

### Phenyl derivatives as PGE2 receptor modulators

The present invention relates to phenyl derivatives of formula (I) and their use in the treatment of cancer by modulating an immune response comprising a reactivation of the immune system in the tumor. The present invention further relates to novel pyrimidine derivatives of formula (III) and their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I) / formula (III), and their use as modulators of the PGE2 receptors EP2 (alias PTGER2, alias PGE2 Receptor EP2 Subtype) and/or EP4 (alias PTGER4, alias EP4R, alias PGE2 Receptor EP4 Subtype). The compounds of formula (I) / formula (III) may especially be used as single agents or in combination with one or more therapeutic agents and/or chemotherapy and/or radiotherapy and/or immunotherapy in the prevention/prophylaxis or treatment of cancers; in particular the prevention/prophylaxis or treatment of melanoma; lung cancer; bladder cancer; renal carcinomas; gastro-intestinal cancers; endometrial cancer; ovarian cancer; cervical cancer; and neuroblastoma.

Prostaglandin E2 (PGE2) is a bioactive lipid that can elicit a wide range of biological effects associated with inflammation and cancer. PGE2 belongs to the prostanoid family of lipids. Cyclooxygenase (COX) is the rate-limiting enzyme in the synthesis of biological mediators termed prostanoids, consisting of prostaglandin PGD2, PGE2, PGF2 $\alpha$ , prostacyclin PGI2, and thromboxane TXA2. Prostanoids function via activation of seven transmembrane G-protein-coupled receptors (GPCRs), in particular EP1, EP2, EP3, and EP4 are receptors for PGE2. Activation of both EP2 and EP4 by PGE2 stimulates adenylate cyclase, resulting in elevation of cytoplasmic cAMP levels to initiate multiple downstream events via its prototypical effector Protein kinase A. In addition, PGE2 is also able to signal via PI3K/AKT and Ras-MAPK/ERK signalling

Cancers figure among the leading causes of death worldwide. 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 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 to grow such as angiogenic factors (promoting ingrowth of blood vessels) or that can help to evade the attack of the host immune response. PGE2 is such an immuno-modulatory factor produced in tumors.

It is well established that COX2, mainly via PGE2, promotes overall growth of tumors and is upregulated and correlates with clinical outcome in a high percentage of common cancers, especially colorectal, gastric, esophageal, pancreatic, breast and ovarian cancer. High COX-2 and PGE2 expression levels are associated with neoplastic transformation, cell growth, angiogenesis, invasiveness, metastasis and immune evasion.

The finding that COX2 is over-expressed and plays an important role in carcinogenesis in gastrointestinal (GI) cancers including among others esophagus, gastric and colorectal cancers has led to the fact that COX-inhibitors (Coxibs), including Celecoxib, and other nonsteroidal anti-inflammatory drugs (NSAID), including aspirin, are

among the most studied cancer chemopreventive agents in development today (for review see for example Wang R et al, *Curr Pharm Des.* 2013;19(1):115-25; Garcia Rodriguez LA et al, *Recent Results Cancer Res.* 2013;191:67-93, Sahin IH et al, *Cancer Lett.* 2014 Apr 10;345(2):249-57; Drew DA et al, *Nat Rev Cancer* 2016, 16:173; Brotons C et al, *Am J Cardiovasc Drugs.* 2015 Apr; 15(2):113)

- 5 In addition to COX2 and PGE2, also EP receptors, especially EP2 and EP4, are aberrantly over-expressed in multiple types of cancers, especially in gastro-intestinal (GI) cancers and pancreatic cancer. Furthermore, the over-expression of PGE2 and/or EP2 and/or EP4 correlates with diseases progression in some cancer types such as oesophageal squamous cell carcinoma (Kuo KT et al, *Ann Surg Onc* 2009; 16(2), 352-60); squamous cell carcinoma of the lung (Alaa M et al, *Int J Oncol* 2009, 34(3); 805-12); prostate cancer (Miyata Y et al, *Urology* 2013, 81(1):136-42); Badawi AF and Badr MZ *Int J Cancer.* 2003, 103(1):84-90); head and neck squamous cell carcinoma (Gallo O et al, *Hum Pathol.* 2002, 33(7):708-14).

- 15 In accordance to studies performed with Coxibs, in mice, knockout of either COX1, COX2, microsomal prostaglandin E synthase 1 (mPTGES1), EP2 or EP4 resulted in reduced tumor incidence and progression in different tumor models. Conversely, overexpression of COX2 or mPTGES1 in transgenic mice resulted in increased tumor incidence and tumor burden (for review see Nakanishi M. and Rosenberg D.W., *Seminars in Immunopathology* 2013, 35: 123–137; Fischer SM et al *Cancer Prev Res (Phila)* 2011 Nov;4(11):1728-35; Fulton AM et al *Cancer Res* 2006; 66(20); 9794-97).

- 20 Several pharmacological studies to inhibit tumor growth and progression using EP receptor antagonists or COX2 inhibitors in different tumor models have been conducted in mice. Among others, EP antagonists and/or COX2 inhibitors reduced tumor growth and metastasis in experimental models of colorectal cancer (e.g Yang L et al *Cancer Res* 2006, 66(19), 9665-9672; Pozzi A. et al *JBC* 279(28); 29797-29804), lung carcinomas (Sharma S et al *Cancer Res* 2005 65(12), 5211-5220), gastro-intestinal cancer (Oshima H et al *Gastroenterology* 2011, 140(2); 596-607; Fu SL et al *World J Gastroenterol* 2004, 10(13); 1971-1974), breast cancer (Kundu N et al, *Breast Cancer Res Treat* 117, 2009; 235-242; Ma X et al, *Oncol Immunology* 2013; Xin X et al *Lab Investigation* 2012, 1-14; Markosyan N et al; *Breast Cancer Res* 2013, 15:R75), prostate cancer (Xu S et al, *Cell Biochem Biophys* 2014, Terada et al *Cancer Res* 70(4) 2010; 1606-1615), pancreatic cancer (Al-Wadei HA et al, *PLOS One* 2012, 7(8):e43376; Funahashi H et al, *Cancer Res* 2007, 67(15):7068-71). COX2 inhibitors were approved for the treatment of familial adenomatous polyposis (FAP) which is an inherited pre-disposition syndrome for colorectal cancer, but later retracted due to cardiovascular side effects.

- 30 Mechanistically, PGE2 signalling is mainly involved in the crosstalk between tumor and stromal cells, thereby creating a microenvironment which is favourable for the tumor to grow. In particular, PGE2 signalling via EP2 and EP4 can for example (i) suppress the cytotoxicity and cytokine production of natural killer cells, (ii) skew the polarization of tumor-associated macrophages towards tumor-promoting M2 macrophages (see for example Nakanishi Y et al *Carcinogenesis* 2011, 32:1333-39), (iii) regulate the activation, expansion and effector function of both Tregs (regulatory T cells) and MDSC (myeloid derived suppressor cells), which are potent immunosuppressive
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cells that accumulate in tumors both in patients and in experimental animal models (see for example Sharma S et al, Cancer Res 2005, 5(12):5211-20; Sinha P et al Cancer Res 2007, 67(9), 4507-4513; Obermajer N et al, Blood 2011, 118(20):5498-5505); (iv) down-regulate IFN- $\gamma$ , TNF- $\alpha$  IL-12 and IL-2 expression in immune cells such as natural killer cells, T-cells, dendritic cells and macrophages, impairing the ability of these immune cells to induce tumor cell apoptosis and restrain tumorigenesis (see for example Bao YS et al, Int Immunopharmacol. 2011;11(10):1599-605; Kim JG and Hahn YS, Immunol Invest. 2000;29(3):257-69; Demeuere CE et al, Eur J Immunol. 1997;27(12):3526-31; Mitsuhashi M et al, J Leukoc Biol. 2004;76(2):322-32; Pockaj BA et al, Ann Surg Oncol. 2004;11(3):328-39; (v) suppress activation, IL-2 responsiveness, expansion and cytotoxicity of T-cells thereby contributing to local immunosuppression (see for example Specht C et al, Int J Cancer 2001;70:705-712); (vi) inhibit maturation of dendritic cells, their ability to present antigens and to produce IL-12, resulting in abortive activation of cytotoxic T-cells (see for example Ahmadi M et al, Cancer Res 2008, 68(18):7250-9; Stolina M et al, J Immunol 2000, 164:361-70); (vii) regulate tumor angiogenesis (formation of new blood vessels for nutrient and oxygen supply) by enhancing endothelial cell motility and survival as well as by increasing the expression of VEGF (vascular endothelial growth factor) (see for example Zhang Y and Daaka Y, Blood 2011;118(19):5355-64; Jain S et al, Cancer Res. 2008; 68(19):7750-9; Wang and Klein, Molecular Carcinogenesis 2007, 46:912-923; (viii) enhance tumor cell survival (via PI3K/AKT and MAPK signalling). For review see for example Kalinski P, J Immunol 2012, 188(1), 21-28; Obermajer N et al, Oncoimmunology 1(5), 762-4; Greenhough A et al, carcinogenesis 2009, 30(3), 377-86; Wang D and Dubois RN, Gut 2006, 55, 115-122; Harris SG et al Trends Immunol 2002, 22, 144-150).

Coxibs have been shown to render tumor cells more sensitive to radiation and chemotherapy and several clinical trials have been performed or are ongoing combining Coxibs with radio- and/or chemotherapy (for review see e.g. Ghosh N et al, Pharmacol Rep. 2010 Mar-Apr;62(2):233-44; Davis TW et al, Am J Clin Oncol. 2003, 26(4):S58-61; see also Higgins JP et al, Cancer Biol Ther 2009, 8:1440-49).

Furthermore, there is some evidence of additive effects and/or synergy between Coxibs and epidermal growth factor receptor (EGFR) inhibitors (see for example Zhang X et al, Clin Cancer Res. 2005, 11(17):6261-9; Yamaguchi NH et al, J Gastrointest Oncol. 2014, 5(1):57-66); and with aromatase inhibitors (see for example Generali D et al, Br J Cancer. 2014;111(1):46-54; Lustberg MB et al, Clin Breast Cancer. 2011 Aug;11(4):221-7; Falandry C et al, Breast Cancer Res Treat. 2009 Aug;116(3):501-8; Chow LW et al, J Steroid Biochem Mol Biol. 2008, 111(1-2):13-7).

Moreover, additive/synergistic effects have been seen in different mouse tumor models when Aspirin (a COX1/2 inhibitor) was combined with anti-VEGF antibody (Motz GT et al; Nat Med 2014 20(6):607) and this combination is currently under investigation in clinical trials (NCT02659384).

Recently, it has been shown that, if combined, different immunotherapeutic approaches can have enhanced anti-tumor efficacy. Due to the immune-modulatory properties of PGE<sub>2</sub>, Coxibs have thus also been used in combination with different immunotherapeutic approaches. In particular, additive or even synergistic effects could be observed when Coxibs were combined with dendritic cell vaccination in a rat glioma model and in a mouse mesothelioma or

melanoma model (Zhang H et al, *Oncol Res.* 2013;20(10):447-55; Veltman JD et al, *BMC Cancer.* 2010;10:464; Toomey D et al, *Vaccine.* 2008 Jun 25;26(27-28):3540-9); with granulocyte-macrophage colony-stimulating factor (GM-CSF) in mouse brain tumors (Eberstål S et al, *Int J Cancer.* 2014 Jun 1;134(11):2748-53); with interferon gamma (IFN- $\gamma$ ) in brain tumors (Eberstål S et al, *Cancer Immunol Immunother.* 2012, 61(8):1191-9); with dendritic cell vaccination or with GM-CSF in a mouse breast cancer model (Hahn T et al, *Int J Cancer.* 2006,118(9):2220-31); and with adenoviral interferon beta (IFN- $\beta$ ) therapy in a mouse mesothelioma model (DeLong P et al, *Cancer Res.* 2003 Nov 15;63(22):7845-52). Along these lines, additive or even synergistic effects of Coxibs and/or EP2 and/or EP4 antagonists can also be envisaged with agents acting on cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) such as anti-CTLA-4 antibodies; anti-TIM-3 antibodies, anti-Lag-3 antibodies; anti-TIGIT antibodies; or, in particular, with agents acting on programmed cell death protein 1 (PD1), such as anti-PD1 or anti-PDL1 (programmed cell death ligand 1) antibodies (Yongkui Li et al *Oncoimmunology* 2016, 5(2):e1074374; Zelenay S et al, *Cell* 2015, 162; 1-14; WO2013/090552, which indicates a synergistic effect of dual EP2 and EP4 blockade in combination with agents acting on PD1).

Adenosine is another endogenous factor with anti-inflammatory properties that is generated through the activity of ectonucleotidases, CD39 and CD73, expressed on various cell types, including regulatory T cells (Treg) (Mandapathil M et al, *J Biol Chem.* 2010; 285(10):7176-86). Immune cells also respond to Adenosine, because they bear receptors for ADO, which are mainly of the A2a/A2b type (Hoskin DW, et al, *Int J Oncol* 2008, 32:527–535). Signaling via Adenosine receptors and EP2/EP4 receptors converges on the cytoplasmic adenylyl cyclase, leading to up-regulation of cAMP. It was shown that Adenosine and PGE2 cooperate in the suppression of immune responses mediated by regulatory T cells (Mandapathil M et al, *J Biol Chem.* 2010; 285(36):27571-80; Caiazzo E et al, *Biochem Pharmacol.* 2016; 112:72-81).

Thus, the present EP2 and/or EP4 antagonists may be useful, alone, or in combination with with one or more therapeutic agents and/or chemotherapy and/or radiotherapy and/or immunotherapy; in particular in combination with chemotherapy, radiotherapy, EGFR inhibitors, aromatase inhibitors, anti-angiogenic drugs, adenosine inhibitors, immunotherapy such as especially PD1 and/or PDL1 blockade, or other targeted therapies; for the prevention / prophylaxis or treatment of cancers, notably for the prevention / prophylaxis or treatment of skin cancer including melanoma including metastatic melanoma; lung cancer including non-small cell lung cancer; bladder cancer including urinary bladder cancer, urothelial cell carcinoma; renal carcinomas including renal cell carcinoma, metastatic renal cell carcinoma, metastatic renal clear cell carcinoma; gastro-intestinal cancers including colorectal cancer, metastatic colorectal cancer, familial adenomatous polyposis (FAP), oesophageal cancer, gastric cancer, gallbladder cancer, cholangiocarcinoma, hepatocellular carcinoma, and pancreatic cancer such as pancreatic adenocarcinoma or pancreatic ductal carcinoma; endometrial cancer; ovarian cancer; cervical cancer; neuroblastoma; prostate cancer including castrate-resistant prostate cancer; brain tumors including brain metastases, malignant gliomas, glioblastoma multiforme, medulloblastoma, meningiomas; breast cancer including triple negative breast carcinoma; oral tumors; nasopharyngeal tumors; thoracic cancer; head and neck cancer; leukemias including acute myeloid leukemia, adult T-cell leukemia; carcinomas; adenocarcinomas; thyroid



carcinoma including papillary thyroid carcinoma; choriocarcinoma; Ewing's sarcoma; osteosarcoma; rhabdomyosarcoma; Kaposi's sarcoma; lymphoma including Burkitt's lymphoma, Hodgkin's lymphoma, MALT lymphoma; multiple myelomas; and virally induced tumors.

In addition, selective or dual EP2 and/or EP4 antagonists may be useful in several other diseases or disorders responding for example to treatment with COX2 inhibitors, with the advantage that EP2 and/or EP4 antagonists should not possess the potential cardiovascular side effects seen with COX2 inhibitors, which are mainly due to interference with PGI<sub>2</sub> and TXA<sub>2</sub> synthesis (see for example Boyd MJ et al, *bioorganic and medicinal chemistry letters* 21, 484, 2011). For example, blockade of prostaglandin production by COX inhibitors is the treatment of choice for pain, including especially inflammatory pain and painful menstruation. Thus EP2 and/or EP4 and/or dual EP2/EP4 antagonists may be useful for the treatment of pain, especially inflammatory pain. Evidence from EP2 knockout mice suggest that EP2 antagonists can be used for the treatment of inflammatory hyperalgesia (Reinold H et al, *J Clin Invest* 2005, 115(3):673-9). In addition, EP4 antagonists have beneficial effect in vivo in inflammatory pain models (eg Murase A, *Eur J Pharmacol* 2008; Clark P, *J Pharmacol Exp Ther.* 2008; Maubach KA *Br J Pharmacol.* 2009; Colucci J *Bioorg Med Chem Lett.* 2010, Boyd MJ et al, *Bioorg Med Chem Lett* 2011, Chn Q et al *Br J Pharmacol* 2010, Nakao K et al, *J Pharmacol Exp Ther.* 2007 Aug;322(2):686-94). Administration of an EP2 in combination with an EP4 antagonist showed significant, but partial inhibition of joint inflammation in mouse collagen-induced arthritis model (Honda T et al *J Exp Med* 2006, 203(2):325-35).

EP2 and/or dual EP2/EP4 antagonists may be of use to decrease female fertility, i.e. they have been shown to prevent pregnancy if used as contraceptive in macaques (Peluffo MC et al *Hum Reprod* 2014). EP2 knockout mice have decreased fertility, smaller litter sizes and reduced cumulus expansion (Matsumoto et al, *Biology of reproduction* 2001, 64; 1557-65; Hitzaki et al, *PNAS* 1999, 96(18), 10501-10506; Tilley SL *J Clin Inves* 1999, 103(11):1539-45; Kennedy CR et al, *Nat Med* 1999 5(2):217-20).

There is also rationale that EP2 and/ or EP4 antagonists may be of use to prevent or treat endometriosis: for example EP2, EP3 and EP4 and COX2 are overexpressed in endometriosis cell lines and tissues (e.g. Santulli P et al *J Clin Endocrinol Metab* 2014, 99(3):881-90); antagonist treatment was shown to inhibit the adhesion of endometrial cells in vitro (Lee J et al *Biol Reprod* 2013, 88(3):77; Lee J et al *Fertil Steril* 201, 93(8):2498-506); COX2 inhibitors have been shown to reduce endometrial lesions in mice via EP2 (Chuang PC et al, *Am J Pathol* 2010, 176(2):850-60); and antagonist treatment has been shown to induce apoptosis of endometrial cells in vitro (Banu SK et al, *MOJ endocrinol* 2009, 23(8) 1291-305).

Dual EP2/EP4 antagonists, or the combination of a selective EP2 antagonists with a selective EP4 antagonist, may be of potential use for autoimmune disorders; e.g. they have been shown to be effective in mouse model for multiple sclerosis (MS) (Esaki Yet al *PNAS* 2010, 107(27):12233-8; Schiffmann S et al, *Biochem Pharmacol.* 2014, 87(4): 625-35; see also Kofler DM et al *J Clin Invest* 2014, 124(6):2513-22). Activation of EP2 / EP 4 signalling in cells in vitro (Kojima F et al *Prostaglandins Other Lipid Mediat* 2009, 89:26-33) linked dual or selective EP2 and/or EP4 antagonists to the treatment of rheumatoid arthritis. Also, elevated levels of PGE<sub>2</sub> have been reported in synovial

fluid and cartilage from patients with osteoarthritis (OA) and it has been shown that PGE2 stimulates matrix degradation in osteoarthritis chondrocytes via the EP4 receptor (Attur M et al, J Immunol. 2008;181(7):5082-8).

EP4 overexpression is associated with enhanced inflammatory reaction in atherosclerotic plaques of patients (Cipollone F et al, Artheroscler Thromb Vasc Biol 2005, 25(9): 1925-31), thus the use of EP4 and/or dual EP2/EP4 antagonists may be indicated for plaque stabilization and prevention / prophylaxis of acute ischemic syndromes. In addition, EP4 deficiency suppresses early atherosclerosis, by compromising macrophage survival (Babaev VR et al, Cell Metab. 2008 Dec;8(6):492-501)

EP2 and/or dual EP2/EP4 antagonists may also be useful in the treatment of pneumonia: intrapulmonary administration of apoptotic cells demonstrated that PGE(2) via EP2 accounts for subsequent impairment of lung recruitment of leukocytes and clearance of Streptococcus pneumoniae, as well as enhanced generation of IL-10 in vivo (Medeiros AI et al J Exp Med 2009 206(1):61-8).

EP2 and/or dual EP2/EP4 antagonists may in addition be useful for the treatment of neurodegenerative diseases (for review see Cimino PJ et al, Curr Med Chem. 2008;15(19):1863-9). EP2 receptor accelerates progression of inflammation in a mouse model of amyotrophic lateral sclerosis (ALS) (Liang X et al, Ann Neurol 2008, 64(3):304-14); COX2 inhibitors have been shown to be neuroprotective in rodent models of stroke, Parkinson disease and ALS (for review see Liang X et al J Mol Neurosci 2007, 33(1):94-9), decreased neurotoxicity was observed in EP2 knockout mice treated with parkinsonian toxin (Jin J et al, J Neuroinflammation 2007, 4:2), PGE2 via EP2 aggravates neurodegeneration in cultured rat cells (Takadera T et al, Life Sci 2006, 78(16): 1878-83); Reduced amyloid burden was observed in Alzheimer's disease mouse model if crossed with EP2 knockout mice (Liang X et al J Neurosci 2005, 25(44):10180-7; Keene CD et al, Am J Pathol. 2010, 177(1):346-54). EP2 null mice are protected from CD14-dependent/ innate immunity mediated neuronal damage in neurodegenerative disease (Shie FS et al Glia 2005, 52(1):70-7); PGE2 via EP2 increases amyloid precursor protein (APP) expression in cultured rat microglial cells (Pooler AM et al Neurosci. Lett. 2004, 362(2):127-30). EP2 antagonist limits oxidative damage from activation of innate immunity (intracranial injection of LPS) in the brain and could be used for Alzheimer or HIV associated dementia (Montine TJ et al, J Neurochem 2002, 83(2):463-70). In an Alzheimer's disease mouse model cognitive function could be improved by genetic and pharmacological inhibition of EP4 (Hoshino T et al, J Neurochem 2012, 120(5):795-805).

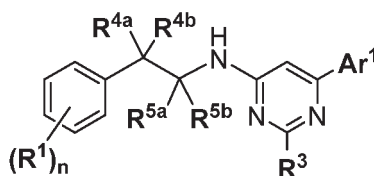
EP2 and/or dual EP2/EP4 antagonists may also be useful to treat autosomal dominant polycystic kidney disease (ADPKD): PGE2 via EP2 induces cystogenesis of human renal epithelial cells; and EP2 was found to be overexpressed in patient samples (Elberg G et al, Am J Physiol Renal Physiol 2007, 293(5):F1622-32).

EP4 and/or dual EP2/EP4 antagonists may also be useful to treat osteoporosis: PGE2 stimulates bone resorption mainly via EP4 and partially via EP2 (Suzawa T et al, Endocrinology. 2000 Apr;141(4):1554-9), EP4 knockout mice show impaired bone resorption (Miyaura C et al, J Biol Chem 2000, 275(26): 19819-23) and an EP4 antagonists showed partial inhibition of PGE(2)-stimulated osteoclastogenesis and osteoclastic bone resorption (Tomita M et al, Bone. 2002 Jan;30(1):159-63).

WO2008/152093 discloses selective EP2 receptor modulators which comprise an indole ring linked to the rest of the molecule in position 3, and a pyrimidine moiety which however is not substituted with a directly linked aromatic substituent. WO2006/044732 discloses pyrimidine compounds which are modulators of PGD2 claimed to be useful e.g. in the treatment of allergic diseases; however, for example the exemplified compound CAS 1001913-77-4 has been tested to be inactive on both the EP2 and the EP4 receptor in the in vitro assay set out in the experimental part below. WO2008/006583 discloses pyrimidin derivatives which are ALK-5 inhibitors. WO2006/044732 and WO2008/039882 disclose certain pyrimidine derivatives as prostaglandin D2 receptor antagonists. Pyrimidin-2-yl derivatives are disclosed in WO2013/020945, WO2012/127032, WO2011/144742, WO2011/022348, WO2009/105220, Bioorg. Med. Chem 2011, 21(13) 4108-4114 and Bioorg. Med. Chem 2011, 21(1) 66-75. Further compounds which are claimed to be active as anti-cancer agents are disclosed in WO2006/128129, WO2008/008059 and Bioorg. Med. Chem 2013, 21(2), 540-546. WO2012/149528 discloses 2-methyl-pyrimidine derivatives as inhibitors of the inducible form of Phosphofructose-Kinase, thought to be useful in the treatment of cancer by decreasing tumor growth by reducing the extremely high rate of glycolysis in cancer cells. WO2018/013840, WO2013/163190, WO2015/058067, and WO2015/058031 disclose certain DNA-PK inhibitors interacting with DNA repair processes. The disclosed compounds are thought to be useful to sensitize cancer cells by directly modulating cancer cell proliferation, and to enhance the efficacy of both cancer chemotherapy and radiotherapy.

The present invention provides phenyl derivatives of formulae (I), (II), or (III) which are modulators of the prostaglandin 2 receptors EP2 and/or EP4. Certain compounds of the present invention are dual antagonists of both the EP2 and the EP4 receptor. The present compounds may, thus, be useful for the prevention / prophylaxis or treatment of diseases which respond to the blockage of the EP2 receptors and/or the EP4 receptors such as especially cancers, wherein a particular aspect is the treatment of cancer by modulating an immune response comprising a reactivation of the immune system in the tumor; as well as pain including especially inflammatory pain and painful menstruation; endometriosis; acute ischemic syndromes in atherosclerotic patients; pneumonia; neurodegenerative diseases including amyotrophic lateral sclerosis, stroke; Parkinson disease, Alzheimer's disease and HIV associated dementia; autosomal dominant polycystic kidney disease; and to control female fertility.

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



Formula (I)

for use in the treatment of a cancer, wherein said cancer is treated by modulating an immune response comprising a reactivation of the immune system in the tumor;

wherein said cancer is notably a cancer selected from melanoma including metastatic melanoma; lung cancer including non-small cell lung cancer; bladder cancer including urinary bladder cancer, urothelial cell carcinoma; renal carcinomas including renal cell carcinoma, metastatic renal cell carcinoma, metastatic renal clear cell carcinoma; gastro-intestinal cancers including colorectal cancer, metastatic colorectal cancer, familial adenomatous polyposis (FAP), oesophageal cancer, gastric cancer, gallbladder cancer, cholangiocarcinoma, hepatocellular carcinoma, and pancreatic cancer such as pancreatic adenocarcinoma or pancreatic ductal carcinoma; endometrial cancer; ovarian cancer; cervical cancer; neuroblastoma; prostate cancer including castrate-resistant prostate cancer; brain tumors including brain metastases, malignant gliomas, glioblastoma multiforme, medulloblastoma, meningiomas; breast cancer including triple negative breast carcinoma; oral tumors; nasopharyngeal tumors; thoracic cancer; head and neck cancer; leukemias including acute myeloid leukemia, adult T-cell leukemia; carcinomas; adenocarcinomas; thyroid carcinoma including papillary thyroid carcinoma; choriocarcinoma; Ewing's sarcoma; osteosarcoma; rhabdomyosarcoma; Kaposi's sarcoma; lymphoma including Burkitt's lymphoma, Hodgkin's lymphoma, MALT lymphoma; multiple myelomas; and virally induced tumors (especially such cancer is selected from melanoma; lung cancer; bladder cancer; renal carcinomas; gastro-intestinal cancers; endometrial cancer; ovarian cancer; cervical cancer; and neuroblastoma);

wherein said compound is optionally used in combination with one or more chemotherapy agents and / or radiotherapy and / or targeted therapy;

wherein in compounds of the formula (I)

$(R^1)_n$  represents one, two or three optional substituents on the phenyl ring (i.e. n represents the integer 0, 1, 2, or 3), wherein said substituents are independently selected from  $(C_{1-3})$ alkyl (especially methyl),  $(C_{1-3})$ alkoxy (especially methoxy),  $-S-(C_{1-3})$ alkyl (especially methylsulfanyl), halogen (especially fluoro, chloro, or bromo),  $(C_{1-3})$ fluoroalkyl (especially trifluoromethyl),  $(C_{1-3})$ fluoroalkoxy (especially trifluoromethoxy), cyano, hydroxy, nitro,  $-CO-O-(C_{1-3})$ alkyl (especially methoxycarbonyl),  $-NR^{N7}R^{N8}$  wherein  $R^{N7}$  and  $R^{N8}$  independently represent hydrogen or  $(C_{1-4})$ alkyl, or  $R^{N7}$  and  $R^{N8}$  together with the nitrogen to which they are attached form a 4- to 6-membered carbocyclic ring (especially such group  $-NR^{N7}R^{N8}$  is methylamino, dimethylamino, pyrrolidin-1-yl);

$R^3$  represents hydrogen, methyl or trifluoromethyl (especially hydrogen);

$R^{4a}$  and  $R^{4b}$  independently represent hydrogen, methyl, or  $R^{4a}$  and  $R^{4b}$  together with the carbon atom to which they are attached represent a cycloprop-1,1-diyl group;

$R^{5a}$  and  $R^{5b}$  independently represent hydrogen, methyl, or  $R^{5a}$  and  $R^{5b}$  together with the carbon atom to which they are attached represent a cycloprop-1,1-diyl group;

$Ar^1$  represents

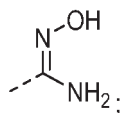
- phenyl, or 5- or 6-membered heteroaryl (notably 5-membered heteroaryl, especially thiophenyl or thiazolyl); wherein said phenyl or 5- or 6-membered heteroaryl independently is mono-, di- or tri-substituted, wherein the substituents are independently selected from

- (C<sub>1-6</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 1-methyl-propan-1-yl, tert.-butyl, 3-methyl-butyl);
  - (C<sub>1-4</sub>)alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy);
  - (C<sub>1-3</sub>)fluoroalkyl, wherein said (C<sub>1-3</sub>)fluoroalkyl is optionally substituted with hydroxy (especially trifluoromethyl, 2,2,2-trifluoro-1-hydroxy-ethyl);
  - (C<sub>1-3</sub>)fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
  - halogen (especially fluoro, chloro, bromo);
  - cyano;
  - (C<sub>3-6</sub>)cycloalkyl, wherein said (C<sub>3-6</sub>)cycloalkyl is unsubstituted or mono-substituted with amino (especially cyclopropyl, 1-amino-cyclopropyl);
  - (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom, wherein said (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy (especially 3-hydroxy-oxetan-3-yl);
  - (C<sub>3-6</sub>)cycloalkyl-oxy (especially cyclobutyl-oxy, cyclopentyl-oxy);
  - hydroxy;
  - -X<sup>1</sup>-CO-R<sup>01</sup>, wherein
    - X<sup>1</sup> represents a direct bond, (C<sub>1-3</sub>)alkylene (especially -CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-), -O-(C<sub>1-3</sub>)alkylene-\* (especially -O-CH<sub>2</sub>-, -O-CH(CH<sub>3</sub>)-, -O-C(CH<sub>3</sub>)<sub>2</sub>-, -O-CH<sub>2</sub>-CH<sub>2</sub>-), -NH-(C<sub>1-3</sub>)alkylene-\* (especially -NH-CH<sub>2</sub>-, -NH-CH(CH<sub>3</sub>)-, -S-CH<sub>2</sub>-, -CF<sub>2</sub>-, -CH=CH-, -CH≡CH-, -NH-CO-, -CO-, or (C<sub>3-5</sub>)cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-R<sup>01</sup> group; and
    - R<sup>01</sup> represents
      - -OH;
      - -O-(C<sub>1-4</sub>)alkyl (especially ethoxy, methoxy);
      - -NH-SO<sub>2</sub>-R<sup>S3</sup> wherein R<sup>S3</sup> represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;
      - -O-CH<sub>2</sub>-CO-R<sup>04</sup>, wherein R<sup>04</sup> represents hydroxy, or (C<sub>1-4</sub>)alkoxy, or -N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>;
      - -O-CH<sub>2</sub>-O-CO-R<sup>05</sup>, wherein R<sup>05</sup> represents (C<sub>1-4</sub>)alkyl or (C<sub>1-4</sub>)alkoxy;
      - -O-CH<sub>2</sub>-CH<sub>2</sub>-N[(C<sub>1-4</sub>)alkyl]<sub>2</sub> (especially -O-CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>); or
      - (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methoxy;
- [wherein in particular such group -X<sup>1</sup>-CO-R<sup>01</sup> represents -COOH, -CO-O-CH<sub>3</sub>, -CO-O-C<sub>2</sub>H<sub>5</sub>, -O-CH<sub>2</sub>-COOH, -O-CH(CH<sub>3</sub>)-COOH, -O-C(CH<sub>3</sub>)<sub>2</sub>-COOH, -O-CH<sub>2</sub>-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -NH-CH(CH<sub>3</sub>)-COOH, -CO-NH-SO<sub>2</sub>-CH<sub>3</sub>, -CO-NH-SO<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>, -CO-NH-SO<sub>2</sub>-cyclopropyl, -CO-NH-SO<sub>2</sub>-C<sub>2</sub>H<sub>5</sub>, -CO-NH-SO<sub>2</sub>-NH<sub>2</sub>, -CO-O-CH<sub>2</sub>-COOH, -CO-O-CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>, -CO-O-CH<sub>2</sub>-CO-N(CH<sub>3</sub>)<sub>2</sub>, -CO-O-CH<sub>2</sub>-O-CO-O-C<sub>2</sub>H<sub>5</sub>, -



CO-O-CH<sub>2</sub>-O-CO-propyl, (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyl-O-CO-, -CH<sub>2</sub>-COOH, -CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -CH<sub>2</sub>-CO-O-C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-COOH, -CH=CH-COOH, -CH≡CH-CO-O-C<sub>2</sub>H<sub>5</sub>, -CF<sub>2</sub>-COOH, -NH-CO-COOH, -CO-COOH, 1-carboxy-cyclopropan-1-yl];

- -CO-CH<sub>2</sub>-OH;



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- 2-hydroxy-3,4-dioxo-cyclobut-1-enyl;
- hydroxy-(C<sub>1-4</sub>)alkyl (especially hydroxymethyl, 1-hydroxy-ethyl);
- dihydroxy-(C<sub>2-4</sub>)alkyl (especially 1,2-dihydroxyethyl);
- hydroxy-(C<sub>2-4</sub>)alkoxy (especially 2-hydroxy-ethoxy);
- 10 ▪ (C<sub>1-4</sub>)alkoxy-(C<sub>2-4</sub>)alkoxy (especially 2-methoxy-ethoxy);
- -(CH<sub>2</sub>)<sub>r</sub>-CO-NR<sup>N3</sup>R<sup>N4</sup> wherein **r** represents the integer 0 or 1; and wherein **R<sup>N3</sup>** and **R<sup>N4</sup>** independently represent hydrogen, (C<sub>1-4</sub>)alkyl, hydroxy-(C<sub>2-4</sub>)alkyl, (C<sub>1-3</sub>)alkoxy-(C<sub>2-4</sub>)alkyl, or hydroxy (wherein preferably at least one of **R<sup>N3</sup>** and **R<sup>N4</sup>** represents hydrogen; and wherein particular examples of such group -CO-NR<sup>N3</sup>R<sup>N4</sup> are -CO-NH<sub>2</sub>, -CO-NH(CH<sub>3</sub>), -CO-NH(C<sub>2</sub>H<sub>5</sub>), -CH<sub>2</sub>-CO-NH<sub>2</sub>, -CO-NH-C<sub>2</sub>H<sub>4</sub>-OH, -CO-NH-C<sub>2</sub>H<sub>4</sub>-OCH<sub>3</sub>, or -CO-N(CH<sub>3</sub>)<sub>2</sub>, -CO-NH-isopropyl, or -CO-NH-OH);
- 15 ▪ -X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup>, wherein **X<sup>2</sup>** represents -(CH<sub>2</sub>)<sub>m</sub>, wherein **m** represents the integer 0 or 1; or **X<sup>2</sup>** represents -O-CH<sub>2</sub>-CH<sub>2</sub>-, wherein the asterisk indicates the bond that is linked to the -NR<sup>N1</sup>R<sup>N2</sup> group; and wherein

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- **R<sup>N1</sup>** and **R<sup>N2</sup>** independently represent hydrogen, (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkoxy-(C<sub>2-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl, or (C<sub>2-3</sub>)fluoroalkyl;
- or **R<sup>N1</sup>** independently represents hydrogen or (C<sub>1-4</sub>)alkyl, and **R<sup>N2</sup>** independently represents -CO-H, -CO-(C<sub>1-3</sub>)alkyl, -CO-(C<sub>1-3</sub>)alkylene-OH, or -CO-O-(C<sub>1-3</sub>)alkyl;
- or **R<sup>N1</sup>** and **R<sup>N2</sup>** together with the nitrogen to which they are attached form a 4-, 5- or 6-membered saturated ring optionally containing one ring oxygen or ring sulfur atom, wherein said ring is unsubstituted, or mono-substituted with oxo on a ring carbon atom, or disubstituted with oxo on a ring sulfur atom;

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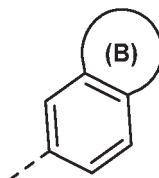
(especially such group -X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup> represents amino, methylamino, ethylamino, propylamino, amino-methyl, methylamino-methyl, isobutylamino-methyl, cyclopropylamino-methyl, cyclobutylamino-methyl, (2-methoxyethyl)amino-methyl, (2,2,2-trifluoro-ethyl)-amino; or -NH-CO-H, -N(C<sub>2</sub>H<sub>5</sub>)-CO-H, -NH-CO-C<sub>2</sub>H<sub>5</sub>, -NH-CO-CH<sub>2</sub>-CH<sub>2</sub>-OH, -NH-CO-O-CH<sub>3</sub>, -N(CH<sub>3</sub>)-CO-O-CH<sub>3</sub>; or pyrrolidin-1-yl, 2-oxo-pyrrolidin-1-yl, 1,1-dioxo-isothiazolidin-2-yl, morpholin-4-yl, azetidin-1-yl, or piperidin-1-yl; or 2-(dimethylamino)-ethoxy);

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- -NH-CO-NR<sup>N5</sup>R<sup>N6</sup> wherein R<sup>N5</sup> and R<sup>N6</sup> independently represent hydrogen or (C<sub>1-4</sub>)alkyl (wherein preferably at least one of R<sup>N5</sup> and R<sup>N6</sup> represents hydrogen; and wherein particular examples of such group -NH-CO-NR<sup>N5</sup>R<sup>N6</sup> are -NH-CO-NH<sub>2</sub>, -NH-CO-NH-C<sub>2</sub>H<sub>5</sub>);
- -SO<sub>2</sub>-R<sup>S1</sup> wherein R<sup>S1</sup> represents hydroxy, (C<sub>1-4</sub>)alkyl (especially methyl), or -NR<sup>N7</sup>R<sup>N8</sup> wherein R<sup>N7</sup> and R<sup>N8</sup> independently represent hydrogen or (C<sub>1-3</sub>)alkyl (wherein preferably at least one of R<sup>N7</sup> and R<sup>N8</sup> represents hydrogen; and wherein particular examples of such group -SO<sub>2</sub>-R<sup>S1</sup> are -SO<sub>2</sub>-CH<sub>3</sub>, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-OH, -SO<sub>2</sub>-NH-CH<sub>3</sub>);
- -S-R<sup>S2</sup> wherein R<sup>S2</sup> represents (C<sub>1-4</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);
- -(CH<sub>2</sub>)<sub>q</sub>-HET<sup>1</sup>, wherein q represents the integer 0, 1 or 2 (especially q is 0, i.e. HET<sup>1</sup> is linked to Ar<sup>1</sup> by a direct bond); and wherein HET<sup>1</sup> represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-hydroxy-[1,2,4]oxadiazol-3-yl), 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl (encompassing its tautomeric form 3-hydroxy-[1,2,4]oxadiazol-5-yl), or 5-thioxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-mercapto-[1,2,4]oxadiazol-3-yl);
- -(CH<sub>2</sub>)<sub>p</sub>-HET, wherein p represents the integer 0 or 1 (especially p is 0, i.e. HET is linked to Ar<sup>1</sup> by a direct bond); and wherein HET represents a 5- or 6-membered heteroaryl (especially 5-membered heteroaryl selected from oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl, and tetrazolyl), wherein said 5- or 6-membered heteroaryl is unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected from (C<sub>1-4</sub>)alkyl (especially methyl), (C<sub>1-4</sub>)alkoxy (especially methoxy), -COOH, hydroxy, hydroxy-(C<sub>1-3</sub>)alkyl (especially hydroxymethyl), (C<sub>3-5</sub>)cycloalkyl optionally containing one ring oxygen atom (especially cyclopropyl, oxetan-3-yl), or -NR<sup>N9</sup>R<sup>N10</sup> wherein R<sup>N9</sup> and R<sup>N10</sup> independently represent hydrogen, (C<sub>1-3</sub>)alkyl (especially methyl), or hydroxy-(C<sub>2-4</sub>)alkyl (especially 2-hydroxy-ethyl); (especially such group -(CH<sub>2</sub>)<sub>p</sub>-HET is 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl, 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, 5-methoxy-[1,2,4]oxadiazol-3-yl, 5-amino-[1,2,4]oxadiazol-3-yl, 5-[(2-hydroxy-ethyl)]-amino-[1,2,4]oxadiazol-3-yl, 5-hydroxymethyl-[1,2,4]oxadiazol-3-yl, 5-(oxetan-3-yl)-[1,2,4]oxadiazol-3-yl, 1H-imidazol-4-yl, 5-methyl-1H-imidazol-4-yl, 2,5-dimethyl-1H-imidazol-4-yl);
- or Ar<sup>1</sup> represents 8- to 10-membered bicyclic heteroaryl (notably 9- or 10-membered bicyclic heteroaryl; especially indazolyl, benzoimidazolyl, indolyl, benzotriazolyl, benzofuranyl, benzooxazolyl, quinoxalyl, isoquinolyl, quinolyl, pyrrolopyridinyl, or imidazopyridinyl); wherein said 8- to 10-membered bicyclic heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C<sub>1-4</sub>)alkyl (especially methyl); (C<sub>1-4</sub>)alkoxy (especially methoxy); (C<sub>1-3</sub>)fluoroalkyl (especially trifluoromethyl); (C<sub>1-3</sub>)fluoroalkoxy (especially trifluoromethoxy); halogen; cyano; hydroxy, or -(C<sub>0-3</sub>)alkylene-COOR<sup>O2</sup> wherein R<sup>O2</sup> represents hydrogen or (C<sub>1-4</sub>)alkyl (especially such group -(C<sub>0-3</sub>)alkylene-COOR<sup>O2</sup> is -

COOH); (especially such 8- to 10-membered bicyclic heteroaryl, if unsubstituted, is 1H-benzoimidazol-5-yl, 1H-indol-6-yl, 1H-indol-5-yl, 1H-indol-2-yl, 1H-indazol-5-yl, isoquinolin-7-yl, quinolin-6-yl; or, if substituted, is 3-carboxy-1H-indol-6-yl, 4-carboxy-1H-indol-2-yl, 5-carboxy-1H-indol-2-yl, 6-carboxy-1H-indol-2-yl, 7-carboxy-1H-indol-2-yl, 5-(methoxycarbonyl)-1H-indol-2-yl, 6-(methoxycarbonyl)-1H-indol-2-yl), 6-carboxy-benzofuran-2-yl, 3-carboxy-benzofuran-6-yl, 2-carboxy-benzofuran-5-yl, or 2-carboxy-benzofuran-6-yl);

- or **Ar<sup>1</sup>** represents a group of the structure (Ar-III):

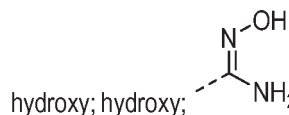


(Ar-III)

wherein ring (B) represents a non-aromatic 5- or 6-membered ring fused to the phenyl group, wherein ring (B) comprises one or two heteroatoms independently selected from nitrogen and oxygen (notably such group (Ar-III) is 2,3-dihydro-benzofuranyl, 2,3-dihydro-1H-indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2,3-dihydro-1H-indazolyl, 2,3-dihydro-1H-benzo[d]imidazolyl, 2,3-dihydrobenzo[d]isoxazolyl, 2,3-dihydro-isindolyl, 2,3-dihydro-benzooxazolyl, 1,2,3,4-tetrahydro-quinazolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, or 1,2,3,4-tetrahydro-phthalazinyl); wherein said ring (B) independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from oxo, (C<sub>1-6</sub>)alkyl (especially methyl, ethyl, propyl, butyl, isobutyl) and -(C<sub>0-3</sub>)alkylene-COOR<sup>03</sup> wherein **R<sup>03</sup>** represents hydrogen or (C<sub>1-3</sub>)alkyl (especially such group (Ar-III) is 2-oxo-2,3-dihydro-benzooxazol-6-yl, 3-methyl-2-oxo-2,3-dihydro-benzooxazol-5-yl, 1-methyl-3-oxo-2,3-dihydro-1H-indazol-6-yl, 2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-7-yl, or 1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl).

In a sub-embodiment, **Ar<sup>1</sup>** especially represents

- phenyl, or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl independently is mono-, di- or tri-substituted (especially di-substituted),
  - wherein one of said substituents is selected from (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom, wherein said (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with



hydroxy; hydroxy; -X<sup>1</sup>-CO-R<sup>01</sup>; 2-hydroxy-3,4-dioxo-cyclobut-1-enyl; hydroxy-(C<sub>2-4</sub>)alkoxy; -(CH<sub>2</sub>)<sub>r</sub>-CO-NR<sup>N3</sup>R<sup>N4</sup>; -NH-CO-NR<sup>N5</sup>R<sup>N6</sup>; -SO<sub>2</sub>-R<sup>S1</sup>; -(CH<sub>2</sub>)<sub>q</sub>-HET<sup>1</sup>; -(CH<sub>2</sub>)<sub>p</sub>-HET;

- and the other of said substituents, if present, independently are selected from (C<sub>1-6</sub>)alkyl; (C<sub>1-4</sub>)alkoxy; (C<sub>1-3</sub>)fluoroalkyl; (C<sub>1-3</sub>)fluoroalkoxy; halogen; cyano; (C<sub>3-6</sub>)cycloalkyl, wherein said (C<sub>3-6</sub>)cycloalkyl is

unsubstituted or mono-substituted with amino; (C<sub>3-6</sub>)cycloalkyl-oxy; hydroxy; hydroxy-(C<sub>1-4</sub>)alkyl; dihydroxy-(C<sub>2-4</sub>)alkyl; hydroxy-(C<sub>2-4</sub>)alkoxy; (C<sub>1-4</sub>)alkoxy-(C<sub>2-4</sub>)alkoxy; -X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup>; -S-R<sup>S2</sup>; wherein the above groups and substituents are as defined in embodiment 1).

- or Ar<sup>1</sup> represents 8- to 10-membered bicyclic heteroaryl as defined in embodiment 1); wherein said 8- to 10-membered bicyclic heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C<sub>1-4</sub>)alkyl; (C<sub>1-4</sub>)alkoxy; (C<sub>1-3</sub>)fluoroalkyl; (C<sub>1-3</sub>)fluoroalkoxy; halogen; cyano; hydroxy, or -(C<sub>0-3</sub>)alkylene-COOR<sup>O2</sup> wherein R<sup>O2</sup> represents hydrogen or (C<sub>1-4</sub>)alkyl;
- or Ar<sup>1</sup> represents a group of the structure (Ar-III) as defined in embodiment 1).

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

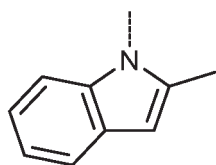
In case a particular compound (or generic structure) is designated as (R)- or (S)-enantiomer, such designation is to be understood as referring to the respective compound (or generic structure) in enriched, especially essentially pure, enantiomeric form. Likewise, in case a specific asymmetric center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

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

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

The present invention also includes isotopically labelled, especially  $^2\text{H}$  (deuterium) labelled compounds of formulae (I), (II), or (III) according to embodiments 1) to 31), which compounds are identical to the compounds of formulae (I), (II), or (III) except that one or more atoms have each been replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Isotopically labelled, especially  $^2\text{H}$  (deuterium) labelled compounds of formulae (I), (II), or (III) and salts thereof are within the scope of the present invention. Substitution of hydrogen with the heavier isotope  $^2\text{H}$  (deuterium) may lead to greater metabolic stability, resulting e.g. in increased *in-vivo* half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of formulae (I), (II), or (III) are not isotopically labelled, or they are labelled only with one or more deuterium atoms. In a sub-embodiment, the compounds of formulae (I), (II), or (III) are not isotopically labelled at all. Isotopically labelled compounds of formulae (I), (II), or (III) may be prepared in analogy to the methods described hereinafter, but using the appropriate isotopic variation of suitable reagents or starting materials.

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



is the 2-methyl-1H-indol-1-yl group.

In some instances, the compounds of formulae (I), (II), or (III) may contain tautomeric forms. Such tautomeric forms are encompassed in the scope of the present invention. In case tautomeric forms exist of a certain residue, and only one form of such residue is disclosed or defined, the other tautomeric form(s) are understood to be encompassed in such disclosed residue. For example the group 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl is to be understood as also encompassing its tautomeric forms 2-hydroxy-1H-benzo[d]imidazol-5-yl and 2-hydroxy-3H-benzo[d]imidazol-5-yl. Similarly, 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (alternatively named 5-oxo-4H-[1,2,4]oxadiazol-3-yl) encompasses its tautomeric form 5-hydroxy-[1,2,4]oxadiazol-3-yl, and 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl (alternatively named 3-oxo-2H-[1,2,4]oxadiazol-5-yl) encompasses its tautomeric form 3-hydroxy-[1,2,4]oxadiazol-5-yl.

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

Any reference to compounds of formulae (I), (II), or (III) according to embodiments 1) to 31) 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 formulae (I), (II), or (III), as defined in any one of embodiments 1) to 22), and, *mutatis mutandis*, throughout the description and the claims unless an otherwise expressly set out definition provides a broader or narrower definition. It is well understood that a definition or preferred definition of a term defines and may replace the respective term independently of (and in combination with) any definition or preferred definition of any or all other terms as defined herein. Whenever the group Ar<sup>1</sup> or substituents thereof are further defined, such definitions are intended to apply *mutatis mutandis* also to the groups (Ar-I), (Ar-II), and (Ar-III) and their respective substituents.

Whenever a substituent is denoted as optional, it is understood that such substituent may be absent (i.e. the respective residue is unsubstituted with regard to such optional substituent), in which case all positions having a free valency (to which such optional substituent could have been attached to; such as for example in an aromatic ring the ring carbon atoms and / or the ring nitrogen atoms having a free valency) are substituted with hydrogen where appropriate. Likewise, in case the term "optionally" is used in the context of (ring) heteroatom(s), the term means that either the respective optional heteroatom(s), or the like, are absent (i.e. a certain moiety does not contain heteroatom(s) / is a carbocycle / or the like), or the respective optional heteroatom(s), or the like, are present as explicitly defined.

The term "halogen" means fluorine, chlorine, bromine, or iodine; especially fluorine, chlorine, or bromine; preferably fluorine or chlorine.

The term "alkyl", used alone or in combination, refers to a saturated straight or branched chain hydrocarbon group containing one to six carbon atoms. The term "(C<sub>x-y</sub>)alkyl" (x and y each being an integer), refers to an alkyl group as defined before, containing x to y carbon atoms. For example a (C<sub>1-6</sub>)alkyl group contains from one to six carbon atoms. Examples of alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, 3-methyl-butyl, 2,2-dimethyl-propyl and 3,3-dimethyl-butyl. For avoidance of any doubt, in case a group is referred to as e.g. propyl or butyl, it is meant to be n-propyl, respectively n-butyl. Preferred are methyl and ethyl. Most preferred is methyl. Preferred for substituents of Ar<sup>1</sup> being phenyl or 5- or 6-membered heteroaryl are methyl, ethyl, propyl, isobutyl, 1-methyl-propan-1-yl, tert.-butyl, 3-methyl-butyl.

The term "(C<sub>x-y</sub>)alkylene-", used alone or in combination, refers to bivalently bound alkyl group as defined before containing x to y carbon atoms. Preferably, the points of attachment of a (C<sub>1-y</sub>)alkylene group are in 1,1-diyl, in 1,2-diyl, or in 1,3-diyl arrangement. In case a (C<sub>0-y</sub>)alkylene group is used in combination with another substituent, the term means that either said substituent is linked through a (C<sub>1-y</sub>)alkylene group to the rest of the molecule, or it is

directly attached to the rest of the molecule (i.e. a (C<sub>0</sub>)alkylene group represents a direct bond linking said substituent to the rest of the molecule). The alkylene group -C<sub>2</sub>H<sub>4</sub>- refers to -CH<sub>2</sub>-CH<sub>2</sub>- if not explicitly indicated otherwise. For the linker **X**<sup>1</sup>, examples of (C<sub>1-3</sub>)alkylene groups are -CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, and -CH<sub>2</sub>-CH<sub>2</sub>-, especially -CH<sub>2</sub>- and -CH<sub>2</sub>-CH<sub>2</sub>-. Examples of (C<sub>0-3</sub>)alkylene groups as used in the substituents -(C<sub>0-3</sub>)alkylene-COOR<sup>02</sup> and (C<sub>0-3</sub>)alkylene-COOR<sup>03</sup>, respectively, are (C<sub>0</sub>)alkylene, and methylene, respectively.

The term "alkoxy", used alone or in combination, refers to an alkyl-O- group wherein the alkyl group is as defined before. The term "(C<sub>x-y</sub>)alkoxy" (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms. For example a (C<sub>1-4</sub>)alkoxy group means a group of the formula (C<sub>1-4</sub>)alkyl-O- in which the term "(C<sub>1-4</sub>)alkyl" has the previously given significance. Examples of alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.-butoxy and tert.-butoxy. Preferred are ethoxy and especially methoxy. Preferred for substituents of **Ar**<sup>1</sup> being phenyl or 5- or 6-membered heteroaryl are methoxy, ethoxy, propoxy, butoxy, isobutoxy.

The term "fluoroalkyl", used alone or in combination, refers to an alkyl group as defined before containing one to three carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. The term "(C<sub>x-y</sub>)fluoroalkyl" (x and y each being an integer) refers to a fluoroalkyl group as defined before containing x to y carbon atoms. For example a (C<sub>1-3</sub>)fluoroalkyl group contains from one to three carbon atoms in which one to seven hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkyl groups include trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl and 2,2,2-trifluoroethyl. Preferred are (C<sub>1</sub>)fluoroalkyl groups such as trifluoromethyl. An example of "(C<sub>1-3</sub>)fluoroalkyl, wherein said (C<sub>1-3</sub>)fluoroalkyl is optionally substituted with hydroxy" is 2,2,2-trifluoro-1-hydroxy-ethyl.

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

The term "cycloalkyl", used alone or in combination, refers to a saturated monocyclic hydrocarbon ring containing three to six carbon atoms. The term "(C<sub>x-y</sub>)cycloalkyl" (x and y each being an integer), refers to a cycloalkyl group as defined before containing x to y carbon atoms. For example a (C<sub>3-6</sub>)cycloalkyl group contains from three to six carbon atoms. Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Preferred are cyclopropyl, cyclobutyl, and cyclopentyl; especially cyclopropyl. An example of cycloalkyl groups containing one ring oxygen atom is especially oxetanyl. Examples of (C<sub>3-6</sub>)cycloalkyl groups wherein said (C<sub>3-6</sub>)cycloalkyl is optionally mono-substituted with amino are cyclopropyl, 1-amino-cyclopropyl. Examples of (C<sub>3-</sub>

<sub>6</sub>)cycloalkyl groups wherein said (C<sub>3-6</sub>)cycloalkyl is mono-substituted with—COOH are 1-carboxy-cyclopropyl, 1-carboxy-cyclopentyl.

The term “-(C<sub>x-y</sub>)cycloalkylene-”, used alone or in combination, refers to bivalently bound cycloalkyl group as defined before containing x to y carbon atoms. Preferably, the points of attachment of any bivalently bound cycloalkyl group are in 1,1-diyl, or in 1,2-diyl arrangement. Examples are cyclopropan-1,1-diyl, cyclopropan-1,2-diyl, and cyclopentan-1,1-diyl; preferred is cyclopropan-1,1-diyl.

Examples of (C<sub>3-6</sub>)cycloalkyl-oxy are cyclobutyl-oxy, and cyclopentyl-oxy.

Alkylated amino groups -N[(C<sub>1-4</sub>)alkyl]<sub>2</sub> as used in groups -X<sup>1</sup>-CO-R<sup>01</sup>, wherein R<sup>01</sup> represents -O-CH<sub>2</sub>-CO-R<sup>04</sup>, wherein R<sup>04</sup> represents -N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>; or wherein R<sup>01</sup> represents -O-CH<sub>2</sub>-CH<sub>2</sub>-N[(C<sub>1-4</sub>)alkyl]<sub>2</sub> are such that the two respective (C<sub>1-4</sub>)alkyl groups are independently selected. A preferred example of such amino group -N[(C<sub>1-4</sub>)alkyl]<sub>2</sub> is -N(CH<sub>3</sub>)<sub>2</sub>.

The term “heterocycle”, used alone or in combination, and if not explicitly defined in a broader or more narrow way, refers to a saturated monocyclic hydrocarbon ring containing one or two (especially one) ring heteroatoms independently selected from nitrogen, sulfur, and oxygen (especially one nitrogen atom, two nitrogen atoms, one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulfur atom). The term “(C<sub>x-y</sub>)heterocycle” refers to such a heterocycle containing x to y ring atoms. Heterocycles are unsubstituted or substituted as explicitly defined.

A group composed of a “non-aromatic 5- or 6-membered ring fused to the phenyl group, wherein ring (B) comprises one or two heteroatoms independently selected from nitrogen and oxygen ” as used for (Ar-III) refers to phenyl groups which are fused to a (C<sub>5-6</sub>)heterocycle as defined before. Examples are 2,3-dihydro-benzofuranyl, 2,3-dihydro-1H-indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2,3-dihydro-1H-indazolyl, 2,3-dihydro-1H-benzo[d]imidazolyl, 2,3-dihydrobenzo[d]isoxazolyl, 2,3-dihydro-isoindolyl, 3-dihydro-benzooxazol-6-yl, 2,3-dihydro-benzooxazol-5-yl, 1,2,3,4-tetrahydro-quinazolin-6-yl, 1,2,3,4-tetrahydro-quinazolin-7-yl, 1,2,3,4-tetrahydro-isoquinolin-6-yl, and 1,2,3,4-tetrahydro-phthalazin-6-yl. The above groups are unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from oxo, (C<sub>1-6</sub>)alkyl, and -(C<sub>0-3</sub>)alkylene-COOR<sup>03</sup> wherein R<sup>03</sup> represents hydrogen or (C<sub>1-3</sub>)alkyl (especially methyl); especially substituents are independently selected from oxo, methyl, ethyl, propyl, butyl, isobutyl, or -COOH; wherein the substituents are attached to the fused 5- or 6-membered non-aromatic ring. Oxo substituents are preferably attached to a ring carbon atom which is in alpha position to a ring nitrogen atom. Preferred examples of such groups are 2,3-dihydro-benzofuranyl, 2,3-dihydro-1H-indolyl, 2,3-dihydro-benzo[1,4]dioxinyl; as well as the oxosubstituted heterocyclyl groups 3-oxo-2,3-dihydro-1H-indazolyl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazolyl, 3-oxo-2,3-dihydrobenzo[d]isoxazolyl, 2-oxo-1,3-dihydro-indolyl, 1-oxo-2,3-dihydro-isoindolyl, 2-oxo-2,3-dihydro-benzooxazolyl, 2-oxo-1,2,3,4-tetrahydro-quinazolinyl, 1-oxo-1,2,3,4-tetrahydro-isoquinolinyl, 1,4-dioxo-1,2,3,4-tetrahydro-phthalazinyl; wherein the above groups optionally carry one (further) substituent independently selected from (C<sub>1-6</sub>)alkyl, and -(C<sub>0-3</sub>)alkylene-COOR<sup>03</sup> wherein R<sup>03</sup> represents hydrogen or (C<sub>1-3</sub>)alkyl (especially methyl). Particular examples are 2-oxo-2,3-dihydro-benzooxazol-6-yl, 3-methyl-

2-oxo-2,3-dihydro-benzooxazol-5-yl, 1-methyl-3-oxo-2,3-dihydro-1H-indazol-6-yl, 2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-7-yl, and 1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl, and, in addition, 2-oxo-1,3-dihydro-indol-5-yl, and 1-methyl-2-oxo-1,3-dihydro-indol-5-yl.

- 5 For avoidance of doubt, certain groups having tautomeric forms which are considered predominantly non-aromatic, such as for example 2-oxo-2,3-dihydro-1H-benzo[d]imidazolyl groups, are defined herein as 8- to 10-membered partially aromatic fused bicyclic heterocyclyl groups, even though their corresponding tautomeric form (2-hydroxy-1H-benzo[d]imidazolyl) could also be considered as a 8- to 10-membered bicyclic heteroaryl group.

10 The term "aryl", used alone or in combination, means phenyl or naphthyl, especially phenyl. The above-mentioned aryl groups are unsubstituted or substituted as explicitly defined.

Examples of the substituent **Ar<sup>1</sup>** representing phenyl are especially those which are at least mono-substituted in para position with respect to the point of attachment of the rest of the molecule. In addition, such group **Ar<sup>1</sup>** representing phenyl may carry one or two further substituents, especially in one or both meta positions with respect to the point of attachment of the rest of the molecule. The respective substituents of such phenyl groups are as explicitly defined.

15 The term "heteroaryl", used alone or in combination, means a 5- to 10-membered monocyclic or bicyclic aromatic ring containing one to a maximum of four heteroatoms, each independently selected from oxygen, nitrogen and sulfur. Examples of such heteroaryl groups are 5-membered heteroaryl groups such as furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl; 6-  
20 membered heteroaryl groups such as pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl; and 8- to 10-membered bicyclic heteroaryl groups such as indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl, thienopyridinyl, quinolinyl, isoquinolinyl, naphthyridinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyrrolopyridinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrrolopyrazinyl, imidazopyridinyl, imidazopyridazinyl, and imidazothiazolyl. The above-mentioned heteroaryl groups are unsubstituted or substituted as explicitly defined.

For the substituent **Ar<sup>1</sup>** representing a "5- or 6-membered heteroaryl", the term means the above-mentioned 5- or 6-membered groups such as especially pyridinyl, pyrimidinyl, pyrrolyl, pyrazolyl, isoxazolyl, thiazolyl or thiophenyl. Notably, the term refers to 5-membered groups such as especially thiazolyl or thiophenyl; in particular thiophen-2-  
30 yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl. Preferred is thiophenyl, especially thiophen-2-yl; or thiazolyl, especially thiazol-2-yl. The above groups are substituted as explicitly defined. Thiophen-2-yl or thiazol-2-yl are especially di-substituted with one substituent being in position 5, and a second substituent in position 4 (and, for thiophen-2-yl, optionally a halogen substituent in position 3).

For the substituent **Ar<sup>1</sup>** representing a "8- to 10-membered bicyclic heteroaryl" the term means the above-mentioned  
35 8- to 10-membered heteroaryl groups. Notably, the term refers to 9- or 10-membered heteroaryl groups, such as

especially indazolyl, benzoimidazolyl, indolyl, benzotriazolyl, benzooxazolyl, quinoxaliny, isoquinoliny, quinoliny, pyrrolopyridiny, and imidazopyridiny, as well as benzofuranyl, benzothiophenyl, and benzothiazolyl. The above groups are unsubstituted or substituted as explicitly defined. Particular examples are 1H-indol-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1-methyl-1H-indol-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-methyl-1H-indazol-6-yl, 3-methyl-1H-indazol-6-yl, 3-methoxy-1H-indazol-6-yl, 6-methoxy-1H-indazol-5-yl, 1H-benzoimidazol-5-yl, 2-methyl-1H-benzoimidazol-5-yl, 2-trifluoromethyl-1H-benzoimidazol-5-yl, 1H-benzotriazol-5-yl, 2-methyl-benzooxazol-5-yl, 2-methyl-benzooxazol-6-yl, quinoxalin-6-yl, isoquinolin-7-yl, quinolin-6-yl, 1H-pyrrolo[2,3-c]pyridin-3-yl, 1H-pyrrolo[2,3-b]pyridin-3-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl, imidazo[1,2-a]pyridin-6-yl, 2-carboxy-1H-indol-5-yl, 3-carboxy-1H-indol-6-yl, 4-carboxy-1H-indol-2-yl, 5-carboxy-1H-indol-2-yl, 6-carboxy-1H-indol-2-yl, 7-carboxy-1H-indol-2-yl, 7-carboxy-1H-indol-4-yl, 7-carboxy-1-methyl-1H-indol-4-yl, 5-(methoxycarbonyl)-1H-indol-2-yl, 6-(methoxycarbonyl)-1H-indol-2-yl, 6-carboxy-benzofuran-2-yl, 3-carboxy-benzofuran-6-yl, 2-carboxy-benzofuran-5-yl, and 2-carboxy-benzofuran-6-yl. Preferred examples are 1H-benzoimidazol-5-yl, 1H-indol-6-yl, 1H-indol-5-yl, 1H-indol-2-yl, 1H-indazol-5-yl, and, in addition, imidazo[1,2-a]pyridin-6-yl; as well as 8- to 10-membered bicyclic heteroaryl which are mono-substituted with  $-(C_{0-3})alkylene-COOR^{02}$  such as 3-carboxy-1H-indol-6-yl, 4-carboxy-1H-indol-2-yl, 5-carboxy-1H-indol-2-yl, 6-carboxy-1H-indol-2-yl, 7-carboxy-1H-indol-2-yl, 5-(methoxycarbonyl)-1H-indol-2-yl, 6-(methoxycarbonyl)-1H-indol-2-yl, 6-carboxy-benzofuran-2-yl, 3-carboxy-benzofuran-6-yl, 2-carboxy-benzofuran-5-yl, and 2-carboxy-benzofuran-6-yl.

For the substituent  $-(CH_2)_p-HET$ , wherein  $p$  represents the integer 0 or 1, and wherein **HET** represents a 5- or 6-membered heteroaryl", such 5- or 6-membered heteroaryl is as defined before; notably a nitrogen containing 5-membered heteroaryl such as especially tetrazolyl, or oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, or triazolyl. The above groups are unsubstituted or substituted as explicitly defined. The group  $-(CH_2)_p-$  is preferably absent, i.e.  $p$  represents the integer 0 and the group **HET** is directly bound to **Ar**<sup>1</sup>. Particular examples of  $-(CH_2)_p-HET$  are especially the  $-(CH_2)_0-HET$  groups 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl; further examples are 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, 5-methoxy-[1,2,4]oxadiazol-3-yl, 5-amino-[1,2,4]oxadiazol-3-yl, 5-[(2-hydroxy-ethyl)]-amino-[1,2,4]oxadiazol-3-yl, 5-hydroxymethyl-[1,2,4]oxadiazol-3-yl, 5-(oxetan-3-yl)-[1,2,4]oxadiazol-3-yl, 1H-imidazol-4-yl, 5-methyl-1H-imidazol-4-yl, and 2,5-dimethyl-1H-imidazol-4-yl; as well as 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 3-methyl-pyrazol-1-yl, 1-methyl-1H-pyrazol-3-yl, 5-methyl-1H-pyrazol-3-yl, 3,5-dimethyl-pyrazol-1-yl, 4-carboxy-1H-pyrazol-3-yl, 1H-imidazol-2-yl, 3-methyl-3H-imidazol-4-yl, 2-methyl-1H-imidazol-4-yl, 1,5-dimethyl-1H-imidazol-2-yl, 1,2-dimethyl-1H-imidazol-4-yl, 1,5-dimethyl-1H-imidazol-4-yl, 2-cyclopropyl-1H-imidazol-4-yl, 2-cyclopropyl-1-methyl-1H-imidazol-4-yl, [1,2,4]oxadiazol-5-yl, 5-methyl-[1,2,4]oxadiazol-3-yl, 3-methyl-[1,2,4]oxadiazol-5-yl, 5-methyl-[1,3,4]oxadiazol-2-yl, isothiazol-5-yl, thiazol-2-yl, thiazol-4-yl, 4-methyl-thiazol-2-yl, 2-methyl-thiazol-4-yl, 2-amino-5-methyl-thiazol-4-yl, 4,5-dimethyl-thiazol-2-yl, 4-carboxy-thiazol-2-yl, 2-carboxy-thiazol-4-yl, 2-hydroxy-thiazol-4-yl, 2-amino-2-oxoethyl-thiazol-4-yl, isoxazol-3-yl, isoxazol-5-yl, 3-methyl-isoxazol-5-yl, 4-methyl-isoxazol-5-yl, 4-carboxy-3-methyl-isoxazol-5-yl, oxazol-5-yl, 2-methyl-oxazol-5-yl, 2-(2-carboxyethyl)-oxazol-5-yl, 2-(2-carboxyethyl)-4-methyl-oxazol-5-yl, 4H-[1,2,4]triazol-3-yl,



1H-[1,2,4]triazol-1-yl, 2-methyl-2H-[1,2,4]triazol-3-yl, pyridin-2-yl, 4-fluoro-pyridin-2-yl, pyrimidin-2-yl, 5-fluoro-pyrimidin-2-yl, 5-methoxy-pyrimidin-2-yl, 4-methoxy-pyrimidin-2-yl, 6-methoxy-pyrimidin-4-yl, 6-dimethylamino-pyrimidin-4-yl, pyrazin-2-yl, 6-methoxy-pyrazin-2-yl, 6-methoxy-pyridazin-3-yl, 3H-imidazol-4-yl, 3H-[1,2,3]triazol-4-yl, oxazol-2-yl, and 4,5-dimethyl-oxazol-2-yl. Particular groups **HET** are selected from 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl, 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, 5-methoxy-[1,2,4]oxadiazol-3-yl, 5-amino-[1,2,4]oxadiazol-3-yl, 5-[(2-hydroxy-ethyl)]-amino)-[1,2,4]oxadiazol-3-yl, 5-hydroxymethyl-[1,2,4]oxadiazol-3-yl, and 5-(oxetan-3-yl)-[1,2,4]oxadiazol-3-yl. For avoidance of doubt, certain groups having tautomeric forms which may be considered predominantly aromatic (such as for example 3-hydroxy-isoxazolyl or 2-hydroxy-[1,3,4]oxadiazolyl groups) are defined herein as heteroaryl groups **HET**, even though their corresponding tautomeric form (3-oxo-2,3-dihydro-2H-isoxazolyl, respectively, 2-oxo-2,3-dihydro-3H-[1,3,4]oxadiazolyl) could also be considered as a non-aromatic group. Likewise, certain groups having tautomeric forms which may be considered predominantly non-aromatic (such as 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl or 5-thioxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl) as defined for the substituent **HET**<sup>1</sup>, are defined herein as not being part of substituted heteroaryl groups as defined for **HET**, even though their corresponding tautomeric form (5-hydroxy-[1,2,4]oxadiazolyl, respectively, 5-mercapto-[1,2,4]oxadiazolyl), could also be considered as an heteroaryl group. It is understood that the corresponding tautomer is encompassed in the respective scope as defined.

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

The term "oxo" refers to a group =O which is preferably attached to a chain or ring carbon or sulfur atom as for example in a carbonyl group -(CO)-, or a sulfonyl group -(SO<sub>2</sub>)-.

Examples of "**-X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup>**" groups as used for substituents of **Ar**<sup>1</sup> being phenyl or 5- or 6-membered heteroaryl are amino, methylamino, ethylamino, propylamino, amino-methyl, methylamino-methyl, isobutylamino-methyl, cyclopropylamino-methyl, cyclobutylamino-methyl, (2-methoxyethyl)amino-methyl, (2,2,2-trifluoro-ethyl)-amino; or -NH-CO-H, -N(C<sub>2</sub>H<sub>5</sub>)-CO-H, -NH-CO-C<sub>2</sub>H<sub>5</sub>, -NH-CO-CH<sub>2</sub>-CH<sub>2</sub>-OH, -NH-CO-O-CH<sub>3</sub>, -N(CH<sub>3</sub>)-CO-O-CH<sub>3</sub>; or pyrrolidin-1-yl, 2-oxo-pyrrolidin-1-yl, 1,1-dioxo-isothiazolidin-2-yl, morpholin-4-yl, azetidin-1-yl, or piperidin-1-yl; and 2-(dimethylamino)-ethoxy.

Examples of a group "**-NH-CO-NR<sup>N5</sup>R<sup>N6</sup>**" as used for substituents of the group **Ar**<sup>1</sup> are ureido (-NH-CO-NH<sub>2</sub>) and 3-ethylureido (-NH-CO-NH-C<sub>2</sub>H<sub>5</sub>).

Examples of a group "**-(CH<sub>2</sub>)<sub>r</sub>-CO-NR<sup>N3</sup>R<sup>N4</sup>**" wherein **r** represents the integer 0 or 1" as used for substituents of the group **Ar**<sup>1</sup> are preferably groups wherein **r** represents the integer 0 and at least one of **R<sup>N3</sup>** and **R<sup>N4</sup>** represents hydrogen (or less preferred, methyl). Particular examples of such group -CO-NR<sup>N3</sup>R<sup>N4</sup> are -CO-NH<sub>2</sub>, -CO-NH(CH<sub>3</sub>), -CO-N(CH<sub>3</sub>)<sub>2</sub>, -CO-NH(C<sub>2</sub>H<sub>5</sub>), -CO-NH-O-methyl, -CO-NH-O-ethyl, -CO-NH-O-isopropyl, -CO-NH-C<sub>2</sub>H<sub>4</sub>-OH, -CO-NH-O-C<sub>2</sub>H<sub>4</sub>-OH, -CO-NH-C<sub>2</sub>H<sub>4</sub>-OCH<sub>3</sub>, -CO-NH-C<sub>2</sub>H<sub>4</sub>-N(CH<sub>3</sub>)<sub>2</sub>, and -CO-NH-O-benzyl. Further examples are -CO-NH-isopropyl and -CO-NH-OH, as well as -CO-N(CH<sub>3</sub>)<sub>2</sub>.

Examples of a group "**-X<sup>1</sup>-CO-R<sup>01</sup>**" as used for substituents of the group **Ar**<sup>1</sup> are especially the following groups:



- a)  $X^1$  represents a direct bond; and  $R^{01}$  represents -OH; (i.e.  $-X^1-CO-R^{01}$  represents -COOH); or
- b)  $X^1$  represents a direct bond; and  $R^{01}$  represents -O-(C<sub>1-4</sub>)alkyl (especially ethoxy, or methoxy); (i.e.  $-X^1-CO-R^{01}$  represents -CO-(C<sub>1-4</sub>)alkoxy (especially ethoxycarbonyl, methoxycarbonyl)); or
- c)  $X^1$  represents a direct bond; and  $R^{01}$  represents -NH-SO<sub>2</sub>-R<sup>S3</sup>; wherein R<sup>S3</sup> represents (C<sub>1-4</sub>)alkyl; (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom; (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom; (C<sub>1-3</sub>)fluoroalkyl; phenyl; or -NH<sub>2</sub>; (i.e.  $-X^1-CO-R^{01}$  represents -CO-NH-SO<sub>2</sub>-R<sup>S3</sup> wherein R<sup>S3</sup> represents the above mentioned groups; notably methyl, ethyl, isopropyl, cyclopropyl, trifluoromethyl, amino; especially  $-X^1-CO-R^{01}$  represents -CO-NH-SO<sub>2</sub>-CH<sub>3</sub>, -CO-NH-SO<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>, -CO-NH-SO<sub>2</sub>-cyclopropyl, -CO-NH-SO<sub>2</sub>-ethyl, or -CO-NH-SO<sub>2</sub>-NH<sub>2</sub>); or
- d)  $X^1$  represents (C<sub>1-3</sub>)alkylene (especially -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-), -O-(C<sub>1-3</sub>)alkylene-\* (especially -O-CH<sub>2</sub>-, -O-CH(CH<sub>3</sub>)-\*, -O-C(CH<sub>3</sub>)<sub>2</sub>-, -O-CH<sub>2</sub>-CH<sub>2</sub>-\*), -NH-(C<sub>1-3</sub>)alkylene-\* (especially -NH-CH<sub>2</sub>-, -NH-CH(CH<sub>3</sub>)-\*), -S-CH<sub>2</sub>-, -CF<sub>2</sub>-, -CH=CH-, or -CH≡CH- [in a sub-embodiment  $X^1$  represents especially -O-CH<sub>2</sub>-, -NH-CH<sub>2</sub>-, -S-CH<sub>2</sub>-, or (C<sub>1-3</sub>)alkylene]; wherein the asterisks indicate the bond that is linked to the -CO-R<sup>01</sup> group; and  $R^{01}$  represents -OH (i.e.  $-X^1-CO-R^{01}$  represents  $-X^1-COOH$  wherein  $X^1$  represents the above mentioned groups; especially  $-X^1-CO-R^{01}$  represents -O-CH<sub>2</sub>-COOH or -NH-CH<sub>2</sub>-COOH; as well as -CH<sub>2</sub>-COOH, -CH<sub>2</sub>-CH<sub>2</sub>-COOH, -CH=CH-COOH, -CH≡CH-COOH, -O-CH<sub>2</sub>-CH<sub>2</sub>-COOH, -O-CH(CH<sub>3</sub>)-COOH, or -NH-CH(CH<sub>3</sub>)-COOH); or
- e)  $-X^1$  represents -NH-CO-\* or -CO-; wherein the asterisk indicates the bond that is linked to the -CO-R<sup>01</sup> group; and  $R^{01}$  represents -OH (i.e.  $-X^1-CO-R^{01}$  represents  $-X^1-COOH$  wherein  $X^1$  represents the above mentioned groups; especially  $-X^1-CO-R^{01}$  represents -NH-CO-COOH, -CO-COOH); or
- f)  $X^1$  represents (C<sub>3-5</sub>)cycloalkylene; and  $R^{01}$  represents -OH; (i.e.  $-X^1-CO-R^{01}$  represents (C<sub>3-5</sub>)cycloalkyl which is mono-substituted with COOH; especially  $-X^1-CO-R^{01}$  represents 1-carboxy-cyclopropan-1-yl or 1-carboxy-cyclopentan-1-yl); or
- g)  $X^1$  represents a direct bond; and  $R^{01}$  represents -O-CH<sub>2</sub>-CO-R<sup>04</sup>, wherein R<sup>04</sup> represents hydroxy, or (C<sub>1-4</sub>)alkoxy, or -N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>; especially  $-X^1-CO-R^{01}$  represents -CO-O-CH<sub>2</sub>-COOH; or
- wherein each of the groups a), b), c), d), e), f), and g) forms a particular sub-embodiment.

