl, or 6-membered heteroaryl, independently is unsubstituted, mono-, di-, or tri-substituted (notably unsubstituted, mono-, or di-substituted), wherein the substituent independently represents

- halogen (especially chlorine, fluorine, bromine, or iodine);
- cyano;
- C₁₋₃-alkyl (especially methyl or ethyl);
- C₁₋₂-fluoroalkyl (especially difluoromethyl, trifluoromethyl, or 1,1-difluoroethyl);
- C₁₋₂-alkoxy (especially methoxy);
- C₃₋₄-cycloalkyl (especially cyclopropyl);
- C₁₋₂-fluoroalkoxy (especially trifluoromethoxy); or
- amino optionally mono- or di-substituted with methyl or ethyl (especially methyl);

R¹ represents

- C₁₋₅-alkyl (notably C₁₋₄-alkyl; especially methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, or sec-butyl);
- hydroxy-C₂₋₄-alkyl (especially 2-hydroxy-1-methyl-ethyl or 2-hydroxy-1,1-dimethyl-ethyl);
- C₁₋₂-alkoxy-C₂₋₄-alkyl (especially 2-methoxyethyl, 2-methoxy-1-methyl-ethyl, or 2-methoxy-1,1-dimethyl-ethyl);
- C₁₋₄-fluoroalkyl (especially 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-fluoro-1-methyl-ethyl, 2-fluoro-1-fluoromethyl-ethyl, 2,2-difluoro-1-methyl-ethyl, 2,2,2-trifluoro-1,1-dimethyl-ethyl, or 2,2,2-trifluoro-1-methyl-ethyl); or
- **-L-Cy**, wherein
 - **-L-** represents a bond (i.e. **Cy** is directly attached to the nitrogen atom) or -CH₂-; and
 - **Cy** represents C₃₋₆-cycloalkyl (especially cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl) optionally containing one oxygen ring atom, wherein said C₃₋₆-cycloalkyl optionally containing one oxygen ring atom is unsubstituted or mono-substituted (especially at the point of attachment of said C₃₋₆-cycloalkyl to the rest of the molecule), wherein the substituent represents fluorine [in particular **-L-Cy** represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetan-3-yl, cyclopropylmethyl, 1-fluoro-cyclopropylmethyl, or cyclobutyl-methyl]; and

R² represents hydrogen or fluorine (especially hydrogen).

Definitions provided herein are intended to apply uniformly to the compounds of Formula (I) as defined in any one of embodiments 1) to 42), 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. If not explicitly defined otherwise in the respective embodiment or claim, groups defined herein are unsubstituted.

The term "halogen", used alone or in combination, means fluorine, chlorine, bromine, or iodine; notably fluorine, chlorine, or bromine.

In one embodiment, the halogen substituent(s) of **Ar** are stable, non-radioactive halogen isotopes; notably fluorine, chlorine, or iodine; most preferred is fluorine.

In another embodiment, the halogen substituent(s) of **Ar** are unstable, radioactive halogen isotopes of fluorine and/or iodine; notably fluorine-18, iodine-123, iodine-124, iodine-125, and iodine-131; especially fluorine-18.

It is understood that when a substituent is referred to as halogen, fluorine, chlorine, bromine, or iodine, said substituent represents halogen, fluorine, chlorine, bromine, or iodine, in its stable, non-radioactive isotope.

The term "amino", used alone or in combination, refers to the group -NH₂.

The term "alkyl", used alone or in combination, refers to a saturated straight or branched hydrocarbon chain 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. In case a C_{x-y}-alkyl group is used in combination with another substituent, the term means that said substituent is linked through a C_{x-y}-alkyl group to the rest of the molecule. For example, a C₁₋₃-alkyl group contains from 1 to 3 carbon atoms. Examples of C₁₋₃-alkyl groups are methyl, ethyl, n-propyl, and isopropyl. For the substituent(s) of **Ar** preferred examples of C₁₋₃-alkyl groups are methyl and ethyl, most preferred is methyl. Examples of C₁₋₅-alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 1-methyl-butyl, 2-methyl-butyl, 3-methyl-butyl, 1,2-dimethyl-propyl, and 1,1-dimethyl-propyl. For the substituent **R**¹ a preferred example of C₁₋₅-alkyl group is C₁₋₄-alkyl i.e., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl; more preferred is C₂₋₄-alkyl i.e., ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl; most preferred are isopropyl and tert-butyl; particularly preferred is isopropyl.

The term "hydroxyalkyl", used alone or in combination, refers to an alkyl group as defined before, wherein one hydrogen atom has been replaced with a hydroxy group. The term "hydroxy-C_{x-y}-alkyl" (x and y each being an integer), used alone or in combination, refers to a hydroxyalkyl group as defined before wherein the alkyl group contains x to y carbon atoms. For example, a hydroxy-C₂₋₄-alkyl group is a hydroxyalkyl group as defined before which contains from 2 to 4 carbon atoms. Examples of hydroxy-C₂₋₄-alkyl groups are 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxy-1-methyl-ethyl, 2-hydroxy-1-methyl-ethyl, and 2-hydroxy-1,1-dimethyl-ethyl. For the substituent **R**¹ preferred examples are 2-hydroxy-1-methyl-ethyl and 2-hydroxy-1,1-dimethyl-ethyl.

The term "fluoroalkyl", used alone or in combination, refers to an alkyl group as defined before in which one or more (and possibly all) hydrogen atoms have been replaced by 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 C₁₋₂-fluoroalkyl

group contains from 1 to 2 carbon atoms in which 1 to 5 hydrogen atoms have been replaced with fluorine. Examples of C₁₋₂-fluoroalkyl groups are fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, and 2,2,2-trifluoroethyl. For the substituent(s) of **Ar** preferred examples of C₁₋₂-fluoroalkyl groups are difluoromethyl, trifluoromethyl, or 1,1-difluoroethyl; more preferred are C₁-fluoroalkyl groups such as difluoromethyl and trifluoromethyl. A C₁₋₄-fluoroalkyl group contains from 1 to 4 carbon atoms in which 1 to 9 hydrogen atoms have been replaced with fluorine. For the substituent **R**¹ preferred examples of a C₁₋₄-fluoroalkyl group are 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 2-fluoro-1-fluoromethyl-ethyl, 1-methyl-2,2-difluoro-ethyl, 1-methyl-1-trifluoromethyl-ethyl, and 2,2,2-trifluoro-1-methyl-ethyl; preferred are 2,2,2-trifluoro-1-methyl-ethyl and 1-methyl-2,2-difluoro-ethyl.

- 10 The term "cycloalkyl", used alone or in combination, refers to a saturated monocyclic hydrocarbon ring containing three to seven carbon atoms (preferably three to six carbon atoms). The term "C_{x-y}-cycloalkyl" (x and y each being an integer), refers to a saturated monocyclic hydrocarbon ring containing x to y carbon atoms. For example, a C₃₋₄-cycloalkyl group contains from 3 to 4 carbon atoms. Examples of C₃₋₄-cycloalkyl groups are cyclopropyl and cyclobutyl. For the substituent(s) of **Ar** a preferred example of C₃₋₄-cycloalkyl group is cyclopropyl. A C₃₋₆-cycloalkyl group contains from 15 3 to 6 carbon atoms. Examples of a C₃₋₆-cycloalkyl group are cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. For the substituent **R**¹ preferred examples of C₃₋₆-cycloalkyl groups are cyclopropyl and cyclobutyl; most preferred is cyclopropyl. The above-mentioned cycloalkyl groups are unsubstituted or substituted as explicitly defined.

The term "C₃₋₆-cycloalkyl optionally containing one oxygen ring atom", used alone or in combination, refers to a C₃₋₆-cycloalkyl group as defined before, wherein one carbon ring atom is optionally replaced with an oxygen atom. Examples 20 of C₃₋₆-cycloalkyl optionally containing one oxygen ring atom are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxiranyl, oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl; preferred C₃₋₆-cycloalkyl groups optionally containing one oxygen ring atom are cyclopropyl and cyclobutyl; particularly preferred is cyclopropyl. The above-mentioned groups are unsubstituted or substituted as explicitly defined.

The term "alkoxy", used alone or in combination, refers to an alkyl group as defined before, wherein one hydrogen 25 atom is replaced with an oxy group (-O-), i.e. the term refers to the group alkyl-O-. The term "C_{x-y}-alkoxy" (x and y each being an integer), used alone or in combination, refers to an alkoxy group as defined before, wherein the alkoxy group contains x to y carbon atoms. For example, a C₁₋₂-alkoxy group is an alkoxy group as defined herein which contains 1 or 2 carbon atoms. Examples of C₁₋₂-alkoxy groups are methoxy and ethoxy. For the substituent(s) of **Ar** a preferred example of a C₁₋₂-alkoxy group is methoxy.

- 30 The term "C₁₋₂-alkoxy-C₂₋₄-alkyl", used alone or in combination, refers to an alkyl group as defined before, wherein one hydrogen atom is replaced by an alkoxy group, wherein said alkoxy group is as defined hereinabove. The term C_{x1-y1}-alkoxy-C_{x2-y2}-alkyl (x₁, y₁, x₂, and y₂, each being an integer), used alone or in combination, refers to an C_{x2-y2}-alkyl group containing x₂ to y₂ carbon atoms, wherein one hydrogen atom is replaced with an C_{x1-y1}-alkoxy group, said C_{x1-y1}-alkoxy group containing x₁ to y₁ carbon atoms. Thus, the term "C₁₋₂-alkoxy-C₂₋₄-alkyl", refers to an C₂₋₄-alkyl group 35 containing 2 to 4 carbon atoms, wherein one hydrogen atom is replaced with an C₁₋₂-alkoxy group containing 1 to 2 carbon atoms. Examples of such C₁₋₂-alkoxy-C₂₋₄-alkyl are 2-methoxyethyl, 2-methoxy-1-methyl-ethyl, or 2-methoxy-1,1-dimethyl-ethyl; preferred is 2-methoxy-1-methyl-ethyl.

The term "fluoroalkoxy", used alone or in combination, refers to an alkoxy group as defined before, wherein 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_{1-2} -fluoroalkoxy group contains from 1 to 2 carbon atoms in which 1 to 5 hydrogen atoms have been replaced with fluorine.

- 5 Examples of C_{1-2} -fluoroalkoxy groups are trifluoromethoxy, difluoromethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, and 2,2,2-trifluoroethoxy. For the substituent(s) of **Ar** a preferred example of a C_{1-2} -fluoroalkoxy group is trifluoromethoxy.

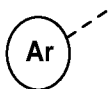
The term "aryl", used alone or in combination, means phenyl or naphthyl, preferably phenyl. The aryl groups are unsubstituted or substituted as explicitly defined.

- 10 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 (notably containing one to a maximum of three 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, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzoxadiazolyl, 15 benzothiadiazolyl, quinolinyl, isoquinolinyl, naphthyridinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyrrolopyridinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrrolopyrazinyl, imidazopyridinyl, imidazopyridazinyl, and imidazothiazolyl.

- 20 The term "5-membered heteroaryl", used alone or in combination, refers to a 5-membered monocyclic aromatic ring containing one to four ring heteroatoms (preferably one to three ring heteroatoms), each independently selected from oxygen, nitrogen, and sulfur. The term "6-membered heteroaryl", used alone or in combination, refers to a 6-membered monocyclic aromatic ring containing one to three ring nitrogen atoms. Examples of 5-membered heteroaryl groups are furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, and tetrazolyl. For **Ar** preferred examples of 5-membered heteroaryl groups are thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, and triazolyl; more preferred are thiophen-2-yl, thiophen-3-yl, 25 thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, [1,3,4]thiadiazol-2-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, isothiazol-5-yl, isoxazol-4-yl, oxazol-5-yl, 1H-[1,2,3]triazol-4-yl, or 2H-[1,2,3]triazol-4-yl; most preferred are thiophenyl such as thiophen-2-yl and thiophen-3-yl, thiazolyl such as thiazol-5-yl, and isothiazolyl such as isothiazol-5-yl; particularly preferred is thiophenyl such as thiophen-2-yl and thiophen-3-yl. For **Ar** preferred examples of 6-membered heteroaryl groups are pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl; more preferred are pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, and pyridazin-3-yl; most preferred is pyridinyl such as pyridin-2-yl, pyridin-3-yl and pyridin-4-yl; particularly preferred is pyridin-3-yl. The above-mentioned heteroaryl groups are unsubstituted or substituted as explicitly defined.

The term "unsubstituted, mono-, di-, or tri-substituted" as used herein refers to "unsubstituted, mono-substituted, di-substituted, or tri-substituted". Likewise, the term "unsubstituted, mono-, or di-substituted" refers to "unsubstituted, mono-substituted, or di-substituted".

- 35 In this patent application, a bond drawn as a dotted line shows the point of attachment of the radical drawn to the rest of the molecule. For example, the radical drawn below



represents phenyl or pyridin-3-yl.

2) One embodiment relates to compounds according to embodiment 1), with the proviso that the following compounds and salts (especially pharmaceutically acceptable salts) thereof, are excluded:

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-dimethylthiophene-3-sulfonamide (i.e. CAS RN 2068756-64-7);

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-5-chlorothiophene-2-sulfonamide (i.e. CAS RN 2068741-89-7);

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,4-dimethylbenzenesulfonamide (i.e. CAS RN 2068738-85-0);

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-3,5-dimethylisoxazole-4-sulfonamide (i.e. CAS RN 2068733-03-7);

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-methoxy-4-methylbenzenesulfonamide (i.e. CAS RN 2068727-35-3);

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,4-difluorobenzenesulfonamide (i.e. CAS RN 2068732-71-6);

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide (i.e. CAS RN 2068712-87-6);

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-4-methoxy-3-methylbenzenesulfonamide (i.e. CAS RN 2068699-30-7);

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-dimethylthiophene-3-sulfonamide (i.e. CAS RN 1783256-82-5);

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-5-chlorothiophene-2-sulfonamide (i.e. CAS RN 1783305-08-7);

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,4-dimethylbenzenesulfonamide (i.e. CAS RN 1783155-99-6);

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-3,5-dimethylisoxazole-4-sulfonamide (i.e. CAS RN 1783110-79-1);

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-methoxy-4-methylbenzenesulfonamide (i.e. CAS RN 1783211-08-4);

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,4-difluorobenzenesulfonamide (i.e. CAS RN 1783040-48-1);

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide (i.e. CAS RN 1783125-47-2); and

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-4-methoxy-3-methylbenzenesulfonamide (i.e. CAS RN 1783136-48-0).

It is understood that when a specific compound without "*cis*-" or "*trans*-" designation is referred to as excluded from the scope of embodiment 2), the *cis*-isomer, the *trans*-isomer, and any mixture of *cis*- and *trans*-isomer, of said compound are also explicitly excluded from the scope of embodiment 2). For example, when the compound *N*-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-dimethylthiophene-3-sulfonamide is referred to as excluded from the scope of embodiment 2), the isomers *N*-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-dimethylthiophene-3-sulfonamide, *N*-(*trans*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-dimethylthiophene-3-sulfonamide, and any mixture thereof, are also excluded from the scope of embodiment 2). For avoidance of doubt, salts (especially pharmaceutically acceptable salts) of the *trans*-isomers of the specific compounds listed in embodiment 2) are also excluded from the scope of embodiment 2).

- 3) Another embodiment relates to compounds according to embodiment 1) or 2), wherein **Ar** represents
- phenyl, wherein said phenyl is unsubstituted, mono-, or di-substituted, wherein the substituent independently represents
 - halogen (especially iodine, chlorine or fluorine);
 - cyano;
 - C₁₋₃-alkyl (especially methyl);
 - C₁₋₂-alkoxy (especially methoxy); or
 - C₁₋₂-fluoroalkoxy (especially trifluoromethoxy);
 - 5-membered heteroaryl containing from one to three ring heteroatoms independently selected from nitrogen, sulfur, and oxygen (notably such 5-membered heteroaryl is selected from thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, and triazolyl; especially selected from thiophen-2-yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, [1,3,4]thiadiazol-2-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, isothiazol-5-yl, isoxazol-4-yl, oxazol-5-yl, 1H-[1,2,3]triazol-4-yl, and 2H-[1,2,3]triazol-4-yl; in particular selected from thiophenyl such as thiophen-2-yl and thiophen-3-yl), wherein said 5-membered heteroaryl is unsubstituted, mono-, or di-substituted, wherein the substituent independently represents
 - halogen (especially chlorine, fluorine, or bromine);
 - cyano;
 - C₁₋₃-alkyl (especially methyl or ethyl);
 - C₁₋₂-fluoroalkyl (especially difluoromethyl or 1,1-difluoroethyl);
 - C₁₋₂-alkoxy (especially methoxy); or
 - C₃₋₄-cycloalkyl (especially cyclopropyl);
 - 6-membered heteroaryl containing from one to three ring nitrogen atoms (notably such 6-membered heteroaryl is selected from pyridinyl, pyrimidinyl, pyrazinyl, or pyridazinyl; especially selected from pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, and pyridazin-3-yl; in particular selected from pyridin-3-yl), wherein said 6-membered heteroaryl is unsubstituted, mono-, di-, or tri-substituted (notably unsubstituted, mono-, or di-substituted), wherein the substituent independently represents
 - halogen (especially chlorine, fluorine, or bromine);
 - cyano;

- C₁₋₃-alkyl (especially methyl or ethyl);
- C₁₋₂-fluoroalkyl (especially difluoromethyl or trifluoromethyl);
- C₁₋₂-alkoxy (especially methoxy);
- C₃₋₄-cycloalkyl (especially cyclopropyl); or
- amino optionally mono- or di-substituted with methyl or ethyl (especially methyl).

4) Another embodiment relates to compounds according to embodiment 1) or 2), wherein **Ar** represents

- phenyl, wherein said phenyl is unsubstituted, mono-, or di-substituted, wherein the substituent independently represents
 - halogen (especially iodine, chlorine or fluorine);
 - C₁₋₃-alkyl (especially methyl); or
 - C₁₋₂-alkoxy (especially methoxy).
- 5-membered heteroaryl containing from one to three ring heteroatoms independently selected from nitrogen, sulfur, and oxygen (notably such 5-membered heteroaryl is selected from thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, and triazolyl; especially selected from thiophen-2-yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, [1,3,4]thiadiazol-2-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, isothiazol-5-yl, isoxazol-4-yl, oxazol-5-yl, 1H-[1,2,3]triazol-4-yl, and 2H-[1,2,3]triazol-4-yl; in particular selected from thiophenyl such as thiophen-2-yl and thiophen-3-yl), wherein said 5-membered heteroaryl is unsubstituted, mono-, or di-substituted, wherein the substituent independently represents
 - halogen (especially chlorine, fluorine, or bromine);
 - C₁₋₃-alkyl (especially methyl or ethyl);
 - C₁₋₂-fluoroalkyl (especially difluoromethyl or 1,1-difluoroethyl);
 - C₁₋₂-alkoxy (especially methoxy); or
 - C₃₋₄-cycloalkyl (especially cyclopropyl);
- 6-membered heteroaryl containing from one to three ring nitrogen atoms (notably such 6-membered heteroaryl is selected from pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; especially selected from pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, and pyridazin-3-yl; in particular selected from pyridin-3-yl), wherein said 6-membered heteroaryl is unsubstituted, mono-, di-, or tri-substituted (notably unsubstituted, mono-, or di-substituted), wherein the substituent independently represents
 - halogen (especially chlorine, fluorine, or bromine);
 - cyano;
 - C₁₋₃-alkyl (especially methyl or ethyl);
 - C₁₋₂-fluoroalkyl (especially difluoromethyl or trifluoromethyl);
 - C₁₋₂-alkoxy (especially methoxy); or
 - C₃₋₄-cycloalkyl (especially cyclopropyl).

5) Another embodiment relates to compounds according to embodiment 1) or 2), wherein **Ar** represents

- phenyl, wherein said phenyl is unsubstituted, mono-, di-, or tri-substituted (notably unsubstituted, mono-, or di-substituted), wherein the substituent independently represents

- halogen (especially iodine, chlorine, fluorine, or bromine);
- cyano;
- C₁₋₃-alkyl (especially methyl or ethyl);
- C₁₋₂-fluoroalkyl (especially difluoromethyl, trifluoromethyl, or 1,1-difluoroethyl);
- C₁₋₂-alkoxy (especially methoxy);
- C₃₋₄-cycloalkyl (especially cyclopropyl);
- C₁₋₂-fluoroalkoxy (especially trifluoromethoxy); or
- amino optionally mono- or di-substituted with methyl or ethyl (especially methyl).

6) Another embodiment relates to compounds according to embodiment 1) or 2), wherein **Ar** represents

- phenyl, wherein said phenyl is unsubstituted; mono-substituted in *meta*-position with regard to the point of attachment of the rest of the molecule; or di-substituted with one substituent in *meta*-position and another substituent in *para*- or *ortho*-position (any one of the *ortho*-positions), with regard to the point of attachment of the rest of the molecule; wherein the substituent independently represents
 - halogen (especially iodine, chlorine, fluorine, or bromine; preferred is fluorine);
 - cyano;
 - C₁₋₃-alkyl (especially methyl or ethyl);
 - C₁₋₂-fluoroalkyl (especially difluoromethyl, trifluoromethyl, or 1,1-difluoroethyl);
 - C₁₋₂-alkoxy (especially methoxy);
 - C₃₋₄-cycloalkyl (especially cyclopropyl);
 - C₁₋₂-fluoroalkoxy (especially trifluoromethoxy); or
 - amino optionally mono- or di-substituted with methyl or ethyl (especially methyl).

7) Another embodiment relates to compounds according to any one of embodiments 1) to 3), wherein **Ar** represents

- phenyl, wherein said phenyl is unsubstituted; mono- substituted in *meta*-position with regard to the point of attachment of the rest of the molecule; or di-substituted with one substituent in *meta*-position and another substituent in *para*- or *ortho*-position (any one of the *ortho*-positions), with regard to the point of attachment of the rest of the molecule; wherein the substituent independently represents
 - halogen (especially iodine, chlorine or fluorine);
 - cyano;
 - C₁₋₃-alkyl (especially methyl);
 - C₁₋₂-alkoxy (especially methoxy); or
 - C₁₋₂-fluoroalkoxy (especially trifluoromethoxy).

8) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein **Ar** represents

- phenyl, wherein said phenyl is unsubstituted; mono- substituted in *meta*-position with regard to the point of attachment of the rest of the molecule; or di-substituted with one substituent in *meta*-position and another substituent in *para*-position, with regard to the point of attachment of the rest of the molecule; wherein the substituent independently represents
 - halogen (especially iodine, chlorine or fluorine);

- C₁₋₃-alkyl (especially methyl); or
- C₁₋₂-alkoxy (especially methoxy).

9) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein **Ar** represents

- phenyl, wherein said phenyl is unsubstituted; mono- substituted in *meta*-position with regard to the point of attachment of the rest of the molecule; or di-substituted with one substituent in *meta*-position and another substituent in *para*-position, with regard to the point of attachment of the rest of the molecule; wherein the substituent independently represents chlorine, fluorine, or methoxy (notably iodine, chlorine or fluorine; especially fluorine).

10) Another embodiment relates to compounds according to embodiment 1) or 2), wherein **Ar** represents

- 5-membered heteroaryl containing from one to three ring heteroatoms independently selected from nitrogen, sulfur, and oxygen (notably such 5-membered heteroaryl is selected from thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, and triazolyl; especially selected from thiophen-2-yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, [1,3,4]thiadiazol-2-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, isothiazol-5-yl, isoxazol-4-yl, oxazol-5-yl, 1H-[1,2,3]triazol-4-yl, and 2H-[1,2,3]triazol-4-yl; in particular selected from thiophen-2-yl and thiophen-3-yl), wherein said 5-membered heteroaryl is unsubstituted, mono-, di-, or tri-substituted (notably unsubstituted, mono-, or di-substituted), wherein the substituent independently represents
 - halogen (especially chlorine, fluorine, or bromine);
 - cyano;
 - C₁₋₃-alkyl (especially methyl or ethyl);
 - C₁₋₂-fluoroalkyl (especially difluoromethyl, trifluoromethyl, or 1,1-difluoroethyl);
 - C₁₋₂-alkoxy (especially methoxy);
 - C₃₋₄-cycloalkyl (especially cyclopropyl);
 - C₁₋₂-fluoroalkoxy (especially trifluoromethoxy); or
 - amino optionally mono- or di-substituted with methyl or ethyl (especially methyl).

11) Another embodiment relates to compounds according to embodiments 1) or 2), wherein **Ar** represents

- 5-membered heteroaryl containing at least one ring sulfur atom and optionally one or two ring nitrogen atoms (notably such 5-membered heteroaryl is selected from thiophenyl, thiazolyl, isothiazolyl, and thiadiazolyl; especially selected from thiophen-2-yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-5-yl, and [1,3,4]thiadiazol-2-yl; in particular selected from thiophenyl such as thiophen-2-yl and thiophen-3-yl); wherein said 5-membered heteroaryl is unsubstituted, mono-, or di-substituted (notably unsubstituted or mono-substituted; especially mono-substituted), wherein the substituent independently represents
 - halogen (especially chlorine, fluorine, or bromine);
 - cyano;
 - C₁₋₃-alkyl (especially methyl or ethyl);
 - C₁₋₂-fluoroalkyl (especially difluoromethyl, trifluoromethyl, or 1,1-difluoroethyl);
 - C₁₋₂-alkoxy (especially methoxy);
 - C₃₋₄-cycloalkyl (especially cyclopropyl);

- C₁₋₂-fluoroalkoxy (especially trifluoromethoxy); or
- amino optionally mono- or di-substituted with methyl or ethyl (especially methyl).

12) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein **Ar** represents

- 5-membered heteroaryl containing at least one ring sulfur atom and optionally one or two ring nitrogen atoms (notably such 5-membered heteroaryl is selected from thiophenyl, thiazolyl, isothiazolyl, and thiadiazolyl; especially selected from thiophen-2-yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-5-yl, and [1,3,4]thiadiazol-2-yl; in particular selected from thiophenyl such as thiophen-2-yl and thiophen-3-yl); wherein said 5-membered heteroaryl is unsubstituted, mono-, or di-substituted (notably unsubstituted or mono-substituted; especially mono-substituted), wherein the substituent independently represents

- halogen (especially chlorine, fluorine, or bromine);
- C₁₋₃-alkyl (especially methyl or ethyl);
- C₁₋₂-fluoroalkyl (especially difluoromethyl);
- C₁₋₂-alkoxy (especially methoxy); or
- C₃₋₄-cycloalkyl (especially cyclopropyl).

13) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein **Ar** represents

- 5-membered heteroaryl selected from thiophen-2-yl, thiophen-3-yl, isothiazol-5-yl, thiazol-5-yl, and [1,3,4]thiadiazol-2-yl (especially thiophen-2-yl and thiophen-3-yl); wherein said 5-membered heteroaryl is mono-substituted (especially at position 3 with regard to the point of attachment of the rest of the molecule), wherein the substituent independently represents

- halogen (especially chlorine, fluorine, or bromine);
- C₁₋₃-alkyl (especially methyl or ethyl);
- C₁₋₂-fluoroalkyl (especially difluoromethyl);
- C₁₋₂-alkoxy (especially methoxy); or
- C₃₋₄-cycloalkyl (especially cyclopropyl).

14) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein **Ar** represents

- 5-membered heteroaryl selected from thiophen-2-yl and thiophen-3-yl; wherein said 5-membered heteroaryl is mono-substituted (especially at position 3 with regard to the point of attachment of the rest of the molecule), wherein the substituent independently represents

- halogen (especially chlorine, fluorine, or bromine);
- C₁₋₃-alkyl (especially methyl or ethyl); or
- C₁₋₂-fluoroalkyl (especially difluoromethyl).

15) Another embodiment relates to compounds according to embodiment 1) or 2), wherein **Ar** represents

- 6-membered heteroaryl containing from one to three ring nitrogen atoms (notably such 6-membered heteroaryl is selected from pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; especially selected from pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, and pyridazin-3-yl; in particular selected from pyridin-3-yl);

wherein said 6-membered heteroaryl is unsubstituted, mono-, di-, or tri-substituted (notably unsubstituted, mono-, or di-substituted), wherein the substituent independently represents

- halogen (especially chlorine, fluorine, or bromine);
- cyano;
- C₁₋₃-alkyl (especially methyl or ethyl);
- C₁₋₂-fluoroalkyl (especially difluoromethyl, trifluoromethyl, or 1,1-difluoroethyl);
- C₁₋₂-alkoxy (especially methoxy);
- C₃₋₄-cycloalkyl (especially cyclopropyl);
- C₁₋₂-fluoroalkoxy (especially trifluoromethoxy); or
- amino optionally mono- or di-substituted with methyl or ethyl (especially methyl).

16) Another embodiment relates to compounds according to embodiment 1) or 2), wherein **Ar** represents

- 6-membered heteroaryl containing one or two ring nitrogen atoms, wherein at least one ring nitrogen atom is in position 3 with regard to the point of attachment of the rest of the molecule (notably such 6-membered heteroaryl is selected from pyridin-3-yl and pyrimidin-5-yl; especially selected from pyridin-3-yl), wherein said 6-membered heteroaryl is unsubstituted, mono-, di-, or tri-substituted (notably mono-, di- or tri-substituted; especially di- or tri-substituted; in particular di-substituted), wherein the substituent independently represents
 - halogen (especially chlorine, fluorine, or bromine);
 - cyano;
 - C₁₋₃-alkyl (especially methyl or ethyl);
 - C₁₋₂-fluoroalkyl (especially difluoromethyl, trifluoromethyl, or 1,1-difluoroethyl);
 - C₁₋₂-alkoxy (especially methoxy);
 - C₃₋₄-cycloalkyl (especially cyclopropyl);
 - C₁₋₂-fluoroalkoxy (especially trifluoromethoxy); or
 - amino optionally mono- or di-substituted with methyl or ethyl (especially methyl).

17) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein **Ar** represents

- 6-membered heteroaryl selected from pyridin-3-yl, wherein said 6-membered heteroaryl is unsubstituted, mono-, di-, or tri-substituted (notably mono-, di- or tri-substituted; especially di- or tri-substituted; in particular di-substituted), wherein the substituent independently represents
 - halogen (especially chlorine, fluorine, or bromine);
 - C₁₋₃-alkyl (especially methyl or ethyl);
 - C₁₋₂-fluoroalkyl (especially difluoromethyl, trifluoromethyl, or 1,1-difluoroethyl);
 - C₁₋₂-alkoxy (especially methoxy); or
 - C₃₋₄-cycloalkyl (especially cyclopropyl);

18) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein **Ar** represents

- 6-membered heteroaryl selected from pyridin-3-yl, wherein said 6-membered heteroaryl is unsubstituted, mono-, di-, or tri-substituted (notably mono-, di- or tri-substituted; especially di- or tri-substituted; in particular

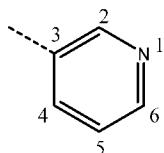
di-substituted), wherein the substituent independently represents chlorine, fluorine, methyl, or methoxy (especially chlorine, fluorine, or methyl).

19) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein **Ar** represents 6-membered heteroaryl selected from pyridin-3-yl, wherein said pyridin-3-yl is unsubstituted, mono-, di-, or tri-substituted (notably mono-, di- or tri-substituted; especially di- or tri-substituted; in particular di-substituted) in position(s) 2 and/or 5 and/or 6, with regard to the nitrogen atom of said pyridin-3-yl; wherein the substituent independently represents chlorine, fluorine, methyl, or methoxy (especially chlorine, fluorine, or methyl).

20) Another embodiment relates to compounds according to any one of embodiments 1) to 4) and 15) to 18), wherein **Ar** represents 6-membered heteroaryl, wherein said 6-membered heteroaryl is selected from pyridin-3-yl, wherein said pyridin-3-yl is unsubstituted, mono-, di-, or tri-substituted (notably mono-, di- or tri-substituted; especially di- or tri-substituted; in particular di-substituted) in position(s) 2 and/or 5 and/or 6, with regard to the nitrogen atom of said pyridin-3-yl; wherein the substituents are as defined for the 6-membered heteroaryl in the corresponding embodiments 1) to 4) and 15) to 18).

21) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein **Ar** represents 6-membered heteroaryl, wherein said 6-membered heteroaryl is selected from pyridin-3-yl, wherein said pyridin-3-yl is unsubstituted, mono-, or di-substituted in position(s) 2 and/or 5 and/or 6, with regard to the nitrogen atom of said pyridin-3-yl; wherein the substituent(s), if present, independently represent methyl or fluorine.

For avoidance of doubt, the numbering of the pyridin-3-yl ring referred to in embodiments 19) and 21) is as follows:



22) Another embodiment relates to compounds according to any one of embodiments 1) to 21), wherein **R¹** represents

- C₁₋₅-alkyl (notably C₁₋₄-alkyl; especially methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, or sec-butyl);
- hydroxy-C₂₋₄-alkyl (especially 2-hydroxy-1-methyl-ethyl or 2-hydroxy-1,1-dimethyl-ethyl);
- C₁₋₂-alkoxy-C₂₋₄-alkyl (especially 2-methoxyethyl, 2-methoxy-1-methyl-ethyl, or 2-methoxy-1,1-dimethyl-ethyl);
- C₁₋₄-fluoroalkyl (especially 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-fluoro-1-methyl-ethyl, 2-fluoro-1-fluoromethyl-ethyl, 2,2-difluoro-1-methyl-ethyl, 2,2,2-trifluoro-1,1-dimethyl-ethyl, or 2,2,2-trifluoro-1-methyl-ethyl); or
- **-L-Cy**, wherein
 - **-L-** represents a bond (i.e. **Cy** is directly attached to the nitrogen atom) or -CH₂-; and
 - **Cy** represents C₃₋₆-cycloalkyl (especially cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl) optionally containing one oxygen ring atom, wherein said C₃₋₆-cycloalkyl optionally containing one

oxygen ring atom is unsubstituted or mono-substituted (especially at the point of attachment of said C₃₋₆-cycloalkyl to the rest of the molecule), wherein the substituent represents fluorine [in particular -L-Cy represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetan-3-yl, cyclopropyl-methyl, 1-fluoro-cyclopropylmethyl, or cyclobutyl-methyl].

- 5 23) Another embodiment relates to compounds according to any one of embodiments 1) to 21), wherein **R¹** represents
- C₁₋₅-alkyl (notably C₁₋₄-alkyl; especially methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, or sec-butyl);
 - C₁₋₄-fluoroalkyl (especially 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 2-fluoro-1-fluoromethyl-ethyl, 1-methyl-2,2-difluoro-ethyl, 1-methyl-1-trifluoromethyl-ethyl, or 2,2,2-trifluoro-1-methyl-ethyl); or
 - **L-Cy**, wherein
 - -L- represents a bond (i.e. **Cy** is directly attached to the nitrogen atom) or -CH₂-; and
 - **Cy** represents C₃₋₆-cycloalkyl, wherein said C₃₋₆-cycloalkyl is unsubstituted or mono-substituted (especially at the point of attachment of said C₃₋₆-cycloalkyl to the rest of the molecule), wherein the substituent represents fluorine (in particular -L-Cy represents cyclopropyl, cyclobutyl, cyclopropyl-methyl, (1-fluoro-cyclopropyl)-methyl, or cyclobutyl-methyl).

- 24) Another embodiment relates to compounds according to any one of embodiments 1) to 21), wherein **R¹** represents
- ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, or sec-butyl; especially isopropyl;
 - 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 2-fluoro-1-fluoromethyl-ethyl, 1-methyl-2,2-difluoro-ethyl, 1-methyl-1-trifluoromethyl-ethyl, or 2,2,2-trifluoro-1-methyl-ethyl; especially 1-methyl-1-trifluoromethyl-ethyl; or
 - cyclopropyl, cyclopropyl-methyl, or (1-fluoro-cyclopropyl)-methyl; especially cyclopropyl.

25) Another embodiment relates to compounds according to any one of embodiments 1) to 24), wherein **R²** represents hydrogen.

- 26) Another embodiment relates to compounds according to embodiment 1), wherein **Ar** represents a 6-membered heteroaryl, wherein said 6-membered heteroaryl is selected from pyridin-3-yl, wherein said pyridin-3-yl is unsubstituted, mono-, or di-substituted in position(s) 2 and/or 5 and/or 6, with regard to the nitrogen atom of said pyridin-3-yl; wherein the substituents independently represent methyl or fluorine; **R¹** represents C₂₋₄-alkyl (notably ethyl, n-propyl, isopropyl, tert-butyl, or sec-butyl; especially isopropyl), cyclopropyl, or 2,2,2-trifluoro-1-methyl-ethyl; and **R²** represents hydrogen;

27) Another embodiment relates to compounds according to embodiment 1) or 2), wherein at least one, especially three of the following characteristics a) and/or b) and/or c) below are present:

- a) the radical  represents:

- phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-iodophenyl, 3-iodophenyl, 3-chlorophenyl, 3-cyanophenyl, 3-methylphenyl, 3-methoxyphenyl, 3-(trifluoromethoxy)-phenyl, 3,4-difluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3-fluoro-4-methoxyphenyl, 3-methyl-4-methoxyphenyl, 3-fluoro-4-methylphenyl, 2-methyl-5-fluorophenyl, 2-fluoro-5-methylphenyl, 3,5-dichlorophenyl, 2-fluoro-5-chlorophenyl, 3-chloro-4-iodophenyl, 3-fluoro-4-iodophenyl, 2-fluoro-4-iodophenyl, 3-cyano-4-iodophenyl, 3-methyl-4-iodophenyl, or 2-chloro-5-fluorophenyl; and/or
 - thiophen-2-yl, 4-methyl-thiophen-2-yl, 3-methyl-thiophen-2-yl, 5-methyl-thiophen-2-yl, 5-chloro-thiophen-2-yl, 5-fluoro-thiophen-2-yl, 5-bromo-thiophen-2-yl, 5-methoxy-thiophen-2-yl, 5-cyclopropyl-thiophene-2-yl, 5-methyl-thiophen-3-yl, 4-methyl-thiazol-2-yl, 2-methyl-thiazol-4-yl, 2-chloro-thiazol-4-yl, thiazol-4-yl, thiazol-5-yl, 2-ethyl-thiazol-5-yl, 2-methyl-thiazol-5-yl, 2-methoxy-thiazole-5-yl, 2-chloro-thiazol-5-yl, 2-cyclopropyl-thiazole-5-yl, 2-(1,1-difluoro-ethyl)-thiazole-5-yl, 2,4-dimethyl-thiazol-5-yl, 2-bromo-4-methyl-thiazol-5-yl, 2-chloro-4-methyl-thiazol-5-yl, 3-methyl-isothiazol-5-yl, 5-methyl-[1,3,4]thiadiazol-2-yl, 1-methyl-1H-pyrazole-4-yl, 3-methyl-isoxazol-4-yl, 2-methyl-oxazol-5-yl, 1-methyl-1H-[1,2,3]triazol-4-yl, 2-methyl-2H-[1,2,3]triazol-4-yl, 1,5-dimethyl-1H-pyrazol-3-yl, 3,5-dimethyl-isoxazole-4-yl, or 5-difluoromethyl-thiophen-3-yl; and/or
 - pyridin-2-yl, pyridin-3-yl, 2-fluoro-pyridin-3-yl, 5-fluoro-pyridin-3-yl, 6-fluoro-pyridin-3-yl, 2-chloro-pyridin-3-yl, 4-chloro-pyridin-3-yl, 5-chloro-pyridin-3-yl, 6-chloro-pyridin-3-yl, 2-bromo-pyridin-3-yl, 2-methyl-pyridin-3-yl, 4-methyl-pyridin-3-yl, 5-methyl-pyridin-3-yl, 6-methyl-pyridin-3-yl, 5-ethyl-pyridin-3-yl, 6-ethyl-pyridin-3-yl, 5-cyclopropyl-pyridin-3-yl, 6-cyclopropyl-pyridin-3-yl, 5-cyano-pyridin-3-yl, 6-cyano-pyridin-3-yl, 6-methoxy-pyridin-3-yl, 6-methylamino-pyridin-3-yl, 2-difluoromethyl-pyridin-3-yl, 5-difluoromethyl-pyridin-3-yl, 6-difluoromethyl-pyridin-3-yl, 5,6-dimethyl-pyridin-3-yl, 2,6-dimethyl-pyridin-3-yl, 2,5-dimethyl-pyridin-3-yl, 4,6-dimethyl-pyridin-3-yl, 5-chloro-6-methyl-pyridin-3-yl, 6-chloro-5-methyl-pyridin-3-yl, 5-fluoro-6-methyl-pyridin-3-yl, 2-fluoro-6-methyl-pyridin-3-yl, 6-fluoro-2-methyl-pyridin-3-yl, 6-fluoro-5-methyl-pyridin-3-yl, 2-chloro-6-methyl-pyridin-3-yl, 2,6-dichloro-pyridin-3-yl, 6-chloro-2-methyl-pyridin-3-yl, 2,6-difluoro-pyridin-3-yl, 6-chloro-5-fluoro-pyridin-3-yl, 5,6-difluoro-pyridin-3-yl, 5,6-dichloro-pyridin-3-yl, 5-fluoro-2-methyl-pyridin-3-yl, 2-fluoro-5-methyl-pyridin-3-yl, 5-chloro-2-methyl-pyridin-3-yl, 2-chloro-5-methyl-pyridin-3-yl, 6-chloro-4-methyl-pyridin-3-yl, 2-chloro-6-fluoro-pyridin-3-yl, 6-trifluoromethyl-pyridin-3-yl, 5-methyl-6-trifluoromethyl-pyridin-3-yl, 5-chloro-6-fluoro-pyridin-3-yl, 5-chloro-2-fluoro-pyridin-3-yl, 2-chloro-6-methoxy-pyridin-3-yl, 5-chloro-2-methoxy-pyridin-3-yl, 6-dimethylamino-pyridin-3-yl, 2-chloro-5,6-dimethyl-pyridin-3-yl, 2-fluoro-5,6-dimethyl-pyridin-3-yl, 2,5,6-trimethyl-pyridin-3-yl, pyridin-4-yl, pyridazin-2-yl, 6-methyl-pyridazin-2-yl, pyrimidin-5-yl, or 2-amino-pyrimidin-5-yl;
- b) **R¹** represents
- methyl, ethyl, cyclopropyl, 2-fluoroethyl, n-propyl, isopropyl, 2-hydroxyethyl, 2-fluoro-1-methyl-ethyl, tert-butyl, sec-butyl, 2,2-difluoro-ethyl, 2-hydroxy-1-methyl-ethyl, 2-methoxy-ethyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetan-3-yl, 1-fluoro-cyclopropylmethyl, cyclobutyl-methyl, 2,2,2-trifluoro-ethyl, 2,2,2-trifluoro-1-methyl-ethyl, 2-fluoro-1-fluoromethyl-ethyl, 2,2-difluoro-1-methyl-ethyl, 2-hydroxy-1,1-dimethyl-ethyl, 2-methoxy-1-methyl-ethyl, or 2-methoxy-1,1-dimethyl-ethyl;
- c) **R²** represents fluorine or hydrogen.

28) Another embodiment relates to compounds according to embodiment 1) or 2), wherein

the radical  represents

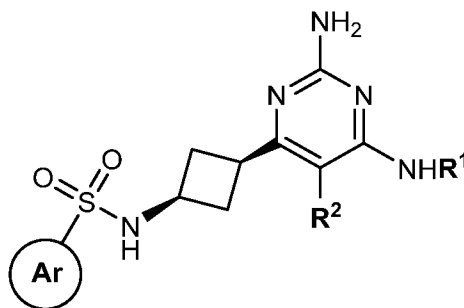
pyridin-3-yl, 2-fluoro-pyridin-3-yl, 5-fluoro-pyridin-3-yl, 6-fluoro-pyridin-3-yl, 2-chloro-pyridin-3-yl, 5-chloro-pyridin-3-yl, 6-chloro-pyridin-3-yl, 2-bromo-pyridin-3-yl, 2-methyl-pyridin-3-yl, 5-methyl-pyridin-3-yl, 6-methyl-pyridin-3-yl, 5-ethyl-pyridin-3-yl, 6-ethyl-pyridin-3-yl, 5-cyclopropyl-pyridin-3-yl, 6-cyclopropyl-pyridin-3-yl, 2-difluoromethyl-pyridin-3-yl, 5,6-dimethyl-pyridin-3-yl, 2,6-dimethyl-pyridin-3-yl, 2,5-dimethyl-pyridin-3-yl, 5-chloro-6-methyl-pyridin-3-yl, 6-chloro-5-methyl-pyridin-3-yl, 5-fluoro-6-methyl-pyridin-3-yl, 2-fluoro-6-methyl-pyridin-3-yl, 6-fluoro-2-methyl-pyridin-3-yl, 6-fluoro-5-methyl-pyridin-3-yl, 2-chloro-6-methyl-pyridin-3-yl, 2,6-dichloro-pyridin-3-yl, 6-chloro-2-methyl-pyridin-3-yl, 2,6-difluoro-pyridin-3-yl, 6-chloro-5-fluoro-pyridin-3-yl, 5,6-difluoro-pyridin-3-yl, 5,6-dichloro-pyridin-3-yl, 5-fluoro-2-methyl-pyridin-3-yl, 2-fluoro-5-methyl-pyridin-3-yl, 5-chloro-2-methyl-pyridin-3-yl, 2-chloro-5-methyl-pyridin-3-yl, 2-chloro-6-fluoro-pyridin-3-yl, 6-trifluoromethyl-pyridin-3-yl, 5-methyl-6-trifluoromethyl-pyridin-3-yl, 5-chloro-6-fluoro-pyridin-3-yl, 5-chloro-2-fluoro-pyridin-3-yl, 2-chloro-5,6-dimethyl-pyridin-3-yl, 2-fluoro-5,6-dimethyl-pyridin-3-yl, or 2,5,6-trimethyl-pyridin-3-yl;

R¹ represents

ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, 1-fluoro-cyclopropylmethyl, 2,2-difluoro-ethyl, or 2,2,2-trifluoro-1-methyl-ethyl; and

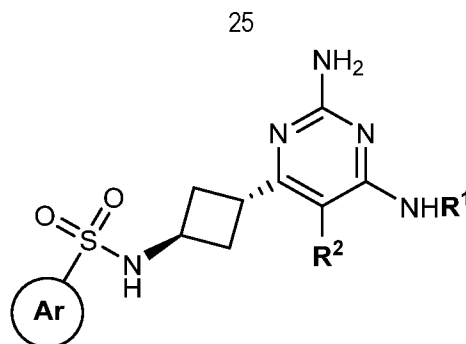
R² represents hydrogen.

29) Another embodiment relates to compounds according to any one of embodiments 1) to 28), which are also compounds of Formula (II) (i.e. the compounds are in *cis*-configuration with respect to the cyclobutan-1,3-diyl ring)



Formula (II).

30) Another embodiment relates to compounds according to any one of embodiments 1) to 28), which are also compounds of Formula (III) (i.e. the compounds are in *trans*-configuration with respect to the cyclobutan-1,3-diyl ring)



Formula (III).

31) Another embodiment relates to compounds according to embodiment 1), which are selected from the following compounds

- 5 *N*-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-4-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-3,4-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide;
- 10 *N*-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,6-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-5-methylbenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-2-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-5-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-2-methylbenzenesulfonamide;
- 15 *N*-(*cis*-3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
- 20 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyridine-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-cyanobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluoro-4-methylbenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-1-methyl-1H-pyrazole-4-sulfonamide;
- 25 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methylbenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3,5-dichlorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)benzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-2-methylbenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-chlorobenzenesulfonamide;
- 30 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-(trifluoromethoxy)benzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluoro-4-methoxybenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methoxybenzenesulfonamide;

- N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chlorothiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3,4-difluorobenzenesulfonamide;
5 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,6-difluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-bromo-4-methylthiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)thiazole-5-sulfonamide;
10 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-ethylthiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylthiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-cyclopropylthiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)thiophene-2-sulfonamide;
15 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3,5-dimethylisoxazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloro-2-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-5-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-6-methoxypyridine-3-sulfonamide;
20 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloro-4-methylpyridine-3-sulfonamide;
2-amino-*N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyrimidine-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methoxypyridine-3-sulfonamide;
N-(*trans*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chlorothiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methyloxazole-5-sulfonamide;
25 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyridine-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methyl-1,3,4-thiadiazole-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloropyridine-3-sulfonamide;
30 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-2-methoxypyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methyl-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(dimethylamino)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-4-methylthiazole-5-sulfonamide;
35 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)thiazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide;

- N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-5-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methoxythiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-chloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-methylthiazole-2-sulfonamide;
5 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methylisoxazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-5-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,4-dimethylthiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyrazine-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoropyridine-3-sulfonamide;
10 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyrimidine-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-1-methyl-1*H*-1,2,3-triazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(1,1-difluoroethyl)thiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chlorothiazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluorothiophene-2-sulfonamide;
15 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-1,5-dimethyl-1*H*-pyrazole-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methylisothiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-(difluoromethyl)thiophene-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methylthiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methyl-2*H*-1,2,3-triazole-4-sulfonamide;
20 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methoxythiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridazine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-methylthiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methylthiophene-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chlorothiophene-2-sulfonamide;
25 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-cyclopropylthiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methylthiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-bromothiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,6-dichloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloro-5-methylpyridine-3-sulfonamide;
30 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-cyanopyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-cyanopyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(difluoromethyl)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloro-5-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methylpyridine-3-sulfonamide;
35 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-6-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-difluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide;

- N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-2-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(difluoromethyl)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-ethylpyridine-3-sulfonamide;
- 5 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-cyclopropylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-cyclopropylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-6-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-(difluoromethyl)pyridine-3-sulfonamide;
- 10 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-ethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-2-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-2-methylpyridine-3-sulfonamide;
- 15 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,5-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dichloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(methylamino)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-bromopyridine-3-sulfonamide;
- 20 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,5,6-trimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylthiazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylthiazole-5-sulfonamide;
- 25 *N*-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloropyridine-3-sulfonamide;
- 30 *N*-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2,6-dimethylpyridine-3-sulfonamide;
- 35 *N*-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;

- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*S*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- 5 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide;
- 10 *N*-(*cis*-3-(2-amino-6-(tert-butylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(tert-butylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclobutylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((cyclobutylmethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(cyclobutylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide;
- 15 *N*-(*cis*-3-(2-amino-6-((cyclobutylmethyl)amino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(cyclobutylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((cyclobutylmethyl)amino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1-hydroxypropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((1-hydroxy-2-methylpropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
- 20 *N*-(*cis*-3-(2-amino-6-(sec-butylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((2,2-difluoroethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((2-fluoroethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((1-fluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
- 25 *N*-(*cis*-3-(2-amino-6-((2-methoxyethyl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1-hydroxypropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1-methoxypropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-((1-methoxy-2-methylpropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
- 30 *N*-(*cis*-3-(2-amino-6-(((1-fluorocyclopropyl)methyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(((1-fluorocyclopropyl)methyl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-((1,3-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
- 35 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;

- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*S*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- 5 *N*-(*cis*-3-(2-amino-6-(oxetan-3-ylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-((1,1,1-trifluoro-2-methylpropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(butylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(isobutylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
- 10 *N*-(*cis*-3-(2-amino-6-(cyclopentylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(cyclohexylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-((cyclopropylmethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
- 15 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-iodobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-iodobenzenesulfonamide;
- N*-(*trans*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-2-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)pyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-fluoropyridine-3-sulfonamide;
- 20 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-5-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-2-methylpyridine-3-sulfonamide;
- 25 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-2-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2,6-dimethylpyridine-3-sulfonamide;
- 30 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-6-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-chloro-4-
- 35 iodobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluoro-4-iodobenzenesulfonamide;

- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-4-iodobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-4-iodobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-cyano-4-iodobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-4-iodo-3-methylbenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(*tert*-butylamino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(*tert*-butylamino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(*tert*-butylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(*tert*-butylamino)pyrimidin-4-yl)cyclobutyl)-2,6-dimethylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(*tert*-butylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-*sec*-butyl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-*sec*-butyl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*S*)-*sec*-butyl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*S*)-*sec*-butyl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide; and
- N*-(*cis*-3-(2-amino-6-(ethylamino)-5-fluoropyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide.
- 32) Another embodiment relates to compounds according to embodiment 1), which are selected from the following compounds
- N*-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,4-difluorobenzenesulfonamide (i.e. CAS RN 2068732-71-6);
- N*-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide (i.e. CAS RN 2068712-87-6);
- N*-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-4-methoxy-3-methylbenzenesulfonamide (i.e. CAS RN 2068699-30-7);
- N*-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,4-difluorobenzenesulfonamide (i.e. CAS RN 1783040-48-1);
- N*-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide (i.e. CAS RN 1783125-47-2); and
- N*-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-4-methoxy-3-methylbenzenesulfonamide (i.e. CAS RN 1783136-48-0).
- 33) Another embodiment relates to compounds according to embodiment 1), which are selected from the following compounds
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)pyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide; and

- 5 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-6-methylpyridine-3-sulfonamide.

Based on the dependencies of the different embodiments 1) to 30) as disclosed hereinabove, the following embodiments are thus possible and intended, and herewith specifically disclosed in individualized form:

- 2+1, 3+1, 3+2+1, 4+1, 4+2+1, 15+1, 15+2+1, 16+1, 16+2+1, 17+1, 17+2+1, 17+3+1, 17+3+2+1, 17+4+1, 17+4+2+1, 18+1,
 10 18+2+1, 18+3+1, 18+3+2+1, 18+4+1, 18+4+2+1, 19+1, 19+2+1, 19+3+1, 19+3+2+1, 19+4+1, 19+4+2+1, 20+1, 20+2+1, 20+3+1,
 20+3+2+1, 20+4+1, 20+4+2+1, 20+15+1, 20+15+2+1, 20+16+1, 20+16+2+1, 20+17+1, 20+17+2+1, 20+17+3+1, 20+17+3+2+1,
 20+17+4+1, 20+17+4+2+1, 20+18+1, 20+18+2+1, 20+18+3+1, 20+18+3+2+1, 20+18+4+1, 20+18+4+2+1, 21+1, 21+2+1,
 21+3+1, 21+3+2+1, 21+4+1, 21+4+2+1, 22+15+1, 22+15+2+1, 22+16+1, 22+16+2+1, 22+17+1, 22+17+2+1, 22+17+3+1,
 22+17+3+2+1, 22+17+4+1, 22+17+4+2+1, 22+18+1, 22+18+2+1, 22+18+3+1, 22+18+3+2+1, 22+18+4+1, 22+18+4+2+1,
 15 22+19+1, 22+19+2+1, 22+19+3+1, 22+19+3+2+1, 22+19+4+1, 22+19+4+2+1, 22+20+1, 22+20+2+1, 22+20+3+1, 22+20+3+2+1,
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 22+20+17+3+1, 22+20+17+3+2+1, 22+20+17+4+1, 22+20+17+4+2+1, 22+20+18+1, 22+20+18+2+1, 22+20+18+3+1,
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 22+21+4+2+1, 23+15+1, 23+15+2+1, 23+16+1, 23+16+2+1, 23+17+1, 23+17+2+1, 23+17+3+1, 23+17+3+2+1, 23+17+4+1,
 20 23+17+4+2+1, 23+18+1, 23+18+2+1, 23+18+3+1, 23+18+3+2+1, 23+18+4+1, 23+18+4+2+1, 23+19+1, 23+19+2+1, 23+19+3+1,
 23+19+3+2+1, 23+19+4+1, 23+19+4+2+1, 23+20+1, 23+20+2+1, 23+20+3+1, 23+20+3+2+1, 23+20+4+1, 23+20+4+2+1,
 23+20+15+1, 23+20+15+2+1, 23+20+16+1, 23+20+16+2+1, 23+20+17+1, 23+20+17+2+1, 23+20+17+3+1, 23+20+17+3+2+1,
 23+20+17+4+1, 23+20+17+4+2+1, 23+20+18+1, 23+20+18+2+1, 23+20+18+3+1, 23+20+18+3+2+1, 23+20+18+4+1,
 23+20+18+4+2+1, 23+21+1, 23+21+2+1, 23+21+3+1, 23+21+3+2+1, 23+21+4+1, 23+21+4+2+1, 24+15+1, 24+15+2+1,
 25 24+16+1, 24+16+2+1, 24+17+1, 24+17+2+1, 24+17+3+1, 24+17+3+2+1, 24+17+4+1, 24+17+4+2+1, 24+18+1, 24+18+2+1,
 24+18+3+1, 24+18+3+2+1, 24+18+4+1, 24+18+4+2+1, 24+19+1, 24+19+2+1, 24+19+3+1, 24+19+3+2+1, 24+19+4+1,
 24+19+4+2+1, 24+20+1, 24+20+2+1, 24+20+3+1, 24+20+3+2+1, 24+20+4+1, 24+20+4+2+1, 24+20+15+1, 24+20+15+2+1,
 24+20+16+1, 24+20+16+2+1, 24+20+17+1, 24+20+17+2+1, 24+20+17+3+1, 24+20+17+3+2+1, 24+20+17+4+1,
 24+20+17+4+2+1, 24+20+18+1, 24+20+18+2+1, 24+20+18+3+1, 24+20+18+3+2+1, 24+20+18+4+1, 24+20+18+4+2+1,
 30 24+21+1, 24+21+2+1, 24+21+3+1, 24+21+3+2+1, 24+21+4+1, or 24+21+4+2+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, “18+3+2+1,” for example refers to embodiment 18) depending on embodiment 3), depending on embodiment 2), depending on embodiment 1), i.e. embodiment “18+3+2+1” corresponds to the compounds of
 35 Formula (I) according to embodiment 1) further limited by all the features of the embodiments 2), 3), and 18).

34) Another aspect relates to a compound of Formula (I) according to any one of embodiments 1) to 25), which is a radiolabeled compound, wherein

- **Ar** is as defined in embodiments 1) to 25), wherein **Ar** independently is mono-, di-, or tri-substituted (notably mono-, or di-substituted), wherein one substituent represents a radioactive isotope of fluorine (especially selected from a group consisting of fluorine-18), wherein the rest of the substituents of **Ar**, if any, independently is/are as defined in embodiments 1) to 25); **R¹** is as defined in embodiments 1) to 25); and **R²** is as defined in any one of embodiments 1) to 25);
- **Ar** is as defined in embodiments 1) to 25), wherein **Ar** independently is mono-, di-, or tri-substituted (notably mono-, or di-substituted), wherein one substituent represents a radioactive isotope of iodine (especially selected from iodine-123, iodine-124, iodine-125, or iodine-131), wherein the rest of the substituents of **Ar**, if any, independently is/are as defined in embodiments 1) to 25); **R¹** is as defined in embodiments 1) to 25); and **R²** is as defined in any one of embodiments 1) to 25); or
- **Ar** is as defined in embodiments 1) to 25), wherein **Ar** independently is unsubstituted, mono-, di-, or tri-substituted (notably unsubstituted, mono-, or di-substituted), wherein the substituent independently is/are as defined in embodiment 1) to 25); **R¹** is as defined in embodiments 1) to 25); and **R²** represents a radioactive isotope of fluorine (especially selected from fluorine-18).