Compounds of Formulae (I), (II), or (III) containing a group " $-X^1-CO-R^{01}$ " wherein  $X^1$  represents -CH=CH- may be in E- or Z-configuration. Preferably, such groups are in E-configuration.

- Whenever a group  $Ar^1$  is substituted with a substituent comprising a carboxylic acid group -COOH (such as in the substituents -(C<sub>0-3</sub>)alkylene-COOR<sup>02</sup> wherein R<sup>02</sup> represents hydrogen; -(C<sub>0-3</sub>)alkylene-COOR<sup>03</sup> wherein R<sup>03</sup> represents hydrogen; or in the substituents  $-X^1-CO-R^{01}$  wherein R<sup>01</sup> represents -OH, especially in the  $-X^1-CO-R^{01}$  groups a), d), e) and f) above) such carboxylic acid group may be present in form of a prodrug group. Such prodrugs are encompassed in the scope of the present invention. In certain instances, compounds comprising such carboxylic acid prodrug groups may as such exhibit biological activity on the EP2 and/or EP4 receptor, whereas in other instances, such compounds comprising such carboxylic acid prodrug groups require (e.g. enzymatic)

cleavage of the prodrug to exhibit biological activity on the EP2 and/or EP4 receptor. Prodrugs of the carboxylic acid functional group are well known in the art (see for example J. Rautio (Ed.) Prodrugs and Targeted Delivery: Towards Better ADME Properties, Volume 47, Wiley 2010, ISBN: 978-3-527-32603-7; H. Maag in Stella, V., Borchardt, R., Hageman, M., Oliyai, R., Maag, H., Tilley, J. (Eds.) Prodrugs: Challenges and Rewards, Springer 2007, ISBN 978-0-387-49785-3).

Particular examples of prodrugs, for example suitable for  $-X^1\text{-COOH}$  groups are:

- ester groups  $-X^1\text{-CO-O-P}^1$  wherein  $P^1$  is for example  $(C_{1-4})$ alkyl;  $(C_{3-6})$ cycloalkyl wherein the  $(C_{3-6})$ cycloalkyl optionally contains a ring oxygen atom;  $(C_{3-6})$ cycloalkyl- $(C_{1-3})$ alkyl wherein the  $(C_{3-6})$ cycloalkyl optionally contains a ring oxygen atom;  $(C_{1-3})$ fluoroalkyl; hydroxy- $(C_{2-4})$ alkyl; or  $(C_{1-4})$ alkoxy- $(C_{2-4})$ alkyl (especially  $P^1$  is  $(C_{1-4})$ alkyl, in particular methyl or ethyl);
- groups  $-X^1\text{-CO-NH-SO}_2\text{-R}^{S3}$  wherein  $R^{S3}$  represents  $(C_{1-4})$ alkyl,  $(C_{3-6})$ cycloalkyl wherein the  $(C_{3-6})$ cycloalkyl optionally contains a ring oxygen atom;  $(C_{3-6})$ cycloalkyl- $(C_{1-3})$ alkyl wherein the  $(C_{3-6})$ cycloalkyl optionally contains a ring oxygen atom;  $(C_{1-3})$ fluoroalkyl,  $-\text{NH}_2$ ; (especially  $R^{S3}$  is  $(C_{1-4})$ alkyl,  $(C_{3-6})$ cycloalkyl; in particular methyl);
- groups  $-X^1\text{-CO-R}^{O1}$  wherein  $R^{O1}$  represents  $-\text{O-CH}_2\text{-CO-R}^{O4}$ , wherein  $R^{O4}$  represents hydroxy, or  $(C_{1-4})$ alkoxy, or  $-\text{N}[(C_{1-4})\text{alkyl}]_2$  (especially  $-\text{CO-O-CH}_2\text{-COOH}$ ,  $-\text{CO-O-CH}_2\text{-CO-N}(\text{CH}_3)_2$ );
- groups  $-X^1\text{-CO-R}^{O1}$  wherein  $R^{O1}$  represents  $-\text{O-CH}_2\text{-O-CO-R}^{O5}$ , wherein  $R^{O5}$  represents  $(C_{1-4})$ alkyl or  $(C_{1-4})$ alkoxy (especially  $-\text{CO-O-CH}_2\text{-O-CO-O-ethyl}$ ,  $-\text{CO-O-CH}_2\text{-O-CO-propyl}$ );
- groups  $-X^1\text{-CO-R}^{O1}$  wherein  $R^{O1}$  represents  $-\text{O-CH}_2\text{-CH}_2\text{-N}[(C_{1-4})\text{alkyl}]_2$  (especially  $-\text{CO-O-CH}_2\text{-CH}_2\text{-N}(\text{CH}_3)_2$ ); and
- groups  $-X^1\text{-CO-R}^{O1}$  wherein  $R^{O1}$  represents 5-methyl-2-oxo-[1,3]dioxol-4-yl)-methoxy-.

Examples of "hydroxy- $(C_{1-4})$ alkyl" groups as used for substituents of the group  $\text{Ar}^1$  are hydroxymethyl and 1-hydroxy-ethyl.

An example of "dihydroxy- $(C_{2-4})$ alkyl" groups as used for substituents of the group  $\text{Ar}^1$  is 1,2-dihydroxyethyl.

An example of "hydroxy- $(C_{2-4})$ alkoxy" groups as used for substituents of the group  $\text{Ar}^1$  is 2-hydroxy-ethoxy.

An example of " $(C_{1-4})$ alkoxy- $(C_{2-4})$ alkoxy" groups as used for substituents of the group  $\text{Ar}^1$  is 2-methoxy-ethoxy.

Examples of a group " $-\text{SO}_2\text{-R}^{S1}$ " as used for substituents of the group  $\text{Ar}^1$  are  $-\text{SO}_2\text{-CH}_3$ ,  $-\text{SO}_2\text{-NH}_2$ ,  $-\text{SO}_2\text{-NH-CH}_3$ .

Examples of a group " $\text{S-R}^{S2}$ " as used for substituents of the group  $\text{Ar}^1$  are methylsulfanyl, ethylsulfanyl, n-propylsulfanyl, isopropylsulfanyl, isobutylsulfanyl, cyclobutylsulfanyl, and (oxetan-3-yl)-sulfanyl.

An example of a " $(C_{1-4})$ alkoxy- $(C_{2-4})$ alkyl" group is 2-methoxyethyl.

An example of a "hydroxy- $(C_{2-4})$ alkoxy" group is 2-hydroxy-ethoxy.

An example of a "hydroxy- $(C_{2-4})$ alkyl" group is 2-hydroxy-ethyl.

An example of a "-CO-(C<sub>1-4</sub>)alkoxy" group as used for substituents of the group **Ar**<sup>1</sup> is ethoxycarbonyl. Such groups may also be useful as produgs of the respective -COOH substituent.

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  
 5 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" 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  
 10 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. Besides, the term "room temperature" as used herein refers to a temperature of about 25°C.

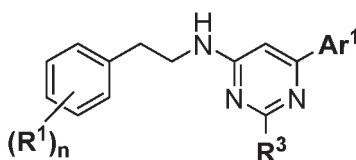
Further embodiments of the invention are presented hereinafter:

2) Another embodiment relates to compounds as defined in to embodiment 1), for use according to embodiment

15 1), wherein **R**<sup>4a</sup> and **R**<sup>4b</sup> both represent hydrogen.

3) Another embodiment relates to compounds as defined in to embodiments 1) or 2), for use according to embodiment 1), wherein **R**<sup>5a</sup> and **R**<sup>5b</sup> both represent hydrogen. Particular compounds of formula (I) are compounds wherein **R**<sup>4a</sup> and **R**<sup>4b</sup> both represent hydrogen; and **R**<sup>5a</sup> and **R**<sup>5b</sup> both represent hydrogen.

4) Another embodiment relates to compounds of formual (I) as defined in embodiment 1), for use according to  
 20 embodiment 1), which compounds are also compounds of the formula (II)



Formula (II)

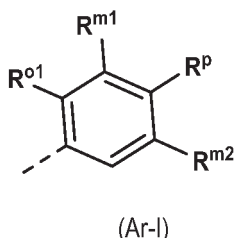
wherein

**(R**<sup>1</sup>**)<sub>n</sub>** represents one, two or three optional substituents on the phenyl ring (i.e. n represents the integer 0, 1, 2, or  
 25 3), wherein said substituents are independently selected from (C<sub>1-3</sub>)alkyl (especially methyl), (C<sub>1-3</sub>)alkoxy (especially methoxy), -S-(C<sub>1-3</sub>)alkyl (especially methylsulfanyl), halogen (especially fluoro, chloro, or bromo), (C<sub>1-3</sub>)fluoroalkyl (especially trifluoromethyl), (C<sub>1-3</sub>)fluoroalkoxy (especially trifluoromethoxy), cyano, hydroxy, nitro, -CO-O-(C<sub>1-3</sub>)alkyl (especially methoxycarbonyl), -NR<sup>N7</sup>R<sup>N8</sup> wherein **R**<sup>N7</sup> and **R**<sup>N8</sup> independently represent hydrogen or (C<sub>1-4</sub>)alkyl, or **R**<sup>N7</sup> and **R**<sup>N8</sup> together with the nitrogen to which they are attached form a 4- to 6-membered carbocyclic ring  
 30 (especially such group -NR<sup>N7</sup>R<sup>N8</sup> is methylamino, dimethylamino, pyrrolidin-1-yl);

**R**<sup>3</sup> represents hydrogen, or methyl (especially hydrogen);

Ar<sup>1</sup> represents

- a phenyl group of the structure (Ar-I):



5 wherein

- R<sup>p</sup> represents

➤ (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom, wherein said (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy (especially 3-hydroxy-oxetan-3-yl);

➤ hydroxy;

10 ➤ -X<sup>1</sup>-CO-R<sup>o1</sup>, wherein

➤ X<sup>1</sup> represents a direct bond, (C<sub>1-3</sub>)alkylene (especially -CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-), -O-(C<sub>1-3</sub>)alkylene-\* (especially -O-CH<sub>2</sub>-, -O-CH(CH<sub>3</sub>)-, -O-C(CH<sub>3</sub>)<sub>2</sub>-, -O-CH<sub>2</sub>-CH<sub>2</sub>-\*), -NH-(C<sub>1-3</sub>)alkylene-\* (especially -NH-CH<sub>2</sub>-, -NH-CH(CH<sub>3</sub>)-, -CH=CH-, -NH-CO-\*, or (C<sub>3-5</sub>)cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-R<sup>o1</sup> group; and

➤ R<sup>o1</sup> represents

- -OH;

- -O-(C<sub>1-4</sub>)alkyl (especially ethoxy, methoxy);

20 ▪ -NH-SO<sub>2</sub>-R<sup>s3</sup> wherein R<sup>s3</sup> represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;

- -O-CH<sub>2</sub>-CO-R<sup>o4</sup>, wherein R<sup>o4</sup> represents hydroxy, or (C<sub>1-4</sub>)alkoxy, or -N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>;

- -O-CH<sub>2</sub>-O-CO-R<sup>o5</sup>, wherein R<sup>o5</sup> represents (C<sub>1-4</sub>)alkyl or (C<sub>1-4</sub>)alkoxy;

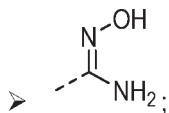
25 ▪ -O-CH<sub>2</sub>-CH<sub>2</sub>-N[(C<sub>1-4</sub>)alkyl]<sub>2</sub> (especially -O-CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>); or

- (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methoxy;

[wherein in particular such group -X<sup>1</sup>-CO-R<sup>o1</sup> represents -COOH, -CO-O-CH<sub>3</sub>, -CO-O-C<sub>2</sub>H<sub>5</sub>, -O-CH<sub>2</sub>-COOH, -O-CH(CH<sub>3</sub>)-COOH, -O-C(CH<sub>3</sub>)<sub>2</sub>-COOH, -O-CH<sub>2</sub>-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -NH-CH(CH<sub>3</sub>)-COOH, -CO-NH-SO<sub>2</sub>-CH<sub>3</sub>, -CO-NH-SO<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>, -CO-NH-SO<sub>2</sub>-cyclopropyl, -CO-NH-SO<sub>2</sub>-C<sub>2</sub>H<sub>5</sub>, -CO-NH-SO<sub>2</sub>-NH<sub>2</sub>, -CO-O-CH<sub>2</sub>-COOH, -CO-O-CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>, -CO-O-CH<sub>2</sub>-CO-N(CH<sub>3</sub>)<sub>2</sub>, -CO-O-CH<sub>2</sub>-O-CO-O-C<sub>2</sub>H<sub>5</sub>, -CO-O-CH<sub>2</sub>-O-CO-propyl, (5-

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methyl-2-oxo-[1,3]dioxol-4-yl)-methyl-O-CO-, -CH<sub>2</sub>-COOH, -CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -CH<sub>2</sub>-CO-O-C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-COOH, -CH=CH-COOH, -NH-CO-COOH, 1-carboxy-cyclopropan-1-yl];



- 2-hydroxy-3,4-dioxo-cyclobut-1-enyl;
- 5 ➤ hydroxy-(C<sub>1-4</sub>)alkyl (especially hydroxymethyl, 1-hydroxy-ethyl);
- hydroxy-(C<sub>2-4</sub>)alkoxy (especially 2-hydroxy-ethoxy);
- -(CH<sub>2</sub>)<sub>r</sub>-CO-NR<sup>N3</sup>R<sup>N4</sup> wherein **r** represents the integer 0 or 1; and wherein **R<sup>N3</sup>** and **R<sup>N4</sup>** independently represent hydrogen, (C<sub>1-4</sub>)alkyl, hydroxy-(C<sub>2-4</sub>)alkyl, (C<sub>1-3</sub>)alkoxy-(C<sub>2-4</sub>)alkyl, or hydroxy (wherein preferably at least one of **R<sup>N3</sup>** and **R<sup>N4</sup>** represents hydrogen; and wherein particular examples of such group -CO-NR<sup>N3</sup>R<sup>N4</sup> are -CO-NH<sub>2</sub>, -CO-NH(CH<sub>3</sub>), -CO-NH(C<sub>2</sub>H<sub>5</sub>), -CH<sub>2</sub>-CO-NH<sub>2</sub>, -CO-NH-C<sub>2</sub>H<sub>4</sub>-OH, -CO-NH-C<sub>2</sub>H<sub>4</sub>-OCH<sub>3</sub>, or -CO-N(CH<sub>3</sub>)<sub>2</sub>, -CO-NH-isopropyl, or -CO-NH-OH);
- 10 ➤ -NR<sup>N1</sup>R<sup>N2</sup>, wherein **R<sup>N1</sup>** independently represents hydrogen or (C<sub>1-4</sub>)alkyl, and **R<sup>N2</sup>** independently represents -CO-H, -CO-(C<sub>1-3</sub>)alkyl, or -CO-(C<sub>1-3</sub>)alkylene-OH; (especially such group -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>N1</sup>R<sup>N2</sup> represents -NH-CO-H, -N(C<sub>2</sub>H<sub>5</sub>)-CO-H, -NH-CO-C<sub>2</sub>H<sub>5</sub>, or -NH-CO-CH<sub>2</sub>-CH<sub>2</sub>-OH);
- 15 ➤ -NH-CO-NR<sup>N5</sup>R<sup>N6</sup> wherein **R<sup>N5</sup>** and **R<sup>N6</sup>** independently represent hydrogen or (C<sub>1-4</sub>)alkyl (wherein preferably at least one of **R<sup>N5</sup>** and **R<sup>N6</sup>** represents hydrogen; and wherein particular examples of such group -NH-CO-NR<sup>N5</sup>R<sup>N6</sup> are -NH-CO-NH<sub>2</sub>, -NH-CO-NH-C<sub>2</sub>H<sub>5</sub>);
- -SO<sub>2</sub>-R<sup>S1</sup> wherein **R<sup>S1</sup>** represents (C<sub>1-4</sub>)alkyl (especially methyl), or -NR<sup>N7</sup>R<sup>N8</sup> wherein **R<sup>N7</sup>** and **R<sup>N8</sup>** independently represent hydrogen or (C<sub>1-3</sub>)alkyl (wherein preferably at least one of **R<sup>N7</sup>** and **R<sup>N8</sup>** represents hydrogen; and wherein particular examples of such group -SO<sub>2</sub>-R<sup>S1</sup> are -SO<sub>2</sub>-CH<sub>3</sub>, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-NH-CH<sub>3</sub>);
- 20 ➤ -(CH<sub>2</sub>)<sub>q</sub>-HET<sup>1</sup>, wherein **q** represents the integer 0, 1 or 2 (especially **q** is 0, i.e. **HET<sup>1</sup>** is linked to **Ar<sup>1</sup>** by a direct bond); and wherein **HET<sup>1</sup>** represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-hydroxy-[1,2,4]oxadiazol-3-yl), 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl (encompassing its tautomeric form 3-hydroxy-[1,2,4]oxadiazol-5-yl), or 5-thioxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-mercapto-[1,2,4]oxadiazol-3-yl);
- 25 ➤ -(CH<sub>2</sub>)<sub>p</sub>-HET, wherein **p** represents the integer 0 or 1 (especially **p** is 0, i.e. **HET** is linked to **Ar<sup>1</sup>** by a direct bond); and wherein **HET** represents a 5-membered heteroaryl (especially oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl, or tetrazolyl), wherein said 5-membered heteroaryl is unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected from (C<sub>1-4</sub>)alkyl (especially methyl), (C<sub>1-4</sub>)alkoxy (especially methoxy), -COOH, hydroxy, hydroxy-(C<sub>1-3</sub>)alkyl (especially hydroxymethyl), (C<sub>3-5</sub>)cycloalkyl optionally containing one ring oxygen atom (especially cyclopropyl, oxetan-3-yl), or -NR<sup>N9</sup>R<sup>N10</sup> wherein **R<sup>N9</sup>** and **R<sup>N10</sup>** independently
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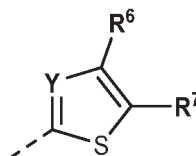
represent hydrogen, (C<sub>1-3</sub>)alkyl (especially methyl), or hydroxy-(C<sub>2-4</sub>)alkyl (especially 2-hydroxy-ethyl); (especially such group -(CH<sub>2</sub>)<sub>p</sub>-HET is 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl, 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, 5-methoxy-[1,2,4]oxadiazol-3-yl, 5-amino-[1,2,4]oxadiazol-3-yl, 5-[(2-hydroxy-ethyl)]-amino-[1,2,4]oxadiazol-3-yl, 5-hydroxymethyl-[1,2,4]oxadiazol-3-yl, 5-(oxetan-3-yl)-[1,2,4]oxadiazol-3-yl, 1H-imidazol-4-yl, 5-methyl-1H-imidazol-4-yl, 2,5-dimethyl-1H-imidazol-4-yl);

▪ **R<sup>m1</sup>** represents

- hydrogen;
- (C<sub>1-6</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl);
- (C<sub>1-4</sub>)alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy);
- (C<sub>1-3</sub>)fluoroalkyl (especially trifluoromethyl);
- (C<sub>1-3</sub>)fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
- halogen (especially fluoro or chloro);
- (C<sub>3-6</sub>)cycloalkyl (especially cyclopropyl);
- (C<sub>3-6</sub>)cycloalkyl-oxy (especially cyclopropyl-oxy, cyclobutyl-oxy, cyclopentyl-oxy);
- hydroxy;
- hydroxy-(C<sub>2-4</sub>)alkoxy (especially 2-hydroxy-ethoxy);
- -X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup>, wherein **X<sup>2</sup>** represents a direkt bond; or **X<sup>2</sup>** represents -O-CH<sub>2</sub>-CH<sub>2</sub>\*, wherein the asterisk indicates the bond that is linked to the -NR<sup>N1</sup>R<sup>N2</sup> group; and wherein **R<sup>N1</sup>** and **R<sup>N2</sup>** independently represent hydrogen, (C<sub>1-4</sub>)alkyl (especially methyl), or (C<sub>3-6</sub>)cycloalkyl (especially cyclopropyl); (especially such group -X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup> represents amino, methylamino, ethylamino, propylamino; or 2-(dimethylamino)-ethoxy);
- -S-R<sup>S2</sup> wherein **R<sup>S2</sup>** represents (C<sub>1-4</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);

wherein in a sub-embodiment, **R<sup>m1</sup>** especially is different from hydrogen;

- **R<sup>m2</sup>** represents hydrogen, methyl, fluoro, or chloro; and
- **R<sup>o1</sup>** represents hydrogen; or, in case **R<sup>m2</sup>** represents hydrogen, **R<sup>o1</sup>** represents hydrogen or fluoro;
- or **Ar<sup>1</sup>** represents a 5-membered heteroaryl group of the structure (Ar-II):

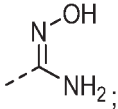


(Ar-II)

wherein

- Y represents  $\text{CR}^8$  wherein  $\text{R}^8$  represents especially hydrogen, or halogen (notably fluoro, chloro); or Y represents N;
- $\text{R}^7$  represents
  - $(\text{C}_{4-6})$ cycloalkyl containing a ring oxygen atom, wherein said  $(\text{C}_{4-6})$ cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy (especially 3-hydroxy-oxetan-3-yl);
  - $-\text{X}^1-\text{CO}-\text{R}^{01}$ , wherein
    - $\text{X}^1$  represents a direct bond,  $(\text{C}_{1-3})$ alkylene (especially  $-\text{CH}_2-$ ,  $-\text{CH}(\text{CH}_3)-$ ,  $-\text{C}(\text{CH}_3)_2-$ ,  $-\text{CH}_2-\text{CH}_2-$ ),  $-\text{O}-(\text{C}_{1-3})$ alkylene-\* (especially  $-\text{O}-\text{CH}_2-$ \*,  $-\text{O}-\text{CH}(\text{CH}_3)-$ \*,  $-\text{O}-\text{C}(\text{CH}_3)_2-$ \*,  $-\text{O}-\text{CH}_2-\text{CH}_2-$ \*),  $-\text{NH}-(\text{C}_{1-3})$ alkylene-\* (especially  $-\text{NH}-\text{CH}_2-$ \*,  $-\text{NH}-\text{CH}(\text{CH}_3)-$ \*),  $-\text{CH}=\text{CH}-$ ,  $-\text{NH}-\text{CO}-$ \*, or  $(\text{C}_{3-6})$ cycloalkylene; wherein the asterisks indicate the bond that is linked to the  $-\text{CO}-\text{R}^{01}$  group; and
    - $\text{R}^{01}$  represents
      - $-\text{OH}$ ;
      - $-\text{O}-(\text{C}_{1-4})$ alkyl (especially ethoxy, methoxy);
      - $-\text{NH}-\text{SO}_2-\text{R}^{\text{S}3}$  wherein  $\text{R}^{\text{S}3}$  represents  $(\text{C}_{1-4})$ alkyl,  $(\text{C}_{3-6})$ cycloalkyl wherein the  $(\text{C}_{3-6})$ cycloalkyl optionally contains a ring oxygen atom,  $(\text{C}_{3-6})$ cycloalkyl- $(\text{C}_{1-3})$ alkylene wherein the  $(\text{C}_{3-6})$ cycloalkyl optionally contains a ring oxygen atom,  $(\text{C}_{1-3})$ fluoroalkyl, or  $-\text{NH}_2$ ;
      - $-\text{O}-\text{CH}_2-\text{CO}-\text{R}^{04}$ , wherein  $\text{R}^{04}$  represents hydroxy, or  $(\text{C}_{1-4})$ alkoxy, or  $-\text{N}[(\text{C}_{1-4})\text{alkyl}]_2$ ;
      - $-\text{O}-\text{CH}_2-\text{O}-\text{CO}-\text{R}^{05}$ , wherein  $\text{R}^{05}$  represents  $(\text{C}_{1-4})$ alkyl or  $(\text{C}_{1-4})$ alkoxy;
      - $-\text{O}-\text{CH}_2-\text{CH}_2-\text{N}[(\text{C}_{1-4})\text{alkyl}]_2$  (especially  $-\text{O}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2$ ); or
      - (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methoxy-;

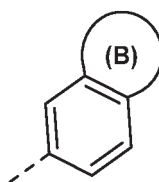
[wherein in particular such group  $-\text{X}^1-\text{CO}-\text{R}^{01}$  represents  $-\text{COOH}$ ,  $-\text{CO}-\text{O}-\text{CH}_3$ ,  $-\text{CO}-\text{O}-\text{C}_2\text{H}_5$ ,  $-\text{O}-\text{CH}_2-\text{COOH}$ ,  $-\text{O}-\text{CH}(\text{CH}_3)-\text{COOH}$ ,  $-\text{O}-\text{C}(\text{CH}_3)_2-\text{COOH}$ ,  $-\text{O}-\text{CH}_2-\text{CH}_2-\text{COOH}$ ,  $-\text{NH}-\text{CH}_2-\text{COOH}$ ,  $-\text{NH}-\text{CH}_2-\text{CO}-\text{O}-\text{CH}_3$ ,  $-\text{NH}-\text{CH}(\text{CH}_3)-\text{COOH}$ ,  $-\text{CO}-\text{NH}-\text{SO}_2-\text{CH}_3$ ,  $-\text{CO}-\text{NH}-\text{SO}_2-\text{C}(\text{CH}_3)_2$ ,  $-\text{CO}-\text{NH}-\text{SO}_2$ -cyclopropyl,  $-\text{CO}-\text{NH}-\text{SO}_2-\text{C}_2\text{H}_5$ ,  $-\text{CO}-\text{NH}-\text{SO}_2-\text{NH}_2$ ,  $-\text{CO}-\text{O}-\text{CH}_2-\text{COOH}$ ,  $-\text{CO}-\text{O}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2$ ,  $-\text{CO}-\text{O}-\text{CH}_2-\text{CO}-\text{N}(\text{CH}_3)_2$ ,  $-\text{CO}-\text{O}-\text{CH}_2-\text{O}-\text{CO}-\text{O}-\text{C}_2\text{H}_5$ ,  $-\text{CO}-\text{O}-\text{CH}_2-\text{O}-\text{CO}$ -propyl, (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyl-O-CO-,  $-\text{CH}_2-\text{COOH}$ ,  $-\text{CH}_2-\text{CO}-\text{O}-\text{CH}_3$ ,  $-\text{CH}_2-\text{CO}-\text{O}-\text{C}_2\text{H}_5$ ,  $-\text{CH}_2-\text{CH}_2-\text{COOH}$ ,  $-\text{CH}=\text{CH}-\text{COOH}$ ,  $-\text{NH}-\text{CO}-\text{COOH}$ , 1-carboxy-cyclopropan-1-yl];

  - ;
    - 2-hydroxy-3,4-dioxo-cyclobut-1-enyl;
    - hydroxy- $(\text{C}_{1-4})$ alkyl (especially hydroxymethyl, 1-hydroxy-ethyl);
    - hydroxy- $(\text{C}_{2-4})$ alkoxy (especially 2-hydroxy-ethoxy);
    - $-(\text{CH}_2)_r-\text{CO}-\text{NR}^{\text{N}3}\text{R}^{\text{N}4}$  wherein r represents the integer 0 or 1; and wherein  $\text{R}^{\text{N}3}$  and  $\text{R}^{\text{N}4}$  independently represent hydrogen,  $(\text{C}_{1-4})$ alkyl, hydroxy- $(\text{C}_{2-4})$ alkyl,  $(\text{C}_{1-3})$ alkoxy- $(\text{C}_{2-4})$ alkyl, or hydroxy (wherein

preferably at least one of  $R^{N3}$  and  $R^{N4}$  represents hydrogen; and wherein particular examples of such group  $-CO-NR^{N3}R^{N4}$  are  $-CO-NH_2$ ,  $-CO-NH(CH_3)$ ,  $-CO-NH(C_2H_5)$ ,  $-CH_2-CO-NH_2$ ,  $-CO-NH-C_2H_4-OH$ ,  $-CO-NH-C_2H_4-OCH_3$ , or  $-CO-N(CH_3)_2$ ,  $-CO-NH$ -isopropyl, or  $-CO-NH-OH$ ;

- $-NR^{N1}R^{N2}$ , wherein  $R^{N1}$  independently represents hydrogen or  $(C_{1-4})$ alkyl, and  $R^{N2}$  independently represents  $-CO-H$ ,  $-CO-(C_{1-3})$ alkyl, or  $-CO-(C_{1-3})$ alkylene- $-OH$ ; (especially such group  $-(CH_2)_m-NR^{N1}R^{N2}$  represents  $-NH-CO-H$ ,  $-N(C_2H_5)-CO-H$ ,  $-NH-CO-C_2H_5$ , or  $-NH-CO-CH_2-CH_2-OH$ );
- $-NH-CO-NR^{N5}R^{N6}$  wherein  $R^{N5}$  and  $R^{N6}$  independently represent hydrogen or  $(C_{1-4})$ alkyl (wherein preferably at least one of  $R^{N5}$  and  $R^{N6}$  represents hydrogen; and wherein particular examples of such group  $-NH-CO-NR^{N5}R^{N6}$  are  $-NH-CO-NH_2$ ,  $-NH-CO-NH-C_2H_5$ );
- $-SO_2-R^{S1}$  wherein  $R^{S1}$  represents  $(C_{1-4})$ alkyl (especially methyl), or  $-NR^{N7}R^{N8}$  wherein  $R^{N7}$  and  $R^{N8}$  independently represent hydrogen or  $(C_{1-3})$ alkyl (wherein preferably at least one of  $R^{N7}$  and  $R^{N8}$  represents hydrogen; and wherein particular examples of such group  $-SO_2-R^{S1}$  are  $-SO_2-CH_3$ ,  $-SO_2-NH_2$ ,  $-SO_2-NH-CH_3$ );
- $-(CH_2)_q-HET^1$ , wherein  $q$  represents the integer 0, 1 or 2 (especially  $q$  is 0, i.e.  $HET^1$  is linked to  $Ar^1$  by a direct bond); and wherein  $HET^1$  represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-hydroxy-[1,2,4]oxadiazol-3-yl), 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl (encompassing its tautomeric form 3-hydroxy-[1,2,4]oxadiazol-5-yl), or 5-thioxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-mercapto-[1,2,4]oxadiazol-3-yl);
- $-(CH_2)_p-HET$ , wherein  $p$  represents the integer 0 or 1 (especially  $p$  is 0, i.e.  $HET$  is linked to  $Ar^1$  by a direct bond); and wherein  $HET$  represents a 5-membered heteroaryl (especially oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl, or tetrazolyl), wherein said 5-membered heteroaryl is unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected from  $(C_{1-4})$ alkyl (especially methyl),  $(C_{1-4})$ alkoxy (especially methoxy),  $-COOH$ , hydroxy, hydroxy- $(C_{1-3})$ alkyl (especially hydroxymethyl),  $(C_{3-5})$ cycloalkyl optionally containing one ring oxygen atom (especially cyclopropyl, oxetan-3-yl), or  $-NR^{N9}R^{N10}$  wherein  $R^{N9}$  and  $R^{N10}$  independently represent hydrogen,  $(C_{1-3})$ alkyl (especially methyl), or hydroxy- $(C_{2-4})$ alkyl (especially 2-hydroxy-ethyl); (especially such group  $-(CH_2)_p-HET$  is 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl, 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, 5-methoxy-[1,2,4]oxadiazol-3-yl, 5-amino-[1,2,4]oxadiazol-3-yl, 5-[(2-hydroxy-ethyl)]-amino-[1,2,4]oxadiazol-3-yl, 5-hydroxymethyl-[1,2,4]oxadiazol-3-yl, 5-(oxetan-3-yl)-[1,2,4]oxadiazol-3-yl, 1H-imidazol-4-yl, 5-methyl-1H-imidazol-4-yl, 2,5-dimethyl-1H-imidazol-4-yl);
- $R^6$  represents
  - $(C_{1-6})$ alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl);
  - $(C_{1-4})$ alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy);
  - $(C_{1-3})$ fluoroalkyl (especially trifluoromethyl);

- (C<sub>1-3</sub>)fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
- halogen (especially fluoro or chloro);
- hydroxy;
- (C<sub>3-6</sub>)cycloalkyl (especially cyclopropyl);
- 5 ➤ (C<sub>3-6</sub>)cycloalkyl-oxy (especially cyclopropyl-oxy, cyclobutyl-oxy, cyclopentyl-oxy);
- hydroxy-(C<sub>2-4</sub>)alkoxy (especially 2-hydroxy-ethoxy);
- -X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup>, wherein X<sup>2</sup> represents a direkt bond; or X<sup>2</sup> represents -O-CH<sub>2</sub>-CH<sub>2</sub>-, wherein the asterisk indicates the bond that is linked to the -NR<sup>N1</sup>R<sup>N2</sup> group; and wherein R<sup>N1</sup> and R<sup>N2</sup> independently represent hydrogen, (C<sub>1-4</sub>)alkyl, or (C<sub>3-6</sub>)cycloalkyl; (especially such group -X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup> represents amino, methylamino, ethylamino, propylamino; or 2-(dimethylamino)-ethoxy);
- 10 ➤ -S-R<sup>S2</sup> wherein R<sup>S2</sup> represents (C<sub>1-4</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);
- or Ar<sup>1</sup> represents 8- to 10-membered bicyclic heteroaryl (notably 9- or 10-membered bicyclic heteroaryl; especially indazolyl, benzoimidazolyl, indolyl, benzofuranyl, benzooxazolyl, quinoxaliny, isoquinoliny, or quinoliny); wherein said 8- to 10-membered bicyclic heteroaryl independently is mono-substituted with -(C<sub>0-3</sub>)alkylene-COOR<sup>O2</sup> wherein R<sup>O2</sup> represents hydrogen or (C<sub>1-4</sub>)alkyl (especially methyl) (wherein especially such group -(C<sub>0-3</sub>)alkylene-COOR<sup>O2</sup> is -COOH); (especially such 8- to 10-membered bicyclic heteroaryl is 3-carboxy-1H-indol-6-yl, 4-carboxy-1H-indol-2-yl, 5-carboxy-1H-indol-2-yl, 6-carboxy-1H-indol-2-yl, 7-carboxy-1H-indol-2-yl, 5-(methoxycarbonyl)-1H-indol-2-yl, 6-(methoxycarbonyl)-1H-indol-2-yl), 6-carboxy-benzofuran-2-yl, 3-carboxy-benzofuran-6-yl, 2-carboxy-benzofuran-5-yl, or 2-carboxy-benzofuran-6-yl);
- 20 • or Ar<sup>1</sup> represents a group of the structure (Ar-III):

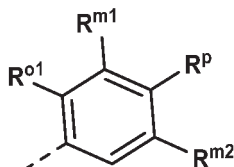


(Ar-III)

- which is selected from 2-oxo-2,3-dihydro-benzooxazol-6-yl, 3-methyl-2-oxo-2,3-dihydro-benzooxazol-5-yl, 1-methyl-3-oxo-2,3-dihydro-1H-indazol-6-yl, 2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-7-yl, and 1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl.

5) Another embodiment relates to compounds as defined in embodiment 4), for use according to embodiment 1), wherein **Ar**<sup>1</sup> represents

- a phenyl group of the structure (Ar-I):



(Ar-I)

wherein

- **R**<sup>p</sup> represents

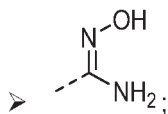
- **-X**<sup>1</sup>-CO-**R**<sup>o1</sup>, wherein

- **X**<sup>1</sup> represents a direct bond, (C<sub>1-3</sub>)alkylene (especially -CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-), -O-(C<sub>1-3</sub>)alkylene-\* (especially -O-CH<sub>2</sub>-, -O-CH(CH<sub>3</sub>)-\*, -O-C(CH<sub>3</sub>)<sub>2</sub>-, -O-CH<sub>2</sub>-CH<sub>2</sub>-\*), -NH-(C<sub>1-3</sub>)alkylene-\* (especially -NH-CH<sub>2</sub>-, -NH-CH(CH<sub>3</sub>)-\*), -CH=CH-, -NH-CO-\*, or (C<sub>3-5</sub>)cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-**R**<sup>o1</sup> group; and

- **R**<sup>o1</sup> represents

- -OH;
- -O-(C<sub>1-4</sub>)alkyl (especially ethoxy, methoxy);
- -NH-SO<sub>2</sub>-**R**<sup>s3</sup> wherein **R**<sup>s3</sup> represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;
- -O-CH<sub>2</sub>-CO-**R**<sup>o4</sup>, wherein **R**<sup>o4</sup> represents hydroxy, or (C<sub>1-4</sub>)alkoxy, or -N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>;
- -O-CH<sub>2</sub>-O-CO-**R**<sup>o5</sup>, wherein **R**<sup>o5</sup> represents (C<sub>1-4</sub>)alkyl or (C<sub>1-4</sub>)alkoxy;
- -O-CH<sub>2</sub>-CH<sub>2</sub>-N[(C<sub>1-4</sub>)alkyl]<sub>2</sub> (especially -O-CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>); or
- (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methoxy;

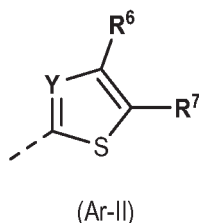
[wherein in particular such group **-X**<sup>1</sup>-CO-**R**<sup>o1</sup> represents -COOH, -CO-O-CH<sub>3</sub>, -CO-O-C<sub>2</sub>H<sub>5</sub>, -O-CH<sub>2</sub>-COOH, -O-CH(CH<sub>3</sub>)-COOH, -O-C(CH<sub>3</sub>)<sub>2</sub>-COOH, -O-CH<sub>2</sub>-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -NH-CH(CH<sub>3</sub>)-COOH, -CO-NH-SO<sub>2</sub>-CH<sub>3</sub>, -CO-NH-SO<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>, -CO-NH-SO<sub>2</sub>-cyclopropyl, -CO-NH-SO<sub>2</sub>-C<sub>2</sub>H<sub>5</sub>, -CO-NH-SO<sub>2</sub>-NH<sub>2</sub>, -CO-O-CH<sub>2</sub>-COOH, -CO-O-CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>, -CO-O-CH<sub>2</sub>-CO-N(CH<sub>3</sub>)<sub>2</sub>, -CO-O-CH<sub>2</sub>-O-CO-O-C<sub>2</sub>H<sub>5</sub>, -CO-O-CH<sub>2</sub>-O-CO-propyl, (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyl-O-CO-, -CH<sub>2</sub>-COOH, -CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -CH<sub>2</sub>-CO-O-C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-COOH, -CH=CH-COOH, -NH-CO-COOH, 1-carboxy-cyclopropan-1-yl];



- 5
- $-(CH_2)_q$ -**HET**<sup>1</sup>, wherein **q** represents the integer 0, 1 or 2 (especially **q** is 0, i.e. **HET**<sup>1</sup> is linked to **Ar**<sup>1</sup> by a direct bond); and wherein **HET**<sup>1</sup> represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-hydroxy-[1,2,4]oxadiazol-3-yl), or 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl (encompassing its tautomeric form 3-hydroxy-[1,2,4]oxadiazol-5-yl);
  - $-(CH_2)_p$ -**HET**, wherein **p** represents the integer 0 or 1 (especially **p** is 0, i.e. **HET** is linked to **Ar**<sup>1</sup> by a direct bond); and wherein **HET** represents a group selected from 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl, 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, and 5-amino-[1,2,4]oxadiazol-3-yl;
- 10
- **R**<sup>m1</sup> represents
    - hydrogen;
    - (C<sub>1-6</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl);
    - (C<sub>1-4</sub>)alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy);
    - (C<sub>1-3</sub>)fluoroalkyl (especially trifluoromethyl);
    - 15 ➤ (C<sub>1-3</sub>)fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
    - halogen (especially fluoro or chloro);
    - (C<sub>3-6</sub>)cycloalkyl (especially cyclopropyl);
    - (C<sub>3-6</sub>)cycloalkyl-oxy (especially cyclopropyl-oxy, cyclobutyl-oxy, cyclopentyl-oxy);
    - hydroxy;
    - 20 ➤ hydroxy-(C<sub>2-4</sub>)alkoxy (especially 2-hydroxy-ethoxy);
    - **-X**<sup>2</sup>-**NR**<sup>N1</sup>**R**<sup>N2</sup>, wherein **X**<sup>2</sup> represents a direct bond; or **X**<sup>2</sup> represents -O-CH<sub>2</sub>-CH<sub>2</sub>-, wherein the asterisk indicates the bond that is linked to the -**NR**<sup>N1</sup>**R**<sup>N2</sup> group; and wherein **R**<sup>N1</sup> and **R**<sup>N2</sup> independently represent hydrogen, (C<sub>1-4</sub>)alkyl (especially methyl), or (C<sub>3-6</sub>)cycloalkyl (especially cyclopropyl); (especially such group **-X**<sup>2</sup>-**NR**<sup>N1</sup>**R**<sup>N2</sup> represents amino, methylamino, ethylamino, propylamino; or 2-(dimethylamino)-ethoxy);
    - 25 ➤ **-S-R**<sup>S2</sup> wherein **R**<sup>S2</sup> represents (C<sub>1-4</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);
- wherein in a sub-embodiment, **R**<sup>m1</sup> especially is different from hydrogen;
- **R**<sup>m2</sup> represents hydrogen, methyl, fluoro, or chloro; and
  - 30 ▪ **R**<sup>o1</sup> represents hydrogen; or, in case **R**<sup>m2</sup> represents hydrogen, **R**<sup>o1</sup> represents hydrogen or fluoro;

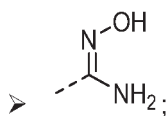


- or **Ar**<sup>1</sup> represents a 5-membered heteroaryl group of the structure (Ar-II):



wherein

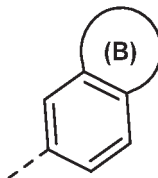
- 5     ▪ **Y** represents **CR**<sup>8</sup> wherein **R**<sup>8</sup> represents especially hydrogen, or halogen (notably fluoro, chloro); or **Y** represents N;
  - **R**<sup>7</sup> represents
    - (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom, wherein said (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy (especially 3-hydroxy-oxetan-3-yl);
    - 10   ➤ **-X**<sup>1</sup>-CO-**R**<sup>01</sup>, wherein
      - **X**<sup>1</sup> represents a direct bond, (C<sub>1-3</sub>)alkylene (especially -CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-), -O-(C<sub>1-3</sub>)alkylene-\* (especially -O-CH<sub>2</sub>-, -O-CH(CH<sub>3</sub>)-, -O-C(CH<sub>3</sub>)<sub>2</sub>-, -O-CH<sub>2</sub>-CH<sub>2</sub>-), -NH-(C<sub>1-3</sub>)alkylene-\* (especially -NH-CH<sub>2</sub>-, -NH-CH(CH<sub>3</sub>)-, -CH=CH-, -NH-CO-, or (C<sub>3-5</sub>)cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-**R**<sup>01</sup> group; and
      - 15   ➤ **R**<sup>01</sup> represents
        - -OH;
        - -O-(C<sub>1-4</sub>)alkyl (especially ethoxy, methoxy);
        - -NH-SO<sub>2</sub>-**R**<sup>S3</sup> wherein **R**<sup>S3</sup> represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;
        - 20   ▪ -O-CH<sub>2</sub>-CO-**R**<sup>04</sup>, wherein **R**<sup>04</sup> represents hydroxy, or (C<sub>1-4</sub>)alkoxy, or -N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>;
        - -O-CH<sub>2</sub>-O-CO-**R**<sup>05</sup>, wherein **R**<sup>05</sup> represents (C<sub>1-4</sub>)alkyl or (C<sub>1-4</sub>)alkoxy;
        - -O-CH<sub>2</sub>-CH<sub>2</sub>-N[(C<sub>1-4</sub>)alkyl]<sub>2</sub> (especially -O-CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>); or
        - 25   ▪ (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methoxy-;
- [wherein in particular such group **-X**<sup>1</sup>-CO-**R**<sup>01</sup> represents -COOH, -CO-O-CH<sub>3</sub>, -CO-O-C<sub>2</sub>H<sub>5</sub>, -O-CH<sub>2</sub>-COOH, -O-CH(CH<sub>3</sub>)-COOH, -O-C(CH<sub>3</sub>)<sub>2</sub>-COOH, -O-CH<sub>2</sub>-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -NH-CH(CH<sub>3</sub>)-COOH, -CO-NH-SO<sub>2</sub>-CH<sub>3</sub>, -CO-NH-SO<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>, -CO-NH-SO<sub>2</sub>-cyclopropyl, -CO-NH-SO<sub>2</sub>-C<sub>2</sub>H<sub>5</sub>, -CO-NH-SO<sub>2</sub>-NH<sub>2</sub>, -CO-O-CH<sub>2</sub>-COOH, -CO-O-CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>, -CO-O-CH<sub>2</sub>-CO-N(CH<sub>3</sub>)<sub>2</sub>, -CO-O-CH<sub>2</sub>-O-CO-O-C<sub>2</sub>H<sub>5</sub>, -CO-O-CH<sub>2</sub>-O-CO-propyl, (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyl-O-CO-, -CH<sub>2</sub>-COOH, -CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -CH<sub>2</sub>-CO-O-C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-COOH, -CH=CH-COOH, -NH-CO-COOH, 1-carboxy-cyclopropan-1-yl];



- $-\text{NH}-\text{CO}-\text{NR}^{\text{N}5}\text{R}^{\text{N}6}$  wherein  $\text{R}^{\text{N}5}$  and  $\text{R}^{\text{N}6}$  independently represent hydrogen or  $(\text{C}_{1-4})$ alkyl (wherein preferably at least one of  $\text{R}^{\text{N}5}$  and  $\text{R}^{\text{N}6}$  represents hydrogen; and wherein particular examples of such group  $-\text{NH}-\text{CO}-\text{NR}^{\text{N}5}\text{R}^{\text{N}6}$  are  $-\text{NH}-\text{CO}-\text{NH}_2$ ,  $-\text{NH}-\text{CO}-\text{NH}-\text{C}_2\text{H}_5$ );
- 5 ➤  $-(\text{CH}_2)_q-\text{HET}^1$ , wherein  $q$  represents the integer 0, 1 or 2 (especially  $q$  is 0, i.e.  $\text{HET}^1$  is linked to  $\text{Ar}^1$  by a direct bond); and wherein  $\text{HET}^1$  represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-hydroxy-[1,2,4]oxadiazol-3-yl), 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl (encompassing its tautomeric form 3-hydroxy-[1,2,4]oxadiazol-5-yl);
- $-(\text{CH}_2)_p-\text{HET}$ , wherein  $p$  represents the integer 0 or 1 (especially  $p$  is 0, i.e.  $\text{HET}$  is linked to  $\text{Ar}^1$  by a direct bond); and wherein  $\text{HET}$  represents a group selected from 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl, 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, 5-methoxy-[1,2,4]oxadiazol-3-yl, 5-amino-[1,2,4]oxadiazol-3-yl, 5-[(2-hydroxy-ethyl)]-amino-[1,2,4]oxadiazol-3-yl, 5-hydroxymethyl-[1,2,4]oxadiazol-3-yl, and 5-(oxetan-3-yl)-[1,2,4]oxadiazol-3-yl;
- 10
- 15 ■  $\text{R}^6$  represents
  - $(\text{C}_{1-6})$ alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl);
  - $(\text{C}_{1-4})$ alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy);
  - $(\text{C}_{1-3})$ fluoroalkyl (especially trifluoromethyl);
  - $(\text{C}_{1-3})$ fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
  - 20 ➤ halogen (especially fluoro or chloro);
  - $(\text{C}_{3-6})$ cycloalkyl-oxy (especially cyclopropyl-oxy, cyclobutyl-oxy, cyclopentyl-oxy);
  - hydroxy- $(\text{C}_{2-4})$ alkoxy (especially 2-hydroxy-ethoxy);
  - $-\text{X}^2-\text{NR}^{\text{N}1}\text{R}^{\text{N}2}$ , wherein  $\text{X}^2$  represents a direct bond; or  $\text{X}^2$  represents  $-\text{O}-\text{CH}_2-\text{CH}_2^*$ , wherein the asterisk indicates the bond that is linked to the  $-\text{NR}^{\text{N}1}\text{R}^{\text{N}2}$  group; and wherein  $\text{R}^{\text{N}1}$  and  $\text{R}^{\text{N}2}$
  - 25 independently represent hydrogen,  $(\text{C}_{1-4})$ alkyl, or  $(\text{C}_{3-6})$ cycloalkyl; (especially such group  $-\text{X}^2-\text{NR}^{\text{N}1}\text{R}^{\text{N}2}$  represents amino, methylamino, ethylamino, propylamino; or 2-(dimethylamino)-ethoxy);
  - $-\text{S}-\text{R}^{\text{S}2}$  wherein  $\text{R}^{\text{S}2}$  represents  $(\text{C}_{1-4})$ alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or  $(\text{C}_{3-6})$ cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);
- or  $\text{Ar}^1$  represents 8- to 10-membered bicyclic heteroaryl selected from indazolyl, benzoimidazolyl, indolyl, benzofuranyl, and benzooxazolyl; wherein said 8- to 10-membered bicyclic heteroaryl independently is mono-substituted with  $-(\text{C}_{0-3})$ alkylene- $\text{COOR}^{\text{O}2}$  wherein  $\text{R}^{\text{O}2}$  represents hydrogen or  $(\text{C}_{1-4})$ alkyl (especially methyl) (wherein especially such group  $-(\text{C}_{0-3})$ alkylene- $\text{COOR}^{\text{O}2}$  is  $-\text{COOH}$ ); (especially such 8- to 10-membered bicyclic heteroaryl is 3-carboxy-1H-indol-6-yl, 4-carboxy-1H-indol-2-yl, 5-carboxy-1H-indol-2-yl, 6-carboxy-1H-indol-2-yl, 7-carboxy-1H-indol-2-yl, 5-(methoxycarbonyl)-1H-indol-2-yl, 6-(methoxycarbonyl)-1H-indol-2-yl, 6-
- 30

carboxy-benzofuran-2-yl, 3-carboxy-benzofuran-6-yl, 2-carboxy-benzofuran-5-yl, or 2-carboxy-benzofuran-6-yl);

- or **Ar<sup>1</sup>** represents a group of the structure (Ar-III):



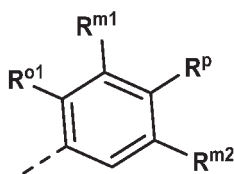
(Ar-III)

which is selected from 2-oxo-2,3-dihydro-benzooxazol-6-yl, 3-methyl-2-oxo-2,3-dihydro-benzooxazol-5-yl, 1-methyl-3-oxo-2,3-dihydro-1H-indazol-6-yl, 2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-7-yl, and 1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl (in particular methyl-3-oxo-2,3-dihydro-1H-indazol-6-yl);

wherein in a sub-embodiment, **Ar<sup>1</sup>** especially is a phenyl group of the structure (Ar-I) (wherein in particular **R<sup>m1</sup>** especially is different from hydrogen), or a 5-membered heteroaryl group of the structure (Ar-II), as defined herein above.

6) Another embodiment relates to compounds defined in embodiment 4), for use according to embodiment 1), wherein **Ar<sup>1</sup>** represents

- a phenyl group of the structure (Ar-I):



(Ar-I)

wherein

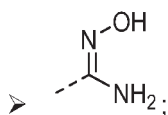
- **R<sup>p</sup>** represents
  - (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom, wherein said (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy (especially 3-hydroxy-oxetan-3-yl);
  - hydroxy;
  - **-X<sup>1</sup>-CO-R<sup>o1</sup>**, wherein
    - **X<sup>1</sup>** represents a direct bond, (C<sub>1-3</sub>)alkylene (especially -CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-), -O-(C<sub>1-3</sub>)alkylene-\* (especially -O-CH<sub>2</sub>-, -O-CH(CH<sub>3</sub>)-\*, -O-C(CH<sub>3</sub>)<sub>2</sub>-, -O-CH<sub>2</sub>-CH<sub>2</sub>-\*),

-NH-(C<sub>1-3</sub>)alkylene-\* (especially -NH-CH<sub>2</sub>\*, -NH-CH(CH<sub>3</sub>)\*, -CH=CH-, or -NH-CO-\*; wherein the asterisks indicate the bond that is linked to the -CO-R<sup>01</sup> group; and

➤ R<sup>01</sup> represents

- -OH;
- -O-(C<sub>1-4</sub>)alkyl (especially ethoxy, methoxy);
- -NH-SO<sub>2</sub>-R<sup>S3</sup> wherein R<sup>S3</sup> represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;

[wherein in particular such group -X<sup>1</sup>-CO-R<sup>01</sup> represents -COOH, -CO-O-CH<sub>3</sub>, -CO-O-C<sub>2</sub>H<sub>5</sub>, -O-CH<sub>2</sub>-COOH, -O-CH(CH<sub>3</sub>)-COOH, -O-C(CH<sub>3</sub>)<sub>2</sub>-COOH, -O-CH<sub>2</sub>-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -NH-CH(CH<sub>3</sub>)-COOH, -CO-NH-SO<sub>2</sub>-CH<sub>3</sub>, -CO-NH-SO<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>, -CO-NH-SO<sub>2</sub>-cyclopropyl, -CO-NH-SO<sub>2</sub>-C<sub>2</sub>H<sub>5</sub>, -CO-NH-SO<sub>2</sub>-NH<sub>2</sub>, -CH<sub>2</sub>-COOH, -CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -CH<sub>2</sub>-CO-O-C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-COOH, -CH=CH-COOH, -NH-CO-COOH];



➤ -(CH<sub>2</sub>)<sub>q</sub>-HET<sup>1</sup>, wherein q represents the integer 0, 1 or 2 (especially q is 0, i.e. HET<sup>1</sup> is linked to Ar<sup>1</sup> by a direct bond); and wherein HET<sup>1</sup> represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-hydroxy-[1,2,4]oxadiazol-3-yl), 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl (encompassing its tautomeric form 3-hydroxy-[1,2,4]oxadiazol-5-yl), or 5-thioxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-mercapto-[1,2,4]oxadiazol-3-yl);

➤ -(CH<sub>2</sub>)<sub>p</sub>-HET, wherein p represents the integer 0 or 1 (especially p is 0, i.e. HET is linked to Ar<sup>1</sup> by a direct bond); and wherein HET represents a group selected from 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl, 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, 5-methoxy-[1,2,4]oxadiazol-3-yl, 5-amino-[1,2,4]oxadiazol-3-yl, 5-[(2-hydroxy-ethyl)]-amino-[1,2,4]oxadiazol-3-yl, 5-hydroxymethyl-[1,2,4]oxadiazol-3-yl, and 5-(oxetan-3-yl)-[1,2,4]oxadiazol-3-yl;

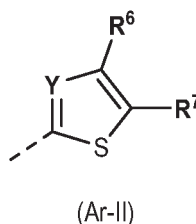
▪ R<sup>m1</sup> represents

- hydrogen;
- (C<sub>1-6</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl);
- (C<sub>1-4</sub>)alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy);
- (C<sub>1-3</sub>)fluoroalkyl (especially trifluoromethyl);
- (C<sub>1-3</sub>)fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
- halogen (especially fluoro or chloro);

- (C<sub>3-6</sub>)cycloalkyl-oxy (especially cyclopropyl-oxy, cyclobutyl-oxy, cyclopentyl-oxy);
- hydroxy;
- hydroxy-(C<sub>2-4</sub>)alkoxy (especially 2-hydroxy-ethoxy);
- -X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup>, wherein X<sup>2</sup> represents a direkt bond; or X<sup>2</sup> represents -O-CH<sub>2</sub>-CH<sub>2</sub>-, wherein the asterisk indicates the bond that is linked to the -NR<sup>N1</sup>R<sup>N2</sup> group; and wherein R<sup>N1</sup> and R<sup>N2</sup> independently represent hydrogen, (C<sub>1-4</sub>)alkyl (especially methyl), or (C<sub>3-6</sub>)cycloalkyl (especially cyclopropyl); (especially such group -X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup> represents amino, methylamino, ethylamino, propylamino; or 2-(dimethylamino)-ethoxy);
- -S-R<sup>S2</sup> wherein R<sup>S2</sup> represents (C<sub>1-4</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);

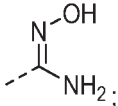
wherein in a sub-embodiment, R<sup>m1</sup> especially is different from hydrogen;

- R<sup>m2</sup> represents hydrogen, methyl, fluoro, or chloro; and
- R<sup>o1</sup> represents hydrogen; or, in case R<sup>m2</sup> represents hydrogen, R<sup>o1</sup> represents hydrogen or fluoro;
- or Ar<sup>1</sup> represents a 5-membered heteroaryl group of the structure (Ar-II):



wherein

- Y represents CR<sup>8</sup> wherein R<sup>8</sup> represents especially hydrogen, or halogen (notably fluoro, chloro); or Y represents N;
- R<sup>7</sup> represents
  - (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom, wherein said (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy (especially 3-hydroxy-oxetan-3-yl);
  - -X<sup>1</sup>-CO-R<sup>o1</sup>, wherein
    - X<sup>1</sup> represents a direct bond, (C<sub>1-3</sub>)alkylene (especially -CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-), -O-(C<sub>1-3</sub>)alkylene-\* (especially -O-CH<sub>2</sub>-, -O-CH(CH<sub>3</sub>)-, -O-C(CH<sub>3</sub>)<sub>2</sub>-, -O-CH<sub>2</sub>-CH<sub>2</sub>-), -NH-(C<sub>1-3</sub>)alkylene-\* (especially -NH-CH<sub>2</sub>-, -NH-CH(CH<sub>3</sub>)-, -CH=CH-, -NH-CO-, or (C<sub>3-5</sub>)cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-R<sup>o1</sup> group; and
    - R<sup>o1</sup> represents
      - -OH;
      - -O-(C<sub>1-4</sub>)alkyl (especially ethoxy, methoxy);

- -NH-SO<sub>2</sub>-R<sup>S3</sup> wherein R<sup>S3</sup> represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;
  - 5     ▪ -O-CH<sub>2</sub>-CO-R<sup>O4</sup>, wherein R<sup>O4</sup> represents hydroxy, or (C<sub>1-4</sub>)alkoxy, or -N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>;
  - -O-CH<sub>2</sub>-O-CO-R<sup>O5</sup>, wherein R<sup>O5</sup> represents (C<sub>1-4</sub>)alkyl or (C<sub>1-4</sub>)alkoxy;
  - -O-CH<sub>2</sub>-CH<sub>2</sub>-N[(C<sub>1-4</sub>)alkyl]<sub>2</sub> (especially -O-CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>); or
  - (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methoxy-;
- [wherein in particular such group -X<sup>1</sup>-CO-R<sup>O1</sup> represents -COOH, -CO-O-CH<sub>3</sub>, -CO-O-C<sub>2</sub>H<sub>5</sub>, -O-CH<sub>2</sub>-COOH, -O-CH(CH<sub>3</sub>)-COOH, -O-C(CH<sub>3</sub>)<sub>2</sub>-COOH, -O-CH<sub>2</sub>-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -NH-CH(CH<sub>3</sub>)-COOH, -CO-NH-SO<sub>2</sub>-CH<sub>3</sub>, -CO-NH-SO<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>, -CO-NH-SO<sub>2</sub>-cyclopropyl, -CO-NH-SO<sub>2</sub>-C<sub>2</sub>H<sub>5</sub>, -CO-NH-SO<sub>2</sub>-NH<sub>2</sub>, -CO-O-CH<sub>2</sub>-COOH, -CO-O-CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>, -CO-O-CH<sub>2</sub>-CO-N(CH<sub>3</sub>)<sub>2</sub>, -CO-O-CH<sub>2</sub>-O-CO-O-C<sub>2</sub>H<sub>5</sub>, -CO-O-CH<sub>2</sub>-O-CO-propyl, (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyl-O-CO-, -CH<sub>2</sub>-COOH, -CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -CH<sub>2</sub>-CO-O-C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-COOH, -CH=CH-COOH, -NH-CO-COOH, 1-carboxy-cyclopropan-1-yl];
- 10
- 15
- ; N=CN
- hydroxy-(C<sub>1-4</sub>)alkyl (especially hydroxymethyl, 1-hydroxy-ethyl);
- hydroxy-(C<sub>2-4</sub>)alkoxy (especially 2-hydroxy-ethoxy);
- -(CH<sub>2</sub>)<sub>r</sub>-CO-NR<sup>N3</sup>R<sup>N4</sup> wherein r represents the integer 0 or 1; and wherein R<sup>N3</sup> and R<sup>N4</sup> independently represent hydrogen, or (C<sub>1-4</sub>)alkyl (wherein preferably at least one of R<sup>N3</sup> and R<sup>N4</sup> represents hydrogen; and wherein particular examples of such group -CO-NR<sup>N3</sup>R<sup>N4</sup> are -CO-NH<sub>2</sub>, -CO-NH(CH<sub>3</sub>), -CO-NH(C<sub>2</sub>H<sub>5</sub>), or -CH<sub>2</sub>-CO-NH<sub>2</sub>);
- 20
- -NH-CO-NR<sup>N5</sup>R<sup>N6</sup> wherein R<sup>N5</sup> and R<sup>N6</sup> independently represent hydrogen or (C<sub>1-4</sub>)alkyl (wherein preferably at least one of R<sup>N5</sup> and R<sup>N6</sup> represents hydrogen; and wherein particular examples of such group -NH-CO-NR<sup>N5</sup>R<sup>N6</sup> are -NH-CO-NH<sub>2</sub>, -NH-CO-NH-C<sub>2</sub>H<sub>5</sub>);
- 25
- -SO<sub>2</sub>-R<sup>S1</sup> wherein R<sup>S1</sup> represents (C<sub>1-4</sub>)alkyl (especially methyl), or -NR<sup>N7</sup>R<sup>N8</sup> wherein R<sup>N7</sup> and R<sup>N8</sup> independently represent hydrogen or (C<sub>1-3</sub>)alkyl (wherein preferably at least one of R<sup>N7</sup> and R<sup>N8</sup> represents hydrogen; and wherein particular examples of such group -SO<sub>2</sub>-R<sup>S1</sup> are -SO<sub>2</sub>-CH<sub>3</sub>, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-NH-CH<sub>3</sub>);
- 30
- -(CH<sub>2</sub>)<sub>q</sub>-HET<sup>1</sup>, wherein q represents the integer 0, 1 or 2 (especially q is 0, i.e. HET<sup>1</sup> is linked to Ar<sup>1</sup> by a direct bond); and wherein HET<sup>1</sup> represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-hydroxy-[1,2,4]oxadiazol-3-yl), 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl (encompassing its tautomeric form 3-hydroxy-[1,2,4]oxadiazol-5-yl), or 5-thioxo-



4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-mercapto-[1,2,4]oxadiazol-3-yl);

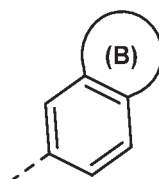
- $-(CH_2)_p$ -HET, wherein **p** represents the integer 0 or 1 (especially **p** is 0, i.e. HET is linked to **Ar**<sup>1</sup> by a direct bond); and wherein HET represents a group selected from 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl, 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, 5-methoxy-[1,2,4]oxadiazol-3-yl, 5-amino-[1,2,4]oxadiazol-3-yl, 5-[(2-hydroxy-ethyl)]-amino-[1,2,4]oxadiazol-3-yl, 5-hydroxymethyl-[1,2,4]oxadiazol-3-yl, and 5-(oxetan-3-yl)-[1,2,4]oxadiazol-3-yl;

▪ **R**<sup>6</sup> represents

- (C<sub>1-6</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl);
- (C<sub>1-4</sub>)alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy);
- (C<sub>1-3</sub>)fluoroalkyl (especially trifluoromethyl);
- (C<sub>1-3</sub>)fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
- halogen (especially fluoro or chloro);
- (C<sub>3-6</sub>)cycloalkyl-oxy (especially cyclopropyl-oxy, cyclobutyl-oxy, cyclopentyl-oxy);
- hydroxy-(C<sub>2-4</sub>)alkoxy (especially 2-hydroxy-ethoxy);
- $-X^2-NR^{N1}R^{N2}$ , wherein **X**<sup>2</sup> represents a direct bond; or **X**<sup>2</sup> represents  $-O-CH_2-CH_2-^*$ , wherein the asterisk indicates the bond that is linked to the  $-NR^{N1}R^{N2}$  group; and wherein **R**<sup>N1</sup> and **R**<sup>N2</sup> independently represent hydrogen, (C<sub>1-4</sub>)alkyl, or (C<sub>3-6</sub>)cycloalkyl; (especially such group  $-X^2-NR^{N1}R^{N2}$  represents amino, methylamino, ethylamino, propylamino; or 2-(dimethylamino)-ethoxy);
- $-S-R^{S2}$  wherein **R**<sup>S2</sup> represents (C<sub>1-4</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);

- or **Ar**<sup>1</sup> represents 8- to 10-membered bicyclic heteroaryl selected from indazolyl, benzoimidazolyl, indolyl, benzofuranyl, and benzooxazolyl; wherein said 8- to 10-membered bicyclic heteroaryl independently is mono-substituted with  $-(C_{0-3})alkylene-COOR^{O2}$  wherein **R**<sup>O2</sup> represents hydrogen or (C<sub>1-4</sub>)alkyl (especially methyl) (wherein especially such group  $-(C_{0-3})alkylene-COOR^{O2}$  is  $-COOH$ ); (especially such 8- to 10-membered bicyclic heteroaryl is 3-carboxy-1H-indol-6-yl, 4-carboxy-1H-indol-2-yl, 5-carboxy-1H-indol-2-yl, 6-carboxy-1H-indol-2-yl, 7-carboxy-1H-indol-2-yl, 5-(methoxycarbonyl)-1H-indol-2-yl, 6-(methoxycarbonyl)-1H-indol-2-yl, 6-carboxy-benzofuran-2-yl, 3-carboxy-benzofuran-6-yl, 2-carboxy-benzofuran-5-yl, or 2-carboxy-benzofuran-6-yl);

- or **Ar**<sup>1</sup> represents a group of the structure (Ar-III):



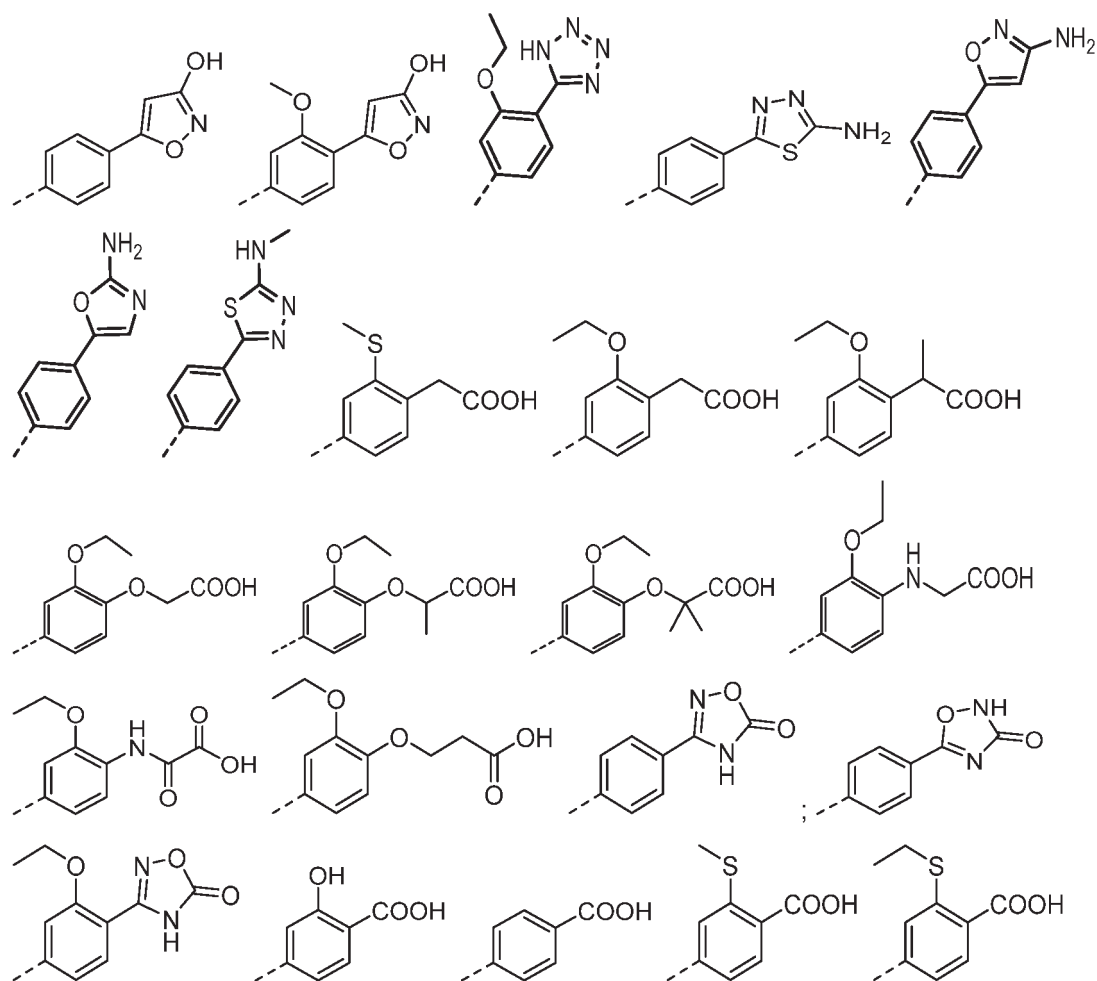
(Ar-III)

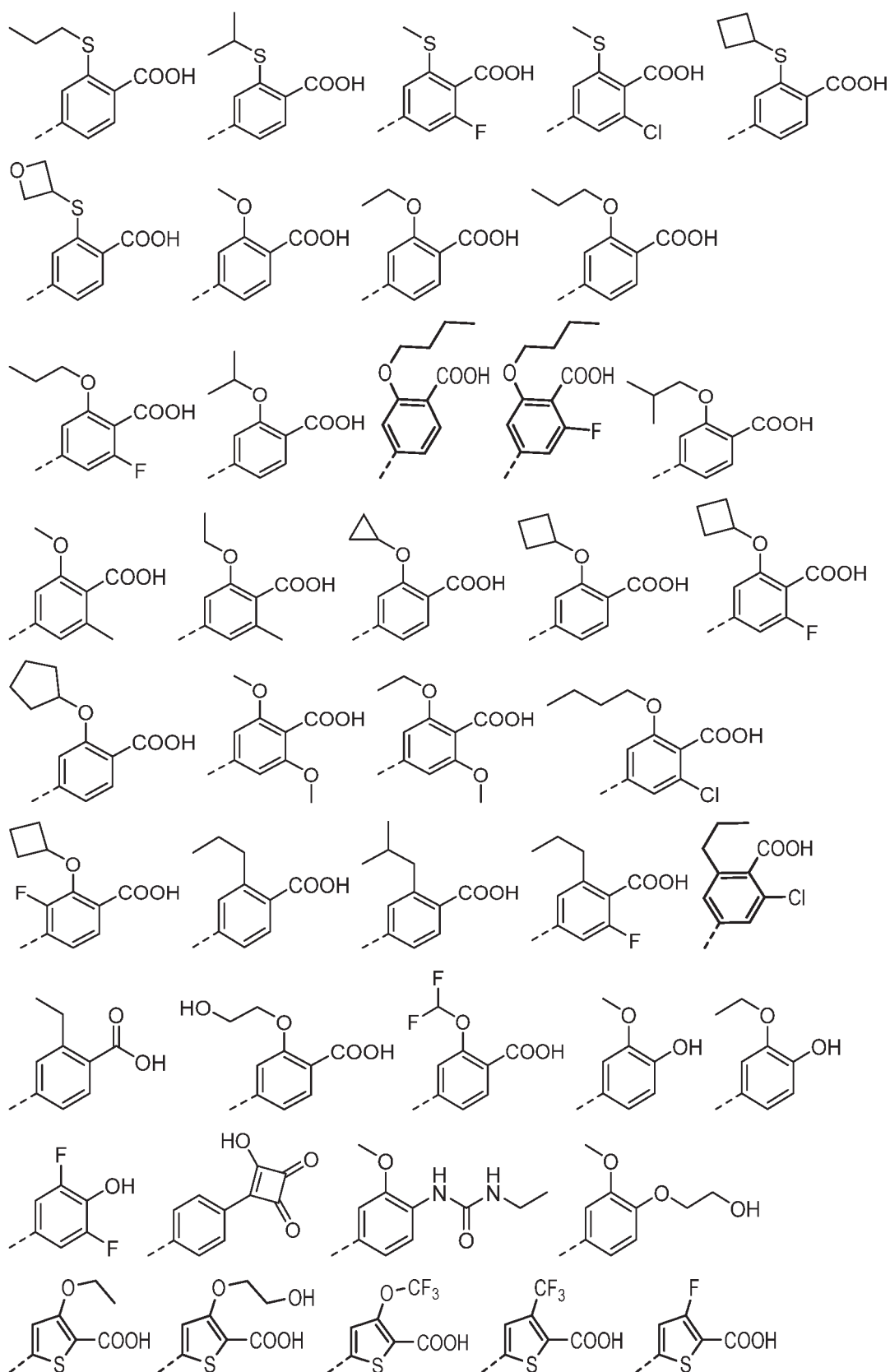
which is selected from 2-oxo-2,3-dihydro-benzooxazol-6-yl, 3-methyl-2-oxo-2,3-dihydro-benzooxazol-5-yl, 1-methyl-3-oxo-2,3-dihydro-1H-indazol-6-yl, 2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-7-yl, and 1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl (in particular methyl-3-oxo-2,3-dihydro-1H-indazol-6-yl);

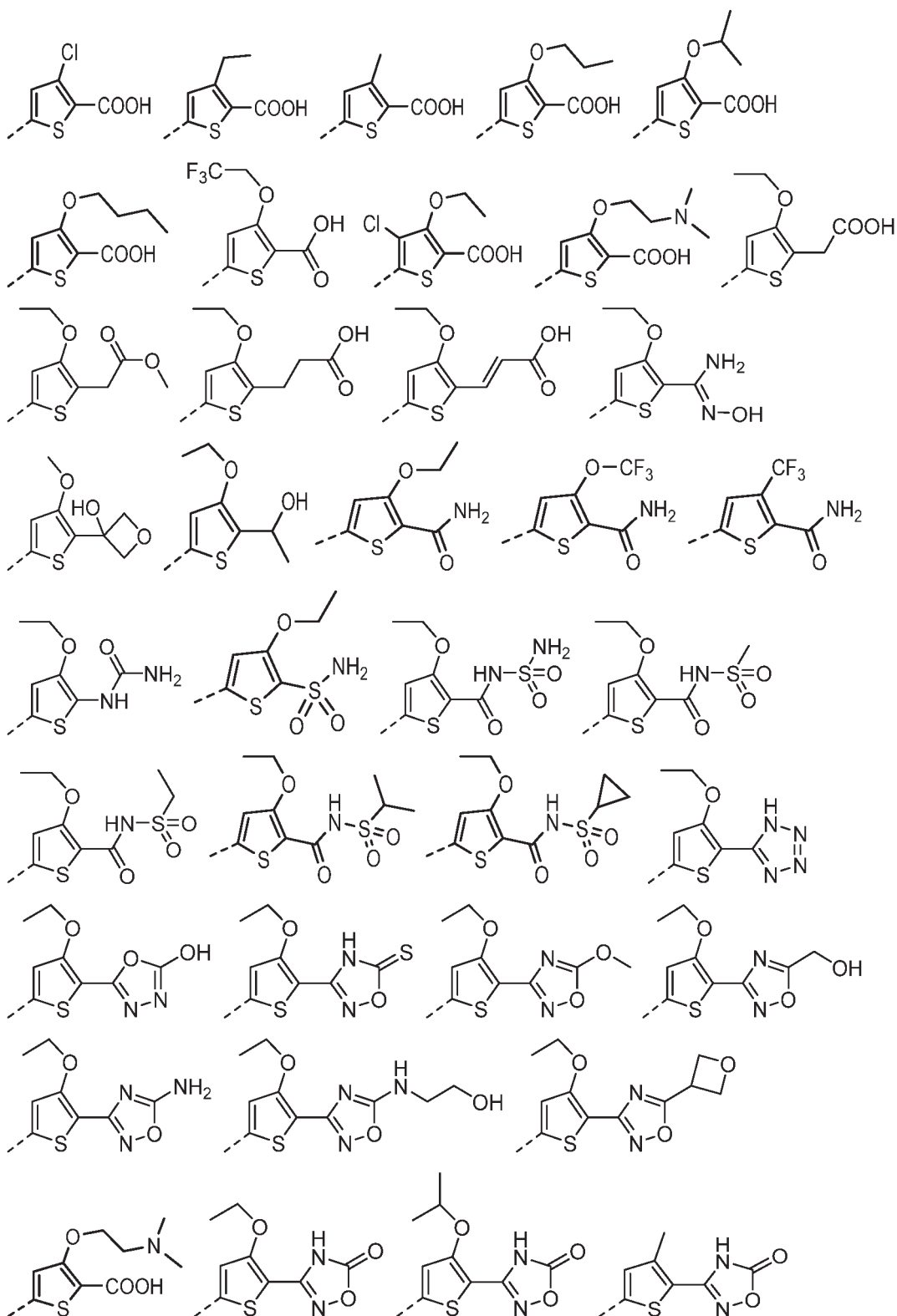
wherein in a sub-embodiment, **Ar<sup>1</sup>** especially is a phenyl group of the structure (Ar-I) (wherein in particular **R<sup>m1</sup>** especially is different from hydrogen), or a 5-membered heteroaryl group of the structure (Ar-II), as defined herein above.

10 7) Another embodiment relates to compounds defined in embodiment 4), for use according to embodiment 1), wherein **Ar<sup>1</sup>** represents a group selected from:

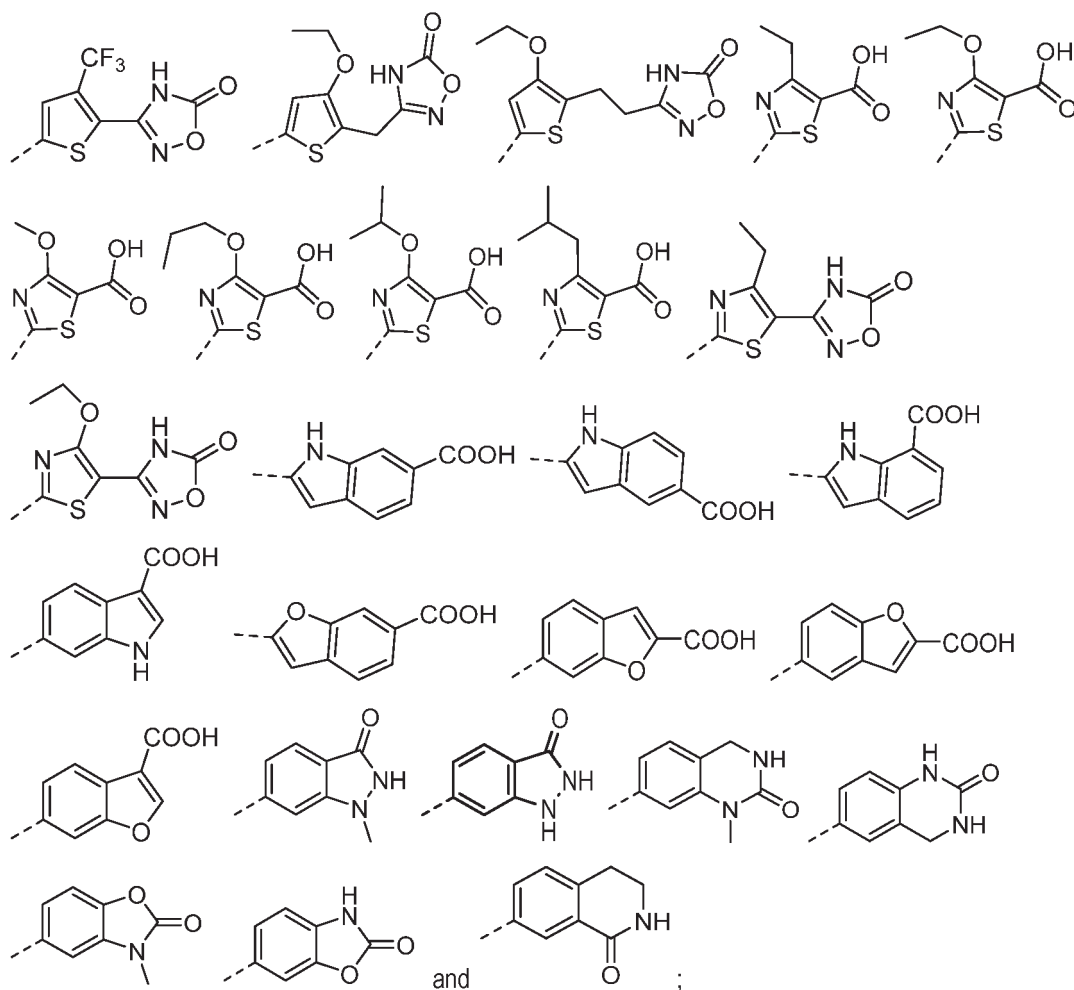
A)







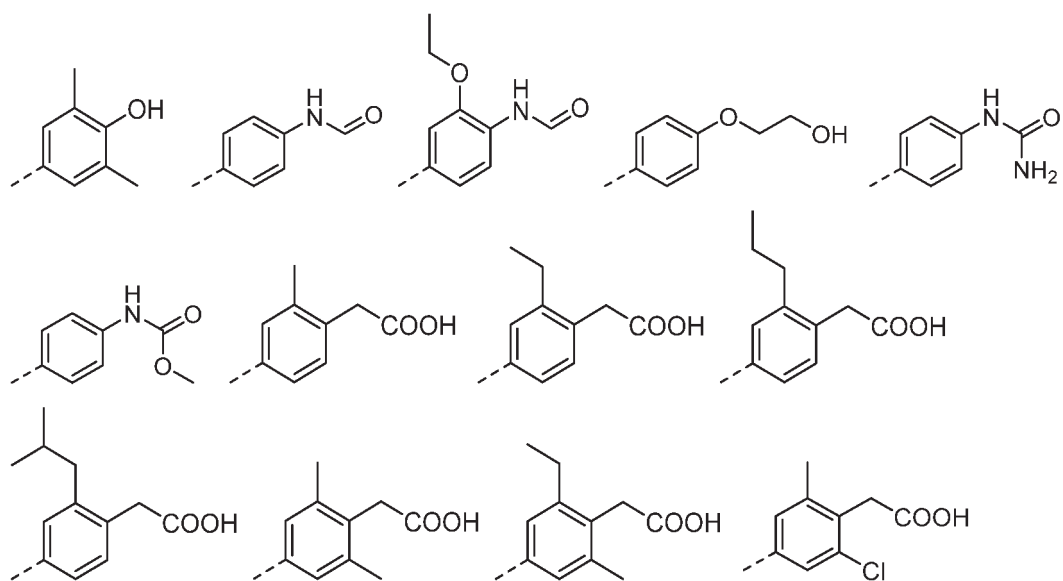
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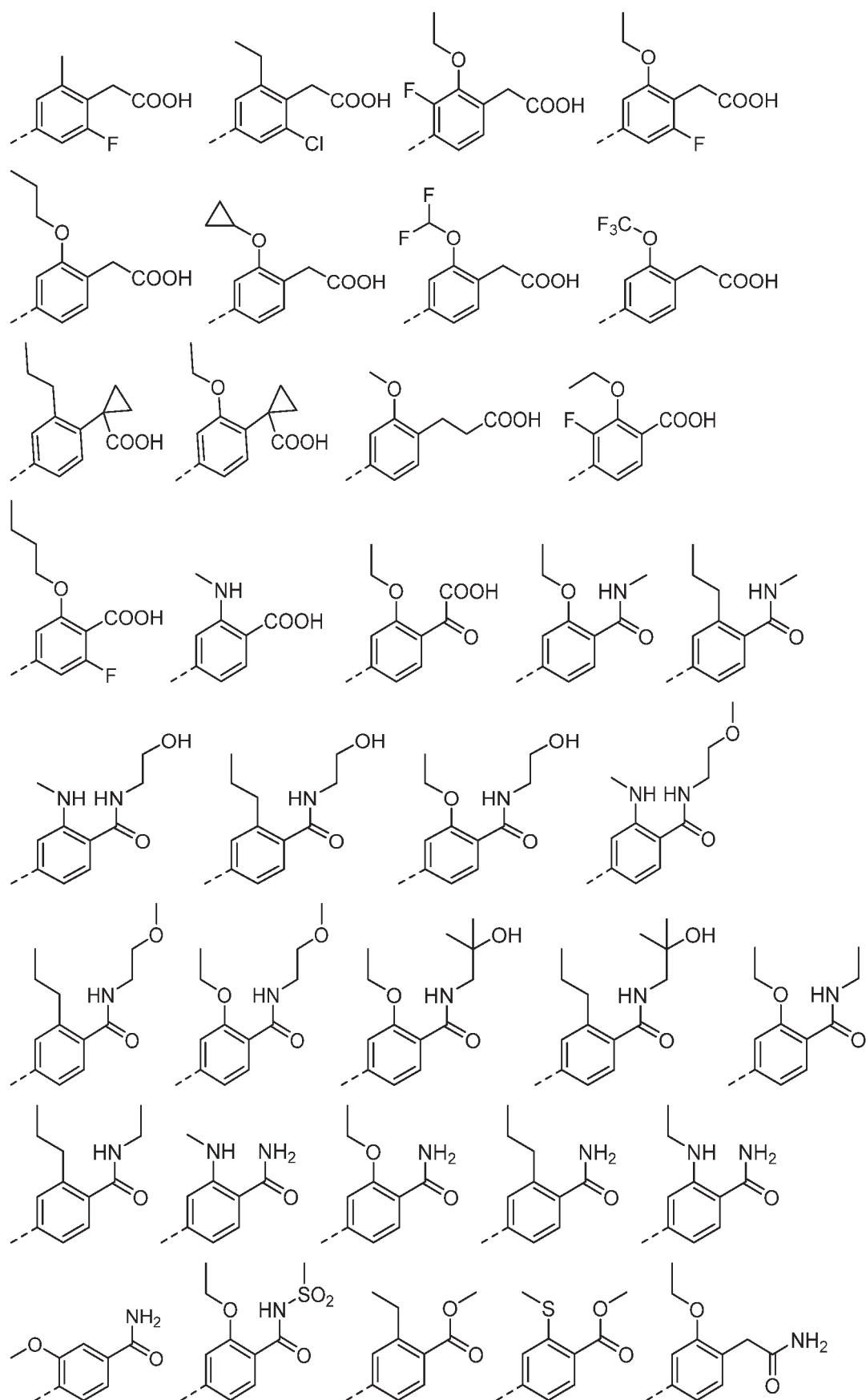
or, in addition,  $\text{Ar}^1$  represents a group selected from:

B)

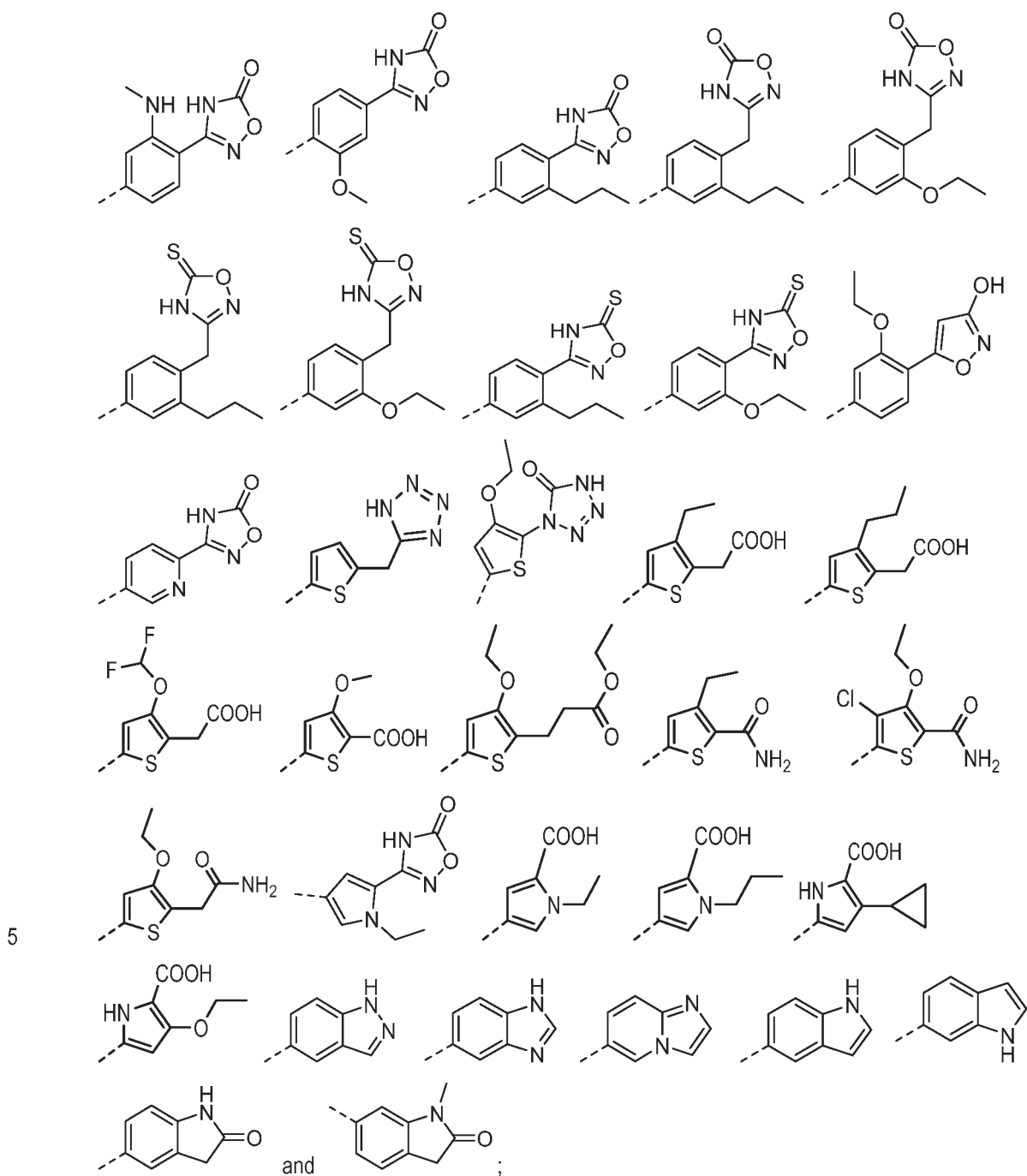


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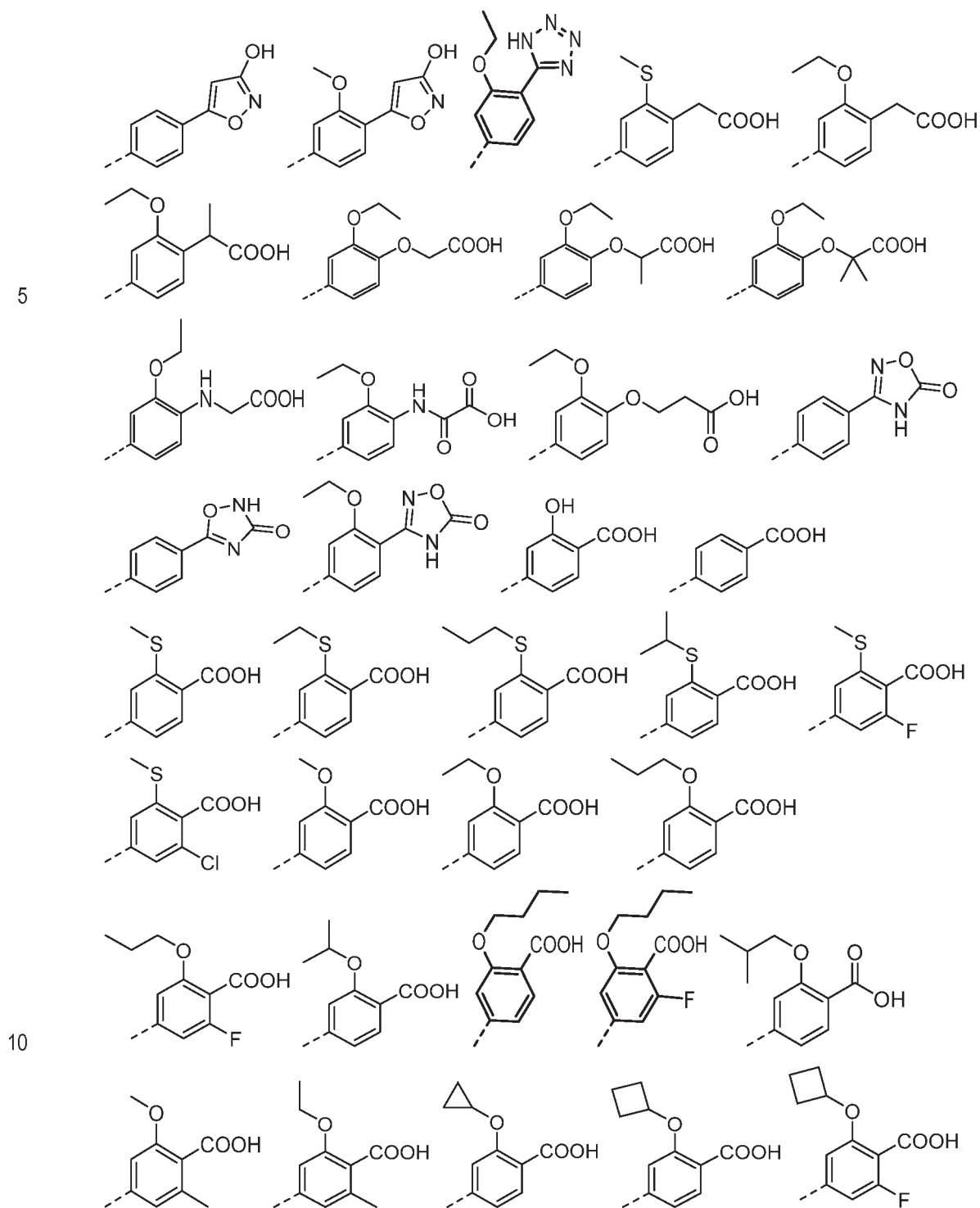


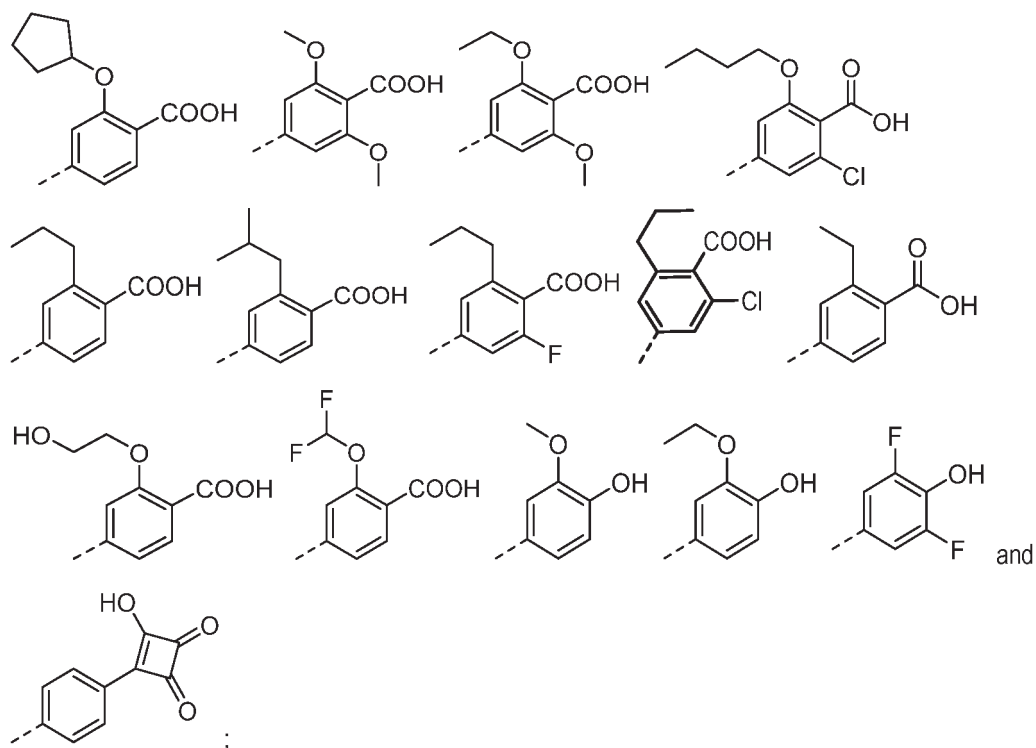
wherein each of the groups A) and B) forms a particular sub-embodiment;

wherein in a further sub-embodiment, **Ar<sup>1</sup>** especially is a phenyl group (in particular a di-substituted phenyl group),  
 10 or a thiophenyl group, or a thiazolyl group, as defined in groups A) and/or B) herein above.

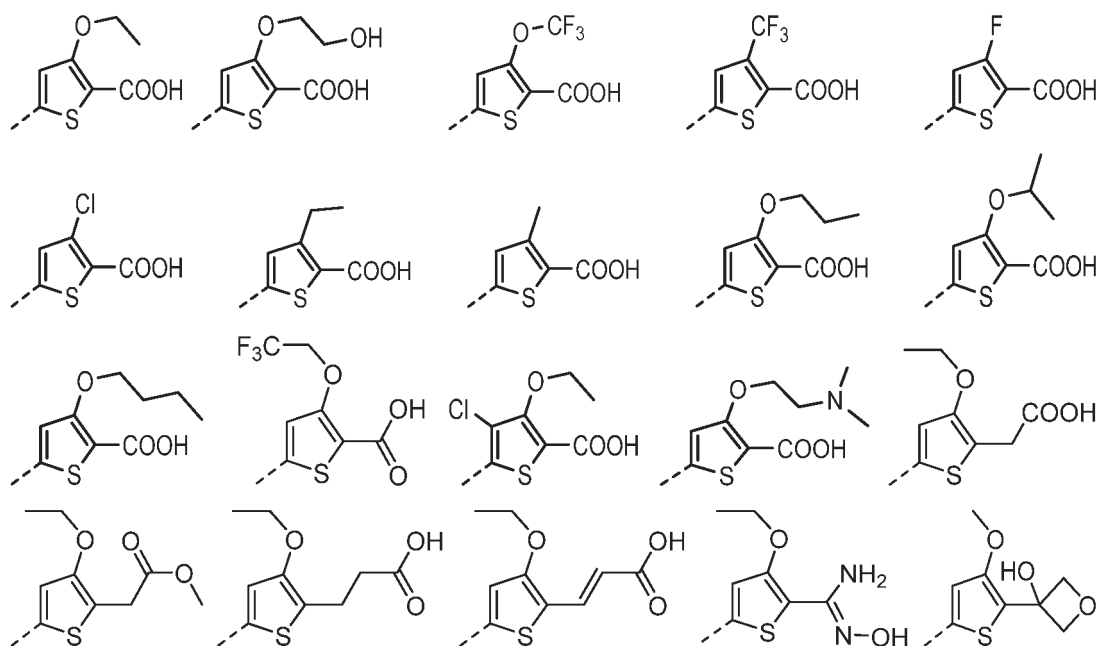
8) Another embodiment relates to compounds defined in embodiment 4), for use according to embodiment 1), wherein

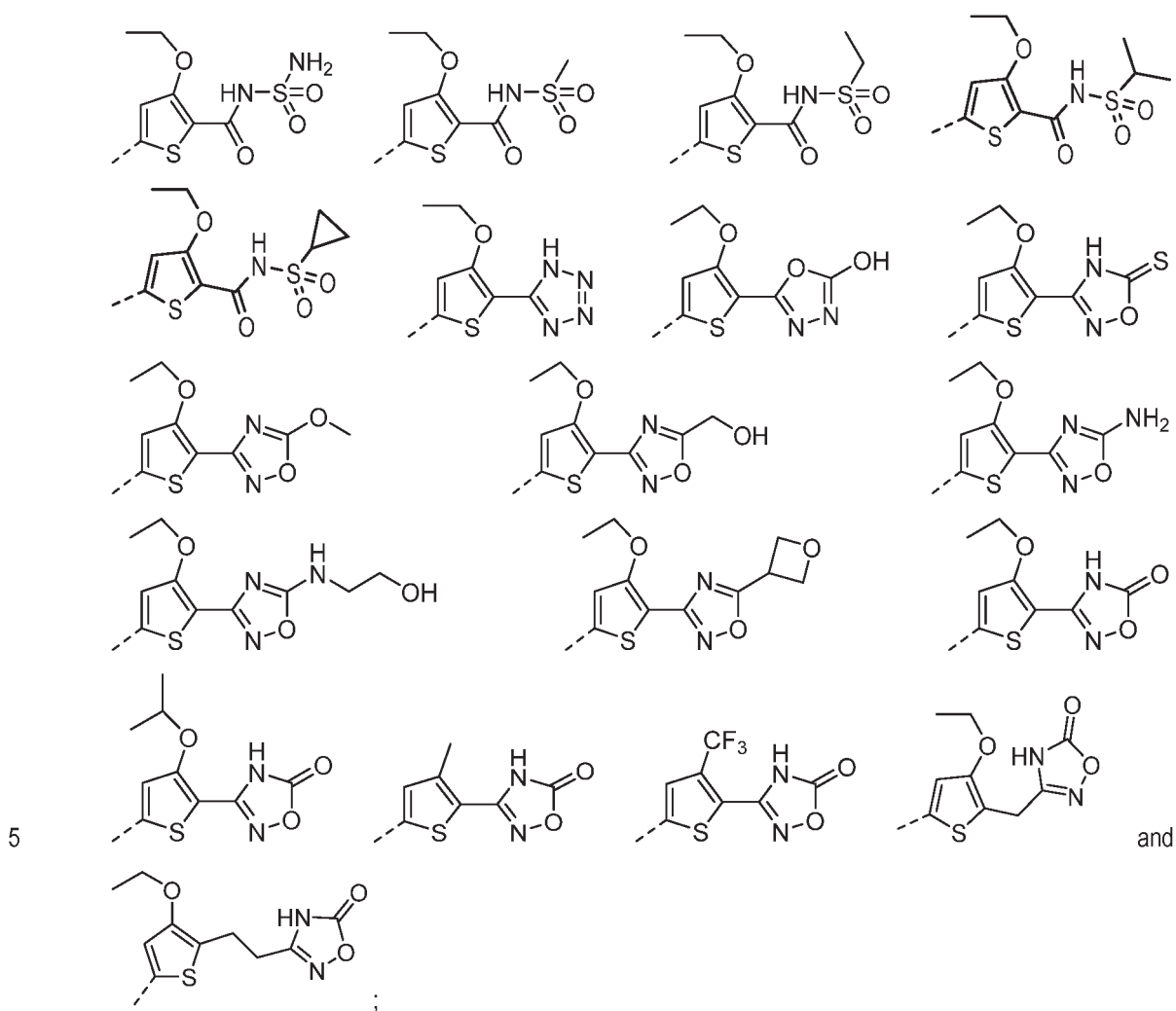
(i) **Ar<sup>1</sup>** represents a phenyl group selected from:



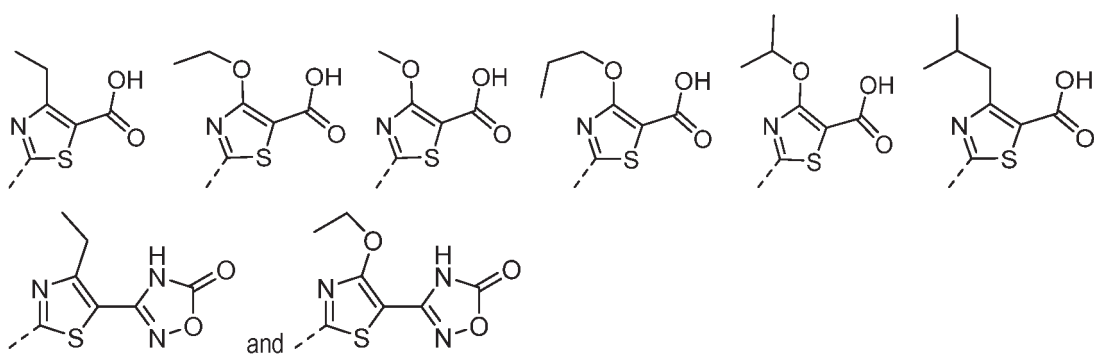


5 (ii) or  $\text{Ar}^1$  represents a thiophenyl group selected from:

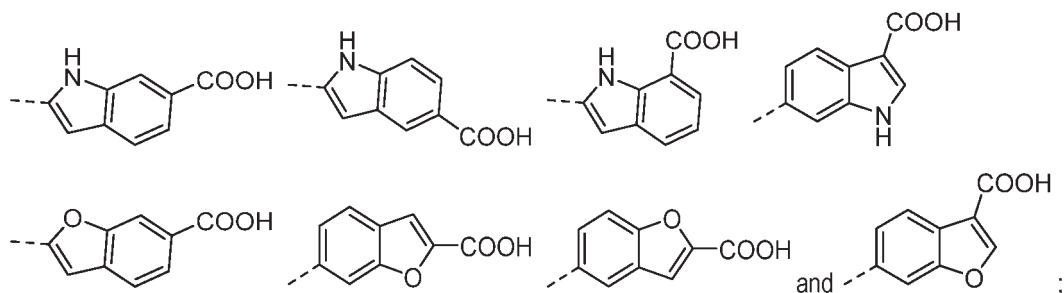




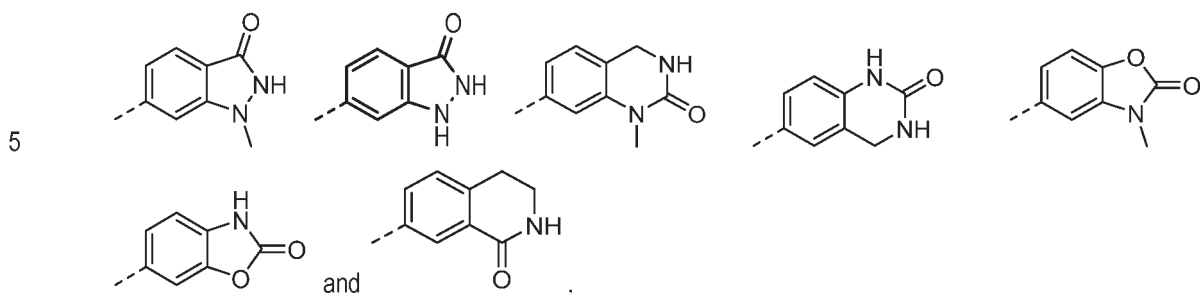
(iii) or **Ar<sup>1</sup>** represents a thiazolyl group selected from:



(iv) or **Ar<sup>1</sup>** represents 9- or 10-membered bicyclic heteroaryl selected from



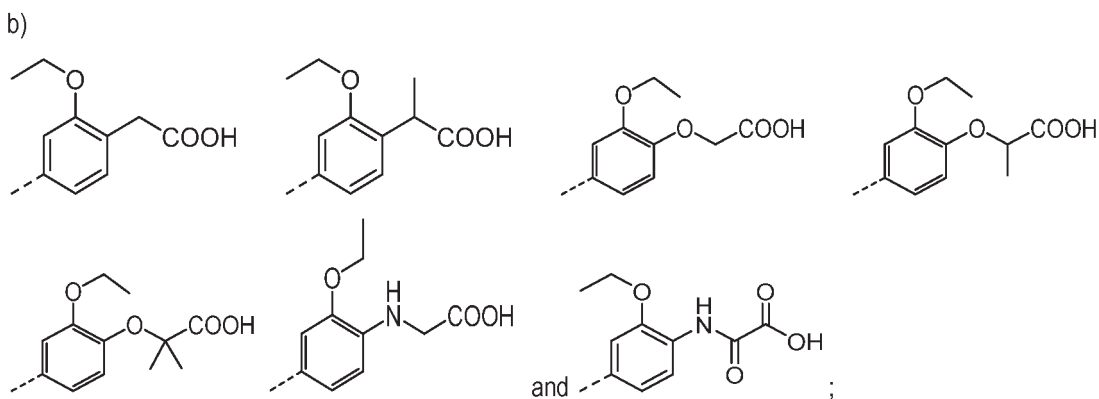
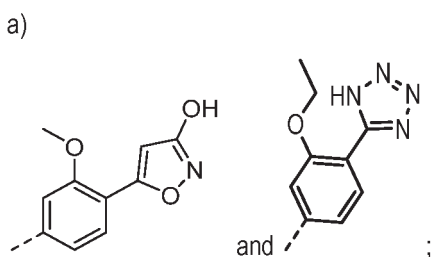
(v) or **Ar<sup>1</sup>** represents a group selected from:



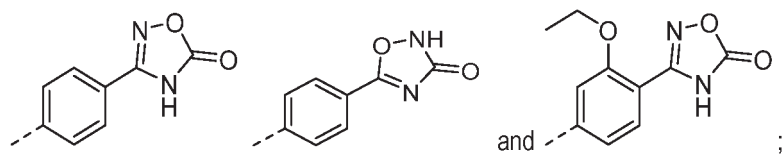
wherein in a sub-embodiment, **Ar<sup>1</sup>** especially is a phenyl group (in particular a di-substituted phenyl group), or a thiophenyl group, or a thiazolyl group, as defined herein above.

9) Another embodiment relates to compounds defined in embodiment 4), for use according to embodiment 1), wherein

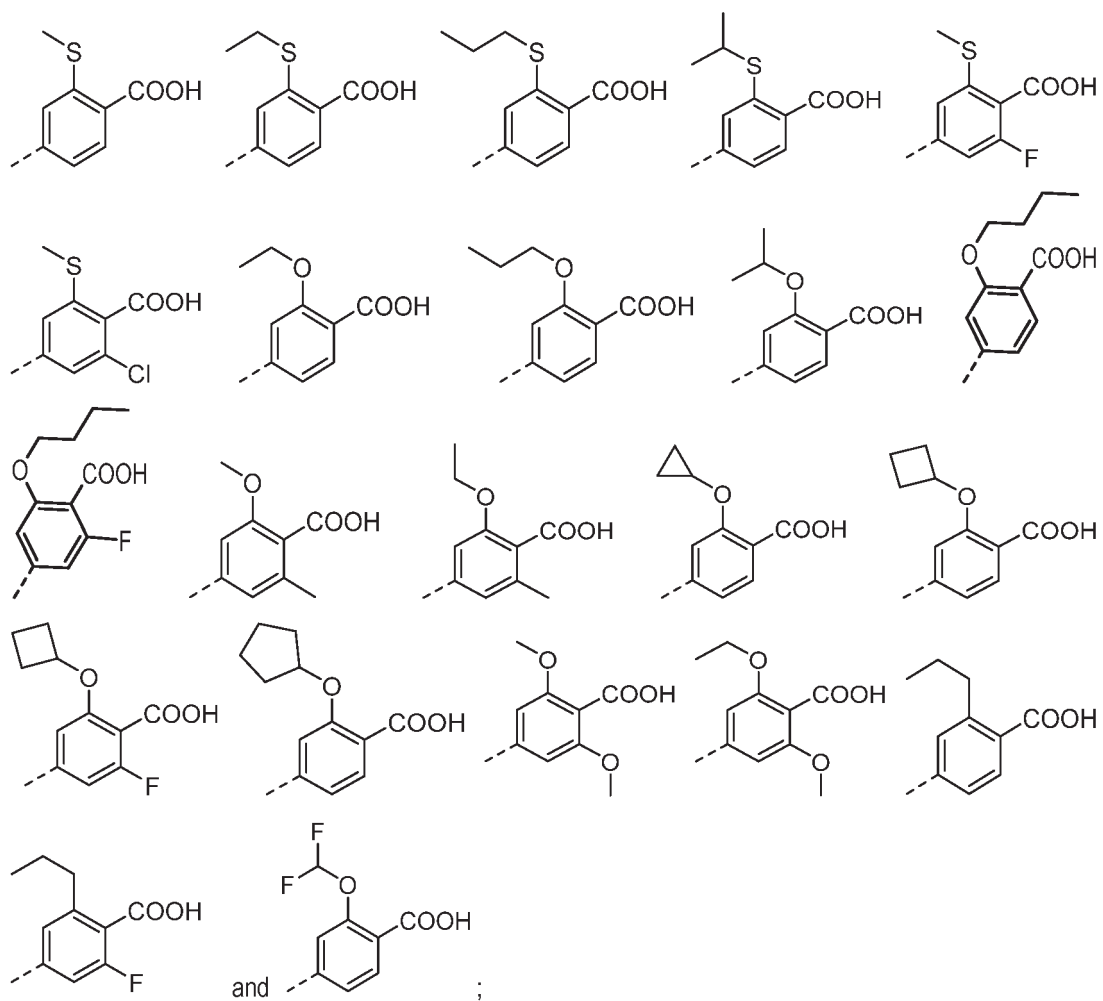
(i) **Ar<sup>1</sup>** represents a phenyl group selected from:



c)

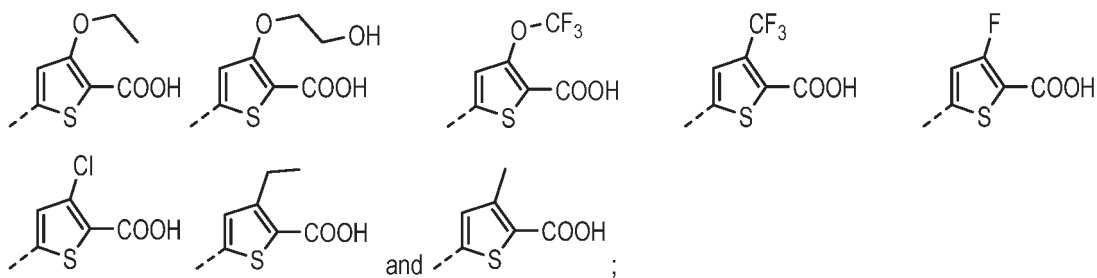


d)



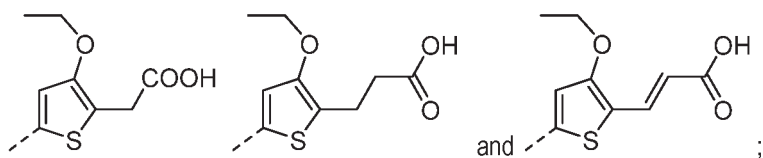
(ii) or **Ar<sup>1</sup>** represents a thiophenyl group selected from:

a)

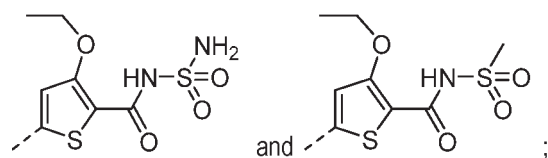


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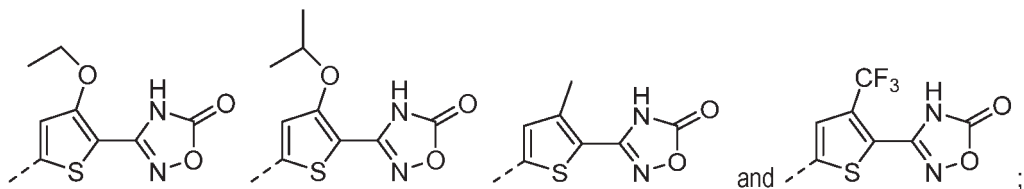
b)



c)

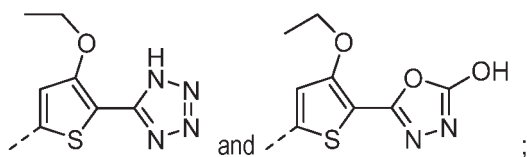


d)



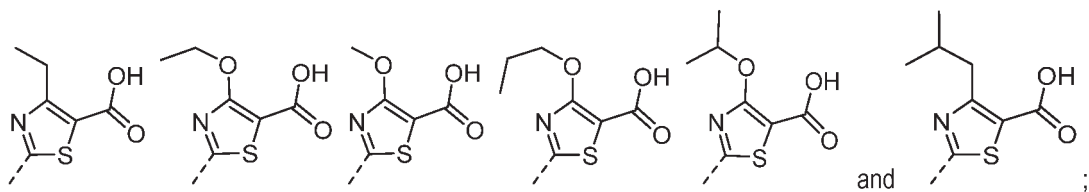
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e)



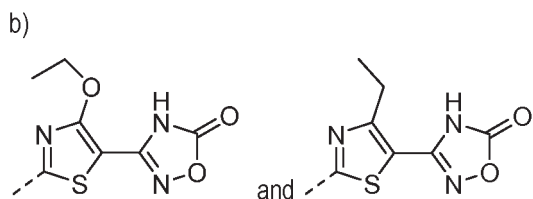
(iii) or **Ar<sup>1</sup>** represents a thiazolyl group selected from:

a)



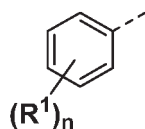
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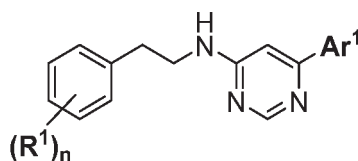
wherein in a sub-embodiment, **Ar<sup>1</sup>** especially is a phenyl group (in particular a di-substituted phenyl group), or a thiophenyl group, or a thiazolyl group, as defined herein above.

- 5 10) A second embodiment relates to compounds as defined in any one of embodiments 1) to 9), for use according to embodiment 1), wherein **R<sup>3</sup>** represents hydrogen.
- 11) Another embodiment relates to compounds as defined in any one of embodiments 1) to 9), for use according to embodiment 1), wherein **R<sup>3</sup>** represents methyl.
- 12) Another embodiment relates to compounds as defined in any one of embodiments 1) to 9), wherein the
- 10 characteristics defined for the fragment



according to embodiments 14), or 16) to 20) below apply *mutatis mutandis*.

- 13) Another embodiment relates to compounds as defined in any one of embodiments 1) to 9), wherein the characteristics defined for the substituent **Ar<sup>1</sup>** according to embodiments 14) or 15) below apply *mutatis mutandis*.
- 15 14) A third aspect of the invention relates to novel compounds of the formula (III)



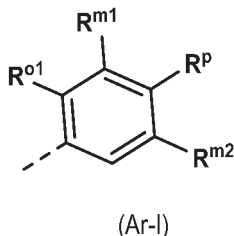
Formula (III)

wherein in compounds of the formula (III)

- (R<sup>1</sup>)<sub>n</sub>** represents one, two or three optional substituents on the phenyl ring (i.e. n represents the integer 0, 1, 2, or
- 20 3), wherein said substituents are independently selected from (C<sub>1-3</sub>)alkyl (especially methyl), (C<sub>1-3</sub>)alkoxy (especially methoxy), -S-(C<sub>1-3</sub>)alkyl (especially methylsulfanyl), halogen (especially fluoro, chloro, or bromo), (C<sub>1-3</sub>)fluoroalkyl (especially trifluoromethyl), (C<sub>1-3</sub>)fluoroalkoxy (especially trifluoromethoxy), cyano, hydroxy, nitro, -CO-O-(C<sub>1-3</sub>)alkyl (especially methoxycarbonyl), -NR<sup>N7</sup>R<sup>N8</sup> wherein **R<sup>N7</sup>** and **R<sup>N8</sup>** independently represent hydrogen or (C<sub>1-4</sub>)alkyl, or **R<sup>N7</sup>** and **R<sup>N8</sup>** together with the nitrogen to which they are attached form a 4- to 6-membered carbocyclic ring
- 25 (especially such group -NR<sup>N7</sup>R<sup>N8</sup> is methylamino, dimethylamino, pyrrolidin-1-yl);

and **Ar<sup>1</sup>** represents

- a phenyl group of the structure (Ar-I):



5 wherein

- **R<sup>p</sup>** represents

➤ **-X<sup>1</sup>-CO-R<sup>o1</sup>**, wherein

➤ **X<sup>1</sup>** represents a direct bond, (C<sub>1-3</sub>)alkylene (especially -CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-), -O-(C<sub>1-3</sub>)alkylene-\* (especially -O-CH<sub>2</sub>-, -O-CH(CH<sub>3</sub>)-, -O-C(CH<sub>3</sub>)<sub>2</sub>-, -O-CH<sub>2</sub>-CH<sub>2</sub>-\*), -NH-(C<sub>1-3</sub>)alkylene-\* (especially -NH-CH<sub>2</sub>-, -NH-CH(CH<sub>3</sub>)-, -CH=CH-, -NH-CO-\*, or (C<sub>3-5</sub>)cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-**R<sup>o1</sup>** group; and

➤ **R<sup>o1</sup>** represents

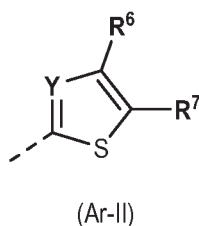
- -OH;
- -O-(C<sub>1-4</sub>)alkyl (especially ethoxy, methoxy);
- -NH-SO<sub>2</sub>-**R<sup>s3</sup>** wherein **R<sup>s3</sup>** represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;

[wherein in particular such group **-X<sup>1</sup>-CO-R<sup>o1</sup>** represents -COOH, -CO-O-CH<sub>3</sub>, -CO-O-C<sub>2</sub>H<sub>5</sub>, -O-CH<sub>2</sub>-COOH, -O-CH(CH<sub>3</sub>)-COOH, -O-C(CH<sub>3</sub>)<sub>2</sub>-COOH, -O-CH<sub>2</sub>-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -NH-CH(CH<sub>3</sub>)-COOH, -CO-NH-SO<sub>2</sub>-CH<sub>3</sub>, -CO-NH-SO<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>, -CO-NH-SO<sub>2</sub>-cyclopropyl, -CO-NH-SO<sub>2</sub>-C<sub>2</sub>H<sub>5</sub>, -CO-NH-SO<sub>2</sub>-NH<sub>2</sub>, -CH<sub>2</sub>-COOH, -CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -CH<sub>2</sub>-CO-O-C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-COOH, -CH=CH-COOH, -NH-CO-COOH, 1-carboxy-cyclopropan-1-yl];

➤ **HET<sup>1</sup>**, wherein **HET<sup>1</sup>** represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-hydroxy-[1,2,4]oxadiazol-3-yl), or 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl (encompassing its tautomeric form 3-hydroxy-[1,2,4]oxadiazol-5-yl); or

➤ **HET**, wherein **HET** represents a group selected from 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl, 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, 5-amino-[1,2,4]oxadiazol-3-yl; especially **HET** is 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, or 2-hydroxy-[1,3,4]oxadiazol-4-yl;

- **R<sup>m1</sup>** represents
  - (C<sub>1-6</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl);
  - (C<sub>1-4</sub>)alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy);
  - (C<sub>1-3</sub>)fluoroalkyl (especially trifluoromethyl);
  - 5 ➤ (C<sub>1-3</sub>)fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
  - halogen (especially fluoro or chloro);
  - (C<sub>3-6</sub>)cycloalkyl (especially cyclopropyl);
  - (C<sub>3-6</sub>)cycloalkyl-oxy (especially cyclopropyl-oxy, cyclobutyl-oxy, cyclopentyl-oxy);
  - hydroxy-(C<sub>2-4</sub>)alkoxy (especially 2-hydroxy-ethoxy); or
  - 10 ➤ -S-**R<sup>s2</sup>** wherein **R<sup>s2</sup>** represents (C<sub>1-4</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);
- **R<sup>m2</sup>** represents hydrogen, methyl, fluoro, or chloro; and
- **R<sup>o1</sup>** represents hydrogen;
- or **Ar<sup>1</sup>** represents a 5-membered heteroaryl group of the structure (Ar-II):



wherein

- **Y** represents CH or N;
- **R<sup>7</sup>** represents
  - 20 ➤ -**X<sup>1</sup>**-CO-**R<sup>o1</sup>**, wherein
    - **X<sup>1</sup>** represents a direct bond, (C<sub>1-3</sub>)alkylene (especially -CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-), -O-(C<sub>1-3</sub>)alkylene-\* (especially -O-CH<sub>2</sub>-, -O-CH(CH<sub>3</sub>)-, -O-C(CH<sub>3</sub>)<sub>2</sub>-, -O-CH<sub>2</sub>-CH<sub>2</sub>-), -NH-(C<sub>1-3</sub>)alkylene-\* (especially -NH-CH<sub>2</sub>-, -NH-CH(CH<sub>3</sub>)-, -CH=CH-, -NH-CO-, or (C<sub>3-5</sub>)cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-**R<sup>o1</sup>** group; and
    - 25 ➤ **R<sup>o1</sup>** represents
      - -OH;
      - -O-(C<sub>1-4</sub>)alkyl (especially ethoxy, methoxy);
      - -NH-SO<sub>2</sub>-**R<sup>s3</sup>** wherein **R<sup>s3</sup>** represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;

[wherein in particular such group -X<sup>1</sup>-CO-R<sup>01</sup> represents -COOH, -CO-O-CH<sub>3</sub>, -CO-O-C<sub>2</sub>H<sub>5</sub>, -O-CH<sub>2</sub>-COOH, -O-CH(CH<sub>3</sub>)-COOH, -O-C(CH<sub>3</sub>)<sub>2</sub>-COOH, -O-CH<sub>2</sub>-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-COOH, -NH-CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -NH-CH(CH<sub>3</sub>)-COOH, -CO-NH-SO<sub>2</sub>-CH<sub>3</sub>, -CO-NH-SO<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>, -CO-NH-SO<sub>2</sub>-cyclopropyl, -CO-NH-SO<sub>2</sub>-C<sub>2</sub>H<sub>5</sub>, -CO-NH-SO<sub>2</sub>-NH<sub>2</sub>, -CH<sub>2</sub>-COOH, -CH<sub>2</sub>-CO-O-CH<sub>3</sub>, -CH<sub>2</sub>-CO-O-C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-COOH, -CH=CH-COOH, -NH-CO-COOH, 1-carboxy-cyclopropan-1-yl];

5

- **HET<sup>1</sup>**, wherein **HET<sup>1</sup>** represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-hydroxy-[1,2,4]oxadiazol-3-yl), or 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl (encompassing its tautomeric form 3-hydroxy-[1,2,4]oxadiazol-5-yl); or
- **HET**, wherein **HET** represents a group selected from 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl, 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, 5-amino-[1,2,4]oxadiazol-3-yl; especially **HET** is 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, or 2-hydroxy-[1,3,4]oxadiazol-4-yl;

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- $\mathbf{R}^6$  represents

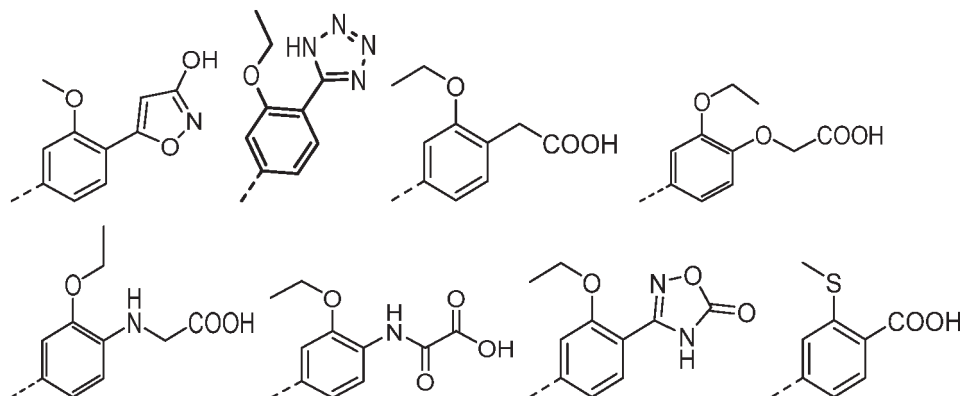
- (C<sub>1-6</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl);
- (C<sub>1-4</sub>)alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy);
- (C<sub>1-3</sub>)fluoroalkyl (especially trifluoromethyl);
- (C<sub>1-3</sub>)fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
- halogen (especially fluoro or chloro);
- (C<sub>3-6</sub>)cycloalkyl (especially cyclopropyl);
- (C<sub>3-6</sub>)cycloalkyl-oxy (especially cyclopropyl-oxy, cyclobutyl-oxy, cyclopentyl-oxy);
- hydroxy-(C<sub>2-4</sub>)alkoxy (especially 2-hydroxy-ethoxy); or
- -S-R<sup>S2</sup> wherein R<sup>S2</sup> represents (C<sub>1-4</sub>)alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl).

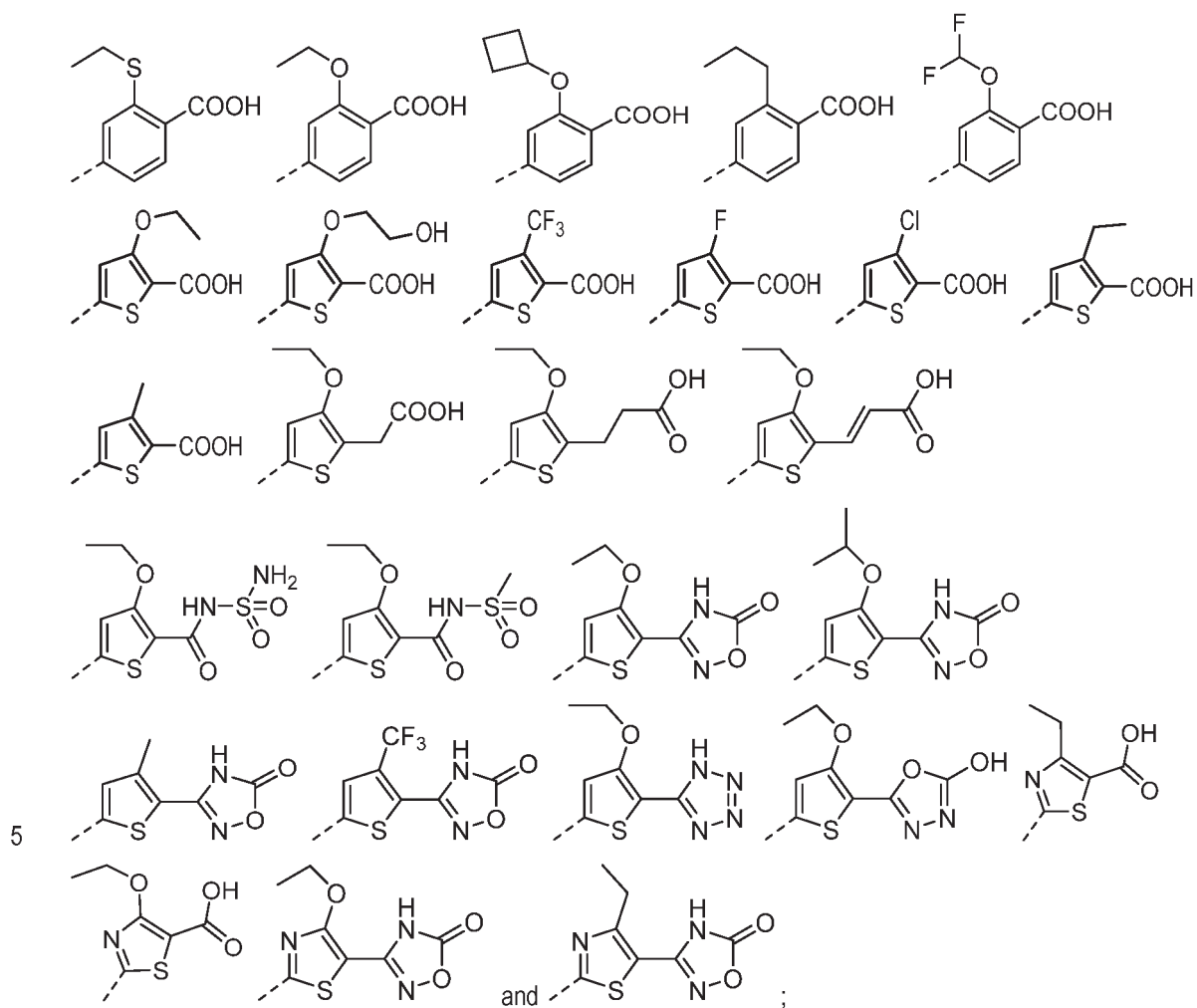
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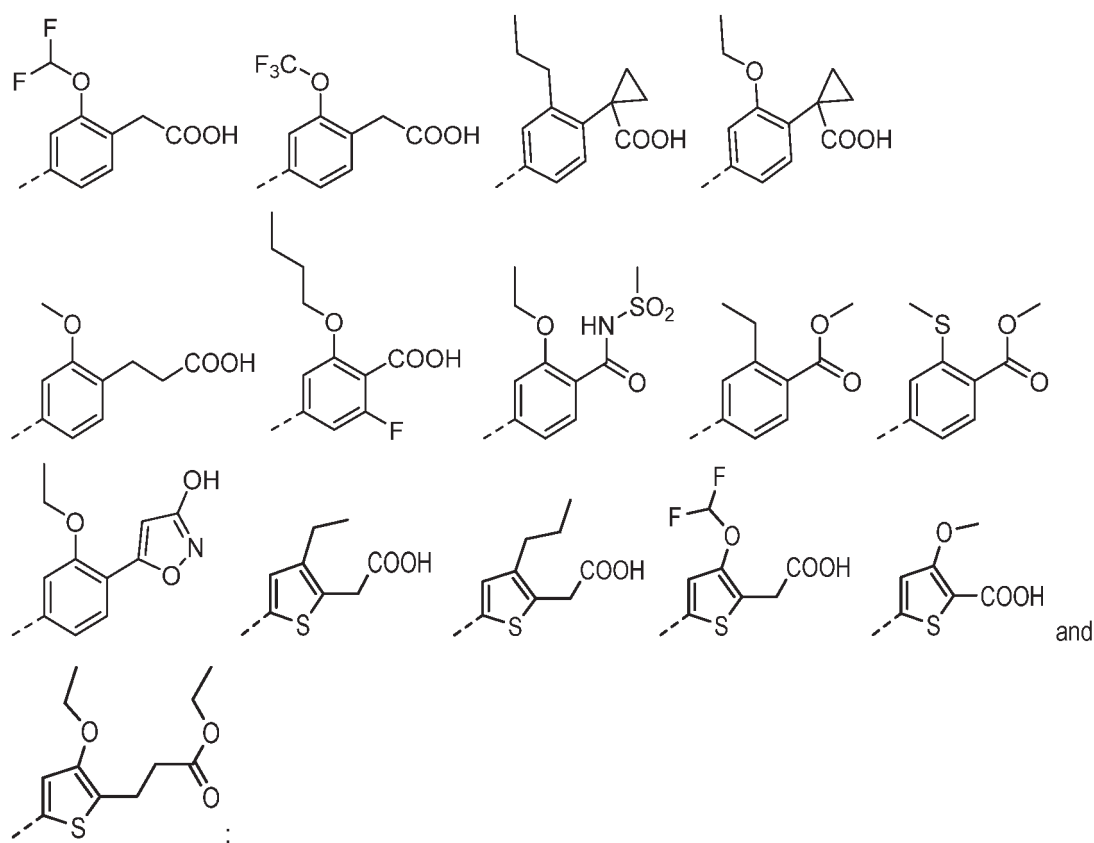
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15) Another embodiment relates to compounds as defined in any one of embodiments 1) to 13), for use according to embodiment 1), and to compounds according to embodiment 14), wherein **Ar<sup>1</sup>** represents a group selected from A)

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5 wherein each of the groups A) and B) forms a particular sub-embodiment.

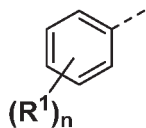
16) Another embodiment relates to compounds as defined in any one of embodiments 1) to 13), for use according to embodiment 1), and to compounds according to embodiments 14) or 15), wherein

(R<sup>1</sup>)<sub>n</sub> represents one, two or three substituents on the phenyl ring (i.e. n represents the integer 1, 2, or 3), wherein said substituents are independently selected from (C<sub>1-3</sub>)alkyl (especially methyl), (C<sub>1-3</sub>)alkoxy (especially methoxy, ethoxy, n-propoxy), -S-(C<sub>1-3</sub>)alkyl (especially methylsulfanyl), halogen (especially fluoro, chloro, or bromo), (C<sub>1-3</sub>)fluoroalkyl (especially trifluoromethyl), (C<sub>1-3</sub>)fluoroalkoxy (especially trifluoromethoxy), cyano, hydroxy, nitro, -CO-O-(C<sub>1-3</sub>)alkyl (especially methoxycarbonyl), -NR<sup>N7</sup>R<sup>N8</sup> wherein R<sup>N7</sup> and R<sup>N8</sup> independently represent hydrogen or (C<sub>1-4</sub>)alkyl, or R<sup>N7</sup> and R<sup>N8</sup> together with the nitrogen to which they are attached form a 4- to 6-membered carbocyclic ring (especially such group -NR<sup>N7</sup>R<sup>N8</sup> is methylamino, dimethylamino, pyrrolidin-1-yl).

15 17) Another embodiment relates to compounds as defined in any one of embodiments 1) to 13), for use according to embodiment 1), and to compounds according to embodiments 14) or 15), wherein

(R<sup>1</sup>)<sub>n</sub> represents one, two or three substituents on the phenyl ring (i.e. n represents the integer 1, 2, or 3), wherein said substituents are independently selected from (C<sub>1-3</sub>)alkyl (especially methyl), (C<sub>1-3</sub>)alkoxy (especially methoxy, ethoxy, n-propoxy), -S-(C<sub>1-3</sub>)alkyl (especially methylsulfanyl), halogen (especially fluoro, chloro, or bromo), (C<sub>1-3</sub>)fluoroalkyl (especially trifluoromethyl), (C<sub>1-3</sub>)fluoroalkoxy (especially trifluoromethoxy), cyano, or hydroxy.

18) Another embodiment relates to compounds as defined in any one of embodiments 1) to 13), for use according to embodiment 1), and to compounds according to embodiments 14) or 15), wherein the fragment



represents a group selected from

5 A)

phenyl, 4-bromo-phenyl, 3-bromo-phenyl, 2-bromo-phenyl, 4-chloro-phenyl, 3-chloro-phenyl, 2-chloro-phenyl, 4-fluoro-phenyl, 3-fluoro-phenyl, 2-fluoro-phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 4-hydroxy-phenyl, 4-methoxy-phenyl, 3-methoxy-phenyl, 2-methoxy-phenyl, 4-bromo-2-methyl-phenyl, 4-bromo-3-methyl-phenyl, 2,4-dimethyl-phenyl, 3,4-dimethyl-phenyl, 2,4-dichloro-phenyl, 3,4-dichloro-phenyl, 2,6-difluoro-phenyl, 4-bromo-3-chloro-phenyl, 4-bromo-2-chloro-phenyl, 2-bromo-5-chloro-phenyl, 4-bromo-3-fluoro-phenyl, 4-bromo-2-fluoro-phenyl, 4-chloro-2,6-difluoro-phenyl, 3-chloro-2,6-difluoro-phenyl, 2-chloro-3,6-difluoro-phenyl, 2,4,6-trifluoro-phenyl, 4-bromo-2,5-difluoro-phenyl, 4-bromo-2,6-difluoro-phenyl, 4-bromo-2-ethyl-phenyl, 4-bromo-5-fluoro-2-methyl-phenyl, 4-bromo-2-fluoro-5-methyl-phenyl, 3-hydroxy-4-methoxy-phenyl, 4-hydroxy-3-methoxy-phenyl, 3-chloro-4-methoxy-phenyl, 4-bromo-3-methoxy-phenyl, 3-bromo-4-methoxy-phenyl, 2-fluoro-4-methoxy-phenyl, 4-bromo-2-methoxy-phenyl, 5-bromo-2-methoxy-phenyl, 2-ethoxy-phenyl, 5-chloro-2-cyano-phenyl, 4-chloro-2-cyano-phenyl, 4-fluoro-2-cyano-phenyl, 4-chloro-2-methylamino-phenyl, 4-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 2-trifluoromethyl-phenyl, 2,5-dimethoxy-phenyl, 2,3-dimethoxy-phenyl, 2,4-dimethoxy-phenyl, 3,5-dimethoxy-phenyl, 3-(methoxy-carbonyl)-phenyl, 2-methoxy-5-(methylsulfanyl)-phenyl, 2-methoxy-4-(methylsulfanyl)-phenyl, 4-fluoro-2-ethoxy-phenyl, 4-bromo-2-ethoxy-phenyl, 2-ethyl-4-methoxy-phenyl, 2-methoxy-4,5-dimethyl-phenyl, 4-chloro-6-fluoro-2-methoxy-phenyl, 4-bromo-6-fluoro-2-methoxy-phenyl, 4-dimethylamino-2-fluoro-phenyl, 2-dimethylamino-4-bromo-phenyl, 4-chloro-2-nitro-phenyl, 2-fluoro-4-trifluoromethyl-phenyl, 4-bromo-2,6-dimethoxy-phenyl, 4-bromo-2-*n*-propoxy-phenyl, 4-bromo-2-trifluoromethoxy-phenyl, 4-bromo-2-(pyrrolidin-1-yl)-phenyl, and 2-ethoxy-4-trifluoromethyl-phenyl;

25 or, in addition to the above-listed, said fragment represents a group selected from

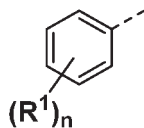
B)

3,4-dichloro-2-methyl-phenyl, 5-bromo-2-methylsulfanyl-phenyl, 2-fluoro-6-methoxy-phenyl, 2-methoxy-6-methyl-phenyl, 2-methoxy-4,6-dimethyl-phenyl, 4,5-difluoro-2-methoxy-phenyl, 2,6-difluoro-4-methoxy-phenyl, 4-difluoromethoxy-2-methoxy-phenyl, 4-difluoromethyl-5-fluoro-2-methoxy-phenyl, 2-methoxy-4-trifluoromethyl-phenyl, 4-difluoromethyl-2-methoxy-5-methyl-phenyl, 2-methoxy-4-trifluoromethoxy-phenyl, 2-fluoro-6-methoxy-4-trifluoromethyl-phenyl, 5-chloro-2-methoxy-4-trifluoromethyl-phenyl, and 2-difluoromethoxy-4-trifluoromethyl-phenyl;

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



19) Another embodiment relates to compounds as defined in any one of embodiments 1) to 13), for use according to embodiment 1), and to compounds according to embodiments 14) or 15), wherein the fragment



represents a group selected from 4-bromo-phenyl, 4-chloro-phenyl, 4-methyl-phenyl, 2,4-dichloro-phenyl, 3,4-dichloro-phenyl, 2,6-difluoro-phenyl, 4-bromo-3-chloro-phenyl, 4-bromo-2-chloro-phenyl, 2-bromo-5-chloro-phenyl, 4-bromo-2-fluoro-phenyl, 4-chloro-2,6-difluoro-phenyl, 3-chloro-2,6-difluoro-phenyl, 2-chloro-3,6-difluoro-phenyl, 2,4,6-trifluoro-phenyl, 4-bromo-2,5-difluoro-phenyl, 4-bromo-2,6-difluoro-phenyl, 4-bromo-2-fluoro-5-methyl-phenyl, 4-hydroxy-3-methoxy-phenyl, 4-bromo-3-methoxy-phenyl, 2-fluoro-4-methoxy-phenyl, 4-bromo-2-methoxy-phenyl, 5-bromo-2-methoxy-phenyl, 2,5-dimethoxy-phenyl, 2,3-dimethoxy-phenyl, 2,4-dimethoxy-phenyl, 2-methoxy-4-(methylsulfanyl)-phenyl, 4-bromo-2-ethoxy-phenyl, 2-ethyl-4-methoxy-phenyl, 2-methoxy-4,5-dimethyl-phenyl, 4-chloro-6-fluoro-2-methoxy-phenyl, 4-bromo-2,6-dimethoxy-phenyl, 4-bromo-2-*n*-propoxy-phenyl, and 2-ethoxy-4-trifluoromethyl-phenyl.

20) The invention, thus, relates to compounds of the formula (I) as defined in embodiment 1) for use according to embodiment 1), or to such compounds further limited by the characteristics of any one of embodiments 2) to 19), under consideration of their respective dependencies; to pharmaceutically acceptable salts thereof; and to the use of such compounds according to embodiment 1), and as further described herein below. For avoidance of any doubt, especially the following embodiments relating to the compounds of formula (I) are thus possible and intended and herewith specifically disclosed in individualized form:

1, 4+1, 5+4+1, 6+4+1, 7+4+1, 8+4+1, 9+4+1, 10+4+1, 10+5+4+1, 10+6+4+1, 10+7+4+1, 10+8+4+1, 10+9+4+1, 16+4+1, 16+5+4+1, 16+6+4+1, 16+7+4+1, 16+8+4+1, 16+9+4+1, 16+10+4+1, 16+10+5+4+1, 16+10+6+4+1, 16+10+7+4+1, 16+10+8+4+1, 16+10+9+4+1, 17+4+1, 17+5+4+1, 17+6+4+1, 17+7+4+1, 17+8+4+1, 17+9+4+1, 17+10+4+1, 17+10+5+4+1, 17+10+6+4+1, 17+10+7+4+1, 17+10+8+4+1, 17+10+9+4+1, 18+4+1, 18+5+4+1, 18+6+4+1, 18+7+4+1, 18+8+4+1, 18+9+4+1, 18+10+4+1, 18+10+5+4+1, 18+10+6+4+1, 18+10+7+4+1, 18+10+8+4+1, 18+10+9+4+1, 19+4+1, 19+5+4+1, 19+6+4+1, 19+7+4+1, 19+8+4+1, 19+9+4+1, 19+10+4+1, 19+10+5+4+1, 19+10+6+4+1, 19+10+7+4+1, 19+10+8+4+1, 19+10+9+4+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, “19+9+4+1” for example refers to embodiment 19) depending on embodiment 9), depending on embodiment 4), depending on embodiment 1), i.e. embodiment “19+9+4+1” corresponds to the compounds of formula (I) as defined in embodiment 1) for use according to embodiment 1), further limited by all the structural features of the embodiments 4), 9), and 19).

21) The invention, thus, further relates to compounds of the formula (III) as defined in embodiment 14), or to such compounds further limited by the characteristics of any one of embodiments 15) to 19), under consideration of their

respective dependencies; to pharmaceutically acceptable salts thereof; and to the use of such compounds as medicaments especially in the prevention / prophylaxis or treatment of diseases which respond to the blockage of the EP2 receptors and/or the EP4 receptors as described herein below. For avoidance of any doubt, especially the following embodiments relating to the compounds of formula (III) are thus possible and intended and herewith specifically disclosed in individualized form:

14, 15+14, 16+14, 16+15+14, 17+14, 17+15+14, 18+14, 18+15+14, 19+14, 19+15+14.

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, "19+15+14" for example refers to embodiment 19) depending on embodiment 15), depending on embodiment 14), i.e. embodiment "19+15+14" corresponds to the compounds of formula (III) according to embodiment 14) further limited by all the features of the embodiments 15), and 19).

22) Another embodiment relates to compounds of formula (I) as defined in embodiment 1) for use according to embodiment 1) which are selected from the following compounds:

5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;  
2-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acetamide;  
2-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-propionic acid;  
3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol].

23) In addition to the compounds listed in embodiment 22), further compounds of formula (I) as defined in embodiment 1) for use according to embodiment 1) are selected from the following compounds:

3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1-ethyl-1H-pyrrol-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1-ethyl-1H-pyrrol-2-yl)-[1,2,4]oxadiazol-5-ol];  
3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methoxy-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methoxy-phenyl)-[1,2,4]oxadiazol-5-ol];  
5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-1H-pyrrole-2-carboxylic acid;  
5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-cyclopropyl-1H-pyrrole-2-carboxylic acid; and  
3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-pyridin-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-pyridin-2-yl)-[1,2,4]oxadiazol-5-ol].

24) Another embodiment relates to compounds of formula (II) as defined in embodiment 4) which are selected from the following compounds:

2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1H-indole-4-carboxylic acid;

3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazole-5(4H)-thione  
 5 [tautomeric form: 3-(5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)-[1,2,4]oxadiazole-5-thiol].