The term “radioactive isotope” (also known as “radionuclide”, “radioisotope”, “radioactive label”, or “label”), as used in the context of the present invention, is a radioactive nuclide useful in radiopharmaceutical therapy (RPT) or diagnosis such as medical imaging by positron emission tomography (PET), single-photon emission computed tomography (SPECT), autoradiography including drug or substrate tissue distribution assays, and the like. It is understood that a radiolabeled compound may represent a mixture of unmodified (non-radioactive or “cold”) compound and a compound comprising said radioactive isotope (modified or “hot” compound).

With regard to the radiolabeled compounds, when a substituent of the molecule is designated as representing a radioactive isotope, it is understood that the abundance of said radioactive isotope at that position is substantially greater than the natural abundance of the same radioactive isotope, that is this substituent is substantially enriched of said radioactive isotope allowing for sufficient therapeutic radiopharmaceutical activity or for a detectable signal in PET, SPECT, autoradiography, and the like.

35) One embodiment relates to a compound according to embodiment 34), which is a radiolabeled compound, wherein **Ar** represents a 6-membered heteroaryl, wherein said 6-membered heteroaryl is selected from pyridin-3-yl, wherein said pyridin-3-yl is mono-, or di-substituted in position(s) 2 and/or 5 and/or 6 with regard to the nitrogen atom of said pyridin-3-yl; wherein one substituent represents fluorine-18 and the other substituent, if present, represents methyl; **R¹** represents C₂₋₄-alkyl (notably ethyl, n-propyl, isopropyl, tert-butyl, or sec-butyl; notably isopropyl), cyclopropyl, or 2,2,2-trifluoro-1-methyl-ethyl [especially **R¹** represents isopropyl or 2,2,2-trifluoro-1-methyl-ethyl]; and **R²** represents hydrogen.

36) One embodiment relates to compounds of Formula (I) according to embodiment 34), which is a radiolabeled compound, wherein said compound is selected from

N-(cis-3-(2-amino-6-(tert-butylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-6-methylpyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(tert-butylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-pyridine-3-sulfonamide;

- N-(cis-3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-pyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(((S)-sec-butyl)amino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-pyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(((R)-sec-butyl)amino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-pyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-6-methylpyridine-3-sulfonamide;
5 N-(cis-3-(2-amino-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-2-methylpyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-5-methylpyridine-3-sulfonamide;
10 N-(cis-3-(2-amino-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-pyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-6-methylpyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-5,6-dimethylpyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-pyridine-3-sulfonamide;
15 N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-2-methylpyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-6-methylpyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-5-methylpyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-5-methylpyridine-3-sulfonamide;
20 N-(cis-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-pyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-pyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-6-fluoropyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-(fluoro-¹⁸F)-pyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-pyridine-3-sulfonamide;
25 N-(cis-3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-benzenesulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-benzenesulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-4-methoxybenzenesulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-4-fluorobenzenesulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluoro-4-(fluoro-¹⁸F)-benzenesulfonamide;
30 N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-5-fluorobenzenesulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-5-(fluoro-¹⁸F)-benzenesulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-(fluoro-¹⁸F)-pyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-(fluoro-¹⁸F)-thiophene-2-sulfonamide;
N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-(fluoro-¹⁸F)-6-methylpyridine-3-sulfonamide;
35 N-(cis-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-(fluoro-¹⁸F)-2-methylpyridine-3-sulfonamide;
N-(cis-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-benzenesulfonamide;
N-(cis-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-5-(fluoro-¹⁸F)-pyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-benzenesulfonamide;

N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5-(fluoro-¹⁸F)-2-methylpyridine-3-sulfonamide;

5 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5-(fluoro-¹⁸F)-6-methylpyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-4-iodobenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-4-

10 iodobenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-benzenesulfonamide;

N-(*cis*-3-(2-amino-6-(*tert*-butylamino)pyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-benzenesulfonamide;

N-(*cis*-3-(2-amino-6-(*sec*-butylamino)pyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-benzenesulfonamide;

N-(*cis*-3-(2-amino-6-((1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-benzenesulfonamide;

15 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-benzenesulfonamide;

N-(*cis*-3-(2-amino-6-(ethylamino)-5-fluoropyrimidin-4-yl)cyclobutyl)-3-(fluoro-¹⁸F)-benzenesulfonamide;

N-(*cis*-3-(2-amino-6-(ethylamino)-5-(fluoro-¹⁸F)-pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-pyridine-3-sulfonamide;

20 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-pyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-5-methylpyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-6-methylpyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-2-methylpyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-pyridine-3-

25 sulfonamide;

N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-5-methylpyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-2-methylpyridine-3-sulfonamide; and

30 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-6-methylpyridine-3-sulfonamide.

37) One embodiment relates to compounds of Formula (I) according to embodiment 34), which is a radiolabeled compound, wherein said compound is selected from

N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-pyridine-3-sulfonamide;

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N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-pyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-5-methylpyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-6-methylpyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-2-methylpyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-pyridine-3-sulfonamide;

5 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-5-methylpyridine-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro-¹⁸F)-2-methylpyridine-3-sulfonamide; and

10 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro-¹⁸F)-6-methylpyridine-3-sulfonamide;

38) Another aspect relates to a pharmaceutical composition comprising a compound of Formula (I) according to any one of embodiments 34) to 37), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

15 39) Another aspect relates to a compound of Formula (I) according to any one of embodiments 34) to 37), which is a radiolabeled compound, or a pharmaceutically acceptable salt thereof, for use as a medicament.

40) Another aspect relates to a compound of Formula (I) according to embodiment 34), which is a radiolabeled compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer by radiopharmaceutical therapy, wherein said compound, or a pharmaceutically acceptable salt thereof, comprise a radioactive isotope of iodine (especially iodine-125 or iodine-131).

20 41) Another aspect relates to a compound of Formula (I) according to any one of embodiments 34) to 37), which is a radiolabeled compound, or a pharmaceutically acceptable salt thereof, for use in the diagnosis of cancer (e.g. by medical imaging such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), or autoradiography including drug or substrate tissue distribution assays).

25 42) Another aspect relates to a compound of Formula (I) according to any one of embodiments 34) to 37), which is a radiolabeled compound, or a pharmaceutically acceptable salt thereof, for use in diagnostic imaging of CCR8 receptors in humans, said method comprising:

(a) administering to the human a detectable quantity of a compound according to any one of embodiments 34) to 37), which is a radiolabeled compound, (especially wherein said compound comprises fluorine-18), or of a pharmaceutically acceptable salt thereof; and

30 (b) detecting said compound when associated with CCR8 receptors.

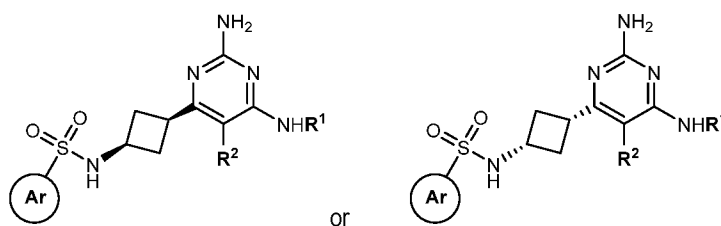
A detectable quantity is a quantity of a compound which is required to render the compound detectable in the human body or in a sample as the case may be by the detection method chosen e.g. PET. The amount of compound to be introduced into a patient/sample in order to provide for detection can be determined by those skilled in the art.

35 The present invention also includes ²H (deuterium) labelled compounds of Formula (I), 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

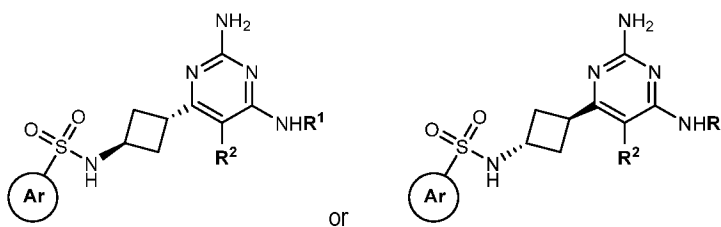
atomic number but an atomic mass different from the atomic mass usually found in nature. ^2H (deuterium) labelled compounds of Formula (I) and salts thereof are within the scope of the present invention. Substitution of hydrogen with the heavier isotope ^2H (deuterium) may lead to greater metabolic stability, resulting e.g. in increased *in-vivo* half-life and/or reduced dosage requirements, and/or may lead to a modified metabolism pathway, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of Formula (I) are not isotopically labelled, or they are labelled only with one or more deuterium atoms. In a sub-embodiment, the compounds of formula (I) are not isotopically labelled at all. Isotopically labelled compounds of Formula (I) may be prepared in analogy to the methods described hereinafter but using the appropriate isotopic variation of suitable reagents or starting materials.

The invention 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 42), under consideration of their respective dependencies; to pharmaceutically acceptable salts thereof; and to the use of such compounds as medicaments especially in the treatment of diseases or disorders where CCR8 receptors are involved as described hereinbelow.

For avoidance of doubt, compounds designated as "cis" are compounds that may be represented by any one of the following formulas:



Likewise, compounds designated as "trans" are compounds that may be represented by any one of the following formulas:



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, pharmaceutical composition, disease or the like.

Any reference to compounds of Formula (I) according to embodiments 1) to 42) 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 Pharmaceutical 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 Formula (I), as defined in any one of embodiments 1) to 42), 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.

The compounds of Formula (I) may encompass compounds with one or more asymmetric centers, such as one or more asymmetric carbon atoms, which may be present in (R)- as well as (S)-configuration. The compounds of Formula (I) 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 Formula (I) may thus be present as mixtures of stereoisomers or preferably in stereoisomerically enriched form, especially as essentially 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 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 compounds of Formula (I) according to embodiments 1) to 37) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral (such especially oral) or parenteral administration (subcutaneous, intraperitoneal, intravenous, intradermal, intramuscular, topical, 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.

One embodiment of the present invention relates to a pharmaceutical composition comprising a compound of Formula (I) according to any one of embodiments 1) to 37), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier/excipient.

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 °C and 80 °C, this means that the end points 40 °C and 80 °C 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" (or alternatively the term "around") 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 10 °C to Y plus 10 °C, and preferably to an interval extending from Y minus 5 °C to Y plus 5 °C.

The compounds of Formula (I) of the present invention may be useful as single therapeutic agents or in combination with one or more therapeutic agents and/or therapies, for the prevention / prophylaxis or treatment of diseases or disorders relating to the CCR8 receptor or its ligands, which are diseases or disorders relating to a dysfunction of the CCR8 receptor, or dysfunction of ligands signaling through the CCR8 (i.e. CCL1, CCL8, CCL16, and/or CCL18, especially CCL1), or dysfunction of CCR8 ligands signaling through their other receptors (i.e. CCL8, CCL16, and/or CCL18).

The compounds of Formula (I) of the present invention may be useful as single therapeutic agents or in combination with one or more therapeutic agents and/or therapies, for the prevention / prophylaxis or treatment of diseases or disorders involving CCR8 and/or CCL1 and/or CCL18 mediated metastasis, chemotaxis, cell adhesion, trans-endothelial migration, cell proliferation and/or survival; especially in regulating the process of metastasis invasion e.g. in melanoma or bladder cancer patients.

The compounds of Formula (I) of the present invention may be useful as single therapeutic agents or in combination with one or more therapeutic agents and/or therapies, for the prevention / prophylaxis or treatment of diseases or disorders, where CCR8 receptors are involved i.e. diseases or disorders ameliorated by modulating, especially by antagonizing CCR8 receptors; wherein such diseases or disorders are defined as cancer.

The term "cancer" as used hereinabove and hereinbelow includes 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.

The term "cancer" as used hereinabove and hereinbelow notably refers to 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; gastro-esophageal junction cancer; esophageal cancer; Kaposi sarcoma; leukemias including acute myeloid leukemia, chronic myeloid leukemia, adult T-cell leukemia, acute lymphoblastic leukemia, and chronic lymphocytic leukemia; leukemic phase of lymphoma; 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 "cancer" as used hereinabove and hereinbelow especially refers to oral squamous cell carcinoma; head and neck squamous cell carcinoma; liver cancer including hepatocellular carcinoma; cholangiosarcoma including extrahepatic cholangiosarcoma; gastrointestinal stromal tumors; colorectal cancer; lung cancer including non-small cell lung cancer; bladder cancer; kidney cancer; breast cancer; lymphoma including T cell lymphoma, cutaneous T cell lymphoma, and systemic ALK-negative anaplastic large cell lymphoma; endometrial tumors; Kaposi sarcoma; melanoma; and basal cell carcinoma.

The term "cancer" as used hereinabove and hereinbelow also refers to cancer types infiltrated with intratumoral regulatory T cells (Tregs) expressing CCR8.

The term "cancer" as used hereinabove and hereinbelow particularly refers to gastrointestinal cancer, colorectal cancer, non-small cell lung cancer, lung squamous cell carcinoma, liver cancer, bladder cancer, kidney cancer, breast cancer, melanoma, oral squamous cell carcinoma, Kaposi sarcoma, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma, and pancreatic ductal adenocarcinoma.

The term "cancer" as used hereinabove and hereinbelow also refers to solid tumors such as renal cancer, breast cancer including triple-negative breast cancer, stomach cancer, colorectal cancer, ovarian cancer, head and neck cancer, melanoma, and pancreatic cancer.

The compounds of Formula (I) of the present invention comprising a radioactive isotope may be useful in radiopharmaceutical therapy (RPT) of cancer, wherein cancer is as defined hereinabove.

The compounds of Formula (I) of the present invention comprising a radioactive isotope may be useful in the diagnosis e.g. in medical imaging such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) of cancer, wherein cancer is as defined hereinabove.

The compounds of Formula (I) of the present invention may be useful as single therapeutic agents or in combination with one or more further therapeutic agents and/or further therapies, for the prevention / prophylaxis or treatment of diseases or disorders, where CCR8 receptors are involved i.e. diseases or disorders ameliorated by modulating, especially by antagonizing CCR8 receptors; wherein such diseases or disorders are defined as atopic diseases; fibrotic diseases; neuropathic pain; sepsis; septic peritonitis; infections associated with immune suppression including infections resulting from burn injury; chronic obstructive pulmonary disease; organ transplantation including allogeneic kidney transplantation; peritoneal adhesions; pathological bondings of serosal membranes related to surgery or inflammation; and autoimmune encephalomyelitis. Notably, atopic diseases; fibrotic diseases; and neuropathic pain. Especially, fibrotic diseases including fibrosis.

The term “atopic diseases”, as used herein, includes all sorts of type 2 inflammatory diseases and immunoglobulin E (IgE) mediated diseases such as atopic dermatitis, allergic enteritis, allergic asthma (e.g. fungal-allergic asthma), allergic rhinitis, allergic conjunctivitis, IgE-mediated drug allergy, food allergy, insect bites, urticaria, angioedema, and anaphylactic shock. Notably, the term refers to atopic dermatitis, allergic enteritis, allergic asthma and (e.g. fungal-allergic asthma).

The term “fibrotic diseases”, as used herein, includes all sorts of diseases defined by deleterious accumulation of extracellular matrix components such as collagen and fibronectin at sites of inflammation or tissue damage that can lead to permanent scarring and/or organ dysfunction. The term “fibrotic diseases” may be referred to “fibrosis”. Said term comprises, among others, liver fibrosis, pulmonary fibrosis, fibrosis associated with IgG4-related disease (e.g. salivary gland fibrosis and sclerosing cholangitis), systemic sclerosis, skin fibrosis including skin fibrosis associated with human chronic graft-versus-host disease, and fibrosis associated with organ transplantation including fibrosis associated with allogeneic kidney transplantation.

The term “pulmonary fibrosis”, as used herein, includes all sorts of fibrotic disorders affecting the lungs, e.g. idiopathic pulmonary fibrosis and pulmonary fibrosis associated with human chronic graft-versus-host disease, and optionally non-idiopathic interstitial pulmonary fibrosis/interstitial lung disease.

The term “liver fibrosis”, as used herein, includes all sorts of fibrotic disorders affecting the liver, including those related to chronic viral liver infections such as Hepatitis C and Hepatitis B, chronic alcohol use, nonalcoholic steatohepatitis, chronic cholestatic disorders such as primary biliary cirrhosis and primary sclerosis cholangitis, and autoimmune hepatitis.

The term “neuropathic pain”, as used herein, refers to both central and peripheral neuropathic pain and includes all sorts of conditions affecting the somatosensory system that result in painful sensations such as dysesthesia and allodynia, including those caused by spinal cord injury, multiple sclerosis, all types of diabetes mellitus, cancer and cancer treatments as defined herein, metabolic disorders, herpes zoster infection, human immunodeficiency virus infection, nutritional deficiencies, exposure to toxins, autoimmune disorders, and physical trauma.

The compounds of Formula (I), or a pharmaceutically acceptable salt thereof, may be useful for the treatment and/or prevention of neuropathic pain, wherein said compounds or a pharmaceutically acceptable salt thereof are used as a single therapeutic agent or in combination with one or more opioid and/or one or more non-opioid analgesics.

5 The compounds of Formula (I), or a pharmaceutically acceptable salt thereof, may be useful for potentiating the analgesic effects of opioids such as methadone, oxycodone, hydrocodone, and the like.

The compounds of Formula (I), or a pharmaceutically acceptable salt thereof, may be useful in the treatment and/or prevention of fibrotic diseases (especially liver fibrosis), wherein said compounds or a pharmaceutically acceptable salt thereof are used as a single therapeutic agent or in combination with one or more further treatment or therapy, wherein said further treatment or therapy is aimed at the treatment and/or prevention of the underlying cause of the fibrotic disease (especially liver fibrosis).

10 When used for the prevention / prophylaxis or treatment of a cancer, such use includes use of the present compounds as single therapeutic agents and their use in combination with one or more chemotherapy agents and / or radiotherapy and / or targeted therapy (especially in combination with targeted therapy).

The terms "radiotherapy" or "radiation therapy" or "radiation oncology", refer to the medical use of ionizing radiation in the prevention (adjuvant therapy) and / or treatment of cancer, including external and internal radiotherapy.

15 The term "targeted therapy" refers to the prevention / prophylaxis (adjuvant therapy) and / or treatment of cancer with one or more anti-neoplastic agents such as small molecules or antibodies which act on specific types of cancer cells or stromal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells. Other types of targeted therapies help the immune system kill cancer cells (immunotherapies); or deliver toxic substances directly to cancer cells and kill them. An example of a targeted therapy which is in particular suitable to be combined with the compounds of the present invention is immunotherapy, especially immunotherapy targeting the programmed cell death receptor 1 (PD-1 receptor) or its ligand PD-L1 (Feig C et al, PNAS 2013).

20 Immunotherapy further refers to (i) an agonist of a stimulatory (including a co-stimulatory) receptor or (ii) an antagonist of an inhibitory (including a co-inhibitory) signal on T cells, both of which result in amplifying antigen-specific T cell responses (often referred to as immune checkpoint regulators). Certain of the stimulatory and inhibitory molecules are members of the immunoglobulin super family (IgSF). One important family of membrane-bound ligands that bind to co-stimulatory or co-inhibitory receptors is the B7 family, which includes B7-1, B7-2, B7-H1 (PD-L1), B7-DC (PD-L2), B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. Another family of membrane bound ligands that bind to co-stimulatory or co-inhibitory receptors is the TNF family of molecules that bind to cognate TNF receptor family members, which includes CD40 and CD40L, OX-40, OX-40L, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, TACI, APRIL, BCMA, LT α R, LIGHT, DcR3, HVEM, VEGI/TLIA, TRAMP/DR3, EDAR, EDAI, XEDAR, EDA2, TNFR1, Lymphotoxin α /TNF β , TNFR2, TNF α , LTPR, Lymphotoxin α 1p2, FAS, FASL, RELT, DR6, TROY, NGFR.

35 When used in combination with the compounds of Formula (I), the term "targeted therapy" especially refers to agents such as:

- a) Epidermal growth factor receptor (EGFR) inhibitors or blocking antibodies (such as Gefitinib, Erlotinib, Afatinib, Icotinib, Lapatinib, Panitumumab, Neratinib, Osimertinib, Dacomitinib, Almonertinib, Tucatinib, Zalutumumab, Nimotuzumab, Matuzumab, Cetuximab), as well as trastuzumab (HERCEPTIN);
- b) RAS/RAF/MEK pathway inhibitors (such as Vemurafenib, Sorafenib, Dabrafenib, GDC-0879, PLX-4720, Encorafenib (LGX818), RG7304, Trametinib (GSK1120212), Cobimetinib (GDC-0973/XL518), Binimetinib (MEK162, ARRY-162), Selumetinib (AZD6244), Sotorasib, Adagrasib, as well as various mutant KRAS-specific, pan RAS, SOS1, and SHP2 inhibitors (Punekar et al., Nature Rev Clin Oncology, 19(10):637-655));
- c) Janus kinase (JAK) inhibitors (such as Ruxolitinib, Itacitinib, Momelotinib, Fedratinib);
- d) Aromatase inhibitors (such as Exemestane, Letrozole, Anastrozole, Vorozole, Formestane, Fadrozole);
- e) Signal transduction inhibitors (STI) that selectively inhibit one or more vital steps in signaling pathways in the normal function of cancer cells, thereby leading to apoptosis, especially (i) bcr/abl kinase inhibitors (such as STI 571 (GLEEVEC®), Dasatinib, Ponatinib, Imatinib, Nilotinib, Radotinib); (ii) inhibitors of Akt family kinases or the Akt pathway (such as Sirolimus, Everolimus, Temsirolimus); (iii) cell cycle kinase inhibitors (such as Palbociclib, Ribociclib, Abemaciclib); (iv) phosphatidyl inositol kinase inhibitors (such as Copanlisib, Duvelisib, Idelalisib, Leniolisib, Alpelisib, Umbralisib); (v) ALK inhibitors (such as Crizotinib, Ceritinib, Alectinib, Lorlatinib); (vi) BTK inhibitors (such as Ibrutinib, Acalabrutinib, Zanubrutinib); (vii) IDH inhibitors (such as Enasidenib, Ivosidenib); (viii) RET inhibitors (such as Selpercatinib); (ix) BCL-2 inhibitors (such as Venetoclax); or (x) c-MET inhibitors (such as Capmatinib, Tepotinib);
- f) Angiogenesis inhibitors, especially VEGF signalling inhibitors (such as Bevacuzimab (Avastin), Ramucirumab, Sorafenib, Axitinib);
- g) Poly-ADP-Ribose-Polymerase (PARP) inhibitors (such as Olaparib, Niraparib, Rucaparib, Talazoparib);
- h) Proteasome inhibitors (such as Bortezomib, Carfilzomib, Ixazomib);
- i) HDAC inhibitors (such as Vorinostat, Romidepsin, Belinostat, Panobinostat, Tucidinostat);
- j) EZH2 inhibitors (such as Tazemetostat);
- k) Immune Checkpoint inhibitors (for example: anti-PD1 antibodies such as Pembrolizumab (Lambrolizumab, MK-3475), Nivolumab, Pidilizumab (CT-011), AMP-514/MED10680, PDR001, SHR-1210, REGN2810, BGBA317, PF-06801591, MGA-012, TSR042, JS-001, BCD100, IBI-308, BI-754091, Toripalimab; fusion proteins targeting PD-1 such as AMP-224; small molecule anti-PD1 agents such as compounds disclosed in WO2015/033299, WO2015/044900 and WO2015/034820; anti-PD1L antibodies, such as BMS-936559, Atezolizumab (MPDL3280A, RG7446), Avelumab (MSB0010718C), Durvalumab (MEDI4736); anti-PDL2 antibodies, such as AMP224; anti-CTLA-4 antibodies, such as Ipilimumab, Tremelimumab; anti-Lymphocyte-activation gene 3 (LAG-3) antibodies such as Relatlimab (BMS-986016), IMP701, IMP731, MK-4280, ImmuFact IMP321; anti-T cell immunoglobulin mucin-3 (TIM-3) antibodies, such as MBG453, TSR-022; anti-T cell immunoreceptor with Ig and ITIM domains (TIGIT) antibodies, such as RG6058 (anti-TIGIT, MTIG7192A); anti-Killer-cell immunoglobulin-like receptors (KIR) antibodies such as Lirilumab (IPH2102/BMS-986015); antagonists of Galectins (such as of Galectin-1, Galectin-9); anti-B and T lymphocyte attenuator (BTLA) antibodies such as JS004;

- l) Vaccination approaches (such as dendritic cell vaccination, DNA, RNA, peptide or protein vaccination (for example with gp100 peptide or MAGE-A3 peptide));
- m) Re-introduction of patient derived or allogenic (non-self) cancer cells genetically modified to secrete immunomodulatory factors such as granulocyte monocyte colony stimulating factor (GM-CSF), gene-transfected tumor cell vaccine (GVAX) or Fms-related tyrosine kinase 3 (Flt-3) ligand gene-transfected tumor cell vaccine (FVAX), or Toll like receptor enhanced GM-CSF tumor based vaccine (TEGVAX);
- n) T-cell based adoptive immunotherapies, including chimeric antigen receptor (CAR) engineered T-cells (such as CTL019);
- o) Cytokine or immunocytokine based therapy (such as Interferon alpha, interferon beta, interferon gamma, interleukin 2, interleukin 6, interleukin 10, interleukin 15, TGF- β);
- p) Toll-like receptor (TLR) agonists (such as resiquimod, imiquimod, glucopyranosyl lipid A, CpG oligodesoxynucleotides);
- q) Thalidomide analogues (such as Lenalidomide, Pomalidomide);
- r) Indoleamin-2,3-Dioxygenase (IDO) and/or Tryptophane-2,3-Dioxygenase (TDO) inhibitors (such as RG6078 / NLG919 / GDC-0919; Indoximod / 1MT (1-methyltryptophan), INCB024360 / Epacadostat, PF-06840003 (EOS200271), F001287);
- s) Activators of T-cell co-stimulatory receptors (for example anti-CD137/4-1BB antibodies, such as BMS-663513 / Urelumab, Utomilumab (PF-05082566), and second generation 4-1BB agonistic drugs (Claus et al., MABS 2023, VOL. 15(1), 2167189)); anti-OX40/CD134 (Tumor necrosis factor receptor superfamily, member 4) antibodies (including agonist antibodies) and fusion proteins, such as RG7888 (MOXR0916), 9B12, MEDI6469, GSK3174998, MEDI6383, MEDI0562), anti-OX40-Ligand/CD252; anti-glucocorticoid-induced TNFR family related gene (GITR) antibodies and fusion proteins (such as TRX518, MEDI1873, MK-4166, BMS-986156, BMS-986153); anti-CD40 (TNF receptor superfamily member 5) antibodies (such as Dacetuzumab (SGN-40), HCD122, CP-870,893, RG7876, ADC-1013, APX005M, SEA-CD40); anti-CD40-Ligand antibodies (such as BG9588); anti-CD27 antibodies (such as Varlilumab); anti-CD28 antibodies; anti-ICOS antibodies;
- t) Molecules binding a tumor specific antigen as well as a T-cell surface marker such as bispecific antibodies (for example RG7802 targeting CEA and CD3) or antibody fragments; antibody mimetic proteins such as designed ankyrin repeat proteins (DARPINS), bispecific T-cell engager (BITE, for example Blinatumomab, Amivantanab, Tebentafusp, and more in clinical development (Wei et al., Frontiers in Immunology, 2022,13:1035276));
- u) Antibodies or small molecular weight inhibitors targeting colony-stimulating factor-1 receptor (CSF-1R) (for example Emactuzumab (RG7155), Cabiralizumab (FPA-008), PLX3397);
- v) Agents targeting immune cell check points on natural killer cells such as antibodies against Killer-cell immunoglobulin-like receptors (KIR) for example Lirilumab (IPH2102/BMS-986015);
- w) Agents targeting the Adenosine receptors or the ectonucleases CD39 and CD73 that convert ATP to Adenosine, such as MEDI9447 (anti-CD73 antibody), PBF-509, CPI-444 (Adenosine A2a receptor antagonist);

- x) Antagonists of chemokine receptors including CCR2 or CCR4;
- y) Agents that deplete or inhibit T regulatory cells (for example anti-CD25 monoclonal antibodies (such as Daclizumab) or by *ex vivo* anti-CD25 bead depletion) or that reverse/prevent T cell anergy or exhaustion
- z) Antibody or biologic-based disease-modifying antirheumatic drugs (DMARDS) useful for the treatment of autoimmune diseases such as antibodies (including modified antibodies); biologics targeting CD20 (for example Rituximab), CD3 (for example Teplizumab), TNF alpha (for example Etanercept), IFN alpha (for example Anifrolumab), CD80 or CD86 (for example Abatacept), VLA-4 (for example Natalizumab), IL-1 (for example Anakinra), IL-6 (for example Sarilumab), IL-17 (for example Secukinumab), IL-23 (for example Guselkumab), or IL12/23 (for example Ustekinumab); small molecule DMARDS such as methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, or Janus kinase (JAK) inhibitors;
- bb) Glucocorticoids;
- cc) Antibody-drug conjugates, such as Mirvetuximab soravtansine, Tisotumab vedotin-tftv, Loncastuximab tesirine-lpyl, Belantamab mafodotin-blmf, Sacituzumab govitecan, Trastuzumab deruxtecan, Enfortumab vedotin, Polatuzumab vedotin-piiq, Moxetumomab pasudotox, Inotuzumab ozogamicin, Trastuzumab emtansine, Brentuximab vedotin, or Gemtuzumab ozogamicin;
- dd) Radioligand therapies such as ¹⁷⁷Lu-Lutathera or ¹⁷⁷Lu-PSMA-617.