25) In addition to the compounds listed in embodiment 24), further compounds of formula (II) according to embodiment 4), are selected from the following compounds:

2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1H-indole-5-carboxylic acid;

10 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylamino-benzamide;

4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethylamino-benzamide;

4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylamino-benzoic acid;

3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5(4H)-one

[tautomeric form: 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5-  
 15 ol];

N-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-formamide;

3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-4-hydroxy-cyclobut-3-ene-1,2-dione;

4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2,6-dimethyl-phenol;

[2-(4-Bromo-2,6-difluoro-phenyl)-ethyl]-[6-(1H-indol-5-yl)-pyrimidin-4-yl]-amine;

20 7-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1-methyl-3,4-dihydro-1H-quinazolin-2-one;

2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1H-indole-7-carboxylic acid;

[2-(4-Bromo-2,6-difluoro-phenyl)-ethyl]-[6-(1H-indazol-5-yl)-pyrimidin-4-yl]-amine;

4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-ethyl)-2-methylamino-benzamide;

4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-N-(2-methoxy-ethyl)-2-methylamino-benzamide;

25 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid amide;

5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethyl-thiophene-2-carboxylic acid amide;

3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzyl)-[1,2,4]oxadiazol-5(4H)-one

[tautomeric form: 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzyl)-  
 [1,2,4]oxadiazol-5-ol];

30 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazole-5(4H)-thione [tautomeric form: 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazole-5-thiol];

5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-chloro-3-ethoxy-thiophene-2-carboxylic acid amide;

- 1-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-1,4-dihydro-tetrazol-5-one [tautomeric form: 1-(5-{6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl}-3-ethoxythiophen-2-yl)-1H-tetrazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazole-5(4H)-thione [tautomeric form: 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazole-5-thiol];
- 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylamino-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylamino-phenyl)-[1,2,4]oxadiazol-5-ol];
- 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzamide;
- 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-2-methyl-propyl)-2-propyl-benzamide;
- 2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1H-indole-6-carboxylic acid;
- 6-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3H-benzooxazol-2-one;
- 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methoxy-benzamide;
- 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzamide; and
- 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-ethyl)-2-propyl-benzamide.
- 26) Another embodiment relates to compounds of formula (III) according to embodiment 14), which are selected from the following compounds:
- 3-Fluoro-5-{6-[2-(p-tolyl-ethylamino)-pyrimidin-4-yl]-thiophene-2-carboxylic acid};
- 4-{6-[2-(2-Methoxy-4-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
- 4-{6-[2-(2-Methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
- 3-Ethoxy-5-{6-[2-(2-methoxy-4-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;
- 3-Ethoxy-5-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;
- 2-Ethoxy-4-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
- 3-(4-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-((4-bromophenethyl)amino)pyrimidin-4-yl}-2-ethoxyphenyl)-[1,2,4]oxadiazol-5-ol];
- 4-{6-[2-(3,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
- 4-{6-[2-(4-Bromo-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
- [2-(4-Bromo-2,6-difluoro-phenyl)-ethyl]-{6-[3-ethoxy-4-(1H-tetrazol-5-yl)-phenyl]-pyrimidin-4-yl}-amine;
- N-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-oxalamic acid;
- 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-chloro-3-ethoxy-thiophene-2-carboxylic acid;
- 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid;
- 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethyl-thiophene-2-carboxylic acid;
- 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-chloro-thiophene-2-carboxylic acid;

- 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-(2-hydroxy-ethoxy)-thiophene-2-carboxylic acid;
- 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
- 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-isobutyl-benzoic acid;
- 5 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-difluoromethoxy-benzoic acid;
- 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-propionic acid;
- 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-propionic acid;
- (E)-3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-acrylic acid;
- (5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-acetic acid;
- 10 (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid;
- 5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;
- 3-Ethoxy-5-{6-[2-(4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;
- 3-Ethoxy-5-{6-[2-(3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;
- 5-[6-(2-p-Tolyl-ethylamino)-pyrimidin-4-yl]-3-trifluoromethyl-thiophene-2-carboxylic acid;
- 15 5-{6-[2-(4-Chloro-2-nitro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;
- 5-{6-[2-(2,4-Dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;
- 5-{6-[2-(3,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;
- 5-{6-[2-(5-Bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;
- 5-{6-[2-(2,5-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;
- 20 5-{6-[2-(2,4-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;
- 5-{6-[2-(4-Chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;
- 3-(5-{6-[2-(4-Bromo-2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 25 3-(5-{6-[2-(4-Chloro-2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-chloro-2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 30 pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-2,6-dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-2-propoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-propoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 35 [1,2,4]oxadiazol-5-ol];

- 3-(3-Ethoxy-5-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(3-Ethoxy-5-{6-[2-(2-fluoro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2-fluoro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(2-Bromo-5-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(2-bromo-5-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(3-Ethoxy-5-{6-[2-(2-ethoxy-4-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2-ethoxy-4-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 5-Chloro-2-(2-((6-(4-ethoxy-5-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)thiophen-2-yl)pyrimidin-4-yl)amino)ethyl)benzonitrile [tautomeric form: 5-chloro-2-(2-{6-[4-ethoxy-5-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-thiophen-2-yl]-pyrimidin-4-ylamino}-ethyl)-benzonitrile];
- 2-(2-((6-(4-Ethoxy-5-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)thiophen-2-yl)pyrimidin-4-yl)amino)ethyl)-5-fluorobenzonitrile [tautomeric form: 2-(2-{6-[4-ethoxy-5-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-thiophen-2-yl]-pyrimidin-4-ylamino}-ethyl)-5-fluoro-benzonitrile];
- 3-(5-{6-[2-(3-Chloro-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(3-chloro-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(3-Ethoxy-5-{6-[2-(2-ethyl-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-Ethoxy-5-{6-[2-(2-ethyl-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(2-Chloro-3,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(2-chloro-3,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(3-Ethoxy-5-{6-[2-(2,4,6-trifluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2,4,6-trifluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(3-Ethoxy-5-{6-[2-(2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(2,6-Difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];



- 3-(5-{6-[2-(4-Chloro-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-chloro-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-3-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-3-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-2,5-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,5-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-3-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-3-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-5-fluoro-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-5-fluoro-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-3-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-3-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-2-fluoro-5-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-fluoro-5-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(2,4-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(2,4-dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(3-Ethoxy-5-{6-[2-(4-hydroxy-3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(4-hydroxy-3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(2,3-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(2,3-dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];



- 3-(5-{6-[2-(5-Bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(5-bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(3,4-Dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one  
5 [tautomeric form: 3-(5-{6-[2-(3,4-dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(2,4-Dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one  
[tautomeric form: 3-(5-{6-[2-(2,4-dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 10 3-(5-{6-[2-(4-Bromo-2-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-  
15 [1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-  
20 [1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 25 [2-(4-Bromo-phenyl)-ethyl]-{6-[4-ethoxy-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-pyrimidin-4-yl}-amine;
- 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 30 2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethoxy-thiazole-5-carboxylic acid;
- 2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethyl-thiazole-5-carboxylic acid;
- 3-(2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethoxy-thiazol-5-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethoxy-thiazol-5-yl)-  
35 [1,2,4]oxadiazol-5-ol];

3-(2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethyl-thiazol-5-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(2-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethyl-thiazol-5-yl)-[1,2,4]oxadiazol-5-ol];

5 5-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,3,4]oxadiazol-2-ol [tautomeric form: 5-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,3,4]-oxadiazol-2(3H)-one];

N-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carbonyl)-methanesulfonamide;

5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxy-N-sulfamoylthiophene-2-carboxamide;

10 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-2-methyl-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-2-methyl-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];

3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-2-methyl-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-phenyl)-ethylamino]-2-methyl-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]; and

15 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-isopropoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-isopropoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol].

27) In addition to the compounds listed in embodiment 26), further compounds of formula (III) according to  
20 embodiment 14), are selected from the following compounds:

4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-(2-hydroxy-ethoxy)-benzoic acid;

4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid;

4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid;

4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethylsulfanyl-benzoic acid;

25 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-benzoic acid;

4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-butoxy-benzoic acid;

4-{6-[2-(4-Bromo-2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

5-{6-[2-(2,6-Difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethyl-thiophene-2-carboxylic acid; and

3-Ethoxy-5-{6-[2-(2-o-tolyl-ethylamino)-pyrimidin-4-yl]-thiophene-2-carboxylic acid.

28) In addition to the compounds listed in embodiments 26) and 27), further compounds of formula (III) according  
30 to embodiment 14), are selected from the following compounds:

3-Fluoro-5-{6-[2-(4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

3-Ethoxy-5-{6-[2-(4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

5-{6-[2-(2,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophene-2-carboxylic acid;

35 5-{6-[2-(3-Bromo-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

3-Ethoxy-5-{6-[2-(3-methoxycarbonyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

- 3-(5-{6-[2-(3,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(3,4-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(3-Ethoxy-5-{6-[2-(2-fluoro-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2-fluoro-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(3-Ethoxy-5-{6-[2-(3-hydroxy-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(3-hydroxy-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
- 3-(5-{6-[2-(3-Chloro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(3-chloro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]; and
- 3-(5-{6-[2-(4-Dimethylamino-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-dimethylamino-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol].
- 29) In addition to the compounds listed in embodiments 26) to 28), further compounds of formula (III) according to embodiment 14), are selected from the following compounds:
- 5-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-isoxazol-3-ol [tautomeric form: 5-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-isoxazol-3(2H)-one];
- 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methoxy-thiophene-2-carboxylic acid;
- 5-{6-[2-(3,4-Dichloro-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;
- 2-Cyclobutoxy-4-{6-[2-(4-difluoromethyl-5-fluoro-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
- 5-{6-[2-(4-Difluoromethyl-5-fluoro-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;
- 2-Cyclobutoxy-4-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
- 3-Ethoxy-5-{6-[2-(2-methoxy-4,6-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;
- 2-Ethoxy-4-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid ;
- 4-{6-[2-(2-Ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
- (2-Ethoxy-4-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid;
- 3-Ethoxy-5-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;
- 5-{6-[2-(4-Difluoromethoxy-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;
- 3-Ethoxy-5-{6-[2-(2-fluoro-6-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;
- 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazol-5-ol];

(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-chloro-6-ethyl-phenyl)-acetic acid;  
 (5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethyl-thiophen-2-yl)-acetic acid;  
 5-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-isoxazol-3-ol [tautomeric form: 5-(4-{6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl}-2-ethoxyphenyl)isoxazol-3(2H)-one];  
 5 3-(5-{6-[2-(5-Bromo-2-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(5-bromo-2-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];  
 (5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-propyl-thiophen-2-yl)-acetic acid; and  
 (5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-difluoromethoxy-thiophen-2-yl)-acetic acid.

10 30) In addition to the compounds listed in embodiments 26) to 29), further compounds of formula (III) according to embodiment 14), are selected from the following compounds:

4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-butoxy-6-fluoro-benzoic acid;  
 3-Ethoxy-5-{6-[2-(2-methoxy-6-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;  
 4-{6-[2-(2-Ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid;  
 15 4-{6-[2-(4-Difluoromethoxy-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid,  
 4-{6-[2-(2,6-Difluoro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;  
 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-isobutoxy-benzoic acid;  
 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-cyclopropoxy-benzoic acid; and  
 N-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoyl)-methanesulfonamide.

20 31) In addition to the compounds listed in embodiments 26) to 30), further compounds of formula (III) according to embodiment 14), are selected from the following compounds:

5-{6-[2-(5-Chloro-2-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;  
 3-Ethoxy-5-{6-[2-(2-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;  
 25 3-Ethoxy-5-{6-[2-(2-methoxy-4-trifluoromethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;  
 5-{6-[2-(2-Difluoromethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid; and  
 3-(2-Ethoxy-4-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-propionic acid.

30 The compounds of formulae (I), (II), or (III) according to embodiments 1) to 31) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral (such especially oral e.g. in form of a tablet or a capsule) or parenteral administration (including topical application or inhalation).

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5,  
 35 "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds

of formulae (I), (II), or (III) 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.

5 The present invention also relates to a method for the prevention / prophylaxis or treatment of a disease or disorder mentioned herein comprising administering to a subject a pharmaceutically active amount of a compound of formulae (I), (II), or (III) according to embodiments 1) to 31).

In a preferred embodiment of the invention, the administered amount is comprised between 1 mg and 2000 mg per day, particularly between 5 mg and 1000 mg per day, more particularly between 25 mg and 500 mg per day, especially between 50 mg and 200 mg per day.

10 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.

15 Unless used regarding temperatures, the term "about" placed before a numerical value "X" refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term "about" placed before a temperature "Y" refers in the current application to an interval extending from the temperature Y minus 10 °C to Y plus 10 °C, and preferably to an interval extending from Y minus 5 °C to Y plus 5 °C.

20 For avoidance of any doubt, if compounds are described as useful for the prevention / prophylaxis or treatment of certain diseases, such compounds are likewise suitable for use in the preparation of a medicament for the prevention / prophylaxis or treatment of said diseases. Likewise, such compounds are also suitable in a method for the prevention / prophylaxis or treatment of such diseases, comprising administering to a subject (mammal, especially human) in need thereof, an effective amount of such compound.

25 The compounds of formulae (I), (II), or (III) according to embodiments 1) to 31) are useful for the prevention / prophylaxis or treatment of disorders relating to the EP2 and/or EP4 receptors.

Certain compounds of formulae (I), (II), or (III) according to embodiments 1) to 31) exhibit their biological activity as modulators of the prostaglandin 2 receptors EP2 and/or EP4 in a biological environment, (i.e. in the presence of one or more enzymes capable of breaking a covalent bond linked to a carbonyl group such as an amidase, an esterase or any suitable equivalent thereof capable of removing a prodrug group from a carboxylic acid group.

30 Diseases or disorders relating to the EP2 and/or EP4 receptors are especially

- cancer (notably melanoma including metastatic melanoma; lung cancer including non-small cell lung cancer; bladder cancer including urinary bladder cancer, urothelial cell carcinoma; renal carcinomas including renal cell carcinoma, metastatic renal cell carcinoma, metastatic renal clear cell carcinoma; gastro-intestinal cancers including colorectal cancer, metastatic colorectal cancer, familial adenomatous

polyposis (FAP), oesophageal cancer, gastric cancer, gallbladder cancer, cholangiocarcinoma, hepatocellular carcinoma, and pancreatic cancer such as pancreatic adenocarcinoma or pancreatic ductal carcinoma; endometrial cancer; ovarian cancer; cervical cancer; neuroblastoma; prostate cancer including castrate-resistant prostate cancer; brain tumors including brain metastases, malignant gliomas, glioblastoma multiforme, medulloblastoma, meningiomas; breast cancer including triple negative breast carcinoma; oral tumors; nasopharyngeal tumors; thoracic cancer; head and neck cancer; leukemias including acute myeloid leukemia, adult T-cell leukemia; carcinomas; adenocarcinomas; thyroid carcinoma including papillary thyroid carcinoma; choriocarcinoma; Ewing's sarcoma; osteosarcoma; rhabdomyosarcoma; Kaposi's sarcoma; lymphoma including Burkitt's lymphoma, Hodgkin's lymphoma, MALT lymphoma; multiple myelomas; and virally induced tumors; especially melanoma; lung cancer; bladder cancer; renal carcinomas; gastro-intestinal cancers; endometrial cancer; ovarian cancer; cervical cancer; and neuroblastoma);

as well as further diseases or disorders relating to the EP2 and/or EP4 receptors such as:

- pain (notably inflammatory pain and painful menstruation);
- endometriosis;
- autosomal dominant polycystic kidney disease;
- acute ischemic syndromes in atherosclerotic patients;
- pneumonia; and
- neurodegenerative diseases including amyotrophic lateral sclerosis, stroke; Parkinson disease, Alzheimer's disease and HIV associated dementia;
- and EP2 and/or EP4 antagonists may further be used to control female fertility.

The compounds of formulae (I), (II), or (III) according to any one of embodiments 1) to 31) are in particular useful as therapeutic agents for the prevention / prophylaxis or treatment of a cancer. They can be used as single therapeutic agents or in combination with one or more chemotherapy agents and / or radiotherapy and / or targeted therapy. Such combined treatment may be effected simultaneously, separately, or over a period of time.

The invention, thus, also relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier material, and:

- a compound of formulae (I), (II), or (III) according to any one of embodiments 1) to 31);
- and one or more cytotoxic chemotherapy agents.

The invention, thus, further relates to a kit comprising

- a pharmaceutical composition, said composition comprising a pharmaceutically acceptable carrier material, and:
  - a compound of formulae (I), (II), or (III) according to any one of embodiments 1) to 31);
- and instructions how to use said pharmaceutical composition for the prevention / prophylaxis or the treatment of a cancer, in combination with chemotherapy and / or radiotherapy and / or targeted therapy.



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

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 inhibit angiogenesis, the growth and formation of new blood vessels in the tumor; 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 (Zelenay et al., **2015**, Cell 162, 1-14; Yongkui Li et al., Oncoimmunology 2016, 5(2):e1074374).

When used in combination with the compounds of formulae (I), (II), or (III), the term "targeted therapy" especially refers to agents such as:

- a) Epidermal growth factor receptor (EGFR) inhibitors or blocking antibodies (for example Gefitinib, Erlotinib, Afatinib, Icotinib, Lapatinib, Panitumumab, Zalutumumab, Nimotuzumab, Matuzumab and Cetuximab);
- b) RAS/RAF/MEK pathway inhibitors (for example Vemurafenib, Sorafenib, Dabrafenib, GDC-0879, PLX-4720, LGX818, RG7304, Trametinib (GSK1120212), Cobimetinib (GDC-0973/XL518), Binimetinib (MEK162, ARRY-162), Selumetinib (AZD6244));
- c) Aromatase inhibitors (for example Exemestane, Letrozole, Anastrozole, Vorozole, Formestane, Fadrozole);
- d) Angiogenesis inhibitors, especially VEGF signalling inhibitors such as Bevacuzimab (Avastin), Ramucirumab, Sorafenib or Axitinib;
- e) 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; fusion proteins targeting PD-1 such as AMP-224; small molecule anti-PD1 agents such as for example compounds disclosed in WO2015/033299, WO2015/044900 and WO2015/034820; anti-PD1L antibodies, such as BMS-936559, atezolizumab (MPDL3280A, RG7446), MEDI4736, avelumab (MSB0010718C), durvalumab (MEDI4736); anti-PDL2 antibodies, such as AMP224; anti-CTLA-4 antibodies, such as ipilimumab, tremilumab; anti-Lymphocyte-activation gene 3 (LAG-3) antibodies, such as BMS-986016, IMP701, MK-4280, ImmuFact IMP321; anti T cell immunoglobulin mucin-3 (TIM-3) antibodies, such as MBG453; anti-CD137/4-1BB antibodies, such as BMS-663513 / urelumab, PF-05082566; anti T cell immunoreceptor with Ig and ITIM domains (TIGIT) antibodies, such as RG6058 (anti-TIGIT, MTIG7192A);



- f) Vaccination approaches (for example dendritic cell vaccination, peptide or protein vaccination (for example with gp100 peptide or MAGE-A3 peptide);
- g) 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);
- h) T-cell based adoptive immunotherapies, including chimeric antigen receptor (CAR) engineered T-cells (for example CTL019);
- i) Cytokine or immunocytokine based therapy (for example Interferon alpha, interferon beta, interferon gamma, interleukin 2, interleukin 15);
- j) Toll-like receptor (TLR) agonists (for example resiquimod, imiquimod, glucopyranosyl lipid A, CpG oligodesoxynucleotides);
- k) Thalidomide analogues (for example Lenalidomide, Pomalidomide);
- l) Indoleamine-2,3-Dioxygenase (IDO) and/or Tryptophan-2,3-Dioxygenase (TDO) inhibitors (for example RG6078 / NLG919 / GDC-0919; Indoximod / 1MT (1-methyltryptophan), INCB024360 / Epcadostat, PF-06840003 (EOS200271), F001287);
- m) Activators of T-cell co-stimulatory receptors (for example anti-OX40/CD134 (Tumor necrosis factor receptor superfamily, member 4, such as RG7888 (MOXR0916), 9B12; MEDI6469, GSK3174998, MEDI0562), anti OX40-Ligand/CD252; anti-glucocorticoid-induced TNFR family related gene (GITR) (such as TRX518, MEDI1873, MK-4166, BMS-986156), 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);
- n) 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 AMG103, AMG330);
- o) Antibodies or small molecular weight inhibitors targeting colony-stimulating factor-1 receptor (CSF-1R) (for example Emactuzumab (RG7155), Cabiralizumab (FPA-008), PLX3397);
- p) 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);
- q) 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).

When used in combination with the compounds of formulae (I), (II), or (III), immune checkpoint inhibitors such as those listed under d), and especially those targeting the programmed cell death receptor 1 (PD-1 receptor) or its ligand PD-L1, are preferred.

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 cytotoxic chemotherapeutic agents which act by killing cells that divide rapidly, one of the main properties of most cancer cells. Chemotherapy may use one  
5 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 formulae (I), (II),  
10 or (III), the term especially refers to conventional cytotoxic chemotherapy agents such as:

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

When used in combination with the compounds of formulae (I), (II), or (III), preferred cytotoxic chemotherapy agents  
25 are the above-mentioned alkylating agents (notably fotemustine, cyclophosphamide, ifosfamide, carmustine, dacarbazine and prodrugs thereof such as especially temozolomide or pharmaceutically acceptable salts of these compounds; in particular temozolomide); mitotic inhibitors (notably paclitaxel, docetaxel, ixabepilone,; or pharmaceutically acceptable salts of these compounds; in particular paclitaxel); platinum drugs (notably cisplatin, oxaliplatin and carboplatin); as well etoposide and gemcitabine.

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

- Combined modality chemotherapy is the use of drugs with other cancer treatments, such as radiation therapy or surgery.
- Induction chemotherapy is the first line treatment of cancer with a chemotherapeutic drug. This type of chemotherapy is used for curative intent.

- 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.
- Intensification chemotherapy is identical to consolidation chemotherapy but a different drug than the induction chemotherapy is used.
- Combination chemotherapy involves treating a patient with a number of different drugs simultaneously. The drugs differ in their mechanism and side effects. The biggest advantage is minimising the chances of resistance developing to any one agent. Also, the drugs can often be used at lower doses, reducing toxicity.
- 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 micrometastatic disease.
- Adjuvant chemotherapy is given after a local treatment (radiotherapy or surgery). It can be used when there is little 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 micrometastases can be treated with adjuvant chemotherapy and can reduce relapse rates caused by these disseminated cells.
- Maintenance chemotherapy is a repeated low-dose treatment to prolong remission.
- Salvage chemotherapy or palliative chemotherapy is given without curative intent, but simply to decrease tumor load and increase life expectancy. For these regimens, a better toxicity profile is generally expected.

"Simultaneously", when referring to an administration type, means in the present application that the administration type concerned consists in the administration of two or more active ingredients and/or treatments at approximately the same time; wherein it is understood that a simultaneous administration will lead to exposure of the subject to the two or more active ingredients and/or treatments at the same time. When administered simultaneously, said two or more active ingredients may be administered in a fixed dose combination, or in an equivalent non-fixed dose combination (e.g. by using two or more different pharmaceutical compositions to be administered by the same route of administration at approximately the same time), or by a non-fixed dose combination using two or more different routes of administration; wherein said administration leads to essentially simultaneous exposure of the subject to the two or more active ingredients and/or treatments. For example, when used in combination with chemotherapy and/or suitable targeted therapy, the present EP2/EP4 antagonists would possibly be used "simultaneously".

"Fixed dose combination", when referring to an administration type, means in the present application that the administration type concerned consists in the administration of one single pharmaceutical composition comprising the two or more active ingredients.

"Separately", when referring to an administration type, means in the present application that the administration type concerned consists in the administration of two or more active ingredients and/or treatments at different points in time; wherein it is understood that a separate administration will lead to a treatment phase (e.g. at least 1 hour, notably at least 6 hours, especially at least 12 hours) where the subject is exposed to the two or more active

ingredients and/or treatments at the same time; but a separate administration may also lead to a treatment phase where for a certain period of time (e.g. at least 12 hours, especially at least one day) the subject is exposed to only one of the two or more active ingredients and/or treatments. Separate administration especially refers to situations wherein at least one of the active ingredients and/or treatments is given with a periodicity substantially different from daily (such as once or twice daily) administration (e.g. wherein one active ingredient and/or treatment is given e.g. once or twice a day, and another is given e.g. every other day, or once a week or at even longer distances). For example, when used in combination with radiotherapy, the present EP2/EP4 antagonists would possibly be used "separately".

By administration "over a period of time" is meant in the present application the subsequent administration of two or more active ingredients and/or treatments at different times. The term in particular refers to an administration method according to which the entire administration of one of the active ingredients and/or treatments is completed before the administration of the other / the others begins. In this way it is possible to administer one of the active ingredients and/or treatments for several months before administering the other active ingredient(s) and/or treatment(s).

Administration "over a period of time" also encompasses situations wherein the compound of formulae (I), (II), or (III) would be used in a treatment that starts after termination of an initial chemotherapeutic (for example an induction chemotherapy) and/or radiotherapeutic treatment and/or targeted therapy treatment, wherein optionally said treatment would be in combination with a further / an ongoing chemotherapeutic and/or radiotherapeutic treatment and/or targeted therapy treatment (for example in combination with a consolidation chemotherapy, an intensification chemotherapy, an adjuvant chemotherapy, or a maintenance chemotherapy; or radiotherapeutic equivalents thereof); wherein such further / ongoing chemotherapeutic and/or radiotherapeutic treatment and/or targeted therapy treatment would be simultaneously, separately, or over a period of time in the sense of "not given with the same periodicity".

The compounds of formulae (I), (II), or (III) as defined in embodiments 1) to 31) are also useful in a method of modulating an immune response in a subject having a tumor, comprising the administration of an effective amount of the compound of formulae (I), (II), or (III) [wherein notably said administration of said effective amount results in the pharmacologically active blockage of the EP2 receptors, or of the EP4 receptors, or of both the EP2 and the EP4 receptors]; wherein said effective amount reactivates the immune system in the tumor of said subject; wherein especially said effective amount:

- counteracts the polarization of tumor-associated macrophages towards tumor-promoting M2 macrophages; and/or
- down-regulates the activation, expansion and/or the effector function of immunosuppressive cells that have accumulated in a tumor (especially of regulatory T cells (Tregs) and/or myeloid derived suppressor cells (MDSC)); and/or

- up-regulates IFN- $\gamma$  and/or TNF- $\alpha$  and/or IL-12 and/or IL-2 expression in immune cells such as natural killer cells, T-cells, dendritic cells and macrophages (leading to the induction of tumor cell apoptosis and/or restrained tumorigenesis); and/or
- directly or indirectly counteracts the suppressed activation, IL-2 responsiveness and expansion of cytotoxic T-cells (thereby decreasing local immunosuppression).

The compounds of formulae (I), (II), or (III) as defined in embodiments 1) to 31) are also useful in a method of diminishing tumor growth and/or reducing tumor size in a subject having a tumor, comprising the administration of an effective amount of the compound of formulae (I), (II), or (III) [wherein notably said administration of said effective amount results in the pharmacologically active blockage of the EP2 receptors, or of the EP4 receptors, or of both the EP2 and the EP4 receptors]; wherein said effective amount down-regulates tumor angiogenesis (especially by decreasing endothelial cell motility and/or survival, and/or by decreasing the expression of VEGF (vascular endothelial growth factor)); and/or wherein said effective amount diminishes tumor cell survival and/or induces tumor cell apoptosis (especially via inhibition of PI3K/AKT and MAPK signalling).

The compounds of formulae (I), (II), or (III) as defined in embodiments 1) to 31) are also useful in a method of modulating an immune response in a subject having a tumor, comprising the administration of an effective amount of the compound of formulae (I), (II), or (III) [wherein notably said administration of said effective amount results in the pharmacologically active blockage of the EP2 receptors, or of the EP4 receptors, or of both the EP2 and the EP4 receptors]; wherein said effective amount reactivates the immune system in the tumor of said subject; wherein said effective amount activates the cytotoxicity and cytokine production of natural killer cells and/or cytotoxic T-cells.

Besides, any preferences and (sub-)embodiments indicated for the compounds of formulae (II) or (III) (whether for the compounds themselves, salts thereof, compositions containing the compounds or salts thereof, or uses of the compounds or salts thereof, etc.) apply *mutatis mutandis* to compounds of formula (I).

#### **Preparation of compounds of formulae (I), (II), or (III):**

The compounds of formulae (I), (II), or (III) can be prepared by well-known literature methods, by the methods given below, by the methods given in the experimental part below or by analogous methods. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by a person skilled in the art by routine optimisation procedures. In some cases the order of carrying out the following reaction schemes, and/or reaction steps, may be varied to facilitate the reaction or to avoid unwanted reaction products. In the general sequence of reactions outlined below, the generic groups **R<sup>1</sup>**, **R<sup>3</sup>**, **R<sup>4a</sup>**, **R<sup>4b</sup>**, **R<sup>5a</sup>**, **R<sup>5b</sup>** and **Ar<sup>1</sup>** are as defined for formulae (I), (II), or (III). Other abbreviations used herein are explicitly defined, or are as defined in the experimental section. In some instances the generic groups **R<sup>1</sup>**, **R<sup>3</sup>**, **R<sup>4a</sup>**, **R<sup>4b</sup>**, **R<sup>5a</sup>**, **R<sup>5b</sup>** and **Ar<sup>1</sup>** might be incompatible with the assembly illustrated in the schemes below and so will require the use of protecting groups (PG). The use of protecting groups is well known in the art (see for example "Protective Groups in Organic Synthesis", T.W. Greene, P.G.M. Wuts, Wiley-Interscience, 1999). For the purposes of this discussion, it will be assumed that such

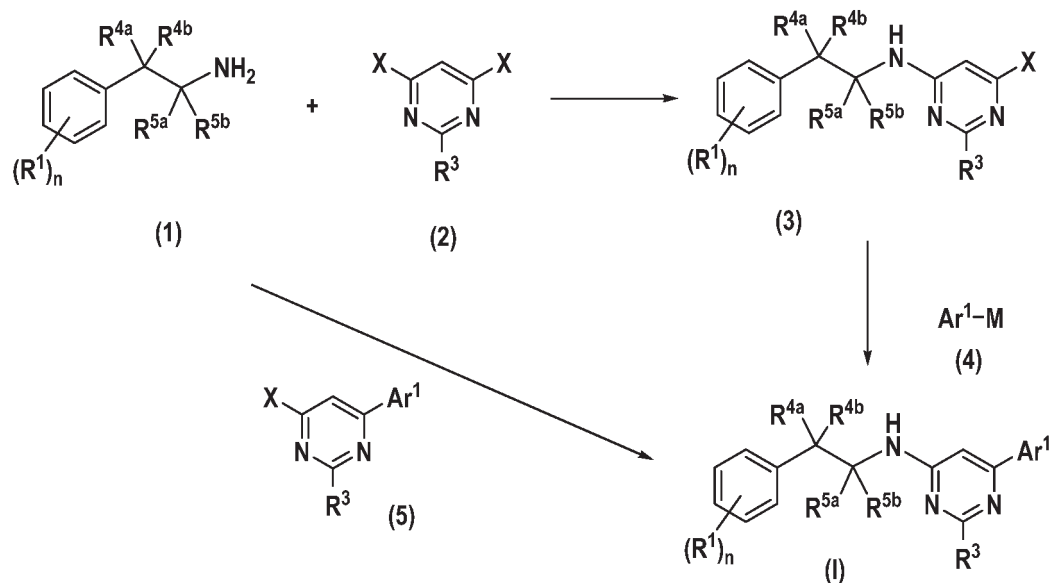
protecting groups as necessary are in place. In some cases the final product may be further modified, for example, by manipulation of substituents to give a new final product. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, hydrolysis and transition-metal catalysed cross-coupling reactions which are commonly known to those skilled in the art. The compounds obtained may also be converted into salts, especially pharmaceutically acceptable salts, in a manner known *per se*.

Compounds of formulae (I), (II), or (III) of the present invention can be prepared according to the general sequence of reactions outlined below.

A general synthetic route allowing the preparation of compounds of formula (I) is presented in *scheme 1*. Thus, precursors **(3)** can be obtained by nucleophilic aromatic substitutions between primary amines **(1)** and pyrimidines **(2)** (wherein **X** is a chlorine, a bromine or an iodine), in the presence of a base such as TEA, DIPEA or K<sub>2</sub>CO<sub>3</sub>, in a solvent such as isopropanol, butanol, DMF or THF, at RT or at elevated temperatures. Compounds of formula (I) can be produced via metal-catalyzed cross-coupling reactions of the pyrimidine halide derivatives **(3)** with a compound of formula **(4)**, for example Suzuki couplings when compounds **(4)** are boronic acids or boronate esters. Typical Suzuki cross-coupling reactions may be carried out in the presence of a base such as K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, or CsF and a catalyst such as Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd(dppf)Cl<sub>2</sub> or Pd(OAc)<sub>2</sub>, in a solvent like ethanol, THF, water, or mixtures thereof, typically at elevated temperatures. Boronic acids or boronate esters **(4)** can be obtained from commercial sources, or synthesized by methods described in the literature, or by methods known by a person skilled in the art. A boronic acid derivative can be formed by the Miyaura borylation reaction, by cross-coupling of bis(pinacolato)diboron with aryl halides or triflates, in the presence of a base such as potassium acetate and a catalyst such as Pd(dppf)Cl<sub>2</sub>. Alternatively, a boronic acid derivative can be formed by a lithiation/borylation sequence, typically at low temperatures, using butyllithium or lithium diisopropylamide as the base, and triisopropylborate or isopropoxyboronic acid pinacol ester, in a solvent such as Et<sub>2</sub>O or THF. In a variant, compounds of formula (I) can be prepared via nucleophilic aromatic substitutions between primary amines **(1)** and substituted pyrimidine halides **(5)**, wherein **X** is a chlorine, a bromine or an iodine (*scheme 1*).

Alternatively, compounds of formula (I) can be synthesized by reacting a compound of formula **(1)** with a compound of formula **(5)** wherein **X** represents OH, in presence of a coupling agent such as (benzotriazol-1-yloxy)-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), (benzotriazol-1-yl-oxy)-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP) or hexachlorocyclotriphosphazene, in presence of a base such as DBU, DIPEA or TEA in a solvent such as THF, MeCN or DMF, at low temperatures, or at RT or at elevated temperatures.



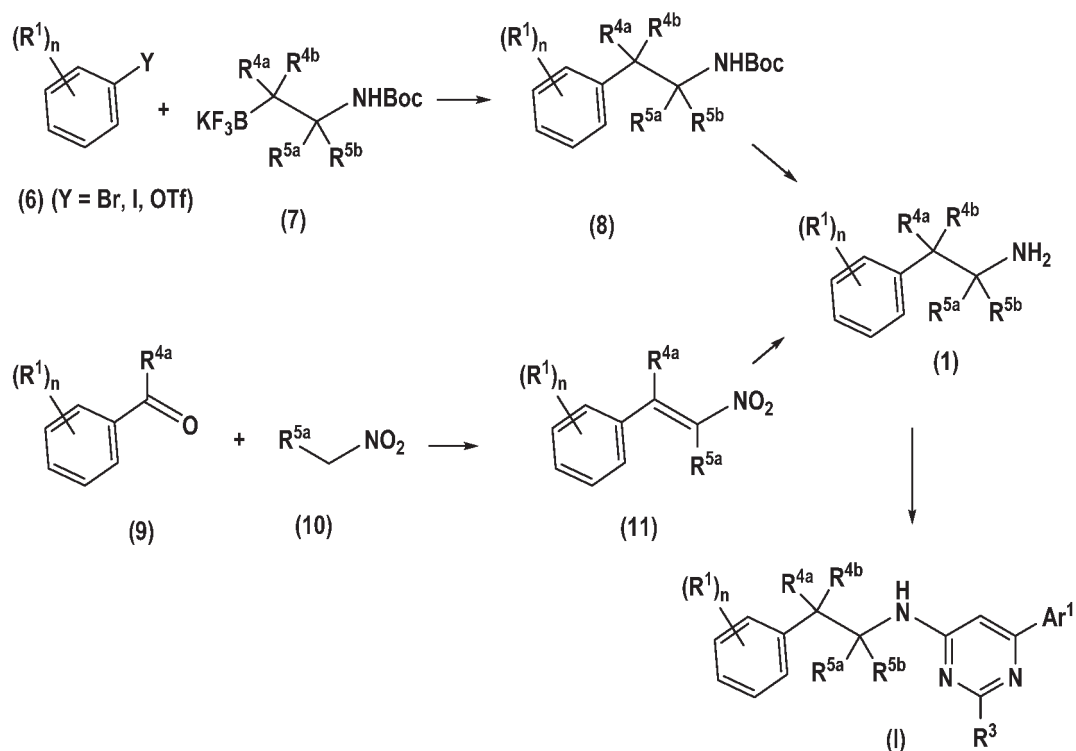


Scheme 1: General preparations of compounds of formula (I)

Preparations of the required primary amines **1** are described in *scheme 2*. Aminoethylated aromatics (**8**) can be produced via Suzuki-Miyaura cross-coupling reactions of the corresponding aromatic electrophiles (**6**) (bromides, iodides or triflates) with Boc-protected potassium  $\beta$ -aminoethyltrifluoroborates (**7**). Such cross-coupling reactions can be performed using described conditions [Pd(dppf)Cl<sub>2</sub> or combination of Pd(OAc)<sub>2</sub> and RuPhos as the catalytic system, Cs<sub>2</sub>CO<sub>3</sub> as a base, in a mixture of toluene/H<sub>2</sub>O, at elevated temperatures]. The corresponding primary amines (**1**) can be obtained after Boc-deprotection of derivatives (**8**), under acidic conditions, and can be converted into compounds of formula (I) with the synthetic sequences described in *scheme 1*. In a variant presented in *scheme 2*, primary amines (**1**) can be prepared starting from carbonyl precursors (**9**) and nitro compounds (**10**) via Henry reaction (butylamine/acetic acid/molecular sieves/90°C) and subsequent reduction of the produced nitroalkenes (**11**) (lithium aluminum hydride/THF, or NaBH<sub>4</sub>/BF<sub>3</sub>·Et<sub>2</sub>O/THF).

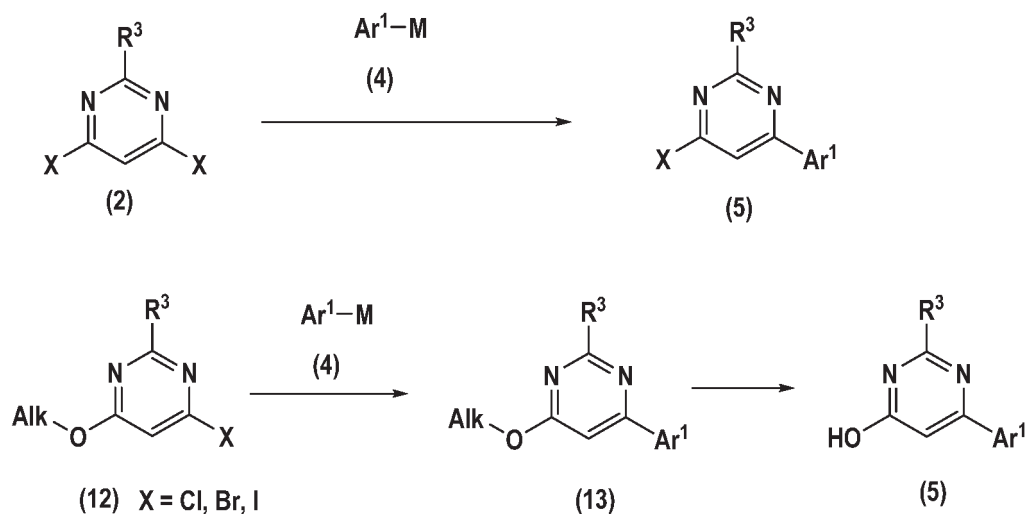


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Scheme 2. Preparations of substituted  $\beta$ -aminoethyl aromatics (1)

The pyrimidines of formula (5) can be obtained by cross-coupling reactions between compounds of formula (4), typically boronic acids or esters, and di-halo-pyrimidines of formula (2), wherein  $X = \text{Cl, Br or I}$  (Scheme 3).

- 5 Compounds of formula (5) wherein  $X = \text{OH}$  can be obtained by de-alkylation of compounds of formula (13), wherein Alk is typically Me or Et, under acidic conditions (HCl, HBr or  $\text{BBr}_3$ ). In turn, (13) can be formed by a cross-coupling reaction between compounds of formula (12), wherein  $X = \text{Cl, Br, I}$ , and compounds of formula (4), typically boronic acids or esters.



10 Scheme 3. Preparations of pyrimidines (5)

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**

### **I. Chemistry**

- 5 All temperatures are stated in °C. Commercially available starting materials were used as received without further purification. Unless otherwise specified, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. Compounds were purified by flash column chromatography on silica gel or by preparative HPLC. Compounds described in the invention are characterised by LC-MS data (retention time  $t_R$  is given in min; molecular weight obtained from the mass spectrum is given in g/mol) using the conditions listed below. In cases where  
10 compounds of the present invention appear as a mixture of conformational isomers, particularly visible in their LC-MS spectra, the retention time of the most abundant conformer is given. In some cases compounds are isolated after purification in form of the corresponding ammonium salt (\*1), the respective formic acid salt (\*2) or the hydrochloride salt (\*3); such compounds are marked accordingly.

#### **Analytical LC-MS equipment:**

- 15 HPLC pump: Binary gradient pump, Agilent G4220A or equivalent  
Autosampler: Gilson LH215 (with Gilson 845z injector) or equivalent  
Column compartment: Dionex TCC-3000RS or equivalent  
Degasser: Dionex SRD-3200 or equivalent  
Make-up pump: Dionex HPG-3200SD or equivalent  
20 DAD detector: Agilent G4212A or equivalent  
MS detector: Single quadrupole mass analyzer, Thermo Finnigan MSQPlus or equivalent  
ELS detector: Sedere SEDEX 90 or equivalent

#### **LC-MS with acidic conditions**

- Method A:** Column: Zorbax SB-aq (3.5  $\mu$ m, 4.6 x 50 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent  
25 B]. Gradient: 95% B  $\rightarrow$  5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

**Method B:** Column: Zorbax RRHD SB-aq (1.8  $\mu$ m, 2.1 x 50 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B  $\rightarrow$  5% B over 2.0 min (flow: 0.8 mL/min). Detection: UV/Vis + MS.

- Method C:** Waters Acquity Binary, Solvent Manager, MS: Waters SQ Detector, DAD: Acquity UPLC PDA Detector, ELSD: Acquity UPLC ELSD. Column ACQUITY UPLC CSH C18 1.7 $\mu$ m 2.1x50 mm from Waters, thermostated in  
30 the Acquity UPLC Column Manager at 60°C. Eluents: A: H<sub>2</sub>O + 0.05% formic acid; B: MeCN + 0.045% formic acid. Method: Gradient: 2% B 98% B over 2.0 min. Flow: 1.0 mL/min. Detection: UV 214nm and ELSD, and MS,  $t_R$  is given in min.

**Method E:** Column: Waters BEH C18 (2.5  $\mu$ m, 2.1 x 50 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B  $\rightarrow$  5% B over 2.0 min (flow: 0.8 mL/min). Detection: UV/Vis + MS.

LC-MS with basic conditions

**Method D:** Column: Waters BEH C<sub>18</sub>, 3.0 x 50mm, 2.5µm, Eluents: A: Water/NH<sub>3</sub> [c(NH<sub>3</sub>) = 13 mmol/l], B: MeCN, Method: 5%B to 95%B in 1.2min, Flow 1.6ml/min, Detection UV: 214nm

Preparative HPLC equipment:

- 5 Gilson 333/334 HPLC pump equipped with Gilson LH215, Dionex SRD-3200 degasser, Dionex ISO-3100A make-up pump, Dionex DAD-3000 DAD detector, Single quadrupole mass analyzer MS detector, Thermo Finnigan MSQ Plus, MRA100-000 flow splitter, Polymer Laboratories PL-ELS1000 ELS detector

Preparative HPLC with basic conditions

- Column: Waters XBridge (10 µm, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% NH<sub>4</sub>OH (25% aq.) [eluent B]; Gradient see **Table 1** (flow: 75 mL/min), the starting percentage of Eluent A (x) is determined depending on the polarity of the compound to purify. Detection: UV/Vis + MS

**Table 1**

|              |       |       |     |     |       |       |
|--------------|-------|-------|-----|-----|-------|-------|
| t (min)      | 0     | 0.01  | 4.0 | 6.0 | 6.2   | 6.6   |
| Eluent A (%) | x     | x     | 95  | 95  | x     | x     |
| Eluent B (%) | 100-x | 100-x | 5   | 5   | 100-x | 100-x |

Preparative HPLC with acidic conditions

- 15 Column: Waters Atlantis T3 (10 µm, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% HCO<sub>2</sub>H [eluent B]; Gradient see **Table 2** (flow: 75 mL/min), the starting percentage of Eluent A (x) is determined depending on the polarity of the compound to purify. Detection: UV/Vis + MS

**Table 2**

|              |       |       |     |     |       |       |
|--------------|-------|-------|-----|-----|-------|-------|
| t (min)      | 0     | 0.01  | 4.0 | 6.0 | 6.2   | 6.6   |
| Eluent A (%) | x     | x     | 95  | 95  | x     | x     |
| Eluent B (%) | 100-x | 100-x | 5   | 5   | 100-x | 100-x |

20 **Abbreviations** (as used hereinbefore or hereinafter):

AcOH acetic acid

aq. aqueous

atm atmosphere

Boc tert-butyloxycarbonyl

- 25 BOP (benzotriazol-1-yloxy)-tris(dimethylamino)-phosphonium hexafluorophosphate

|    |                   |                                                                                                |
|----|-------------------|------------------------------------------------------------------------------------------------|
|    | d                 | days                                                                                           |
|    | DBU               | 1,8-diazabicyclo[5.4.0]undec-7-ene                                                             |
|    | DCM               | dichloromethane                                                                                |
|    | DIBAL/DIBAL-H     | diisobutylaluminium hydride                                                                    |
| 5  | DIPEA             | diisopropyl-ethylamine, Hünig's base                                                           |
|    | DMAP              | 4-Dimethylaminopyridine                                                                        |
|    | DMF               | dimethylformamide                                                                              |
|    | DMSO              | dimethylsulfoxide                                                                              |
|    | dppf              | 1,1'-bis(diphenylphosphino)ferrocene                                                           |
| 10 | EDC               | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide                                                  |
|    | Et                | ethyl                                                                                          |
|    | Et <sub>2</sub> O | diethylether                                                                                   |
|    | EtOAc             | ethyl acetate                                                                                  |
|    | EtOH              | ethanol                                                                                        |
| 15 | Ex.               | example                                                                                        |
|    | FC                | flash chromatography on silica gel                                                             |
|    | h                 | hour(s)                                                                                        |
|    | HATU              | (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate |
| 20 | hept              | heptane(s)                                                                                     |
|    | HOBT              | 1-hydroxybenzotriazol                                                                          |
|    | HPLC              | high performance liquid chromatography                                                         |
|    | HV                | high vacuum conditions                                                                         |
|    | <sup>i</sup> Bu   | isobutyl                                                                                       |
| 25 | <sup>i</sup> Pr   | isopropyl                                                                                      |
|    | LAH               | Lithium aluminium hydride                                                                      |
|    | LC-MS             | liquid chromatography – mass spectrometry                                                      |
|    | Lit.              | Literature                                                                                     |
|    | Me                | methyl                                                                                         |
| 30 | MeCN              | acetonitrile                                                                                   |
|    | MeOH              | methanol                                                                                       |
|    | mL                | milliliter                                                                                     |
|    | min               | minute(s)                                                                                      |
|    | MW                | microwave                                                                                      |
| 35 | NMP               | N-methyl-2-pyrrolidone                                                                         |
|    | <sup>n</sup> Pr   | n-propyl                                                                                       |

|    |                                  |                                                                        |
|----|----------------------------------|------------------------------------------------------------------------|
|    | OAc                              | acetate                                                                |
|    | Pd <sub>2</sub> dba <sub>3</sub> | Tris(dibenzylideneacetone)dipalladium(0)                               |
|    | Pd(dppf)Cl <sub>2</sub>          | [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (II)          |
|    | Pd(dppf)Cl <sub>2</sub> ·DCM     | [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (II) complex  |
| 5  |                                  | with dichloromethane                                                   |
|    | Ph                               | phenyl                                                                 |
|    | PPh <sub>3</sub>                 | triphenyl phosphine                                                    |
|    | prep.                            | preparative                                                            |
|    | PyBOP                            | (benzotriazol-1-yl-oxy)-tripyrrolidino-phosphonium hexafluorophosphate |
| 10 | rac                              | racemic                                                                |
|    | RM                               | reaction mixture                                                       |
|    | RT                               | room temperature                                                       |
|    | s                                | second(s)                                                              |
|    | sat.                             | saturated                                                              |
| 15 | tBu                              | tert-butyl = tertiary butyl                                            |
|    | TEA                              | triethylamine                                                          |
|    | TFA                              | trifluoroacetic acid                                                   |
|    | THF                              | tetrahydrofuran                                                        |
|    | TLC                              | thin layer chromatography                                              |
| 20 | tosyl                            | p-toluene-sulfonyl                                                     |
|    | t <sub>R</sub>                   | retention time                                                         |
|    | triflate                         | trifluoromethanesulfonate                                              |

### General procedures

#### 25 General procedure A: Nitro-aldol condensation and dehydration

To a solution of aromatic aldehyde (10 mmol) in nitromethane (20 mL) at RT are added butylamine (0.117 mL, 1.18 mmol), Acetic acid (0.116 mL, 2.04 mmol) and 4Å molecular sieves (100 mg). The RM is stirred at 90°C for 1h, then cooled to RT and concentrated in vacuo. The residue is partitioned between EtOAc and water. The organic phase is washed once more with water then with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The crude product is purified by preparative HPLC or by FC if needed.

#### General procedure B: Nitrostyrene reduction with NaBH<sub>4</sub> and BF<sub>3</sub>·Et<sub>2</sub>O

To a solution of sodium borohydride (251 mg, 6.51 mmol) in THF (7 mL) at 0°C is added BF<sub>3</sub>·Et<sub>2</sub>O (1.06 mL, 8.14 mmol). The RM is stirred 10 min at 0°C then 15 min at RT. A solution of nitrostyrene (1.36 mmol) in THF (3 mL) is added dropwise and the RM is refluxed overnight. The RM is cooled at 0°C and treated carefully with 2N HCl (8.8 mL, 17.6 mmol). The RM is heated for 1h at 80°C, then cooled to RT, and the organic solvent is removed under reduced pressure. The remaining aqueous layer is extracted with Et<sub>2</sub>O. The aqueous layer is treated with 10%

NaOH to reach pH>12 and extracted 3 times with EtOAc. The combined organic layers are washed with brine, dried over MgSO<sub>4</sub> and concentrated in vacuo. The crude product is purified by preparative HPLC or by FC if needed.

**General procedure C: Suzuki Miyaura coupling with trifluoroborates**

- 5 A reaction vessel is charged with the aryl-bromide or triflate (1.91 mmol), potassium tert-butyl n-[2-(trifluoroboranuidyl)ethyl]carbamate (555 mg, 2.1 mmol), cesium carbonate (2489 mg, 7.64 mmol), palladium(II) acetate (21.5 mg, 0.0955 mmol), RuPhos (93.8 mg, 0.191 mmol) and toluene (15 mL) and water (5 mL). The RM is flushed with argon, then heated at 95°C overnight. The RM is cooled to RT and filtered through a glass microfiber. The filtrate is concentrated under reduced pressure. The residue is partitioned between DCM and NH<sub>4</sub>Cl saturated  
10 solution. Phases are separated and the aqueous layer is extracted twice more with DCM. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and evaporated in vacuo. The crude product is purified by preparative HPLC or by FC if needed.

**General procedure D: Boc deprotection (TFA)**

- 15 To a solution of Boc-protected amine (1.91 mmol) in DCM (40 mL) at 0°C is added TFA (10 mL). The RM is stirred for 2h, letting the temperature rise to RT. It is then concentrated in vacuo. The residue is dissolved again in DCM and evaporated in vacuo (twice), affording the free amine as TFA salt. Alternatively, the residue after evaporation is taken up in DCM and washed with 1N NaOH. The organic layer is dried over MgSO<sub>4</sub>, filtered and evaporated in vacuo. The crude product is purified by preparative HPLC or by FC if needed.

**General procedure E: Boc deprotection (HCl)**

- 20 A solution of Boc-protected amine (1.91 mmol) in DCM (40 mL) at 0°C is added HCl (4N in dioxane, 10 mL). The RM is stirred for 2h, letting the temperature rise to RT. It is then concentrated in vacuo, affording the free amine as HCl salt. Alternatively, the residue after evaporation is taken up in DCM and washed with 1N NaOH. The organic layer is dried over MgSO<sub>4</sub>, filtered and evaporated in vacuo. The crude product is purified by preparative HPLC or by FC if needed.

25 **General procedure F: SNAr of 4,6-di-halo-pyrimidine**

- A solution of aryl-ethylamine (21.1 mmol), 4,6-dichloropyrimidine (3.00 g, 20.1 mmol) and TEA (3.08 mL, 22.2 mmol) in 2-propanol (50 mL) is refluxed for 2h, then allowed to cool to RT and concentrated under reduced pressure. The residue is partitioned between sat. aq. NaHCO<sub>3</sub> solution and EtOAc. The layers are separated and the aqueous layer is extracted once more with EtOAc. The combined organic layers are washed with water, brine, dried over  
30 MgSO<sub>4</sub>, filtered and the solvent is removed in vacuo. The crude product is purified by preparative HPLC or by FC if needed.

**General procedure G: Suzuki coupling with Pd(PPh<sub>3</sub>)<sub>4</sub>**

- A mixture of the respective pyrimidine halide derivative (3) (0.15 mmol), the respective boronic acid derivative (4) (0.18 mmol), and K<sub>2</sub>CO<sub>3</sub> 2M (0.3 mL, 0.6 mmol) in ethanol (3 mL) is purged with argon, tetrakis-  
35 (triphenylphosphine)-palladium (0.0075 mmol) is added, and the reaction mixture is heated at 90°C overnight.

Alternatively, the reaction can be performed in a MW apparatus, at 120°C for 15 - 30 min. The reaction mixture is filtered through a 0.45 µm Glass MicroFiber filter, washed with EtOH/MeCN and DMF. The filtrate is purified either by preparative HPLC or FC. Alternatively, it is diluted with water, if needed the pH is adjusted, and extracted with EtOAc (3x). The combined organic extracts are dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue is purified by preparative HPLC or by FC.

**General procedure H: Suzuki coupling with Pd(PPh<sub>3</sub>)<sub>4</sub> followed by ester hydrolysis**

A mixture of the respective pyrimidine halide derivative (3) (0.15 mmol), the respective boronic acid derivative (4) (0.18 mmol), and K<sub>2</sub>CO<sub>3</sub> 2M (0.3 mL, 0.6 mmol) in EtOH (3 mL) is purged with argon, Pd(PPh<sub>3</sub>)<sub>4</sub> (0.0075 mmol) is added, and the reaction mixture is heated at 90°C overnight. Alternatively, the reaction can be performed in a MW apparatus, at 120°C for 15 - 30 min. NaOH (32% solution, 0.5 mL) is added, and the reaction mixture is stirred at RT for 2 - 20h or at 90°C for 0.5 - 20h. It is then filtered through a 0.45 µm Glass MicroFiber filter, washed with EtOH and water. The filtrate is either purified directly by preparative HPLC or diluted with 1N HCl, and extracted 3x with EtOAc. The combined organic extracts are dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue is purified by preparative HPLC or by FC if needed.

**General procedure I: phosphonium-mediated SNAr**

To a solution of 6-hydroxy-pyrimidine derivative (5) (0.196 mmol) in DMF (2 mL) and TEA (0.109 mL, 0.784 mmol) is added PyBOP (163 mg, 0.313 mmol). The yellow solution is stirred at RT for 15 min, then the respective aryl-ethylamine (1) (0.245 mmol) is added and the RM is stirred at 80°C overnight. The RM is cooled to RT and treated with a few drops of water and purified by preparative HPLC. Alternatively, the RM is diluted with EtOAc and washed twice with brine. The organic layer is dried over MgSO<sub>4</sub>, filtered and concentrated. The residue is purified by preparative HPLC or by FC if needed.

Alternatively, a solution of 6-hydroxy-pyrimidine derivative (5) (0.1 mmol) in DMF (1 mL) is treated with DBU (0.15 mmol) and BOP (0.13 mmol). The solution is stirred at RT for 15 min - 1h, then the respective aryl-ethylamine (1) (0.125 mmol) is added, and the RM is stirred at 80°C for 2 - 20h. The RM is cooled to RT and treated with a few drops of water and purified by preparative HPLC. Or the RM is diluted with EtOAc and washed twice with brine. The organic layer is dried over MgSO<sub>4</sub>, filtered and concentrated. The residue is purified by preparative HPLC or by FC if needed.

**A- Preparation of precursors and intermediates**

**A.1. Synthesis of phenethyl amine derivatives of formula (1)**

**A.1.1. 2-(4-Bromo-2-(trifluoromethoxy)phenyl)ethan-1-amine**

The title compound is prepared according to the general procedure B described above, using (*E*)-4-bromo-1-(2-nitrovinyl)-2-(trifluoromethoxy)benzene, and obtained as a white solid. LC-MS B: t<sub>R</sub> = 0.64 min; [M+H]<sup>+</sup> = 284.02.

**A.1.1.1. (*E*)-4-Bromo-1-(2-nitrovinyl)-2-(trifluoromethoxy)benzene**

The title compound is prepared according to the general procedure A described above, using 4-bromo-2-(trifluoromethoxy)benzaldehyde, and obtained as a yellow solid. LC-MS B: t<sub>R</sub> = 1.06 min; no ionization.



**A.1.2. 2-(4-Bromo-2-ethoxyphenyl)ethan-1-amine**

The title compound is prepared according to the general procedure B described above, using (*E*)-4-bromo-2-ethoxy-1-(2-nitrovinyl)benzene, and obtained as a brown solid. LC-MS B:  $t_R$  = 0.62 min;  $[M+H]^+$  = 244.18.

**A.1.2.1. (*E*)-4-Bromo-2-ethoxy-1-(2-nitrovinyl)benzene**

5 The title compound is prepared according to the general procedure A described above, using 4-bromo-2-ethoxybenzaldehyde, and obtained as a yellow solid. LC-MS B:  $t_R$  = 1.09 min; no ionization.

**A.1.3. 2-(4-Chloro-2-fluoro-6-methoxyphenyl)ethan-1-amine**

The title compound is prepared according to the general procedure B described above, using (*E*)-5-chloro-1-fluoro-3-methoxy-2-(2-nitrovinyl)benzene, and obtained as a pink solid. LC-MS B:  $t_R$  = 0.56 min;  $[M+H]^+$  = 204.29.

10 **A.1.3.1. (*E*)-5-Chloro-1-fluoro-3-methoxy-2-(2-nitrovinyl)benzene**

The title compound is prepared according to the general procedure A described above, using 4-chloro-2-fluoro-6-methoxybenzaldehyde, and obtained as a pale yellow solid. LC-MS B:  $t_R$  = 0.98 min; no ionization.

**A.1.4. 2-(4-Bromo-2-fluoro-6-methoxyphenyl)ethan-1-amine**

15 The title compound is prepared according to the general procedure B described above, using (*E*)-5-bromo-1-fluoro-3-methoxy-2-(2-nitrovinyl)benzene, and obtained as a pale yellow solid. LC-MS B:  $t_R$  = 0.59 min;  $[M+H]^+$  = 250.08.

**A.1.4.1. (*E*)-5-Bromo-1-fluoro-3-methoxy-2-(2-nitrovinyl)benzene**

The title compound is prepared according to the general procedure A described above, using 4-bromo-2-fluoro-6-methoxybenzaldehyde, and obtained as a pale yellow solid. LC-MS B:  $t_R$  = 1.03 min; no ionization.

**A.1.5. 2-(4-Bromo-2,6-dimethoxyphenyl)ethan-1-amine**

20 The title compound is prepared according to the general procedure B described above, using (*E*)-5-bromo-1,3-dimethoxy-2-(2-nitrovinyl)benzene, and obtained as a beige solid. LC-MS B:  $t_R$  = 0.59 min;  $[M+H]^+$  = 260.15.

**A.1.5.1. (*E*)-5-bromo-1,3-dimethoxy-2-(2-nitrovinyl)benzene**

The title compound is prepared according to the general procedure A described above, using 4-bromo-2,6-dimethoxybenzaldehyde, and obtained as a yellow solid. LC-MS B:  $t_R$  = 1.08 min; no ionization.

25 **A.1.6. 2-(4-Bromo-2-propoxyphenyl)ethan-1-amine**

The title compound is prepared according to the general procedure B described above, using (*E*)-4-bromo-1-(2-nitrovinyl)-2-propoxybenzene, and obtained as an orange solid. LC-MS B:  $t_R$  = 0.67 min;  $[M+H]^+$  = 257.99.

**A.1.6.1. (*E*)-4-Bromo-1-(2-nitrovinyl)-2-propoxybenzene**

30 The title compound is prepared according to the general procedure A described above, using 4-bromo-2-propoxybenzaldehyde, and obtained as a yellow solid. LC-MS B:  $t_R$  = 1.11 min; no ionization.

**A.1.7. 2-(2-Ethoxy-4-(trifluoromethyl)phenyl)ethan-1-amine**

The title compound is prepared according to the general procedure D described above, using tert-butyl (2-ethoxy-4-(trifluoromethyl)phenethyl)carbamate, and obtained as a yellow oil. LC-MS B:  $t_R$  = 0.67 min;  $[M+H]^+$  = 234.30.

**A.1.7.1. Tert-butyl (2-ethoxy-4-(trifluoromethyl)phenethyl)carbamate**

The title compound is prepared according to the general procedure C described above, using 4-bromo-3-ethoxybenzotrifluoride, and obtained as a yellow solid. LC-MS B:  $t_R$  = 1.09 min;  $[M+H]^+$  = 334.21.

**A.1.8. 2-(2-Aminoethyl)-5-chloro-N-methylaniline**

- 5 The title compound is prepared according to the general procedure D described above, using tert-butyl (4-chloro-2-(methylamino)phenethyl)carbamate, and obtained as a dark oil. LC-MS B:  $t_R$  = 0.56 min;  $[M+H]^+$  = 185.26.

**A.1.8.1. Tert-butyl (4-chloro-2-(methylamino)phenethyl)carbamate**

- 10 The title compound is prepared according to the general procedure C described above, using N-methyl 2-bromo-5-chloroaniline hydrochloride, and obtained as a pale yellow oil. LC-MS B:  $t_R$  = 1.00 min;  $[M+H]^+$  = 284.56.

**A.1.9. 2-(2-Methoxy-4-(methylthio)phenyl)ethan-1-amine hydrochloride**

The title compound is prepared according to the general procedure E described above, using tert-butyl (2-methoxy-4-(methylthio)phenethyl)carbamate, and obtained as a white solid. LC-MS B:  $t_R$  = 0.55 min;  $[M+H]^+$  = 198.18.

**A.1.9.1. Tert-butyl (2-methoxy-4-(methylthio)phenethyl)carbamate**

- 15 The title compound is prepared according to the general procedure C described above, using 1-bromo-2-methoxy-4-(methylsulfanyl)benzene, and obtained as a white foam. LC-MS B:  $t_R$  = 1.01 min;  $[M+H]^+$  = 298.17.

**A.1.10. 2-(4-(Difluoromethoxy)-2-methoxyphenyl)ethan-1-amine**

- 20 The title compound is prepared according to the general procedure E described above, using tert-butyl (4-(difluoromethoxy)-2-methoxyphenethyl)carbamate, and obtained as a yellow solid. LC-MS B:  $t_R$  = 0.59 min;  $[M+H]^+$  = 218.22.

**A.1.10.1. Tert-butyl (4-(difluoromethoxy)-2-methoxyphenethyl)carbamate**

The title compound is prepared according to the general procedure C described above, using 1-bromo-4-(difluoromethoxy)-2-methoxybenzene, and obtained as a yellow oil. LC-MS B:  $t_R$  = 1.02 min; no ionization.

**A.1.11. 2-(2-Fluoro-6-methoxy-4-(trifluoromethyl)phenyl)ethan-1-amine**

- 25 The title compound is prepared according to the general procedure B described above, using (*E*)-1-fluoro-3-methoxy-2-(2-nitrovinyl)-5-(trifluoromethyl)benzene, and obtained as an amber oil. LC-MS B:  $t_R$  = 0.64 min;  $[M+H]^+$  = 238.22.

**A.1.11.1. (*E*)-1-Fluoro-3-methoxy-2-(2-nitrovinyl)-5-(trifluoromethyl)benzene**

- 30 The title compound is prepared according to the general procedure A described above, using 2-fluoro-6-methoxy-4-(trifluoromethyl)benzaldehyde, and obtained as a light orange solid. LC-MS B:  $t_R$  = 1.05 min; no ionization.

**A.1.11.2. 2-Fluoro-6-methoxy-4-(trifluoromethyl)benzaldehyde**

A solution of 2-fluoro-6-hydroxy-4-(trifluoromethyl)benzaldehyde (1.00 g, 4.81 mmol) in anh. DMF (20 mL) is treated at RT with cesium carbonate (1.879 g, 5.77 mmol) and iodomethane (0.604 mL, 9.61 mmol) and the

RM is stirred at RT, under nitrogen, for 2h. Water is added and the mixture is extracted three times with Et<sub>2</sub>O. The combined organic layers are then washed twice with water, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (heptane/EtOAc = 1/1) affords 2-fluoro-6-methoxy-4-(trifluoromethyl)benzaldehyde as a colorless solid (962 mg, 90%). LC-MS B: t<sub>R</sub> = 0.91 min; no ionization.

5 **A.1.12. 2-(5-Chloro-2-methoxy-4-(trifluoromethyl)phenyl)ethan-1-amine**

The title compound is prepared according to the general procedure E described above, using tert-butyl (5-chloro-2-methoxy-4-(trifluoromethyl)phenethyl)carbamate, and obtained as a colorless solid. LC-MS B: t<sub>R</sub> = 0.66 min; [M+H]<sup>+</sup> = 254.24.

**A.1.12.1. Tert-butyl (5-chloro-2-methoxy-4-(trifluoromethyl)phenethyl)carbamate**

10 The title compound is prepared according to the general procedure C described above, using 1-bromo-5-chloro-2-methoxy-4-(trifluoromethyl)benzene, and obtained as a light yellow solid. LC-MS B: t<sub>R</sub> = 1.08 min; no ionization.

**A.1.12.2. 1-Bromo-5-chloro-2-methoxy-4-(trifluoromethyl)benzene**

15 A solution of 2-bromo-4-chloro-5-(trifluoromethyl)phenol (3.00 g, 10.40 mmol) in anh. DMF (40 mL) is treated at RT with cesium carbonate (4.050 g, 12.40 mmol) and iodomethane (1.30 mL, 20.70 mmol) and the RM is stirred at RT, under nitrogen, for 1h. Water is added and the mixture is extracted three times with Et<sub>2</sub>O. The combined organic layers are then washed twice with water, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (heptane/EtOAc = 7/3) affords 1-bromo-5-chloro-2-methoxy-4-(trifluoromethyl)benzene as a colorless solid (2.748 g, 92%). LC-MS B: t<sub>R</sub> = 1.06 min; no ionization.

20 **A.1.13. 2-(2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl)ethan-1-amine**

The title compound is prepared according to the general procedure E described above, using tert-butyl (2-(difluoromethoxy)-4-(trifluoromethyl)phenethyl)carbamate, and obtained as a yellow solid. LC-MS B: t<sub>R</sub> = 0.66 min; [M+H]<sup>+</sup> = 256.22.

**A.1.13.1. Tert-butyl (2-(difluoromethoxy)-4-(trifluoromethyl)phenethyl)carbamate**

25 The title compound is prepared according to the general procedure C described above, using 1-bromo-2-(difluoromethoxy)-4-(trifluoromethyl)benzene, and obtained as a yellow oil. LC-MS B: t<sub>R</sub> = 1.06 min; no ionization.

**A.1.14. 2-(3,4-Dichloro-2-methylphenyl)ethan-1-amine**

30 The title compound is prepared according to the general procedure E described above, using tert-butyl (3,4-dichloro-2-methylphenethyl)carbamate, and obtained as an orange solid. LC-MS B: t<sub>R</sub> = 0.62 min; [M+H]<sup>+</sup> = 204.21.

**A.1.14.1. Tert-butyl (3,4-dichloro-2-methylphenethyl)carbamate**

The title compound is prepared according to the general procedure C described above, using 1-bromo-3,4-dichloro-2-methylbenzene, and obtained as a yellow oil. LC-MS B: t<sub>R</sub> = 1.08 min; no ionization.

**A.1.15. 2-(4-(Difluoromethyl)-5-fluoro-2-methoxyphenyl)ethan-1-amine**

The title compound is prepared according to the general procedure E described above, using tert-butyl (4-(difluoromethyl)-5-fluoro-2-methoxyphenethyl)carbamate, and obtained as a colorless solid. LC-MS B:  $t_R$  = 0.57 min;  $[M+H]^+$  = 220.12.

**5 A.1.15.1. Tert-butyl (4-(difluoromethyl)-5-fluoro-2-methoxyphenethyl)carbamate**

The title compound is prepared according to the general procedure C described above, using 1-bromo-4-(difluoromethyl)-5-fluoro-2-methoxybenzene, and obtained as a yellow oil. LC-MS B:  $t_R$  = 1.02 min; no ionization.

**A.1.15.2. 1-Bromo-4-(difluoromethyl)-5-fluoro-2-methoxybenzene**

10 To a mixture of 4-bromo-2-fluoro-5-methoxybenzaldehyde (1.500 g, 6.11 mmol) in DCM (30 mL) is added dropwise (diethylamino)sulfur trifluoride (1.37 mL, 10.40 mmol) and the RM is stirred overnight at RT. The RM is then treated with sat. aq.  $\text{NaHCO}_3$  and DCM. The aq. layer is further extracted with DCM and the combined organic layers are dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (heptane/EtOAc = 1/1) affords 1-bromo-4-(difluoromethyl)-5-fluoro-2-methoxybenzene as a beige solid.  
15 LC-MS B:  $t_R$  = 0.97 min; no ionization.

**A.1.16. 2-(4-(Difluoromethyl)-2-methoxy-5-methylphenyl)ethan-1-amine**

The title compound is prepared according to the general procedure E described above, using tert-butyl (4-(difluoromethyl)-2-methoxy-5-methylphenethyl)carbamate, and obtained as a yellow solid. LC-MS B:  $t_R$  = 0.60 min;  $[M+H]^+$  = 216.17.

**20 A.1.16.1. Tert-butyl (4-(difluoromethyl)-2-methoxy-5-methylphenethyl)carbamate**

To a mixture of tert-butyl (4-formyl-2-methoxy-5-methylphenethyl)carbamate (112 mg, 0.38 mmol) in DCM (4 mL) is added dropwise (diethylamino)sulfur trifluoride (85  $\mu\text{L}$ , 0.64 mmol) and the RM is stirred overnight at RT. Additional (diethylamino)sulfur trifluoride (85  $\mu\text{L}$ , 0.64 mmol) is then added and the RM is further stirred at RT for 2h. The RM is then treated with sat. aq.  $\text{NaHCO}_3$  and DCM. The aq. layer is further extracted with  
25 DCM and the combined organic layers are washed with brine, dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (heptane/EtOAc = 1/1) affords tert-butyl (4-(difluoromethyl)-2-methoxy-5-methylphenethyl)carbamate as a yellow solid. LC-MS B:  $t_R$  = 1.04 min; no ionization.

**A.1.16.2. Tert-butyl (4-formyl-2-methoxy-5-methylphenethyl)carbamate**

30 The title compound is prepared according to the general procedure C described above, using 4-formyl-2-methoxy-5-methylphenyl trifluoromethanesulfonate, and obtained as a pale yellow solid. LC-MS B:  $t_R$  = 0.96 min; no ionization.

**A.1.16.3. 4-Formyl-2-methoxy-5-methylphenyl trifluoromethanesulfonate**

A solution of 4-(difluoromethyl)-2-methoxy-5-methylphenol (220 mg, 1.17 mmol) and TEA (0.42 mL, 3.04 mmol) in anh. DCM (11 mL) is treated portionwise at RT with 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (506 mg, 1.40 mmol) and the RM is stirred at RT, under nitrogen, overnight. The RM is then concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords 4-formyl-2-methoxy-5-methylphenyl trifluoromethanesulfonate as a colorless oil (155 mg). LC-MS B:  $t_R$  = 1.01 min; no ionization.

#### A.1.16.4. 4-(Difluoromethyl)-2-methoxy-5-methylphenol

A mixture of 1-(benzyloxy)-4-(difluoromethyl)-2-methoxy-5-methylbenzene (426 mg, 1.53 mmol) and 10% palladium over activated charcoal (42 mg) is placed under nitrogen before methanol (30 ml) is carefully added. The resulting suspension is placed under vacuum, then under hydrogen (1 atm), and the reaction mixture is vigorously stirred at rt overnight. The reaction mixture is filtered over a pad of celite, and concentrated under reduced pressure to afford 4-(difluoromethyl)-2-methoxy-5-methylphenol as a green solid which is further dried under HV (220 mg; 76%). LC-MS B:  $t_R$  = 0.79 min; no ionization.

#### A.1.16.5. 1-(Benzyloxy)-4-(difluoromethyl)-2-methoxy-5-methylbenzene

To a mixture of 4-(benzyloxy)-5-methoxy-2-methylbenzaldehyde (740 mg, 2.89 mmol) in DCM (20 mL) is added dropwise (diethylamino)sulfur trifluoride (0.64 mL, 4.91 mmol) and the RM is stirred overnight at RT. Additional (diethylamino)sulfur trifluoride (0.30 mL, 2.34 mmol) is then added and the RM is further stirred at RT for 8h. The RM is then treated with sat. aq.  $\text{NaHCO}_3$  and DCM. The aq. layer is further extracted with DCM and the combined organic layers are washed with brine, dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (heptane/EtOAc = 1/1) affords 1-(benzyloxy)-4-(difluoromethyl)-2-methoxy-5-methylbenzene as a colorless solid. LC-MS B:  $t_R$  = 1.05 min; no ionization.

#### A.1.16.6. 4-(Benzyloxy)-5-methoxy-2-methylbenzaldehyde

To a cooled ( $-78^\circ\text{C}$ ) solution of 1-(benzyloxy)-4-bromo-2-methoxy-5-methylbenzene (1.130 g, 3.68 mmol) in anh. THF (40 mL) is added a solution of BuLi (1.6 M in hexanes, 3.45 mL, 5.52 mmol) and the RM is further stirred at  $-78^\circ\text{C}$ , under nitrogen, for 1 min. Anh. DMF (538 mg, 7.36 mmol) is then added dropwise to the previous mixture and stirring at  $-78^\circ\text{C}$  is continued for 30 min. The RM is then treated dropwise with sat. aq.  $\text{NH}_4\text{Cl}$  and is allowed to warm-up to RT. Water and  $\text{Et}_2\text{O}$  are then added and the layers are separated. The aq. layer is further extracted with  $\text{Et}_2\text{O}$  and the combined organic layers are dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (heptane/EtOAc = 1/1) affords 4-(benzyloxy)-5-methoxy-2-methylbenzaldehyde as a colorless solid (0.816 g, 87%). LC-MS B:  $t_R$  = 0.98 min;  $[\text{M}+\text{H}]^+ = 257.27$ .

#### A.1.16.7. 1-(Benzyloxy)-4-bromo-2-methoxy-5-methylbenzene

A solution of 2-(benzyloxy)-1-methoxy-4-methylbenzene (1.025 g, 4.49 mmol) in anh. MeCN (20 mL) is treated portionwise with N-bromosuccinimide (879 mg, 4.94 mmol). The RM is further stirred at RT overnight. Sat. aq.  $\text{NaHCO}_3$  and DCM are added and the layers are separated. The organic layer is further washed with sat. aq.  $\text{NaHCO}_3$ , dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from

heptane to EtOAc) affords 1-(benzyloxy)-4-bromo-2-methoxy-5-methylbenzene as a pale yellow solid (1.35 g, 98%). LC-MS B:  $t_R$  = 1.09 min;  $[M+H]^+$  = 307.02.

#### A.1.16.8. 2-(Benzyloxy)-1-methoxy-4-methylbenzene

To a solution of 2-methoxy-5-methylphenol (1.00 g, 7.09 mmol) in anh. MeCN (22 mL) at RT are added successively benzyl bromide (0.92 mL, 7.80 mmol), potassium carbonate (2.00 g, 14.20 mmol) and potassium iodide (119 mg, 0.70 mmol). The RM is heated to 80°C, under nitrogen, overnight. The RM is then allowed to cool to RT, filtered and the obtained filtrate is concentrated under reduced pressure. Purification by FC (heptane/EtOAc = 1/1) affords 2-(benzyloxy)-1-methoxy-4-methylbenzene as a colorless solid (1.65 g, quantitative). LC-MS B:  $t_R$  = 1.02 min;  $[M+H]^+$  = 229.28.

### 10 A.2. Synthesis of pyrimidine halide derivatives of formula (3)

#### A.2.1. 6-Chloro-N-(4-methylphenethyl)pyrimidin-4-amine

The title compound is prepared according to the general procedure F described above, using 2-(p-tolyl)ethylamine and 4,6-dichloropyrimidine, and obtained as an off-white solid. LC-MS A:  $t_R$  = 0.87 min;  $[M+H]^+$  = 248.18.

15 Following the procedure described for the synthesis of A.2.1. described above, the following pyrimidine-halide derivatives are synthesized, starting from the corresponding commercially available phenethylamines or the phenethylamines A.1.1. – A.1.9. and 4,6-dichloropyrimidine or 4,6-diiodopyrimidine (see table 3).

**Table 3: Pyrimidine halide derivatives A.2.2. – A.2.11.**

| No.     | Compound                                                        | $t_R$ [min]<br>(LC-MS) | MS Data<br>m/z<br>$[M+H]^+$ |
|---------|-----------------------------------------------------------------|------------------------|-----------------------------|
| A.2.2.  | N-(4-bromophenethyl)-6-iodopyrimidin-4-amine                    | 0.84 (A)               | 403.95                      |
| A.2.3.  | 6-chloro-N-(3,4-dimethylphenethyl)pyrimidin-4-amine             | 1.00 (B)               | 262.30                      |
| A.2.4.  | N-(4-bromo-2-fluorophenethyl)-6-iodopyrimidin-4-amine           | 0.93 (B)               | 423.87                      |
| A.2.5.  | 6-chloro-N-(4-(trifluoromethyl)phenethyl)pyrimidin-4-amine      | 0.91 (A)               | 302.08                      |
| A.2.6.  | N-(4-bromo-2,6-difluorophenethyl)-6-iodopyrimidin-4-amine       | 0.95 (B)               | 440.99                      |
| A.2.7.  | N-(4-bromo-2-methoxyphenethyl)-6-iodopyrimidin-4-amine          | 0.97 (B)               | 433.81                      |
| A.2.8.  | N-(4-bromo-2-ethoxyphenethyl)-6-iodopyrimidin-4-amine           | 1.01 (B)               | 448.06                      |
| A.2.9.  | N-(4-bromo-2,6-dimethoxyphenethyl)-6-iodopyrimidin-4-amine      | 1.00 (B)               | 463.92                      |
| A.2.10. | 6-chloro-N-(2-methoxy-4-(methylthio)phenethyl)pyrimidin-4-amine | 0.99 (B)               | 310.14                      |
| A.2.11. | 6-chloro-N-(2-methoxy-4,5-dimethylphenethyl)pyrimidin-4-amine   | 1.02 (B)               | 292.15                      |



**A.2.12. 6-chloro-N-(2-ethoxy-4-(trifluoromethyl)phenethyl)pyrimidin-4-amine**

Following the general procedure F, using 4,6-dichloropyrimidine and 2-(2-ethoxy-4-(trifluoromethyl)phenyl)ethan-1-amine (A.1.7.), the title compound is obtained as a white powder. LC-MS B:  $t_R$  = 1.08 min;  $[M+H]^+$  = 346.09.