The term "chemotherapy" refers to the treatment of cancer with one or more cytotoxic anti-neoplastic agents ("cytotoxic chemotherapy agents"). Chemotherapy is often used in conjunction with other cancer treatments, such as radiation therapy or surgery. The term especially refers to conventional chemotherapeutic agents which act by killing cells that divide rapidly, one of the main properties of most cancer cells. Chemotherapy may use one drug at a time (single-agent chemotherapy) or several drugs at once (combination chemotherapy or polychemotherapy). Chemotherapy using drugs that convert to cytotoxic activity only upon light exposure is called photochemotherapy or photodynamic therapy.

The term "cytotoxic chemotherapy agent" or "chemotherapy agent" as used herein refers to an active anti-neoplastic agent inducing apoptosis or necrotic cell death. When used in combination with the compounds of Formula (I), the term especially refers to conventional cytotoxic chemotherapy agents such as:

- a) alkylating agents (for example mechlorethamine, chlorambucil, cyclophosphamide, ifosfamide, streptozocin, carmustine, lomustine, melphalan, busulfan, dacarbazine, temozolomide, thiotepa or altretamine; in particular temozolomide);
- b) platinum drugs (for example cisplatin, carboplatin or oxaliplatin);
- c) antimetabolite drugs (for example 5-fluorouracil, capecitabine, 6-mercaptopurine, methotrexate, gemcitabine, cytarabine, fludarabine or pemetrexed);
- d) anti-tumor antibiotics (for example daunorubicin, doxorubicin, epirubicin, idarubicin, actinomycin-D, bleomycin, mitomycin-C or mitoxantrone);
- e) mitotic inhibitors (for example paclitaxel, docetaxel, ixabepilone, vinblastine, vincristine, vinorelbine, vindesine or estramustine); or
- f) topoisomerase inhibitors (for example etoposide, teniposide, topotecan, irinotecan, diflomotecan or elomotecan).

When used in combination with the compounds of Formula (I) of the present invention, preferred cytotoxic chemotherapy agents are the above-mentioned alkylating agents (notably mechlorethamine, chlorambucil, cyclophosphamide, ifosfamide, streptozocin, carmustine, lomustine, melphalan, busulfan, dacarbazine, 3-methyl-(triazene-1-yl)imidazole-4-carboxamide (MTIC) and prodrugs thereof such as especially temozolomide, thiotepa, altretamine; or pharmaceutically acceptable salts of these compounds; in particular temozolomide); and mitotic inhibitors (notably paclitaxel, docetaxel, ixabepilone, vinblastine, vincristine, vinorelbine, vindesine, estramustine; or pharmaceutically acceptable salts of these compounds; in particular paclitaxel). Most preferred cytotoxic chemotherapy agents to be used in combination with the compounds of formula (I) are those routinely used in the treatment of glioblastoma multiforme, in particular temozolomide. Equally preferred is radiotherapy.

Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms.

- a) Combined modality chemotherapy is the use of drugs with other cancer treatments, such as radiation therapy or surgery.
- b) Induction chemotherapy is the first line treatment of cancer with a chemotherapeutic drug. This type of chemotherapy is used for curative intent.
- 15 c) Consolidation chemotherapy is the given after remission in order to prolong the overall disease-free time and improve overall survival. The drug that is administered is the same as the drug that achieved remission.
- d) Intensification chemotherapy is identical to consolidation chemotherapy but a different drug than the induction chemotherapy is used.
- e) Combination chemotherapy involves treating a patient with a number of different drugs simultaneously. The drugs
20 differ in their mechanism and side effects. The biggest advantage is minimizing the chances of resistance developing to any one agent. Also, the drugs can often be used at lower doses, reducing toxicity.
- f) Neoadjuvant chemotherapy is given prior to a local treatment such as surgery, and is designed to shrink the primary tumor. It is also given to cancers with a high risk of micro-metastatic disease.
- g) Adjuvant chemotherapy is given after a local treatment (radiotherapy or surgery). It can be used when there is little
25 evidence of cancer present, but there is risk of recurrence. It is also useful in killing any cancerous cells that have spread to other parts of the body. These micro-metastases can be treated with adjuvant chemotherapy and can reduce relapse rates caused by these disseminated cells.
- h) Maintenance chemotherapy is a repeated low-dose treatment to prolong remission.
- i) Salvage chemotherapy or palliative chemotherapy is given without curative intent, but simply to decrease tumor
30 load and increase life expectancy. For these regimens, a better toxicity profile is generally expected.

When used in combination with the compounds of Formula (I) of the present invention, preventive or curative forms of chemotherapy (or *mutatis mutandis*: radiotherapy) such as those listed under a), b) c), d), e), and especially g) and / or h) above are preferred.

When used in combination with the compounds of Formula (I) of the present invention, chemotherapy, radiotherapy, EGFR inhibitors, aromatase inhibitors, and immunotherapy are preferred. Immunotherapy such as especially those targeting the programmed cell death receptor 1 (PD-1 receptor) or its ligand PD-L1 i.e. PD1 and/or PDL1 blockade; and/or CTLA4 blockade; and/or TIGIT blockade and/or LAG3 blockade; or other targeted therapies are especially preferred. Most preferred immunotherapy used in combination with the compounds of Formula (I) of the present invention is PD1 and/or PDL1 blockade.

For avoidance of any doubt, if compounds of the present invention are described as useful as single therapeutic agents or in combination with one or more therapeutic agents and/or therapies, for the prevention / prophylaxis or treatment of diseases or disorders, such compounds are likewise suitable for use in the preparation of a medicament for the prevention / prophylaxis or treatment of diseases or disorders.

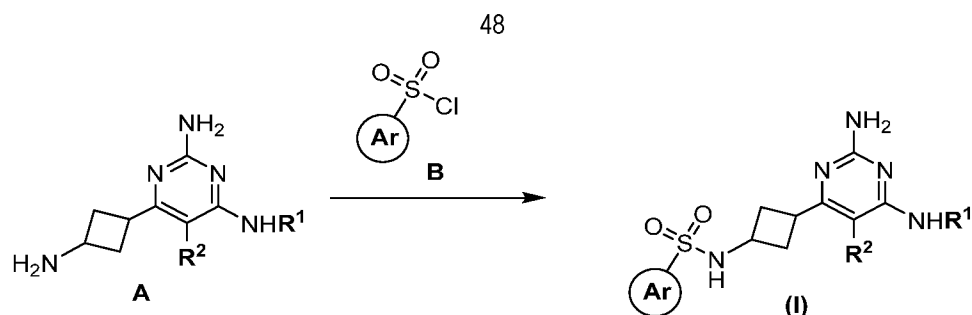
The present invention also relates to a method for the prevention / prophylaxis or treatment of diseases or disorders mentioned hereinabove or hereinbelow, said method comprising administering to a subject in need of such prevention / prophylaxis or treatment a pharmaceutically active amount of a compound of Formula (I) of the present invention, either alone or in combination with other pharmacologically active compounds and/or therapies.

In a preferred embodiment of the present invention, the administered amount is comprised between 1 mg and 1000 mg per day, particularly between 5 mg and 500 mg per day, more particularly between 25 mg and 400 mg per day, especially between 50 mg and 200 mg per day.

Synthesis of compounds of Formula (I)

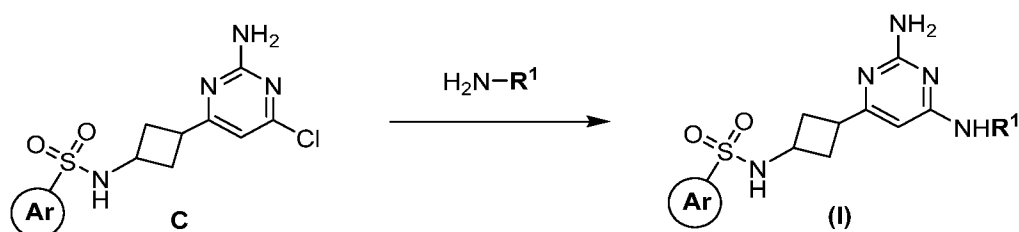
A further aspect of the invention is a process for the preparation of compounds of Formula (I) as defined in any one of embodiments 1) to 37). Compounds of Formula (I) can be prepared from commercially available or well-known starting materials according to the methods described in the experimental part, by analogous methods; or according to the general sequence of reactions outlined below, wherein **Ar**, **R¹**, and **R²** are as defined for Formula (I). 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 optimization procedures. Other abbreviations used herein are explicitly defined or are as defined in the experimental section. In some instances of the preparation described hereinbelow, protecting groups (PG) may be required. 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) and for the purposes of this discussion, it will be assumed that such protecting groups as necessary are in place. The compounds obtained may be converted into salts, especially pharmaceutically acceptable salts thereof in a manner known *per se*.

Generally, compounds of Formula (I) are obtained by reaction of an intermediate of Formula A with a sulfonylchloride of Formula B following a typical sulfonamide coupling reaction scheme in the presence of a base such as TEA or DIPEA in a solvent such as THF, DMF, DCM or a mixture at RT or at elevated temperature (Scheme 1).



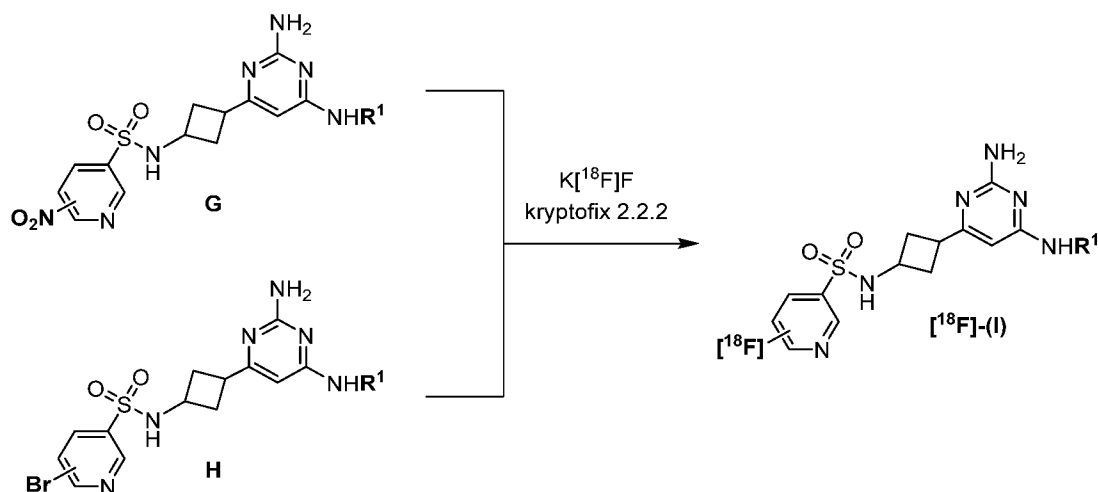
Scheme 1

Alternatively, compounds of Formula (I) are obtained by reaction of an intermediate of Formula C with an amine following a typical S_NAr coupling reaction scheme in the presence of a base such as TEA or DIPEA in a solvent such as THF, DMF, MeOH, EtOH or the like at RT or at elevated temperature (Scheme 2).



Scheme 2

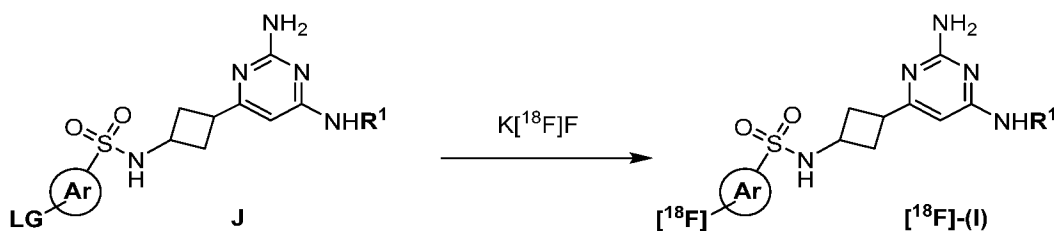
[¹⁸F]-labelled compounds of Formula [¹⁸F]-(I) are obtained by reaction of an intermediate of Formula G or an intermediate of Formula H with K[¹⁸F]F in the presence of kryptofix 2.2.2, potassium oxalate and a base such as K₂CO₃ in a solvent such as DMF or DMSO at RT or at elevated temperature (Scheme 3).



Scheme 3

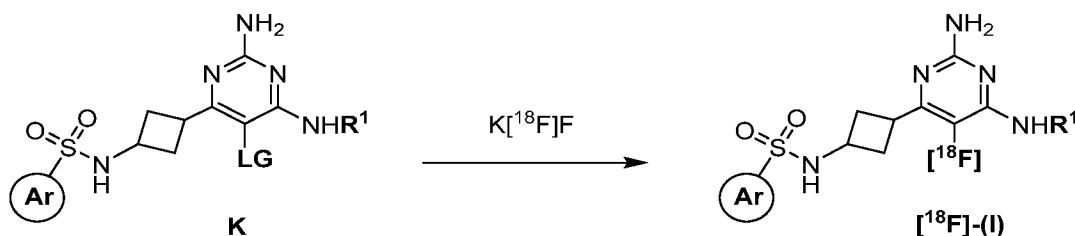
Generally, [¹⁸F]-labelled compounds of Formula [¹⁸F]-(I) are obtained by standard methodologies known to a person skilled in the art (see for example Halder, R. et al. J. Org. Chem. 2021, 86, 13873; or Liu, Z. et al. Frontiers in Chemistry 2022, 10, 883866). For example, compounds of Formula [¹⁸F]-(I) are obtained by reaction of an intermediate of Formula J with K[¹⁸F]F under various conditions to displace a leaving group (LG) such as a boronic acid ($-\text{B}(\text{OH})_2$), boronic ester

(-B(OR)₂), phenol (-OH), iodonium salt (-I⁺R), sulfonium salt (-S⁺R₂), stannane (-SnR₃), halogen (-Cl, -Br, -I) or ammonium salt (-N⁺R₃) in intermediates of Formula J (Scheme 4).



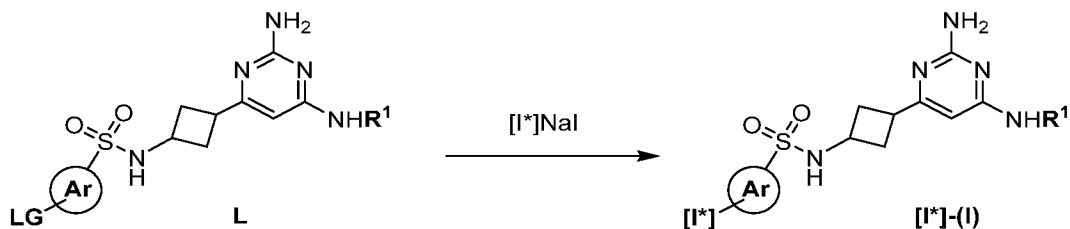
Scheme 4

- 5 Alternatively, [¹⁸F]-labelled compounds of Formula [¹⁸F]-(I) are obtained by reaction of an intermediate of Formula K with K[¹⁸F]F under various conditions to displace a leaving group (LG) (Scheme 5).



Scheme 5

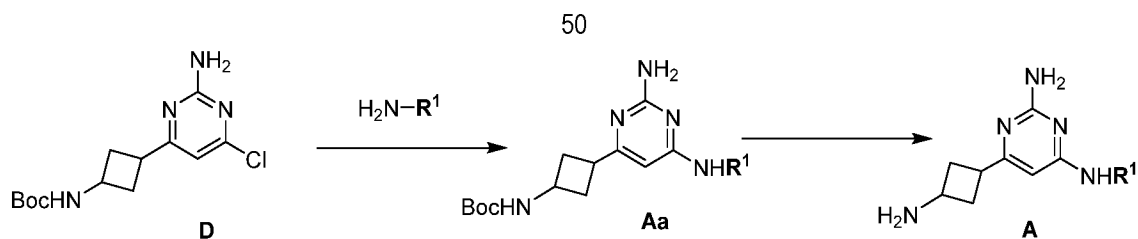
Generally, radioiodine-labelled compounds of Formula [^{I*}]-(*I*) may be obtained by standard methodologies known to a person skilled in the art (see for example Petrov, S. A. et al. Int. J. Mol. Sci. 2022, 23, 137896). The symbol "^{I*}" refers to any one of the radioactive isotopes of iodine suitable for the intended use (therapy or diagnostic). For example, compounds of Formula [^{I*}]-(*I*) may be obtained by reaction of an intermediate of Formula L with radiolabeled [^{I*}]-NaI under various conditions to displace a leaving group (LG) such as a boronic acid (-B(OH)₂), boronic ester (-B(OR)₂), silane (-SiR₃), stannane (-SnR₃), halogen (-Cl, -Br) or diazonium salt (-N₂⁺) in intermediates of Formula L (Scheme 5i).



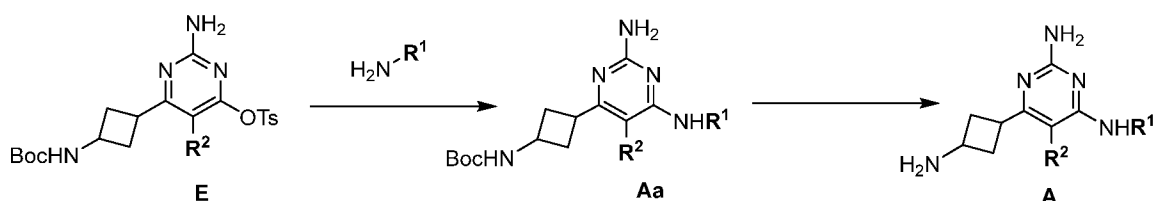
Scheme 5i

Synthesis of intermediates of Formula A

Generally, intermediates of Formula A are obtained by reaction of a chloropyrimidine of Formula D with an amine, followed by reaction of an intermediate of Formula Aa with an acid (Scheme 6). In a typical experiment, intermediate D is stirred at RT or at elevated temperature with an appropriate amine in a solvent such as EtOH, MeOH or the like. The resulting tert-butyl carbamate intermediate of Formula Aa is then treated at RT or at elevated temperature with an acid such as TFA, HCl, H₂SO₄, H₃PO₄ or the like in a solvent such as DCM, MeCN, THF, toluene or the like.

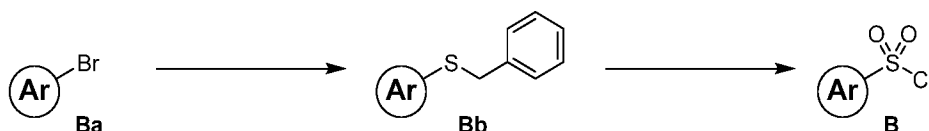


Alternatively, intermediates of Formula A are obtained by reaction of a pyrimidine *p*-toluenesulfonate of Formula E with an amine, followed by reaction of an intermediate of Formula Aa with an acid (Scheme 7). In a typical experiment, intermediate E is stirred at RT or at elevated temperature with an appropriate amine in a solvent such as EtOH, MeOH or the like. The resulting tert-butyl carbamate intermediate of Formula Aa is then treated at RT or at elevated temperature with an acid such as TFA, HCl, H₂SO₄, H₃PO₄ or the like in a solvent such as DCM, MeCN, THF, toluene or the like.



Synthesis of intermediates of Formula B

Generally, intermediates of Formula B are either commercially available or are obtained by reaction of an aryl bromide Ba with benzyl mercaptane followed by oxidation of the thioether intermediate of Formula Bb (Scheme 8). In a typical experiment, an aryl bromide of Formula Ba is stirred at elevated temperature in a solvent such as dioxane or toluene or the like in the presence of benzyl mercaptane, a palladium catalyst such as Pd₂(dba)₃, a phosphine ligand such as XantPhos and a base such as DIPEA or the like. For a typical thioether oxidation, the resulting intermediate Bb is stirred at RT or at elevated temperature in a solvent such as MeCN in the presence of an aqueous solution of HCl and an oxidant such as NCS or the like.

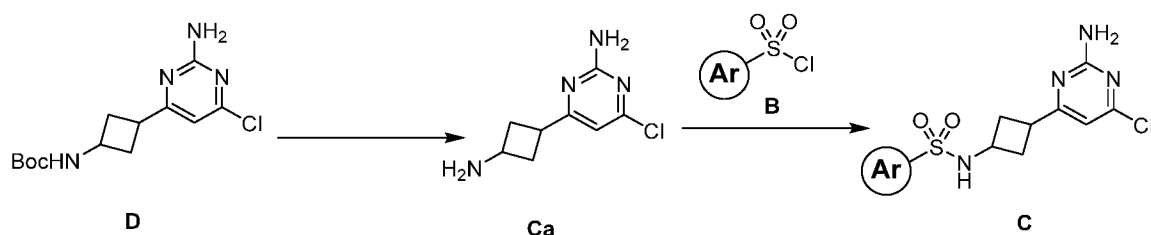


Synthesis of intermediates of Formula C

Generally, intermediates of Formula C are obtained by reaction of a chloropyrimidine of Formula D with an acid followed by reaction of an intermediate of Formula Ca with a sulfonylchloride of Formula B under typical sulfonamide coupling conditions (Scheme 9). In a typical experiment, an intermediate of Formula D is treated at RT or at elevated temperature with an acid such as TFA, HCl, H₂SO₄, H₃PO₄ or the like in a solvent such as DCM, MeCN, THF, toluene or the like. The resulting chloropyrimidine intermediate of Formula Ca is treated with a sulfonyl chloride of Formula B in the

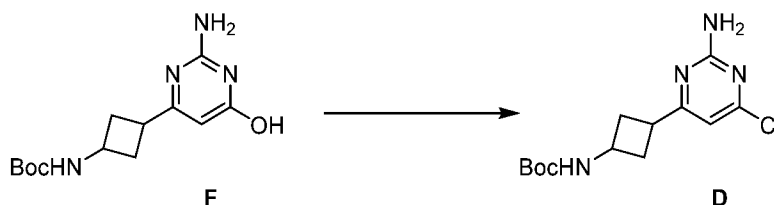
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presence of a base such as TEA or DIPEA in a solvent such as THF, DMF, DCM or a mixture at RT or at elevated temperature.



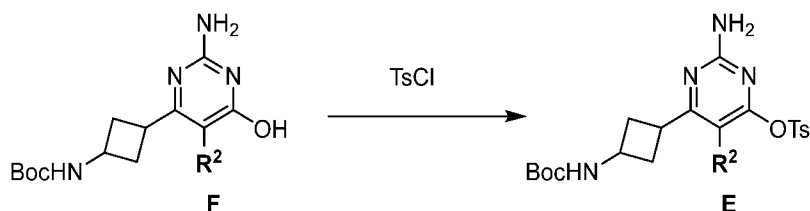
5 Synthesis of intermediates of Formula D

Generally, intermediates of Formula D are obtained by reaction of intermediate F with a chlorinating reagent such as POCl₃ in the presence of a base such as TEA, DIPEA or the like in solvent such as MeCN, toluene, DCM or the like at RT or at elevated temperature (Scheme 10).



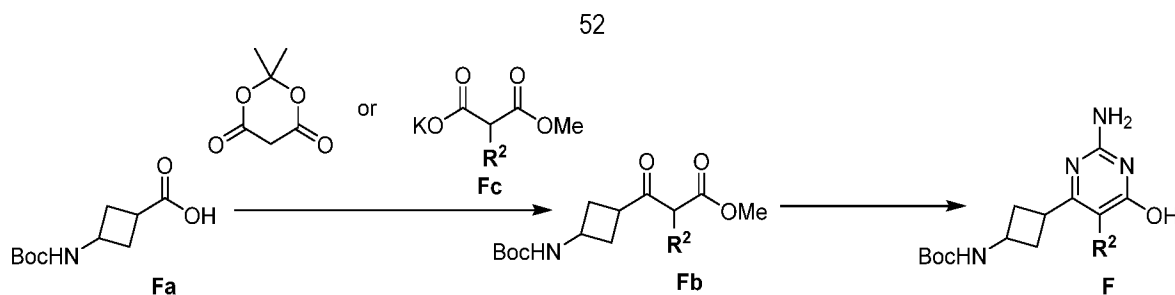
10 Synthesis of intermediates of Formula E

Generally, intermediates of Formula E are obtained by reaction of intermediate F with *p*-toluenesulfonyl chloride in the presence of a base such as TEA, DIPEA or the like in solvent such as MeCN, toluene, DCM or the like at RT or at elevated temperature (Scheme 11).



15 Synthesis of intermediates of Formula F

Generally, intermediates of Formula F are obtained by reaction of commercially available acid Fa to produce intermediate ketoester Fb, followed by condensation with guanidine (Scheme 12). In a typical experiment, a commercially available acid of Formula Fa is treated with 2,2-dimethyl-1,3-dioxane-4,6-dione or a 3-methoxy-3-oxopropanoic acid potassium salt of Formula Fc in the presence of an acid activating reagent such as EDC, CDI or the like and a base such as DMAP in a solvent such as DCM, followed by treatment with MeOH at RT or at elevated temperature. The resulting ketoester intermediate of Formula Fb is treated with guanidine hydrochloride in the presence of a base such as NaOEt, KOtBu or the like in a solvent such as EtOH, MeOH or the like at RT or at elevated temperature.



Whenever the compounds of Formula (I) are obtained in the form of mixtures of enantiomers, the enantiomers can be separated using methods known to one skilled in the art: e.g. by formation and separation of diastereomeric salts or by HPLC or SFC over a chiral stationary phase such as a Regis Whelk-O1(R,R) (10 μ m) column, a Daicel ChiralCel OD-H (5-10 μ m) column, or a Daicel ChiralPak IA (10 μ m), IA, IB, IC, IE, or IF (5 μ m) or AD-H (5 μ m) column. Typical conditions of chiral HPLC or SFC are an isocratic mixture of eluent A (EtOH, in presence or absence of an amine such as triethylamine or diethylamine) and eluent B (heptane or CO₂), at a flow rate of 0.8 to 150 mL/min.

The following examples are provided to illustrate the invention. These examples are illustrative only and should not be construed as limiting the invention in any way.

Experimental Part

Chemistry

All temperatures are stated in °C.

Preparative HPLC conditions:

The conditions for preparative HPLC purifications were chosen among the possibilities given below depending on the properties of the compounds to be purified. More than one option per problem can lead to a successful result.

Equipment: HPLC pumps: Gilson 333/334 or equivalent; Autosampler: Gilson LH215 (with Gilson 845z injector) or equivalent; Degasser: Dionex SRD-3200 or equivalent; Make-up pump: Dionex ISO-3100A or equivalent; DAD detector: Dionex DAD-3000 or equivalent; MS detector: Single quadrupole mass analyzer Thermo Finnigan MSQ Plus or equivalent; MRA splitter: MRA100-000 flow splitter or equivalent; ELS detector: Polymer Laboratories PL-ELS1000 or equivalent. **Method:** Column: variable, Agilent Zorbax SB-Aq 30x75 mm 5 μ m (acidic conditions), Waters Xbridge C18, 30 x 75 mm 10 μ m (acidic/basic conditions), Waters Xbridge C18, 50 x 150 mm 10 μ m (acidic/basic conditions); Flow rate: variable 75 mL/min (for columns with dimension 30x75 mm), 150 mL/min (for columns with dimension 50x150 mm). Mobile phase: gradient mode, A1: Water + 0.5% formic acid (acidic conditions), A2: Water + 0.5% ammonium hydroxide solution (25%) (basic conditions), B: Acetonitrile (acidic/basic conditions); Gradient: variable, e.g. for 75 mL/min: "extremely polar": at 0.0 min 0%B, at 1.0 min 0%B, at 3.5 min 20%B, at 4.0 min 95%B, at 6.0 min 95%B, at 6.2 min 0%B, at 6.6 min 0%B; "very polar": at 0.0 min 5%B, at 0.1 min 5%B, at 3.0 min 50%B, at 4.0 min 95%B, at 6.0 min 95%B, at 6.2 min 5%B, at 6.6 min 5%B; "polar": at 0.0 min 10%B, at 0.01 min 10%B, at 4.0 min 95%B, at 6.0 min 95%B, at 6.2 min 10%B, at 6.6 min 10%B; "normal": at 0.0 min 20%B, at 0.01 min 20%B, at 4.0 min 95%B, at 6.0 min 95%B, at 6.2 min 20%B, at 6.6 min 20%B; "lypophilic": at 0.0 min 30%B, at 0.01 min 30%B, at 3.5 min 95%B, at 6.0 min 95%B, at 6.2 min 30%B, at 6.6 min 30%B; "very lypophilic": at 0.0 min 50%B, at 0.01 min 50%B, at 3.0 min 95%B, at 6.0 min 95%B, at 6.2 min 50%B, at 6.6 min 50%B. Injection volume: 100-2500 μ L. Collection: UV / MS / ELSD if

available, and all possible combinations; Make-up flow rate: 0.50 mL/min. Make-up eluent MS: acetonitrile/water/TFA 70:30:0.025 (V/V/V); MS ionization mode: ESI+.

LC-MS conditions:

Conditions A: Column: Waters BEH C18, 2.1x50 mm, 2.5 μ m; Temperature: 40°C; Injection volume: 0.15 μ L; Eluent A: water/NH₃ with c(NH₃) = 13 mmol/L; Eluent B: Acetonitrile; Ionization: ESI+; Gradient: at 0.0 min = 5% B, 1.20 min = 95% B, at 1.90 min = 95% B, at 2.10 min = 5% B; Flow = 0.8 mL/min. Detection: UV 210 nm and MS.

Conditions B: Column: Zorbax RRHD SB-Aq, 2.1x50 mm, 1.8 μ m; Temperature: 40°C; Injection volume: 0.15 μ L; Eluent A: water 0.04% TFA; Eluent B: Acetonitrile; Ionization: ESI+; Gradient: at 0.0 min = 5% B, at 1.20 min = 95% B, at 1.90 min = 95% B, at 2.10 min = 5% B; Flow = 0.8 mL/min. Detection: UV 210 nm and MS.

Conditions C: Column: Waters BEH C18, 2.1x50 mm, 1.7 μ m; Temperature: 40°C; Injection volume: 3.0 μ L; Eluent A: 95% water 7 mM CH₃COONH₄ / 5% acetonitrile; Eluent B: Acetonitrile; Ionization: ESI+; Gradient: at 0.0 min = 5% B, at 1.00 min = 95% B, at 2.6 min = 95% B, at 2.8 min = 5% B, at 3.30 min = 5% B; Flow = 0.5 mL/min. Detection: UV 210 nm and MS.

QC conditions: Column: Waters Acquity UPLC CSH C18 2.1x50 mm, 1.7 μ m; Temperature: 60°C; Injection volume: 0.20 μ L; Eluent A1: H₂O + 0.05% v/v Formic Acid; Eluent B1 : Acetonitrile + 0.045% v/v Formic Acid; Ionization: ESI+; Gradient: at 0.0 min = 2% B, at 1.50 min = 95% B, at 1.90 min = 95% B, at 1.95 min = 2% B; Run time: 2.00 min; Flow = 1.0 mL/min. Detection: UV 214 nm and MS.

Chiral SFC conditions:

Chiral A conditions: Column: Chiralcel OZ-H 4.6x250mm, 5 μ m; Temperature: 40°C; Injection volume: 10.0 μ L; Eluent A: CO₂; Eluent B: EtOH 0.1% diethylamine; Gradient: isocratic 30% B over 5 min.; Flow = 4.0 mL/min. Detection: UV 220 nm.

Chiral B conditions: Column: Chiralcel OZ-H 4.6x250mm, 5 μ m; Temperature: 40°C; Injection volume: 10.0 μ L; Eluent A: CO₂; Eluent B: EtOH 0.1% diethylamine; Gradient: isocratic 35% B over 5 min.; Flow = 4.0 mL/min. Detection: UV 220 nm.

Abbreviations (as used hereinbefore or hereinafter):

Ac	acetate
Aq.	Aqueous
Boc	<i>tert</i> -butoxycarbonyl
BPR	back pressure regulator
BSA	bovine serum albumin
CDI	1,1'-carbonyldiimidazole (CAS # 530-62-1)
DCM	dichloromethane
DIPEA	<i>N,N</i> -diisopropylethylamine (Hünig's base; CAS # 7087-68-5)
DMAP	4-(dimethylamino)pyridine
DMEM	Dulbecco's modified eagle medium
DMF	dimethylformamide
DMSO	dimethylsulfoxide

	EDC	<i>N</i> -(3-dimethylaminopropyl)- <i>N</i> -ethylcarbodiimide HCl (CAS # 25952-53-8)
	ESI	electrospray ionization
	Et	ethyl
	EtOAc	ethyl acetate
5	Et ₂ O	diethyl ether
	EtOH	ethanol
	FC	flash chromatography
	FLIPR	fluorescent imaging plate reader
	h	hour(s)
10	Hepes	2-[4-(2-Hydroxyethyl)piperazin-1-yl]ethane-1-sulfonic acid
	HBSS	Hanks' Balanced Salt Solution
	HPLC	high pressure liquid chromatography
	LC-MS	liquid chromatography-mass spectrometry
	Me	methyl
15	MeCN	acetonitrile
	MeOH	methanol
	min.	minute(s)
	MS	mass spectrometry
	NCS	<i>N</i> -chlorosuccinimide (CAS # 128-09-6)
20	n-Bu	n-butyl
	NEt ₃	triethylamine
	NMR	nuclear magnetic resonance spectrometry
	org.	organic
	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0) (CAS # 51364-51-3)
25	POCl ₃	phosphorus(V) oxychloride
	prepHPLC	preparative HPLC
	RT	room temperature
	sat.	saturated
	SFC	supercritical fluid chromatography
30	SNAr	nucleophilic aromatic substitution
	TBME	tert-butyl methyl ether
	<i>t</i> -Bu	tert-butyl
	TEA	triethylamine
	TFA	trifluoroacetic acid
35	THF	tetrahydrofuran
	t _R	retention time
	Ts	p-toluenesulfonate
	UV	ultraviolet

XantPhos 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (CAS # 161265-03-8) INTERMEDIATES F

Intermediate F1: *tert*-butyl (*cis*-3-(2-amino-6-hydroxypyrimidin-4-yl)cyclobutyl)carbamate

Step 1: methyl 3-(*cis*-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)-3-oxopropanoate Fb1 (CAS # 2407860-80-2)

To a suspension of *cis*-3-(*tert*-butoxycarbonylamino)cyclobutanecarboxylic acid (CAS # 1008773-79-2) (15 g, 68.3 mmol) in DCM (400 mL) is added 2,2-dimethyl-1,3-dioxane-4,6-dione (12 g, 82 mmol), DMAP (12.6 g, 102 mmol) and EDC (15.7 g, 82 mmol). The mixture is stirred at RT for 1.5h. An aq. 0.5 M KHSO₄ solution (500 mL) is added, and the mixture is stirred at RT for 5 min. The aq. phase is extracted with DCM (150 mL). The org. phase is washed with water (3x250 mL), dried (MgSO₄), filtered and concentrated. The resulting solid is dissolved in MeOH (400 mL) and stirred at reflux for 3h. The mixture is concentrated and purified by FC (SiO₂, EtOAc/heptane) to give 15 g of intermediate Fb1. LC-MS (conditions B): *t_R* = 0.78 min; [M+H]⁺ = 272.24. ¹H NMR (400 MHz, DMSO) δ: 7.13 (d, *J* = 8.0 Hz, 1 H), 3.87 (m, 1 H), 3.62 (s, 3 H), 3.56 (s, 2 H), 2.98 (m, 1 H), 2.31 (m, 2 H), 1.94-2.02 (m, 2 H), 1.36 (s, 9 H).

Step 2: *tert*-butyl (*cis*-3-(2-amino-6-hydroxypyrimidin-4-yl)cyclobutyl)carbamate F1

To a solution of guanidine hydrochloride (CAS # 50-01-1) (16.4 g, 169 mmol) in EtOH (160 mL) is added a solution of NaOEt (21wt% in EtOH, 63 mL, 169 mmol) and the mixture is stirred at RT for 10 min. A solution of intermediate Fb1 (15.3 g, 56 mmol) in EtOH (160 mL) is added over 5 min. The suspension is heated to 80°C and stirred for 1h. The reaction mixture is filtered and concentrated. The residue is taken up in water (50 mL) and the pH is adjusted to pH 5 by addition of an aq. 1N HCl solution (100 mL). The resulting beige suspension is filtered and the collected solid is washed sequentially with water (50 mL), water/MeOH 1:1 (50 mL) and Et₂O (100 mL). The solid is dried by azeotropic distillation with toluene and then under vacuum for 1h. The solid is taken up in MeOH (70 mL) and stirred at RT for 1h. The suspension is filtered and the solid is collected and dried under high vacuum to give 11.8 g of intermediate F1. LC-MS (conditions B): *t_R* = 0.54 min; [M+H]⁺ = 281.27. ¹H NMR (400 MHz, DMSO) δ: 10.60 (d, *J* = 0.4 Hz, 1 H), 7.10 (d, *J* = 7.8 Hz, 1 H), 6.47 (d, *J* = 0.6 Hz, 2 H), 5.38 (s, 1 H), 3.85 (m, 1 H), 2.69-2.74 (m, 1 H), 2.37 (m, 2 H), 1.93 (m, 2 H), 1.37 (s, 9 H).

Intermediate F2: *tert*-butyl (*trans*-3-(2-amino-6-hydroxypyrimidin-4-yl)cyclobutyl)carbamate

Step 1: methyl 3-(*trans*-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)-3-oxopropanoate Fb2 (CAS # 2260789-10-2)

To a suspension of *trans*-3-(*tert*-butoxycarbonylamino)cyclobutanecarboxylic acid (CAS # 939400-34-7) (1 g, 4.4 mmol) in DCM (40 mL) is added 2,2-dimethyl-1,3-dioxane-4,6-dione (780 mg, 5.3 mmol), DMAP (809 mg, 6.6 mmol) and EDC (1.02 g, 5.3 mmol). The mixture is stirred at RT for 18h. An aq. 0.5 M KHSO₄ solution (100 mL) is added, and the mixture is stirred at RT for 5 min. The aq. phase is extracted with DCM (100 mL). The org. phase is washed with water (3x50 mL), dried (MgSO₄), filtered and concentrated. The resulting solid is dissolved in MeOH (40 mL) and stirred at reflux for 3h. The mixture is concentrated and the solid is dried under vacuum to give 1.2 g of intermediate Fb2. LC-MS (conditions B): *t_R* = 0.78 min; [M+H]⁺ = 216.23. ¹H NMR (400 MHz, DMSO) δ: 7.11-7.27 (m, 1 H), 3.83-3.93 (m, 1 H), 3.54-3.66 (m, 5 H), 3.17-3.28 (m, 1 H), 2.26-2.40 (m, 2 H), 1.94-2.16 (m, 2 H), 1.33-1.41 (m, 9 H).

Step 2: *tert*-butyl (*trans*-3-(2-amino-6-hydroxypyrimidin-4-yl)cyclobutyl)carbamate F2

To a solution of intermediate Fb2 (1.2 g, 4.6 mmol) in MeOH (10 mL) is added guanidine hydrochloride (CAS # 50-01-1) (550 mg, 5.6 mmol) and KOtBu (2.9 g, 25 mmol). The reaction is heated to 60°C for 5 min and then stirred at RT for 18h. The mixture is filtered, and the filtrate is diluted with water (10 mL). The pH is adjusted to pH 5 by addition of 2 M

aq. HCl. The resulting suspension is filtered and the solid is dried under vacuum to give 870 mg of intermediate F2. LC-MS (conditions B): t_R = 0.54 min; $[M+H]^+$ = 281.29. 1H NMR (400 MHz, DMSO) δ : 10.78-11.06 (m, 1 H), 7.10 (d, J = 8.0 Hz, 1 H), 6.65-6.66 (m, J_1 = 1.1 Hz, J_2 = 2.8 Hz, 2 H), 5.41 (s, 1 H), 3.83-3.90 (m, 1 H), 2.73 (m, 1 H), 2.35-2.41 (m, 2 H), 1.94 (m, 2 H), 1.37 (s, 9 H).

5 **Intermediate F3: *tert*-butyl (*cis*-3-(2-amino-5-fluoro-6-hydroxypyrimidin-4-yl)cyclobutyl)carbamate**

Intermediate F3 is made according to the procedure reported for intermediate F1 using *cis*-3-(*tert*-butoxycarbonylamino)cyclobutanecarboxylic acid (CAS # 1008773-79-2) and intermediate F3c as starting materials. LC-MS (conditions B): t_R = 0.64 min; $[M+H]^+$ = 299.21.

Intermediate F3c: 2-fluoro-3-methoxy-3-oxopropanoic acid, potassium salt

- 10 To a solution of dimethyl 2-fluoromalonate (CAS # 344-14-9) (500 mg, 3.3 mmol) in MeOH (10 mL) is added a solution of KOH (1M in MeOH, 3 mL). The reaction is stirred at RT for 1.5h. The mixture is concentrated to give 500 mg of intermediate F3c.

INTERMEDIATES E

- 15 **Intermediate E1: 2-amino-6-(*cis*-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)pyrimidin-4-yl 4-methylbenzenesulfonate**

- To a solution of intermediate F1 (5 g, 17.8 mmol) in DCM (110 mL) is added NEt_3 (22.6 mL, 161 mmol) and *p*-toluenesulfonyl chloride (CAS # 98-59-9) (4.2 g, 21.4 mmol). The mixture is stirred for 18h at RT. The reaction is diluted with water (100 mL) and DCM (100 mL). The phases are separated, and the aq. phase is extracted with DCM (100 mL). The combined org. phases are washed with aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$), filtered and concentrated. The residue is purified by FC (SiO_2 , EtOAc/heptane) to give 6.8 g of intermediate E1. LC-MS (conditions B): t_R = 0.95 min; $[M+H]^+$ = 435.67. 1H NMR (400 MHz, DMSO) δ : 7.97 (d, J = 8.3 Hz, 2 H), 7.48 (d, J = 8.3 Hz, 2 H), 7.14 (d, J = 8.1 Hz, 1 H), 6.97 (s, 2 H), 6.17 (s, 1 H), 3.91 (m, 1 H), 2.95 (m, 1 H), 2.43 (m, 5 H), 1.95-2.03 (m, 2 H), 1.37 (s, 9 H).

- Intermediate E2: 2-amino-6-(*cis*-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)-5-fluoropyrimidin-4-yl 4-methylbenzenesulfonate**

- 25 Intermediate E2 is made according to the abovementioned procedure described for the synthesis of intermediate E1 using intermediate F3 as starting material. LC-MS (conditions B): t_R = 1.04 min; $[M+H]^+$ = 453.18.

INTERMEDIATES D

Intermediate D1: *tert*-butyl (*cis*-3-(2-amino-6-chloropyrimidin-4-yl)cyclobutyl)carbamate

- 30 To a solution of intermediate F1 (2.7 g, 9.6 mmol) in MeCN (50 mL) is added DIPEA (5.1 mL, 30 mmol) and $POCl_3$ (2.7 mL, 30 mmol). The mixture is stirred for 18h at RT. The reaction mixture is poured into aq. $NaHCO_3$ (250 mL). The aq. phase is extracted with DCM (2x250 mL). The combined org. phases are washed with water (250 mL), dried ($MgSO_4$), filtered and concentrated to give 2.3 g of intermediate D1. LC-MS (conditions B): t_R = 0.82 min; $[M+H]^+$ = 299.11. 1H NMR (400 MHz, DMSO) δ : 7.13-7.15 (m, 1 H), 7.03 (s, 2 H), 6.59 (s, 1 H), 3.89-3.96 (m, 1 H), 2.92-2.99 (m, 1 H), 2.44-2.46 (m, 2 H), 2.01-2.08 (m, 2 H), 1.38 (s, 9 H).

- 35 **Intermediate D2: *tert*-butyl (*trans*-3-(2-amino-6-chloropyrimidin-4-yl)cyclobutyl)carbamate**

Intermediate D2 is made according to the abovementioned procedure described for the synthesis of intermediate D1 using intermediate F2 as starting material. LC-MS (conditions B): t_R = 0.82 min; $[M+H]^+$ = 299.25.

INTERMEDIATES A

Intermediate A1: 6-(*cis*-3-aminocyclobutyl)-*N*⁴-methylpyrimidine-2,4-diamine hydrochloride**Step 1: *tert*-butyl (*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)carbamate Aa1**

A vial is charged with a solution of intermediate D1 (500 mg, 1.7 mmol) in EtOH (7.5 mL), DIPEA (0.6 mL, 3.4 mmol) and methylamine (30wt% in EtOH, 0.3 mL, 2.5 mmol). The vial is closed, and the mixture is heated to 90°C and stirred for 18h. More methylamine (30wt% in EtOH, 0.1 mL, 0.84 mmol) is added and the mixture is heated to 90°C and stirred for another 18h. The mixture is diluted with aq. NaHCO₃ (100 mL) and EtOAc (100 mL). The phases are separated, and the aq. phase is extracted with EtOAc (100 mL). The combined org. phases are dried (MgSO₄), filtered and concentrated. The residue is purified by FC (SiO₂, MeOH/DCM) to give 495 mg of intermediate Aa1. LC-MS (conditions B): *t*_R = 0.59 min; [M+H]⁺ = 294.37. ¹H NMR (500 MHz, DMSO) δ: 7.10 (d, *J* = 7.8 Hz, 1 H), 6.61-6.62 (m, 1 H), 5.79 (s, 2 H), 5.55 (s, 1 H), 3.83-3.88 (m, 1 H), 2.71-2.75 (m, 4 H), 2.37 (qd, *J*₁ = 2.6 Hz, *J*₂ = 7.7 Hz, 2 H), 1.96 (m, 2 H), 1.37 (s, 9 H).

Step 2: 6-(*cis*-3-aminocyclobutyl)-*N*⁴-methylpyrimidine-2,4-diamine hydrochloride A1

To a solution of intermediate Aa1 (525 mg, 1.8 mmol) in dioxane (5.2 mL) is added a solution of HCl (4N in dioxane, 4.5 mL, 18 mmol) and MeOH (2.6 mL). The reaction is stirred at RT for 1h. The mixture is concentrated and the solid is dried under vacuum to give 550 mg of intermediate A1. LC-MS (conditions A): *t*_R = 0.42 min; [M+H]⁺ = 194.39. ¹H NMR (400 MHz, DMSO) δ: 12.75 (s, 1 H), 8.96 (d, *J* = 4.8 Hz, 1 H), 8.42-8.50 (m, 2 H), 6.66-6.80 (m, 2 H), 3.70-3.76 (m, 1 H), 3.24 (m, 1 H), 2.86 (d, *J* = 4.7 Hz, 3 H), 2.56-2.63 (m, 2 H), 2.33-2.41 (m, 2 H).

Intermediate A2: 6-(*cis*-3-aminocyclobutyl)-*N*⁴-ethylpyrimidine-2,4-diamine hydrochloride

Intermediate A2 is prepared according to the procedure described for intermediate A1, using ethylamine and intermediate D1 as starting materials. LC-MS (conditions A): *t*_R = 0.49 min; [M+H]⁺ = 208.34. ¹H NMR (400 MHz, DMSO) δ: 12.72 (s, 1 H), 8.95 (t, *J* = 5.4 Hz, 1 H), 8.39-8.40 (m, 2 H), 6.18-6.31 (m, 2 H), 3.70-3.78 (m, 1 H), 3.33-3.41 (m, 2 H), 3.21-3.28 (m, 1 H), 2.56-2.63 (m, 2 H), 2.33-2.40 (m, 2 H), 1.13 (t, *J* = 7.2 Hz, 3 H).

Intermediate A3: 6-(*cis*-3-aminocyclobutyl)-*N*⁴-isopropylpyrimidine-2,4-diamine hydrochloride**Step 1: *tert*-butyl (*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)carbamate Aa3**

To a solution of intermediate E1 (1.5 g, 3.45 mmol) in EtOH (15 mL) is added isopropylamine (1.5 mL, 17.3 mmol). The reaction is heated to 80°C for 18h. The mixture is concentrated, and water (100 mL) is added. The aq. phase is extracted with DCM (2x100 mL). The combined org. phases are washed with aq. NaHCO₃ (100 mL), dried (MgSO₄), filtered and concentrated. The residue is purified by FC (SiO₂, NH₃ in MeOH/DCM) to give 630 mg of intermediate Aa3. LC-MS (conditions B): *t*_R = 0.68 min; [M+H]⁺ = 321.94. ¹H NMR (400 MHz, DMSO) δ: 7.11 (d, *J* = 7.6 Hz, 1 H), 6.57-6.59 (m, 1 H), 5.78 (m, 2 H), 5.54 (s, 1 H), 4.03 (m, 1 H), 3.85 (m, 1 H), 2.68-2.74 (m, 1 H), 2.33-2.39 (m, 2 H), 1.95 (m, 2 H), 1.37 (s, 9 H), 1.09 (d, *J* = 6.4 Hz, 6 H).

Step 2: 6-(*cis*-3-aminocyclobutyl)-*N*⁴-isopropylpyrimidine-2,4-diamine hydrochloride A3

To a solution of intermediate Aa3 (1.9 g, 5.9 mmol) in DCM (40 mL) is added HCl (4N in dioxane, 7.4 mL, 30 mmol). The reaction is stirred at RT for 3h. The mixture is concentrated and the solid is dried under vacuum to give 1.7 g of intermediate A3. LC-MS (conditions B): *t*_R = 0.37 min; [M+H]⁺ = 222.31. ¹H NMR (400 MHz, DMSO) δ: 12.71-12.80 (m,

1 H), 8.92 (d, *J* = 7.7 Hz, 1 H), 8.43-8.57 (m, 3 H), 5.93 (s, 1 H), 4.17 (m, 1 H), 3.70-3.76 (m, 1 H), 3.22 (m, 1 H), 2.53-2.62 (m, 2 H), 2.33-2.40 (m, 2 H), 1.16 (d, *J* = 6.6 Hz, 6 H).

Intermediate A3.1: 6-(*trans*-3-aminocyclobutyl)-*N*⁴-isopropylpyrimidine-2,4-diamine hydrochloride

Intermediate A3.1 is made according to the abovementioned procedure described for the synthesis of intermediate A1 using intermediate D2 and isopropylamine as starting materials. LC-MS (conditions B): *t*_R = 0.37 min; [M+H]⁺ = 222.20. The intermediates from **Table 1** below are made according to the abovementioned procedures described for the synthesis of intermediates A1 or A3 using intermediates D1, D2 or E1 and the appropriate amine or amine hydrochloride as starting materials.

Table 1

			LC-MS	
Intermediate number	Intermediate Name	Amine precursor	<i>t</i> _R (min)	[M+H] ⁺
A4	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -cyclopropylpyrimidine-2,4-diamine hydrochloride	Cyclopropylamine CAS # 765-30-0	0.31 (conditions B)	220.14
A5	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -((<i>R</i>)-1,1,1-trifluoropropan-2-yl)pyrimidine-2,4-diamine hydrochloride	(<i>R</i>)-1,1,1-Trifluoro-2-propanamine CAS # 779303-24-1	0.40 (conditions B)	276.18
A6	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -propylpyrimidine-2,4-diamine hydrochloride	Propylamine CAS # 107-10-8	0.54 (conditions A)	222.33
A7	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(<i>tert</i> -butyl)pyrimidine-2,4-diamine hydrochloride	<i>tert</i> -Butylamine CAS # 75-64-9	0.45 (conditions B)	236.26
A10.1	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -cyclobutylpyrimidine-2,4-diamine hydrochloride	Cyclobutylamine CAS # 2516-34-9	0.38 (conditions B)	234.16
A10.2	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(cyclobutylmethyl)pyrimidine-2,4-diamine hydrochloride	Cyclobutanemethanamine CAS # 4415-83-2	0.43 (conditions B)	248.17
A10.3	(<i>S</i>)-2-((2-amino-6-(<i>cis</i> -3-aminocyclobutyl)pyrimidin-4-yl)amino)propan-1-ol hydrochloride	L-Alaninol CAS # 2749-11-3	0.41 (conditions A)	238.36

A10.4	2-((2-amino-6-(<i>cis</i> -3-aminocyclobutyl)pyrimidin-4-yl)amino)-2-methylpropan-1-ol hydrochloride	2-Amino-2-methyl-1-propanol CAS # 124-68-5	0.50 (conditions A)	252.39
A10.5	rac-6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(<i>sec</i> -butyl)pyrimidine-2,4-diamine hydrochloride	(±)- <i>sec</i> -Butylamine CAS # 13952-84-6	0.39 (conditions B)	No ionization
A10.6	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(2,2-difluoroethyl)pyrimidine-2,4-diamine hydrochloride	2,2-Difluoro-ethanamine CAS # 430-67-1	0.27 (conditions B)	244.13
A10.7	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(2,2,2-trifluoroethyl)pyrimidine-2,4-diamine hydrochloride	2,2,2-Trifluoroethylamine CAS # 753-90-2	0.33 (conditions B)	262.13
A10.8	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(2-fluoroethyl)pyrimidine-2,4-diamine hydrochloride	2-Fluoroethylamine CAS # 406-34-8	0.25 (conditions B)	226.16
A10.9	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(1-fluoropropan-2-yl)pyrimidine-2,4-diamine hydrochloride	1-Fluoro-2-propanamine CAS # 66679-45-6	0.33 (conditions B)	240.13
A10.10	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(2-methoxyethyl)pyrimidine-2,4-diamine hydrochloride	2-Methoxyethylamine CAS # 109-85-3	0.44 (conditions B)	238.34
A10.11	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -((<i>S</i>)-1-methoxypropan-2-yl)pyrimidine-2,4-diamine hydrochloride	(<i>S</i>)-2-Amino-1-methoxypropane CAS # 99636-32-5	0.34 (conditions B)	No ionization
A10.12	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(1-methoxy-2-methylpropan-2-yl)pyrimidine-2,4-diamine hydrochloride	1-Methoxy-2-methyl-2-propanamine CAS # 20719-68-0	0.40 (conditions B)	No ionization
A10.13	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -((<i>S</i>)-1,1,1-trifluoropropan-2-yl)pyrimidine-2,4-diamine hydrochloride	(<i>S</i>)-1,1,1-Trifluoropropan-2-amine CAS # 125278-10-6	0.40 (conditions B)	276.19
A10.14	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -((1-fluorocyclopropyl)methyl)pyrimidine-2,4-diamine hydrochloride	1-Fluorocyclopropane-methanamine hydrochloride CAS # 1462885-86-4	0.38 (conditions B)	252.22
A10.15	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(1,3-difluoropropan-2-yl)pyrimidine-2,4-diamine hydrochloride	1,3-Difluoro-2-propanamine hydrochloride CAS # 760-25-8	0.32 (conditions B)	No ionization

A10.16	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(1,1,1-trifluoro-2-methylpropan-2-yl)pyrimidine-2,4-diamine hydrochloride	1,1,1-Trifluoro-2-methyl-2-propanamine hydrochloride CAS # 174886-04-5	0.47 (conditions B)	289.88
A10.17	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -butylpyrimidine-2,4-diamine hydrochloride	Butylamine CAS # 109-73-9	0.92 (conditions C)	236.3
A10.18	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -isobutylpyrimidine-2,4-diamine hydrochloride	Isobutylamine CAS # 78-81-9	0.89 (conditions C)	236.2
A10.19	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -cyclopentylpyrimidine-2,4-diamine hydrochloride	Cyclopentylamine CAS # 1003-03-8	0.93 (conditions C)	248.3
A10.20	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -cyclohexylpyrimidine-2,4-diamine hydrochloride	Cyclohexylamine CAS # 108-91-8	1.00 (conditions C)	262.2
A10.21	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(cyclopropylmethyl)pyrimidine-2,4-diamine hydrochloride	Cyclopropanemethanamine CAS # 2516-47-4	0.86 (conditions C)	234.2
A10.22	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -((<i>R</i>)- <i>sec</i> -butyl)pyrimidine-2,4-diamine hydrochloride	(<i>R</i>)- <i>sec</i> -Butylamine CAS # 13250-12-9	0.39 (conditions B)	No ionization
A10.23	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -((<i>S</i>)- <i>sec</i> -butyl)pyrimidine-2,4-diamine hydrochloride	(<i>S</i>)- <i>sec</i> -Butylamine CAS # 513-49-5	0.39 (conditions B)	No ionization
A11	rac-6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -(1,1-difluoropropan-2-yl)pyrimidine-2,4-diamine hydrochloride	1,1-Difluoro-2-propanamine hydrochloride CAS # 1384427-90-0	0.36 (conditions B)	257.94
A12	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -((<i>S</i>)-1,1-difluoropropan-2-yl)pyrimidine-2,4-diamine hydrochloride	(2 <i>S</i>)-1,1-difluoropropan-2-amine hydrochloride CAS # 2287236-82-0	0.36 (conditions B)	258.05
A13	6-(<i>cis</i> -3-aminocyclobutyl)- <i>N</i> ⁴ -((<i>R</i>)-1,1-difluoropropan-2-yl)pyrimidine-2,4-diamine hydrochloride	(2 <i>R</i>)-1,1-difluoropropan-2-amine hydrochloride CAS # 1018434-72-4	0.35 (conditions B)	258.03

Intermediate A14: 6-(*cis*-3-aminocyclobutyl)-*N*⁴-ethyl-5-fluoropyrimidine-2,4-diamine hydrochloride

Intermediate A14 is made according to the abovementioned procedure described for the synthesis of intermediate A1 using intermediate E2 and ethylamine as starting materials. LC-MS (conditions B): *t*_R = 0.32 min; [M+H]⁺ = 226.22.

INTERMEDIATES B

Intermediate B1: 5,6-dimethylpyridine-3-sulfonyl chloride (CAS # 1781875-71-5)**Step 1: 5-(benzylthio)-2,3-dimethylpyridine B1a**

A mixture of 5-bromo-2,3-dimethylpyridine (CAS # 27063-90-7) (500 mg, 2.58 mmol), Pd₂(dba)₃ (122 mg, 0.13 mmol), XantPhos (152 mg, 0.26 mmol), benzylmercaptan (0.37 mL, 3.1 mmol) and dioxane (10 mL) is put under N₂ and heated to 100°C for 18h. The mixture is diluted with water (50 mL) and the aq. phase is extracted with EtOAc (2x50 mL). The combined org. phases are washed with brine (50 mL), dried (MgSO₄), filtered and concentrated. The residue is purified by FC (SiO₂, EtOAc/heptane) to give 420 mg of intermediate B1a. LC-MS (conditions B): t_R = 0.66 min; [M+H]⁺ = 230.16. ¹H NMR (400 MHz, DMSO) δ: 8.15 (s, 1 H), 7.53 (s, 1 H), 7.22-7.30 (m, 5 H), 4.21 (s, 2 H), 2.36 (s, 3 H), 2.20 (s, 3 H).

Step 2: 5,6-dimethylpyridine-3-sulfonyl chloride B1

A solution of NCS (939 mg, 7.0 mmol) in MeCN (8 mL) is cooled to 0°C. 2M aq. HCl (1 mL, 1.9 mmol) is added, and the mixture is stirred at 0°C for 10 min. A solution of intermediate B1a (420 mg, 1.8 mmol) in MeCN (4 mL) is added. The reaction is stirred at RT for 30 min. The mixture is diluted with water (50 mL) and the aq. phase is extracted with DCM (2x50 mL). The combined org. phases are dried (MgSO₄), filtered and concentrated. The residue is purified by FC (SiO₂, EtOAc/heptane) to give 138 mg of intermediate B1. LC-MS (conditions B): t_R = 0.85 min; [M+H]⁺ = 206.11. ¹H NMR (400 MHz, DMSO) δ: 8.66 (s, 1 H), 8.50 (s, 1 H), 2.66 (s, 3 H), 2.44 (s, 3 H).