5 **A.2.13. 6-Chloro-N-(2,6-difluoro-4-methoxyphenethyl)pyrimidin-4-amine**

Following the general procedure F, using 4,6-dichloropyrimidine and 2-(2,6-difluoro-4-methoxyphenyl)ethan-1-amine, the title compound is obtained as a brown powder. LC-MS B:  $t_R$  = 0.96 min;  $[M+H]^+$  = 300.15.

**A.2.14. 6-Chloro-N-(2-methoxy-4,6-dimethylphenethyl)pyrimidin-4-amine**

10 The title compound is prepared according to the general procedure F described above, using 2-(2-methoxy-4,6-dimethylphenyl)ethan-1-amine and 4,6-dichloropyrimidine, and obtained as an off-white solid. LC-MS B:  $t_R$  = 1.03 min;  $[M+H]^+$  = 292.25.

**A.2.15. 6-Chloro-N-(2-methoxy-5-(methylthio)phenethyl)pyrimidin-4-amine**

15 The title compound is prepared according to the general procedure F described above, using 2-(2-methoxy-5-(methylthio)phenyl)ethan-1-amine and 4,6-dichloropyrimidine, and obtained as a yellow solid. LC-MS B:  $t_R$  = 0.99 min;  $[M+H]^+$  = 310.14.

**A.2.16. 6-Chloro-N-(4-(difluoromethoxy)-2-methoxyphenethyl)pyrimidin-4-amine**

The title compound is prepared according to the general procedure F described above, using 2-(4-(difluoromethoxy)-2-methoxyphenyl)ethan-1-amine (A.1.10.) and 4,6-dichloropyrimidine, and obtained as a colorless solid. LC-MS B:  $t_R$  = 0.99 min;  $[M+H]^+$  = 330.10.

20 **A.2.17. 6-Chloro-N-(2-methoxy-4-(trifluoromethyl)phenethyl)pyrimidin-4-amine**

The title compound is prepared according to the general procedure F described above, using 2-(2-methoxy-4-(trifluoromethyl)phenyl)ethan-1-amine and 4,6-dichloropyrimidine, and obtained as a colorless solid. LC-MS B:  $t_R$  = 1.04 min;  $[M+H]^+$  = 332.14.

**A.2.18. 6-Chloro-N-(2-fluoro-6-methoxy-4-(trifluoromethyl)phenethyl)pyrimidin-4-amine**

25 The title compound is prepared according to the general procedure F described above, using 2-(2-fluoro-6-methoxy-4-(trifluoromethyl)phenyl)ethan-1-amine (A.1.11.) and 4,6-dichloropyrimidine, and obtained as a light orange solid. LC-MS B:  $t_R$  = 1.05 min;  $[M+H]^+$  = 350.05.

**A.2.19. 6-Chloro-N-(5-chloro-2-methoxy-4-(trifluoromethyl)phenethyl)pyrimidin-4-amine**

30 The title compound is prepared according to the general procedure F described above, using 2-(5-chloro-2-methoxy-4-(trifluoromethyl)phenyl)ethan-1-amine (A.1.12.) and 4,6-dichloropyrimidine, and obtained as a colorless solid. LC-MS B:  $t_R$  = 1.07 min;  $[M+H]^+$  = 366.09.



**A.2.20. 6-Chloro-N-(2-(difluoromethoxy)-4-(trifluoromethyl)phenethyl)pyrimidin-4-amine**

The title compound is prepared according to the general procedure F described above, using 2-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)ethan-1-amine (A.1.13.) and 4,6-dichloropyrimidine, and obtained as an off-white solid. LC-MS B:  $t_R$  = 1.04 min;  $[M+H]^+$  = 368.07.

**5 A.2.21. 6-Chloro-N-(3,4-dichloro-2-methylphenethyl)pyrimidin-4-amine**

The title compound is prepared according to the general procedure F described above, using 2-(3,4-dichloro-2-methylphenyl)ethan-1-amine (A.1.14.) and 4,6-dichloropyrimidine, and obtained as a yellow solid. LC-MS B:  $t_R$  = 1.05 min;  $[M+H]^+$  = 316.06.

**A.2.22. 6-Chloro-N-(2-fluoro-6-methoxyphenethyl)pyrimidin-4-amine**

10 The title compound is prepared according to the general procedure F described above, using 2-(2-fluoro-6-methoxyphenyl)ethan-1-amine and 4,6-dichloropyrimidine, and obtained as a colorless solid. LC-MS B:  $t_R$  = 0.95 min;  $[M+H]^+$  = 282.23.

**A.2.23. 6-Chloro-N-(4,5-difluoro-2-methoxyphenethyl)pyrimidin-4-amine**

15 The title compound is prepared according to the general procedure F described above, using 2-(4,5-difluoro-2-methoxyphenyl)ethan-1-amine and 4,6-dichloropyrimidine, and obtained as a colorless solid. LC-MS B:  $t_R$  = 0.97 min;  $[M+H]^+$  = 300.16.

**A.2.24. 6-Chloro-N-(2-methoxy-4-(trifluoromethoxy)phenethyl)pyrimidin-4-amine**

20 The title compound is prepared according to the general procedure F described above, using 2-(2-methoxy-4-(trifluoromethoxy)phenyl)ethan-1-amine and 4,6-dichloropyrimidine, and obtained as a colorless solid. LC-MS B:  $t_R$  = 1.05 min;  $[M+H]^+$  = 348.07.

**A.2.25. 6-Chloro-N-(4-(difluoromethyl)-5-fluoro-2-methoxyphenethyl)pyrimidin-4-amine**

The title compound is prepared according to the general procedure F described above, using 2-(4-(difluoromethyl)-5-fluoro-2-methoxyphenyl)ethan-1-amine (A.1.15.) and 4,6-dichloropyrimidine, and obtained as a colorless solid. LC-MS B:  $t_R$  = 0.99 min;  $[M+H]^+$  = 332.13.

**25 A.2.26. 6-Chloro-N-(4-(difluoromethyl)-2-methoxy-5-methylphenethyl)pyrimidin-4-amine**

The title compound is prepared according to the general procedure F described above, using 2-(4-(difluoromethyl)-2-methoxy-5-methylphenyl)ethan-1-amine (A.1.16.) and 4,6-dichloropyrimidine, and obtained as a beige solid. LC-MS B:  $t_R$  = 1.00 min;  $[M+H]^+$  = 328.13.A.3.

**Synthesis of boronic acid derivatives of formula (4)****30 A.3.1. 3-Fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylic acid**

To a solution of lithium diisopropylamide (2.0 M in THF/heptane/ethylbenzene, 9.84 mL, 39.4 mmol) in THF (74 mL) at -78°C is added dropwise a solution of 3-fluoro-2-thiophenecarboxylic acid (2.00 g, 13.1 mmol) in THF (37 mL). The RM is stirred for 10 min at -78°C then a solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.1 mL, 19.7 mmol) in THF (37 mL) is added dropwise, the RM is stirred for 20 min at -78°C then it is allowed to

warm to RT and stirred for 1h. HCl 1N (105 mL, 105 mmol) is added to the RM at 0°C, and it is stirred for 5 min. The mixture is extracted with EtOAc (3 times). The combined organic layers are washed with brine, dried over MgSO<sub>4</sub> and concentrated to dryness. The crude is purified by FC (DCM/MeOH 1:0 to 9:1) to afford the title compound as a green-yellow solid (2.64 g, 74%). LC-MS A: t<sub>R</sub> = 0.46 min; no ionization.

5 **A.3.2. Methyl 3-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate**

The title compound is prepared according to the synthesis of A.3.1. using methyl 3-ethylthiophene-2-carboxylate; LC-MS B: t<sub>R</sub> = 1.10 min; [M+H]<sup>+</sup> = 297.27.

**A.3.3. 3-Ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylic acid**

10 The title compound is prepared according to the synthesis of A.3.1. using 3-ethoxythiophene-2-carboxylic acid. LC-MS A: t<sub>R</sub> = 0.48 min; [M+H]<sup>+</sup> = 217.07 (boronic acid, from hydrolysis of the pinacol ester on the LC-MS-column).

**A.3.4. 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)thiophene-2-carboxylic acid**

The title compound is prepared according to the procedure described for A.3.1., starting with 3-(trifluoromethyl)thiophene-2-carboxylic acid. LC-MS A: t<sub>R</sub> = 0.59 min; no ionization.

**A3.4.1. 3-(Trifluoromethyl)thiophene-2-carboxylic acid**

15 To a -78°C solution of 3-(trifluoromethyl)thiophene (0.4 mL, 3.68 mmol) in dry THF (10 mL) is added dropwise a solution of butyllithium (1.38M in hexane, 2.93 mL, 4.05 mmol) and the RM is stirred for 30 min. The reaction mixture is then poured over an excess of freshly crushed dry ice carbon dioxide. Once the RM is back at RT, HCl 1N is added until pH<3 and the mixture is extracted with DCM (3x). The organic layer is dried over MgSO<sub>4</sub> and concentrated under vacuum, affording the title compound as a pale yellow solid (0.72 g, quantitative). LC-MS A: t<sub>R</sub> = 0.69 min; no ionization.

**A.3.5. 5-(2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-tetrazole**

25 A MW vial is charged with 2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (500 mg, 1.83 mmol), azidotributyltin(IV) (0.768 mL, 2.75 mmol), and dry toluene (4 mL), it is sealed and heated at 180°C for 1h under MW irradiation. The mixture is cooled to RT, treated with HCl 0.1N and extracted with EtOAc. The organic layer is dried over MgSO<sub>4</sub> and concentrated under vacuum. The residue is purified via FC (Heptane:EtOAc 100:0 to 10:90), affording the title compound as a white solid (135 mg, 23%). LC-MS B: t<sub>R</sub> = 0.87 min; [M+H]<sup>+</sup> = 317.14.

**A.3.5.1. 2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile**

30 A solution of 2-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.50 g, 6.12 mmol), K<sub>2</sub>CO<sub>3</sub> (1.69 g, 12.2 mmol) in DMF (4 mL) and iodoethane (0.596 mL, 7.34 mmol) is heated at 120°C for 30 min. The reaction mixture is cooled down to RT, partitioned between DCM and 1N NaHCO<sub>3</sub>. The aqueous layer is re-extracted with DCM, the combined organics are dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. This afforded the title compound as a beige solid (1.31 g, 78%). LC-MS B: t<sub>R</sub> = 0.96 min; [M+CH<sub>3</sub>CN+H]<sup>+</sup> = 315.10.

**A.3.6. 2-(Difluoromethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid**

To a solution of 4-bromo-2-(difluoromethoxy)benzoic acid (1.00 g, 3.56 mmol) in DMF (20 mL) are added at RT bis(pinacolato)diboron (1.355 g, 5.34 mmol), KOAc (1.047 g, 10.7 mmol) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium (II) (208 mg, 0.285 mmol). The RM is stirred at 100°C for 17h, then cooled to RT and filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted (x2) with EtOAc. Organic layers are combined, washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue is purified by FC eluting with DCM to afford the title compound as an orange solid (846 mg, 76%). LC-MS A: t<sub>R</sub> = 0.37 min; [M+H]<sup>+</sup> = 313.11.

Following the procedure described for the synthesis of A.3.6. described above, the following boronic acid derivatives are synthesized, starting from the corresponding commercially available halides (see table 4).

**Table 4: Boronic acid derivatives A.3.7. – A.3.11.**

| No.            | Compound                                                                              | t <sub>R</sub> [min]<br>(LC-MS) | MS Data<br>m/z<br>[M+H] <sup>+</sup> |
|----------------|---------------------------------------------------------------------------------------|---------------------------------|--------------------------------------|
| <b>A.3.7.</b>  | 2-Cyclobutoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid             | 0.91 (A)                        | 319.11                               |
| <b>A.3.8.</b>  | 1-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3H-indazol-3-one | 0.77 (A)                        | 275.27                               |
| <b>A.3.9.</b>  | 5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoxazol-3-ol                | 0.85 (A)                        | 288.17                               |
| <b>A.3.10.</b> | 5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,2,4]-oxadiazol-3-ol      | 0.82 (B)                        | 290.10                               |
| <b>A.3.11.</b> | Methyl 2-(methylthio)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate         | 0.96 (A)                        | 309.18                               |

#### **A.3.12. 2-Fluoro-6-propyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid**

The title compound is prepared according to the procedure described for A.3.6., starting with 4-bromo-2-fluoro-6-propylbenzoic acid. LC-MS D: t<sub>R</sub> = 0.48 min; [M-H]<sup>+</sup> = 307.11.

##### **A.3.12.1. 4-Bromo-2-fluoro-6-propylbenzoic acid**

To a solution of 4-bromo-2,6-difluorobenzoic acid (5.00 g, 21.1 mmol) in THF (50 mL) at 0°C is added dropwise over 30 min n-propylmagnesium bromide (2M in THF, 21.6 mL, 43.2 mmol). The RM is allowed to reach RT and stirred for 17h, then quenched carefully at 0°C with MeOH (10 mL). After stirring for 5 min, the solvent is removed under reduced pressure. The residue is partitioned between EtOAc and 2N HCl. The aqueous phase is re-extracted with EtOAc (2x). The combined org. phases are washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The residue is purified by FC (heptane/EtOAc 100:0 to 70:30) to afford the title compound as a white solid (4.45 g, 81%). LC-MS A: t<sub>R</sub> = 0.84 min; no ionization.

#### **A.3.13. 3-(2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,2,4]oxadiazol-5(4H)-one**

The title compound is prepared according to the procedure described for A.3.6., starting with 3-(4-bromo-2-ethoxyphenyl)-[1,2,4]oxadiazol-5(4H)-one. LC-MS A:  $t_R$  = 0.89 min;  $[M+H]^+$  = 333.06.

**A.3.13.1. 3-(4-Bromo-2-ethoxyphenyl)-[1,2,4]oxadiazol-5(4H)-one**

5 The solution of 4-bromo-2-ethoxy-N'-hydroxybenzimidamide (1.395 g, 5.38 mmol), 1,1'-carbonyldiimidazole (1.31 g, 8.08 mmol) and DBU (1.23 mL, 8.08 mmol) in dioxane (20 mL) is stirred at 90 °C for 4h30min. Once at RT, the product precipitated upon addition of HCl 1M. Dioxane is partially evaporated via N<sub>2</sub> stream prior to filtering off the solid under vacuum, washing with water. The title compound is obtained as a white solid (1.375 g, 90%). LC-MS A:  $t_R$  = 0.81min,  $[M+MeCN]^+$  = 325.89.

**A.3.13.2. 4-Bromo-2-ethoxy-N'-hydroxybenzimidamide**

10 A suspension of 4-bromo-2-ethoxybenzonitrile (1.50 g, 6.5 mmol), hydroxylamine hydrochloride (913 mg, 13 mmol) and NaHCO<sub>3</sub> (1.365 g, 16.3 mmol) in water (1.32 mL) and EtOH (26.6 mL) is stirred in a sealed tube at 90 °C for 3h. Once at RT, the product precipitated from the RM upon addition of water. The solid is filtered off, washing with water and some Et<sub>2</sub>O. A first crop of pure title compound (947mg) is thus obtained as a white solid. The filtrate is extracted with EtOAc. The organic layer is then washed twice with brine, dried over MgSO<sub>4</sub>,  
15 filtered and concentrated. The residue is purified by FC (hept/EtOAc 1:1) to yield another crop of the pure title compound as a white solid (448 mg), merged with the first batch from precipitation. The title compound is obtained as a white solid (1.395 g, 83%). LC-MS A:  $t_R$  = 0.53 min,  $[M+H]^+$  = 259.03.

**A.3.14. 3-(2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)propanoic acid**

20 The title compound is prepared according to the procedure described for A.3.6., starting with 3-(4-bromo-2-ethoxyphenoxy)propanoic acid. LC-MS D:  $t_R$  = 0.45 min;  $[M-H]^+$  = 335.18.

**A.3.14.1. 3-(4-Bromo-2-ethoxyphenoxy)propanoic acid**

A MW vial is charged with 4-bromo-2-ethoxyphenol (1300 mg, 5.98 mmol), H<sub>2</sub>O (5 mL), NaOH 32% (1.332 mL, 14.38 mmol) and 3-chloropropionic acid (674 mg, 6.08 mmol). It is sealed and irradiated at 120°C, for 40 min. The RM is diluted in water and pH is decreased to pH9 with HCl 2N then is extracted twice with EtOAc.  
25 The basic aqueous layer is then acidified to pH2 and extracted twice with EtOAc, the combined organic extracts are washed with water, brine, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness, yielding the title compound as a white powder (0.448 g, 56%). LC-MS A:  $t_R$  = 0.89 min;  $[M+H]^+$  = 289.10.

**A.3.15. Methyl (E)-3-(3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acrylate**

30 The title compound is prepared according to the procedure described for A.3.1., starting with methyl (E)-3-(3-ethoxythiophen-2-yl)acrylate. LC-MS A:  $t_R$  = 1.02 min;  $[M+H]^+$  = 339.14.

**A.3.15.1. Methyl (E)-3-(3-ethoxythiophen-2-yl)acrylate**

A suspension of 3-ethoxythiophene-2-carbaldehyde (2.90 g, 18.6 mmol), methyl bromoacetate (3.07 mL, 33.4 mmol), and triphenylphosphine (7.305 g, 27.8 mmol) in aq saturated NaHCO<sub>3</sub> (100 mL) is stirred at RT for 5h. THF (30 mL) is added and the RM is stirred overnight at RT. It is then extracted twice with DCM. The  
35 combined organic layers are dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The crude is purified

by FC (Hept/EtOAc 9:1) to afford the title compound as a dark orange oil (2.9 g, 100%). LC-MS A:  $t_R$  = 0.69 min;  $[M+MeCN]^+$  = 198.26.

**A.3.16. 3-(3-Ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)propanoic acid**

To a solution of methyl (*E*)-3-(3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acrylate  
5 [A.3.15.] (250 mg, 0.786 mmol) in MeOH (15 mL) is added Pd/C 5% wet (50 mg). Then the vessel is inertized with  $N_2$  and flushed with  $H_2$ . The mixture is placed in a autoclave and it is stirred overnight at RT under 4 Bar of  $H_2$ , then for 1d at 50°C under 4 bar of  $H_2$ . After filtration on whatman filter, NaOH 10% (1.18 mL, 11.8 mmol) is added and the RM is stirred for 1h at RT. It is then treated with HCl 2N until pH<1 and extracted twice with EtOAc. The organic layer is dried over  $MgSO_4$  and concentrated, to afford the title compound as a dark yellow oil (287 mg, 74%). LC-  
10 MS A:  $t_R$  = 0.86 min;  $[M+H]^+$  = 327.09.

**A.3.17. 3-(3-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)oxetan-3-ol**

The title compound is prepared according to the procedure described for A.3.1., starting with 3-(3-methoxythiophen-2-yl)oxetan-3-ol. LC-MS A:  $t_R$  = 0.78 min;  $[M-H_2O]^+$  = 295.12.

**A.3.17.1. 3-(3-Methoxythiophen-2-yl)oxetan-3-ol**

To a stirred solution of 3-methoxythiophene (1.00 g, 8.58 mmol) and N,N,N',N'-tetramethylethylenediamine  
15 (1.55 mL, 10.3 mmol) in  $Et_2O$  (30 mL) is added butyllithium (1.6M in Hexane, 6.4 mL, 10.3 mmol) dropwise at 0°C. The RM is stirred at RT for 30 min, then 3-oxetanone (0.761 mL, 12.9 mmol) is added dropwise and the RM is stirred at RT for 35min, then diluted with water, the aqueous layer is extracted three times with EtOAc and the combined organic layers are dried over  $MgSO_4$ , filtered and concentrated under  
20 reduced pressure. The residue is purified by FC (Hept to Hept/EtOAc 8:2) to give the title compound as a light-yellow oil (1.123 g, 70%). LC-MS A:  $t_R$  = 0.53 min;  $[M-H_2O]^+$  = 169.04.

**A.3.18. Methyl 2-(3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acetate**

A suspension of methyl 2-(3-ethoxythiophen-2-yl)acetate (815 mg, 4.07 mmol), bis(pinacolato)diboron (633 mg, 2.44 mmol), (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (28.9 mg, 0.0437 mmol) and 4,4'-di-tert-butyl-2,2'-  
25 dipyriddy (26.8 mg, 0.0999 mmol) in THF (19.3 mL) is degassed with a nitrogen stream for 15min and then stirred at 80°C overnight. The RM is concentrated under reduced pressure and the residue is purified by FC (Hept to Hept/EtOAc 9:1) to afford the title compound as a colourless oil which crystallized upon standing. LC-MS B:  $t_R$  = 1.03 min;  $[M+H]^+$  = 327.14.

**A.3.18.1. Methyl 2-(3-ethoxythiophen-2-yl)acetate**

Silver benzoate (1800 mg, 7.78 mmol) is added portionwise to a solution of 2-diazo-1-(3-ethoxythiophen-2-yl)ethan-1-one (2025 mg, 10.3 mmol) and TEA (4.31 mL, 31 mmol) in MeOH (52.7 mL) and the RM is stirred at RT for 2h. It is then diluted with EtOAc and filtered over celite. The filtrate is washed twice with sat. aq.  $NaHCO_3$  and once with brine. The organic layer is dried over  $MgSO_4$ , filtered and concentrated. The residue is purified by FC (Hept to Hept/EtOAc 95:5) to yield the title compound as a light yellow oil (817 mg, 40%).  
35 LC-MS B:  $t_R$  = 0.86 min,  $[M+H]^+$  = 201.14.

**A.3.18.2. 2-Diazo-1-(3-ethoxythiophen-2-yl)ethan-1-one**

A solution of 3-ethoxythiophene-2-carboxylic acid (2500 mg, 14.1 mmol) in DCM (120 mL) is treated with thionyl chloride (1.56 mL, 21.1 mmol), dropwise. The RM is stirred at RT overnight, it is then concentrated in vacuo, and the residue is dissolved in MeCN (80 mL). TEA (2.2 mL, 15.8 mmol) is added dropwise and the solution is cooled down to 0°C. (Trimethylsilyl)diazomethane (2M solution, 15 mL, 30 mmol) is added dropwise and the RM is stirred at RT for 2d. It is then carefully quenched by dropwise addition of AcOH, until no more bubbling is observed. The RM is then concentrated and the residue is partitioned between EtOAc and water. The organic layer is then washed with sat. aq. NaHCO<sub>3</sub> and with brine, dried (MgSO<sub>4</sub>) and concentrated. The residue is purified by FC (Hept to Hept/EtOAc 8:2) to yield the title compound as an intense yellow solid (2.028 g, 73%). LC-MS B: t<sub>R</sub> = 0.78 min, [M+H]<sup>+</sup> = 197.15.

**A.3.19. Ethyl 2-((2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxoacetate**

The title compound is prepared according to the procedure described for A.3.6., starting with ethyl 2-((4-bromo-2-ethoxyphenyl)amino)-2-oxoacetate. LC-MS A: t<sub>R</sub> = 0.98 min; [M+H]<sup>+</sup> = 364.21.

**A.3.19.1. Ethyl 2-((4-bromo-2-ethoxyphenyl)amino)-2-oxoacetate**

To a solution of 4-bromo-2-ethoxyaniline (1.10 g, 4.84 mmol) in DCM (35 mL) is added TEA (0.748 mL, 5.32 mmol) at RT. The RM is cooled to 0°C and ethyl oxalyl chloride (0.61 mL, 5.32 mmol) is added dropwise. The RM is stirred for 30 min at 0°C then allowed to warm to RT and stirred for 30 min. The RM is partitioned between EtOAc and sat. aq. NaHCO<sub>3</sub>. The two layers are separated and the organic layers washed with water, brine then dried over MgSO<sub>4</sub>, filtered and solvent removed under vacuo, affording the title compound as a brown solid (1.52 g, 99%). LC-MS A: t<sub>R</sub> = 0.92 min; [M+MeCN]<sup>+</sup> = 316.04.

**A.3.20. 2-(2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethan-1-ol**

A solution of 4-hydroxy-3-methoxyphenylboronic acid, pinacol ester (100 mg, 0.4 mmol) in DMF (4 mL) is successively added cesium carbonate (456 mg, 1.4 mmol) and 2-iodoethanol (0.0563 mL, 0.72 mmol). The RM is then stirred at 100°C for 4h. The RM is cooled down to RT and 2-iodoethanol (0.0281 mL, 0.36 mmol) is added. The RM is heated up to 100°C and stirred for 1h, then cooled to RT, diluted with EtOAc and washed with water (3x). The organic layer is dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue is purified by acidic prep. HPLC to afford the title compound as a beige solid (23 mg, 20%). LC-MS B: t<sub>R</sub> = 0.83 min; [M+H]<sup>+</sup> = 295.25.

**A.3.21. 3-Ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-sulfonamide**

A MW vial is charged with 3-ethoxythiophene-2-sulfonamide (308 mg, 1.49 mmol), bis(pinacolato)diboron (578 mg, 2.23 mmol), (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (49.3 mg, 0.0743 mmol) and 4,4'-di-tert-butyl-2,2'-dipyridyl (32.6 mg, 0.119 mmol) in cyclohexane (12 mL), it is capped and the RM is stirred at 120°C for 30 min under MW irradiation. The RM is concentrated and purified by FC (DCM/(MeOH/NH<sub>3</sub> 98:2), from 100:0 to 80:20), affording the title compound as an orange solid (670 mg, quantitative). LC-MS B: t<sub>R</sub> = 0.47 min; [M+H]<sup>+</sup> = 252.26 (mass from boronic acid from pinacol ester cleavage during LC-MS analysis).



**A.3.21.1. 3-Ethoxythiophene-2-sulfonamide**

EtOH (2 mL, 34.3 mmol) followed by NaH (241 mg, 10 mmol) are added at RT to a solution of 3-fluorothiophene-2-sulfonamide (607 mg, 3.35 mmol) in DMF (3 mL). The RM is stirred overnight at 90°C. It is cooled to RT, NaH (241 mg, 10 mmol) and EtOH (1 mL) are added and the RM is stirred at 90°C for 4h. It is cooled to RT, quenched with water, and extracted twice with EtOAc. The combined organic layers are washed with brine, dried on anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue is purified by FC (heptane/EtOAc, 100:0 to 1:1), affording the title compound as a white solid (308 mg, 44%). LC-MS B: t<sub>R</sub> = 0.56 min; [M+H]<sup>+</sup> = 208.28.

**A.3.22. Methyl 2-(2-hydroxyethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate**

The title compound is prepared according to the procedure described for A.3.6., starting with methyl 4-bromo-2-(2-hydroxyethoxy)benzoate. LC-MS B: t<sub>R</sub> = 0.89 min; [M+H]<sup>+</sup> = 323.26.

**A.3.22.1. Methyl 4-bromo-2-(2-hydroxyethoxy)benzoate**

NaH (101 mg, 4.2 mmol) is added portionwise to a 0°C solution of methyl 4-bromo-2-hydroxybenzoate (500 mg, 2.1 mmol) in DMF (5 mL). The RM is stirred for a few minutes at 0°C, then 2-bromoethanol (0.235 mL, 3.15 mmol) is added and the RM is stirred at 90°C for 2h45, then cooled to RT. Water is added to the RM and it is extracted twice with EtOAc. The combined organic layers are washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue is purified by FC (heptane/EtOAc, 1:0 to 6:4), affording the title compound as a colorless oil (358 mg, 62%). LC-MS B: t<sub>R</sub> = 0.77 min; [M+H]<sup>+</sup> = 275.14.

**A.3.23. 7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-5H-thieno[3,2-e][1,4]dioxepin-5-one**

The title compound is prepared according to the procedure described for A.3.21., starting with 2,3-dihydro-5H-thieno[3,2-e][1,4]dioxepin-5-one. LC-MS B: t<sub>R</sub> = 0.51 min; [M+H]<sup>+</sup> = 215.41 (mass from boronic acid from pinacol ester cleavage during LC-MS analysis).

**A.3.23.1. 2,3-Dihydro-5H-thieno[3,2-e][1,4]dioxepin-5-one**

A MW vial is charged with K<sub>2</sub>CO<sub>3</sub> (623 mg, 4.5 mmol), methyl 3-hydroxythiophene-2-carboxylate (250 mg, 1.5 mmol) and DMF (5 mL). The RM is stirred for a few minutes then 2-bromoethanol (0.146 mL, 1.95 mmol) is added, the vial is capped and heated at 100°C for 2h under MW irradiation. 2-Bromoethanol (0.0319 mL, 0.45 mmol) is added and the RM is stirred at 90°C overnight, under thermal conditions. Once at RT, water is added and the RM is extracted thrice with EtOAc. The combined organic layers are dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure, affording the crude title compound as a brownish solid (338 mg, quantitative). LC-MS B: t<sub>R</sub> = 0.61 min; [M+H]<sup>+</sup> = 170.94.

**A.3.24. Methyl 4-chloro-3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate**

The title compound is prepared according to the procedure described for A.3.21., starting with methyl 4-chloro-3-ethoxythiophene-2-carboxylate. LC-MS B: t<sub>R</sub> = 0.75 min; no ionization.

**A.3.24.1. Methyl 4-chloro-3-ethoxythiophene-2-carboxylate**



To a solution of methyl 4-chloro-3-hydroxythiophene-2-carboxylate (528 mg, 2.74 mmol) in DMF (27 mL) at RT is added potassium carbonate (792 mg, 5.62 mmol). The RM is stirred for 15min at 60°C then iodoethane (0.267 mL, 3.29 mmol) is added and the RM is stirred at 60°C for 1h30, cooled to RT, and partitioned between EtOAc and water. The organic layer is washed once more with water, then brine, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness yielding the title compound as a yellow oil (570mg, 94%). LC-MS B: t<sub>R</sub> = 0.92 min; [M+H]<sup>+</sup> = 221.03.

**A.3.25. 3-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,2,4]oxadiazol-5(4H)-one**

The title compound is prepared according to the procedure described for A.3.6., starting with 3-(4-bromophenyl)-[1,2,4]oxadiazol-5(4H)-one. LC-MS B: t<sub>R</sub> = 0.90 min; [M+MeCN]<sup>+</sup> = 330.12.

**A.3.26. 3-(2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,2,4]oxadiazol-5(4H)-one**

The title compound is prepared according to the procedure described for A.3.6., starting with 3-(4-bromo-2-ethoxyphenyl)-[1,2,4]oxadiazol-5(4H)-one. LC-MS B: t<sub>R</sub> = 0.98 min; [M+H]<sup>+</sup> = 333.18.

**A.3.26.1. 3-(4-Bromo-2-ethoxyphenyl)-[1,2,4]oxadiazol-5(4H)-one**

A solution of (Z)-4-bromo-2-ethoxy-N'-hydroxybenzimidamide (1.25 g, 4.82 mmol), 1,1'-carbonyldiimidazole (1.17 g, 7.24 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.1 mL, 7.24 mmol) in dioxane (18 mL) is stirred at 90°C for 90min. Once at RT, the product precipitated upon addition of HCl 1M. Dioxane is partially evaporated via N<sub>2</sub> stream prior to filtering off the solid under vacuum, washing with water. The title compound is obtained as a white solid (1.096 g, 80%). LC-MS B: t<sub>R</sub> = 0.53 min, no ionization; <sup>1</sup>H NMR (500 MHz, d<sub>6</sub>-DMSO) δ: 12.22-12.56 (m, 1 H), 7.54 (d, J = 8.2 Hz, 1 H), 7.45 (d, J = 1.7 Hz, 1 H), 7.30-7.33 (m, 1 H), 4.14-4.25 (m, 2 H), 1.33-1.39 (m, 3 H).

**A.3.26.2. (Z)-4-Bromo-2-ethoxy-N'-hydroxybenzimidamide**

A suspension of 4-bromo-2-ethoxybenzonitrile (1.50 g, 6.5 mmol), hydroxylamine hydrochloride (913 mg, 13 mmol) and NaHCO<sub>3</sub> (1.365 g, 16.3 mmol) in water (1.32 mL) and EtOH (26.6 mL) is stirred in a sealed tube at 90°C for 6h. Once at RT, the product precipitated from the RM upon addition of water. The solid is filtered off under high vacuum, washing with water and some Et<sub>2</sub>O. A first crop of pure title compound (947mg) was thus obtained as white solid. The filtrate is extracted with EtOAc. The organic layer is then washed twice with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The residue is purified by FC (hept/EtOAc 1:1) to yield another crop of the pure title compound as a white solid (448 mg), merged with the first batch from precipitation. The title compound is obtained as a white solid (1.395 g, 83%). LC-MS B: t<sub>R</sub> = 0.53min, [M+H]<sup>+</sup> = 259.12.

**A.3.27. 1-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinazolin-2(1H)-one**

The title compound is prepared according to the procedure described for A.3.6., starting with 7-bromo-1-methyl-3,4-dihydroquinazolin-2(1H)-one. LC-MS A: t<sub>R</sub> = 0.80 min; [M+H]<sup>+</sup> = 289.18.

**A.3.28. Ethyl 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-oxoacetate**

The title compound is prepared according to the procedure described for A.3.6., starting with ethyl 2-(4-bromo-2-ethoxyphenyl)-2-oxoacetate. LC-MS A:  $t_R$  = 0.98 min;  $[M+H]^+$  = 349.19.

#### A.3.28.1. Ethyl 2-(4-bromo-2-ethoxyphenyl)-2-oxoacetate

To a solution of 2-(4-bromo-2-hydroxyphenyl)-2-oxoacetic acid (1.00 g, 3.88 mmol) and  $K_2CO_3$  (1.605 g,) in DMF (10 mL) is added iodethane (0.799 mL, 9.69 mmol) and the RM is stirred at 50°C for 2 d.  $K_2CO_3$  (1.605 g, 11.6 mmol) and iodethane (0.799 mL, 9.69 mmol) are added and the RM is stirred at 60°C for 20h. The RM is filtered, rinsed with DCM and concentrated under reduced. The residue is purified by FC (Hept/EtOAc 1:0 to 4:1) to afford the title compound as a beige solid (0.921 g, 79%). LC-MS A:  $t_R$  = 0.92 min;  $[M+H]^+$  = 303.03.

#### 10 A.3.29. Methyl (2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)glycinate

The title compound is prepared according to the procedure described for A.3.6., starting with methyl (4-bromo-2-ethoxyphenyl)glycinate. LC-MS B:  $t_R$  = 0.93 min;  $[M+H]^+$  = 336.28.

#### A.3.29.1. Methyl (4-bromo-2-ethoxyphenyl)glycinate

To a solution of 4-bromo-2-ethoxyaniline (0.60 g, 2.64 mmol) in DMF (2.5 mL) is added DiPEA (0.673 mL, 3.96 mmol) followed by methyl bromoacetate (0.275 mL, 2.9 mmol). The mixture is stirred at 90°C for 1h in the microwave apparatus. The DMF is evaporated under high vacuum and the residue is purified by FC, eluting with Hept/EtOAc 1:0 to 17:3 affording the title compound as a dark red oil (0.71 g, 94%). LC-MS A:  $t_R$  = 0.89 min;  $[M+H]^+$  = 288.08.

#### A.3.30. 3-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylic acid

To a solution of methyl 3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (650 mg, 1.85 mmol) in MeOH (12 mL), THF (4 mL) and  $H_2O$  (4 mL) at RT is added NaOH 10% (3.71 mL, 9.26 mmol) is added and the RM is stirred at RT overnight. The solvents are removed in vacuo. The basic aqueous layer is acidified to pH=3-4 using HCl 1N and extracted with EtOAc (2x). The combined organic layers are washed with brine, dried over  $MgSO_4$ , filtered and solvent is removed in vacuo yielding the title compound as a brown solid, well dried under HV (365 mg, 69%). LC-MS B:  $t_R$  = 0.44 min;  $[M+H]^+$  = 203.3 (boronic acid, from hydrolysis of the pinacol ester on the LC-MS-column).

#### A.3.30.1. Methyl 3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate

The title compound is prepared according to the procedure described for A.3.18., starting with methyl 3-methoxythiophene-2-carboxylate. LC-MS B:  $t_R$  = 0.56 min;  $[M+H]^+$  = 216.99 (boronic acid, from hydrolysis of the pinacol ester on the LC-MS-column).

#### A.3.31. 2-Ethoxy-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid

Ethyl 2-ethoxy-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (960 mg, 2.38 mmol) is dissolved in MeOH/THF (1:1) (10 mL). Then NaOH 10% (4.77 mL, 11.9 mmol) is added and the RM is stirred at RT for 4h. It is treated with HCl 2N (~10 mL) to reach acidic pH (<2) and extracted with EtOAc. The resulting organic phase is

dried over  $\text{MgSO}_4$  and concentrated, yielding the title compound as a yellow solid (0.735 g, 81%). LC-MS B:  $t_R$  = 0.91 min;  $[\text{M}+\text{H}]^+ = 311.26$ .

**A.3.31.1. Ethyl 2-ethoxy-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate**

5 The title compound is prepared according to the procedure described for A.3.6., starting with ethyl 4-bromo-2-ethoxy-3-fluorobenzoate. LC-MS B:  $t_R$  = 1.10 min;  $[\text{M}+\text{H}]^+ = 339.26$ .

**A.3.31.2. Ethyl 4-bromo-2-ethoxy-3-fluorobenzoate**

10 To a solution of 4-bromo-3-fluoro-2-hydroxybenzoic acid (750 mg, 3.1 mmol) and  $\text{K}_2\text{CO}_3$  (1070 mg, 7.74 mmol) in DMF (6 mL), is added ethyl iodide (0.508 mL, 6.35 mmol). The reaction is stirred for 2.5 d at RT, then it is partitioned between DCM and brine. The aqueous layer is re-extracted with DCM, the combined organics are washed with brine then dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure to afford the title compound as a dark orange oil. LC-MS B:  $t_R$  = 1.03 min;  $[\text{M}+\text{H}]^+ = 291.01$ .

**A.3.32. 2-(Methylamino)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide**

15 2-(Methylamino)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (300 mg, 1.08 mmol) is dissolved in DMF (5 mL), TEA (0.452 mL, 3.25 eq) and HATU (535 mg, 1.41 mmol) are added followed after 2 min stirring by ammonia (0.5 M in dioxane, 2.6 mL, 1.3 mmol). The RM is stirred at RT for 1h, then treated with 1mL of 25% ammonia and extracted with DCM. The organic layer is washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated. The residue is purified by FC (Hept/EtOAc 1:0 to 1:3), affording the title compound as light yellow solid (165 mg, 55%). LC-MS E:  $t_R$  = 0.80 min;  $[\text{M}+\text{H}]^+ = 277.25$ .

**A.3.33. 2-(Ethylamino)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide**

20 The title compound is prepared according to the procedure described for A.3.32., starting with 2-(ethylamino)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid. LC-MS A:  $t_R$  = 0.82 min;  $[\text{M}+\text{H}]^+ = 291.25$ .

**A.3.33.1. 2-(Ethylamino)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid**

The title compound is prepared according to the procedure described for A.3.6., starting with 4-bromo-2-(ethylamino)benzoic acid. LC-MS A:  $t_R$  = 0.85 min;  $[\text{M}+\text{H}]^+ = 292.18$ .

25 **A.3.34. N-(2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)formamide**

The title compound is prepared according to the procedure described for A.3.6., starting with N-(4-bromo-2-ethoxyphenyl)formamide. LC-MS B:  $t_R$  = 0.94 min;  $[\text{M}+\text{H}]^+ = 292.23$ .

**A.3.34.1. N-(4-bromo-2-ethoxyphenyl)formamide**

30 A mixture of 4-bromo-2-ethoxyaniline (1283 mg, 5.64 mmol), ethyl formate (18.5 mL, 226 mmol) and TEA (3.14 mL, 22.6 mmol) is stirred in a sealed tube at 85°C for 5 days. The RM is concentrated under reduced pressure. The residue is purified by FC (EtOAc:Hept 0:1 to 4:6) to afford the title compound as a brown solid (788 mg, 57%). LC-MS B:  $t_R$  = 0.84 min;  $[\text{M}+\text{H}]^+ = 285.06$ .

**A.3.35. 2-Butoxy-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid**

The title compound is prepared according to the procedure described for A.3.6., starting with 4-bromo-2-butoxy-6-fluorobenzoic acid. LC-MS A:  $t_R$  = 0.92 min;  $[M+H]^+$  = 339.21.

#### A.3.35.1. 4-Bromo-2-butoxy-6-fluorobenzoic acid

5 Methyl 4-bromo-2-butoxy-6-fluorobenzoate (1246 mg, 3.94 mmol) is dissolved in EtOH (15 mL). NaOH 32% (1.82 mL, 19.7 mmol) is added and the RM is heated up to 60°C for 1h. It is cooled to RT and diluted with EtOAc. HCl 2N (~10 mL) is added to reach acidic pH (<2). The aq. layer is extracted twice with EtOAc. The resulting organic phase is dried over  $MgSO_4$  and concentrated, to afford the title compound as a white powder (1.15g, 99%). LC-MS D:  $t_R$  = 0.52 min;  $[M-H]^+$  = 290.89.

#### A.3.35.2. Methyl 4-bromo-2-butoxy-6-fluorobenzoate

10 To a solution of methyl 4-bromo-2-fluoro-6-hydroxybenzoate (1.00 g, 4.02 mmol) in DMF (10 mL), is added  $Cs_2CO_3$  (2.62 g, 8.03 mmol) followed by 1-iodobutane (0.685 mL, 6.02 mmol). The RM is stirred at 120°C for 2h in the microwave. The RM is concentrated under reduced pressure, the residue is partitioned between DCM and water. The aqueous layer is re-extracted with DCM, the combined organics are dried ( $MgSO_4$ ), and concentrated under reduced pressure. Purification by FC (Hept/EtOAc 1:0 to 19:1) affords the title compound as a colourless oil (1.24 g, 99%). LC-MS A:  $t_R$  = 0.98 min;  $[M+H]^+$  = 306.84.

#### A.3.36. Methyl 3-(3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)propanoate

20 A MW vial under argon is charged with methyl 3-(3-ethoxythiophen-2-yl)propanoate (593 mg, 2.77 mmol), bis(pinacolato)diboron (574 mg, 2.22 mmol), (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (91.8 mg, 0.138 mmol), 4,4'-di-tert-butyl-2,2'-dipyridyl (59.5 mg, 0.222 mmol) in cyclohexane (20 mL). The vial is purged with argon, sealed and heated at 130°C for 15 min in the MW apparatus. The RM is concentrated under reduced pressure, and the residue is purified by FC (Hept/DCM 1:1 to 0:1), affording the title compound as a clear yellow oil (2.178 g, 77%). LC-MS B:  $t_R$  = 1.07 min;  $[M+H]^+$  = 341.12.

#### A.3.36.1. Methyl 3-(3-ethoxythiophen-2-yl)propanoate

25 To a solution of methyl (*E/Z*)-3-(3-ethoxythiophen-2-yl)acrylate (1818 mg, 8.31 mmol) in MeOH (30 mL) is added Pd/C 10% wet (300 mg). Then the vessel is inertized with  $N_2$  and flushed with  $H_2$ . The mixture is heated at 50°C overnight under 5 bar of  $H_2$ . Pd/C 10% wet (300 mg) is added to the mixture and it is further heated at 50°C under 6 Bar of  $H_2$  for 4 days. The mixture is filtered on Whatman 0.45um, rinsed with MeOH and concentrated, affording the title compound as a colourless oil (1.78 g, 100%). LC-MS B:  $t_R$  = 0.90 min;  $[M+H]^+$  = 215.36.

#### A.3.36.2. Methyl (*E/Z*)-3-(3-ethoxythiophen-2-yl)acrylate

30 A suspension of 3-ethoxythiophene-2-carbaldehyde (2.90 g, 18.6 mmol), methyl bromoacetate (3.07 mL, 33.4 mmol), and triphenylphosphine (7.305 g, 27.8 mmol) in aq saturated  $NaHCO_3$  (100 mL) is stirred at RT for 5h. THF (30 mL) is added and the RM is stirred overnight at RT. It is then extracted twice with DCM. The combined organic layers are dried over  $MgSO_4$ , filtered, and concentrated under vacuum. The crude is

purified by FC (Hept/EtOAc 9:1) to afford the title compound as a dark orange oil (3.10 g, 79%). LC-MS A:  $t_R$  = 0.86 min;  $[M+H]^+$  = 213.25.

**A.3.37. 3-Ethoxy-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclobut-3-ene-1,2-dione**

3-Ethoxy-4-(tributylstannyl)cyclobut-3-ene-1,2-dione (335 mg, 0.807 mmol) and 4-iodophenylboronic acid, pinacol ester (298 mg, 0.904 mmol) are dissolved in DMF (4 mL) with  $N_2$  bubbling for 5 min. Trans-benzyl(chloro)bis(triphenylphosphine)palladium(II) (36.7 mg, 0.0484 mmol) and CuI (15.4 mg, 0.0807 mmol) are added and the RM is stirred at RT for 3h., then filtered over a microglass filter, concentrated under vacuum and purified by FC (Hept.:EtOAc 100:0 to 80:20) to obtain the title compound as a yellow solid (127 mg, 48%). LC-MS A:  $t_R$  = 0.97 min;  $[M+MeCN]^+$  = 370.07.

**A.3.38. 2-(2-Propoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid**

To a solution of propyl 2-(2-propoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (308 mg, 0.85 mmol) in EtOH (9 mL) is added NaOH (10% aq. Solution, 3.4 mL) and the mixture is stirred at RT for 2h. EtOH is removed in vacuo. pH of the resulting basic aqueous layer is adjusted to pH=3-4 using HCl 1N and extracted twice with EtOAc. The combined organic layers are washed with water, brine, dried over  $MgSO_4$ , filtered and solvent is removed in vacuo, yielding the title compound as a white powder (0.238 g, 87%). LC-MS A:  $t_R$  = 0.88 min;  $[M+H]^+$  = 321.08.

**A.3.38.1. Propyl 2-(2-propoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**

The title compound is prepared according to the procedure described for A.3.6., starting with propyl 2-(4-bromo-2-propoxyphenyl)acetate. LC-MS A:  $t_R$  = 1.04 min;  $[M+H]^+$  = 363.12.

**A.3.38.2. Propyl 2-(4-bromo-2-propoxyphenyl)acetate**

To a solution of 4-bromo-2-hydroxyphenylacetic acid (1.50 g, 6.37 mmol) in DMF (50 mL) is added 1-iodopropane (1.38 mL, 14 mmol, 2.2 eq) and  $Cs_2CO_3$  (6.23 g, 19.1 mmol). The RM is stirred at 100°C overnight, then cooled to RT. Water is added, and the DMF is removed under reduced pressure. The residue is partitioned between EtOAc and water. The aqueous layer is re-extracted twice with EtOAc. The combined organic extracts are washed with brine, dried ( $MgSO_4$ ) and concentrated in vacuo. The residue is purified by FC (Hept:EtOAc 100:0 to 90:10), affording the title compound as a colourless oil (0.775 g, 39%). LC-MS A:  $t_R$  = 1.00 min;  $[M+H]^+$  = 315.07.

**A.3.39. 2-(2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid**

Following the synthesis of A.3.38., with ethyl 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate, the title compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.92 min;  $[M+H]^+$  = 307.25.

**A.3.39.1. Ethyl 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**

The title compound is prepared according to the procedure described for A.3.6., starting with ethyl 2-(4-bromo-2-ethoxyphenyl)acetate LC-MS A:  $t_R$  = 1.01 min;  $[M+H]^+$  = 287.04.

**A.3.39.2. Ethyl 2-(4-bromo-2-ethoxyphenyl)acetate**

Following the synthesis of A.2.38.2., with 4-bromo-2-hydroxyphenylacetic acid and iodoethane, the title compound is obtained as a colorless oil. LC-MS B:  $t_R$  = 1.02 min;  $[M+H]^+$  = 287.10.

**A.3.40. 5-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoxazol-3-ol**

Butyllithium solution 2.5M (2 mL, 5.03 mmol) is added dropwise, at -78 °C under nitrogen, to the stirred solution of 5-(4-bromo-2-ethoxyphenyl)isoxazol-3-ol (286 mg, 1.01 mmol) and 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.733 mL, 3.52 mmol) in dry THF (15 mL). The RM is stirred at -78 °C for 15 min then water is added at -78 °C and mixture is left stirring at RT for 40min. A saturated solution of  $NH_4Cl$  is added and the aqueous phase is extracted with EtOAc. The organic layer is washed twice with brine, then it is dried over  $MgSO_4$ , filtered and concentrated. The crude residue is purified by FC (Hept to Hept/EtOAc 1:1), to afford the title compound as a white solid (390 mg, quant.). LC-MS B:  $t_R$  = 0.98 min;  $[M+H]^+$  = 332.34 &  $[M+H+MeCN]^+$  = 373.55 .

**A.3.40.1. 5-(4-bromo-2-ethoxyphenyl)isoxazol-3-ol**

To a solution of ethyl 3-(4-bromo-2-ethoxyphenyl)propionate (1017 mg, 3.42 mmol) in EtOH (30 mL), Hydroxylamine hydrochloride (721 mg, 10.3 mmol) is added followed by dropwise addition of NaOH 10% (6.85 mL, 18.8 mmol); the RM is stirred overnight at RT. The solvent is distilled off under reduced pressure, the residue obtained is suspended in water, and the suspension is adjusted to pH 2-3 with a 2N aqueous HCl solution. The resultant solid is filtered off to afford the title compound as a white solid (380 mg, 39%). LC-MS B:  $t_R$  = 0.91 min;  $[M+H]^+$  = 284.17/286.25 .

**A.3.40.2. Ethyl 3-(4-bromo-2-ethoxyphenyl)propionate**

A  $CO_2$  (gas) inlet is set up in the reaction apparatus and  $CO_2$  is bubbled continuously into a stirred solution of ((4-bromo-2-ethoxyphenyl)ethynyl)trimethylsilane (1950 mg, 6.56 mmol) in DMSO (20 mL). Cesium fluoride (1220 mg, 7.87 mmol) is added and the RM is stirred at RT for 2 h.  $CO_2$  bubbling is stopped and iodoethane (0.639 mL, 7.87 mmol) is added dropwise. The RM is further stirred at RT for 3 h and then poured into water. The aqueous phase is extracted twice with EtOAc and the combined organic layers are washed back with water and finally brine. The organic phase is dried over  $MgSO_4$  and concentrated to dryness. Purification by FC (Hept:EtOAc 100:0 to 85:15) yields the tile compound as an orange oil (1.017 g, 52%). LC-MS B:  $t_R$  = 1.08 min;  $[M+H]^+$  = 297.20/299.23 .

**A.3.40.3. ((4-Bromo-2-ethoxyphenyl)ethynyl)trimethylsilane**

To a solution of 4-bromo-2-ethoxy-1-iodobenzene (2120 mg, 6.48 mmol) in THF (20 mL) are added TEA (2.71 mL, 19.5 mmol), ethynyltrimethylsilane (1.12 mL, 7.78 mmol) and copper iodide (61.7 mg, 0.324 mmol). The RM is degassed and put under argon 3 times. Then trans-dichlorobis(triphenylphosphine)palladium(II) (91 mg, 0.13 mmol) is added and the RM is degassed a last time, put under argon and stirred at 70 °C for 16 h. The mixture is cooled to RT and partitioned between EtOAc and water. The organic layer is washed with brine, dried over  $Na_2SO_4$ , filtered and the solvent is evaporated. The resulting residue is purified by FC (Hept:EtOAc 100:0 to 90:10) to yield the title compound as an orange oil (1.95 g, 100%). LC-MS B:  $t_R$  = 1.18 min; no ionization;  $^1H$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$ :



7.31 (d,  $J$  = 8.2 Hz, 1 H), 7.24 (d,  $J$  = 1.6 Hz, 1 H), 7.10 (dd,  $J_1$  = 1.7 Hz,  $J_2$  = 8.1 Hz, 1 H), 4.09 (q,  $J$  = 7.0 Hz, 2 H), 1.33 (t,  $J$  = 6.8 Hz, 3 H), 0.22 (s, 9 H)

#### A.3.41. Methyl 2-(2-(methylthio)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate

To a solution of methyl 2-(4-bromo-2-(methylthio)phenyl)acetate (1.45 g, 5.27 mmol) in anh. DMF (12 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.352 g, 5.27 mmol), potassium acetate (2.069 g, 21.10 mmol) and Pd(dppf)Cl<sub>2</sub> (428 mg, 0.58 mmol). The RM is heated to 90°C, under nitrogen, for 17h. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to EtOAc) affords methyl 2-(2-(methylthio)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a pale yellow solid (664 mg, 39%). LC-MS B:  $t_R$  = 1.04 min;  $[M+H]^+$  = 323.16.

##### A.3.41.1. Methyl 2-(4-bromo-2-(methylthio)phenyl)acetate

To a solution of 2-(4-bromo-2-(methylthio)phenyl)acetic acid (1.86 g, 7.12 mmol) in anh. DMF (17 mL) at RT are added cesium carbonate (2.901 g, 8.90 mmol) and iodomethane (0.667 mL, 10.70 mmol) and the RM is stirred at RT, under nitrogen, for 1h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(4-bromo-2-(methylthio)phenyl)acetate as a yellow oil (1.45 g, 74%). LC-MS B:  $t_R$  = 0.97 min; no ionization.

##### A.3.41.2. 2-(4-Bromo-2-(methylthio)phenyl)acetic acid

A mixture of 2-(4-bromo-2-(methylthio)phenyl)acetonitrile (1.76 g, 7.27 mmol), water (7 mL), 95% sulfuric acid (7.8 mL) and acetic acid (5.4 mL) is heated to 110°C, under nitrogen, for 4.5h. The RM is then allowed to cool to RT and is poured onto ice/water. The mixture is extracted twice with DCM and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure affording 2-(4-bromo-2-(methylthio)phenyl)acetic acid as a yellow solid (1.86 g, 98%). LC-MS B:  $t_R$  = 0.82 min;  $[M+H]^+$  = 260.70.

##### A.3.41.3. 2-(4-Bromo-2-(methylthio)phenyl)acetonitrile

A solution of (5-bromo-2-(chloromethyl)phenyl)(methyl)sulfane (2.45 g, 9.74 mmol) in MeCN (26 mL) and water (3.4 mL) is treated with sodium cyanide (646 mg, 12.70 mmol) and the RM is heated to 80°C, under nitrogen, for 16h. Additional sodium cyanide (238 mg, 4.85 mmol) is then added and the mixture is heated to 80°C for 4h. The RM is then allowed to cool to RT and is diluted with water. Acetonitrile is removed under reduced pressure and the RM is extracted twice with DCM. The combined organic layers are dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords 2-(4-bromo-2-(methylthio)phenyl)acetonitrile as a pale yellow solid (1.76 g, 75%). LC-MS B:  $t_R$  = 0.95 min;  $[M+H]^+$  = 241.81.



**A.3.41.4. (5-Bromo-2-(chloromethyl)phenyl)(methyl)sulfane**

A cooled (0°C) mixture of (4-bromo-2-(methylthio)phenyl)methanol (2.31 g, 9.91 mmol) and zinc chloride (33.8 mg, 0.248 mmol) in anh. DCM (20 mL) is treated dropwise with thionyl chloride (1.45 mL, 19.80 mmol) and the RM is stirred at 0°C for 3h, and then at RT for 15h. The RM is concentrated under reduced pressure affording (5-bromo-2-(chloromethyl)phenyl)(methyl)sulfane as a yellow oil (2.45 g, 98%). LC-MS B:  $t_R$  = 1.04 min; no ionization.

**A.3.41.5. (4-Bromo-2-(methylthio)phenyl)methanol**

To a cooled (-78°C) solution of methyl 4-bromo-2-(methylthio)benzoate (2.87 g, 11.00 mmol) in anh. THF (30 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in toluene, 33.0 mL, 33.0 mmol). The mixture is further stirred at -78°C, under nitrogen, for 15 min and is then allowed to warm-up to 0°C. Stirring at 0°C is continued for 15 min, and the cooled RM is treated successively with water (31 mL) and with 2.8 N aq. NaOH (22 mL). The mixture is then allowed to warm-up to RT, EtOAc is added and the layers are separated. The aqueous layer is extracted twice with EtOAc. The combined organic layers are dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords (4-bromo-2-(methylthio)phenyl)methanol as a colorless solid (2.31 g, 90%). LC-MS B:  $t_R$  = 0.83 min;  $[M+H]^+$  = 232.99.

**A.3.41.6. Methyl 4-bromo-2-(methylthio)benzoate**

To a solution of 4-bromo-2-mercaptobenzoic acid (3.00 g, 12.20 mmol) in anh. DMF (20 mL) at RT is added cesium carbonate (11.952 g, 36.70 mmol) and the mixture is stirred at RT for 15 min. The cooled (0°C) mixture is then treated with iodomethane (1.92 mL, 30.60 mmol) and the RM is stirred at RT for 16h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure affording methyl 4-bromo-2-(methylthio)benzoate as a pale orange solid (2.87 g, 90%). LC-MS B:  $t_R$  = 0.96 min;  $[M+H]^+$  = 261.06.

**A.3.42. Methyl 2-(2-propyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**

To a solution of methyl 2-(4-bromo-2-propylphenyl)acetate (2.380 g, 8.78 mmol) in anh. DMF (20 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.251 g, 8.78 mmol), potassium acetate (3.446 g, 35.10 mmol) and Pd(dppf)Cl<sub>2</sub> (714 mg, 0.96 mmol). The RM is heated to 90°C, under nitrogen, for 16h. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(2-propyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a colorless oil (2.230 g, 80%). LC-MS B:  $t_R$  = 1.10 min;  $[M+H]^+$  = 319.31.

**A.3.42.1. Methyl 2-(4-bromo-2-propylphenyl)acetate**

To a solution of 2-(4-bromo-2-propylphenyl)acetic acid (2.770 g, 10.80 mmol) in anh. DMF (20 mL) at RT are added cesium carbonate (5.265 g, 16.20 mmol) and iodomethane (1.02 mL, 16.20 mmol) and the RM is stirred at RT, under nitrogen, for 1h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(4-bromo-2-propylphenyl)acetate as a yellow oil (2.380 g, 81%). LC-MS B: t<sub>R</sub> = 1.04 min; no ionization.

**A.3.42.2. 2-(4-Bromo-2-propylphenyl)acetic acid**

A mixture of 2-(4-bromo-2-propylphenyl)acetonitrile (2.570 g, 10.80 mmol), water (10 mL), 95% sulfuric acid (11.5 mL) and acetic acid (8 mL) is heated to 110°C, under nitrogen, for 3h. The RM is then allowed to cool to RT and is poured onto ice/water. The mixture is extracted twice with DCM and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure affording crude 2-(4-bromo-2-propylphenyl)acetic acid as a pale grey solid (3.390 g, quantitative). LC-MS B: t<sub>R</sub> = 0.91 min; no ionization.

**A.3.42.3. 2-(4-Bromo-2-propylphenyl)acetonitrile**

A solution of 4-bromo-1-(chloromethyl)-2-propylbenzene (2.980 g, 12.00 mmol) in MeCN (32 mL) and water (3.9 mL) is treated with sodium cyanide (767 mg, 15.60 mmol) and the RM is heated to 80°C, under nitrogen, overnight. The RM is then allowed to cool to RT and is diluted with water. Acetonitrile is removed under reduced pressure and the RM is extracted twice with DCM. The combined organic layers are dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to EtOAc) affords 2-(4-bromo-2-propylphenyl)acetonitrile as a pale yellow oil (2.570 g, 90%). LC-MS B: t<sub>R</sub> = 1.02 min; no ionization.

**A.3.42.4. 4-Bromo-1-(chloromethyl)-2-propylbenzene**

A cooled (0°C) mixture of (4-bromo-2-propylphenyl)methanol (2.650 g, 11.60 mmol) and zinc chloride (39.4 mg, 0.289 mmol) in anh. DCM (23 mL) is treated dropwise with thionyl chloride (1.69 mL, 23.10 mmol) and the RM is stirred at 0°C for 3h, and then at RT overnight. The RM is concentrated under reduced pressure affording crude 4-bromo-1-(chloromethyl)-2-propylbenzene as a grey oil (2.98 g, quantitative). LC-MS B: t<sub>R</sub> = 1.10 min; no ionization.

**A.3.42.5. (4-Bromo-2-propylphenyl)methanol**

To a cooled (-78°C) solution of methyl 4-bromo-2-propylbenzoate (3.300 g, 12.80 mmol) in anh. THF (60 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in toluene, 38.5 mL, 38.5 mmol). The mixture is further stirred at -78°C, under nitrogen, for 15 min and is then allowed to warm-up to 0°C. Stirring at 0°C is continued for 45 min, and the cooled RM is treated successively with water (1.5 mL), 2.8 N aq. NaOH (1.5 mL) and water (4 mL). The mixture is then allowed to warm-up to RT and stirring was continued for 30 min.

The resulting mixture was filtered over celite washing with THF and the filtrate was concentrated to dryness under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords (4-bromo-2-propylphenyl)methanol as a colorless oil (2.650 g, 90%). LC-MS B:  $t_R$  = 0.91 min; no ionization.

#### A.3.42.6. Methyl 4-bromo-2-propylbenzoate

5 To a solution of 4-bromo-2-propylbenzoic acid (3.590 g, 14.80 mmol) in anh. DMF (30 mL) at RT are added successively cesium carbonate (9.623 g, 29.50 mmol) and iodomethane (1.86 mL, 29.50 mmol) and the RM is stirred at RT for 16h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1)  
10 affords methyl 4-bromo-2-propylbenzoate as a colorless oil (3.300 g, 87%). LC-MS B:  $t_R$  = 1.05 min; no ionization.

#### A.3.42.7. 4-Bromo-2-propylbenzoic acid

To a cooled (0°C) solution of 4-bromo-2-fluorobenzoic acid (5.000 g, 22.40 mmol) in anh. THF (40 mL) is added dropwise a solution of propylmagnesium bromide (2.0 M in THF, 33.50 mL, 67.00 mmol) and the RM  
15 is further stirred at RT, under nitrogen, overnight. MeOH (10 mL) is then added dropwise to the cooled (0°C) reaction mixture that is further stirred at 0°C for 5 min. The resulting mixture is then concentrated to dryness under reduced pressure and the residue is partitioned between EtOAc and 2 M aq. HCl. The layers are separated, and the aq. layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from  
20 heptane to heptane/EtOAc = 3/2) affords 4-bromo-2-propylbenzoic acid as a colorless solid (3.590 g, 66%). LC-MS B:  $t_R$  = 0.93 min; no ionization.

#### A.3.43. Methyl 2-(2-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate

To a solution of methyl 2-(4-bromo-2-ethylphenyl)acetate (900 mg, 3.24 mmol) in anh. DMF (15 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (832 mg, 3.24 mmol), potassium acetate (1.274 g,  
25 13.00 mmol) and Pd(dppf)Cl<sub>2</sub> (264 mg, 0.35 mmol). The RM is heated to 90°C, under nitrogen, overnight. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 4/1) affords methyl 2-(2-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a  
30 light yellow oil (708 mg, 72%). LC-MS B:  $t_R$  = 1.05 min; [M+H]<sup>+</sup> = 305.22.

#### A.3.43.1. Methyl 2-(4-bromo-2-ethylphenyl)acetate

To a solution of 2-(4-bromo-2-ethylphenyl)acetic acid (2.118 g, 8.05 mmol) in anh. DMF (20 mL) at RT are added cesium carbonate (5.246 g, 16.10 mmol) and iodomethane (1.01 mL, 16.10 mmol) and the RM is stirred at RT, under nitrogen, for 1h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is  
35 extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>,

filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(4-bromo-2-ethylphenyl)acetate as a light yellow oil (2.043 g, 99%). LC-MS B:  $t_R$  = 0.99 min; no ionization.

#### **A.3.43.2. 2-(4-Bromo-2-ethylphenyl)acetic acid**

5 A mixture of 2-(4-bromo-2-ethylphenyl)acetonitrile (1.859 g, 7.99 mmol), water (7.5 mL), 95% sulfuric acid (8.3 mL) and acetic acid (5.8 mL) is heated to 110°C, under nitrogen, for 4h. The RM is then allowed to cool to RT and is poured onto ice/water. The mixture is extracted twice with DCM and the combined organic layers are washed with brine, dried over anh.  $MgSO_4$ , filtered and concentrated under reduced pressure affording crude 2-(4-bromo-2-ethylphenyl)acetic acid as an amber solid (2.118 g, quantitative). LC-MS B:  $t_R$  = 0.85 min; no ionization.

#### **A.3.43.3. 2-(4-Bromo-2-ethylphenyl)acetonitrile**

15 A solution of 4-bromo-1-(chloromethyl)-2-ethylbenzene (2.050 g, 8.34 mmol) in MeCN (24 mL) and water (3 mL) is treated with sodium cyanide (553 mg, 10.80 mmol) and the RM is heated to 80°C, under nitrogen, overnight. The RM is then allowed to cool to RT and is diluted with water. Acetonitrile is removed under reduced pressure and the RM is extracted twice with DCM. The combined organic layers are dried over anh.  $MgSO_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords 2-(4-bromo-2-ethylphenyl)acetonitrile as a colorless solid (1.859 g, 99%). LC-MS B:  $t_R$  = 0.95 min; no ionization.

#### **A.3.43.4. 4-Bromo-1-(chloromethyl)-2-ethylbenzene**

20 A cooled (0°C) mixture of (4-bromo-2-ethylphenyl)methanol (1.854 g, 8.30 mmol) and zinc chloride (28.3 mg, 0.208 mmol) in anh. DCM (20 mL) is treated dropwise with thionyl chloride (1.21 mL, 16.60 mmol) and the RM is stirred at 0°C for 2h. The RM is concentrated under reduced pressure affording crude 4-bromo-1-(chloromethyl)-2-ethylbenzene as a light purple oil (2.050 g, quantitative). LC-MS B:  $t_R$  = 1.04 min; no ionization.

#### **A.3.43.5. (4-Bromo-2-ethylphenyl)methanol**

25 To a cooled (-78°C) solution of methyl 4-bromo-2-ethylbenzoate (2.219 g, 9.01 mmol) in anh. THF (60 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in toluene, 27.0 mL, 27.0 mmol). The mixture is further stirred at -78°C, under nitrogen, for 15 min and is then allowed to warm-up to 0°C. Stirring at 0°C is continued for 45 min, and the cooled RM is treated successively with water (1 mL), 2.8 N aq. NaOH (1 mL) and water (3 mL). The mixture is then allowed to warm-up to RT and is further stirred for 30 min. The resulting mixture is filtered over celite, washing with THF and the filtrate is concentrated to dryness under reduced pressure. EtOAc and water are added and the layers are separated. The aqueous layer is extracted twice with EtOAc and the combined organic layers are dried over anh.  $MgSO_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords (4-bromo-2-ethylphenyl)methanol (1.854 g, 96%). LC-MS B:  $t_R$  = 0.84 min; no ionization.

**A.3.43.6. Methyl 4-bromo-2-ethylbenzoate**

To a solution of 4-bromo-2-ethylbenzoic acid (3.003 g, 12.80 mmol) in anh. DMF (30 mL) at RT are added cesium carbonate (8.355 g, 25.60 mmol) and iodomethane (1.61 mL, 25.60 mmol) and the RM is stirred at RT for 1h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 4-bromo-2-ethylbenzoate as a clear oil (2.735 g, 88%). LC-MS B: t<sub>R</sub> = 1.02 min; no ionization.

**A.3.43.7. 4-Bromo-2-ethylbenzoic acid**

To a cooled (0°C) solution of 4-bromo-2-fluorobenzoic acid (5.000 g, 22.40 mmol) in anh. THF (40 mL) is added dropwise a solution of ethylmagnesium bromide (1.0 M in THF, 67.1 mL, 67.1 mmol) and the RM is further stirred at RT, under nitrogen, for 3h. MeOH (15 mL) is then added dropwise to the cooled (0°C) reaction mixture that is further stirred at 0°C for 5 min. The resulting mixture is then concentrated to dryness under reduced pressure and the residue is partitioned between EtOAc and 2 M aq. HCl. The layers are separated, and the aq. layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords 4-bromo-2-ethylbenzoic acid as a colorless solid (3.003 g, 59%). LC-MS B: t<sub>R</sub> = 0.87 min; no ionization.

**A.3.44. Methyl 2-(2-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**

To a solution of methyl 2-(4-bromo-2-isobutylphenyl)acetate (2.271 g, 7.13 mmol) in anh. DMF (25 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.828 g, 7.13 mmol), potassium acetate (2.798 g, 28.50 mmol) and Pd(dppf)Cl<sub>2</sub> (579 mg, 0.78 mmol). The RM is heated to 95°C, under nitrogen, for 16h. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(2-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a yellow oil (1.822 g, 77%). LC-MS B: t<sub>R</sub> = 1.13 min; [M+H]<sup>+</sup> = 333.24.

**A.3.44.1. Methyl 2-(4-bromo-2-isobutylphenyl)acetate**

To a solution of 2-(4-bromo-2-isobutylphenyl)acetic acid (2.457 g, 8.64 mmol) in anh. DMF (30 mL) at RT are added cesium carbonate (5.633 g, 17.30 mmol) and iodomethane (1.09 mL, 17.30 mmol) and the RM is stirred at RT, under nitrogen, for 1h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(4-bromo-2-isobutylphenyl)acetate as a clear oil (2.271 g, 92%). LC-MS B: t<sub>R</sub> = 1.06 min; no ionization.

**A.3.44.2. 2-(4-Bromo-2-isobutylphenyl)acetic acid**

A mixture of 2-(4-bromo-2-isobutylphenyl)acetonitrile (2.162 g, 8.41 mmol), water (8 mL), 95% sulfuric acid (9 mL) and acetic acid (6 mL) is heated to 110°C, under nitrogen, overnight. The RM is then allowed to cool to RT and is poured onto ice/water. The mixture is extracted twice with DCM and the combined organic layers are washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure affording crude 2-(4-bromo-2-isobutylphenyl)acetic acid as an amber oil (2.457 g, quantitative). LC-MS B:  $t_R$  = 0.96 min; no ionization.

**A.3.44.3. 2-(4-Bromo-2-isobutylphenyl)acetonitrile**

A solution of 4-bromo-1-(chloromethyl)-2-isobutylbenzene (2.381 g, 9.00 mmol) in MeCN (24 mL) and water (3 mL) is treated with sodium cyanide (597 mg, 11.70 mmol) and the RM is heated to 80°C, under nitrogen, overnight. The RM is then allowed to cool to RT and is diluted with water. Acetonitrile is removed under reduced pressure and the RM is extracted twice with DCM. The combined organic layers are dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords 2-(4-bromo-2-isobutylphenyl)acetonitrile as a clear oil (2.162 g, 95%). LC-MS B:  $t_R$  = 1.05 min; no ionization.

**A.3.44.4. 4-Bromo-1-(chloromethyl)-2-isobutylbenzene**

A cooled (0°C) mixture of (4-bromo-2-isobutylphenyl)methanol (2.192 g, 8.83 mmol) and zinc chloride (30.1 mg, 0.221 mmol) in anhydrous DCM (20 mL) is treated dropwise with thionyl chloride (1.29 mL, 17.70 mmol) and the RM is stirred at 0°C for 4h. The RM is concentrated under reduced pressure affording crude 4-bromo-1-(chloromethyl)-2-isobutylbenzene as a light pink oil (2.381 g, quantitative). LC-MS B:  $t_R$  = 1.13 min; no ionization.

**A.3.44.5. (4-Bromo-2-isobutylphenyl)methanol**

To a cooled (-78°C) solution of methyl 4-bromo-2-isobutylbenzoate (2.712 g, 9.71 mmol) in anhydrous THF (60 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in toluene, 29.1 mL, 29.1 mmol). The mixture is further stirred at -78°C, under nitrogen, for 15 min and is then allowed to warm-up to 0°C. Stirring at 0°C is continued for 30 min, and the cooled RM is treated successively with water (1 mL), 2.8 N aq. NaOH (1 mL) and water (3 mL). The mixture is then allowed to warm-up to RT and is further stirred for 30 min. The resulting mixture is filtered over celite, washing with THF and the filtrate is concentrated to dryness under reduced pressure. EtOAc and water are added and the layers are separated. The aqueous layer is extracted twice with EtOAc and the combined organic layers are dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords (4-bromo-2-isobutylphenyl)methanol (2.192 g, 93%). LC-MS B:  $t_R$  = 0.96 min; no ionization.

**A.3.44.6. Methyl 4-bromo-2-isobutylbenzoate**

To a solution of 4-bromo-2-isobutylbenzoic acid (4.254 g, 14.30 mmol) in anhydrous DMF (50 mL) at RT are added successively cesium carbonate (9.304 g, 28.60 mmol) and iodomethane (1.80 mL, 28.60 mmol) and the RM



is stirred at RT for 1h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 4-bromo-2-isobutylbenzoate as a light yellow oil (3.462 g, 89%). LC-MS B: t<sub>R</sub> = 1.11 min; no ionization.

5      **A.3.44.7. 4-Bromo-2-isobutylbenzoic acid**

To a cooled (0°C) solution of 4-bromo-2-fluorobenzoic acid (5.000 g, 22.40 mmol) in anh. THF (40 mL) is added dropwise a solution of isobutylmagnesium bromide (2.0 M in Et<sub>2</sub>O, 33.5 mL, 67.0 mmol) and the RM is further stirred at RT, under nitrogen, overnight. MeOH (10 mL) is then added dropwise to the cooled (0°C) reaction mixture that is further stirred at 0°C for 5 min. The resulting mixture is then concentrated to dryness under reduced pressure and the residue is partitioned between EtOAc and 2 M aq. HCl. The layers are separated, and the aq. layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords 4-bromo-2-isobutylbenzoic acid as a light yellow solid (4.254 g, 74%). LC-MS B: t<sub>R</sub> = 0.97 min; no ionization.

15      **A.3.45. Methyl 2-(2-ethyl-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**

To a solution of methyl 2-(4-bromo-2-ethyl-6-methylphenyl)acetate (1.176 g, 4.34 mmol) in anh. DMF (15 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.112 g, 4.34 mmol), potassium acetate (1.703 g, 17.30 mmol) and Pd(dppf)Cl<sub>2</sub> (353 mg, 0.47 mmol). The RM is heated to 90°C, under nitrogen, for 16h. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(2-ethyl-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a light green oil (895 mg, 65%). LC-MS B: t<sub>R</sub> = 1.08 min; [M+H]<sup>+</sup> = 319.28.

25      **A.3.45.1. Methyl 2-(4-bromo-2-ethyl-6-methylphenyl)acetate**

To a solution of 2-(4-bromo-2-ethyl-6-methylphenyl)acetic acid (2.993 g, 11.60 mmol) in anh. DMF (20 mL) at RT are added cesium carbonate (7.585 g, 23.30 mmol) and iodomethane (1.46 mL, 23.30 mmol) and the RM is stirred at RT, under nitrogen, for 5h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(4-bromo-2-ethyl-6-methylphenyl)acetate as a yellow oil (1.176 g, 37%). LC-MS B: t<sub>R</sub> = 1.03 min; no ionization.

30      **A.3.45.2. 2-(4-Bromo-2-ethyl-6-methylphenyl)acetic acid**

A mixture of 2-(4-bromo-2-ethyl-6-methylphenyl)acetonitrile (2.477 g, 10.40 mmol), water (10 mL), 95% sulfuric acid (11 mL) and acetic acid (7.5 mL) is heated to 110°C, under nitrogen, for 1.5h. The RM is then allowed to cool to RT and is poured onto ice/water. The mixture is extracted twice with DCM and the combined



organic layers are washed with brine, dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure affording crude 2-(4-bromo-2-ethyl-6-methylphenyl)acetic acid as an off-white solid (2.993 g, quantitative). LC-MS B:  $t_R$  = 0.81 min; no ionization.

**A.3.45.3. 2-(4-Bromo-2-ethyl-6-methylphenyl)acetonitrile**

5 A solution of 5-bromo-2-(chloromethyl)-1-ethyl-3-methylbenzene (2.849 g, 11.50 mmol) in MeCN (30 mL) and water (3.7 mL) is treated with sodium cyanide (764 mg, 15.00 mmol) and the RM is heated to 80°C, under nitrogen, for 1h. The RM is then allowed to cool to RT and is diluted with water. Acetonitrile is removed under reduced pressure and the RM is extracted twice with DCM. The combined organic layers are dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords 2-(4-bromo-2-ethyl-6-methylphenyl)acetonitrile as a clear oil (2.477 g, 90%). LC-MS B:  $t_R$  = 0.99 min; no ionization.

**A.3.45.4. 5-Bromo-2-(chloromethyl)-1-ethyl-3-methylbenzene**

15 A cooled (0°C) mixture of (4-bromo-2-ethyl-6-methylphenyl)methanol (2.525 g, 11.00 mmol) and zinc chloride (37.6 mg, 0.276 mmol) in anh. DCM (30 mL) is treated dropwise with thionyl chloride (1.61 mL, 22.00 mmol) and the RM is stirred at 0°C for 1h. The RM is concentrated under reduced pressure affording crude 5-bromo-2-(chloromethyl)-1-ethyl-3-methylbenzene as a light brown oil (2.849 g, quantitative). LC-MS B:  $t_R$  = 1.08 min; no ionization.