The intermediates from **Table 2** below are made according to the abovementioned procedure described for the synthesis of intermediate B1 using the appropriate arylbromide starting material. Reaction time goes up to 24h, with purification by FC or no purification.

Table 2

Intermediate number	Intermediate Name	Arylbromide precursor	LC-MS	
			t _R (min)	[M+H] ⁺
B2	6-(difluoromethyl)pyridine-3-sulfonyl chloride	5-Bromo-2-(difluoromethyl)pyridine CAS # 845827-13-6	0.86 (conditions B)	no ionization
B3	5-fluoro-6-methylpyridine-3-sulfonyl chloride	5-Bromo-3-fluoro-2-methylpyridine CAS # 1162674-74-9	0.82 (conditions B)	no ionization
B4	2-fluoro-6-methylpyridine-3-sulfonyl chloride	3-Bromo-2-fluoro-6-methylpyridine CAS # 375368-78-8	0.87 (conditions B)	no ionization

B5	6-fluoro-2-methylpyridine-3-sulfonyl chloride	3-Bromo-6-fluoro-2-methylpyridine CAS # 375368-83-5	0.88 (conditions B)	no ionization
B6	2-(difluoromethyl)pyridine-3-sulfonyl chloride	3-Bromo-2-(difluoromethyl)pyridine CAS # 1211520-77-2	0.80 (conditions B)	no ionization
B7	5-chloro-6-methylpyridine-3-sulfonyl chloride	5-Bromo-3-chloro-2-methylpyridine CAS # 914358-72-8	0.89 (conditions B)	no ionization
B8	6-ethylpyridine-3-sulfonyl chloride	5-Bromo-2-ethylpyridine CAS # 38749-90-5	0.87 (conditions B)	206.18
B9	6-cyclopropylpyridine-3-sulfonyl chloride	5-Bromo-2-cyclopropylpyridine CAS # 579475-29-9	0.93 (conditions B)	218.13
B10	5-cyclopropylpyridine-3-sulfonyl chloride	3-Bromo-5-cyclopropylpyridine CAS # 1044210-57-2	0.90 (conditions B)	218.13
B11	2-chloro-6-fluoropyridine-3-sulfonyl chloride	3-Bromo-2-chloro-6-fluoropyridine CAS # 1211578-75-4	0.89 (conditions B)	no ionization
B12	2-chloro-5,6-dimethylpyridine-3-sulfonyl chloride	3-Bromo-2-chloro-5,6-dimethylpyridine CAS # 1780882-71-4	0.94 (conditions B)	no ionization
B13	5-ethylpyridine-3-sulfonyl chloride	3-Bromo-5-ethylpyridine CAS # 142337-95-9	0.88 (conditions B)	206.16
B14	2,6-dimethylpyridine-3-sulfonyl chloride	3-Bromo-2,6-dimethylpyridine CAS # 3430-31-7	0.84 (conditions B)	206.18
B15	5-chloro-2-methylpyridine-3-sulfonyl chloride	3-Bromo-5-chloro-2-methylpyridine CAS # 131036-39-0	0.90 (conditions B)	no ionization
B16	5-chloro-2-fluoropyridine-3-sulfonyl chloride	3-Bromo-5-chloro-2-fluoropyridine CAS # 884494-87-5	0.88 (conditions B)	no ionization

B17	5-fluoro-2-methylpyridine-3-sulfonyl chloride	3-Bromo-5-fluoro-2-methylpyridine CAS # 1211542-29-8	0.84 (conditions B)	no ionization
B18	2-fluoro-5,6-dimethylpyridine-3-sulfonyl chloride	3-Bromo-2-fluoro-5,6-dimethylpyridine CAS # 2137579-23-6	0.91 (conditions B)	no ionization
B19	6-(methylamino)pyridine-3-sulfonyl chloride	5-Bromo-N-methyl-2-pyridinamine CAS # 84539-30-0	1.14 (conditions C)	207.2
B20	2,5,6-trimethylpyridine-3-sulfonyl chloride	3-Bromo-2,5,6-trimethylpyridine CAS # 1780024-77-2	0.90 (conditions B)	220.11
B22	2-nitropyridine-3-sulfonyl chloride	3-Bromo-2-nitropyridine CAS # 54231-33-3	0.84 (conditions B)	no ionization
B23	6-methyl-2-nitropyridine-3-sulfonyl chloride	3-Bromo-6-methyl-2-nitropyridine CAS # 1379359-54-2	0.90 (conditions B)	no ionization
B24	6-nitropyridine-3-sulfonyl chloride	5-Bromo-2-nitropyridine CAS # 39856-50-3	0.79 (conditions B)	no ionization
B25	2-methyl-6-nitropyridine-3-sulfonyl chloride	3-Bromo-2-methyl-6-nitropyridine CAS # 1231930-13-4	0.86 (conditions B)	no ionization
B26	5-methyl-6-nitropyridine-3-sulfonyl chloride	5-Bromo-3-methyl-2-nitropyridine CAS # 114042-02-3	0.90 (conditions B)	no ionization

Intermediate B21: 3-cyano-4-iodobenzenesulfonyl chloride

5 A solution of 5-amino-2-iodobenzonitrile (CAS # 1082454-14-5) (107 mg, 0.42 mmol) in conc. HCl (0.13 mL, 4.2 mmol) is cooled to 0°C. A solution of sodium nitrite (35 mg, 0.5 mmol) in water (80 µL, 4.6 mmol) is added slowly. The reaction is stirred at 0°C for 1h. In a separate flask, a solution of thionyl chloride (90 µL, 1.25 mmol) in water (0.12 mL, 6.7 mmol) is cooled to 0°C and CuCl (4 mg, 0.042 mmol) is added. The two solutions are combined, and the reaction is stirred at RT for 20 min. The mixture is diluted with water (50 mL) and the aq. phase is extracted with TBME (2x50 mL). The combined org. phases are washed with brine (50 mL), dried (MgSO₄), filtered and concentrated to give the crude product, which was directly used for the next step. LC-MS (conditions B): t_R = 0.97 min; no ionization.

INTERMEDIATES G and H

Intermediate G1: *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-nitropyridine-3-sulfonamide

To a solution of intermediate A5 (415 mg, 1.33 mmol) in THF (10 mL) is added NEt₃ (0.93 mL, 6.6 mmol) and sulfonyl chloride B22 (824 mg, 3.7 mmol). The reaction is stirred at RT for 30 min. Purification by prepHPLC (basic conditions) gives 260 mg of intermediate G1. LC-MS (QC conditions): t_R = 0.601 min; [M+H]⁺ = 462.3. ¹H NMR (500 MHz, DMSO) δ: 8.81 (dd, J₁ = 1.5 Hz, J₂ = 4.7 Hz, 1 H), 8.55 (dd, J₁ = 1.5 Hz, J₂ = 8.0 Hz, 1 H), 8.04 (dd, J₁ = 4.7 Hz, J₂ = 8.0 Hz, 1 H), 7.21-7.23 (m, 1 H), 5.99 (s, 2 H), 5.60 (s, 1 H), 4.92-4.98 (m, 1 H), 3.70-3.75 (m, 1 H), 2.75-2.82 (m, 1 H), 2.29 (qd, J₁ = 3.7 Hz, J₂ = 7.4 Hz, 2 H), 1.96-2.03 (m, 2 H), 1.25 (d, J = 7.0 Hz, 3 H).

The intermediates from **Table 3** below are made according to the abovementioned procedure described for the synthesis of intermediate G1 using the appropriate intermediate A and the appropriate sulfonyl chloride B. Reaction time goes up to 24h, with purification by prepHPLC (acidic or basic conditions).

Table 3

				LC-MS (QC conditions)	
Intermediate number	Intermediate Name	Amine precursor A	Sulfonyl chloride precursor B	t _R (min)	[M+H] ⁺
G2	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-nitropyridine-3-sulfonamide	A3	B22	0.564	408.4
H2	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-bromopyridine-3-sulfonamide	A3	2-Bromo-3-pyridinesulfonyl chloride (CAS # 1060811-59-7)	0.521	443.3
G3	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methyl-6-nitropyridine-3-sulfonamide	A3	B26	0.603	422.4

G4	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methyl-2-nitropyridine-3-sulfonamide	A3	B23	0.608	422.4
G5	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methyl-6-nitropyridine-3-sulfonamide	A3	B25	0.571	422.4
G6	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-nitropyridine-3-sulfonamide	A5	B24	0.573	462.3
H6	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-bromopyridine-3-sulfonamide	A5	6-Bromo-3-pyridinesulfonyl chloride CAS # 886371-20-6	0.615	497.3
G7	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5-methyl-6-nitropyridine-3-sulfonamide	A5	B26	0.642	476.3
G8	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-methyl-6-nitropyridine-3-sulfonamide	A5	B25	0.612	476.4
G9	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-methyl-2-nitropyridine-3-sulfonamide	A5	B23	0.649	476.4

SYNTHESIS OF EXAMPLES

Example 1.1: *N*-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,4-difluorobenzenesulfonamide

To a solution of intermediate A1 (15 mg, 0.05 mmol) in DCM (0.3 mL) is added NEt₃ (0.03 mL, 0.25 mmol) and 2,4-difluorobenzenesulfonyl chloride (CAS # 13918-92-8) (11 mg, 0.05 mmol). The reaction is stirred at RT for 30 min.

5 Purification by prepHPLC (basic conditions) gives 14 mg of Example 1.1. LC-MS (QC conditions): t_R = 0.486 min;

[M+H]⁺ = 370.2. ¹H NMR (500 MHz, DMSO) δ : 8.35 (m, 1 H), 7.86 (m, 1 H), 7.53-7.58 (m, 1 H), 7.29 (td, J_1 = 2.2 Hz, J_2 = 8.4 Hz, 1 H), 6.61-6.63 (m, 1 H), 5.79 (s, 2 H), 5.47 (s, 1 H), 3.61-3.65 (m, 1 H), 2.69-2.73 (m, 4 H), 2.20 (qd, J_1 = 2.7 Hz, J_2 = 7.7 Hz, 2 H), 1.92-1.98 (m, 2 H).

The examples from **Table 4** below are made according to the abovementioned procedure described for the synthesis of Example 1.1 using intermediate A1 and the appropriate sulfonylchloride B as starting materials. Reaction time goes up to 24h, at RT, with purification by prepHPLC (acidic or basic conditions).

Table 4

Example number	Example Name	Sulfonyl chloride precursor B	LC-MS (QC conditions)	
			t_R (min)	[M+H] ⁺
Example 1.2	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-4-methoxy-3-methylbenzenesulfonamide	4-Methoxy-3-methylbenzenesulfonyl chloride CAS # 84910-98-5	0.554	378.2
Example 1.3	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide	2,5-Difluorobenzenesulfonyl chloride CAS # 26120-86-5	0.497	370.2
Example 1.4	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-fluorobenzenesulfonamide	2-Fluorobenzenesulfonyl chloride CAS # 2905-21-7	0.461	352.3
Example 1.5	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.486	352.2
Example 1.6	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-4-fluorobenzenesulfonamide	4-Fluorobenzenesulfonyl chloride CAS # 349-88-2	0.483	352.3
Example 1.7	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-3,4-difluorobenzenesulfonamide	3,4-Difluorobenzenesulfonyl chloride CAS # 145758-05-0	0.525	370.2
Example 1.8	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide	2,3-Difluorobenzenesulfonyl chloride CAS # 210532-24-4	0.499	370.3
Example 1.9	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,6-difluorobenzenesulfonamide	2,6-Difluorobenzenesulfonyl chloride CAS # 60230-36-6	0.449	370.2

Example 1.10	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-5-methylbenzenesulfonamide	2-Fluoro-5-methylbenzenesulfonyl chloride CAS # 870704-14-6	0.530	366.3
Example 1.11	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-2-fluorobenzenesulfonamide	5-Chloro-2-fluorobenzenesulfonyl chloride CAS # 351003-49-1	0.561	386.2
Example 1.12	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-5-fluorobenzenesulfonamide	2-Chloro-5-fluorobenzenesulfonyl chloride CAS # 82875-86-3	0.533	386.2
Example 1.13	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-2-methylbenzenesulfonamide	5-Fluoro-2-methylbenzenesulfonyl chloride CAS # 445-05-6	0.549	366.3

Example 2.1: *N*-(*cis*-3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide

To a solution of intermediate A2 (65 mg, 0.205 mmol) in DCM (3 mL) is added NEt₃ (1.44 mL, 1.03 mmol) and 3-fluorobenzene-1-sulfonyl chloride (CAS # 701-27-9) (42 mg, 0.205 mmol). The reaction is stirred at RT for 18h.

- 5 Purification by prepHPLC (basic conditions) gives 71 mg of Example 2.1. LC-MS (QC conditions): *t_R* = 0.541 min; [M+H]⁺ = 366.4. ¹H NMR (500 MHz, DMSO) δ: 8.09 (d, *J* = 8.5 Hz, 1 H), 7.66-7.68 (m, 2 H), 7.58-7.61 (m, 1 H), 7.51-7.55 (m, 1 H), 6.70-6.70 (m, 1 H), 5.80 (s, 2 H), 5.45 (s, 1 H), 3.63 (m, 1 H), 3.19 (m, 2 H), 2.70 (m, 1 H), 2.18 (qd, *J*₁ = 2.7 Hz, *J*₂ = 7.6 Hz, 2 H), 1.82-1.88 (m, 2 H), 1.06 (t, *J* = 7.2 Hz, 3 H).

The examples from **Table 5** below are made according to the abovementioned procedure described for the synthesis of Example 2.1 using intermediate A2 and the appropriate sulfonylchloride B as starting materials. Reaction time goes up to 24h, at RT, with purification by prepHPLC (acidic or basic conditions).

Table 5

Example number	Example Name	Sulfonyl chloride precursor B	LC-MS (QC conditions)	
			<i>t_R</i> (min)	[M+H] ⁺
Example 2.2	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide	2,3-Difluorobenzenesulfonyl chloride CAS # 210532-24-4	0.538	384.2
Example 2.3	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide	2,5-Difluorobenzenesulfonyl chloride CAS # 26120-86-5	0.533	384.2
Example 2.4	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide	B1	0.471	377.3

Example 2.5	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide	2-Fluoro-3-pyridinesulfonyl chloride CAS # 1089330-70-0	0.435	367.2
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Example 3.1: *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide

To a solution of intermediate A3 (198 mg, 0.673 mmol) in DCM (10 mL) is added NEt₃ (0.47 mL, 3.36 mmol) and 3-fluorobenzene-1-sulfonyl chloride (CAS # 701-27-9) (138 mg, 0.673 mmol). The reaction is stirred at RT for 18h.

- 5 Purification by prepHPLC (basic conditions) gives 142 mg of Example 3.1. LC-MS (QC conditions): *t*_R = 0.574 min; [M+H]⁺ = 380.2. ¹H NMR (500 MHz, DMSO) δ: 8.09 (s, 1 H), 7.66-7.68 (m, 2 H), 7.58-7.60 (m, 1 H), 7.52-7.53 (m, 1 H), 6.51 (d, *J* = 6.5 Hz, 1 H), 5.71 (s, 2 H), 5.42 (s, 1 H), 3.94-4.04 (m, 1 H), 3.60-3.64 (m, 1 H), 2.68 (m, 1 H), 2.17 (qd, *J*₁ = 2.7 Hz, *J*₂ = 7.6 Hz, 2 H), 1.84 (m, 2 H), 1.07 (d, *J* = 6.5 Hz, 6 H).

Example 3.2: *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide

- 10 Example 3.2 is made according to the abovementioned procedure described for the synthesis of Example 3.1 using intermediate A3 and 2-fluoro-3-pyridinesulfonyl chloride (CAS # 1089330-70-0) as starting materials. LC-MS (QC conditions): *t*_R = 0.491 min; [M+H]⁺ = 381.3. ¹H NMR (500 MHz, DMSO) δ: 8.51-8.54 (m, 2 H), 8.34 (m, 1 H), 7.59 (ddd, *J*₁ = 1.6 Hz, *J*₂ = 4.9 Hz, *J*₃ = 7.4 Hz, 1 H), 6.54-6.55 (m, 1 H), 5.74 (s, 2 H), 5.45 (s, 1 H), 3.99-4.04 (m, 1 H), 3.67 (m, 1 H), 2.66-2.73 (m, 1 H), 2.19 (m, 2 H), 1.94 (m, 2 H), 1.08 (d, *J* = 6.5 Hz, 6 H).

- 15 **Example 3.3: *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide**

Example 3.3 is made according to the abovementioned procedure described for the synthesis of Example 3.1 using intermediate A3 and sulfonylchloride B1 as starting materials. LC-MS (QC conditions): *t*_R = 0.516 min; [M+H]⁺ = 391.5.

- 20 ¹H NMR (500 MHz, DMSO) δ: 8.63 (d, *J* = 2.2 Hz, 1 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 7.89 (d, *J* = 1.8 Hz, 1 H), 6.50 (d, *J* = 6.6 Hz, 1 H), 5.71 (s, 2 H), 5.44 (s, 1 H), 3.99-4.00 (m, 1 H), 3.62 (m, 1 H), 2.64-2.72 (m, 1 H), 2.51 (s, 3 H), 2.35 (s, 3 H), 2.18 (qd, *J*₁ = 2.7 Hz, *J*₂ = 7.6 Hz, 2 H), 1.81-1.87 (m, 2 H), 1.07 (d, *J* = 6.5 Hz, 6 H).

The examples from **Table 6** below are made according to the abovementioned procedure described for the synthesis of Example 3.1 using the appropriate intermediate A3 or A3.1 and the appropriate sulfonylchloride B as starting materials. Reaction time goes up to 24h, at RT, with purification by prepHPLC (acidic or basic conditions).

- 25 **Table 6**

LC-MS (QC conditions)

Example number	Example Name	Amine precursor A	Sulfonyl chloride precursor B	t_R (min)	$[M+H]^+$
Example 3.4	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyridine-2-sulfonamide	A3	2-Pyridinesulfonyl chloride CAS # 66715-65-9	0.458	363.2
Example 3.5	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-cyanobenzenesulfonamide	A3	3-Cyanobenzenesulfonyl chloride CAS # 56542-67-7	0.543	387.2
Example 3.6	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluoro-4-methylbenzenesulfonamide	A3	3-Fluoro-4-methylbenzenesulfonyl chloride CAS # 90260-13-2	0.633	394.2
Example 3.7	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-1-methyl-1H-pyrazole-4-sulfonamide	A3	1-Methyl-1H-pyrazole-4-sulfonyl chloride CAS # 288148-34-5	0.425	366.2
Example 3.8	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methylbenzenesulfonamide	A3	3-Methylbenzenesulfonyl chloride CAS # 1899-93-0	0.599	376.3
Example 3.9	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3,5-dichlorobenzenesulfonamide	A3	3,5-Dichlorobenzenesulfonyl chloride CAS # 705-21-5	0.713	430.1
Example 3.10	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)benzenesulfonamide	A3	Benzenesulfonyl chloride CAS # 98-09-9	0.542	362.2

Example 3.11	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-2-methylbenzenesulfonamide	A3	5-Fluoro-2-methylbenzenesulfonyl chloride CAS # 445-05-6	0.633	394.3
Example 3.12	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-chlorobenzenesulfonamide	A3	3-Chlorobenzenesulfonyl chloride CAS # 2888-06-4	0.627	396.2
Example 3.13	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-(trifluoromethoxy)benzenesulfonamide	A3	3-(Trifluoromethoxy)benzenesulfonyl chloride CAS # 220227-84-9	0.716	446.3
Example 3.14	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluoro-4-methoxybenzenesulfonamide	A3	3-Fluoro-4-methoxybenzenesulfonyl chloride CAS # 67475-55-2	0.590	410.3
Example 3.15	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methoxybenzenesulfonamide	A3	3-Methoxybenzenesulfonyl chloride CAS # 10130-74-2	0.592	392.3
Example 3.16	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyridine-3-sulfonamide	A3	3-Pyridinesulfonyl chloride CAS # 16133-25-8	0.452	363.3
Example 3.17	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide	A3	2,3-Difluorobenzenesulfonyl chloride CAS # 210532-24-4	0.586	398.2
Example 3.18	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chlorothiazole-5-sulfonamide	A3	2-Chloro-5-thiazolesulfonyl chloride CAS # 88917-11-7	0.574	403.2

Example 3.19	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3,4-difluorobenzenesulfonamide	A3	3,4-Difluorobenzenesulfonyl chloride CAS # 145758-05-0	0.606	398.2
Example 3.20	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide	A3	6-Methyl-3-pyridinesulfonyl chloride CAS # 478264-00-5	0.491	377.3
Example 3.21	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,6-difluoropyridine-3-sulfonamide	A3	2,6-Difluoro-3-pyridinesulfonyl chloride CAS # 1261843-52-0	0.558	399.3
Example 3.22	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4,6-dimethylpyridine-3-sulfonamide	A3	4,6-Dimethyl-3-pyridinesulfonyl chloride CAS # 1023814-93-8	0.506	391.3
Example 3.23	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-bromo-4-methylthiazole-5-sulfonamide	A3	2-Bromo-4-methyl-5-thiazolesulfonyl chloride CAS # 1421601-62-8	0.630	463.2
Example 3.24	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)thiazole-5-sulfonamide	A3	5-Thiazolesulfonyl chloride CAS # 1820741-28-3	0.458	369.2
Example 3.25	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-ethylthiazole-5-sulfonamide	A3	2-Ethyl-5-thiazolesulfonyl chloride CAS # 1314915-12-2	0.552	397.2
Example 3.26	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylthiazole-5-sulfonamide	A3	2-Methyl-5-thiazolesulfonyl chloride CAS # 1314977-63-3	0.497	383.3

Example 3.27	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-cyclopropylthiazole-5-sulfonamide	A3	2-Cyclopropyl-5-thiazolesulfonyl chloride CAS # 1989659-05-3	0.576	409.2
Example 3.28	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloropyridine-3-sulfonamide	A3	6-Chloro-3-pyridinesulfonyl chloride CAS # 6684-39-5	0.561	397.2
Example 3.29	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)thiophene-2-sulfonamide	A3	2-Thiophenesulfonyl chloride CAS # 16629-19-9	0.525	368.2
Example 3.30	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3,5-dimethylisoxazole-4-sulfonamide	A3	3,5-Dimethylisoxazole-4-sulfonyl chloride CAS # 80466-79-1	0.535	381.3
Example 3.31	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloro-2-methylpyridine-3-sulfonamide	A3	6-Chloro-2-methyl-3-pyridinesulfonyl chloride CAS # 889944-74-5	0.596	411.3
Example 3.32	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoropyridine-3-sulfonamide	A3	6-Fluoro-3-pyridinesulfonyl chloride CAS # 1025509-80-1	0.507	381.2
Example 3.33	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-5-methylpyridine-3-sulfonamide	A3	2-Chloro-5-methyl-3-pyridinesulfonyl chloride CAS # 1208081-98-4	0.555	411.3
Example 3.34	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-6-methoxypyridine-3-sulfonamide	A3	2-Chloro-6-methoxy-3-pyridinesulfonyl chloride CAS # 1208081-26-8	0.603	427.2

Example 3.35	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloro-4-methylpyridine-3-sulfonamide	A3	6-Chloro-4-methyl-3-pyridinesulfonyl chloride CAS # 889944-76-7	0.601	411.3
Example 3.36	2-amino- <i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyrimidine-5-sulfonamide	A3	2-Amino-5-pyrimidinesulfonyl chloride CAS # 289484-00-0	0.412	379.3
Example 3.37	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methoxypyridine-3-sulfonamide	A3	6-Methoxy-3-pyridinesulfonyl chloride CAS # 312300-42-8	0.541	393.2
Example 3.38	<i>N</i> -(<i>trans</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chlorothiazole-5-sulfonamide	A3.1	2-Chloro-5-thiazolesulfonyl chloride CAS # 88917-11-7	0.596	403.3
Example 3.39	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methyloxazole-5-sulfonamide	A3	2-Methyl-5-oxazolesulfonyl chloride CAS # 1909316-63-7	0.481	367.4
Example 3.40	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyridine-4-sulfonamide	A3	4-Pyridinesulfonyl chloride CAS # 134479-04-2	0.455	363.3
Example 3.41	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloropyridine-3-sulfonamide	A3	2-Chloro-3-pyridinesulfonyl chloride CAS # 6684-06-6	0.507	397.3
Example 3.42	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methyl-1,3,4-thiadiazole-2-sulfonamide	A3	5-Methyl-1,3,4-thiadiazole-2-sulfonyl chloride CAS # 184222-90-0	0.481	384.2

Example 3.43	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide	A3	2-Methyl-3-pyridinesulfonyl chloride CAS # 872001-95-1	0.481	377.3
Example 3.44	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloropyridine-3-sulfonamide	A3	5-Chloro-3-pyridinesulfonyl chloride CAS # 1060802-18-7	0.550	397.2
Example 3.45	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-2-methoxypyridine-3-sulfonamide	A3	5-Chloro-2-methoxy-3-pyridinesulfonyl chloride CAS # 1261451-92-6	0.627	427.3
Example 3.46	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-6-methylpyridine-3-sulfonamide	A3	2-Chloro-6-methyl-3-pyridinesulfonyl chloride CAS # 1208081-60-0	0.548	411.3
Example 3.47	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methyl-6-(trifluoromethyl)pyridine-3-sulfonamide	A3	5-Methyl-6-(trifluoromethyl)-3-pyridinesulfonyl chloride CAS # 2166663-13-2	0.667	445.3
Example 3.48	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(dimethylamino)pyridine-3-sulfonamide	A3	6-(Dimethylamino)-3-pyridinesulfonyl chloride CAS # 680591-58-6	0.527	406.5
Example 3.49	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-4-methylthiazole-5-sulfonamide	A3	2-Chloro-4-methyl-5-thiazolesulfonyl chloride CAS # 292138-59-1	0.611	417.3
Example 3.50	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(trifluoromethyl)pyridine-3-sulfonamide	A3	6-(Trifluoromethyl)-3-pyridinesulfonyl chloride CAS # 959996-58-8	0.623	431.3

Example 3.51	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)thiazole-4-sulfonamide	A3	4-Thiazolesulfonyl chloride CAS # 89501-99-5	0.438	369.2
Example 3.52	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-methylpyridine-3-sulfonamide	A3	4-Methyl-3-pyridinesulfonyl chloride CAS # 372198-42-0	0.481	377.3
Example 3.53	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide	A3	2,5-Difluorobenzenesulfonyl chloride CAS # 26120-86-5	0.581	398.2
Example 3.54	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-5-methylpyridine-3-sulfonamide	A3	2-Fluoro-5-methyl-3-pyridinesulfonyl chloride CAS # 2055931-49-0	0.546	395.3
Example 3.55	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methoxythiazole-5-sulfonamide	A3	2-Methoxy-5-thiazolesulfonyl chloride CAS # 1803608-63-0	0.483	399.3
Example 3.56	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-chloropyridine-3-sulfonamide	A3	4-Chloro-3-pyridinesulfonyl chloride CAS # 33263-44-4	0.496	397.3
Example 3.57	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-methylthiazole-2-sulfonamide	A3	4-Methyl-2-thiazolesulfonyl chloride CAS # 459843-97-1	0.519	383.3
Example 3.58	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methylisoxazole-4-sulfonamide	A3	3-Methyl-4-isoxazolesulfonyl chloride CAS # 858489-87-9	0.494	367.2

Example 3.59	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-5-methylpyridine-3-sulfonamide	A3	6-Fluoro-5-methyl-3-pyridinesulfonyl chloride CAS # 2243510-24-7	0.566	395.3
Example 3.60	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,4-dimethylthiazole-5-sulfonamide	A3	2,4-Dimethylthiazole-5-sulfonyl chloride CAS # 80466-80-4	0.524	397.3
Example 3.61	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyrazine-2-sulfonamide	A3	2-Pyrazinesulfonyl chloride CAS # 184170-48-7	0.436	364.3
Example 3.62	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoropyridine-3-sulfonamide	A3	5-Fluoro-3-pyridinesulfonyl chloride CAS # 1060802-49-4	0.501	381.3
Example 3.63	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyrimidine-5-sulfonamide	A3	5-Pyrimidinesulfonyl chloride CAS # 856596-17-3	0.438	364.3
Example 3.64	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-1-methyl-1 <i>H</i> -1,2,3-triazole-4-sulfonamide	A3	1-Methyl-1 <i>H</i> -1,2,3-triazole-4-sulfonyl chloride CAS # 1351676-71-5	0.417	367.2
Example 3.65	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(1,1-difluoroethyl)thiazole-5-sulfonamide	A3	2-(1,1-Difluoroethyl)-5-thiazolesulfonyl chloride CAS # 2648962-47-2	0.646	433.3
Example 3.66	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chlorothiazole-4-sulfonamide	A3	2-Chloro-4-thiazolesulfonyl chloride CAS # 1934444-85-5	0.531	403.2