**A.3.45.5. (4-Bromo-2-ethyl-6-methylphenyl)methanol**

20 To a cooled (-78°C) solution of methyl 4-bromo-2-ethyl-6-methylbenzoate (3.355 g, 13.00 mmol) in anh. THF (60 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in toluene, 39.0 mL, 39.0 mmol). The mixture is further stirred at -78°C, under nitrogen, for 15 min and is then allowed to warm-up to 0°C. Stirring at 0°C is continued for 1h, and the cooled RM is treated successively with water (1 mL), 2.8 N aq. NaOH (1 mL) and water (3 mL). The mixture is then allowed to warm-up to RT and is further stirred for 30 min. The resulting mixture is filtered over celite, washing with THF and the filtrate is concentrated to dryness under reduced pressure. EtOAc and water are added and the layers are separated. The aqueous layer is extracted twice with EtOAc and the combined organic layers are dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords (4-bromo-2-ethyl-6-methylphenyl)methanol (2.525 g, 84%). LC-MS B:  $t_R$  = 0.87 min; no ionization.

**A.3.45.6. Methyl 4-bromo-2-ethyl-6-methylbenzoate**

30 To a solution of 4-bromo-2-ethyl-6-methylbenzoic acid (3.465 g, 14.30 mmol) in anh. DMF (35 mL) at RT are added cesium carbonate (9.288 g, 28.50 mmol) and iodomethane (1.79 mL, 28.50 mmol) and the RM is stirred at RT for 1h. Water and  $\text{Et}_2\text{O}$  are added and the layers are separated. The aqueous layer is extracted twice with  $\text{Et}_2\text{O}$  and the combined organic layers are washed with brine, dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 3/1) affords methyl 4-bromo-2-ethyl-6-methylbenzoate as a clear oil (3.355 g, 92%). LC-MS B:  $t_R$  = 1.02 min; no ionization.

**A.3.45.7. 4-Bromo-2-ethyl-6-methylbenzoic acid**

To a cooled (0°C) solution of 4-bromo-2-fluoro-6-methylbenzoic acid (4.000 g, 16.30 mmol) in anh. THF (40 mL) is added dropwise a solution of ethylmagnesium bromide (1.0 M in THF, 49.0 mL, 49.0 mmol) and the RM is further stirred at RT, under nitrogen, overnight. MeOH (15 mL) is then added dropwise to the cooled (0°C) reaction mixture that is further stirred at 0°C for 5 min. The resulting mixture is then concentrated to dryness under reduced pressure and the residue is partitioned between EtOAc and 2 M aq. HCl. The layers are separated, and the aq. layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 3/1) affords 4-bromo-2-ethyl-6-methylbenzoic acid as a colorless solid (3.465 g, 87%). LC-MS B: t<sub>R</sub> = 0.86 min; no ionization.

**A.3.46. Methyl 2-(2-chloro-6-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**

To a solution of methyl 2-(4-bromo-2-chloro-6-ethylphenyl)acetate (254 mg, 0.87 mmol) in anh. DMF (10 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (223 mg, 0.87 mmol), potassium acetate (342 mg, 3.48 mmol) and Pd(dppf)Cl<sub>2</sub> (70 mg, 0.095 mmol). The RM is heated to 90°C, under nitrogen, for 5.5h. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(2-chloro-6-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a pale yellow oil (126 mg, 43%). LC-MS B: t<sub>R</sub> = 1.14 min; [M+H]<sup>+</sup> = 339.35.

**A.3.46.1. Methyl 2-(4-bromo-2-chloro-6-ethylphenyl)acetate**

To a solution of 2-(4-bromo-2-chloro-6-ethylphenyl)acetic acid (259 mg, 0.93 mmol) in anh. DMF (9 mL) at RT are added cesium carbonate (456 mg, 1.40 mmol) and iodomethane (70 µL, 1.12 mmol) and the RM is stirred at RT, under nitrogen, for 30 min. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(4-bromo-2-chloro-6-ethylphenyl)acetate as a pale yellow solid (254 mg, 93%). LC-MS B: t<sub>R</sub> = 1.03 min; no ionization.

**A.3.46.2. 2-(4-Bromo-2-chloro-6-ethylphenyl)acetic acid**

A mixture of 2-(4-bromo-2-chloro-6-ethylphenyl)acetonitrile (511 mg, 1.98 mmol), potassium hydroxide (333 mg, 5.93 mmol) in EtOH (15 mL) and water (15 mL) is heated to 110°C, under nitrogen, for 24h. The RM is then allowed to cool to RT and is concentrated under reduced pressure. 1 M aq. HCl and DCM are successively added, the layers are then separated and the aqueous layer is extracted twice with DCM. The combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure affording crude 2-(4-bromo-2-chloro-6-ethylphenyl)acetic acid as an off-white solid (259 mg). LC-MS B: t<sub>R</sub> = 0.90 min; no ionization.

**A.3.46.3. 2-(4-Bromo-2-chloro-6-ethylphenyl)acetonitrile**

A solution of 5-bromo-1-chloro-2-(chloromethyl)-3-ethylbenzene (740 mg, 2.76 mmol) in MeCN (14 mL) and water (2 mL) is treated with sodium cyanide (176 mg, 3.59 mmol) and the RM is heated to 80°C, under nitrogen, overnight. The RM is then allowed to cool to RT and is diluted with water. Acetonitrile is removed under reduced pressure and the mixture is extracted twice with DCM. The combined organic layers are dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords 2-(4-bromo-2-chloro-6-ethylphenyl)acetonitrile as a colorless oil (511 mg, 72%). LC-MS B: t<sub>R</sub> = 0.99 min; no ionization.

**A.3.46.4. 5-Bromo-1-chloro-2-(chloromethyl)-3-ethylbenzene**

A cooled (0°C) mixture of (4-bromo-2-chloro-6-ethylphenyl)methanol (645 mg, 2.58 mmol) and zinc chloride (9 mg, 0.064 mmol) in anh. DCM (10 mL) is treated dropwise with thionyl chloride (0.37 mL, 5.17 mmol) and the RM is stirred at 0°C for 3h, and then at RT overnight. The RM is concentrated under reduced pressure affording crude 5-bromo-1-chloro-2-(chloromethyl)-3-ethylbenzene as a grey oil (740 mg, quantitative). LC-MS B: t<sub>R</sub> = 1.09 min; no ionization.

**A.3.46.5. (4-Bromo-2-chloro-6-ethylphenyl)methanol**

To a cooled (-78°C) solution of methyl 4-bromo-2-chloro-6-ethylbenzoate (2.115 g, 7.62 mmol) in anh. THF (50 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in toluene, 45.7 mL, 45.7 mmol). The mixture is further stirred at -78°C, under nitrogen, for 15 min and is then allowed to warm-up to 0°C. Stirring at 0°C is continued for 45 min, and the cooled RM is treated successively with water (2 mL), 2.8 N aq. NaOH (2 mL) and water (5 mL). The mixture is then allowed to warm-up to RT and is further stirred for 30 min. The resulting mixture is filtered over celite, washing with THF and the filtrate is concentrated to dryness under reduced pressure. EtOAc and water are added and the layers are separated. The aqueous layer is extracted twice with EtOAc and the combined organic layers are dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords pure (4-bromo-2-chloro-6-ethylphenyl)methanol (645 mg, 34%). LC-MS B: t<sub>R</sub> = 0.89 min; no ionization.

**A.3.46.6. Methyl 4-bromo-2-chloro-6-ethylbenzoate**

To a solution of 4-bromo-2-chloro-6-ethylbenzoic acid (2.660 g, 10.10 mmol) in anh. DMF (20 mL) at RT are added cesium carbonate (4.933 g, 15.10 mmol) and iodomethane (0.76 mL, 12.10 mmol) and the RM is stirred at RT for 1.5h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 4-bromo-2-chloro-6-ethylbenzoate as a colorless oil (1.930 g, 69%). LC-MS B: t<sub>R</sub> = 1.03 min; no ionization.

**A.3.46.7. 4-Bromo-2-chloro-6-ethylbenzoic acid**

To a cooled (0°C) solution of 4-bromo-2-chloro-6-fluorobenzoic acid (4.530 g, 17.00 mmol) in anh. THF (40 mL) is added dropwise a solution of ethylmagnesium bromide (1.0 M in THF, 67.9 mL, 67.9 mmol) and the RM is further stirred at RT, under nitrogen, for 50 min. MeOH (20 mL) is then added dropwise to the cooled (0°C) reaction mixture that is further stirred at 0°C for 5 min. The resulting mixture is then concentrated to dryness under reduced pressure and the residue is partitioned between EtOAc and 2 M aq. HCl. The layers are separated, and the aq. layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords 4-bromo-2-chloro-6-ethylbenzoic acid as a colorless solid (2.660 g, 59%). LC-MS B: t<sub>R</sub> = 0.86 min; no ionization.

**A.3.47. Methyl 2-(2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**

To a solution of methyl 2-(4-bromo-2-chloro-6-methylphenyl)acetate (2.614 g, 9.42 mmol) in anh. DMF (25 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.416 g, 9.42 mmol), potassium acetate (3.697 g, 37.70 mmol) and Pd(dppf)Cl<sub>2</sub> (766 mg, 1.04 mmol). The RM is heated to 90°C, under nitrogen, overnight. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a light green oil (1.939 g, 63%). LC-MS B: t<sub>R</sub> = 1.08 min; [M+H]<sup>+</sup> = 325.19.

**A.3.47.1. Methyl 2-(4-bromo-2-chloro-6-methylphenyl)acetate**

To a solution of 2-(4-bromo-2-chloro-6-methylphenyl)acetic acid (2.648 g, 10.00 mmol) in anh. DMF (25 mL) at RT are added cesium carbonate (6.548 g, 20.10 mmol) and iodomethane (1.26 mL, 20.10 mmol) and the RM is stirred at RT, under nitrogen, for 1h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(4-bromo-2-chloro-6-methylphenyl)acetate as a clear oil (2.614 g, 94%). LC-MS B: t<sub>R</sub> = 1.00 min; no ionization.

**A.3.47.2. 2-(4-Bromo-2-chloro-6-methylphenyl)acetic acid**

A mixture of 2-(4-bromo-2-chloro-6-methylphenyl)acetonitrile (2.504 g, 10.20 mmol), water (9 mL), 95% sulfuric acid (11 mL) and acetic acid (7 mL) is heated to 110°C, under nitrogen, for 4h. The RM is then allowed to cool to RT and is poured onto ice/water. The mixture is extracted twice with DCM and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure affording crude 2-(4-bromo-2-chloro-6-methylphenyl)acetic acid as an off-white solid (2.648 g, 98%). LC-MS B: t<sub>R</sub> = 0.86 min; no ionization.

**A.3.47.3. 2-(4-Bromo-2-chloro-6-methylphenyl)acetonitrile**

A solution of 5-bromo-1-chloro-2-(chloromethyl)-3-methylbenzene (2.752 g, 10.80 mmol) in MeCN (30 mL) and water (4 mL) is treated with sodium cyanide (719 mg, 14.10 mmol) and the RM is heated to 80°C, under nitrogen, for 1h. The RM is then allowed to cool to RT and is diluted with water. Acetonitrile is removed under reduced pressure and the mixture is extracted twice with DCM. The combined organic layers are dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords 2-(4-bromo-2-chloro-6-methylphenyl)acetonitrile as a colorless solid (2.504 g, 94%). LC-MS B: t<sub>R</sub> = 0.96 min; no ionization.

**A.3.47.4. 5-Bromo-1-chloro-2-(chloromethyl)-3-methylbenzene**

A cooled (0°C) mixture of (4-bromo-2-chloro-6-methylphenyl)methanol (2.529 g, 10.70 mmol) and zinc chloride (36.6 mg, 0.268 mmol) in anhydrous DCM (30 mL) is treated dropwise with thionyl chloride (1.57 mL, 21.50 mmol) and the RM is stirred at 0°C for 4h. The RM is concentrated under reduced pressure affording crude 5-bromo-1-chloro-2-(chloromethyl)-3-methylbenzene as a dark pink solid (2.752 g, quantitative). LC-MS B: t<sub>R</sub> = 1.05 min; no ionization.

**A.3.47.5. (4-Bromo-2-chloro-6-methylphenyl)methanol**

To a cooled (-78°C) solution of methyl 4-bromo-2-chloro-6-methylbenzoate (3.450 g, 12.60 mmol) in anhydrous THF (60 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in toluene, 38.0 mL, 38.0 mmol). The mixture is further stirred at -78°C, under nitrogen, for 30 min and is then allowed to warm-up to RT. Stirring at RT is continued for 1.5h, and the cooled RM is then treated successively with water (1 mL), 2.8 N aq. NaOH (1 mL) and water (3 mL). The mixture is allowed to warm-up to RT and is further stirred for 30 min. The resulting mixture is filtered over celite, washing with THF and the filtrate is concentrated to dryness under reduced pressure. EtOAc and water are added and the layers are separated. The aqueous layer is extracted twice with EtOAc and the combined organic layers are dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords pure (4-bromo-2-chloro-6-methylphenyl)methanol (2.529 g, 85%). LC-MS B: t<sub>R</sub> = 0.90 min; no ionization.

**A.3.47.6. Methyl 4-bromo-2-chloro-6-methylbenzoate**

To a solution of 4-bromo-2-chloro-6-methylbenzoic acid (3.500 g, 13.30 mmol) in anhydrous DMF (35 mL) at RT are added successively cesium carbonate (8.685 g, 26.70 mmol) and iodomethane (1.68 mL, 26.70 mmol) and the RM is stirred at RT for 1h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 4-bromo-2-chloro-6-methylbenzoate as a dark orange oil (3.450 g, 98%). LC-MS B: t<sub>R</sub> = 0.99 min; no ionization.

**A.3.48. Methyl 2-(2-fluoro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**

To a solution of methyl 2-(4-bromo-2-fluoro-6-methylphenyl)acetate (974 mg, 3.73 mmol) in anh. DMF (15 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (957 mg, 3.73 mmol), potassium acetate (1.464 g, 14.90 mmol) and Pd(dppf)Cl<sub>2</sub> (303 mg, 0.41 mmol). The RM is heated to 95°C, under nitrogen, overnight.

5 The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(2-fluoro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a yellow oil (918 mg, 80%). LC-MS B: t<sub>R</sub> = 1.05 min; [M+H]<sup>+</sup> = 309.23.

**10 A.3.48.1. Methyl 2-(4-bromo-2-fluoro-6-methylphenyl)acetate**

To a solution of 2-(4-bromo-2-fluoro-6-methylphenyl)acetic acid (980 mg, 3.97 mmol) in anh. DMF (15 mL) at RT are added cesium carbonate (2.585 g, 7.93 mmol) and iodomethane (0.499 mL, 7.93 mmol) and the RM is stirred at RT, under nitrogen, for 1h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh.

15 MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(4-bromo-2-fluoro-6-methylphenyl)acetate as a clear oil (974 mg, 94%). LC-MS B: t<sub>R</sub> = 0.96 min; no ionization.

**A.3.48.2. 2-(4-Bromo-2-fluoro-6-methylphenyl)acetic acid**

A mixture of 2-(4-bromo-2-fluoro-6-methylphenyl)acetonitrile (897 mg, 3.93 mmol), water (4 mL), 95% sulfuric acid (4 mL) and acetic acid (3 mL) is heated to 110°C, under nitrogen, for 2h. The RM is then allowed to cool to RT and is poured onto ice/water. The mixture is extracted twice with DCM and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure affording crude 2-(4-bromo-2-fluoro-6-methylphenyl)acetic acid as a colorless solid (980 mg, quantitative). LC-MS B: t<sub>R</sub> = 0.82 min; no ionization.

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**25 A.3.48.3. 2-(4-Bromo-2-fluoro-6-methylphenyl)acetonitrile**

A solution of 5-bromo-2-(chloromethyl)-1-fluoro-3-methylbenzene (1.027 g, 4.32 mmol) in MeCN (12 mL) and water (1.5 mL) is treated with sodium cyanide (287 mg, 5.62 mmol) and the RM is heated to 80°C, under nitrogen, for 2.5h. The RM is then allowed to cool to RT and is diluted with water. Acetonitrile is removed under reduced pressure and the RM is extracted twice with DCM. The combined organic layers are dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords 2-(4-bromo-2-fluoro-6-methylphenyl)acetonitrile as a light yellow solid (897 mg, 91%). LC-MS B: t<sub>R</sub> = 0.91 min; no ionization.

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**A.3.48.4. 5-Bromo-2-(chloromethyl)-1-fluoro-3-methylbenzene**

A cooled (0°C) mixture of (4-bromo-2-fluoro-6-methylphenyl)methanol (1.000 g, 4.38 mmol) and zinc chloride (14.9 mg, 0.11 mmol) in anh. DCM (10 mL) is treated dropwise with thionyl chloride (0.639 mL, 8.77 mmol)

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and the RM is stirred at 0°C for 2h. The RM is concentrated under reduced pressure affording crude 5-bromo-2-(chloromethyl)-1-fluoro-3-methylbenzene as a brown oil (1.027 g, 99%). LC-MS B:  $t_R$  = 1.02 min; no ionization.

**A.3.49. Methyl 2-(2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**

To a solution of methyl 2-(4-bromo-2,6-dimethylphenyl)acetate (2.575 g, 10.00 mmol) in anh. DMF (25 mL) are added at RT 4,4,4',4',5,5,5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.569 g, 10.00 mmol), potassium acetate (3.931 g, 40.10 mmol) and Pd(dppf)Cl<sub>2</sub> (814 mg, 1.10 mmol). The RM is heated to 95°C, under nitrogen, overnight. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 3/1) affords methyl 2-(2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a light yellow solid (2.333 g, 77%). LC-MS B:  $t_R$  = 1.05 min; [M+H]<sup>+</sup> = 305.23.

**A.3.49.1. Methyl 2-(4-bromo-2,6-dimethylphenyl)acetate**

To a solution of 2-(4-bromo-2,6-dimethylphenyl)acetic acid (2.553 g, 10.50 mmol) in anh. DMF (25 mL) at RT are added cesium carbonate (6.843 g, 21.00 mmol) and iodomethane (1.32 mL, 21.00 mmol) and the RM is stirred at RT, under nitrogen, for 1h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(4-bromo-2,6-dimethylphenyl)acetate as a clear oil (2.575 g, 95%). LC-MS B:  $t_R$  = 0.99 min; no ionization.

**A.3.49.2. 2-(4-Bromo-2,6-dimethylphenyl)acetic acid**

A mixture of 2-(4-bromo-2,6-dimethylphenyl)acetonitrile (3.048 g, 13.50 mmol), water (12.5 mL), 95% sulfuric acid (14 mL) and acetic acid (10 mL) is heated to 110°C, under nitrogen, for 4h. The RM is then allowed to cool to RT and is poured onto ice/water. The mixture is extracted twice with DCM and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure affording crude 2-(4-bromo-2,6-dimethylphenyl)acetic acid as a colorless solid (2.553 g, 78%). LC-MS B:  $t_R$  = 0.85 min; no ionization.

**A.3.49.3. 2-(4-Bromo-2,6-dimethylphenyl)acetonitrile**

A solution of 5-bromo-2-(chloromethyl)-1,3-dimethylbenzene (3.328 g, 14.30 mmol) in MeCN (30 mL) and water (3.5 mL) is treated with sodium cyanide (946 mg, 18.50 mmol) and the RM is heated to 80°C, under nitrogen, for 2h. The RM is then allowed to cool to RT and is diluted with water. Acetonitrile is removed under reduced pressure and the mixture is extracted twice with DCM. The combined organic layers are dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords 2-(4-bromo-2,6-dimethylphenyl)acetonitrile as a colorless solid (3.048 g, 95%). LC-MS B:  $t_R$  = 0.95 min; no ionization.



**A.3.49.4. 5-Bromo-2-(chloromethyl)-1,3-dimethylbenzene**

A cooled (0°C) mixture of (4-bromo-2,6-dimethylphenyl)methanol (3.000 g, 13.90 mmol) and zinc chloride (47.5 mg, 0.349 mmol) in anh. DCM (30 mL) is treated dropwise with thionyl chloride (2.03 mL, 27.90 mmol) and the RM is stirred at 0°C for 2h. The RM is concentrated to dryness under reduced pressure affording crude 5-bromo-2-(chloromethyl)-1,3-dimethylbenzene as a colorless solid (3.328 g, quantitative). LC-MS B:  $t_R$  = 1.04 min; no ionization.

**A.3.50. Methyl 2-(2-ethoxy-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**

To a solution of methyl 2-(4-bromo-2-ethoxy-6-fluorophenyl)acetate (1.370 g, 4.71 mmol) in anh. DMF (12 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.207 g, 4.71 mmol), potassium acetate (1.847 g, 18.80 mmol) and Pd(dppf)Cl<sub>2</sub> (383 mg, 0.51 mmol). The RM is heated to 90°C, under nitrogen, overnight. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(2-ethoxy-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a colorless solid (0.970 g, 61%). LC-MS B:  $t_R$  = 1.09 min; [M+H]<sup>+</sup> = 339.21.

**A.3.50.1. Methyl 2-(4-bromo-2-ethoxy-6-fluorophenyl)acetate**

To a solution of 2-(4-bromo-2-ethoxy-6-fluorophenyl)acetic acid (1.440 g, 5.20 mmol) in anh. DMF (15 mL) at RT are added cesium carbonate (2.117 g, 6.50 mmol) and iodomethane (0.48 mL, 7.80 mmol) and the RM is stirred at RT, under nitrogen, for 15 min. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(4-bromo-2-ethoxy-6-fluorophenyl)acetate as a colorless oil (1.370 g, 91%). LC-MS B:  $t_R$  = 1.01 min; [M+H]<sup>+</sup> = 290.99.

**A.3.50.2. 2-(4-Bromo-2-ethoxy-6-fluorophenyl)acetic acid**

A mixture of 2-(4-bromo-2-ethoxy-6-fluorophenyl)acetonitrile (1.440 g, 5.58 mmol), water (5 mL), 95% sulfuric acid (6 mL) and acetic acid (7 mL) is heated to 110°C, under nitrogen, for 3h. The RM is then allowed to cool to RT and is poured onto ice/water. The mixture is extracted twice with DCM and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure affording crude 2-(4-bromo-2-ethoxy-6-fluorophenyl)acetic acid as a colorless solid (1.440 g, 93%). LC-MS B:  $t_R$  = 0.88 min; no ionization.

**A.3.50.3. 2-(4-Bromo-2-ethoxy-6-fluorophenyl)acetonitrile**

A solution of 5-bromo-2-(chloromethyl)-1-ethoxy-3-fluorobenzene (2.860 g, 10.10 mmol) in MeCN (27 mL) and water (3.5 mL) is treated with sodium cyanide (669 mg, 13.10 mmol) and the RM is heated to 80°C, under nitrogen, overnight. The RM is then allowed to cool to RT and is diluted with water. Acetonitrile is removed under reduced pressure and the mixture is extracted twice with DCM. The combined organic layers are dried

over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords 2-(4-bromo-2-ethoxy-6-fluorophenyl)acetonitrile as a colorless solid (1.440 g, 55%). LC-MS B:  $t_R$  = 0.97 min; no ionization.

**A.3.50.4. 5-Bromo-2-(chloromethyl)-1-ethoxy-3-fluorobenzene**

A cooled ( $0^\circ\text{C}$ ) mixture of (4-bromo-2-ethoxy-6-fluorophenyl)methanol (2.180 g, 8.75 mmol) and zinc chloride (29.8 mg, 0.219 mmol) in anh. DCM (17 mL) is treated dropwise with thionyl chloride (1.28 mL, 17.50 mmol) and the RM is stirred at  $0^\circ\text{C}$  for 2h. The RM is concentrated under reduced pressure affording crude 5-bromo-2-(chloromethyl)-1-ethoxy-3-fluorobenzene as a pale pink oil (2.330 g, 99%). LC-MS B:  $t_R$  = 1.07 min; no ionization.

**A.3.50.5. (4-Bromo-2-ethoxy-6-fluorophenyl)methanol**

To a cooled ( $-78^\circ\text{C}$ ) solution of methyl 4-bromo-2-ethoxy-6-fluorobenzoate (3.150 g, 11.40 mmol) in anh. THF (30 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in toluene, 34.1 mL, 34.1 mmol). The mixture is further stirred at  $-78^\circ\text{C}$ , under nitrogen, for 15 min and is then allowed to warm-up to  $0^\circ\text{C}$ . Stirring at  $0^\circ\text{C}$  is continued for 45 min, and the cooled RM is then treated successively with water (35 mL) and 2.8 N aq. NaOH (25 mL). The mixture is allowed to warm-up to RT and is further stirred for 30 min. The resulting mixture is filtered over celite, washing with THF. EtOAc and water are added and the layers are separated. The aqueous layer is extracted twice with EtOAc and the combined organic layers are dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to EtOAc) affords (4-bromo-2-ethoxy-6-fluorophenyl)methanol as a colorless solid (2.680 g, 95%). LC-MS B:  $t_R$  = 0.84 min; no ionization.

**A.3.50.6. Methyl 4-bromo-2-ethoxy-6-fluorobenzoate**

To a solution of methyl 4-bromo-2-fluoro-6-hydroxybenzoate (2.930 g, 11.20 mmol) in anh. DMF (14 mL) at RT are added successively cesium carbonate (3.642 g, 11.20 mmol) and iodoethane (0.90 mL, 11.20 mmol) and the RM is stirred at RT for 30 min. Additional cesium carbonate (3.729 g, 11.40 mmol) and iodoethane (0.92 mL, 11.40 mmol) are then added and the RM is stirred at RT for 20 min. Water and  $\text{Et}_2\text{O}$  are added and the layers are separated. The aqueous layer is extracted twice with  $\text{Et}_2\text{O}$  and the combined organic layers are washed with brine, dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 4-bromo-2-ethoxy-6-fluorobenzoate as a yellow oil (3.150 g, quantitative). LC-MS B:  $t_R$  = 0.97 min;  $[\text{M}+\text{H}]^+ = 277.08$ .

**A.3.51. Methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethoxy)phenyl)acetate**

To a solution of methyl 2-(4-bromo-2-(trifluoromethoxy)phenyl)acetate (1.896 g, 5.58 mmol) in anh. DMF (25 mL) are added at RT 4,4',4'',5,5',5''-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.432 g, 5.58 mmol), potassium acetate (2.192 g, 22.30 mmol) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (454 mg, 0.61 mmol). The RM is heated to  $95^\circ\text{C}$ , under nitrogen, overnight. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with  $\text{Et}_2\text{O}$ . The filtrate is washed with water and the aqueous layer is extracted twice with  $\text{Et}_2\text{O}$ . The combined organic layers are then washed with

brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethoxy)phenyl)acetate as a green oil (1.574 g, 78%). LC-MS B:  $t_R$  = 1.09 min;  $[M+H]^+$  = 361.13.

#### A.3.51.1. Methyl 2-(4-bromo-2-(trifluoromethoxy)phenyl)acetate

5 To a solution of 2-(4-bromo-2-(trifluoromethoxy)phenyl)acetic acid (2.000 g, 6.56 mmol) in anh. DMF (30 mL) at RT are added cesium carbonate (4.277 g, 13.10 mmol) and iodomethane (0.82 mL, 13.10 mmol) and the RM is stirred at RT, under nitrogen, for 1h. Water and  $\text{Et}_2\text{O}$  are added and the layers are separated. The aqueous layer is extracted twice with  $\text{Et}_2\text{O}$  and the combined organic layers are washed with brine, dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(4-bromo-2-(trifluoromethoxy)phenyl)acetate as a clear oil (1.896 g, 92%). LC-MS B:  $t_R$  = 1.01 min; no ionization.

#### A.3.52. Methyl 2-(2-(difluoromethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate

To a solution of methyl 2-(4-bromo-2-(difluoromethoxy)phenyl)acetate (800 mg, 2.71 mmol) in anh. DMF (20 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (695 mg, 2.71 mmol), potassium acetate (1.064 g, 10.80 mmol) and  $\text{Pd(dppf)Cl}_2$  (220 mg, 0.29 mmol). The RM is heated to 90°C, under nitrogen, overnight. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(2-(difluoromethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a yellow oil (367 mg, 40%). LC-MS B:  $t_R$  = 1.03 min; no ionization.

#### A.3.52.1. Methyl 2-(4-bromo-2-(difluoromethoxy)phenyl)acetate

To a solution of 2-(4-bromo-2-(difluoromethoxy)phenyl)acetic acid (3.560 g, 12.70 mmol) in anh. DMF (20 mL) at RT are added cesium carbonate (6.191 g, 19.00 mmol) and iodomethane (0.95 mL, 15.20 mmol) and the RM is stirred at RT, under nitrogen, for 1h. Water and  $\text{Et}_2\text{O}$  are added and the layers are separated. The aqueous layer is extracted twice with  $\text{Et}_2\text{O}$  and the combined organic layers are washed with brine, dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(4-bromo-2-(difluoromethoxy)phenyl)acetate as a colorless oil (2.390 g, 64%). LC-MS B:  $t_R$  = 0.94 min; no ionization.

#### A.3.52.2. 2-(4-Bromo-2-(difluoromethoxy)phenyl)acetic acid

30 To a mixture of 2-(4-bromo-2-(difluoromethoxy)phenyl)acetonitrile (3.460 g, 13.20 mmol) in EtOH (100 mL) and water (100 mL) at RT is added potassium hydroxide (2.222 g, 39.60 mmol) and the RM is heated at reflux, under nitrogen, overnight. The RM is then allowed to cool to RT and ethanol is removed under reduced pressure. The resulting mixture is treated with 1 M aq. HCl and is extracted twice with DCM. The combined organic layers are washed with brine, dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced

pressure affording crude 2-(4-bromo-2-(difluoromethoxy)phenyl)acetic acid as an off-white solid (3.560 g, 96%). LC-MS B:  $t_R$  = 0.82 min; no ionization.

**A.3.52.3. 2-(4-Bromo-2-(difluoromethoxy)phenyl)acetonitrile**

5 A solution of 4-bromo-1-(chloromethyl)-2-(difluoromethoxy)benzene (3.890 g, 14.30 mmol) in MeCN (38 mL) and water (5 mL) is treated with sodium cyanide (913 mg, 18.60 mmol) and the RM is heated to 85°C, under nitrogen, for 3h. The RM is then allowed to cool to RT and is diluted with water. Acetonitrile is removed under reduced pressure and the mixture is extracted twice with DCM. The combined organic layers are dried over anhydrous  $MgSO_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to EtOAc) affords 2-(4-bromo-2-(difluoromethoxy)phenyl)acetonitrile as a pale yellow solid (3.560 g, 95%). LC-MS B:  $t_R$  = 0.92 min; no ionization.

**A.3.52.4. 4-Bromo-1-(chloromethyl)-2-(difluoromethoxy)benzene**

15 A cooled (0°C) mixture of (4-bromo-2-(difluoromethoxy)phenyl)methanol (3.580 g, 14.10 mmol) and zinc chloride (48.2 mg, 0.354 mmol) in anhydrous DCM (28 mL) is treated dropwise with thionyl chloride (2.06 mL, 28.30 mmol) and the RM is stirred at 0°C for 3.5h. The RM is concentrated under reduced pressure affording crude 4-bromo-1-(chloromethyl)-2-(difluoromethoxy)benzene as a colorless oil (3.890 g, quantitative). LC-MS B:  $t_R$  = 1.00 min; no ionization.

**A.3.52.5. (4-Bromo-2-(difluoromethoxy)phenyl)**

20 To a cooled (0°C) solution of 4-bromo-2-(difluoromethoxy)benzaldehyde (3.820 g, 15.20 mmol) in anhydrous MeOH (75 mL) is added portionwise sodium borohydride (1.727 g, 45.70 mmol) and the mixture is further stirred at 0°C, under nitrogen, for 1h. Methanol is then removed under reduced pressure. DCM and water are added and the layers are separated. The aqueous layer is extracted twice with DCM and the combined organic layers are dried over anhydrous  $MgSO_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords (4-bromo-2-(difluoromethoxy)phenyl)methanol as a colorless oil (3.890 g, quantitative). LC-MS B:  $t_R$  = 0.81 min; no ionization.

**A.3.52.6. 4-Bromo-2-(difluoromethoxy)benzaldehyde**

25 To a cooled (0°C) solution of 4-bromo-2-hydroxybenzaldehyde (5.000 g, 24.40 mmol) in MeCN (135 mL) and water (135 mL) is added potassium hydroxide (27.355 g, 488.00 mmol). The mixture is stirred at RT for 30 min, and is then cooled to -30°C. Diethyl (bromodifluoromethyl)phosphonate (13.283 g, 48.80 mmol) is added in one portion to the cooled mixture and stirring is then continued at RT for 2h.  $Et_2O$  is added, the layers are separated and the aqueous layer is further extracted with  $Et_2O$ . The combined organic layers are successively washed with 1 M aq. NaOH, water and brine and are then dried over anhydrous  $MgSO_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords 4-bromo-2-(difluoromethoxy)benzaldehyde as a pale yellow solid (3.820 g, 62%). LC-MS B:  $t_R$  = 0.92 min; no ionization.

**A.3.53. Methyl 2-(3-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acetate**

A mixture of methyl 2-(3-ethylthiophen-2-yl)acetate (1.340 g, 7.27 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.119 g, 4.36 mmol), bis(1,5-cyclooctadiene)diiridium(I) dichloride (50.4 mg, 0.0727 mmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (47.8 mg, 0.175 mmol) in THF (35 mL) is degassed with a nitrogen stream and then stirred at 80°C, under nitrogen, overnight. The RM is concentrated under reduced pressure and the residue is purified by FC (from heptane to heptane/EtOAc = 4/1) to afford methyl 2-(3-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acetate as a pale yellow oil (1.781 g, 79%). LC-MS B:  $t_R$  = 1.04 min;  $[M+H]^+$  = 311.22.

**A.3.53.1. Methyl 2-(3-ethylthiophen-2-yl)acetate**

To a solution of 2-(3-ethylthiophen-2-yl)acetic acid (1.248 g, 7.33 mmol) in anh. DMF (20 mL) at RT are added cesium carbonate (3.581 g, 11.00 mmol) and iodomethane (0.55 mL, 8.79 mmol) and the RM is stirred at RT, under nitrogen, for 40 min. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(3-ethylthiophen-2-yl)acetate as a yellow oil (1.340 g, 99%). LC-MS B:  $t_R$  = 0.87 min;  $[M+H]^+$  = 185.19.

**A.3.53.2. 2-(3-Ethylthiophen-2-yl)acetic acid**

To a mixture of 2-(3-ethylthiophen-2-yl)acetonitrile (1.150 g, 7.60 mmol) in EtOH (6 mL) and water (6 mL) at RT is added potassium hydroxide (1.280 g, 22.80 mmol) and the RM is heated at reflux, under nitrogen, for 75 min. The RM is then allowed to cool to RT and ethanol is removed under reduced pressure. The resulting mixture is treated with 1 M aq. HCl and is extracted twice with DCM. The combined organic layers are dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure affording crude 2-(3-ethylthiophen-2-yl)acetic acid as a yellow oil (1.247 g, 96%). LC-MS B:  $t_R$  = 0.72 min;  $[M+H]^+$  = 170.94.

**A.3.53.3. 2-(3-Ethylthiophen-2-yl)acetonitrile**

A solution of 2-(chloromethyl)-3-ethylthiophene (506 mg, 3.15 mmol) in anhydrous DMSO (20 mL) is treated with sodium cyanide (617 mg, 12.60 mmol) and the RM is heated to 80°C, under nitrogen, for 40 min. The RM is then allowed to cool to RT and is diluted with water. The resulting mixture is extracted three times with EtOAc and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords 2-(3-ethylthiophen-2-yl)acetonitrile as a yellow oil (360 mg, 76%). LC-MS B:  $t_R$  = 0.83 min; no ionization.

**A.3.53.4. 2-(Chloromethyl)-3-ethylthiophene**

To a cooled (0°C) solution of (3-ethylthiophen-2-yl)methanol (500 mg, 3.52 mmol) in anh. DCM (18 mL) are added successively triethylamine (0.63 mL, 4.57 mmol) and 4-dimethylaminopyridine (43 mg, 0.35 mmol). Methanesulfonyl chloride (0.32 mL, 4.22 mmol) is then added dropwise and the resulting mixture is stirred at RT, under nitrogen, for 1h. The RM is then diluted with water, the layers are separated and the aqueous layer

is extracted twice with DCM. The combined organic layers are dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure affording crude 2-(chloromethyl)-3-ethylthiophene as a yellow oil (505 mg, 90%). LC-MS B:  $t_R$  = 0.86 min; no ionization.

**A.3.53.5. (3-Ethylthiophen-2-yl)methanol**

5 To a cooled ( $-78^\circ\text{C}$ ) solution of methyl 3-ethylthiophene-2-carboxylate (2.270 g, 13.30 mmol) in anh. THF (80 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in toluene, 40.0 mL, 40.0 mmol). The mixture is further stirred at  $-78^\circ\text{C}$ , under nitrogen, for 10 min and is then allowed to warm-up to  $0^\circ\text{C}$ . Stirring at  $0^\circ\text{C}$  is continued for 30 min, and the cooled RM is then treated successively with water (1.5 mL), 15% aq. NaOH (1.5 mL) and water (4 mL). The mixture is allowed to warm-up to RT and is further stirred for 1h. The  
10 resulting mixture is filtered over celite, washing with THF. EtOAc and water are added and the layers are separated. The aqueous layer is extracted twice with EtOAc and the combined organic layers are dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords (3-ethylthiophen-2-yl)methanol as a colorless oil (2.030 g, quantitative). LC-MS B:  $t_R$  = 0.66 min; no ionization.

15 **A.3.53.6. Methyl 3-ethylthiophene-2-carboxylate**

To a solution of 3-ethylthiophene-2-carboxylic acid (3.130 g, 19.00 mmol) in anh. DMF (20 mL) at RT are added successively cesium carbonate (9.303 g, 28.60 mmol) and iodomethane (1.44 mL, 22.80 mmol) and the RM is stirred at RT for 1.5h. Water and  $\text{Et}_2\text{O}$  are added and the layers are separated. The aqueous layer is extracted twice with  $\text{Et}_2\text{O}$  and the combined organic layers are washed with brine, dried over anh.  $\text{MgSO}_4$ ,  
20 filtered and concentrated under reduced pressure affording methyl 3-ethylthiophene-2-carboxylate as a yellow oil (3.340 g, quantitative). LC-MS B:  $t_R$  = 0.89 min;  $[\text{M}+\text{H}]^+ = 171.04$ .

**A.3.54. Ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxylate**

To a solution of ethyl 6-bromobenzofuran-3-carboxylate (1.850 g, 6.87 mmol) in anh. DMF (20 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.763 g, 6.87 mmol), potassium acetate (2.699 g,  
25 27.50 mmol) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (559 mg, 0.75 mmol). The RM is heated to  $95^\circ\text{C}$ , under nitrogen, overnight. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with  $\text{Et}_2\text{O}$ . The filtrate is washed with water and the aqueous layer is extracted twice with  $\text{Et}_2\text{O}$ . The combined organic layers are then washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxylate as a  
30 light yellow solid (1.528 g, 70%). LC-MS B:  $t_R$  = 1.11 min;  $[\text{M}+\text{H}]^+ = 317.23$ .

**A.3.55. Methyl 2-(2-cyclopropoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**

To a solution of methyl 2-(4-bromo-2-cyclopropoxyphenyl)acetate (2.009 g, 7.05 mmol) in anh. 1,4-dioxane (30 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.807 g, 7.05 mmol), potassium acetate (2.766 g, 28.20 mmol) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (573 mg, 0.77 mmol). The RM is heated to  $95^\circ\text{C}$ , under nitrogen, overnight.  
35 The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is



washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(2-cyclopropoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a yellow oil (1.912 g, 82%). LC-MS B: t<sub>R</sub> = 1.04 min; [M+H]<sup>+</sup> = 333.25.

5      **A.3.55.1. Methyl 2-(4-bromo-2-cyclopropoxyphenyl)acetate**

A cooled (0°C) solution of diethylzinc (1 M in hexanes, 32.6 mL, 32.6 mmol) in anh. DCM (30 mL) is treated dropwise with trifluoroacetic acid (1.72 mL, 22.30 mmol) and the mixture is stirred at 0°C, under nitrogen, for 10 min. Diiodomethane (5.35 mL, 65.20 mmol) is then added dropwise to the cooled mixture and stirring at 0°C is continued for 10 min. A solution of methyl 2-(4-bromo-2-(vinylloxy)phenyl)acetate (2.396 g, 8.57 mmol) in anh. DCM (40 mL) is then added dropwise and the resulting mixture is further stirred at 0°C for 30 min, and then at RT for 5h. The RM is then treated with aq. sat. NH<sub>4</sub>Cl and the layers are separated. The aqueous layer is extracted twice with DCM and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 3/1) affords methyl 2-(4-bromo-2-cyclopropoxyphenyl)acetate as a light yellow oil (2.009 g, 82%). LC-MS B: t<sub>R</sub> = 0.99 min; no ionization.

**A.3.55.2. Methyl 2-(4-bromo-2-(vinylloxy)phenyl)acetate**

To a solution of methyl 2-(4-bromo-2-hydroxyphenyl)acetate (3.160 g, 12.90 mmol) in anh. toluene (35 mL) at RT are added successively sodium carbonate (820 mg, 7.74 mmol) and bis(1,5-cyclooctadiene)diiridium(I) dichloride (89.3 mg, 0.129 mmol), and the mixture is degassed with nitrogen. Vinyl acetate (2.4 mL, 25.80 mmol) is then added and the resulting mixture is heated to 100°C, under nitrogen, for 5h. The RM is allowed to cool to RT and water is added. The mixture is extracted three times with EtOAc and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(4-bromo-2-(vinylloxy)phenyl)acetate as a yellow oil (2.253 g, 64%). LC-MS B: t<sub>R</sub> = 0.96 min; no ionization.

25      **A.3.55.3. Methyl 2-(4-bromo-2-hydroxyphenyl)acetate**

A solution of 2-(4-bromo-2-hydroxyphenyl)acetic acid (3.000 g, 12.30 mmol) in anh. MeOH (45 mL) is treated dropwise with a solution of concentrated HCl (12 M, 1.02 mL, 12.30 mmol) in anh. MeOH (15 mL) and the resulting solution is heated to 70°C, under nitrogen, for 2h. The RM is then allowed to cool to RT and methanol is removed under reduced pressure. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(4-bromo-2-hydroxyphenyl)acetate as a colorless solid (2.733 g, 90%). LC-MS B: t<sub>R</sub> = 0.80 min; no ionization.



**A.3.56. Methyl 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-2-carboxylate**

To a solution of methyl 4-bromo-1-ethyl-1H-pyrrole-2-carboxylate (1.567 g, 6.75 mmol) in anh. DMF (15 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.715 g, 6.75 mmol), potassium acetate (2.651 g, 27.00 mmol) and Pd(dppf)Cl<sub>2</sub> (494 mg, 0.67 mmol). The RM is heated to 90°C, under nitrogen, overnight.

5 The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 3/1) affords methyl 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-2-carboxylate as a light yellow oil (841 mg, 45%). LC-MS B: t<sub>R</sub> = 0.96 min; [M+H]<sup>+</sup> = 280.24.

**10 A.3.56.1. Methyl 4-bromo-1-ethyl-1H-pyrrole-2-carboxylate**

To a solution of methyl 4-bromo-1H-pyrrole-2-carboxylate (1.500 g, 7.21 mmol) in anh. DMF (15 mL) at RT are added potassium carbonate (1.494 g, 10.80 mmol) and iodoethane (1.43 mL, 8.65 mmol) and the RM is stirred at RT, under nitrogen, for 2.5h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh.

15 MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 4-bromo-1-ethyl-1H-pyrrole-2-carboxylate as a clear oil (1.567 g, 94%). LC-MS B: t<sub>R</sub> = 0.94 min; no ionization.

**A.3.57. Methyl 1-propyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-2-carboxylate**

To a solution of methyl 4-bromo-1-propyl-1H-pyrrole-2-carboxylate (1.721 g, 6.99 mmol) in anh. DMF (15 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.776 g, 6.99 mmol), potassium acetate (2.745 g, 28.00 mmol) and Pd(dppf)Cl<sub>2</sub> (512 mg, 0.69 mmol). The RM is heated to 90°C, under nitrogen, overnight.

20 The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 3/1) affords methyl 1-propyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-2-carboxylate as a yellow oil (1.036 g, 51%). LC-MS B: t<sub>R</sub> = 1.02 min; [M+H]<sup>+</sup> = 294.33.

**A.3.57.1. Methyl 4-bromo-1-propyl-1H-pyrrole-2-carboxylate**

To a solution of methyl 4-bromo-1H-pyrrole-2-carboxylate (1.500 g, 7.21 mmol) in anh. DMF (15 mL) at RT are added potassium carbonate (1.494 g, 10.80 mmol) and 1-iodopropane (0.84 mL, 8.65 mmol) and the RM is stirred at RT, under nitrogen, overnight. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh.

30 MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 4-bromo-1-propyl-1H-pyrrole-2-carboxylate as a clear oil (1.721 g, 97%). LC-MS B: t<sub>R</sub> = 0.99 min; no ionization.

**A.3.58. Methyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-2-carboxylate**

A mixture of methyl 3-ethoxy-1H-pyrrole-2-carboxylate (265 mg, 1.57 mmol), 4,4,4',4',5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (402 mg, 1.57 mmol), (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (15.9 mg, 0.0235 mmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (15 mg, 0.054 mmol) in THF (5 mL) is degassed with a nitrogen stream and then stirred at RT, under nitrogen, for 1h. The RM is concentrated under reduced pressure and the residue is purified by FC (from heptane to heptane/EtOAc = 7/3) to afford methyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-2-carboxylate as a clear oil (490 mg, quantitative). LC-MS B:  $t_R$  = 0.88 min;  $[M+H]^+$  = 296.25.

**A.3.58.1. Methyl 3-ethoxy-1H-pyrrole-2-carboxylate**

To a solution of methyl 3-hydroxy-1H-pyrrole-2-carboxylate (300 mg, 2.06 mmol) in anh. DMF (8 mL) at RT are added potassium carbonate (299 mg, 2.17 mmol) and iodoethane (0.174 mL, 2.17 mmol) and the RM is stirred at RT, under nitrogen, overnight. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to EtOAc) affords methyl 3-ethoxy-1H-pyrrole-2-carboxylate as a light yellow solid (265 mg, 76%). LC-MS B:  $t_R$  = 0.60 min;  $[M+H]^+$  = 170.09.

**A.3.59. Ethyl 3-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-2-carboxylate**

A mixture of ethyl 3-cyclopropyl-1H-pyrrole-2-carboxylate (300 mg, 1.59 mmol), 4,4,4',4',5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (408 mg, 1.59 mmol), (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (16.1 mg, 0.0239 mmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (15.2 mg, 0.055 mmol) in THF (2.5 mL) is degassed with a nitrogen stream and then stirred at RT, under nitrogen, for 1h. The RM is concentrated under reduced pressure and the residue is purified by FC (from heptane to heptane/EtOAc = 7/3) to afford ethyl 3-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-2-carboxylate as a yellow solid (389 mg, 80%). LC-MS B:  $t_R$  = 1.03 min;  $[M+H]^+$  = 306.04.

**A.3.60. 1-(2-Propyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carboxylic acid**

The title compound is prepared according to the procedure described for A.3.6., starting with 1-(4-bromo-2-propylphenyl)cyclopropane-1-carboxylic acid. LC-MS B:  $t_R$  = 1.02 min;  $[M+MeCN]^+$  = 372.47.

**A.3.60.1. 1-(4-Bromo-2-propylphenyl)cyclopropane-1-carboxylic acid**

In a flask containing 1-(4-bromo-2-propylphenyl)cyclopropane-1-carbonitrile (465 mg, 1.69 mmol) and equipped with a condenser, are added successively H<sub>2</sub>O (1.6 mL), AcOH (1.2 mL) and H<sub>2</sub>SO<sub>4</sub> (1.8 mL). The RM is stirred at 110°C for 3 d, then cooled to RT. The RM is poured into ice water and the mixture is extracted with DCM (3x). The combined organic layers are washed with NaOH 1N. The basic aqueous layer is extracted once more with EtOAc. The aqueous layer is acidified till pH2-3 by addition of 2N HCl. This acidic aqueous layer is then extracted twice with EtOAc. These organic layers (acidic extraction) are combined, washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure,

affording the title compound as a white solid (283mg, 65%). LC-MS B:  $t_R$  = 0.96 min; no ionization.  $^1H$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$ : 12.13-12.49 (m, 1 H), 7.36-7.41 (m, 1 H), 7.23-7.33 (m, 1 H), 7.13-7.22 (m, 1 H), 2.59-2.67 (m, 2 H), 1.61 (m, 2 H), 1.43-1.56 (m, 2 H), 1.06-1.15 (m, 2 H), 0.81-0.98 (m, 3 H).

**A.3.60.2. 1-(4-Bromo-2-propylphenyl)cyclopropane-1-carbonitrile**

5 To a solution of 2-(4-bromo-2-propylphenyl)acetonitrile (A.3.42.3., 1180 mg, 4.81 mmol) in toluene (25 mL) are added at RT under argon 1,2-dibromoethane (1.26 mL, 14.4 mmol), benzyltriethylammonium chloride (89.4 mg, 0.385 mmol) and NaOH (1346 mg, 33.6 mmol). The RM is stirred over 2 nights at 110°C, it is then cooled to RT and 1,2-dibromoethane (1.26 mL, 14.4 mmol), benzyltriethylammonium chloride (89.4 mg, 0.385 mmol) and NaOH (1346 mg, 33.6 mmol) are added and the RM is stirred  
10 overnight at 110°C. Once at RT, the RM is quenched with water and concentrated in vacuo. The residue is partitioned between EtOAc and water. The aqueous is extracted once more with EtOAc. The combined organic layers are washed with water, brine, dried over  $MgSO_4$ , filtered and concentrated in vacuo. The residue is purified by FC (Hept:EtOAc, 100:0 to 95:5), affording the title compound as a yellow oil (468mg 37%). LC-MS B:  $t_R$  = 1.06 min;  $[M+H]^+$  = 263.92.

**A.3.61. 1-(2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carboxylic acid**

The title compound is prepared according to the procedure described for A.3.6., starting with 1-(4-bromo-2-ethoxyphenyl)cyclopropane-1-carboxylic acid. LC-MS B:  $t_R$  = 0.96 min;  $[M+H]^+$  = 333.44.

**A.3.61.1. 1-(4-Bromo-2-ethoxyphenyl)cyclopropane-1-carboxylic acid**

The title compound is prepared according to the procedure described for A.3.60.1., starting with 1-(4-bromo-2-ethoxyphenyl)cyclopropane-1-carbonitrile. LC-MS B:  $t_R$  = 0.90 min;  $[M+H]^+$  = 285.17.  
20

**A.3.61.2. 1-(4-Bromo-2-ethoxyphenyl)cyclopropane-1-carbonitrile**

The title compound is prepared according to the procedure described for A.3.60.2., starting with 2-(4-bromo-2-ethoxyphenyl)acetonitrile(Example 282-d). LC-MS B:  $t_R$  = 1.00 min;  $[M+H]^+$  = 265.94.

**A.3.62. 5-(2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoxazol-3-ol**

25 Butyllithium (1.6M in hexane, 1.1 mL, 1.76 mmol) is added dropwise, at -78 °C under nitrogen, to a stirred solution of 5-(4-bromo-2-methoxyphenyl)isoxazol-3-ol (158 mg, 0.585 mmol) in dry THF (4 mL). The RM is stirred at -78 °C for 25 min, then isopropoxyboronic acid, pinacol ester (0.418 mL, 2.05 mmol) is added dropwise and the RM is stirred at -78 °C for 45 min then at RT for 40min. The RM is quenched with sat. aq.  $NH_4Cl$  and extracted with EtOAc. The organic layer is washed twice with brine, dried over  $MgSO_4$ , filtered and concentrated. The residue is  
30 purified by FC (Hept:EtOAc 9:1 to 8:2) to afford the expected product as a white solid (42 mg, 23%). LC-MS A:  $t_R$  = 0.86 min;  $[M+H]^+$  = 318.14.

**A.3.62.1. 5-(4-Bromo-2-methoxyphenyl)isoxazol-3-ol**

HCl conc. (6.8 mL) is added dropwise at RT to a stirred suspension of 3-(4-bromo-2-methoxyphenyl)-3-oxo-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide (284 mg, 0.763 mmol) in MeOH (1.7 mL). The RM is

stirred at RT for 30 min. Water (4 mL) is added and the precipitate is filtered off, washing with 1.2 mL water to afford the expected product as a white solid (169 mg, 82%) LC-MS A:  $t_R$  = 0.79 min,  $[M+H]^+$  = 271.99.

**A.3.62.2. 3-(4-Bromo-2-methoxyphenyl)-3-oxo-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide**

5 To a solution of ethyl 3-(4-bromo-2-methoxyphenyl)-3-oxopropanoate (971 mg, 1.33 mmol) in NMP (15.7 mL) are sequentially added O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (512 mg, 4.19 mmol) and DMAP (433 mg, 3.55 mmol) at RT. The RM is heated to 115°C and stirred overnight, then cooled to RT. The mixture is partitioned between 40 mL HCl 0.5M (pH 2) and 40 mL EtOAc. The organic layer is washed three times with 40 mL NaCl sat. The aqueous layer is reextracted with 40 mL EtOAc. The organic layers  
10 are combined, dried over  $MgSO_4$ , filtered and concentrated. The residue is purified by FC (Hept:EtOAc), affording the title compound as a white solid (301 mg, 25%). LC-MS A:  $t_R$  = 0.76 min,  $[M+H]^+$  = 373.98.

**A.3.62.3. Ethyl 3-(4-bromo-2-methoxyphenyl)-3-oxopropanoate**

1-(4-bromo-2-methoxyphenyl)ethanone (1.00 g, 4.37 mmol) is dissolved in diethyl carbonate (5.6 mL, 46.2 mmol). NaH (66% suspension in oil, 384 mg, 9.6 mmol) is added carefully. The RM is stirred overnight at RT. Water is  
15 added carefully and the mixture is extracted two times with EtOAc. The organic layers are washed with water, brine, dried over  $MgSO_4$ , filtered and concentrated. The residue is purified by FC (Hept-EtOAc, affording the title compound as a light yellow oil (933mg, 71%). LC-MS A:  $t_R$  = 0.87min,  $[M+H]^+$  = 303.01.

**A.3.63. Methyl 3-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate**

To a solution of methyl 3-(4-bromo-2-methoxyphenyl)propanoate (0.899 g, 3.26 mmol) in anh. DMF (10 mL) are  
20 added at RT 4,4,4',4',5,5,5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.835 g, 3.26 mmol), potassium acetate (1.278 g, 13.00 mmol) and  $Pd(dppf)Cl_2$  (265 mg, 0.35 mmol). The mixture is heated to 90°C, under nitrogen, overnight. The RM is allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are washed with brine, dried over  $MgSO_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane  
25 to heptane/EtOAc = 4/1) affords methyl 3-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate as a light yellow oil (0.752 g, 72%). LC-MS B:  $t_R$  = 1.02 min;  $[M+H]^+$  = 321.22.

**A.3.63.1. Methyl 3-(4-bromo-2-methoxyphenyl)propanoate**

To a solution of 3-(4-bromo-2-methoxyphenyl)propanoic acid (1.000 g, 3.86 mmol) in anh. DMF (10 mL) at  
RT are added cesium carbonate (2.515 g, 7.72 mmol) and iodomethane (0.485 mL, 7.72 mmol) and the  
30 mixture is stirred at RT, under nitrogen, for 1h. Water and  $Et_2O$  are added and the layers are separated. The aqueous layer is extracted twice with  $Et_2O$  and the combined organic layers are washed with brine, dried over anh.  $MgSO_4$ , filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 3-(4-bromo-2-methoxyphenyl)propanoate as a clear oil (0.899 g, 85%). LC-MS B:  $t_R$  = 0.96 min; no ionization.

**A.3.64. Methyl 2-(2-ethoxy-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**

To a solution of methyl 2-(4-bromo-2-ethoxy-3-fluorophenyl)acetate (1.939 g, 6.66 mmol) in anh. DMF (20 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.708 g, 6.66 mmol), potassium acetate (2.615 g, 26.60 mmol) and Pd(dppf)Cl<sub>2</sub> (0.542 g, 0.73 mmol). The mixture is heated to 90°C, under nitrogen, overnight. The RM is allowed to cool to RT and is filtered through a pad of celite, washing with EtOAc. The filtrate is washed with water and the aqueous layer is extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(2-ethoxy-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a dark green oil (1.254 g, 56%). LC-MS B: t<sub>R</sub> = 1.05 min; [M+H]<sup>+</sup> = 339.23.

**A.3.64.1. Methyl 2-(4-bromo-2-ethoxy-3-fluorophenyl)acetate**

To a solution of 2-(4-bromo-2-ethoxy-3-fluorophenyl)acetic acid (2.186 g, 7.28 mmol) in anh. DMF (20 mL) at RT are added cesium carbonate (3.213 g, 9.86 mmol) and iodomethane (0.738 mL, 11.80 mmol) and the mixture is stirred at RT, under nitrogen, for 15 min. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(4-bromo-2-ethoxy-3-fluorophenyl)acetate as a clear oil (1.939 g, 91%). LC-MS B: t<sub>R</sub> = 0.99 min; [M+H]<sup>+</sup> = 291.10.

**A.3.64.2. 2-(4-Bromo-2-ethoxy-3-fluorophenyl)acetic acid**

A mixture of 2-(4-bromo-2-ethoxy-3-fluorophenyl)acetonitrile (1.879 g, 7.28 mmol), water (7 mL), 95% sulfuric acid (8 mL) and acetic acid (9 mL) is heated to 110°C, under nitrogen, for 1.5h. The RM is then allowed to cool to RT and is poured onto ice/water. The mixture is extracted twice with DCM and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure affording 2-(4-bromo-2-ethoxy-3-fluorophenyl)acetic acid as an off-white solid (2.186 g, quantitative). LC-MS B: t<sub>R</sub> = 0.85 min; no ionization.

**A.3.64.3. 2-(4-Bromo-2-ethoxy-3-fluorophenyl)acetonitrile**

A solution of 1-bromo-4-(chloromethyl)-3-ethoxy-2-fluorobenzene (2.124 g, 7.94 mmol) in MeCN (24 mL) and water (3 mL) is treated with sodium cyanide (0.527 g, 10.30 mmol) and the mixture is heated to 80°C, under nitrogen, overnight. The RM is allowed to cool to RT and is diluted with water. Acetonitrile is removed under reduced pressure and the mixture is extracted twice with DCM. The combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords 2-(4-bromo-2-ethoxy-3-fluorophenyl)acetonitrile as a colorless solid (1.879 g, 92%). LC-MS B: t<sub>R</sub> = 0.97 min; no ionization.

**A.3.64.4. 1-Bromo-4-(chloromethyl)-3-ethoxy-2-fluorobenzene**

A cooled (0°C) mixture of (4-bromo-2-ethoxy-3-fluorophenyl)methanol (1.947 g, 7.82 mmol) and zinc chloride (26.6 mg, 0.19 mmol) in anh. DCM (25 mL) is treated dropwise with thionyl chloride (1.14 mL, 15.60 mmol)



and the mixture is stirred at 0°C for 2h. The RM is concentrated under reduced pressure affording 1-bromo-4-(chloromethyl)-3-ethoxy-2-fluorobenzene as a clear oil (2.124 g, quantitative). LC-MS B:  $t_R$  = 1.06 min; no ionization.

#### **A.3.64.5. (4-Bromo-2-ethoxy-3-fluorophenyl)methanol**

5 To a cooled (-78°C) solution of ethyl 4-bromo-2-ethoxy-3-fluorobenzoate (2.920 g, 10.00 mmol) in anh. THF (30 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in toluene, 30.1 mL, 30.1 mmol) and the mixture is further stirred at -78°C, under nitrogen, for 45 min. The RM is then allowed to warm-up to 0°C and is treated successively with water and with 2.8 N aq. NaOH. EtOAc is added, the layers are separated and the aqueous layer is extracted twice with EtOAc. The combined organic layers are dried over anh. MgSO<sub>4</sub>,  
10 filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords (4-bromo-2-ethoxy-3-fluorophenyl)methanol as a colorless solid (1.947 g, 78%). LC-MS B:  $t_R$  = 0.85 min; no ionization.

#### **A.3.64.6. Ethyl 4-bromo-2-ethoxy-3-fluorobenzoate**

15 To a solution of 4-bromo-3-fluoro-2-hydroxybenzoic acid (3.000 g, 12.80 mmol) in anh. DMF (25 mL) at RT are added potassium carbonate (3.529 g, 25.50 mmol) and iodoethane (2.05 mL, 25.50 mmol) and the mixture is stirred at 80°C, under nitrogen, overnight. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 3/1) affords ethyl 4-bromo-2-ethoxy-3-fluorobenzoate as a yellow oil (2.920 g, 79%). LC-MS  
20 B:  $t_R$  = 1.04 min; [M+H]<sup>+</sup> = 291.09.

#### **A.3.65. Methyl 2-(3-propyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acetate**

A mixture of methyl 2-(3-propylthiophen-2-yl)acetate (0.600 g, 3.03 mmol), 4,4,4',4',5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.470 g, 1.82 mmol), (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (21.5 mg, 0.0325 mmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (20 mg, 0.074 mmol) in THF (15 mL) is degassed with a nitrogen stream  
25 and stirred at 80°C, under nitrogen, overnight. The RM is concentrated under reduced pressure and the residue is purified by FC (from heptane to heptane/EtOAc = 7/3) to afford methyl 2-(3-propyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acetate as a clear oil (0.671 g, 68%). LC-MS B:  $t_R$  = 1.07 min; [M+H]<sup>+</sup> = 325.24.

##### **A.3.65.1. Methyl 2-(3-propylthiophen-2-yl)acetate**

30 A mixture of methyl 2-(3-bromothiophen-2-yl)acetate (1.655 g, 7.04 mmol), potassium n-propyltrifluoroborate (1.223 g, 7.74 mmol) and cesium carbonate (6.881 g, 21.10 mmol) in toluene (24 mL) and water (12 mL) is degassed three times with nitrogen. Palladium(II) acetate (79 mg, 0.35 mmol) and RuPhos (0.346 g, 0.70 mmol) are then added and the mixture is heated to 95°C, under nitrogen, overnight. The RM is allowed to cool to RT, water is added and the mixture is extracted three times with EtOAc. The combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification

by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(3-propylthiophen-2-yl)acetate as a yellow oil (1.336 g, 96%). LC-MS B:  $t_R$  = 0.94 min;  $[M+H]^+$  = 199.26.

#### A.3.65.2. Methyl 2-(3-bromothiophen-2-yl)acetate

5 To a solution of 2-(3-bromothiophen-2-yl)acetic acid (2.000 g, 9.05 mmol) in anh. DMF (20 mL) at RT are added cesium carbonate (5.895 g, 18.10 mmol) and iodomethane (1.14 mL, 18.10 mmol) and the mixture is stirred at RT, under nitrogen, for 1h. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-(3-bromothiophen-2-yl)acetate as a yellow oil (2.183 g, quantitative). LC-MS B:  $t_R$  = 10 0.86 min; no ionization.

#### A.3.66. Methyl 2-(3-(difluoromethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acetate

A mixture of methyl 2-(3-(difluoromethoxy)thiophen-2-yl)acetate (0.365 g, 1.64 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.253 g, 0.98 mmol), (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (11 mg, 0.0164 mmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (11 mg, 0.039 mmol) in THF (8 mL) is degassed with a nitrogen stream and stirred at 80°C, under nitrogen, overnight. The RM is concentrated under reduced pressure and the residue is purified by FC (from heptane to heptane/EtOAc = 4/1) to afford methyl 2-(3-(difluoromethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acetate as a yellow oil (0.473 g, 83%). LC-MS B:  $t_R$  = 1.02 min;  $[M+H]^+$  = 349.15.

#### A.3.66.1. Methyl 2-(3-(difluoromethoxy)thiophen-2-yl)acetate

20 To a solution of 2-(3-(difluoromethoxy)thiophen-2-yl)acetic acid (0.401 g, 1.93 mmol) in anh. DMF (8 mL) at RT are added cesium carbonate (0.941 g, 2.89 mmol) and iodomethane (0.145 mL, 2.31 mmol) and the mixture is stirred at RT, under nitrogen, for 30 min. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 4/1) affords methyl 2-(3-(difluoromethoxy)thiophen-2-yl)acetate as a pale yellow oil (0.364 g, 85%). LC-MS B:  $t_R$  = 0.83 min; no ionization.

#### A.3.66.2. 2-(3-(Difluoromethoxy)thiophen-2-yl)acetic acid

30 A mixture of 2-(3-(difluoromethoxy)thiophen-2-yl)acetonitrile (0.306 g, 1.62 mmol), potassium hydroxide (0.272 g, 4.85 mmol) in EtOH (3 mL) and water (3 mL) is heated to 110°C, under nitrogen, for 2.5h. The RM is allowed to cool to RT and is concentrated under reduced pressure. 1 M aq. HCl and DCM are successively added, the layers are separated and the aqueous layer is extracted twice with DCM. The combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure affording 2-(3-(difluoromethoxy)thiophen-2-yl)acetic acid as an orange oil (0.296 g, 88%). LC-MS B:  $t_R$  = 0.68 min; no ionization.



**A.3.66.3. 2-(3-(Difluoromethoxy)thiophen-2-yl)acetonitrile**

A solution of 2-(chloromethyl)-3-(difluoromethoxy)thiophene (0.426 g, 2.14 mmol) in anhydrous DMSO (10.5 mL) is treated with sodium cyanide (0.217 g, 4.29 mmol) and the mixture is heated to 80°C, under nitrogen, for 75 min. The RM is allowed to cool to RT and is diluted with water. The resulting mixture is extracted three times with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 4/1) affords 2-(3-(difluoromethoxy)thiophen-2-yl)acetonitrile as a pale yellow oil (0.306 g, 75%). LC-MS B: t<sub>R</sub> = 0.78 min; no ionization.

**A.3.66.4. 2-(Chloromethyl)-3-(difluoromethoxy)thiophene**

A cooled (0°C) mixture of (3-(difluoromethoxy)thiophen-2-yl)methanol (0.360 g, 2.00 mmol) and zinc chloride (7 mg, 0.049 mmol) in anh. DCM (20 mL) is treated dropwise with thionyl chloride (0.291 mL, 3.99 mmol) and the mixture is stirred at RT for 3h. The mixture is cooled to 0°C, treated dropwise with thionyl chloride (0.291 mL, 3.99 mmol) and further stirred at RT for 1h. The RM is concentrated under reduced pressure to afford 2-(chloromethyl)-3-(difluoromethoxy)thiophene as a black oil (0.328 g, 83%). LC-MS B: t<sub>R</sub> = 0.82 min; no ionization.

**A.3.66.5. (3-(Difluoromethoxy)thiophen-2-yl)methanol**

To a cooled (-78°C) solution of methyl 3-(difluoromethoxy)thiophene-2-carboxylate (1.450 g, 6.97 mmol) in anh. THF (50 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in THF, 21.0 mL, 21.0 mmol). The mixture is further stirred at -78°C, under nitrogen, for 20 min and is then allowed to warm-up to 0°C. Stirring at 0°C is continued for 20 min, and the RM is treated successively with water (1 mL), 2.8 N aq. NaOH (1 mL) and water (2 mL). The mixture is then allowed to warm-up to RT and stirred for 1h. The resulting mixture was filtered over celite washing with THF and the filtrate was concentrated to dryness under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords (3-(difluoromethoxy)thiophen-2-yl)methanol as a pale yellow oil (1.075 g, 86%). LC-MS B: t<sub>R</sub> = 0.63 min; no ionization.

**A.3.66.6. Methyl 3-(difluoromethoxy)thiophene-2-carboxylate**

To a solution of 3-(difluoromethoxy)thiophene-2-carboxylic acid (0.500 g, 2.45 mmol) in anh. DMF (4 mL) at RT are added successively cesium carbonate (1.196 g, 3.67 mmol) and iodomethane (0.185 mL, 2.94 mmol) and the mixture is stirred at RT for 40 min. Water and Et<sub>2</sub>O are added and the layers are separated. The aqueous layer is extracted twice with Et<sub>2</sub>O and the combined organic layers are washed with brine, dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 3-(difluoromethoxy)thiophene-2-carboxylate as a colorless oil (0.495 g, 97%). LC-MS B: t<sub>R</sub> = 0.81 min; no ionization.

**B- Preparation of examples**

Compounds of Examples 1 - 54 listed in Table 5 below are prepared by applying either General Procedure G or H to the pyrimidine halide derivatives A.2.1. – A.2.11. coupled with commercially available boronic acid derivatives or with boronic acid derivatives A.3.1. – A.3.24.

5 **Table 5: Examples 1 - 54**

| Ex. | Compound                                                                                                                                                                                    | t <sub>R</sub> [min]<br>(method) | MS Data<br>m/z<br>[M+H] <sup>+</sup> |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|--------------------------------------|
| 1   | 3-Fluoro-5-[6-(2-p-tolyl-ethylamino)-pyrimidin-4-yl]-thiophene-2-carboxylic acid (*1)                                                                                                       | 1.1 (C)                          | 357.9                                |
| 2   | 4-{6-[2-(2-Methoxy-4-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid                                                                                       | 0.9 (C)                          | 442.1                                |
| 3   | 4-{6-[2-(2-Methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid                                                                                           | 0.9 (C)                          | 424.3                                |
| 4   | 3-Ethoxy-5-{6-[2-(2-methoxy-4-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid                                                                                | 1.0 (C)                          | 446.2                                |
| 5   | 3-Ethoxy-5-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid                                                                                    | 1.1 (C)                          | 428.3                                |
| 6   | 2-Ethoxy-4-{6-[2-(2-methoxy-4-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid                                                                                               | 0.9 (C)                          | 440.3                                |
| 7   | 2-Ethoxy-4-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid                                                                                                   | 0.9 (C)                          | 422.3                                |
| 8   | 2-Cyclobutoxy-4-{6-[2-(2-methoxy-4-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid                                                                                          | 1.0 (C)                          | 466.3                                |
| 9   | 6-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-1-methyl-1,2-dihydro-indazol-3-one                                                                                                     | 0.7 (C)                          | 424.4                                |
| 10  | 4-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenol                                                                                                                       | 0.7 (C)                          | 400                                  |
| 11  | 4-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)                                                                                                             | 0.9 (C)                          | 442                                  |
| 12  | 4-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-2,6-difluoro-phenol                                                                                                                    | 0.9 (C)                          | 406                                  |
| 13  | 3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methoxy-thiophen-2-yl)-oxetan-3-ol                                                                                                | 0.9 (C)                          | 462.4                                |
| 14  | 3-(4-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)phenyl)-[1,2,4]oxadiazol-5-ol] | 0.9 (C)                          | 438.4                                |

|    |                                                                                                                                                                                                               |         |        |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------|
| 15 | 3-(4-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-((4-bromophenethyl)amino)pyrimidin-4-yl}-2-ethoxyphenyl)-[1,2,4]oxadiazol-5-ol] | 1.0 (C) | 482.2  |
| 16 | 2-(4-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenoxy)-ethanol                                                                                                                            | 0.7 (C) | 443.9  |
| 17 | (5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-acetic acid                                                                                                                     | 1.0 (C) | 462.2  |
| 18 | 4-{6-[2-(3,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)                                                                                                                  | 0.9 (C) | 394.1  |
| 19 | 4-{6-[2-(3,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)                                                                                                                          | 0.9 (C) | 392.3  |
| 20 | 2-Cyclobutoxy-4-{6-[2-(3,4-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)                                                                                                                     | 1.0 (C) | 418.4  |
| 21 | 4-{6-[2-(4-Bromo-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)                                                                                                                      | 0.9 (C) | 460.2  |
| 22 | 3-Fluoro-5-{6-[2-(4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (*1)                                                                                                      | 1.1 (C) | 412.2  |
| 23 | [2-(4-Bromo-2,6-difluoro-phenyl)-ethyl]-{6-[3-ethoxy-4-(1H-tetrazol-5-yl)-phenyl]-pyrimidin-4-yl}-amine                                                                                                       | 1.0 (C) | 502    |
| 24 | N-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-oxalamic acid                                                                                                           | 0.9 (C) | 521.2  |
| 25 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-(2-hydroxy-ethoxy)-benzoic acid (*1)                                                                                                      | 0.8 (C) | 494.18 |
| 26 | 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (*1)                                                                                                            | 1.1 (C) | 440.12 |
| 27 | 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-chloro-3-ethoxy-thiophene-2-carboxylic acid (*1)                                                                                          | 1.3 (C) | 518.1  |
| 28 | 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid (*1)                                                                                                   | 1.1 (C) | 454    |
| 29 | 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethyl-thiophene-2-carboxylic acid (*1)                                                                                                    | 1.2 (C) | 468.1  |
| 30 | 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-sulfonic acid amide                                                                                                    | 1.1 (C) | 519.1  |
| 31 | 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-chloro-thiophene-2-carboxylic acid (*1)                                                                                                   | 1.2 (C) | 474.3  |
| 32 | 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-(2-hydroxy-ethoxy)-thiophene-2-carboxylic acid (*1)                                                                                       | 1.0 (C) | 500.1  |

|    |                                                                                                                                                                                                                       |          |        |
|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|--------|
| 33 | 5-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-isoxazol-3-ol [tautomeric form: 5-(4-{6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl}phenyl)isoxazol-3(2H)-one]                  | 0.9 (C)  | 473.2  |
| 34 | 5-(4-{6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl}phenyl)-[1,2,4]oxadiazol-3(2H)-one [tautomeric form: 5-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-3-ol] | 0.9 (C)  | 474    |
| 35 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid                                                                                                                               | 1.0 (C)  | 476.4  |
| 36 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid                                                                                                                              | 1.0 (C)  | 492.2  |
| 37 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid                                                                                                                       | 1.0 (C)  | 480.2  |
| 38 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-isobutyl-benzoic acid                                                                                                                             | 1.1 (C)  | 489.9  |
| 39 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-fluoro-6-propyl-benzoic acid                                                                                                                      | 1.1 (C)  | 494.2  |
| 40 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethylsulfanyl-benzoic acid                                                                                                                        | 1.0 (C)  | 494.1  |
| 41 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-difluoromethoxy-benzoic acid                                                                                                                      | 1.0 (C)  | 500    |
| 42 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-benzoic acid (*1)                                                                                                                     | 1.1 (C)  | 504.3  |
| 43 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-butoxy-benzoic acid                                                                                                                               | 1.1 (C)  | 506.2  |
| 44 | 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-propionic acid                                                                                                           | 1.1 (C)  | 512.3  |
| 45 | 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-propionic acid (*1)                                                                                                            | 0.8 (C)  | 522.4  |
| 46 | 2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1H-indole-4-carboxylic acid                                                                                                                         | 1.0 (C)  | 473.3  |
| 47 | (E)-3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-acrylic acid                                                                                                         | 1.2 (C)  | 510.3  |
| 48 | (5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-acetic acid                                                                                                                | 0.89 (B) | 497.90 |
| 49 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid                                                                                                                       | 0.9 (C)  | 492.2  |

|    |                                                                                                    |         |       |
|----|----------------------------------------------------------------------------------------------------|---------|-------|
| 50 | 4-{6-[2-(4-Bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)          | 0.9 (C) | 472.2 |
| 51 | 4-{6-[2-(4-Bromo-2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*2)           | 1.0 (C) | 486.1 |
| 52 | 4-{6-[2-(4-Bromo-2,6-dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)      | 0.9 (C) | 502   |
| 53 | 5-{6-[2-(2,6-Difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethyl-thiophene-2-carboxylic acid (*1) | 1.1 (C) | 390.2 |
| 54 | 5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid          | 1.0 (C) | 448.2 |

**Example 55: 3-Ethoxy-5-[6-(2-o-tolyl-ethylamino)-pyrimidin-4-yl]-thiophene-2-carboxylic acid (\*1)**

Following the general procedure F with 5-(6-chloropyrimidin-4-yl)-3-ethoxythiophene-2-carboxylic acid and 2-methylphenethylamine, the title compound is obtained as a white solid. LC-MS A:  $t_R = 0.75$  min;  $[M+H]^+ = 285.06$ .

**5 a) 5-(6-Chloropyrimidin-4-yl)-3-ethoxythiophene-2-carboxylic acid**

A mixture of 3-ethoxy-5-(6-hydroxypyrimidin-4-yl)thiophene-2-carboxylic acid (2410 mg, 9.05 mmol) and phosphorus(V) oxychloride (25 mL) is heated to 100 °C for 1h15min. POCl<sub>3</sub> is removed under reduced pressure and the residue is diluted with EtOAc and washed with water. The organic layer is concentrated under reduced pressure, and the residual acid chloride is taken up in EtOAc and acetonitrile, then water is added. The RM is stirred over the week-end. The layers are separated and the aqueous layer is extracted again with EtOAc. The combined organic extracts are dried over MgSO<sub>4</sub>, filtered, and the solvent removed under reduced pressure, affording the title compound as a beige solid (1.8860 g, 73%). LC-MS A:  $t_R = 0.75$  min;  $[M+MeCN]^+ = 326.02$ .

**b) 3-Ethoxy-5-(6-hydroxypyrimidin-4-yl)thiophene-2-carboxylic acid**

A suspension of methyl 3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxylate (2664 mg, 9.05 mmol) in dioxane (12.5 mL) and HCl conc aq. (16.3 mL) is heated to 50°C and stirred for 24h, then over the week end at RT. The suspension is filtered and washed with heptane then with MeOH. The filtrate is concentrated under reduced pressure and the residue is dissolved in THF/ H<sub>2</sub>O 10:1 (60 mL) and NaOH 2M (70 mL) is added and the RM is stirred for 1h at RT. The RM is neutralised with 2M HCl, then concentrated under reduced pressure to ca 1/3 of its volume. Acetonitrile is added, and the solid that precipitated is filtered off and washed with MeCN, dried under high vacuum, affording the title compound as a light brown solid (2.718 g, quantitative). LC-MS A:  $t_R = 0.54$  min;  $[M+H]^+ = 267.10$ .

**c) Methyl 3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxylate**

A mixture of 4-chloro-6-methoxypyrimidine (7124 mg, 48.3 mmol), methyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (3141 mg, 10.1 mmol), potassium phosphate tribasic monohydrate (6951 mg, 30.2 mmol) and Pd(dppf)Cl<sub>2</sub>·DCM (822 mg, 1.01 mmol) in DMF (50 mL) and water

(1.09 mL, 60.4 mmol) is degassed for 15 min under a nitrogen stream, then stirred at RT overnight. It is then partitioned between sat. aq. NaHCO<sub>3</sub> and EtOAc. The aqueous layer is extracted twice with EtOAc, then it is adjusted to pH = 1 with HCl 2M and extracted once with EtOAc. This last organic layer is further washed (3x) with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The residue is purified by FC (Heptane/EtOAc 7:1) to give the title compound as a pale yellow solid (2.402 g, 81%). LC-MS A: t<sub>R</sub> = 0.54 min; [M+H]<sup>+</sup> = 267.10.

**d) Methyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate**

The title compound is prepared according to the synthesis of A.3.1. using methyl 3-ethoxythiophene-2-carboxylate, and obtained as a white solid; LC-MS A: t<sub>R</sub> = 0.63 min; [M+H]<sup>+</sup> = 313.13.

Compounds of Examples 56 - 82 listed in Table 6 below are prepared by applying the same method as described for the synthesis of Example 55, by reacting 5-(6-chloropyrimidin-4-yl)-3-ethoxythiophene-2-carboxylic acid (example 55-a) with the corresponding commercially available phenethylamines.

**Table 6: Examples 56 - 82**

| Ex. | Compound                                                                                                     | t <sub>R</sub> [min]<br>(LC-MS C) | MS Data<br>m/z<br>[M+H] <sup>+</sup> |
|-----|--------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------|
| 56  | 3-Ethoxy-5-{6-[2-(2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid                   | 1.0                               | 388.2                                |
| 57  | 5-{6-[2-(2,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid (*3)          | 1.1                               | 397.9                                |
| 58  | 3-Ethoxy-5-{6-[2-(4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid          | 1.1                               | 438                                  |
| 59  | 3-Ethoxy-5-{6-[2-(3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (*3)             | 0.9                               | 400.3                                |
| 60  | 3-Ethoxy-5-{6-[2-(4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (*3)             | 0.9                               | 400.4                                |
| 61  | 3-Ethoxy-5-{6-[2-(3-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (*3)     | 1.1                               | 438.2                                |
| 62  | 5-[6-(2-p-Tolyl-ethylamino)-pyrimidin-4-yl]-3-trifluoromethyl-thiophene-2-carboxylic acid (*1)               | 1.2                               | 407.9                                |
| 63  | 5-{6-[2-(3-Methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophene-2-carboxylic acid (*1)    | 1.1                               | 424.2                                |
| 64  | 5-{6-[2-(2,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophene-2-carboxylic acid (*1) | 1.3                               | 422.2                                |
| 65  | 5-{6-[2-(4-Chloro-2-nitro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid           | 1.0                               | 449.2                                |



|    |                                                                                                     |     |       |
|----|-----------------------------------------------------------------------------------------------------|-----|-------|
| 66 | 5-{6-[2-(2,4-Dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid      | 1.1 | 438.3 |
| 67 | 5-{6-[2-(3,5-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid     | 0.9 | 430.1 |
| 68 | 5-{6-[2-(3,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid      | 1.1 | 398   |
| 69 | 3-Ethoxy-5-{6-[2-(4-hydroxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid         | 0.7 | 386.2 |
| 70 | 5-{6-[2-(2-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid           | 1.0 | 448.3 |
| 71 | 5-{6-[2-(5-Bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid | 1.1 | 478.1 |
| 72 | 5-{6-[2-(2,5-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid     | 0.9 | 430.1 |
| 73 | 5-{6-[2-(2,4-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid     | 0.9 | 430   |
| 74 | 5-{6-[2-(3-Bromo-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid | 1.0 | 478.4 |
| 75 | 3-Ethoxy-5-(6-phenethylamino-pyrimidin-4-yl)-thiophene-2-carboxylic acid                            | 0.9 | 370.2 |
| 76 | 3-Ethoxy-5-{6-[2-(3-methoxycarbonyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid | 0.9 | 428.1 |
| 77 | 5-{6-[2-(3-Chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid          | 1.0 | 404.2 |
| 78 | 5-{6-[2-(2-Chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid          | 1.0 | 404.3 |
| 79 | 5-{6-[2-(3-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid           | 1.0 | 448   |
| 80 | 3-Ethoxy-5-{6-[2-(4-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid          | 0.9 | 388.2 |
| 81 | 3-Ethoxy-5-{6-[2-(3-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid          | 1.0 | 388.2 |
| 82 | 5-{6-[2-(4-Chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid          | 1.0 | 404.3 |

**Example 83:** 3-(5-{6-[2-(3,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(3,4-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]

Following the general procedure I with 3-(3-ethoxy-5-(6-hydroxypyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol and 2-(3,4-dimethylphenyl)ethan-1-amine, the title compound is obtained as a yellow solid. LC-MS A:  $t_R$  = 0.98 min;  $[M+H]^+$  = 438.17.

**a) 3-(3-Ethoxy-5-(6-hydroxypyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol**

A suspension of 3-(3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol (5180 mg, 12.1 mmol) in HCl (4M in dioxane, 100 mL) is heated at 100°C overnight, cooled down to RT, and the solvent is partially removed. The solid residue is filtered off washing with water, and dried under high vacuum, affording the title compound as a light yellow solid. LC-MS B:  $t_R$  = 0.66 min;  $[M+H]^+$  = 307.01.

**b) 3-(3-Ethoxy-5-(6-methoxypyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol**

To a mixture of 3-ethoxy-N'-hydroxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboximidamide (6930 mg, 22.6 mmol) and DBU (8.62 mL, 56.5 mmol) in Dioxane/DMSO (3:2, 220 mL) is added CDI (5498 mg, 33.9 mmol). The RM is stirred at 100°C for 30min, then cooled to RT. Evaporation of the solvent and trituration in 2N HCl afforded the title compound as a yellow solid (7.15 g, 99%). LC-MS A:  $t_R$  = 0.89 min;  $[M+H]^+$  = 321.14.

**c) 3-Ethoxy-N'-hydroxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboximidamide**

A suspension of 3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carbonitrile (6860 mg, 24.7 mmol), TEA (10.3 mL, 74 mmol) and hydroxylamine hydrochloride (2.59 mL, 61.7 mmol) in EtOH (220 mL) is refluxed for 3h, then cooled to RT and treated with water (30 mL). The yellow solid is filtered off and dried under high vacuum. The filtrate is concentrated and the solid is triturated in water, filtered off and combined with the first crop. The title compound is obtained as a yellow solid (6.93 g, 95%). LC-MS B:  $t_R$  = 0.62 min;  $[M+H]^+$  = 295.23.

**d) 3-Ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carbonitrile**

Cyanuric chloride (6248 mg, 33.5 mmol) is added portionwise at 0°C to a suspension of 3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxamide (6940 mg, 22.4 mmol) in DMF (130 mL). The RM is then stirred at RT for 45 min. It is cooled at 0°C and diluted with water. The solid is filtered off, washing with water and then EtOAc, and dried under high vacuum. The filtrate is extracted twice with EtOAc, combined organic layers are washed with brine, dried over  $MgSO_4$ , filtered and concentrated under reduced pressure. Both solids are combined to afford the title compound as a beige solid (5.49 g, 94%). LC-MS A:  $t_R$  = 1.00 min;  $[M+H]^+$  = 262.26.

**e) 3-Ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxamide**

CDI (4861 mg, 29.1 mmol) is added to a solution of 3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxylic acid (7410 mg, 26.4 mmol) in THF (140 mL) at RT. The RM is stirred for 30 min, then  $NH_4OH$  (25% solution, 61.1 mL, 397 mmol) is added, and the RM is stirred at RT for 30min, then concentrated under reduced pressure, and the residue is triturated in 2N HCl. The title compound is filtered off, dried under high vacuum, and obtained as a yellow solid (6.94 g, 94%). LC-MS A:  $t_R$  = 0.79 min;  $[M+H]^+$  = 280.22.

**f) 3-Ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxylic acid**

A suspension of methyl 3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxylate (7870 mg, 26.2 mmol) in MeOH (210 mL) and NaOH 2M (38.8 mL, 419 mmol) is stirred overnight at RT. It is then acidified with HCl 8N (60mL), MeOH is removed under vacuum and the slurry is filtered, to afford the title compound as a yellow solid (7.41 g, 99% ). LC-MS A:  $t_R$  = 0.77 min;  $[M+H]^+$  = 281.19.

**g) Methyl 3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxylate**

A mixture of methyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (10520 mg, 30 mmol), 4-chloro-6-methoxypyrimidine (4645 mg, 31.5 mmol), Pd(dppf)Cl<sub>2</sub>·DCM (2449 mg, 3 mmol) and potassium phosphate tribasic monohydrate (20719 mg, 90 mmol) in water (4 mL) and DMF (150 mL) is degassed for 20 min under a nitrogen stream, then stirred at RT for 1h15. The RM is filtered through celite, the filtrate is concentrated under vacuum, the residue is partitioned between water and EtOAc. The organic layer is further washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. Purification by FC (heptane/EtOAc, from 1:0 to 0:1) afforded the title compound as a yellow solid (7.87 g, 89% ). LC-MS A:  $t_R$  = 0.93 min;  $[M+H]^+$  = 295.18.

**h) Methyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate**

The title compound is prepared according to the synthesis of A.2.1. using methyl 3-ethoxythiophene-2-carboxylate, and obtained as a white solid; LC-MS A:  $t_R$  = 0.63 min;  $[M+H]^+$  = 313.13.

Following the procedure described for the synthesis of Example 83, the following examples are synthesized, starting from 3-(3-ethoxy-5-(6-hydroxypyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol and the corresponding commercially available phenethylamines or the phenethylamines A.1.1. – A.1.8. described above (see table 7).

**Table 7: Examples 84 - 127**

| Ex. | Compound                                                                                                                                                                                                                                                                    | $t_R$ [min]<br>(method) | MS Data<br>m/z $[M+H]^+$ |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------------------|
| 84  | 3-(5-{6-[2-(4-Bromo-2-trifluoromethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]   | 1.3 (C)                 | 572.1                    |
| 85  | 3-(5-{6-[2-(4-Bromo-2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                       | 1.2 (C)                 | 532.1                    |
| 86  | 3-(5-{6-[2-(4-Chloro-2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-chloro-2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol] | 1.2 (C)                 | 492                      |

|    |                                                                                                                                                                                                                                                                           |         |       |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------|
| 87 | 3-(5-{6-[2-(4-Bromo-2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol] | 1.2 (C) | 536.1 |
| 88 | 3-(5-{6-[2-(4-Bromo-2,6-dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]           | 1.2 (C) | 547.9 |
| 89 | 3-(5-{6-[2-(4-Bromo-2-propoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-propoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                   | 1.3 (C) | 546.1 |
| 90 | 3-(3-Ethoxy-5-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol] | 1.2 (C) | 522.3 |
| 91 | 3-(5-{6-[2-(4-Chloro-2-methylamino-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-chloro-2-methylamino-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]         | 1.2 (C) | 473.1 |
| 92 | 3-(3-Ethoxy-5-{6-[2-(2-fluoro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2-fluoro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                 | 1.1 (C) | 458   |
| 93 | 3-(3-Ethoxy-5-{6-[2-(2-fluoro-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2-fluoro-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol] | 1.2 (C) | 496.2 |
| 94 | 3-(5-{6-[2-(2-Bromo-5-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(2-bromo-5-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                     | 1.2 (C) | 522.1 |
| 95 | 3-(3-Ethoxy-5-{6-[2-(2-ethoxy-4-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2-ethoxy-4-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                   | 1.2 (C) | 472.1 |

|     |                                                                                                                                                                                                                                                                        |         |       |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------|
| 96  | 5-Chloro-2-(2-((6-(4-ethoxy-5-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)thiophen-2-yl)pyrimidin-4-yl)amino)ethyl)benzonitrile [tautomeric form: 5-chloro-2-(2-{6-[4-ethoxy-5-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-thiophen-2-yl]-pyrimidin-4-ylamino}-ethyl)-benzonitrile] | 1.1 (C) | 469.2 |
| 97  | 2-(2-((6-(4-Ethoxy-5-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)thiophen-2-yl)pyrimidin-4-yl)amino)ethyl)-5-fluorobenzonitrile [tautomeric form: 2-(2-{6-[4-ethoxy-5-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-thiophen-2-yl]-pyrimidin-4-ylamino}-ethyl)-5-fluorobenzonitrile]  | 1.0 (C) | 453.4 |
| 98  | 3-(5-{6-[2-(3-Chloro-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(3-chloro-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]        | 1.1 (C) | 480.1 |
| 99  | 3-(3-Ethoxy-5-{6-[2-(2-ethyl-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2-ethyl-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                | 1.1 (C) | 468   |
| 100 | 3-(5-{6-[2-(2-Chloro-3,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(2-chloro-3,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]        | 1.1 (C) | 480.2 |
| 101 | 3-(3-Ethoxy-5-{6-[2-(2,4,6-trifluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2,4,6-trifluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                    | 1.1 (C) | 464.2 |
| 102 | 3-(3-Ethoxy-5-{6-[2-(2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                                  | 1.1 (C) | 454   |
| 103 | 3-(5-{6-[2-(2,6-Difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                          | 1.1 (C) | 446.2 |
| 104 | 3-(5-{6-[2-(4-Bromo-2-ethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-ethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                    | 1.3 (C) | 516.2 |
| 105 | 3-(5-{6-[2-(4-Chloro-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-chloro-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]        | 1.2 (C) | 480.1 |

|            |                                                                                                                                                                                                                                                                         |         |       |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------|
| <b>106</b> | 3-(5-{6-[2-(4-Bromo-3-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-3-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                   | 1.2 (C) | 522.1 |
| <b>107</b> | 3-(5-{6-[2-(4-Bromo-2,5-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,5-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]           | 1.2 (C) | 524.1 |
| <b>108</b> | 3-(5-{6-[2-(4-Bromo-3-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-3-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                   | 1.2 (C) | 506.2 |
| <b>109</b> | 3-(5-{6-[2-(4-Bromo-2-dimethylamino-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-dimethylamino-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]     | 1.2 (C) | 531.1 |
| <b>110</b> | 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]           | 1.2 (C) | 524.1 |
| <b>111</b> | 3-(5-{6-[2-(4-Bromo-5-fluoro-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-5-fluoro-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol] | 1.2 (C) | 520.2 |
| <b>112</b> | 3-(5-{6-[2-(4-Bromo-2-pyrrolidin-1-yl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-pyrrolidin-1-yl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol] | 1.3 (C) | 556.9 |
| <b>113</b> | 3-(5-{6-[2-(4-Bromo-3-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-3-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]                   | 1.2 (C) | 502.2 |
| <b>114</b> | 3-(5-{6-[2-(4-Bromo-2-fluoro-5-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-fluoro-5-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol] | 1.2 (C) | 520   |

|     |                                                                                                                                                                                                                                                             |          |        |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|--------|
| 115 | 3-(5-{6-[2-(4-Bromo-3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]     | 1.1 (C)  | 518.1  |
| 116 | 3-(5-{6-[2-(2,4-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(2,4-dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]             | 1.1 (C)  | 470    |
| 117 | 3-(3-Ethoxy-5-{6-[2-(3-hydroxy-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(3-hydroxy-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol] | 0.9 (C)  | 456    |
| 118 | 3-(3-Ethoxy-5-{6-[2-(4-hydroxy-3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-{6-[2-(4-hydroxy-3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol] | 0.9 (C)  | 456.2  |
| 119 | 3-(5-{6-[2-(2,3-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(2,3-dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]             | 1.0 (C)  | 470.3  |
| 120 | 3-(5-{6-[2-(5-Bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(5-bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]     | 1.2 (C)  | 518.1  |
| 121 | 3-(5-{6-[2-(3,4-Dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(3,4-dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]               | 1.2 (C)  | 478.1  |
| 122 | 3-(5-{6-[2-(3-Chloro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(3-chloro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]   | 1.1 (C)  | 474.1  |
| 123 | 3-(5-{6-[2-(2,4-Dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(2,4-dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]               | 1.2 (C)  | 478    |
| 124 | 3-(5-{6-[2-(4-Bromo-2-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]       | 1.02 (B) | 521.89 |



|            |                                                                                                                                                                                                                                                         |         |       |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------|
| <b>125</b> | 3-(5-{6-[2-(4-Bromo-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]   | 1.2 (C) | 506.4 |
| <b>126</b> | 3-(5-{6-[2-(4-Bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol] | 1.2 (C) | 518   |
| <b>127</b> | 3-(5-{6-[2-(4-Bromo-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]   | 1.2 (C) | 502.2 |

**Example 128: 5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid amide**

To a solution of 5-{6-[2-(4-bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid (Example 54, 366 mg, 0.816 mmol, 1 eq) in DMF (3 mL) is added EDC.HCl (172 mg, 0.898 mmol) and HOBT (121 mg, 0.898 mmol) and the RM is stirred at RT for 1h. It is then cooled down to 0°C and 25% ammonia solution (1.24 mL) is added. The RM is stirred for 1h at RT, then concentrated under reduced pressure, and the residue is partitioned between EtOAc and NaOH 1M (pH 10). The aqueous layer is re-extracted with EtOAc. The combined organic layers are washed with brine, dried (MgSO<sub>4</sub>) and concentrated, affording the title compound as a beige solid (342mg, 94%). LC-MS A: t<sub>R</sub> = 0.78 min; [M+H]<sup>+</sup> = 446.98.

**Example 129: 5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-N-hydroxy-thiophene-2-carboxamidine**

A mixture of 5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophene-2-carbonitrile (84 mg, 0.196 mmol), hydroxylamine hydrochloride (27.5 mg, 0.391 mmol) and TEA (0.0545 mL, 0.391 mmol) in EtOH (2.52 mL) is stirred in a sealed tube at 90°C for 3h. Once at RT, the RM is diluted with water and the precipitate is filtered off washing with water and EtOH, thus affording the title compound as a yellow solid (49 mg, 55%). LC-MS A: t<sub>R</sub> = 0.73 min; [M+H]<sup>+</sup> = 463.93.

**a) 5-(6-((4-Bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophene-2-carbonitrile**

To a suspension of 5-{6-[2-(4-bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid amide (Example 128, 190 mg, 0.425 mmol) in DMF (1.3 mL) at 0°C is added portionwise cyanuric chloride (117 mg, 0.637 mmol). The RM is then allowed to warm to RT and stirred for 15min. It is then diluted with water and extracted with EtOAc (3x). The combined organic layers are washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. Purification by FC (Heptane to Heptane/EtOAc 1:4) affords the title compound as a white solid (84 mg, 46%). LC-MS A: t<sub>R</sub> = 0.98 min; [M+H]<sup>+</sup> = 431.05.

**Example 130:** 3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]

A mixture of 5-{6-[2-(4-bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-N-hydroxy-thiophene-2-carboxamidine (Example 129, 48.6 mg, 0.105 mmol), 1,1'-carbonyldiimidazole (25.6 mg, 0.158 mmol) and DBU (0.0273 mL, 0.179 mmol) in dioxane (1 mL) is stirred at 90°C for 1h. Once at RT, HCl 1M is added, the precipitate is filtered off, washing with water and Et<sub>2</sub>O, thus affording the pure expected product as a yellow solid (42 mg, 81%). LC-MS A: t<sub>R</sub> = 0.88 min; [M+H]<sup>+</sup> = 489.88.

**Example 131:** [2-(4-Bromo-phenyl)-ethyl]-{6-[4-ethoxy-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-pyrimidin-4-yl}-amine

To a suspension of 5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophene-2-carbonitrile (Example 129-a, 100 mg, 0.233 mmol) in toluene (1.80 mL) is added trimethylsilylazide (0.0459 mL, 0.349 mmol) and dibutyltin oxide (5.8 mg, 0.0233 mmol). The RM is stirred in a sealed tube at 110°C for 8h. It is cooled down to RT, trimethylsilylazide (0.0153 mL, 0.116 mmol) and dibutyltin oxide (5.8 mg, 0.0233 mmol) are added. The RM is stirred at 110°C overnight. Once at RT, the RM is concentrated under reduced pressure, and the residue is purified by basic prep HPLC, affording the title compound as a yellow solid (50 mg, 50%). LC-MS A: t<sub>R</sub> = 0.83 min; [M+H]<sup>+</sup> = 474.01.

**Example 132:** 3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazole-5(4H)-thione [tautomeric form: 3-(5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)-[1,2,4]oxadiazole-5-thiol]

Following the same method as described for example 130, using 1,1'-thiocarbonyldiimidazole, the title compound is obtained as a yellow solid. LC-MS A: t<sub>R</sub> = 1.08 min; [M+H]<sup>+</sup> = 503.91.

**Example 133:** 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]

Following the same method as described for example 130, using 1,1'-carbonyldiimidazole and 5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N'-hydroxy-3-(trifluoromethyl)thiophene-2-carboximidamide, the title compound is obtained as a pale yellow solid. LC-MS B: t<sub>R</sub> = 1.04 min; [M+H]<sup>+</sup> = 547.49.

**a) 5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N'-hydroxy-3-(trifluoromethyl)thiophene-2-carboximidamide**

Following the same method as described for example 129, using 5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-(trifluoromethyl)thiophene-2-carbonitrile, the title compound is obtained as a yellow oil. LC-MS B: t<sub>R</sub> = 0.90 min; [M+H]<sup>+</sup> = 521.81.

**b) 5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-(trifluoromethyl)thiophene-2-carbonitrile**

Following the general procedure F, using 2-(4-bromo-2,6-difluorophenyl)ethan-1-amine and 5-(6-chloropyrimidin-4-yl)-3-(trifluoromethyl)thiophene-2-carbonitrile, the title compound is obtained as a red powder. LC-MS B:  $t_R$  = 1.19 min;  $[M+H]^+$  = 488.89.

**c) 5-(6-Chloropyrimidin-4-yl)-3-(trifluoromethyl)thiophene-2-carbonitrile**

5 Following the procedure described for Example 83-d, using 5-(6-chloropyrimidin-4-yl)-3-(trifluoromethyl)thiophene-2-carboxamide, the title compound is obtained as a white solid. LC-MS A:  $t_R$  = 0.94 min; no ionization.

**d) 5-(6-Chloropyrimidin-4-yl)-3-(trifluoromethyl)thiophene-2-carboxamide**

10 Following the procedure described for Example 83-e, using 5-(6-chloropyrimidin-4-yl)-3-(trifluoromethyl)thiophene-2-carboxylic acid, the title compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.75 min;  $[M+H]^+$  = 307.97.

**e) 5-(6-Chloropyrimidin-4-yl)-3-(trifluoromethyl)thiophene-2-carboxylic acid**

15 Following the procedure described for Example 55-c, using 4,6-dichloropyrimidine and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)thiophene-2-carboxylic acid (A.3.4.), the title compound is obtained as a beige solid. LC-MS B:  $t_R$  = 0.83 min;  $[M+MeCN]^+$  = 349.91.

**Example 134: 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophene-2-carboxylic acid amide**

The title compound is formed as a side-product in the synthesis of Example 133-a, and isolated as a white powder. LC-MS A:  $t_R$  = 0.95 min;  $[M+H]^+$  = 506.81.

**20 Example 135: 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]**

25 Following the same method as described for example 130, using 1,1'-carbonyldiimidazole and 5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N'-hydroxythiophene-2-carboximidamide, the title compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.91 min;  $[M+H]^+$  = 479.9.

**a) 5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N'-hydroxythiophene-2-carboximidamide**

30 Following the same method as described for example 129, using 5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)thiophene-2-carbonitrile, the title compound is obtained as a grey powder. LC-MS B:  $t_R$  = 0.74 min;  $[M+H]^+$  = 455.93.

**b) 5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)thiophene-2-carbonitrile**

Following the procedure described for Example 55-c, using N-(4-bromo-2,6-difluorophenethyl)-6-iodopyrimidin-4-amine (A.2.6.) and 5-cyanothiophene-2-boronic acid, the title compound is obtained as a beige powder. LC-MS B:  $t_R$  = 1.04 min;  $[M+H]^+$  = 420.78.

**Example 136:** 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]

Following the same method as described for example 130, using 1,1'-carbonyldiimidazole and 5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N'-hydroxy-3-methylthiophene-2-carboximidamide, the title compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.94 min;  $[M+H]^+$  = 493.89.

**a) 5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N'-hydroxy-3-methylthiophene-2-carboximidamide**

Following the same method as described for example 129, using 5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-methylthiophene-2-carbonitrile, the title compound is obtained as a crude mixture used without further purification. LC-MS B:  $t_R$  = 0.72 min;  $[M+H]^+$  = 467.75.

**b) 5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-methylthiophene-2-carbonitrile**

Following the procedure described for Example 55-c, using N-(4-bromo-2,6-difluorophenethyl)-6-iodopyrimidin-4-amine (A.2.6.) and 5-cyano-4-methylthiophene-2-boronic acid, the title compound is obtained as a pale yellow powder. LC-MS B:  $t_R$  = 1.07 min;  $[M+H]^+$  = 436.81.

**Example 137:** 3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-ylmethyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-ylmethyl)-[1,2,4]oxadiazol-5-ol]

Following the same method as described for example 130, using 1,1'-carbonyldiimidazole and 2-(5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)-N'-hydroxyacetimidamide, the title compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.81 min;  $[M+H]^+$  = 502.08.

**a) 2-(5-(6-((4-Bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)-N'-hydroxyacetimidamide**

Following the same method as described for example 129, using 2-(5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)acetonitrile, the title compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.66 min;  $[M+H]^+$  = 476.16.

**b) 2-(5-(6-((4-Bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)acetonitrile**

A solution of sodium cyanide (83.1 mg, 1.7 mmol) in water (0.4 mL) is added dropwise at RT to a stirred suspension of N-(4-bromophenethyl)-6-(5-(chloromethyl)-4-ethoxythiophen-2-yl)pyrimidin-4-amine (192 mg, 0.424 mmol) in DMF (3.5 mL). The RM is stirred at RT for 30min, then diluted with EtOAc and washed twice with sat. aq.  $\text{NaHCO}_3$  and once with brine. The organic layer is dried over  $\text{MgSO}_4$ , filtered and concentrated. The residue is purified by FC (Heptane to Heptane/EtOAc 1:1), affording the title compound as a white powder (117 mg, 63%). LC-MS B:  $t_R$  = 0.89 min;  $[M+H]^+$  = 443.22.

**c) N-(4-Bromophenethyl)-6-(5-(chloromethyl)-4-ethoxythiophen-2-yl)pyrimidin-4-amine**

Thionyl chloride (0.0191 mL, 0.259 mmol) is added at RT to a solution of 5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)methanol (75 mg, 0.173 mmol) in DCM (1.7 mL), and the RM is stirred for 1h. It is then concentrated under vacuum to afford the crude expected product as a greyish solid (82 mg, quantitative). LC-MS B:  $t_R$  = 0.88 min;  $[M+H]^+$  = 450.06.

5 **d) 5-(6-((4-Bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)methanol**

Diisobutylaluminium hydride (1.0 M in DCM, 6.2 mL, 6.78 mmol) is added dropwise at -78 °C to a solution of methyl 5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophene-2-carboxylate (550 mg, 1.13 mmol) in THF (20 mL) and the RM is stirred for 3h. Diisobutylaluminium hydride (1.0 M in DCM, 3.1 mL, 3.39 mmol) is added dropwise, and the RM is stirred for 3h. It is then carefully quenched at -78 °C by dropwise addition  
10 of sat. aq.  $NH_4Cl$ . Once at RT, DCM and a saturated solution of Rochelle's salt are added, the biphasic mixture is vigorously stirred at RT, then filtered over celite. The layers are separated, then the organic layer is washed twice with brine, separated through phase separator cartridge and concentrated. The solid residue is triturated in  $Et_2O$ . The solid is filtered off washing with  $Et_2O$  and dried under vacuum to afford the pure expected product as a beige solid (375 mg, 76%). LC-MS A:  $t_R$  = 0.78 min;  $[M+H]^+$  = 434.09.

15 **e) Methyl 5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophene-2-carboxylate**

Following the procedure described for Example 55-c, using N-(4-bromophenethyl)-6-iodopyrimidin-4-amine (A.2.2.) and methyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (Example 83-h), the title compound is obtained as a beige powder. LC-MS B:  $t_R$  = 0.96 min;  $[M+H]^+$  = 462.15.

20 **Example 138: 3-(5-(6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl)-3-ethoxy-thiophen-2-ylmethyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-(6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl)-3-ethoxy-thiophen-2-ylmethyl)-[1,2,4]oxadiazol-5-ol]**

Following the same method as described for example 130, using 1,1'-carbonyldiimidazole and 2-(5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)-N'-hydroxyacetimidamide, the title compound is obtained as a beige solid. LC-MS B:  $t_R$  = 0.86 min;  $[M+H]^+$  = 538.02.

25 **a) 2-(5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)-N'-hydroxyacetimidamide**

Following the same method as described for example 129, using 2-(5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)acetonitrile, the title compound is obtained as a light yellow solid. LC-MS B:  $t_R$  = 0.70 min;  $[M+H]^+$  = 511.90.

30 **b) 2-(5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)acetonitrile**

Following the general procedure I with 2-(3-ethoxy-5-(6-hydroxypyrimidin-4-yl)thiophen-2-yl)acetonitrile and 2-(4-bromo-2,6-difluorophenyl)ethan-1-amine, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 0.94 min;  $[M+H]^+$  = 479.07.

**c) 2-(3-Ethoxy-5-(6-hydroxypyrimidin-4-yl)thiophen-2-yl)acetonitrile**

Following the same method as described for Example 83-a, using 2-(3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophen-2-yl)acetonitrile, the title compound is obtained as a pink solid. LC-MS B:  $t_R$  = 0.70 min;  $[M+H]^+$  = 262.07.

**d) 2-(3-Ethoxy-5-(6-methoxypyrimidin-4-yl)thiophen-2-yl)acetonitrile**

5 Following the same method as described for Example 137-b, using 4-(5-(chloromethyl)-4-ethoxythiophen-2-yl)-6-methoxypyrimidine, the title compound is obtained as a light yellow solid. LC-MS B:  $t_R$  = 0.93 min;  $[M+H]^+$  = 276.12.

**e) 4-(5-(Chloromethyl)-4-ethoxythiophen-2-yl)-6-methoxypyrimidine**

10 Following the same method as described for Example 137-c, using (3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophen-2-yl)methanol, the title compound is obtained as a greyish solid. LC-MS B:  $t_R$  = 0.94 min; no ionization.

**f) (3-Ethoxy-5-(6-methoxypyrimidin-4-yl)thiophen-2-yl)methanol**

15 Following the same method as described for Example 137-d, using methyl 3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxylate (Example 83-g), the title compound is obtained as a light yellow solid. LC-MS B:  $t_R$  = 0.78 min;  $[M+H]^+$  = 267.10.

**Example 139: {6-[5-(5-Amino-[1,2,4]oxadiazol-3-yl)-4-ethoxy-thiophen-2-yl]-pyrimidin-4-yl}-[2-(4-bromophenyl)-ethyl]-amine**

20 N-(4-Bromophenethyl)-6-(4-ethoxy-5-(5-(trichloromethyl)-[1,2,4]oxadiazol-3-yl)thiophen-2-yl)pyrimidin-4-amine (17 mg, 0.0259 mmol) is dissolved at RT in  $NH_3$  (7M in MeOH, 0.5 mL), and the RM is stirred at RT for 1h. It is then concentrated and the residue is purified by prep. HPLC, affording the title compound as a white solid. LC-MS B:  $t_R$  = 0.83 min;  $[M+H]^+$  = 487.07.

**a) N-(4-Bromophenethyl)-6-(4-ethoxy-5-(5-(trichloromethyl)-[1,2,4]oxadiazol-3-yl)thiophen-2-yl)pyrimidin-4-amine**

25 Trichloroacetic anhydride (0.0169 mL, 0.0908 mmol) is added at RT to a suspension of 5-{6-[2-(4-bromophenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-N-hydroxy-thiophene-2-carboxamide (Example 129, 50 mg, 0.0757 mmol) in toluene (0.35 mL). The suspension is stirred at 115 °C for 30min, then cooled to RT. It is then diluted with EtOAc and washed twice with sat. aq.  $NaHCO_3$  and once with brine. The organic layer is dried over  $MgSO_4$ , filtered and concentrated. The residue is purified by FC (Heptane to Heptane/EtOAc 1:1), yielding the title compound as a light yellow solid /17 mg, 38%). LC-MS B:  $t_R$  = 1.16 min;  $[M+H]^+$  = 590.20.

30 **Example 140: [2-(4-Bromo-phenyl)-ethyl]-{6-[4-ethoxy-5-(5-methoxy-[1,2,4]oxadiazol-3-yl)-thiophen-2-yl]-pyrimidin-4-yl}-amine**

Sodium methoxide (0.5 M in methanol, 0.082 mL, 0.0412 mmol) is added dropwise at RT to a solution of N-(4-bromophenethyl)-6-(4-ethoxy-5-(5-(trichloromethyl)-[1,2,4]oxadiazol-3-yl)thiophen-2-yl)pyrimidin-4-amine (Example 139-a, 18 mg, 0.0275 mmol) in DMF (0.275 mL). The RM is stirred at RT for 1h, quenched with water,



and purified by prep. HPLC to yield the title compound as a white solid (3 mg, 20%). LC-MS D:  $t_R$  = 1.15 min;  $[M-H]^+$  = 501.90.

**Example 141: 2-[3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ylamino]-ethanol**

- 5 Following the same method as described for example 139, using N-(4-Bromophenethyl)-6-(4-ethoxy-5-(5-(trichloromethyl)-[1,2,4]oxadiazol-3-yl)thiophen-2-yl)pyrimidin-4-amine (139-a) and ethanolamine, the compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.81 min;  $[M+H]^+$  = 531.07.

**Example 142: [2-(4-Bromo-phenyl)-ethyl]-{6-[4-ethoxy-5-(5-oxetan-3-yl)-[1,2,4]oxadiazol-3-yl]-thiophen-2-yl}-pyrimidin-4-yl)-amine**

- 10 Oxetane-3-carboxylic acid (9.27 mg, 0.0908 mmol) is dissolved in DMF (0.746 mL) and TBTU (29.2 mg, 0.0908 mmol) and DIPEA (0.0311 mL, 0.182 mmol) are added in succession. After 5min stirring at RT, 5-{6-[2-(4-bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-N-hydroxy-thiophene-2-carboxamidine (Example 129, 40 mg, 0.0606 mmol) is added and the RM is stirred at RT overnight, then at 120°C for 1h40min. Once cooled at RT, the RM is purified directly by prep. HPLC, affording the title compound as a yellow solid (4 mg, 12%). LC-MS B:  $t_R$  = 0.95 min;  $[M+H]^+$  = 527.95.
- 15

**Example 143: [3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-yl]-methanol**

- Acetoxyacetic acid (5.42 mg, 0.0454 mmol) is dissolved in DMF (0.561 mL) and TBTU (14.6 mg, 0.0454 mmol) and DIPEA (0.0183 mL, 0.107 mmol) are added in succession. After 5min stirring at RT, 5-{6-[2-(4-bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-N-hydroxy-thiophene-2-carboxamidine (Example 129, 30 mg, 0.0454 mmol) is added and the RM is stirred at RT for 1h, then at 120 °C for 1h. Once cooled at RT, the RM is purified directly by prep. HPLC, affording the title compound as a yellow solid (2.4 mg, 11%). LC-MS D:  $t_R$  = 1.01 min;  $[M-H]^+$  = 501.87.
- 20

**Example 144: 3-[2-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-ethyl]-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-[2-(5-{6-[2-(4-bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-ethyl]-[1,2,4]oxadiazol-5-ol]**

25

Following the same method as described for example 130, using 3-(5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)-N'-hydroxypropanimidamide and 1,1'-carbonyldiimidazole, the compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.83 min;  $[M+H]^+$  = 515.90.

- a) 3-(5-(6-((4-Bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)-N'-hydroxypropanimidamide**
- 30

Following the same method as described for example 129, starting with 3-(5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)propanenitrile, the title compound is obtained as a light yellow solid. LC-MS B:  $t_R$  = 0.68 min;  $[M+H]^+$  = 490.12.

**b) 3-(5-(6-((4-Bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)propanenitrile**



To a mixture of 5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)methanol (Example 137-d, 266 mg, 0.612 mmol) and (cyanomethyl)trimethylphosphonium iodide (391 mg, 1.53 mmol), propionitrile (1.22 mL) and DIPEA (0.335 mL, 1.96 mmol) are added. The RM is stirred at 95°C in a sealed tube for 3h. At RT, water (66 mg, 3.67 mmol) is added carefully, and the RM is stirred at 95°C for 2h. The RM is cooled to RT, diluted with water (10 mL) and HCl (1 M, 1 mL), and extracted with EtOAc (3 times). The combined extracts are washed with brine, dried (MgSO<sub>4</sub>), and concentrated. The residue is purified by FC, affording the title compound is obtained as a yellow solid (43 mg, 15%). LC-MS B: t<sub>R</sub> = 0.89 min; [M+H]<sup>+</sup> = 457.10.

**Example 145: 1-(5-(6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl)-3-ethoxy-thiophen-2-yl)-ethanol**

Sodium borohydride (27.5 mg, 0.728 mmol) is added at 0 °C to a solution of 1-(5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)ethan-1-one (65 mg, 0.146 mmol) in EtOH (2 mL), then the RM is stirred at RT over the weekend. Sodium borohydride (27.5 mg, 0.728 mmol) is added, and stirring continued for 1h. The RM is quenched by dropwise addition of acetone and concentrated under reduced pressure. The residue is partitioned between water and EtOAc, then the organic layer is dried over MgSO<sub>4</sub>, filtered and concentrated. Purification by prep. HPLC afforded the title compound as a white solid (38 mg, 57%). LC-MS A: t<sub>R</sub> = 0.77 min; [M+H]<sup>+</sup> = 447.87.

**a) 1-(5-(6-((4-Bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)ethan-1-one**

To a flame-dried flask containing 5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxy-N-methoxy-N-methylthiophene-2-carboxamide (115 mg, 0.234 mmol) in THF (2 mL), methylmagnesium bromide (3M in THF, 0.25 mL, 0.75 mmol) is added dropwise at 0 °C, then the solution is stirred at RT for 1h, and quenched with sat. aq. NH<sub>4</sub>Cl and diluted with EtOAc. Some product remains insoluble at the interface of the two layers and is therefore filtered off to afford 24mg (23%) of pure product as a beige solid. The phases of the filtrate are separated, the organic layer is washed with brine (2x), dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated to afford the expected product as a light yellow solid (65mg, 62%). LC-MS A: t<sub>R</sub> = 0.90 min; [M+H]<sup>+</sup> = 446.03.

**b) 5-(6-((4-Bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxy-N-methoxy-N-methylthiophene-2-carboxamide**

A mixture of 5-(6-[2-(4-bromo-phenyl)-ethylamino]-pyrimidin-4-yl)-3-ethoxy-thiophene-2-carboxylic acid (Example 54, 194 mg, 0.427 mmol), N,O-dimethylhydroxylamine hydrochloride (63.8 mg, 0.641 mmol), TEA (0.178 mL, 1.28 mmol) and HATU (244 mg, 0.641 mmol) in DMF (1.5 mL) is stirred at RT for 1h, and purified by prep. HPLC to afford the title compound as a beige solid (115mg, 55%). LC-MS A: t<sub>R</sub> = 0.81 min; [M+H]<sup>+</sup> = 490.96.

**Example 146: (5-(6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl)-3-ethoxy-thiophen-2-yl)-urea**

TEA (0.01 mL, 0.0718 mmol) and trichloroacetyl isocyanate (0.01 mL, 0.0809 mmol) are successively added at RT to a solution of 6-(5-amino-4-ethoxythiophen-2-yl)-N-(4-bromophenethyl)pyrimidin-4-amine hydrochloride (19.3 mg,

0.0424 mmol) in DCM (0.5 mL). The RM is stirred at RT for 1h30min, it is concentrated and the residue is taken up in NH<sub>3</sub> (7M in MeOH, 0.5 mL) and stirred at RT for 1h. The RM is diluted with DCM and water. The product precipitated as a yellow solid, which was filtered off and dried under high vacuum (11 mg, 58%). LC-MS A:  $t_R$  = 0.72 min;  $[M+H]^+$  = 462.00.

5      **a) 6-(5-Amino-4-ethoxythiophen-2-yl)-N-(4-bromophenethyl)pyrimidin-4-amine hydrochloride**

A solution of tert-butyl (5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)carbamate (22 mg, 0.0424 mmol) in HCl 4M in dioxane (1 mL) is stirred at RT for 2h, then it is concentrated under reduced pressure to afford the title compound as an orange solid (19.3 mg, 99%). LC-MS A:  $t_R$  = 0.75 min;  $[M+H]^+$  = 419.09.

10      **b) Tert-butyl (5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)carbamate**

5-[6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl]-3-ethoxy-thiophene-2-carboxylic acid (Example 54, 100 mg, 0.22 mmol) is suspended in tert-butanol (0.75mL) and diphenyl phosphoryl azide (0.0474 mL, 0.22 mmol) is added, followed by TEA (0.0311 mL, 0.221 mmol), at RT. The RM is heated at 90°C and stirred for 5h. Once at RT, it is diluted with sat. aq. NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer is washed twice  
15 with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. Purification by FC (heptane to heptane/EtOAc 1:1) afforded the title compound as a light yellow solid (23 mg, 20%). LC-MS A:  $t_R$  = 0.86 min;  $[M+H]^+$  = 519.06.

**Example 147: 3-(3-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5-ol]**

Following the same method as described for example 130, using 1,1'-carbonyldiimidazole and 3-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)-N'-hydroxybenzimidamide, the title compound is obtained as a white solid.  
20 LC-MS A:  $t_R$  = 0.72 min;  $[M+H]^+$  = 437.99.

**a) 3-(6-((4-Bromophenethyl)amino)pyrimidin-4-yl)-N'-hydroxybenzimidamide**

Following the same method as described for example 129, using 3-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)benzonitrile, the title compound is obtained as a white solid. LC-MS A:  $t_R$  = 0.59 min;  $[M+H]^+$  = 412.07.

25      **b) 3-(6-((4-Bromophenethyl)amino)pyrimidin-4-yl)benzonitrile**

Following the general procedure G with N-(4-bromophenethyl)-6-iodopyrimidin-4-amine (A.2.2.) and 3-cyanophenylboronic acid, the title compound is obtained as a white solid. LC-MS A:  $t_R$  = 0.76 min;  $[M+H]^+$  = 381.05.

30      **Example 148: 2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethoxy-thiazole-5-carboxylic acid**

To a solution of ethyl 4-ethoxy-2-(6-hydroxypyrimidin-4-yl)thiazole-5-carboxylate (59 mg, 0.2 mmol) in DMF (2 mL) are added TEA (0.151 mL, 1.08 mmol) and PyBop (150 mg, 0.288 mmol). The RM is stirred at RT for a few minutes until complete dissolution and 2-(4-bromo-2,6-difluorophenyl)ethan-1-amine (59 mg, 0.25 mmol) is added. The RM is heated at 100 °C for 30 min in the MW apparatus. NaOH 10% (0.721 mL, 2 mmol) is added and the RM is stirred

at 70°C overnight. Purification by prep. LC-MS afforded the title compound as a yellow solid. LC-MS B:  $t_R$  = 0.97 min;  $[M+H]^+$  = 486.95.

**a) Ethyl 4-ethoxy-2-(6-hydroxypyrimidin-4-yl)thiazole-5-carboxylate**

Following the procedure described for the synthesis of Example 83-a with ethyl 4-ethoxy-2-(6-methoxypyrimidin-4-yl)thiazole-5-carboxylate, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 0.78 min;  $[M+H]^+$  = 296.15.

**b) Ethyl 4-ethoxy-2-(6-methoxypyrimidin-4-yl)thiazole-5-carboxylate**

To a solution of ethyl 4-hydroxy-2-(6-methoxypyrimidin-4-yl)thiazole-5-carboxylate (1730 mg, 6.15 mmol) in DMF (40 mL) at RT under argon is added  $K_2CO_3$  (2168 mg, 15.4 mmol), and the RM is heated at 60°C. Iodoethane (0.749 mL, 9.23 mmol) is added and the RM is stirred at 75°C overnight. It is then cooled to RT, and water (75 mL) is added. The aq layer is extracted with DCM, the organic extracts are dried ( $MgSO_4$ ), filtered and concentrated under reduced pressure, affording the crude title compound as an orange solid (1.75 g, 76%). LC-MS B:  $t_R$  = 1.04 min;  $[M+H]^+$  = 310.24.

**c) Ethyl 4-hydroxy-2-(6-methoxypyrimidin-4-yl)thiazole-5-carboxylate**

To a solution of 6-methoxypyrimidine-4-carbothioamide (1000 mg, 5.85 mmol) in toluene (40 mL) is added pyridine (1.9 mL, 23.4 mmol) at RT, followed by diethyl bromomalonate (1.52 mL, 8.19 mmol). The RM is heated at reflux overnight, then cooled to RT and treated with HCl 2N. The product is filtered off. The layers of the filtrate are separated and the aq layer is extracted twice with EtOAc. The combined organic layers are dried over  $MgSO_4$ , filtered, evaporated to dryness. The residue is combined with the first crop, yielding the title compound as a brown solid (1.73 g, 99%). LC-MS B:  $t_R$  = 0.89 min;  $[M+H]^+$  = 282.18.

**Example 149: 2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethyl-thiazole-5-carboxylic acid**

Following the procedure described for the synthesis of Example 148, using ethyl 4-ethyl-2-(6-hydroxypyrimidin-4-yl)thiazole-5-carboxylate and 2-(4-bromo-2,6-difluorophenyl)ethan-1-amine, the title compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.97 min;  $[M+H]^+$  = 470.90.

**a) Ethyl 4-ethyl-2-(6-hydroxypyrimidin-4-yl)thiazole-5-carboxylate**

Following the procedure described for the synthesis of Example 83-a with ethyl 4-ethyl-2-(6-ethoxypyrimidin-4-yl)thiazole-5-carboxylate, the title compound is obtained as a beige solid. LC-MS B:  $t_R$  = 0.73 min;  $[M+H]^+$  = 266.26.

**b) Ethyl 4-ethyl-2-(6-ethoxypyrimidin-4-yl)thiazole-5-carboxylate**

To a solution of methyl 2-chloro-3-oxovalerate (0.96 mL, 6.5 mmol) in EtOH (30 mL) is added 6-methoxypyrimidine-4-carbothioamide (1000 mg, 5.91 mmol) and the mixture is refluxed overnight. Methyl 2-chloro-3-oxovalerate (1.31 mL, 8.86 mmol) is added and the RM is further refluxed for 24h, then cooled at RT and treated with water (15 mL), cooled down to 0°C. The precipitate is filtered off, rinsed with MeOH and dried under high vacuum, affording the title compound as a pinkish solid (485 mg, 28%). LC-MS B:  $t_R$  = 1.07 min;  $[M+H]^+$  = 294.20.

**Example 150: 3-(2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethoxy-thiazol-5-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(2-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethoxy-thiazol-5-yl)-[1,2,4]oxadiazol-5-ol]**

Following the procedure described for the synthesis of Example 148, using 3-(4-ethoxy-2-(6-hydroxypyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol and 2-(4-bromo-2,6-difluorophenyl)ethan-1-amine, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 1.10 min;  $[M+H]^+$  = 524.05.

**a) 3-(4-Ethoxy-2-(6-hydroxypyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol**

Following the procedure described for the synthesis of Example 83-a with 3-(4-ethoxy-2-(6-methoxypyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol, the title compound is obtained as a yellowish solid. LC-MS B:  $t_R$  = 0.68 min;  $[M+H]^+$  = 308.17.

**b) 3-(4-Ethoxy-2-(6-methoxypyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol**

Following the procedure described for the synthesis of Example 83-b with 4-ethoxy-N'-hydroxy-2-(6-methoxypyrimidin-4-yl)thiazole-5-carboximidamide, the title compound is obtained as a beige solid. LC-MS B:  $t_R$  = 0.94 min;  $[M+H]^+$  = 321.93.

**c) 4-Ethoxy-N'-hydroxy-2-(6-methoxypyrimidin-4-yl)thiazole-5-carboximidamide**

Following the procedure described for the synthesis of Example 83-c with 4-ethoxy-2-(6-methoxypyrimidin-4-yl)thiazole-5-carbonitrile, the title compound is obtained as a deep yellow solid. LC-MS B:  $t_R$  = 0.67 min;  $[M+H]^+$  = 296.17.

**d) 4-Ethoxy-2-(6-methoxypyrimidin-4-yl)thiazole-5-carbonitrile**

NH<sub>4</sub>OH (25%, 4.05 mL, 26.3 mmol) and I<sub>2</sub> (1824 mg, 7.19 mmol) are added at 0°C to a solution of 4-ethoxy-2-(6-methoxypyrimidin-4-yl)thiazole-5-carbaldehyde (465 mg, 1.75 mmol) in THF (15 mL) and the mixture is stirred at RT for 3h. It is then poured in 10mL of NaHSO<sub>3</sub> 40% (15 mL) and extracted with EtOAc, dried over MgSO<sub>4</sub> and concentrated under vacuum, to afford the title compound as an orange solid. LC-MS B:  $t_R$  = 1.02 min;  $[M+H]^+$  = 263.25.

**e) 4-Ethoxy-2-(6-methoxypyrimidin-4-yl)thiazole-5-carbaldehyde**

A mixture of ethyl 4-ethoxy-2-(6-methoxypyrimidin-4-yl)thiazole-5-carboxylate (Example 148-b, 706 mg, 2.64 mmol) in THF (20 mL) is cooled down to -78°C and DiBAL-H (1M in THF, 5.28 mL, 5.28 mmol) is added dropwise. The mixture is stirred at RT overnight. The mixture is quenched at 0°C by dropwise addition of water (200 uL), then NaOH 10% (400uL) and finally water (600 uL). The aluminium precipitate is filtered over a pad of Celite and rinsed with EtOAc. The filtrate is dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue is dissolved in DCM (20 mL) and MnO<sub>2</sub> (2701 mg, 26.4 mmol) is added. The mixture is stirred 5h at RT, then filtered over a pad of Celite and rinsed with EtOAc. The filtrate is concentrated under reduced pressure, affording the title compound as a light orange solid. LC-MS B:  $t_R$  = 0.97 min;  $[M+H]^+$  = 266.25.

**Example 151:** 3-(2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethyl-thiazol-5-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(2-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethyl-thiazol-5-yl)-[1,2,4]oxadiazol-5-ol]

Following the procedure described for the synthesis of Example 148, using 3-(4-ethyl-2-(6-hydroxypyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol and 2-(4-bromo-2,6-difluorophenyl)ethan-1-amine, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 1.03 min;  $[M+H]^+$  = 510.98.

**a) 3-(4-Ethyl-2-(6-hydroxypyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol**

Following the procedure described for the synthesis of Example 83-a with 3-(4-ethyl-2-(6-ethoxypyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol, the title compound is obtained as a grey solid. LC-MS B:  $t_R$  = 0.64 min;  $[M+H]^+$  = 292.17.

**b) 3-(4-Ethyl-2-(6-ethoxypyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol**

Following the procedure described for the synthesis of Example 83-b with 4-ethyl-N'-hydroxy-2-(6-ethoxypyrimidin-4-yl)thiazole-5-carboximidamide, the title compound is obtained as a light orange solid. LC-MS B:  $t_R$  = 0.92 min;  $[M+H]^+$  = 320.21.

**c) 4-Ethyl-N'-hydroxy-2-(6-ethoxypyrimidin-4-yl)thiazole-5-carboximidamide**

Following the procedure described for the synthesis of Example 83-c with 4-ethyl-2-(6-ethoxypyrimidin-4-yl)thiazole-5-carbonitrile, the title compound is obtained as a light yellow solid. LC-MS B:  $t_R$  = 0.66 min;  $[M+H]^+$  = 294.21.

**d) 4-Ethyl-2-(6-ethoxypyrimidin-4-yl)thiazole-5-carbonitrile**

Following the procedure described for the synthesis of Example 83-d with 2-(6-ethoxypyrimidin-4-yl)-4-ethylthiazole-5-carboxamide, the title compound is obtained as a beige solid. LC-MS B:  $t_R$  = 1.04 min;  $[M+H]^+$  = 261.29.

**e) 2-(6-Ethoxypyrimidin-4-yl)-4-ethylthiazole-5-carboxamide**

Following the procedure described for the synthesis of Example 83-e with 2-(6-ethoxypyrimidin-4-yl)-4-ethylthiazole-5-carboxylic acid, the title compound is obtained as an orange solid. LC-MS B:  $t_R$  = 0.79 min;  $[M+H]^+$  = 279.25.

**f) 2-(6-Ethoxypyrimidin-4-yl)-4-ethylthiazole-5-carboxylic acid**

An ice-chilled solution of ethyl 4-ethyl-2-(6-ethoxypyrimidin-4-yl)thiazole-5-carboxylate (Example 149-b, 1000 mg, 3.09 mmol) in THF/MeOH 1:1 (15 mL) is treated with NaOH 10% (5.58 mL, 15.5 mmol) and stirred at RT for 20h. The solvents are removed under reduced pressure, the aqueous phase is extracted once with Et<sub>2</sub>O. The aqueous phase is then acidified with 2N HCl and extracted with EtOAc (3 x). The combined organic extracts are dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure, yielding the title compound as a greenish solid (522 mg, 64%). LC-MS B:  $t_R$  = 0.88 min;  $[M+H]^+$  = 280.24.

**Example 152:** 5-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,3,4]-oxadiazol-2-ol [tautomeric form: 5-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,3,4]-oxadiazol-2(3H)-one]

Following the procedure described for the synthesis of Example 83, using 5-(3-ethoxy-5-(6-hydroxypyrimidin-4-yl)thiophen-2-yl)-[1,3,4]-oxadiazol-2-ol, 2-(4-bromo-2,6-difluorophenyl)ethan-1-amine and BOP, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 0.94 min;  $[M+H]^+$  = 526.01.

**a) 5-(3-Ethoxy-5-(6-hydroxypyrimidin-4-yl)thiophen-2-yl)-[1,3,4]-oxadiazol-2-ol**

5 Following the procedure described for the synthesis of Example 83-a with tert-butyl (5-(3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophen-2-yl)-[1,3,4]-oxadiazol-2-yl) carbonate, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 0.64 min;  $[M+H]^+$  = 307.04.

**b) Tert-butyl (5-(3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophen-2-yl)-[1,3,4]-oxadiazol-2-yl) carbonate**

10 Di-tert.butyl-dicarbonate (693 mg, 3.18 mmol) is added portionwise, at RT, to a solution of 3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carbohydrazide (150 mg, 0.635 mmol) and DMAP (7.84 mg, 0.0635 mmol) in THF (6 mL). The RM is stirred at RT overnight, then partitioned between DCM and sat. aq.  $\text{NaHCO}_3$ . The two layers are separated via a phase separator syringe and the organic layer is concentrated to dryness. Purification by prep HPLC affords the title compound as a yellow solid (31 mg, 43%). LC-MS B:  $t_R$  = 1.10 min;  $[M+H]^+$  = 421.16.

15 **c) 3-Ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carbohydrazide**

To a solution of methyl 3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxylate (Example 83-g, 257 mg, 0.873 mmol) in EtOH (2 mL) is added hydrazine monohydrate (0.216 mL, 4.37 mmol). The RM is stirred at 80°C for 3 h, then concentrated to dryness, affording the title compound as a yellow solid (253 mg, 99%). LC-MS B:  $t_R$  = 0.68 min;  $[M+H]^+$  = 295.16.

20 **Example 153: 5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophene-2-carboxylic acid**

Following the general procedure G using N-(4-bromo-2,6-difluorophenethyl)-6-iodopyrimidin-4-amine (A.2.6.) and 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylic acid (A.3.3.), the title compound is obtained as a light yellow solid. LC-MS B:  $t_R$  = 0.89 min;  $[M+H]^+$  = 485.96.

25 **Example 154: N-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carbonyl)-methanesulfonamide**

5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophene-2-carboxylic acid (Example 153, 70 mg, 0.145 mmol) is dissolved in DMSO/THF (2:1) (3 mL) and CDI (35.2 mg, 0.217 mmol) is added. The RM is heated at 60°C for 1h, cooled to RT and treated with methanesulfonamide (31.2 mg, 0.318 mmol) and DBU (0.054 mL, 0.361 mmol). The RM is stirred at RT for 2h30. THF is removed under reduced pressure, a few drops of TEA are added, and the mixture is filtrated through a whatman filter and purified by prep HPLC, affording the title compound as a white solid. LC-MS B:  $t_R$  = 1.03 min;  $[M+H]^+$  = 563.03.

30 **Example 155: 5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxy-N-sulfamoylthiophene-2-carboxamide**



Following the procedure described for the synthesis of Example 154, using 5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophene-2-carboxylic acid (Example 153) and sulfamide, the title compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.94 min;  $[M+H]^+$  = 561.78.

**Example 156: 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-2-methyl-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-2-methyl-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]**

Following the procedure described for the synthesis of Example 83, using 3-(3-ethoxy-5-(6-hydroxy-2-methylpyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol and 2-(4-bromo-2,6-difluorophenyl)ethan-1-amine, the title compound is obtained as a pale yellow solid. LC-MS B:  $t_R$  = 0.90 min;  $[M+H]^+$  = 540.05.

**a) 3-(3-Ethoxy-5-(6-hydroxy-2-methylpyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol**

Following the procedure described for the synthesis of Example 83-a using 3-(3-ethoxy-5-(6-methoxy-2-methylpyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 0.71 min;  $[M+H]^+$  = 321.04.

**b) 3-(3-Ethoxy-5-(6-methoxy-2-methylpyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol**

Following the procedure described for the synthesis of Example 83-b using 3-ethoxy-N'-hydroxy-5-(6-methoxy-2-methylpyrimidin-4-yl)thiophene-2-carboximidamide, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 0.95 min;  $[M+H]^+$  = 335.05.

**c) 3-Ethoxy-N'-hydroxy-5-(6-methoxy-2-methylpyrimidin-4-yl)thiophene-2-carboximidamide**

Following the procedure described for the synthesis of Example 83-c using 3-ethoxy-5-(6-methoxy-2-methylpyrimidin-4-yl)thiophene-2-carbonitrile, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 0.66 min;  $[M+H]^+$  = 309.09.

**d) 3-Ethoxy-5-(6-methoxy-2-methylpyrimidin-4-yl)thiophene-2-carbonitrile**

Following the procedure described for the synthesis of Example 83-d using 3-ethoxy-5-(6-methoxy-2-methylpyrimidin-4-yl)thiophene-2-carboxamide, the title compound is obtained as a beige solid. LC-MS B:  $t_R$  = 1.06 min;  $[M+H]^+$  = 276.18.

**e) 3-Ethoxy-5-(6-methoxy-2-methylpyrimidin-4-yl)thiophene-2-carbonitrile**

A solution of methyl 3-ethoxy-5-(6-methoxy-2-methylpyrimidin-4-yl)thiophene-2-carboxylate (450 mg, 1.46 mmol) is dissolved in  $NH_3$  (7M in MeOH, 15 mL) is stirred at 80°C for 3 d, then it is concentrated reduced pressure to afford the title compound as a yellow solid (449 mg, 99%). LC-MS B:  $t_R$  = 0.84 min;  $[M+H]^+$  = 294.13.

**f) Methyl 3-ethoxy-5-(6-methoxy-2-methylpyrimidin-4-yl)thiophene-2-carboxylate**

Following the procedure described for the synthesis of Example 83-g, using methyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (Example 83-h) and 4-chloro-6-methoxy-2-methylpyrimidine, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 0.99 min;  $[M+H]^+$  = 309.10.

**Example 157:** 3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-2-methyl-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-phenyl)-ethylamino]-2-methyl-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]

Following the procedure described for the synthesis of Example 83, using 3-(3-ethoxy-5-(6-hydroxy-2-methylpyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol (Example 156-a) and 4-bromophenethylamine, the title compound is obtained as a pale yellow solid. LC-MS B:  $t_R$  = 0.86 min;  $[M+H]^+$  = 504.07.

**Example 158:** 2-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acetamide

Following the procedure described for the synthesis of Example 156-e, using methyl 2-(5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)thiophen-2-yl)acetate and  $NH_3$  in MeOH, the title compound is obtained as a beige solid. LC-MS B:  $t_R$  = 0.69 min;  $[M+H]^+$  = 417.05.

**a) Methyl 2-(5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)thiophen-2-yl)acetate**

Following the procedure described for the synthesis of Example 83-g using N-(4-bromophenethyl)-6-iodopyrimidin-4-amine (A.2.2.) and methyl 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acetate, the title compound is obtained as a beige solid. LC-MS B:  $t_R$  = 0.82 min;  $[M+H]^+$  = 431.94.

**b) Methyl 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acetate**

Following the procedure described for the synthesis of A.3.18. using methyl thiophene-2-acetate, the title compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.97 min;  $[M+H]^+$  = 283.14.

**Example 159:** rac-2-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-propionic acid

A mixture of 2-(5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)thiophen-2-yl)propanenitrile (30 mg, 0.0726 mmol) in HCl Conc. (0.35 mL) is stirred in a sealed tube at 85 °C for 45min. It is then cooled down to 0 °C, basified with  $NH_4OH$  and purified by prep. HPLC, yielding the title compound as a white solid (23 mg, 73%). LC-MS B:  $t_R$  = 0.78 min;  $[M+H]^+$  = 432.06.

**a) 2-(5-(6-((4-Bromophenethyl)amino)pyrimidin-4-yl)thiophen-2-yl)propanenitrile**

Following the procedure described for the synthesis of Example 83-g using N-(4-bromophenethyl)-6-iodopyrimidin-4-amine (A.2.2.) and 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)propanenitrile, the title compound is obtained as a beige solid. LC-MS B:  $t_R$  = 0.87 min;  $[M+H]^+$  = 413.07.

**b) 2-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)propanenitrile**

Following the procedure described for the synthesis of A.3.18. using 2-(thiophen-2-yl)propanenitrile, the title compound is obtained as a white solid. LC-MS A:  $t_R$  = 1.00 min; no ionization.

**Example 160:** 4-Chloro-2-(2-{6-[4-ethoxy-5-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-thiophen-2-yl]-pyrimidin-4-ylamino}-ethyl)-benzonitrile [tautomeric form: 4-chloro-2-(2-{6-[4-ethoxy-5-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-thiophen-2-yl]-pyrimidin-4-ylamino}-ethyl)-benzonitrile]

A MW vial is charged 3-(5-{6-[2-(2-bromo-5-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one (Example 94, 28 mg, 0.0536 mmol), copper(I) cyanide (0.00415 mL, 0.134 mmol) and DMF (1 mL). It is capped and heated at 160 °C for 30min under MW irradiation. Copper(I) cyanide (0.0124 mL, 0.402 mmol) is added and the mixture is further heated at 180 °C for 30 min, then at 170 °C for 1h. The RM is treated

with 0.5 mL of 25% NH<sub>4</sub>OH and filtered through a 0.45 µm Whatman filter, rinsed with MeOH and purified by prep HPLC, yielding the title compound as a beige solid (1 mg, 4%). LC-MS B: t<sub>R</sub> = 0.95 min; [M+H]<sup>+</sup> = 469.16.

**Example 161: 3-(5-{6-[2-(4-Dimethylamino-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-dimethylamino-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]**

A MW vial is charged with 3-(5-{6-[2-(4-bromo-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one (Example 125, 15 mg, 0.0296 mmol), dimethylamine (2.0 M in THF, 0.02 mL, 0.04 mmol), XPhos (3 mg, 0.0061 mmol), tris(dibenzylideneacetone)dipalladium(0) (3 mg, 0.00328 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (30 mg, 0.0921 mmol) in toluene (1 mL). The vial is capped, evacuated and backfilled with N<sub>2</sub> (3x). The RM is heated at 120 °C for 15 min under MW irradiation. Dimethylamine (2.0 M in THF, 0.075 mL, 0.148 mmol) is added and the RM is further heated at 125 °C for 30 min. Dimethylamine (2.0 M in THF, 0.15 mL, 0.296 mmol) is added and the RM is heated at 130 °C for 30 min. Dimethylamine (2.0 M in THF, 0.15 mL, 0.296 mmol), XPhos (3 mg, 0.0061 mmol) and tris(dibenzylideneacetone)dipalladium(0) (3 mg, 0.00328 mmol) are added and the mixture is heated at 150 °C for 1 h. The RM is filtered on a 0.45 µm glass fiber filter, the filtrate is concentrated and the residue is purified by prep HPLC, yielding the title compound as a beige solid (1 mg, 7%). LC-MS B: t<sub>R</sub> = 0.85 min; [M+H]<sup>+</sup> = 471.06.

**Example 162: 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-isopropoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-isopropoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]**

Following the procedure described for the synthesis of Example 83, using 3-(5-(6-hydroxypyrimidin-4-yl)-3-isopropoxythiophen-2-yl)-[1,2,4]oxadiazol-5-ol and 2-(4-bromo-2,6-difluorophenyl)ethan-1-amine, the title compound is obtained as a beige solid. LC-MS B: t<sub>R</sub> = 1.03 min; [M+H]<sup>+</sup> = 538.06.

**a) 3-(5-(6-Hydroxypyrimidin-4-yl)-3-isopropoxythiophen-2-yl)-[1,2,4]oxadiazol-5-ol**

Following the procedure described for the synthesis of Example 83-a using 3-(5-(6-methoxypyrimidin-4-yl)-3-isopropoxythiophen-2-yl)-[1,2,4]oxadiazol-5-ol, the title compound is obtained as a brown solid. LC-MS B: t<sub>R</sub> = 0.71 min; [M+H]<sup>+</sup> = 321.16.

**b) 3-(5-(6-Methoxypyrimidin-4-yl)-3-isopropoxythiophen-2-yl)-[1,2,4]oxadiazol-5-ol**

Following the procedure described for the synthesis of Example 83-b using N'-hydroxy-3-isopropoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboximidamide, the title compound is obtained as a yellow solid. LC-MS B: t<sub>R</sub> = 0.95 min; [M+H]<sup>+</sup> = 335.23.

**c) N'-Hydroxy-3-isopropoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboximidamide**

Following the procedure described for the synthesis of Example 83-c using 3-isopropoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carbonitrile, the title compound is obtained as a yellow solid. LC-MS B: t<sub>R</sub> = 0.66 min; [M+H]<sup>+</sup> = 309.26.

**d) 3-Isopropoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carbonitrile**

Following the procedure described for the synthesis of Example 83-d using 3-isopropoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxamide, the title compound is obtained as a beige solid. LC-MS B:  $t_R = 1.04$  min;  $[M+H]^+ = 276.27$ .

**e) 3-Isopropoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxamide**

5 Following the procedure described for the synthesis of Example 83-e using 3-isopropoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxylic acid, the title compound is obtained as a brown solid. LC-MS B:  $t_R = 0.85$  min;  $[M+H]^+ = 294.23$ .

**f) 3-Isopropoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxylic acid**

10 To a solution of methyl 3-isopropoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxylate (500 mg, 1.62 mmol) in MeOH (16 mL) and THF (10 mL) is added NaOH 1N (16.2 mL, 16.2 mmol). The RM is stirred at RT overnight, then concentrated in vacuo. The residue is partitioned between EtOAc and water. The basic aqueous layer is acidified to pH=2 using HCl 1N and extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over  $MgSO_4$ , filtered and concentrated under reduced pressure, yielding the title compound as a beige solid (322mg, 68%). LC-MS B:  $t_R = 0.93$  min;  $[M+H]^+ = 295.20$ .

15 **g) Methyl 3-isopropoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carboxylate**

Following the procedure described for the synthesis of Example 83-g, using methyl 3-isopropoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate and 4-chloro-6-methoxy-pyrimidine, the title compound is obtained as a yellow solid. LC-MS B:  $t_R = 0.98$  min;  $[M+H]^+ = 309.06$ .

**h) Methyl 3-isopropoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate**

20 Following the procedure described for the synthesis of A.3.3., using methyl 3-isopropoxythiophene-2-carboxylate, the title compound is obtained as a beige solid. LC-MS B:  $t_R = 0.73$  min;  $[M+H]^+ = 259.12$  (boronic acid, from hydrolysis of the pinacol ester on the LC-MS-column).

**i) Methyl 3-isopropoxythiophene-2-carboxylate**

25 To a solution of methyl 3-hydroxythiophene-2-carboxylate (8000 mg, 50.6 mmol) in DMF (100 mL) at 0°C is added NaH (60% in oil, 2529 mg, 63.2 mmol) portionwise. Once the gas evolution is finished, 2-bromopropane (15.84 mL, 166.8 mmol) is added dropwise. After 5 minutes at 0°C the RM is allowed to warm to RT, then to 50°C over the week-end. It is cooled to RT, quenched with a few drops of water, then concentrated under reduced pressure. The residue is partitioned between water and EtOAc. The aqueous layer is re-extracted twice with EtOAc. The combined organic phases are washed with water, brine, dried over  $MgSO_4$ , filtered and concentrated in vacuo yielding the title compound as a brown liquid (9.80 g, 97%). LC-MS B:  $t_R = 0.78$  min;  $[M+H]^+ = 201.24$ .

30

**Example 163: 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-(2-dimethylamino-ethoxy)-thiophene-2-carboxylic acid**

35 To a solution of methyl 5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-hydroxythiophene-2-carboxylate (20 mg, 0.0458 mmol),  $Cs_2CO_3$  (44.8 mg, 0.137 mmol) and TBAI (3.42 mg, 0.00917 mmol) in DMF (1 mL) is added (2-bromoethyl)dimethylamine (33.7 mg, 0.137 mmol) and the RM is heated at 120°C overnight. The

RM is cooled to RT and treated with NaOH 10% (0.0917 mL, 0.229 mmol), and further stirred at RT for 4h. The RM is filtered, rinsed with MeOH and purified by prep HPLC to yield the title compound as a red solid (3 mg, 16%). LC-MS B:  $t_R$  = 0.70 min;  $[M+H]^+$  = 527.07.

**a) Methyl 5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-hydroxythiophene-2-carboxylate**

Following the general procedure G with N-(4-bromo-2,6-difluorophenethyl)-6-iodopyrimidin-4-amine (A.2.6.) and methyl 3-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate, the title compound is obtained as an ochre solid. LC-MS B:  $t_R$  = 1.00 min;  $[M+H]^+$  = 471.99.

**b) Methyl 3-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate**

Following the procedure described for the synthesis of A.3.3., using methyl 3-hydroxythiophene-2-carboxylate, the title compound is obtained as a brown solid. LC-MS B:  $t_R$  = 0.56 min; no ionization.

**Example 164: 3-Ethoxy-5-{6-[2-(2-methoxy-5-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid**

Following the general procedure G using 6-chloro-N-(2-methoxy-4-(methylthio)phenethyl)pyrimidin-4-amine (A.2.10.) and 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylic acid (A.3.3.), the title compound is obtained as a white solid. LC-MS A:  $t_R$  = 0.84 min;  $[M+H]^+$  = 446.12.

**Example 165: 4-{6-[2-(2-Methoxy-5-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanylbenzoic acid**

Following the general procedure H using 6-chloro-N-(2-methoxy-4-(methylthio)phenethyl)pyrimidin-4-amine (A.2.10.) and methyl 2-(methylthio)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (A.3.11.), the title compound is obtained as a white solid. LC-MS A:  $t_R$  = 0.78 min;  $[M+H]^+$  = 442.13.

Compounds of Examples 166 – 274 listed in Table 8 below are prepared by applying either General Procedure G or H to the pyrimidine halide derivatives A.2.1. – A.2.26. coupled with commercially available boronic acid derivatives or with boronic acid derivatives A.3.1. – A.3.59.