Example 3.67	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluorothiophene-2-sulfonamide	A3	5-Fluoro-2-thiophenesulfonyl chloride CAS # 1132652-99-3	0.578	386.2
Example 3.68	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-1,5-dimethyl-1 <i>H</i> -pyrazole-3-sulfonamide	A3	1,5-Dimethyl-1 <i>H</i> -pyrazole-3-sulfonyl chloride CAS # 1354706-13-0	0.473	380.3
Example 3.69	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methylisothiazole-5-sulfonamide	A3	3-Methyl-5-isothiazolesulfonyl chloride CAS # 1355334-86-9	0.555	383.2
Example 3.70	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-(difluoromethyl)thiophene-3-sulfonamide	A3	5-(Difluoromethyl)-3-thiophenesulfonyl chloride CAS # 1781345-13-8	0.601	418.3
Example 3.71	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methylthiophene-2-sulfonamide	A3	5-Methyl-2-thiophenesulfonyl chloride CAS # 55854-45-0	0.584	382.3
Example 3.72	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methyl-2 <i>H</i> -1,2,3-triazole-4-sulfonamide	A3	2-Methyl-2 <i>H</i> -1,2,3-triazole-4-sulfonyl chloride CAS # 1496511-49-9	0.460	367.3
Example 3.73	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methoxythiophene-2-sulfonamide	A3	5-Methoxy-2-thiophenesulfonyl chloride CAS # 1314904-87-4	0.576	398.2
Example 3.74	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridazine-3-sulfonamide	A3	6-Methyl-3-pyridazinesulfonyl chloride CAS # 1250556-77-4	0.451	378.3

Example 3.75	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-methylthiophene-2-sulfonamide	A3	4-Methylthiophene-2-sulfonyl chloride CAS # 69815-97-0	0.604	382.3
Example 3.76	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methylthiophene-3-sulfonamide	A3	5-Methyl-3-thiophenesulfonyl chloride CAS # 89379-25-9	0.601	382.2
Example 3.77	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chlorothiophene-2-sulfonamide	A3	5-Chloro-2-thiophenesulfonyl chloride CAS # 2766-74-7	0.654	402.2
Example 3.78	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-cyclopropylthiophene-2-sulfonamide	A3	5-Cyclopropyl-2-thiophenesulfonyl chloride CAS # 2141875-46-7	0.679	408.3
Example 3.79	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methylthiophene-2-sulfonamide	A3	3-Methyl-2-thiophenesulfonyl chloride CAS # 61714-76-9	0.587	382.2
Example 3.80	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-bromothiophene-2-sulfonamide	A3	5-Bromo-2-thiophenesulfonyl chloride CAS # 55854-46-1	0.667	448.2
Example 3.81	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,6-dichloropyridine-3-sulfonamide	A3	2,6-Dichloro-3-pyridinesulfonyl chloride CAS # 239810-43-6	0.633	431.2
Example 3.82	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloro-5-methylpyridine-3-sulfonamide	A3	6-Chloro-5-methyl-3-pyridinesulfonyl chloride CAS # 37105-10-5	0.616	411.3

Example 3.83	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-cyanopyridine-3-sulfonamide	A3	5-Cyano-3-pyridinesulfonyl chloride CAS # 1060804-15-0	0.511	388.3
Example 3.84	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-cyanopyridine-3-sulfonamide	A3	6-Cyano-3-pyridinesulfonyl chloride CAS # 928139-31-5	0.536	388.3
Example 3.85	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(difluoromethyl)pyridine-3-sulfonamide	A3	B2	0.544	413.4
Example 3.86	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloro-5-fluoropyridine-3-sulfonamide	A3	6-Chloro-5-fluoro-3-pyridinesulfonyl chloride CAS # 1261737-06-7	0.601	415.4
Example 3.87	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methylpyridine-3-sulfonamide	A3	5-Methyl-3-pyridinesulfonyl chloride CAS # 166337-57-1	0.493	377.4
Example 3.88	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-6-methylpyridine-3-sulfonamide	A3	B3	0.547	395.4
Example 3.89	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-6-fluoropyridine-3-sulfonamide	A3	5-Chloro-6-fluoro-3-pyridinesulfonyl chloride CAS # 1261585-97-0	0.606	415.4
Example 3.90	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-difluoropyridine-3-sulfonamide	A3	5,6-Difluoro-3-pyridinesulfonyl chloride CAS # 1261729-75-2	0.586	399.5

Example 3.91	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide	A3	B4	0.537	395.4
Example 3.92	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-2-methylpyridine-3-sulfonamide	A3	B5	0.554	395.4
Example 3.93	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(difluoromethyl)pyridine-3-sulfonamide	A3	B6	0.531	413.3
Example 3.94	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-6-methylpyridine-3-sulfonamide	A3	B7	0.603	411.3
Example 3.95	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-ethylpyridine-3-sulfonamide	A3	B8	0.554	391.4
Example 3.96	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-cyclopropylpyridine-3-sulfonamide	A3	B9	0.595	403.4
Example 3.97	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-cyclopropylpyridine-3-sulfonamide	A3	B10	0.579	403.4
Example 3.98	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-6-fluoropyridine-3-sulfonamide	A3	B11	0.581	415.3

Example 3.99	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-5,6-dimethylpyridine-3-sulfonamide	A3	B12	0.600	425.3
Example 3.100	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-(difluoromethyl)pyridine-3-sulfonamide	A3	5-(Difluoromethyl)-3-pyridinesulfonyl chloride CAS # 1780034-60-7	0.547	413.4
Example 3.101	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-ethylpyridine-3-sulfonamide	A3	B13	0.561	391.4
Example 3.102	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,6-dimethylpyridine-3-sulfonamide	A3	B14	0.507	391.4
Example 3.103	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-2-methylpyridine-3-sulfonamide	A3	B15	0.601	411.3
Example 3.104	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-2-fluoropyridine-3-sulfonamide	A3	B16	0.596	415.3
Example 3.105	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-2-methylpyridine-3-sulfonamide	A3	B17	0.546	395.3
Example 3.106	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,5-dimethylpyridine-3-sulfonamide	A3	2,5-Dimethylpyridine-3-sulfonyl chloride CAS # 1785415-03-3	0.528	391.5

Example 3.107	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-5,6-dimethylpyridine-3-sulfonamide	A3	B18	0.586	409.4
Example 3.108	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dichloropyridine-3-sulfonamide	A3	5,6-Dichloro-3-pyridinesulfonyl chloride CAS # 98121-40-5	0.661	431.4
Example 3.109	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(methylamino)pyridine-3-sulfonamide	A3	B19	0.435	392.5
Example 3.110	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-bromopyridine-3-sulfonamide	A3	2-Bromo-3-pyridinesulfonyl chloride CAS # 1060811-59-7	0.521	443.3
Example 3.111	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,5,6-trimethylpyridine-3-sulfonamide	A3	B20	0.520	405.5
Example 3.112	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-iodobenzenesulfonamide	A3	4-Iodobenzenesulfonyl chloride CAS # 98-61-3	0.661	488.3
Example 3.113	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-iodobenzenesulfonamide	A3	3-Iodobenzenesulfonyl chloride CAS # 50702-38-0	0.656	488.3
Example 3.114	<i>N</i> -(<i>trans</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-2-methylpyridine-3-sulfonamide	A3.1	B5	0.565	395.3

The examples from **Table 7** below are made according to the abovementioned procedure described for the synthesis of Example 3.1 using appropriate intermediate A and the appropriate sulfonylchloride B as starting materials. Reaction time goes up to 24h, at RT, with purification by prepHPLC (acidic or basic conditions).

5 **Table 7**

					LC-MS (QC conditions)
Example number	Example Name	Amine precursor A	Sulfonyl chloride precursor B	t _R (min)	[M+H] ⁺
Example 4.1	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A4	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.553	378.3
Example 4.2	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide	A4	2-Fluoro-3-pyridinesulfonyl chloride CAS # 1089330-70-0	0.467	379.3
Example 4.3	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylthiazole-4-sulfonamide	A4	2-Methyl-4-thiazolesulfonyl chloride CAS # 1382676-48-3	0.451	381.3
Example 4.4	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylthiazole-5-sulfonamide	A4	2-Methyl-5-thiazolesulfonyl chloride CAS # 1314977-63-3	0.470	381.2
Example 4.5	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)pyridine-3-sulfonamide	A4	3-Pyridinesulfonyl chloride CAS # 16133-25-8	0.429	361.5

Example 4.6	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloropyridine-3-sulfonamide	A4	2-Chloro-3-pyridinesulfonyl chloride CAS # 6684-06-6	0.479	395.3
Example 4.7	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide	A4	2-Methyl-3-pyridinesulfonyl chloride CAS # 872001-95-1	0.454	375.4
Example 4.8	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoropyridine-3-sulfonamide	A4	5-Fluoro-3-pyridinesulfonyl chloride CAS # 1060802-49-4	0.476	379.3
Example 4.9	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloropyridine-3-sulfonamide	A4	5-Chloro-3-pyridinesulfonyl chloride CAS # 1060802-18-7	0.530	395.3
Example 4.10	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoropyridine-3-sulfonamide	A4	6-Fluoro-3-pyridinesulfonyl chloride CAS # 1025509-80-1	0.486	379.3
Example 4.11	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloropyridine-3-sulfonamide	A4	6-Chloro-3-pyridinesulfonyl chloride CAS # 6684-39-5	0.530	395.3
Example 4.12	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide	A4	6-Methyl-3-pyridinesulfonyl chloride CAS # 478264-00-5	0.461	375.3
Example 4.13	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide	A4	B4	0.509	393.5

Example 4.14	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2,6-dimethylpyridine-3-sulfonamide	A4	B14	0.497	389.6
Example 4.15	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide	A4	B1	0.476	389.6

Example 5.1: *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide

Example 5.1 is made according to the abovementioned procedure described for the synthesis of Example 3.1 using intermediate A5 and 2-fluoro-3-pyridinesulfonyl chloride (CAS # 1089330-70-0) as starting materials. LC-MS (QC conditions): t_R = 0.543 min; $[M+H]^+$ = 435.4. 1H NMR (500 MHz, DMSO) δ : 8.51-8.53 (m, 2 H), 8.34 (m, 1 H), 7.60 (ddd, J_1 = 1.7 Hz, J_2 = 4.9 Hz, J_3 = 7.5 Hz, 1 H), 7.20 (d, J = 9.0 Hz, 1 H), 5.98 (s, 2 H), 5.59 (s, 1 H), 4.93-4.97 (m, 1 H), 3.67-3.70 (m, 1 H), 2.75 (m, 1 H), 2.19-2.24 (m, 2 H), 1.93-1.99 (m, 2 H), 1.25 (d, J = 7.0 Hz, 3 H).

Example 5.2: *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide

Example 5.2 is made according to the abovementioned procedure described for the synthesis of Example 3.1 using intermediate A5 and sulfonylchloride B1 as starting materials. LC-MS (QC conditions): t_R = 0.568 min; $[M+H]^+$ = 445.4. 1H NMR (500 MHz, DMSO) δ : 8.63 (d, J = 2.1 Hz, 1 H), 8.04 (d, J = 8.4 Hz, 1 H), 7.89 (d, J = 1.8 Hz, 1 H), 7.19 (d, J = 9.0 Hz, 1 H), 5.97 (s, 2 H), 5.58 (s, 1 H), 4.94-4.95 (m, 1 H), 3.64 (m, 1 H), 2.74 (m, 1 H), 2.51 (s, 3 H), 2.35 (s, 3 H), 2.20 (qd, J_1 = 3.7 Hz, J_2 = 7.3 Hz, 2 H), 1.86 (m, 2 H), 1.24 (d, J = 7.0 Hz, 3 H).

The examples from **Table 8** below are made according to the abovementioned procedure described for the synthesis of Example 3.1 using appropriate intermediate A and the appropriate sulfonylchloride B as starting materials. Reaction time goes up to 24h, at RT, with purification by prepHPLC (acidic or basic conditions).

Table 8

Example number	Example Name	Amine precurs or A	Sulfonyl chloride precursor B	LC-MS (QC conditions)	
				t_R (min)	$[M+H]^+$

Example 5.3	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A5	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.617	434.3
Example 5.4	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)pyridine-3-sulfonamide	A5	3-Pyridinesulfonyl chloride CAS # 16133-25-8	0.493	417.3
Example 5.5	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-fluoropyridine-3-sulfonamide	A5	6-Fluoro-3-pyridinesulfonyl chloride CAS # 1025509-80-1	0.551	435.3
Example 5.6	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide	A5	6-Methyl-3-pyridinesulfonyl chloride CAS # 478264-00-5	0.524	431.3
Example 5.7	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-5-methylpyridine-3-sulfonamide	A5	6-Fluoro-5-methyl-3-pyridinesulfonyl chloride CAS # 2243510-24-7	0.604	449.3
Example 5.8	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-2-methylpyridine-3-sulfonamide	A5	B5	0.586	449.4
Example 5.9	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-2-methylpyridine-3-sulfonamide	A5	B17	0.573	449.4
Example 5.10	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide	A5	2-Methyl-3-pyridinesulfonyl chloride CAS # 872001-95-1	0.516	431.4

Example 5.11	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2,6-dimethylpyridine-3-sulfonamide	A5	B14	0.540	445.3
Example 5.12	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide	A5	B4	0.576	449.3
Example 5.13	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-6-methylpyridine-3-sulfonamide	A5	B3	0.583	449.3
Example 5.14	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-chloro-4-iodobenzenesulfonamide	A5	3-Chloro-4-iodobenzenesulfonyl chloride CAS # 1261580-79-3	0.769	576.2
Example 5.15	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluoro-4-iodobenzenesulfonamide	A5	3-Fluoro-4-iodobenzenesulfonyl chloride CAS # 874839-62-0	0.728	560.2
Example 5.16	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-4-iodobenzenesulfonamide	A5	2-Fluoro-4-iodobenzenesulfonyl chloride CAS # 583047-48-7	0.716	560.2
Example 5.17	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-4-iodobenzenesulfonamide	A5	4-Iodobenzenesulfonyl chloride CAS # 98-61-3	0.710	542.2
Example 5.18	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-cyano-4-iodobenzenesulfonamide	A5	B21	0.691	567.2

Example 5.19	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-4-iodo-3-methylbenzenesulfonamide	A5	4-Iodo-3-methylbenzene-1-sulfonyl chloride CAS # 858004-37-2	0.760	556.2
Example 6.1	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A6	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.581	380.2
Example 6.2	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide	A6	2,3-Difluorobenzenesulfonyl chloride CAS # 210532-24-4	0.597	398.2
Example 6.3	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide	A6	2,5-Difluorobenzenesulfonyl chloride CAS # 26120-86-5	0.587	398.2
Example 6.4	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide	A6	B1	0.523	391.2
Example 6.5	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide	A6	2-Fluoro-3-pyridinesulfonyl chloride CAS # 1089330-70-0	0.494	381.3
Example 7.1	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(tert-butylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A7	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.642	394.4
Example 7.2	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(tert-butylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide	A7	B1	0.591	405.5

Example 7.3	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(<i>tert</i> -butylamino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide	A7	2-Methyl-3-pyridinesulfonyl chloride CAS # 872001-95-1	0.544	391.3
Example 7.4	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(<i>tert</i> -butylamino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide	A7	6-Methyl-3-pyridinesulfonyl chloride CAS # 478264-00-5	0.544	391.3
Example 7.5	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(<i>tert</i> -butylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide	A7	2-Fluoro-3-pyridinesulfonyl chloride CAS # 1089330-70-0	0.556	395.3
Example 7.6	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(<i>tert</i> -butylamino)pyrimidin-4-yl)cyclobutyl)-2,6-dimethylpyridine-3-sulfonamide	A7	B14	0.560	405.5
Example 7.7	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(<i>tert</i> -butylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide	A7	B4	0.594	409.3
Example 10.1	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclobutylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.1	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.603	392.2
Example 10.2	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((cyclobutylmethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.2	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.665	406.2
Example 10.3	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclobutylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide	A10.1	2,3-Difluorobenzenesulfonyl chloride CAS # 210532-24-4	0.621	410.2

Example 10.4	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((cyclobutylmethyl)amino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide	A10.2	2,3-Difluorobenzenesulfonyl chloride CAS # 210532-24-4	0.677	424.2
Example 10.5	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclobutylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide	A10.1	2,5-Difluorobenzenesulfonyl chloride CAS # 26120-86-5	0.616	410.2
Example 10.6	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((cyclobutylmethyl)amino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide	A10.2	2,5-Difluorobenzenesulfonyl chloride CAS # 26120-86-5	0.674	424.2
Example 10.7	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>S</i>)-1-hydroxypropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.3	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.491	396.3
Example 10.8	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((1-hydroxy-2-methylpropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.4	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.536	410.3
Example 10.9	<i>rac-N</i> -(<i>cis</i> -3-(2-amino-6-(sec-butylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.5	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.637	394.4
Example 10.10	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((2,2-difluoroethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.6	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.526	402.3
Example 10.11	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.7	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.570	420.3

Example 10.12	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((2-fluoroethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.8	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.452	384.3
Example 10.13	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((1-fluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.9	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.552	398.4
Example 10.14	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((2-methoxyethyl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide	A10.10	2-Fluoro-3-pyridinesulfonyl chloride CAS # 1089330-70-0	0.426	397.3
Example 10.15	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>S</i>)-1-hydroxypropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide	A10.3	2-Fluoro-3-pyridinesulfonyl chloride CAS # 1089330-70-0	0.404	397.2
Example 10.16	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>S</i>)-1-methoxypropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide	A10.11	2-Fluoro-3-pyridinesulfonyl chloride CAS # 1089330-70-0	0.471	411.3
Example 10.17	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((1-methoxy-2-methylpropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide	A10.12	2-Fluoro-3-pyridinesulfonyl chloride CAS # 1089330-70-0	0.544	425.3
Example 10.18	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>S</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide	A10.13	2-Fluoro-3-pyridinesulfonyl chloride CAS # 1089330-70-0	0.542	435.4
Example 10.19	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>S</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.13	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.623	434.4

Example 10.20	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>S</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide	A10.13	B1	0.567	445.5
Example 10.21	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((1-fluorocyclopropyl)methyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.14	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.591	410.5
Example 10.22	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((1-fluorocyclopropyl)methyl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide	A10.14	B1	0.536	421.5
Example 10.23	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((1,3-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.15	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.546	416.4
Example 10.24	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((1,1,1-trifluoro-2-methylpropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide	A10.16	2-Fluoro-3-pyridinesulfonyl chloride CAS # 1089330-70-0	0.598	449.4
Example 10.25	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(butylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.17	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.650	394.4
Example 10.26	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isobutylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.18	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.642	394.4
Example 10.27	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclopentylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.19	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.657	406.4

Example 10.28	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(cyclohexylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.20	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.704	420.4
Example 10.29	<i>N</i> -(<i>cis</i> -3-(2-amino-6-((cyclopropylmethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A10.21	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.603	392.3
Example 10.30	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)- <i>sec</i> -butyl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide	A10.22	B1	0.568	405.4
Example 10.31	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)- <i>sec</i> -butyl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide	A10.22	2-Fluoro-3-pyridinesulfonyl chloride CAS # 1089330-70-0	0.541	395.3
Example 10.32	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>S</i>)- <i>sec</i> -butyl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide	A10.23	B1	0.567	405.5
Example 10.33	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>S</i>)- <i>sec</i> -butyl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide	A10.23	2-Fluoro-3-pyridinesulfonyl chloride CAS # 1089330-70-0	0.541	391.3
Example 14.1	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(ethylamino)-5-fluoropyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide	A14	3-Fluorobenzenesulfonyl chloride CAS # 701-27-9	0.567	384.3

Example 11.1: rac-*N*-(*cis*-3-(2-amino-6-((1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide

Example 11.1 is made according to the abovementioned procedure described for the synthesis of Example 3.1 using the appropriate intermediate A11 and 3-fluorobenzenesulfonylchloride (CAS # 701-27-9) as starting materials. Purification by prepHPLC (basic conditions) gives the title compound. LC-MS (QC conditions): t_R = 0.581 min; $[M+H]^+$

= 416.4. ¹H NMR (500 MHz, DMSO) δ: 8.09 (d, *J* = 8.5 Hz, 1 H), 7.66-7.68 (m, 2 H), 7.58-7.61 (m, 1 H), 7.51-7.55 (m, 1 H), 6.90 (d, *J* = 7.5 Hz, 1 H), 5.87-6.10 (m, 3 H), 5.55 (s, 1 H), 4.40-4.41 (m, 1 H), 3.63 (m, 1 H), 2.71 (m, 1 H), 2.16-2.21 (m, 2 H), 1.82-1.88 (m, 2 H), 1.12 (d, *J* = 7.0 Hz, 3 H).

Examples 11.2 and 11.3: *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide and *N*-(*cis*-3-(2-amino-6-(((*S*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide

23 mg of Example 11.1 are separated on a chiral stationary phase using the method below to give 7 mg of each title compound. Example 11.2: SFC (chiral A): *t_R* = 1.57 min. LC-MS (QC conditions): *t_R* = 0.594; [M+H]⁺ = 416.3. Example 11.3: SFC (chiral A): *t_R* = 2.55 min. LC-MS (QC conditions): *t_R* = 0.596 min; [M+H]⁺ = 416.3.

10 Column: Chiralcel OZ-H 30x250mm, 5 μm; Detector wavelength: 217 nm; Eluent: 70% CO₂ and 30% (EtOH 0.1% diethylamine); Flow: 160.00 mL/min; BPR: 100 bar; Temperature: 40°C. Injection volume: 1000 μL.

Example 11.4: *rac-N*-(*cis*-3-(2-amino-6-((1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide

15 Example 11.4 is made according to the abovementioned procedure described for the synthesis of Example 3.1 using the appropriate intermediate A11 and sulfonylchloride B1 as starting materials. Purification by prepHPLC (basic conditions) gives the title compound. LC-MS (QC conditions): *t_R* = 0.525 min; [M+H]⁺ = 427.5. ¹H NMR (500 MHz, DMSO) δ: 8.63 (d, *J* = 2.2 Hz, 1 H), 8.05 (s, 1 H), 7.89 (d, *J* = 1.9 Hz, 1 H), 6.90 (d, *J* = 7.8 Hz, 1 H), 5.87-6.10 (m, 3 H), 5.56 (s, 1 H), 4.40-4.41 (m, 1 H), 3.61-3.65 (m, 1 H), 2.72 (m, 1 H), 2.51 (s, 3 H), 2.35 (s, 3 H), 2.17-2.22 (m, 2 H), 1.85 (m, 2 H), 1.12 (d, *J* = 7.0 Hz, 3 H).

20 **Example 11.6:** *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide and **Example 11.5** *N*-(*cis*-3-(2-amino-6-(((*S*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide

21 mg of Example 11.4 are separated on a chiral stationary phase using the method below to give 6 mg of each title compound. Example 11.5: SFC (chiral B): *t_R* = 2.17 min. LC-MS (QC conditions): *t_R* = 0.536; [M+H]⁺ = 427.4. Example 25 11.6: SFC (chiral B): *t_R* = 3.30 min. LC-MS (QC conditions): *t_R* = 0.537 min; [M+H]⁺ = 427.4.

Column: Chiralcel OZ-H 30x250mm, 5 μm; Detector wavelength: 214 nm; Eluent: 65% CO₂ and 35% (EtOH 0.1% diethylamine); Flow: 160.00 mL/min; BPR: 100 bar; Temperature: 40°C. Injection volume: 1000 μL.

Alternatively, Example 11.5 can be prepared according to the abovementioned procedure described for the synthesis of Example 3.1 using intermediate A12 and the sulfonylchloride B1 as starting materials. Reaction time goes up to 24h, 30 at RT, with purification by prepHPLC (acidic or basic conditions).

Alternatively, Example 11.6 can be prepared according to the abovementioned procedure described for the synthesis of Example 3.1 using intermediate A13 and the sulfonylchloride B1 as starting materials. Reaction time goes up to 24h, at RT, with purification by prepHPLC (acidic or basic conditions).

Example 12.1: *N*-(*cis*-3-(2-amino-6-(oxetan-3-ylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide

35 **Step 1:** 4-(*cis*-3-aminocyclobutyl)-6-chloropyrimidin-2-amine hydrochloride C1

To a solution of intermediate D1 (75 mg, 0.25 mmol) in dioxane (0.65 mL) is added a solution of HCl (4N in dioxane, 0.63 mL, 2.5 mmol). The reaction is stirred RT for 2h. The mixture is concentrated and the solid is dried under vacuum to give 68 mg of intermediate C1. LC-MS (conditions A): t_R = 0.51 min; $[M+H]^+$ = 199.36.

Step 2: *N*-(*cis*-3-(2-amino-6-chloropyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide Ca1

- 5 To a solution of intermediate C1 (68 mg, 0.25 mmol) in DCM (2 mL) is added 3-fluorobenzenesulfonyl chloride (CAS # 701-27-9) (51 mg, 0.25 mmol) and NEt_3 (0.18 mL, 1.25 mmol). The reaction is stirred at RT for 16h. The mixture is diluted with water (50 mL) and the aq. phase is extracted with DCM (2x50 mL). The combined org. phases are washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to give 90 mg of intermediate Ca1. LC-MS (conditions A): t_R = 0.82 min; $[M+H]^+$ = 357.42. 1H NMR (400 MHz, DMSO) δ : 8.13 (d, J = 8.7 Hz, 1 H), 7.66 (d, J = 3.2 Hz, 2 H), 7.59 (d, J = 8.8 Hz, 1 H), 7.52-7.56 (m, 1 H), 7.02 (s, 2 H), 6.48 (s, 1 H), 3.69 (m, 1 H), 2.94 (m, 1 H), 2.25-2.30 (m, 2 H), 1.90-1.97 (m, 2 H).
- 10

Step 3: *N*-(*cis*-3-(2-amino-6-(oxetan-3-ylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide Example 12.1

- To a solution of intermediate Ca1 (70 mg, 0.2 mmol) in EtOH (0.9 mL) is added DIPEA (0.07 mL, 0.4 mmol) and oxetan-3-amine (CAS # 21635-88-1) (30 mg, 0.4 mmol). The reaction is heated to 85°C for 16h. More oxetan-3-amine (CAS # 21635-88-1) (30 mg, 0.4 mmol) is added, and the mixture is stirred at 85°C for another 24h. Purification by prepHPLC (basic conditions) gives 2 mg of Example 12.1. LC-MS (QC conditions): t_R = 0.476 min; $[M+H]^+$ = 394.3. 1H NMR (500 MHz, DMSO) δ : 8.10 (d, J = 8.3 Hz, 1 H), 7.66-7.68 (m, 2 H), 7.58-7.60 (m, 1 H), 7.52-7.55 (m, 1 H), 6.67-6.69 (m, 1 H), 5.84 (s, 2 H), 5.46 (s, 1 H), 4.88-4.89 (m, 1 H), 4.73 (t, J = 6.5 Hz, 2 H), 4.39 (t, J = 6.4 Hz, 2 H), 3.60-3.65 (m, 1 H), 2.68-2.75 (m, 1 H), 2.18 (qd, J_1 = 2.7 Hz, J_2 = 7.7 Hz, 2 H), 1.85 (m, 2 H).
- 15
- 20

Example [^{18}F]-5.1: *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro- ^{18}F)-pyridine-3-sulfonamide

- $[^{18}F]$ fluoride ions are produced by bombardment of 98% enriched ^{18}O -water via the $^{18}O(p,n)^{18}F$ nuclear reaction. The aqueous solution is transferred from the cyclotron to the hot-cell and trapped on a QMA cartridge (Waters SepPak Accel QMA cartridge carbonate). A mixture of kryptofix 2.2.2 (CAS # 23978-09-8) (5 mg/mL), K_2CO_3 (1 mg/mL) in MeCN/ H_2O (4:1) is applied to elute the radioactivity to the reaction vial. After azeotropic drying with MeCN (3x0.8 mL), 2-3 mg of intermediate G1 dissolved in DMF or DMSO (0.3 mL) is added to the residue and the mixture is heated to 150°C for 10 min in a closed reaction vial. After cooling down the reaction and dilution with 2.7 mL water, the mixture is purified by semi-preparative HPLC (Column: Gemini 5 μ m C18, 250 x 10mm; Eluent A: 0.5% NH_3 in water; Eluent B: MeCN; Gradient: isocratic with 23% A; Retention time: 770-970 seconds). The collected fraction is diluted with 8 mL Milli-Q water and passed through a pre-conditioned C18 light cartridge (Waters, WAT023501). After washing with 5 mL Milli-Q water, the final radioligand is eluted with 1 mL EtOH and diluted with water for quality control. The radiochemical yield of the radioligand is ranging between 2-5 GBq (collected activity) or 2-32 GBq/ μ mol (Molar activity), respectively. The identity of the compounds was confirmed by identical retention time as compared to unlabeled Example 5.1.
- 25
- 30
- 35

The examples from **Table 9** below may be prepared in analogy to the procedure described for example [^{18}F]-5.1 using the appropriate precursor G or H.

Table 9

Example number	Example Name	precursor G or H
Example [¹⁸F]-3.2	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro- ¹⁸ F)-pyridine-3-sulfonamide	G2 or H2
Example [¹⁸F]-3.59	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro- ¹⁸ F)-5-methylpyridine-3-sulfonamide	G3
Example [¹⁸F]-3.91	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro- ¹⁸ F)-6-methylpyridine-3-sulfonamide	G6
Example [¹⁸F]-3.92	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro- ¹⁸ F)-2-methylpyridine-3-sulfonamide	G7
Example [¹⁸F]-5.5	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro- ¹⁸ F)-pyridine-3-sulfonamide	G9 or H9
Example [¹⁸F]-5.7	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro- ¹⁸ F)-5-methylpyridine-3-sulfonamide	G10
Example [¹⁸F]-5.8	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-(fluoro- ¹⁸ F)-2-methylpyridine-3-sulfonamide	G11

Example [¹⁸ F]-5.12	<i>N</i> -(<i>cis</i> -3-(2-amino-6-(((<i>R</i>)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-(fluoro- ¹⁸ F)-6-methylpyridine-3-sulfonamide	G13
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BIOLOGICAL TESTS

FLIPR hCCR8 assay

20'000 HEK293.hCCR8 cells/well were seeded in 50µl of 90% DMEM, 10% none heat inactivated Foetal Bovine Serum, 1% Penicillin/Streptomycin, 800µg/ml G418, 200µg/ml hygromycin B into 384-well plate coated with Poly-L-Lysine. Cells were incubated at 37°C, 5% CO₂ for 24hours. Compounds to be tested were prepared by serial dilution from 10µM to 0.038nM. FLIPR buffer containing HBSS/0.1%BSA/20mM Hepes/2.5mM probenecid was made and FLIPR staining solution was obtained by adding 15ml FLIPR buffer to 10ml calcium 6 for one plate. Medium was removed from cells. 50µl of the above staining solution was added. The plate was centrifugated briefly and incubated at 37°C, 5% CO₂ for 1h30. 10µl of compounds diluted in FLIPR buffer were distributed and incubated for 30 minutes in the dark followed by the addition of 10µl of a 70nM hCCL1 stock solution. The signal is recorded immediately with the FLIPR device. Data were analyzed to generate IC₅₀ values, and the results are summarized in **Table 10**.

Table 10

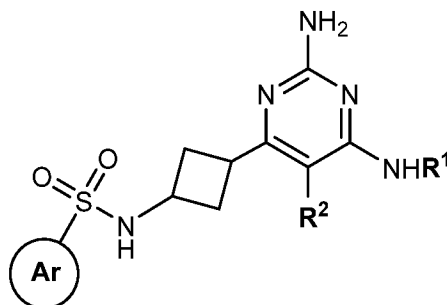
Example Number	hCCR8 (IC ₅₀ in nM)	2.3	89	3.16	14	3.34	99
		2.4	12	3.17	69	3.35	295
		2.5	77	3.18	12	3.36	86
		3.1	21	3.19	37	3.37	73
1.1	716	3.2	10	3.20	8	3.38	178
1.2	1700	3.3	2	3.21	16	3.39	627
1.3	357	3.4	1030	3.22	598	3.40	764
1.4	348	3.5	55	3.23	186	3.41	11
1.5	97	3.6	134	3.24	152	3.42	88
1.6	553	3.7	1480	3.25	55	3.43	7
1.7	236	3.8	119	3.26	22	3.44	28
1.8	444	3.9	389	3.27	79	3.45	2190
1.9	1600	3.10	26	3.28	18	3.46	7
1.10	931	3.11	146	3.29	109	3.47	42
1.11	373	3.12	44	3.30	1140	3.48	3640
1.12	471	3.13	1160	3.31	14	3.49	270
1.13	290	3.14	44	3.32	25	3.50	502
2.1	40	3.15	1640	3.33	619	3.51	842
2.2	117						

3.52	1420	3.86	17	4.6	7	7.1	27
3.53	46	3.87	58	4.7	13	7.2	4
3.54	37	3.88	3	4.8	23	7.3	11
3.55	36	3.89	52	4.9	38	7.4	16
3.56	84	3.90	22	4.10	80	7.5	19
3.57	534	3.91	4	4.11	39	7.6	11
3.58	2940	3.92	4	4.12	9	7.7	23
3.59	6	3.93	26	4.13	14	10.1	105
3.60	299	3.94	2	4.14	4	10.2	125
3.61	614	3.95	42	4.15	5	10.3	337
3.62	12	3.96	24	5.1	2	10.4	359
3.63	240	3.97	1900	5.2	1	10.5	195
3.64	2660	3.98	7	5.3	5	10.6	131
3.65	383	3.99	14	5.4	3	10.7	376
3.66	250	3.100	336	5.5	4	10.8	791
3.67	16	3.101	651	5.6	2	10.9	48
3.68	514	3.102	7	5.7	2	10.10	247
3.69	25	3.103	431	5.8	3	10.11	105
3.70	3	3.104	90	5.9	3	10.12	249
3.71	2	3.105	7	5.10	3	10.13	341
3.72	3430	3.106	787	5.11	2	10.14	2020
3.73	90	3.107	2	5.12	2	10.15	254
3.74	2160	3.108	6	5.13	1	10.16	501
3.75	5	3.109	55	5.14	10	10.17	1120
3.76	1	3.110	23	5.15	19	10.18	382
3.77	2	3.111	19	5.16	11	10.19	1620
3.78	11	3.112	124	5.17	23	10.20	125
3.79	165	3.113	336	5.18	82	10.21	549
3.80	2	3.114	534	5.19	11	10.22	40
3.81	7	4.1	25	6.1	45	10.23	779
3.82	3	4.2	16	6.2	147	10.24	165
3.83	186	4.3	1665	6.3	97	10.25	151
3.84	825	4.4	61	6.4	9	10.26	255
3.85	134	4.5	67	6.5	55	10.27	604

10.28	1770	10.32	7	11.3	48	12.1	1400
10.29	295	10.33	45	11.4	3	14.1	94
10.30	3	11.1	49	11.5	57		
10.31	15	11.2	866	11.6	4		

CLAIMS

1. A compound of Formula (I)



Formula (I),

wherein

Ar represents

- phenyl;
 - 5-membered heteroaryl containing from one to three ring heteroatoms independently selected from nitrogen, sulfur, and oxygen; or
 - 6-membered heteroaryl containing from one to three ring nitrogen atoms;
- wherein said phenyl, 5-membered heteroaryl, or 6-membered heteroaryl, independently is unsubstituted, mono-, di-, or tri-substituted, wherein the substituent independently represents

- halogen;
- cyano;
- C₁₋₃-alkyl;
- C₁₋₂-fluoroalkyl;
- C₁₋₂-alkoxy;
- C₃₋₄-cycloalkyl;
- C₁₋₂-fluoroalkoxy; or
- amino optionally mono- or di-substituted with methyl or ethyl;

R¹ represents

- C₁₋₅-alkyl;
- hydroxy-C₂₋₄-alkyl;
- C₁₋₂-alkoxy-C₂₋₄-alkyl;
- C₁₋₄-fluoroalkyl; or
- -L-Cy, wherein
 - -L- represents a bond or -CH₂-; and

- **Cy** represents C₃₋₆-cycloalkyl optionally containing one oxygen ring atom, wherein said C₃₋₆-cycloalkyl optionally containing one oxygen ring atom is unsubstituted or mono-substituted, wherein the substituent represents fluorine; and

R² represents hydrogen or fluorine;

5 or a pharmaceutically acceptable salt thereof;

with the proviso that the following compounds and salts thereof are excluded:

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-dimethylthiophene-3-sulfonamide;

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-5-chlorothiophene-2-sulfonamide;

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,4-dimethylbenzenesulfonamide;

10 *N*-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-3,5-dimethylisoxazole-4-sulfonamide;

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-methoxy-4-methylbenzenesulfonamide;

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,4-difluorobenzenesulfonamide;

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide;

N-(3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-4-methoxy-3-methylbenzenesulfonamide;

15 *N*-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-dimethylthiophene-3-sulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-5-chlorothiophene-2-sulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,4-dimethylbenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-3,5-dimethylisoxazole-4-sulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-methoxy-4-methylbenzenesulfonamide;

20 *N*-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,4-difluorobenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide; and

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-4-methoxy-3-methylbenzenesulfonamide.

2. A compound according to claim 1, wherein **Ar** represents

- 6-membered heteroaryl containing from one to three ring nitrogen atoms, wherein said 6-membered

25 heteroaryl is unsubstituted, mono-, di-, or tri-substituted, wherein the substituent independently represents

➤ halogen;

➤ cyano;

➤ C₁₋₃-alkyl;

➤ C₁₋₂-fluoroalkyl;

30 ➤ C₁₋₂-alkoxy;

➤ C₃₋₄-cycloalkyl;

➤ C₁₋₂-fluoroalkoxy; or

➤ amino optionally mono- or di-substituted with methyl or ethyl;

or a pharmaceutically acceptable salt thereof.

35 3. A compound according to claim 1, wherein **Ar** represents

- 6-membered heteroaryl selected from pyridin-3-yl, wherein said 6-membered heteroaryl is unsubstituted, mono-, di-, or tri-substituted, wherein the substituent independently represents

- halogen;
- C₁₋₃-alkyl;
- C₁₋₂-fluoroalkyl;
- C₁₋₂-alkoxy; or
- C₃₋₄-cycloalkyl;

or a pharmaceutically acceptable salt thereof.

4. A compound according to any one of claims 1 to 3, wherein **R¹** represents

- C₁₋₅-alkyl;
- hydroxy-C₂₋₄-alkyl;
- C₁₋₂-alkoxy-C₂₋₄-alkyl;
- C₁₋₄-fluoroalkyl; or
- -**L-Cy**, wherein
 - -**L**- represents a bond or -CH₂-; and
 - **Cy** represents C₃₋₆-cycloalkyl optionally containing one oxygen ring atom, wherein said C₃₋₆-cycloalkyl optionally containing one oxygen ring atom is unsubstituted or mono-substituted, wherein the substituent represents fluorine;

or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 3, wherein **R¹** represents

- ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, or sec-butyl;
- 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 2-fluoro-1-fluoromethyl-ethyl, 1-methyl-2,2-difluoro-ethyl, 1-methyl-1-trifluoromethyl-ethyl, or 2,2,2-trifluoro-1-methyl-ethyl; especially 1-methyl-1-trifluoromethyl-ethyl; or
- cyclopropyl, cyclopropyl-methyl, or (1-fluoro-cyclopropyl)-methyl;

or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 5, wherein **R²** represents hydrogen; or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 1, wherein

Ar represents a 6-membered heteroaryl, wherein said 6-membered heteroaryl is selected from pyridin-3-yl, wherein said pyridin-3-yl is unsubstituted, mono-, or di-substituted in position(s) 2 and/or 5 and/or 6, with regard to the nitrogen atom of said pyridin-3-yl; wherein the substituent(s) independently represent methyl or fluorine;

R¹ represents C₂₋₄-alkyl, cyclopropyl, or 2,2,2-trifluoro-1-methyl-ethyl; and

R² represents hydrogen;

or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 6, which is a radiolabeled compound, wherein

- **Ar** is as defined in any one of claims 1 to 6, wherein **Ar** is mono-, di-, or tri-substituted, wherein one substituent represents a radioactive isotope of fluorine, wherein the rest of the substituents of **Ar**, if any, independently

is/are as defined in any one of claims 1 to 6; **R¹** is as defined in any one of claims 1 to 6; and **R²** is as defined in any one of claims 1 to 6; or

- **Ar** is as defined in any one of claims 1 to 6, wherein **Ar** is mono-, di-, or tri-substituted, wherein one substituent represents a radioactive isotope of iodine, wherein the rest of the substituents of **Ar**, if any, independently is/are as defined in any one of claims 1 to 6; **R¹** is as defined in any one of claims 1 to 6; and **R²** is as defined in any one of claims 1 to 6; or

- **Ar** is as defined in any one of claims 1 to 6, wherein **Ar** is unsubstituted, mono-, di-, or tri-substituted, wherein the substituent, if any, independently is/are as defined in any one of claims 1 to 6; **R¹** is as defined in any one of claims 1 to 6; and **R²** represents a radioactive isotope of fluorine;

or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 1, wherein

the radical  represents:

- phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-iodophenyl, 3-iodophenyl, 3-chlorophenyl, 3-cyanophenyl, 3-methylphenyl, 3-methoxyphenyl, 3-(trifluoromethoxy)-phenyl, 3,4-difluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3-fluoro-4-methoxyphenyl, 3-methyl-4-methoxyphenyl, 3-fluoro-4-methylphenyl, 2-methyl-5-fluorophenyl, 2-fluoro-5-methylphenyl, 3,5-dichlorophenyl, 2-fluoro-5-chlorophenyl, 3-chloro-4-iodophenyl, 3-fluoro-4-iodophenyl, 2-fluoro-4-iodophenyl, 3-cyano-4-iodophenyl, 3-methyl-4-iodophenyl, or 2-chloro-5-fluorophenyl; and/or
- thiophen-2-yl, 4-methyl-thiophen-2-yl, 3-methyl-thiophen-2-yl, 5-methyl-thiophen-2-yl, 5-chloro-thiophen-2-yl, 5-fluoro-thiophen-2-yl, 5-bromo-thiophen-2-yl, 5-methoxy-thiophen-2-yl, 5-cyclopropyl-thiophene-2-yl, 5-methyl-thiophen-3-yl, 4-methyl-thiazol-2-yl, 2-methyl-thiazol-4-yl, 2-chloro-thiazol-4-yl, thiazol-4-yl, thiazol-5-yl, 2-ethyl-thiazol-5-yl, 2-methyl-thiazol-5-yl, 2-methoxy-thiazole-5-yl, 2-chloro-thiazol-5-yl, 2-cyclopropyl-thiazole-5-yl, 2-(1,1-difluoro-ethyl)-thiazole-5-yl, 2,4-dimethyl-thiazol-5-yl, 2-bromo-4-methyl-thiazol-5-yl, 2-chloro-4-methyl-thiazol-5-yl, 3-methyl-isothiazol-5-yl, 5-methyl-[1,3,4]thiadiazol-2-yl, 1-methyl-1H-pyrazole-4-yl, 3-methyl-isoxazol-4-yl, 2-methyl-oxazol-5-yl, 1-methyl-1H-[1,2,3]triazol-4-yl, 2-methyl-2H-[1,2,3]triazol-4-yl, 1,5-dimethyl-1H-pyrazol-3-yl, 3,5-dimethyl-isoxazole-4-yl, or 5-difluoromethyl-thiophen-3-yl; and/or
- pyridin-2-yl, pyridin-3-yl, 2-fluoro-pyridin-3-yl, 5-fluoro-pyridin-3-yl, 6-fluoro-pyridin-3-yl, 2-chloro-pyridin-3-yl, 4-chloro-pyridin-3-yl, 5-chloro-pyridin-3-yl, 6-chloro-pyridin-3-yl, 2-bromo-pyridin-3-yl, 2-methyl-pyridin-3-yl, 4-methyl-pyridin-3-yl, 5-methyl-pyridin-3-yl, 6-methyl-pyridin-3-yl, 5-ethyl-pyridin-3-yl, 6-ethyl-pyridin-3-yl, 5-cyclopropyl-pyridin-3-yl, 6-cyclopropyl-pyridin-3-yl, 5-cyano-pyridin-3-yl, 6-cyano-pyridin-3-yl, 6-methoxy-pyridin-3-yl, 6-methylamino-pyridin-3-yl, 2-difluoromethyl-pyridin-3-yl, 5-difluoromethyl-pyridin-3-yl, 6-difluoromethyl-pyridin-3-yl, 5,6-dimethyl-pyridin-3-yl, 2,6-dimethyl-pyridin-3-yl, 2,5-dimethyl-pyridin-3-yl, 4,6-dimethyl-pyridin-3-yl, 5-chloro-6-methyl-pyridin-3-yl, 6-chloro-5-methyl-pyridin-3-yl, 5-fluoro-6-methyl-pyridin-3-yl, 2-fluoro-6-methyl-pyridin-3-yl, 6-fluoro-2-methyl-pyridin-3-yl, 6-fluoro-5-methyl-pyridin-3-yl, 2-chloro-6-methyl-pyridin-3-yl, 2,6-dichloro-pyridin-3-yl, 6-chloro-2-methyl-pyridin-3-yl, 2,6-difluoro-pyridin-3-yl, 6-chloro-

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5-fluoro-pyridin-3-yl, 5,6-difluoro-pyridin-3-yl, 5,6-dichloro-pyridin-3-yl, 5-fluoro-2-methyl-pyridin-3-yl, 2-fluoro-5-methyl-pyridin-3-yl, 5-chloro-2-methyl-pyridin-3-yl, 2-chloro-5-methyl-pyridin-3-yl, 6-chloro-4-methyl-pyridin-3-yl, 2-chloro-6-fluoro-pyridin-3-yl, 6-trifluoromethyl-pyridin-3-yl, 5-methyl-6-trifluoromethyl-pyridin-3-yl, 5-chloro-6-fluoro-pyridin-3-yl, 5-chloro-2-fluoro-pyridin-3-yl, 2-chloro-6-methoxy-pyridin-3-yl, 5-chloro-2-methoxy-pyridin-3-yl, 6-dimethylamino-pyridin-3-yl, 2-chloro-5,6-dimethyl-pyridin-3-yl, 2-fluoro-5,6-dimethyl-pyridin-3-yl, 2,5,6-trimethyl-pyridin-3-yl, pyridin-4-yl, pyridazin-2-yl, 6-methyl-pyridazin-2-yl, pyrimidin-5-yl, or 2-amino-pyrimidin-5-yl;

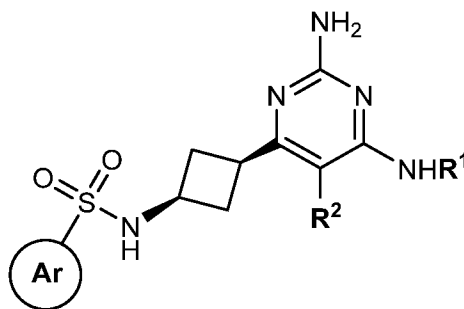
R¹ represents:

methyl, ethyl, cyclopropyl, 2-fluoroethyl, n-propyl, isopropyl, 2-hydroxyethyl, 2-fluoro-1-methyl-ethyl, tert-butyl, sec-butyl, 2,2-difluoro-ethyl, 2-hydroxy-1-methyl-ethyl, 2-methoxy-ethyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetan-3-yl, 1-fluoro-cyclopropylmethyl, cyclobutyl-methyl, 2,2,2-trifluoro-ethyl, 2,2,2-trifluoro-1-methyl-ethyl, 2-fluoro-1-fluoromethyl-ethyl, 2,2-difluoro-1-methyl-ethyl, 2-hydroxy-1,1-dimethyl-ethyl, 2-methoxy-1-methyl-ethyl, or 2-methoxy-1,1-dimethyl-ethyl; and

R² represents fluorine or hydrogen;

or a pharmaceutically acceptable salt thereof.

10. A compound according to any one of claims 1 to 9, which is also a compound of Formula (II)



Formula (II);

or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 1 which is

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-fluorobenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-4-fluorobenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-3,4-difluorobenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2,6-difluorobenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-5-methylbenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-2-fluorobenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-5-fluorobenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(methylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-2-methylbenzenesulfonamide;

N-(*cis*-3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;

- N*-(*cis*-3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
5 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyridine-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-cyanobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluoro-4-methylbenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-1-methyl-1H-pyrazole-4-sulfonamide;
10 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methylbenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3,5-dichlorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)benzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-2-methylbenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-chlorobenzenesulfonamide;
15 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-(trifluoromethoxy)benzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluoro-4-methoxybenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methoxybenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide;
20 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chlorothiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3,4-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,6-difluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4,6-dimethylpyridine-3-sulfonamide;
25 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-bromo-4-methylthiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)thiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-ethylthiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylthiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-cyclopropylthiazole-5-sulfonamide;
30 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)thiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3,5-dimethylisoxazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloro-2-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoropyridine-3-sulfonamide;
35 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-5-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-6-methoxypyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloro-4-methylpyridine-3-sulfonamide;
2-amino-*N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyrimidine-5-sulfonamide;

- N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methoxypyridine-3-sulfonamide;
N-(*trans*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chlorothiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methyloxazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyridine-4-sulfonamide;
- 5 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methyl-1,3,4-thiadiazole-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-2-methoxypyridine-3-sulfonamide;
- 10 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methyl-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(dimethylamino)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-4-methylthiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
- 15 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)thiazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-5-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methoxythiazole-5-sulfonamide;
- 20 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-chloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-methylthiazole-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methylisoxazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-5-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,4-dimethylthiazole-5-sulfonamide;
- 25 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyrazine-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)pyrimidine-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-1-methyl-1*H*-1,2,3-triazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(1,1-difluoroethyl)thiazole-5-sulfonamide;
- 30 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chlorothiazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluorothiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-1,5-dimethyl-1*H*-pyrazole-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methylisothiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-(difluoromethyl)thiophene-3-sulfonamide;
- 35 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methylthiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methyl-2*H*-1,2,3-triazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methoxythiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridazine-3-sulfonamide;

- N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-methylthiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methylthiophene-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chlorothiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-cyclopropylthiophene-2-sulfonamide;
5 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-methylthiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-bromothiophene-2-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,6-dichloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloro-5-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-cyanopyridine-3-sulfonamide;
10 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-cyanopyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(difluoromethyl)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloro-5-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-6-methylpyridine-3-sulfonamide;
15 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-6-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-difluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-2-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-(difluoromethyl)pyridine-3-sulfonamide;
20 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-ethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-cyclopropylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-cyclopropylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-6-fluoropyridine-3-sulfonamide;
25 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloro-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-(difluoromethyl)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-ethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-2-methylpyridine-3-sulfonamide;
30 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloro-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-2-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,5-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dichloropyridine-3-sulfonamide;
35 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-(methylamino)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2-bromopyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-2,5,6-trimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;

- N*-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylthiazole-4-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylthiazole-5-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)pyridine-3-sulfonamide;
- 5 *N*-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-chloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-5-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-5-chloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoropyridine-3-sulfonamide;
- 10 *N*-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-6-chloropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-2,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclopropylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- 15 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- 20 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide;
- 25 *N*-(*cis*-3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(tert-butylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(tert-butylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(cyclobutylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((cyclobutylmethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
- 30 *N*-(*cis*-3-(2-amino-6-(cyclobutylamino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((cyclobutylmethyl)amino)pyrimidin-4-yl)cyclobutyl)-2,3-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(cyclobutylamino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((cyclobutylmethyl)amino)pyrimidin-4-yl)cyclobutyl)-2,5-difluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1-hydroxypropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
- 35 *N*-(*cis*-3-(2-amino-6-((1-hydroxy-2-methylpropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(sec-butylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((2,2-difluoroethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;

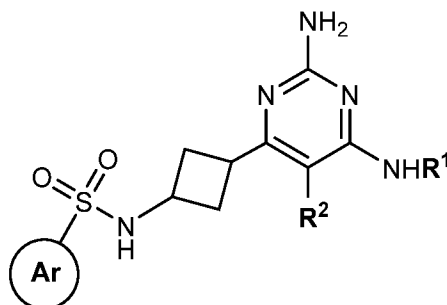
- N*-(*cis*-3-(2-amino-6-((2-fluoroethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((1-fluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((2-methoxyethyl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1-hydroxypropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
5 *N*-(*cis*-3-(2-amino-6-(((*S*)-1-methoxypropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-((1-methoxy-2-methylpropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((1-fluorocyclopropyl)methyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(((1-fluorocyclopropyl)methyl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
10 *N*-(*cis*-3-(2-amino-6-(((1,3-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(((1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(((*R*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
15 *N*-(*cis*-3-(2-amino-6-(((1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*R*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*S*)-1,1-difluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
20 *N*-(*cis*-3-(2-amino-6-(oxetan-3-ylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((1,1,1-trifluoro-2-methylpropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(butylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isobutylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
25 *N*-(*cis*-3-(2-amino-6-(cyclopentylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(cyclohexylamino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-((cyclopropylmethyl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(ethylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
30 *N*-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-4-iodobenzenesulfonamide;
N-(*cis*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-3-iodobenzenesulfonamide;
N-(*trans*-3-(2-amino-6-(isopropylamino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-2-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)pyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-fluoropyridine-3-sulfonamide;
35 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide;
N-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-5-methylpyridine-3-sulfonamide;

- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-6-fluoro-2-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-2-methylpyridine-3-sulfonamide;
- 5 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2,6-dimethylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide;
- 10 *N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-5-fluoro-6-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-chloro-4-iodobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-fluoro-4-
- 15 iodobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-4-iodobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-4-iodobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-3-cyano-4-
- 20 iodobenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclobutyl)-4-iodo-3-methylbenzenesulfonamide;
- N*-(*cis*-3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(propylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
- 25 *N*-(*cis*-3-(2-amino-6-(*tert*-butylamino)pyrimidin-4-yl)cyclobutyl)-2-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(*tert*-butylamino)pyrimidin-4-yl)cyclobutyl)-6-methylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(*tert*-butylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(*tert*-butylamino)pyrimidin-4-yl)cyclobutyl)-2,6-dimethylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(*tert*-butylamino)pyrimidin-4-yl)cyclobutyl)-2-fluoro-6-methylpyridine-3-sulfonamide;
- 30 *N*-(*cis*-3-(2-amino-6-(((*R*)-*sec*-butyl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*R*)-*sec*-butyl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*S*)-*sec*-butyl)amino)pyrimidin-4-yl)cyclobutyl)-5,6-dimethylpyridine-3-sulfonamide;
- N*-(*cis*-3-(2-amino-6-(((*S*)-*sec*-butyl)amino)pyrimidin-4-yl)cyclobutyl)-2-fluoropyridine-3-sulfonamide; or
- N*-(*cis*-3-(2-amino-6-(ethylamino)-5-fluoropyrimidin-4-yl)cyclobutyl)-3-fluorobenzenesulfonamide;
- 35 or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

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13. A compound of Formula (I)



Formula (I),

wherein

5 **Ar** represents

- phenyl;
- 5-membered heteroaryl containing from one to three ring heteroatoms independently selected from nitrogen, sulfur, and oxygen; or
- 6-membered heteroaryl containing from one to three ring nitrogen atoms;

10 wherein said phenyl, 5-membered heteroaryl, or 6-membered heteroaryl, independently is unsubstituted, mono-, di-, or tri-substituted, wherein the substituent independently represents

- halogen;
- cyano;
- C₁₋₃-alkyl;
- C₁₋₂-fluoroalkyl;
- C₁₋₂-alkoxy;
- C₃₋₄-cycloalkyl;
- C₁₋₂-fluoroalkoxy; or
- amino optionally mono- or di-substituted with methyl or ethyl;

20 **R¹** represents

- C₁₋₅-alkyl;
- hydroxy-C₂₋₄-alkyl;
- C₁₋₂-alkoxy-C₂₋₄-alkyl;
- C₁₋₄-fluoroalkyl; or

25 **-L-Cy**, wherein

- **-L** represents a bond or -CH₂-; and
- **Cy** represents C₃₋₆-cycloalkyl optionally containing one oxygen ring atom, wherein said C₃₋₆-cycloalkyl optionally containing one oxygen ring atom is unsubstituted or mono-substituted, wherein the substituent represents fluorine;

30 **R²** represents hydrogen or fluorine;

or a pharmaceutically acceptable salt thereof;
for use as a medicament.

14. A compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use as a medicament.

5 **15.** A compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of

- a disease/disorder selected from a group consisting of cancer, wherein said compound, or a pharmaceutically acceptable salt thereof, is used as a single therapeutic agent or in combination with one or more chemotherapy agent and/or radiotherapy and/or targeted therapy; or

10 • a disease/disorder selected from a group consisting of atopic diseases; fibrotic diseases; neuropathic pain; sepsis; septic peritonitis; infections associated with immune suppression; infections resulting from burn injury; chronic obstructive pulmonary disease; organ transplantation; allogeneic kidney transplantation; peritoneal adhesions; pathological bondings of serosal membranes related to surgery or inflammation; and autoimmune encephalomyelitis, wherein said compound, or a pharmaceutically acceptable salt thereof, is used as a single
15 therapeutic agent or in combination with one or more further therapeutic agent or therapy.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/083499

A. CLASSIFICATION OF SUBJECT MATTER					
INV.	C07D239/48	C07D401/12	C07D403/12	C07D409/12	C07D413/12
	C07D417/12	A61P25/02	A61P31/02	A61P35/00	A61P37/00
	A61K31/505	A61K31/506			
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, EMBASE, 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	NORMAN, DR. P.: "CCR8 antagonists : Astrazeneca: WO2006107252, WO2006107253 and WO2006107254", EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 17, no. 4, 2007, pages 465-469, XP093117065, ISSN: 1354-3776, DOI: 10.1517/13543776.17.4.465 Retrieved from the Internet: URL:https://dx.doi.org/10.1517/13543776.17 .4.465> abstract page 466 ----- -/-				1-15
☒ 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 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family					
Date of the actual completion of the international search 29 January 2024			Date of mailing of the international search report 05/02/2024		
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016			Authorized officer Kiernan, Andrea		

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2023/083499

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JENKINS, T.J. ET AL.: "Design, Synthesis, and Evaluation of Naphthalene-Sulfonamide Antagonists of Human CCR8", JOURNAL OF MEDICINAL CHEMISTRY, vol. 50, no. 3, 2007, pages 566-584, XP055883728, ISSN: 0022-2623, DOI: 10.1021/jm061118e Retrieved from the Internet: URL:https://pubs.acs.org/doi/pdf/10.1021/jm061118e> cited in the application abstract page 570; table 5; compound 37 -----	1-15
A	WO 2013/131010 A2 (ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI) 6 September 2013 (2013-09-06) cited in the application abstract; claims 29-37 -----	1-15
A	WO 2022/000443 A1 (NANJING IMMUNOPHAGE BIOTECH CO., LTD.) 6 January 2022 (2022-01-06) cited in the application abstract; claims page 98; compound 43 page 100; compounds 63, 64 page 103; compounds 89, 90 page 113 - page 114; example 10; compound 100 -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2023/083499

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			EP 4175949 A1 10-05-2023
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			KR 20230035602 A 14-03-2023
			US 2023038589 A1 09-02-2023
			US 2023159446 A1 25-05-2023
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