**Table 8: Examples 166 - 274**

| Ex. | Compound                                                                                                   | $t_R$ [min]<br>(method C) | MS Data<br>m/z $[M+H]^+$ |
|-----|------------------------------------------------------------------------------------------------------------|---------------------------|--------------------------|
| 166 | 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-propionic acid (*1) | 0.849                     | 492.2                    |
| 167 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-butoxy-6-fluoro-benzoic acid           | 1.17                      | 524.2                    |
| 168 | 2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1H-indole-5-carboxylic acid (*1)         | 0.977                     | 471.9                    |

|     |                                                                                                                                                                                                                                   |       |       |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------|
| 169 | 2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1H-indole-6-carboxylic acid                                                                                                                                     | 1.027 | 473.4 |
| 170 | [2-(4-Bromo-2,6-difluoro-phenyl)-ethyl]-[6-(1H-indol-6-yl)-pyrimidin-4-yl]-amine                                                                                                                                                  | 0.814 | 429.1 |
| 171 | 1-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-cyclopropanecarboxylic acid (*1)                                                                                                            | 0.935 | 518.2 |
| 172 | 1-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-phenyl)-cyclopropanecarboxylic acid (*1)                                                                                                            | 0.98  | 516.3 |
| 173 | 2-Cyclobutoxy-4-{6-[2-(2-methoxy-5-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)                                                                                                                           | 0.987 | 464.1 |
| 174 | 5-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-isoxazol-3-ol [tautomeric form: 5-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-isoxazol-3(2H)-one] | 0.985 | 503.1 |
| 175 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-3-fluoro-phenyl)-acetic acid (*1)                                                                                                                     | 0.945 | 510.0 |
| 176 | 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methoxy-thiophene-2-carboxylic acid (*1)                                                                                                                      | 1.057 | 470.1 |
| 177 | 3-Ethoxy-5-{6-[2-(2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid                                                                                                                              | 0.997 | 418.3 |
| 178 | 3-Ethoxy-5-{6-[2-(2-methoxy-6-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid                                                                                                                              | 1.037 | 414.3 |
| 179 | 5-{6-[2-(4,5-Difluoro-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid                                                                                                                          | 1.022 | 436.2 |
| 180 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)                                                                                                                                      | 0.982 | 478.2 |
| 181 | 5-{6-[2-(3,4-Dichloro-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid (*1)                                                                                                                      | 1.193 | 450.1 |
| 182 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenylamino)-acetic acid                                                                                                                              | 0.829 | 507   |
| 183 | 4-{6-[2-(4-Difluoromethyl-5-fluoro-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)                                                                                                                       | 0.908 | 460.2 |
| 184 | 2-Cyclobutoxy-4-{6-[2-(4-difluoromethyl-5-fluoro-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)                                                                                                                  | 1.002 | 486.1 |
| 185 | 5-{6-[2-(4-Difluoromethyl-5-fluoro-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid (*1)                                                                                                        | 1.047 | 466.2 |
| 186 | (4-{6-[2-(4-Difluoromethyl-5-fluoro-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid (*1)                                                                                                               | 0.834 | 474.1 |



|     |                                                                                                                             |       |       |
|-----|-----------------------------------------------------------------------------------------------------------------------------|-------|-------|
| 187 | 4-{6-[2-(4-Difluoromethyl-5-fluoro-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)         | 0.913 | 462   |
| 188 | 2-Cyclobutoxy-4-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)                         | 1.027 | 446.2 |
| 189 | 4-{6-[2-(2-Methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid (*1)                              | 0.987 | 418   |
| 190 | (2-Ethoxy-4-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid (*1)                      | 0.859 | 434.2 |
| 191 | (4-{6-[2-(2-Methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-phenyl)-acetic acid (*1)              | 0.869 | 436.3 |
| 192 | (4-{6-[2-(2-Methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-phenyl)-acetic acid (*1)                      | 0.908 | 432.2 |
| 193 | (2-Ethoxy-6-fluoro-4-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid (*1)             | 0.972 | 452.9 |
| 194 | (4-{6-[2-(2-Methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-phenyl)-acetic acid (*1)                     | 0.913 | 448   |
| 195 | 4-{6-[2-(5-Chloro-2-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)                | 1.042 | 494   |
| 196 | 4-{6-[2-(5-Chloro-2-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)        | 1.047 | 496   |
| 197 | 4-{6-[2-(5-Chloro-2-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid (*1)                | 1.091 | 492.3 |
| 198 | 5-{6-[2-(5-Chloro-2-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid (*1) | 1.17  | 500.1 |
| 199 | 4-{6-[2-(4-Difluoromethyl-2-methoxy-5-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)                 | 0.923 | 456   |
| 200 | 4-{6-[2-(2-Methoxy-4,6-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)                      | 0.947 | 422.1 |
| 201 | 4-{6-[2-(2-Methoxy-4,6-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid (*1)                              | 0.992 | 418   |
| 202 | (2-Ethoxy-4-{6-[2-(2-methoxy-4,6-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid (*1)                      | 0.864 | 434.1 |
| 203 | 3-Ethoxy-5-{6-[2-(2-methoxy-4,6-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (*1)               | 1.101 | 426   |
| 204 | (4-{6-[2-(2-Methoxy-4,6-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-phenyl)-acetic acid (*1)                     | 0.918 | 448.2 |

|     |                                                                                                                            |       |       |
|-----|----------------------------------------------------------------------------------------------------------------------------|-------|-------|
| 205 | 2-Ethoxy-4-{6-[2-(2-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)                        | 0.967 | 460   |
| 206 | 4-{6-[2-(2-Methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)                | 0.972 | 462.4 |
| 207 | 4-{6-[2-(2-Methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid (*1)                        | 1.022 | 458.1 |
| 208 | 3-Ethoxy-5-{6-[2-(2-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (*1)         | 1.106 | 466.2 |
| 209 | 2-Isobutyl-4-{6-[2-(2-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)                      | 1.066 | 472   |
| 210 | 3-Ethoxy-5-{6-[2-(2-methoxy-4-trifluoromethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (*1)        | 1.131 | 482.1 |
| 211 | 2-Ethoxy-4-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)                         | 1.042 | 476.2 |
| 212 | 4-{6-[2-(2-Ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)                 | 1.042 | 475.9 |
| 213 | 4-{6-[2-(2-Ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid (*1)                         | 1.081 | 472.1 |
| 214 | (2-Ethoxy-4-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid (*1)                 | 0.943 | 490.2 |
| 215 | 3-Ethoxy-5-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (*1)          | 1.18  | 480   |
| 216 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylamino-benzamide                                  | 0.809 | 462.1 |
| 217 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethylamino-benzamide                                   | 0.868 | 476.4 |
| 218 | 4-{6-[2-(2-Difluoromethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)        | 1.002 | 498.3 |
| 219 | 5-{6-[2-(2-Difluoromethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid (*1) | 1.126 | 502.1 |
| 220 | 4-{6-[2-(4-Difluoromethoxy-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)                        | 0.883 | 458.3 |
| 221 | 4-{6-[2-(4-Difluoromethoxy-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)                | 0.888 | 460.1 |
| 222 | 4-{6-[2-(4-Difluoromethoxy-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid (*1)                        | 0.937 | 456.2 |

|     |                                                                                                                                                                                                                                                |       |       |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------|
| 223 | 4-{6-[2-(4-Difluoromethoxy-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid (*1)                                                                                                                                     | 0.819 | 472.2 |
| 224 | 5-{6-[2-(4-Difluoromethoxy-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid (*1)                                                                                                                             | 1.022 | 464.1 |
| 225 | 3-(2-Ethoxy-4-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-propionic acid (*1)                                                                                                                                   | 0.834 | 464   |
| 226 | 2-Ethoxy-4-{6-[2-(2-fluoro-6-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)                                                                                                                                   | 1.007 | 478   |
| 227 | 3-Ethoxy-5-{6-[2-(2-fluoro-6-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (*1)                                                                                                                    | 1.136 | 484.1 |
| 228 | 4-{6-[2-(2,6-Difluoro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)                                                                                                                                                 | 0.873 | 430.3 |
| 229 | 4-{6-[2-(2,6-Difluoro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)                                                                                                                                         | 0.883 | 432.3 |
| 230 | 4-{6-[2-(2-Fluoro-6-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)                                                                                                                           | 1.012 | 479.9 |
| 231 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylamino-benzoic acid                                                                                                                                                   | 0.913 | 463.3 |
| 232 | 6-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1-methyl-1,3-dihydro-indol-2-one                                                                                                                                             | 0.839 | 459   |
| 233 | 3-(4-{6-((2,6-Difluorophenethyl)amino)pyrimidin-4-yl}-2-ethoxyphenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-((2,6-difluorophenethyl)amino)pyrimidin-4-yl}-2-ethoxyphenyl)-[1,2,4]oxadiazol-5-ol]                                | 0.937 | 440.3 |
| 234 | 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazol-5-ol] | 1.066 | 518   |
| 235 | 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5-ol]                  | 0.957 | 474.2 |
| 236 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-trifluoromethoxy-phenyl)-acetic acid (*1)                                                                                                                                  | 1.081 | 532   |
| 237 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-isobutoxy-benzoic acid (*1)                                                                                                                                                | 1.131 | 506.1 |
| 238 | N-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-formamide                                                                                                                                                         | 0.765 | 433.2 |

|     |                                                                                                                         |       |       |
|-----|-------------------------------------------------------------------------------------------------------------------------|-------|-------|
| 239 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-oxo-acetic acid                     | 0.918 | 506   |
| 240 | N-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-formamide                         | 0.883 | 477.2 |
| 241 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethyl-phenyl)-acetic acid (*1)                     | 0.873 | 476.2 |
| 242 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-phenyl)-acetic acid (*1)                    | 0.928 | 489.9 |
| 243 | 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-4-hydroxy-cyclobut-3-ene-1,2-dione         | 0.973 | 486.1 |
| 244 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-isobutyl-phenyl)-acetic acid (*1)                  | 0.977 | 504.1 |
| 245 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethyl-benzoic acid methyl ester                     | 1.161 | 476.3 |
| 246 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid methyl ester            | 1.17  | 494   |
| 247 | 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-propionic acid ethyl ester | 1.299 | 540.2 |
| 248 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-phenyl)-acetic acid (*1)                   | 0.942 | 506.2 |
| 249 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethyl-benzoic acid (*1)                             | 0.972 | 462.4 |
| 250 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2,6-dimethyl-phenol                                   | 0.829 | 434.2 |
| 251 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-benzoic acid (*1)                        | 1.056 | 492.2 |
| 252 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-difluoromethoxy-phenyl)-acetic acid (*1)           | 0.972 | 514   |
| 253 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-chloro-6-ethyl-phenyl)-acetic acid (*1)            | 1.042 | 510.2 |
| 254 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methyl-phenyl)-acetic acid (*1)                    | 0.824 | 462.1 |
| 255 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2,6-dimethyl-phenyl)-acetic acid (*1)                | 0.844 | 476.4 |
| 256 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-fluoro-6-methyl-phenyl)-acetic acid (*1)           | 0.938 | 480.4 |

|     |                                                                                                                                                                                                                        |       |       |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------|
| 257 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethyl-6-methyl-phenyl)-acetic acid (*1)                                                                                                           | 0.893 | 490.2 |
| 258 | [2-(4-Bromo-2,6-difluoro-phenyl)-ethyl]-[6-(1H-indol-5-yl)-pyrimidin-4-yl]-amine                                                                                                                                       | 0.809 | 429.2 |
| 259 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-cyclopropoxy-benzoic acid (*1)                                                                                                                     | 0.992 | 490.4 |
| 260 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-cyclopropoxy-phenyl)-acetic acid (*1)                                                                                                             | 0.903 | 504.1 |
| 261 | (5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethyl-thiophen-2-yl)-acetic acid (*1)                                                                                                             | 1.022 | 482.2 |
| 262 | 7-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1-methyl-3,4-dihydro-1H-quinazolin-2-one                                                                                                             | 0.809 | 474   |
| 263 | 2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1H-indole-7-carboxylic acid (*1)                                                                                                                     | 1.141 | 473.2 |
| 264 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-chloro-6-methyl-phenyl)-acetic acid (*1)                                                                                                          | 0.992 | 496.1 |
| 265 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-urea                                                                                                                                        | 0.71  | 448.2 |
| 266 | 6-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3H-benzooxazol-2-one                                                                                                                                 | 0.824 | 447.2 |
| 267 | [2-(4-Bromo-2,6-difluoro-phenyl)-ethyl]-[6-(1H-indazol-5-yl)-pyrimidin-4-yl]-amine                                                                                                                                     | 0.77  | 430.2 |
| 268 | 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-1H-pyrrole-2-carboxylic acid (*1)                                                                                                           | 0.933 | 467.3 |
| 269 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1-ethyl-1H-pyrrole-2-carboxylic acid (*1)                                                                                                            | 0.775 | 451.2 |
| 270 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1-propyl-1H-pyrrole-2-carboxylic acid (*1)                                                                                                           | 0.819 | 465.2 |
| 271 | 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-cyclopropyl-1H-pyrrole-2-carboxylic acid (*1)                                                                                                      | 0.987 | 463   |
| 272 | 6-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-benzofuran-3-carboxylic acid (*1)                                                                                                                    | 0.933 | 474.2 |
| 273 | 5-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-isoxazol-3-ol [tautomeric form: 5-(4-{6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl}-2-ethoxyphenyl)isoxazol-3(2H)-one] | 1.051 | 517.4 |
| 274 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-3-fluoro-benzoic acid (*1)                                                                                                                  | 1.032 | 496.1 |

**Example 275:** 3-(5-{6-[2-(5-Bromo-2-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-{6-[2-(5-bromo-2-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol]

Following the general procedure I with 3-(3-ethoxy-5-(6-hydroxypyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol (Example 83-a) and 2-(5-bromo-2-(methylthio)phenyl)ethan-1-amine hydrochloride, the title compound is obtained as a pale yellow powder. LC-MS D:  $t_R$  = 1.25 min;  $[M+H]^+$  = 534.1.

**Example 276:** 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-ethyl)-2-methylamino-benzamide

4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylamino-benzoic acid (Example 231) (51 mg, 0.11 mmol) and ethanolamine (8  $\mu$ L, 0.132 mmol) are dissolved in DMF (2 mL). N-Ethyl-diisopropylamine (57  $\mu$ L, 0.33 mmol) is added, followed by HATU (52 mg, 0.138 mmol) and the RM is stirred at RT for 1h. It is then diluted with water and MeCN, and purified via prep. HPLC, to afford the title compound as a light yellow solid (52 mg, 93%). LC-MS D:  $t_R$  = 0.789 min;  $[M+H]^+$  = 506.0.

**Example 277:** 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-N-(2-methoxy-ethyl)-2-methylamino-benzamide

Following the procedure described for Example 276, using 2-methoxyethylamine, the title compound is obtained as a light yellow powder. LC-MS D:  $t_R$  = 0.878 min;  $[M+H]^+$  = 520.3.

**Example 278:** 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1-ethyl-1H-pyrrol-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1-ethyl-1H-pyrrol-2-yl)-[1,2,4]oxadiazol-5-ol]

Following the procedure described for example 83-b, using 4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-1-ethyl-N'-hydroxy-1H-pyrrole-2-carboximidamide, the title compound is obtained as a white powder. LC-MS D:  $t_R$  = 0.834 min;  $[M+H]^+$  = 491.2.

**a) 4-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-1-ethyl-N'-hydroxy-1H-pyrrole-2-carboximidamide**

Following the procedure described for example 83-c, using 4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-1-ethyl-1H-pyrrole-2-carbonitrile, the title compound is obtained as a grey solid. LC-MS B:  $t_R$  = 0.68 min;  $[M+H]^+$  = 467.42.

**b) 4-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-1-ethyl-1H-pyrrole-2-carbonitrile**

Following the general procedure G, using N-(4-bromo-2,6-difluorophenethyl)-6-iodopyrimidin-4-amine (A.2.6.) and 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-2-carbonitrile, the title compound is obtained as an ochre powder. LC-MS B:  $t_R$  = 0.84 min;  $[M+H]^+$  = 432.37.

**c) 1-Ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-2-carbonitrile**



The title compound is prepared according to the procedure described for A.3.6., starting with 4-bromo-1-ethyl-1H-pyrrole-2-carbonitrile. LC-MS B:  $t_R$  = 0.97 min; no ionization;  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$ : 7.50-7.58 (m, 1 H), 6.99-7.14 (m, 1 H), 3.99-4.19 (m, 2 H), 1.33-1.43 (m, 3 H), 1.21-1.29 (m, 12 H).

**Example 279: 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid amide**

HATU (72.8 mg, 0.191 mmol) is added to a solution of 5-{6-[(4-bromo-2,6-difluorophenethyl)amino]pyrimidin-4-yl}-3-ethoxythiophene-2-carboxylic acid (Example 153, 64 mg, 0.128 mmol) in DMF (3 mL) at RT. The RM is stirred for 30 minutes. Then 25% ammonia solution (0.197 mL, 1.28 mmol) is added, and the RM is stirred at RT overnight. It is then directly purified by prep LC-MS, affording the title compound as a white solid (55 mg, 89%). LC-MS C:  $t_R$  = 1.072 min;  $[\text{M}+\text{H}]^+ = 483.4$ .

**Example 280: N-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoyl)-methanesulfonamide**

A mixture of 4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (Example 180) (36 mg, 0.0727 mmol), methanesulfonamide (9.27 mg, 0.0945 mmol), EDC (25.1 mg, 0.131 mmol) and DMAP (26.6 mg, 0.218 mmol) is dissolved in DCM (0.7 mL) and stirred at RT for 2 days. The RM is concentrated and purified by prep LC-MS to afford the title compound as a white solid (17 mg, 42 %). LC-MS C:  $t_R$  = 1.081 min;  $[\text{M}+\text{H}]^+ = 555.1$ .

**Example 281: 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethyl-thiophene-2-carboxylic acid amide**

Following the procedure described for Example 83-e, using 5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethyl-thiophene-2-carboxylic acid (Example 29) and 25% ammonium hydroxide solution, the title compound is obtained as a white solid. LC-MS C:  $t_R$  = 1.056 min;  $[\text{M}+\text{H}]^+ = 467.2$ .

**Example 282: 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzyl)-[1,2,4]oxadiazol-5-ol]**

Following the procedure described for Example 83-b, using (*E/Z*)-2-(4-{6-[(4-bromo-2,6-difluorophenethyl)amino]pyrimidin-4-yl}-2-ethoxyphenyl)-*N'*-hydroxyacetimidamide, the title compound is obtained as a white solid. LC-MS C:  $t_R$  = 0.928 min;  $[\text{M}+\text{H}]^+ = 532.1$ .

**a) (*E/Z*)-2-(4-{6-[(4-Bromo-2,6-difluorophenethyl)amino]pyrimidin-4-yl}-2-ethoxyphenyl)-*N'*-hydroxyacetimidamide**

Following the procedure described for Example 83-c, using 2-(4-{6-[(4-bromo-2,6-difluorophenethyl)amino]pyrimidin-4-yl}-2-ethoxyphenyl)acetonitrile, the title compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.66 min;  $[\text{M}+\text{H}]^+ = 506.10$ .

**b) 2-(4-{6-[(4-Bromo-2,6-difluorophenethyl)amino]pyrimidin-4-yl}-2-ethoxyphenyl)acetonitrile**

Following the general procedure G, with N-(4-bromo-2,6-difluorophenethyl)-6-iodopyrimidin-4-amine (A.2.6.) and 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetonitrile, the title compound is obtained as a beige powder. LC-MS B:  $t_R$  = 0.88 min;  $[M+H]^+$  = 473.33.

**c) 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetonitrile**

5 The title compound is prepared according to the procedure described for A.3.6., starting with 2-(4-bromo-2-ethoxyphenyl)acetonitrile. LC-MS B:  $t_R$  = 1.05 min;  $[M+H]^+$  = 288.4.

**d) 2-(4-Bromo-2-ethoxyphenyl)acetonitrile**

10 The title compound is prepared according to the procedure described for Example 83-d, starting with 2-(4-bromo-2-ethoxyphenyl)acetamide. LC-MS B:  $t_R$  = 0.97 min; no ionization.  $^1H$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$ : 7.22-7.42 (m, 2 H), 6.96-7.21 (m, 1 H), 4.13 (q,  $J$  = 6.9 Hz, 2 H), 3.78-3.86 (m, 2 H), 1.36 (m, 3 H).

**e) 2-(4-bromo-2-ethoxyphenyl)acetamide**

The title compound is prepared according to the procedure described for Example 83-e, starting with 2-(4-bromo-2-ethoxyphenyl)acetic acid. LC-MS B:  $t_R$  = 0.76 min;  $[M+H]^+$  = 257.85.

15 **Example 283: 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzyl)-[1,2,4]oxadiazole-5(4H)-thione [tautomeric form: 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzyl)-[1,2,4]oxadiazole-5-thiol]**

20 Following the procedure described for Example 83-b, using (*E/Z*)-2-(4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-ethoxyphenyl)-*N'*-hydroxyacetimidamide (Example 282-a) and 1,1'-thiocarbonyldiimidazole, the title compound is obtained as a white solid. LC-MS C:  $t_R$  = 1.007 min;  $[M+H]^+$  = 548.0.

**Example 284: 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzyl)-[1,2,4]oxadiazol-5-ol]**

25 Following the procedure described for Example 83-b, using (*E/Z*)-2-(4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-propylphenyl)-*N'*-hydroxyacetimidamide, the title compound is obtained as a white solid. LC-MS C:  $t_R$  = 0.963 min;  $[M+H]^+$  = 530.2.

**a) (*E/Z*)-2-(4-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-propylphenyl)-*N'*-hydroxyacetimidamide**

30 Following the procedure described for Example 83-c, using 2-(4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-propylphenyl)acetonitrile, the title compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.70 min;  $[M+H]^+$  = 504.16.

**b) 2-(4-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-propylphenyl)acetonitrile**

Following the general procedure G, with N-(4-bromo-2,6-difluorophenethyl)-6-iodopyrimidin-4-amine (A.2.6.) and 2-(2-propyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetonitrile the title compound is obtained as a white powder. LC-MS B:  $t_R$  = 0.91 min;  $[M+H]^+$  = 471.14.

**c) 2-(2-Propyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetonitrile**

- 5 The title compound is prepared according to the procedure described for A.3.6., starting with 2-(4-bromo-2-propylphenyl)acetonitrile. LC-MS B:  $t_R$  = 1.09 min;  $[M+H]^+$  = 327.25.

**Example 285: 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzyl)-[1,2,4]oxadiazole-5(4H)-thione [tautomeric form: 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzyl)-[1,2,4]oxadiazole-5-thiol]**

- 10 Following the procedure described for Example 83-b, using (E/Z)-2-(4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-propylphenyl)-N'-hydroxyacetimidamide (Example 284-a) and 1,1'-thiocarbonyldiimidazole, the title compound is obtained as a white solid. LC-MS C:  $t_R$  = 1.037 min;  $[M+H]^+$  = 546.4.

**Example 286: 2-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetamide**

- 15 A solution of ethyl 2-(4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-ethoxyphenyl)acetate (91 mg, 0.175 mmol) in  $NH_3$  (7M in MeOH, 3 mL) is stirred in a sealed tube over 3 d at 85 °C. The RM is then concentrated under reduced pressure, and purified by FC (Hept to EtOAc 1: to 0:1) to yield the expected product as a white solid (71 mg, 82%). LC-MS C:  $t_R$  = 0.804 min;  $[M+H]^+$  = 491.4.

**a) Ethyl 2-(4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-ethoxyphenyl)acetate**

- 20 Following the general procedure G, with N-(4-bromo-2,6-difluorophenethyl)-6-iodopyrimidin-4-amine (A.2.6.) and ethyl 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (A.3.39.1.), the title compound is obtained as a white powder. LC-MS B:  $t_R$  = 0.92 min;  $[M+H]^+$  = 520.0.

**Example 287: 2-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-acetamide**

- 25 Following the procedure described for Example 276, using (5-{6-[2-(4-bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-acetic acid (Example 17) and ammonia, the title compound is obtained as a white powder. LC-MS C:  $t_R$  = 0.903 min;  $[M+H]^+$  = 461.3.

**Example 288: [2-(4-Bromo-phenyl)-ethyl]-{6-[5-(1H-tetrazol-5-ylmethyl)-thiophen-2-yl]-pyrimidin-4-yl}-amine**

- 30 To a solution of 2-(5-(6-((4-bromophenethyl)amino)pyrimidin-4-yl)thiophen-2-yl)acetonitrile (50 mg, 0.125 mmol) in toluene (1.05 mL), trimethylsilylazide (0.0247 mL, 0.188 mmol) and dibutyltin oxide (3.12 mg, 0.0125 mmol) are added under nitrogen. The RM is stirred at 110 °C overnight in a sealed tube. It is then cooled to RT, diluted with EtOAc and washed twice with HCl 1M and once with brine. The organic layer is dried over  $MgSO_4$ , filtered and concentrated. The residue is purified by prep. LC-MS to afford the expected product as a white solid (22 mg, 39%).  
35 LC-MS C:  $t_R$  = 0.868 min;  $[M+H]^+$  = 442.2.

**a) 2-(5-(6-((4-Bromophenethyl)amino)pyrimidin-4-yl)thiophen-2-yl)acetonitrile**

A mixture of N-(4-bromophenethyl)-6-iodopyrimidin-4-amine (A.2.2., 438 mg, 1.08 mmol), 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acetonitrile (297 mg, 1.19 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (88.6 mg, 0.108 mmol) and potassium phosphate tribasic (749 mg, 3.25 mmol) in water (0.117 mL, 6.51 mmol) and DMF (11.7 mL) is degassed for 15 min under a nitrogen stream, then stirred at RT overnight. ), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (88.6 mg, 0.108 mmol) is added to the RM, which is degassed again and stirred at RT for 4h. It is then diluted with EtOAc and washed with brine. The organic phase is dried over MgSO<sub>4</sub>, filtered and concentrated. The residue is purified by FC (Hept to Hept/EtOAc 1:1) to yield the expected product as a beige solid (192 mg, 44%). LC-MS B: t<sub>R</sub> = 0.82 min; [M+H]<sup>+</sup> = 399.04.

**b) 2-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acetonitrile**

A mixture of 2-thiopheneacetonitrile (199 mg, 1.57 mmol), bis(pinacolato)diboron (244 mg, 0.941 mmol), (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (5.5 mg, 0.0083 mmol) and 4,4'-di-tert-butyl-2,2'-dipyridyl (5.5 mg, 0.0205 mmol) in THF (7.5 mL) is degassed with a nitrogen stream for 15 min and then stirred at 80°C overnight. It is then cooled to RT, concentrated under reduced pressure and the residue is purified by FC (Hept to Hept/EtOAc 9:1) to obtain the expected product as a colourless oil, which crystallizes upon standing (300 mg, 77%). LC-MS B: t<sub>R</sub> = 0.94 min; no ionization. <sup>1</sup>H NMR (500 MHz, d<sub>6</sub>-DMSO) δ: 7.45 (d, J = 3.5 Hz, 1 H), 7.17 (d, J = 3.5 Hz, 1 H), 4.36 (d, J = 0.7 Hz, 2 H), 1.29 (s, 12 H).

**Example 289: 3-(5-(6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl)-pyridin-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(5-(6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl)-pyridin-2-yl)-[1,2,4]oxadiazol-5-ol]**

Following the procedure described for Example 83-b, using (E/Z)-5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N'-hydroxypicolinimidamide, the title compound is obtained as a white solid. LC-MS C: t<sub>R</sub> = 1.037 min; [M+H]<sup>+</sup> = 475.3.

**a) (E/Z)-5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N'-hydroxypicolinimidamide**

Following the procedure described for Example 83-c, using 5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)picolinonitrile, the title compound is obtained as a beige solid. LC-MS B: t<sub>R</sub> = 0.70 min; [M+H]<sup>+</sup> = 450.98.

**5-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)picolinonitrile**

Following the procedure described for the synthesis of Example 288-a, using N-(4-bromo-2,6-difluorophenethyl)-6-iodopyrimidin-4-amine (A.2.6.) and 2-cyano-5-pyridinylboronic acid, the title compound is obtained as a brown solid. LC-MS B: t<sub>R</sub> = 0.90 min; [M+H]<sup>+</sup> = 417.85.

**Example 290:** 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazole-5(4H)-thione [tautomeric form: 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazole-5-thiol]

Following the procedure described for Example 83-b, using (E/Z)-4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-ethoxy-N'-hydroxybenzimidamide and 1,1'-thiocarbonyldiimidazole, the title compound is obtained as a pale yellow solid. LC-MS C:  $t_R$  = 1.145 min;  $[M+H]^+$  = 534.0.

**a) (E/Z)-4-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-ethoxy-N'-hydroxybenzimidamide**

Following the procedure described for Example 83-c, using 4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-ethoxybenzonitrile, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 0.67 min;  $[M+H]^+$  = 491.83.

**b) 4-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-ethoxybenzonitrile**

Following the general procedure G with N-(4-bromo-2,6-difluorophenethyl)-6-iodopyrimidin-4-amine (A.2.6.) and 4-cyano-3-ethoxyphenylboronic acid, the title compound is obtained as a white powder. LC-MS B:  $t_R$  = 0.93 min;  $[M+H]^+$  = 458.83.

**Example 291:** 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methoxy-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methoxy-phenyl)-[1,2,4]oxadiazol-5-ol]

Following the procedure described for Example 83-b, using 4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N-hydroxy-3-methoxybenzimidamide, the title compound is obtained as a white solid. LC-MS C:  $t_R$  = 0.834 min;  $[M+H]^+$  = 504.2.

**a) 4-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N-hydroxy-3-methoxybenzimidamide**

Following the procedure described for Example 83-c, using 4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-methoxybenzonitrile, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 0.66 min;  $[M+H]^+$  = 478.09.

**b) 4-(6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-methoxybenzonitrile**

Following the general procedure G using N-(4-bromo-2,6-difluorophenethyl)-6-iodopyrimidin-4-amine (A.2.6.) and 3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile, the title compound is obtained as a white solid. LC-MS B:  $t_R$  = 0.84 min;  $[M+H]^+$  = 447.3.

**c) 3-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile**

Following the procedure described for the synthesis of A.3.6., using 4-bromo-3-methoxybenzonitrile, the title compound is obtained as a dark purple solid. LC-MS B:  $t_R$  = 0.97 min; no ionization.

**Example 292:** 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methoxy-benzamide

The title compound is isolated as a by-product in the synthesis of 4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N-hydroxy-3-methoxybenzimidamide (Example 291-a), as a white powder. LC-MS C:  $t_R$  = 0.715 min;  $[M+H]^+$  = 463.2.

**Example 293: 5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-chloro-3-ethoxy-thiophene-2-carboxylic acid amide**

Following the procedure described for the synthesis of Example 279, using 5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-chloro-3-ethoxy-thiophene-2-carboxylic acid (Example 27), the title compound is obtained as a white solid. LC-MS C:  $t_R$  = 1.215 min;  $[M+H]^+$  = 517.1.

**Example 294: 1-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-1,4-dihydro-tetrazol-5-one [tautomeric form: 1-(5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophen-2-yl)-1H-tetrazol-5-ol] (\*1)**

N-(4-bromo-2,6-difluorophenethyl)-6-(4-ethoxy-5-isocyanatothiophen-2-yl)pyrimidin-4-amine (78 mg, 0.162 mmol) is suspended in dioxane (2 mL) then azidotrimethylsilane (0.906 mL, 6.48 mmol) is added and the mixture is heated at 90°C for 4h. The RM is concentrated and purified by prep LC-MS, affording the title compound as a yellow solid (5 mg, 6%). LC-MS C:  $t_R$  = 1.141 min;  $[M+H]^+$  = 524.0.

**a) N-(4-bromo-2,6-difluorophenethyl)-6-(4-ethoxy-5-isocyanatothiophen-2-yl)pyrimidin-4-amine**

To a solution of 5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid (Example 153, 130 mg, 0.268 mmol) in THF (10 mL) are added TEA (0.1 mL, 0.718 mmol) and diphenyl phosphoryl azide (0.07 mL, 0.325 mmol). The RM is refluxed at 70°C for 2h, cooled to RT and concentrated to dryness. The residue is purified by FC (Hept:EtOAc 1:0 to 1:1) to afford the expected isocyanate as a white solid (78 mg, 60%). LC-MS E:  $t_R$  = 1.13 min; no ionization.

**Example 295: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazole-5(4H)-thione [tautomeric form: 3-(5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazole-5-thiol]**

Following the procedure described for Example 83-b, using (E/Z)-5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxy-N'-hydroxythiophene-2-carboximidamide and 1,1'-thiocarbonyldiimidazole, the title compound is obtained as a brown solid. LC-MS C:  $t_R$  = 1.296 min;  $[M+H]^+$  = 540.2.

**a) (E/Z)-5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxy-N'-hydroxythiophene-2-carboximidamide**

Following the procedure described for the synthesis of Example 83-c, using 5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophene-2-carbonitrile, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 0.81 min;  $[M+H]^+$  = 497.87.

**b) 5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxythiophene-2-carbonitrile**



Following the procedure described for the synthesis of Example 83-d, using 5-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid amide (Example 279), the title compound is obtained as a light yellow solid. LC-MS B:  $t_R$  = 1.14 min;  $[M+H]^+$  = 467.19.

**Example 296: 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylamino-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylamino-phenyl)-[1,2,4]oxadiazol-5-ol]**

Following the procedure described for Example 83-b, using (E/Z)-4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N'-hydroxy-2-(methylamino)benzimidamide, the title compound is obtained as a yellow solid. LC-MS C:  $t_R$  = 0.963 min;  $[M+H]^+$  = 502.9.

**a) (E/Z)-4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-N'-hydroxy-2-(methylamino)benzimidamide**

Following the procedure described for the synthesis of Example 83-c, using 4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-(methylamino)benzonitrile, the title compound is obtained as a yellow solid. LC-MS B:  $t_R$  = 0.67 min;  $[M+H]^+$  = 477.25.

**b) 4-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-2-(methylamino)benzonitrile**

Following the procedure described for the synthesis of Example 83-d, using 4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylamino-benzamide (Example 216), the title compound is obtained as a light yellow solid. LC-MS B:  $t_R$  = 0.86 min;  $[M+H]^+$  = 444.24.

**Example 297: 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzamide**

To a solution of 4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (Example 180, 0.08 mmol), ammonium chloride (5.7 mg, 0.096 mmol), DIPEA (0.0438 mL, 0.256 mmol) in DMF (0.6 mL) is added a solution of HATU (31.9 mg, 0.084 mmol) in DMF (0.2 mL). The RM is stirred for 3 d at RT, then directly purified by prep LC-MS, affording the title compound as a white solid (20.3 mg, 53%). LC-MS C:  $t_R$  = 0.91 min;  $[M+H]^+$  = 477.4.

Following the procedure described for Example 297, with 4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (Example 180) and the corresponding commercially available amines, the following examples are synthesized:

| Ex. | Compound                                                                                      | $t_R$ [min]<br>(LC-MS C) | MS Data m/z<br>[M+H] <sup>+</sup> |
|-----|-----------------------------------------------------------------------------------------------|--------------------------|-----------------------------------|
| 298 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-N-methyl-benzamide | 0.955                    | 491.3                             |
| 299 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-N-ethyl-benzamide  | 1.031                    | 505.2                             |

|     |                                                                                                                    |       |       |
|-----|--------------------------------------------------------------------------------------------------------------------|-------|-------|
| 300 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-N-(2-hydroxy-ethyl)-benzamide           | 0.869 | 521.4 |
| 301 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-N-(2-methoxy-ethyl)-benzamide           | 1.011 | 535   |
| 302 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-N-(2-hydroxy-2-methyl-propyl)-benzamide | 0.955 | 549.1 |

Following the procedure described for Example 297, with 4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid (Example 36) and the corresponding commercially available amines, the following examples are synthesized:

| Ex. | Compound                                                                                                           | t <sub>R</sub> [min]<br>(LC-MS C) | MS Data m/z<br>[M+H] <sup>+</sup> |
|-----|--------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------|
| 303 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzamide                               | 0.859                             | 475.3                             |
| 304 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-N-methyl-2-propyl-benzamide                      | 0.9                               | 489.3                             |
| 305 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-N-ethyl-2-propyl-benzamide                       | 0.96                              | 503.3                             |
| 306 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-ethyl)-2-propyl-benzamide           | 0.834                             | 519.2                             |
| 307 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-N-(2-methoxy-ethyl)-2-propyl-benzamide           | 0.945                             | 533.1                             |
| 308 | 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-2-methyl-propyl)-2-propyl-benzamide | 0.91                              | 547.3                             |

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By applying either General Procedure G or H to the pyrimidine halide derivatives A.2.1. – A.2.26. coupled with commercially available boronic acid derivatives or with boronic acid derivatives A.3.1. – A.3.66, the following examples are synthesized:

| Ex. | Compound | t <sub>R</sub> [min]<br>(method C) | MS Data m/z<br>[M+H] <sup>+</sup> |
|-----|----------|------------------------------------|-----------------------------------|
|-----|----------|------------------------------------|-----------------------------------|

|     |                                                                                                                      |       |       |
|-----|----------------------------------------------------------------------------------------------------------------------|-------|-------|
| 309 | [2-(4-Bromo-2,6-difluoro-phenyl)-ethyl]-(6-imidazo[1,2-a]pyridin-6-yl-pyrimidin-4-yl)-amine                          | 0.683 | 430.3 |
| 310 | [6-(1H-Benzoimidazol-5-yl)-pyrimidin-4-yl]-[2-(4-bromo-2,6-difluoro-phenyl)-ethyl]-amine                             | 0.653 | 430.2 |
| 311 | 2-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-ethanol                                | 0.738 | 450.2 |
| 312 | 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-1,3-dihydro-indol-2-one                            | 0.718 | 445.2 |
| 313 | (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-carbamic acid methyl ester                | 0.819 | 463.2 |
| 314 | (5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-propyl-thiophen-2-yl)-acetic acid (*1)          | 1.086 | 496.2 |
| 315 | (5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-difluoromethoxy-thiophen-2-yl)-acetic acid (*1) | 1.126 | 520   |

## II. Biological Assays

Compounds of the present invention may be further characterized with regard to their general pharmacokinetic and pharmacological properties using conventional assays well known in the art such as angiogenesis assays or tumor growth inhibition assays, or for example relating to their bioavailability in different species (such as rat or dog); or for their properties with regard to drug safety and/or toxicological properties using conventional assays well known in the art, for example relating to cytochrome P450 enzyme inhibition and time dependent inhibition, pregnane X receptor (PXR) activation, glutathione binding, or phototoxic behavior.

### EMT-6 mouse tumor model

The EMT-6 cell line is established from a transplantable murine mammary carcinoma that arose in a BALB/cCRGL mouse after implantation of a hyperplastic mammary alveolar nodule (Volence FJ, et al, J Surg Oncol. 1980, 13(1):39-44), obtained from ATCC (American Type culture collection, Manassas, Virginia, USA).

EMT-6 tumour cells are grown as monolayer at 37°C in a humidified atmosphere (5% CO<sub>2</sub>, 95% air) in RPMI 1640 containing 2mM L glutamine supplemented with 10% fetal bovine serum. For experimental use, tumour cells are detached from the culture flask with trypsin. The cells are counted in a hemocytometer and their viability is assessed by trypan blue exclusion.

Tumours are induced in female BALB/c mice by either subcutaneous injection of 1x10<sup>6</sup> EMT-6 cells in 200 µL of RPMI 1640 into the right flank or by injection of 2.5x10<sup>5</sup> EMT-6 cells in 50 µL of RPMI1640 into the mammary fat pad tissue. For the latter injection, female BALB/c mice are anaesthetized with Isoflurane and a 5 mm incision is made in the skin over the lateral thorax to expose the mammary fat pad tissue. After tumor cell injection the thoracic

surface is gently dabbed with a 95% ethanol-dampened cotton-swab to kill tumor cells that may leak from the injection site. The skin of mice is closed with 4-0 crinence sutures.

Animals are monitored daily for behavior and survival and twice weekly for body weight and tumor growth. Tumor size is measured with calipers and tumor volume is calculated according to the following formula: Tumor volume = (width<sup>2</sup> x length)/2.

When tumors reach between 60 and 100mm<sup>3</sup> (depending on the experiment), treatment with EP2 and/or EP4 antagonists is started and compound is given daily for at least 3 weeks.

Tumor weight is measured at the end of the study.

#### **in vitro Assays**

The antagonistic activities of the compounds of formula (I) on the EP2 and EP4 receptors are determined in accordance with the following experimental method.

The assay is using the PathHunter<sup>TM</sup> HEK 293 PTGER2 and PTGER4 b-arrestin cell lines from DiscoverX. The system is based on the Enzyme Fragment Complementation Technology. Two complementing fragments of the b-galactosidase enzyme are expressed within stably transfected cells. The larger portion of b-gal, termed EA for Enzyme Acceptor, is fused to the C-terminus of b-arrestin 2. The smaller fragment, termed ProLink<sup>TM</sup> tag, is fused to PTGER2 (EP2) or PTRGER4 (EP4) at the C-terminus. Upon activation, b-arrestin is recruited which forces the interaction of ProLink and EA, allowing complementation of the two fragments of b-gal and the formation of a functional enzyme which is capable of hydrolysing the substrate and generating a chemiluminescent signal.

#### **hEP2 b-arrestin assay:**

The HEK 293 PTGER2 b-arrestin cells (DiscoverX 93-021-4C1) are detached from culture dishes with a cell dissociation buffer (Invitrogen, 13151-014), and collected in growing medium (GM: DMEM + Glutamax-I (Invitrogen 32430) /10% FCS, 1 % Penicilin/streptomycin). 5000 cells per well of a 384 well plate (white with white bottom Greiner 781080 ) are seeded in 20ul per well of GM. Plate is incubated at 37°C, 5% CO2 for 24 hours.

Stock solutions of test compounds are made at a concentration of 10 mM in DMSO, and serially diluted in DMSO to concentrations required for inhibition dose response curves (tested concentration range 10μM-2nM or 1μM-0.2nM).

PGE2 (Cayman 14010, stock solution: 10mM in DMSO) is used as agonist at 5μM final concentration, corresponding to EC80.

Five microliters of diluted compounds are transferred into the assay plate. Plate is pre-incubated 15 minutes at 37°C. Then five microliters of PGE2 (final conc. 5μM) are transferred into the assay plate. Plate is incubated 120 minutes at 37°C.

PathHunter Glo Detection Kit components are thawed and mix according to manufacturer's instructions : 1 part Galacton Star Substrate with 5 parts Emerald IITM Solution, and 19 parts of PathHunter Cell Assay Buffer,

respectively. Twelve  $\mu$ l of reagent are transferred to the assay plate and incubate for 1 hour at room temperature in the dark. Luminescence counts are read on a BMG Fluostar Optima reader according to manufacturer's instructions.

For each compound concentration calculate of the percentage of activity compared to DMSO control value as average  $\pm$  STDEV. (each concentration is measured in duplicate)

IC<sub>50</sub> values and curves are generated with XLfit software (IDBS) using Dose-Response One Site model 203. When compounds were measured multiple times, mean values are given.

#### **hEP4 b-arrestin assay:**

The HEK 293 PTGER4 b-arrestin cells (DiscoverX 93-030-4C1) are detached from culture dishes with a cell dissociation buffer (Invitrogen, 13151-014), and collected in growing medium (GM: DMEM + Glutamax-I (Invitrogen 32430) /10% FCS, 1 % Penicilin/streptomycin). 5000 cells per well of a 384 well plate (white with white bottom Greiner 781080 ) are seeded in 20ul per well of GM. Plate is incubated at 37°C, 5% CO<sub>2</sub> for 24 hours.

Stock solutions of test compounds are made at a concentration of 10 mM in DMSO, and serially diluted in DMSO to concentrations required for inhibition dose response curves (tested concentration range 10 $\mu$ M-2nM or 1 $\mu$ M-0.2nM).

PGE<sub>2</sub> (Cayman 14010, stock solution: 100uM in DMSO) is used as agonist at 20nM final concentration, corresponding to EC<sub>80</sub>.

Five microliters of diluted compounds are transferred into the assay plate. Plate is pre-incubated 15 minutes at 37°C. Then five microliters of PGE<sub>2</sub> (final conc. 20nM) are transferred into the assay plate. Plate is incubated 120 minutes at 37°C.

PathHunter Glo Detection Kit components are thawed and mix according to manufacturer's instructions : 1 part Galacton Star Substrate with 5 parts Emerald IITM Solution, and 19 parts of PathHunter Cell Assay Buffer, respectively. Twelve  $\mu$ l of reagent are transferred to the assay plate and incubate for 1 hour at room temperature in the dark. Luminescence counts are read on a BMG Fluostar Optima reader according to manufacturer's instructions.

For each compound concentration calculate of the percentage of activity compared to DMSO control value as average  $\pm$  STDEV. (each concentration is measured in duplicate)

IC<sub>50</sub> values and curves are generated with XLfit software (IDBS) using Dose-Response One Site model 203. When compounds were measured multiple times, mean values are given.

The antagonistic activities of the compounds of formula (I) on the EP<sub>2</sub> and EP<sub>4</sub> receptors are also determined in accordance with the following experimental method.

Human tumor cell lines expressing endogenously either EP4 or EP2 are used and cAMP accumulation in cells upon PGE<sub>2</sub> stimulation is monitored. SF295 glioblastoma cells express high endogenous EP2 and no EP4, whereas BT549 breast cancer cells, express high endogenous EP4 levels and very low EP2 levels.

As a detection method for cAMP the HTRF (homogeneous time resolved fluorescence) Cisbio kit (HTRF cAMP dynamic 2 kit 20'000 tests Cisbio Cat. #62AM4PEC) was used, which is based on a competitive immunoassay using a Cryptate-labeled anti-cAMP antibody and d2-labeled cAMP. Native cAMP produced by cells or unlabeled cAMP (for the standard curve) compete with exogenously added d2-labeled cAMP (acceptor) for binding to monoclonal anti-cAMP-Eu3+ Cryptate (donor). A FRET signal (Fluorescence Resonance Energy Transfer) is obtained only if the labeled anti-cAMP antibody binds the d2 labelled cAMP, thus the specific signal (i.e. energy transfer) is inversely proportional to the concentration of cAMP in the standard or sample.

**hEP2 cAMP assay:**

The SF295 cells (NCI/No. 0503170) are detached from culture dishes with a cell dissociation buffer (Invitrogen, 13151-014), and collected in growing medium (GM: RPMI1640 (Invitrogen 21875) /10% FCS, 1 % Penicilin/streptomycin). Cells are counted washed and resuspended in assay buffer (AB; HBSS, 20mM HEPES, 0.2% BSA; 2mM IBMX ). 4'000 cells in 5µl of AB are seeded per well of a small volume 384 well plate (black with flat bottom, Greiner 784076).

Stock solutions of test compounds are made at a concentration of 10 mM in DMSO, and serially diluted in DMSO to concentrations required for inhibition dose response curves (tested concentration range 30µM - 0.4nM; 30µM - 0.015nM or 1µM - 0.01nM).

PGE<sub>2</sub> (Cayman 14010, stock solution: 75µM in DMSO) is used as agonist at 75nM final concentration, corresponding to EC80.

Two point five microliters of diluted compounds are transferred into the assay plate. Plate is pre-incubated 45 minutes at room temperature. Subsequently, 2.5 microliters of PGE<sub>2</sub> (final conc. 75nM) are transferred into the assay plate. Plate is incubated 30 minutes at room temperature. Five µl of each donor (anti-cAMP cryptate) and acceptor (cAMP-d2) are added and the plate is incubated another hour at room temperature in the dark and then read using a BMG LABTECH PHERAstar reader (Excitation : 337nm, Emission : 620 and 665nm).

The obtained Delta F (fluorescence) values (665nm/620nm) are converted into % cAMP values using the measurements of the cAMP calibrator provided in the kit. For each compound concentration the percentage of cAMP compared to DMSO control value as average ± STDEV (each concentration is measured in duplicate) is calculated.

IC<sub>50</sub> values and curves are generated with XLfit software (IDBS) using Dose-Response One Site model 203. When compounds were measured multiple times, mean values are given.

**hEP4 cAMP assay:**



The BT549 cells (NCI/No. 0507282) are detached from culture dishes with a cell dissociation buffer (Invitrogen, 13151-014), and collected in growing medium (GM: RPMI1640 (Invitrogen 21875) /10% FCS, 1 % Penicilin/streptomycin). Cells are counted washed and resuspended in assay buffer (AB; HBSS, 20mM HEPES, 0.2% BSA; 2mM IBMX ). 4'000 cells in 5µl of AB are seeded per well of a small volume 384 well plate (black with flat bottom, Greiner 784076).

Stock solutions of test compounds are made at a concentration of 10 mM in DMSO, and serially diluted in DMSO to concentrations required for inhibition dose response curves (tested concentration range 30µM - 0.4nM; 30µM - 0.015nM or 1µM - 0.01nM).

PGE<sub>2</sub> (Cayman 14010, stock solution: 6µM in DMSO) is used as agonist at 6nM final concentration, corresponding to EC80.

Two point five microliters of diluted compounds are transferred into the assay plate. Plate is pre-incubated 45 minutes at room temperature. Subsequently, 2.5 microliters of PGE<sub>2</sub> (final conc. 6nM) are transferred into the assay plate. Plate is incubated 30 minutes at room temperature. Five µl of each donor (anti-cAMP cryptate) and acceptor (cAMP-d2) are added and the plate is incubated another hour at room temperature in the dark and then read using a BMG LABTECH PHERAstar reader (Excitation : 337nm, Emission : 620 and 665nm).

The obtained Delta F (fluorescence) values (665nm/620nm) are converted into % cAMP values using the measurements of the cAMP calibrator provided in the kit. For each compound concentration the percentage of cAMP compared to DMSO control value as average  $\pm$  STDEV (each concentration is measured in duplicate) is calculated.

IC<sub>50</sub> values and curves are generated with XLfit software (IDBS) using Dose-Response One Site model 203. When compounds were measured multiple times, mean values are given.

Antagonistic activities (IC<sub>50</sub> in nM) in the beta-arrestin and cAMP assays of exemplified compounds are displayed in Table 9:

Table 9:

| Ex. | hEP4<br>b-arr IC <sub>50</sub> | hEP2<br>b-arr IC <sub>50</sub> | hEP2<br>cAMP<br>IC <sub>50</sub> | hEP4<br>cAMP<br>IC <sub>50</sub> | Ex. | hEP4<br>b-arr IC <sub>50</sub> | hEP2<br>b-arr IC <sub>50</sub> | hEP2<br>cAMP<br>IC <sub>50</sub> | hEP4<br>cAMP<br>IC <sub>50</sub> |
|-----|--------------------------------|--------------------------------|----------------------------------|----------------------------------|-----|--------------------------------|--------------------------------|----------------------------------|----------------------------------|
| 1   | 402                            | 240                            | 86                               | 65                               | 159 |                                |                                | 392                              | 602                              |
| 2   | 550                            | 438                            | 79                               | 112                              | 160 | 134                            |                                | 318                              | 256                              |
| 3   | 420                            | 86                             | 45                               | 46                               | 161 | 10                             |                                | 713                              | 40                               |
| 4   |                                |                                | 38                               | 5                                | 162 | 2                              | 20                             | 46                               | 5                                |
| 5   |                                |                                | 45                               | 6                                | 163 | 3250                           | 234                            | 636                              | 792                              |

|    |      |      |     |      |     |     |     |      |      |
|----|------|------|-----|------|-----|-----|-----|------|------|
| 6  | 1210 | 1350 | 702 | 573  | 164 | 102 | 37  | 77   | 39   |
| 7  | 759  | 441  | 205 | 140  | 165 | 582 | 62  | 163  | 480  |
| 8  |      |      | 340 | 262  | 166 | 326 | 154 |      |      |
| 9  |      |      | 642 | 1080 | 167 | 431 | 42  | 198  | 1080 |
| 10 |      |      | 931 | 798  | 168 | 196 | 190 | 1690 | 2000 |
| 11 | 1090 | 358  | 311 | 440  | 169 | 457 | 21  | 74   | 1380 |
| 12 |      |      | 885 | 617  | 170 | 746 | 424 |      |      |
| 13 |      |      | 294 | 636  | 171 | 582 | 680 |      |      |
| 14 |      |      | 257 | 262  | 172 | 401 | 440 |      |      |
| 15 | 56   | 368  | 198 | 42   | 173 | 519 | 107 |      |      |
| 16 |      |      | 795 | 914  | 174 | 108 | 36  | 265  | 94   |
| 17 | 147  | 202  | 189 | 293  | 175 | 461 | 258 |      |      |
| 18 | 168  | 481  | 130 | 173  | 176 | 75  | 22  | 9    | 6    |
| 19 | 705  | 7990 | 649 | 712  | 177 | 343 | 126 |      |      |
| 20 | 446  |      | 498 | 574  | 178 | 404 | 29  | 10   | 134  |
| 21 | 779  | 248  | 193 | 80   | 179 | 315 | 140 |      |      |
| 22 | 187  |      | 759 | 68   | 180 | 674 | 119 | 52   | 221  |
| 23 | 60   | 73   | 28  | 61   | 181 | 96  | 165 | 92   | 34   |
| 24 | 45   | 35   | 93  | 110  | 182 | 208 | 163 |      |      |
| 25 | 2070 | 203  | 71  | 454  | 183 | 661 | 695 |      |      |
| 26 | 104  | 149  | 46  | 115  | 184 | 140 | 127 | 630  | 250  |
| 27 | 168  | 23   | 50  | 97   | 185 | 8   | 51  | 41   | 6    |
| 28 | 80   | 49   | 41  | 41   | 186 | 238 | 945 |      |      |
| 29 | 20   | 29   | 23  | 12   | 187 | 216 | 130 | 260  | 200  |
| 30 | 46   | 239  | 132 | 213  | 188 | 117 | 179 |      |      |
| 31 | 100  | 39   | 8   | 14   | 189 | 338 | 295 |      |      |
| 32 |      |      | 55  | 30   | 190 | 181 | 486 |      |      |

|    |      |     |      |     |     |     |     |     |     |
|----|------|-----|------|-----|-----|-----|-----|-----|-----|
| 33 | 156  |     | 1130 | 149 | 191 | 145 | 322 |     |     |
| 34 | 261  |     | 437  | 676 | 192 | 193 | 380 |     |     |
| 35 | 242  | 109 | 86   | 433 | 193 | 159 | 797 |     |     |
| 36 | 684  | 70  | 91   | 951 | 194 | 207 | 548 |     |     |
| 37 | 215  | 43  | 30   | 185 | 195 | 269 | 837 |     |     |
| 38 | 202  | 277 | 128  | 81  | 196 | 113 | 235 | 400 | 107 |
| 39 | 349  | 122 | 164  | 697 | 197 | 163 | 539 |     |     |
| 40 | 333  | 84  | 25   | 298 | 198 | 4   | 329 |     |     |
| 41 | 342  | 92  | 20   | 107 | 199 | 283 | 163 |     |     |
| 42 | 241  | 59  | 50   | 297 | 200 | 526 | 114 |     |     |
| 43 | 208  | 55  | 66   | 514 | 201 | 482 | 140 |     |     |
| 44 | 62   | 44  | 120  | 38  | 202 | 365 | 597 |     |     |
| 45 | 50   | 81  | 184  | 165 | 203 | 92  | 81  | 27  | 11  |
| 46 | 148  | 105 | 303  | 470 | 204 | 699 | 433 |     |     |
| 47 | 11   | 50  | 129  | 85  | 205 | 681 | 966 |     |     |
| 48 | 25   | 28  | 46   | 51  | 206 | 372 | 315 |     |     |
| 49 | 143  | 139 | 246  | 159 | 207 | 491 | 721 |     |     |
| 50 | 1310 | 264 | 259  | 910 | 208 | 18  | 207 |     |     |
| 51 |      | 39  | 72   | 684 | 209 | 156 | 557 |     |     |
| 52 |      |     | 343  | 626 | 210 | 20  | 294 | 615 | 21  |
| 53 | 472  | 437 | 63   | 221 | 211 | 126 | 106 | 148 | 170 |
| 54 | 17   | 60  | 31   | 10  | 212 | 50  | 26  | 62  | 93  |
| 55 | 1000 | 89  | 65   | 396 | 213 | 217 | 71  | 184 | 300 |
| 56 | 3030 | 717 | 512  | 775 | 214 | 62  | 184 |     |     |
| 57 | 1160 |     | 295  | 166 | 215 | 3   | 10  | 12  | 8   |
| 58 | 11   | 454 | 127  | 20  | 216 | 17  | 21  | 23  | 67  |
| 59 | 169  | 359 | 131  | 51  | 217 | 29  | 20  | 134 | 79  |

|    |      |     |     |     |     |     |     |      |     |
|----|------|-----|-----|-----|-----|-----|-----|------|-----|
| 60 | 139  |     | 376 | 81  | 218 | 917 | 690 |      |     |
| 61 | 363  |     | 715 | 161 | 219 | 96  | 302 | 332  | 42  |
| 62 | 108  | 324 | 176 | 79  | 220 | 839 | 401 |      |     |
| 63 | 233  |     | 644 | 105 | 221 | 268 | 92  |      |     |
| 64 | 205  | 316 | 244 | 38  | 222 | 286 | 231 |      |     |
| 65 | 136  | 111 | 102 | 53  | 223 | 232 | 367 |      |     |
| 66 | 133  | 16  | 27  | 53  | 224 | 23  | 37  |      |     |
| 67 | 261  |     | 712 | 245 | 225 | 97  | 277 |      |     |
| 68 | 33   | 145 | 165 | 25  | 226 | 273 | 907 |      |     |
| 69 | 915  |     | 382 | 170 | 227 | 5   | 81  | 120  | 8   |
| 70 |      | 260 | 139 | 554 | 228 | 777 | 502 |      |     |
| 71 | 100  | 85  | 70  | 53  | 229 | 273 | 81  |      |     |
| 72 | 104  | 77  | 40  | 42  | 230 | 152 | 662 |      |     |
| 73 | 136  | 54  | 30  | 35  | 231 | 94  | 16  | 13   | 43  |
| 74 | 90   |     | 533 | 33  | 232 | 325 | 711 |      |     |
| 75 | 2180 | 727 | 568 | 918 | 233 | 398 | 222 |      |     |
| 76 | 310  | 488 | 234 | 88  | 234 | 49  | 77  | 93   | 23  |
| 77 | 121  |     | 415 | 108 | 235 | 89  | 43  | 203  | 149 |
| 78 |      | 176 | 149 | 458 | 236 | 351 | 265 |      |     |
| 79 | 203  |     | 408 | 106 | 237 | 419 | 72  | 128  | 668 |
| 80 |      |     | 255 | 366 | 238 | 438 | 251 |      |     |
| 81 | 554  |     | 318 | 125 | 239 | 387 | 300 |      |     |
| 82 | 103  | 74  | 66  | 46  | 240 | 72  | 127 | 511  | 405 |
| 83 | 14   |     | 208 | 13  | 241 | 431 | 215 | 574  | 506 |
| 84 | 116  |     | 358 | 166 | 242 | 231 | 145 | 526  | 223 |
| 85 | 6    | 8   | 7   | 12  | 243 | 61  | 41  |      |     |
| 86 | 30   | 16  | 84  | 89  | 244 | 251 | 364 | 1130 | 280 |

|     |     |     |      |     |     |     |     |      |      |
|-----|-----|-----|------|-----|-----|-----|-----|------|------|
| 87  | 5   | 11  | 28   | 17  | 245 | 307 | 392 | 4630 | 6720 |
| 88  | 2   | 9   | 31   | 6   | 246 | 277 | 479 |      |      |
| 89  | 3   | 17  | 10   | 58  | 247 | 278 | 799 |      |      |
| 90  | 3   | 26  | 24   | 10  | 248 | 311 | 226 | 635  | 299  |
| 91  | 42  |     | 2840 | 335 | 249 | 467 | 110 |      |      |
| 92  | 4   | 48  | 68   | 4   | 250 | 169 | 78  | 856  | 887  |
| 93  | 3   |     | 509  | 6   | 251 | 831 | 254 |      |      |
| 94  | 90  | 79  | 82   | 93  | 252 | 484 | 214 | 1910 | 959  |
| 95  | 59  | 30  | 15   | 166 | 253 | 170 | 191 |      |      |
| 96  | 43  | 24  | 58   | 106 | 254 | 880 | 753 |      |      |
| 97  | 95  | 131 | 144  | 127 | 255 | 283 | 344 |      |      |
| 98  | 14  | 53  | 83   | 50  | 256 | 584 | 574 |      |      |
| 99  | 45  | 75  | 80   | 69  | 257 | 239 | 212 |      |      |
| 100 | 27  | 17  | 50   | 59  | 258 | 174 | 77  |      |      |
| 101 | 103 | 44  | 62   | 82  | 259 | 351 | 46  | 45   | 76   |
| 102 | 91  | 34  | 17   | 122 | 260 | 755 | 204 |      |      |
| 103 | 36  | 62  | 39   | 39  | 261 | 42  | 58  | 165  | 101  |
| 104 | 101 |     | 956  | 399 | 262 | 149 | 88  |      |      |
| 105 | 9   | 11  | 40   | 25  | 263 | 73  | 31  | 167  | 73   |
| 106 | 1   | 35  | 49   | 10  | 264 | 465 | 372 |      |      |
| 107 | 2   | 10  | 11   | 7   | 265 | 452 | 242 |      |      |
| 108 | 5   | 28  | 113  | 15  | 266 | 368 | 65  |      |      |
| 109 |     |     | 558  | 254 | 267 | 183 | 70  |      |      |
| 110 | 2   | 6   | 9    | 3   | 268 | 294 | 19  | 21   | 225  |
| 111 | 6   | 31  | 137  | 26  | 269 | 768 | 258 |      |      |
| 112 | 80  |     | 892  | 192 | 270 | 700 | 316 |      |      |
| 113 | 3   | 47  | 113  | 29  | 271 | 380 | 36  | 151  | 1760 |

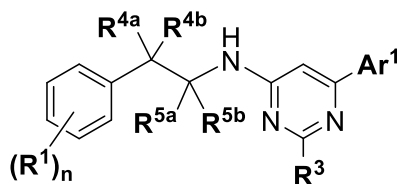
|            |     |     |     |     |            |      |     |      |      |
|------------|-----|-----|-----|-----|------------|------|-----|------|------|
| <b>114</b> | 3   | 15  | 27  | 8   | <b>272</b> | 426  | 174 |      |      |
| <b>115</b> | 16  | 44  | 51  | 12  | <b>273</b> | 56   | 45  | 364  | 211  |
| <b>116</b> | 5   | 10  | 14  | 8   | <b>274</b> | 646  | 160 |      |      |
| <b>117</b> | 16  | 692 | 244 | 26  | <b>275</b> | 90   | 125 | 163  | 18   |
| <b>118</b> | 316 | 488 | 266 | 148 | <b>276</b> | 37   | 23  | 59   | 72   |
| <b>119</b> | 5   | 10  | 17  | 11  | <b>277</b> | 68   | 74  | 221  | 241  |
| <b>120</b> | 21  | 35  | 13  | 69  | <b>278</b> | 42   | 64  | 150  | 89   |
| <b>121</b> | 9   | 66  | 60  | 42  | <b>279</b> | 5    | 46  | 72   | 12   |
| <b>122</b> | 8   |     | 906 | 19  | <b>280</b> | 289  | 20  | 48   | 257  |
| <b>123</b> | 27  | 29  | 32  | 19  | <b>281</b> | 37   | 56  | 47   | 81   |
| <b>124</b> |     |     | 46  | 36  | <b>282</b> | 83   | 135 | 1030 | 380  |
| <b>125</b> | 3   | 11  | 49  | 5   | <b>283</b> | 245  | 118 | 959  | 595  |
| <b>126</b> | 7   | 22  | 74  | 20  | <b>284</b> | 199  | 295 |      |      |
| <b>127</b> | 14  | 29  | 129 | 47  | <b>285</b> | 272  | 163 |      |      |
| <b>128</b> | 34  |     | 629 | 235 | <b>286</b> | 287  | 217 |      |      |
| <b>129</b> | 45  |     | 372 | 247 | <b>287</b> | 315  |     | 868  | 1210 |
| <b>130</b> | 4   | 22  | 63  | 24  | <b>288</b> | 1190 |     | 739  | 775  |
| <b>131</b> | 3   | 18  | 54  | 11  | <b>289</b> | 308  | 80  | 234  | 320  |
| <b>132</b> | 6   |     | 594 | 60  | <b>290</b> | 28   | 48  |      |      |
| <b>133</b> | 13  | 13  | 92  | 44  | <b>291</b> | 77   | 88  | 774  | 154  |
| <b>134</b> | 98  |     | 284 | 718 | <b>292</b> | 893  | 100 |      |      |
| <b>135</b> | 8   | 26  | 15  | 34  | <b>293</b> | 41   | 138 | 900  | 326  |
| <b>136</b> | 6   | 18  | 17  | 18  | <b>294</b> | 18   | 27  | 47   | 22   |
| <b>137</b> | 411 |     | 371 | 963 | <b>295</b> | 2    | 12  | 84   | 2    |
| <b>138</b> | 130 | 34  | 123 | 247 | <b>296</b> | 9    | 12  | 44   | 14   |
| <b>139</b> | 6   |     | 290 | 149 | <b>297</b> | 236  | 21  |      |      |
| <b>140</b> | 12  |     | 345 | 218 | <b>298</b> | 301  | 128 |      |      |



|            |      |     |      |     |            |     |     |     |    |
|------------|------|-----|------|-----|------------|-----|-----|-----|----|
| <b>141</b> | 8    |     | 381  | 168 | <b>299</b> | 255 | 145 |     |    |
| <b>142</b> |      |     | 700  | 571 | <b>300</b> | 230 | 155 |     |    |
| <b>143</b> |      |     | 604  | 344 | <b>301</b> | 640 | 118 |     |    |
| <b>144</b> | 126  |     | 1000 | 433 | <b>302</b> | 565 | 121 |     |    |
| <b>145</b> |      |     | 1120 | 690 | <b>303</b> | 163 | 44  |     |    |
| <b>146</b> | 14   | 39  | 249  | 189 | <b>304</b> | 339 | 126 |     |    |
| <b>147</b> |      |     | 490  | 834 | <b>305</b> | 628 | 203 |     |    |
| <b>148</b> | 9    | 20  | 19   | 8   | <b>306</b> | 403 | 97  |     |    |
| <b>149</b> | 43   | 199 | 67   | 73  | <b>307</b> | 781 | 219 |     |    |
| <b>150</b> | 2    | 13  | 15   | 9   | <b>308</b> | 164 | 156 |     |    |
| <b>151</b> | 3    | 69  | 43   | 29  | <b>309</b> | 875 | 352 |     |    |
| <b>152</b> | 5    | 12  | 9    | 30  | <b>310</b> | 302 | 400 |     |    |
| <b>153</b> | 21   | 5   | 7    | 4   | <b>311</b> | 776 | 216 |     |    |
| <b>154</b> | 33   | 13  | 8    | 66  | <b>312</b> | 703 | 175 |     |    |
| <b>155</b> | 35   | 12  | 20   | 62  | <b>313</b> | 333 | 143 |     |    |
| <b>156</b> | 31   | 9   | 28   | 16  | <b>314</b> | 61  | 55  | 169 | 27 |
| <b>157</b> | 57   | 64  | 99   | 34  | <b>315</b> | 38  | 25  | 17  | 28 |
| <b>158</b> | 2270 |     | 643  | 913 |            |     |     |     |    |

## CLAIMS

1. Use of a compound of formula (I)



Formula (I)

5 in the manufacture of a medicament for the treatment of a cancer, wherein said cancer is treated by modulating an immune response comprising a reactivation of the immune system in the tumor;

wherein said medicament is to be optionally used in combination with one or more chemotherapy agents and / or radiotherapy and / or targeted therapy;

wherein in compounds of the formula (I)

10  $(R^1)_n$  represents one, two or three optional substituents on the phenyl ring, wherein said substituents are independently selected from  $(C_{1-3})$ alkyl,  $(C_{1-3})$ alkoxy,  $-S-(C_{1-3})$ alkyl, halogen,  $(C_{1-3})$ fluoroalkyl,  $(C_{1-3})$ fluoroalkoxy, cyano, hydroxy, nitro,  $-CO-O-(C_{1-3})$ alkyl,  $-NR^{N7}R^{N8}$  wherein  $R^{N7}$  and  $R^{N8}$  independently represent hydrogen or  $(C_{1-4})$ alkyl, or  $R^{N7}$  and  $R^{N8}$  together with the nitrogen to which they are attached form a 4- to 6-membered carbocyclic ring;

15  $R^3$  represents hydrogen, methyl or trifluoromethyl;

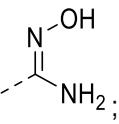
$R^{4a}$  and  $R^{4b}$  independently represent hydrogen, methyl, or  $R^{4a}$  and  $R^{4b}$  together with the carbon atom to which they are attached represent a cycloprop-1,1-diyl group;

$R^{5a}$  and  $R^{5b}$  independently represent hydrogen, methyl, or  $R^{5a}$  and  $R^{5b}$  together with the carbon atom to which they are attached represent a cycloprop-1,1-diyl group;

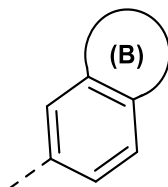
20  $Ar^1$  represents

- phenyl, or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl independently is mono-, di- or tri-substituted, wherein the substituents are independently selected from

- $(C_{1-6})$ alkyl;
- $(C_{1-4})$ alkoxy;
- 25 ▪  $(C_{1-3})$ fluoroalkyl, wherein said  $(C_{1-3})$ fluoroalkyl is optionally substituted with hydroxy;
- $(C_{1-3})$ fluoroalkoxy;
- halogen;
- cyano;
- $(C_{3-6})$ cycloalkyl, wherein said  $(C_{3-6})$ cycloalkyl is unsubstituted or mono-substituted with amino;

- (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom, wherein said (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy;
- (C<sub>3-6</sub>)cycloalkyl-oxy;
- hydroxy;
- 5   ▪ -X<sup>1</sup>-CO-R<sup>01</sup>, wherein
  - X<sup>1</sup> represents a direct bond, (C<sub>1-3</sub>)alkylene, -O-(C<sub>1-3</sub>)alkylene-\*, -NH-(C<sub>1-3</sub>)alkylene-\*, -S-CH<sub>2</sub>\*, -CF<sub>2</sub>-, -CH=CH-, -C≡C-, -NH-CO-\*, -CO-, or (C<sub>3-5</sub>)cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-R<sup>01</sup> group; and
  - R<sup>01</sup> represents
    - 10       • -OH;
    - -O-(C<sub>1-4</sub>)alkyl;
    - -NH-SO<sub>2</sub>-R<sup>S3</sup> wherein R<sup>S3</sup> represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;
    - 15       • -O-CH<sub>2</sub>-CO-R<sup>04</sup>, wherein R<sup>04</sup> represents hydroxy, or (C<sub>1-4</sub>)alkoxy, or -N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>;
    - -O-CH<sub>2</sub>-O-CO-R<sup>05</sup>, wherein R<sup>05</sup> represents (C<sub>1-4</sub>)alkyl or (C<sub>1-4</sub>)alkoxy;
    - -O-CH<sub>2</sub>-CH<sub>2</sub>-N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>; or
    - 20       • (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methoxy-;
- -CO-CH<sub>2</sub>-OH;
- ;
  - 2-hydroxy-3,4-dioxo-cyclobut-1-enyl;
  - hydroxy-(C<sub>1-4</sub>)alkyl;
  - 25   ▪ dihydroxy-(C<sub>2-4</sub>)alkyl;
  - hydroxy-(C<sub>2-4</sub>)alkoxy;
  - (C<sub>1-4</sub>)alkoxy-(C<sub>2-4</sub>)alkoxy;
  - -(CH<sub>2</sub>)<sub>r</sub>-CO-NR<sup>N3</sup>R<sup>N4</sup> wherein r represents the integer 0 or 1; and wherein R<sup>N3</sup> and R<sup>N4</sup> independently represent hydrogen, (C<sub>1-4</sub>)alkyl, hydroxy-(C<sub>2-4</sub>)alkyl, (C<sub>1-3</sub>)alkoxy-(C<sub>2-4</sub>)alkyl, or hydroxy;
  - 30   ▪ -X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup>, wherein X<sup>2</sup> represents -(CH<sub>2</sub>)<sub>m</sub>-, wherein m represents the integer 0 or 1; or X<sup>2</sup> represents -O-CH<sub>2</sub>-CH<sub>2</sub>\*, wherein the asterisk indicates the bond that is linked to the -NR<sup>N1</sup>R<sup>N2</sup> group; and wherein

- 5
- **R<sup>N1</sup>** and **R<sup>N2</sup>** independently represent hydrogen, (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkoxy-(C<sub>2-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl, or (C<sub>2-3</sub>)fluoroalkyl;
  - or **R<sup>N1</sup>** independently represents hydrogen or (C<sub>1-4</sub>)alkyl, and **R<sup>N2</sup>** independently represents -CO-H, -CO-(C<sub>1-3</sub>)alkyl, -CO-(C<sub>1-3</sub>)alkylene-OH, or -CO-O-(C<sub>1-3</sub>)alkyl;
  - or **R<sup>N1</sup>** and **R<sup>N2</sup>** together with the nitrogen to which they are attached form a 4-, 5- or 6-membered saturated ring optionally containing one ring oxygen or ring sulfur atom, wherein said ring is unsubstituted, or mono-substituted with oxo on a ring carbon atom, or disubstituted with oxo on a ring sulfur atom;
    - -NH-CO-NR<sup>N5</sup>R<sup>N6</sup> wherein **R<sup>N5</sup>** and **R<sup>N6</sup>** independently represent hydrogen or (C<sub>1-4</sub>)alkyl;
    - 10   ▪ -SO<sub>2</sub>-R<sup>S1</sup> wherein **R<sup>S1</sup>** represents hydroxy, (C<sub>1-4</sub>)alkyl, or -NR<sup>N7</sup>R<sup>N8</sup> wherein **R<sup>N7</sup>** and **R<sup>N8</sup>** independently represent hydrogen or (C<sub>1-3</sub>)alkyl;
    - -S-R<sup>S2</sup> wherein **R<sup>S2</sup>** represents (C<sub>1-4</sub>)alkyl, or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom;
    - -(CH<sub>2</sub>)<sub>q</sub>-HET<sup>1</sup>, wherein **q** represents the integer 0, 1 or 2; and wherein **HET<sup>1</sup>** represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl, or 5-thioxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl;
    - 15   ▪ -(CH<sub>2</sub>)<sub>p</sub>-HET, wherein **p** represents the integer 0 or 1; and wherein **HET** represents a 5- or 6-membered heteroaryl, wherein said 5- or 6-membered heteroaryl is unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected from (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkoxy, -COOH, hydroxy, hydroxy-(C<sub>1-3</sub>)alkyl, (C<sub>3-5</sub>)cycloalkyl optionally containing one ring oxygen atom, or -NR<sup>N9</sup>R<sup>N10</sup> wherein **R<sup>N9</sup>** and **R<sup>N10</sup>** independently represent hydrogen, (C<sub>1-3</sub>)alkyl, or hydroxy-(C<sub>2-4</sub>)alkyl;
    - 20   • or **Ar<sup>1</sup>** represents 8- to 10-membered bicyclic heteroaryl; wherein said 8- to 10-membered bicyclic heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C<sub>1-4</sub>)alkyl; (C<sub>1-4</sub>)alkoxy; (C<sub>1-3</sub>)fluoroalkyl; (C<sub>1-3</sub>)fluoroalkoxy; halogen; cyano; hydroxy, or -(C<sub>0-3</sub>)alkylene-COOR<sup>O2</sup> wherein **R<sup>O2</sup>** represents hydrogen or (C<sub>1-4</sub>)alkyl;
    - 25   • or **Ar<sup>1</sup>** represents a group of the structure (Ar-III):

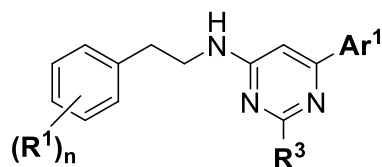


(Ar-III)

- 30   wherein ring (B) represents a non-aromatic 5- or 6-membered ring fused to the phenyl group, wherein ring (B) comprises one or two heteroatoms independently selected from nitrogen and oxygen; wherein said ring (B) independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from oxo, (C<sub>1-6</sub>)alkyl and -(C<sub>0-3</sub>)alkylene-COOR<sup>O3</sup> wherein **R<sup>O3</sup>** represents hydrogen or (C<sub>1-3</sub>)alkyl;

or a pharmaceutically acceptable salt thereof.

2. Use according to claim 1, wherein said compound is a compound of formula (II)



Formula (II)

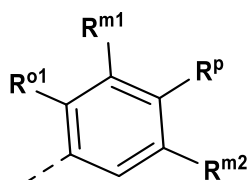
wherein

(R¹)<sub>n</sub> represents one, two or three optional substituents on the phenyl ring, wherein said substituents are independently selected from (C<sub>1-3</sub>)alkyl, (C<sub>1-3</sub>)alkoxy, -S-(C<sub>1-3</sub>)alkyl, halogen, (C<sub>1-3</sub>)fluoroalkyl, (C<sub>1-3</sub>)fluoroalkoxy, cyano, hydroxy, nitro, -CO-O-(C<sub>1-3</sub>)alkyl, -NR<sup>N7</sup>R<sup>N8</sup> wherein R<sup>N7</sup> and R<sup>N8</sup> independently represent hydrogen or (C<sub>1-4</sub>)alkyl, or R<sup>N7</sup> and R<sup>N8</sup> together with the nitrogen to which they are attached form a 4- to 6-membered carbocyclic ring;

R³ represents hydrogen, or methyl;

Ar¹ represents

- a phenyl group of the structure (Ar-I):



(Ar-I)

wherein

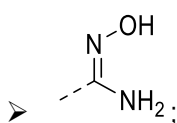
- Rᵖ represents

- (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom, wherein said (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy;
- hydroxy;
- -X¹-CO-R⁰¹, wherein
  - X¹ represents a direct bond, (C<sub>1-3</sub>)alkylene, -O-(C<sub>1-3</sub>)alkylene-\*, -NH-(C<sub>1-3</sub>)alkylene-\*, -CH=CH-, -NH-CO-\*, or (C<sub>3-5</sub>)cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-R⁰¹ group; and

- R⁰¹ represents

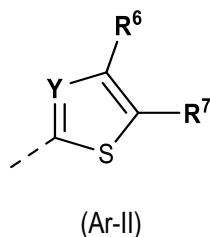
- -OH;

- 5
- -O-(C<sub>1-4</sub>)alkyl;
  - -NH-SO<sub>2</sub>-R<sup>S3</sup> wherein R<sup>S3</sup> represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;
  - -O-CH<sub>2</sub>-CO-R<sup>O4</sup>, wherein R<sup>O4</sup> represents hydroxy, or (C<sub>1-4</sub>)alkoxy, or -N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>;
  - -O-CH<sub>2</sub>-O-CO-R<sup>O5</sup>, wherein R<sup>O5</sup> represents (C<sub>1-4</sub>)alkyl or (C<sub>1-4</sub>)alkoxy;
  - -O-CH<sub>2</sub>-CH<sub>2</sub>-N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>; or
  - 10 ▪ (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methoxy-;



- 2-hydroxy-3,4-dioxo-cyclobut-1-enyl;
- hydroxy-(C<sub>1-4</sub>)alkyl;
- hydroxy-(C<sub>2-4</sub>)alkoxy;
- 15 ➤ -(CH<sub>2</sub>)<sub>r</sub>-CO-NR<sup>N3</sup>R<sup>N4</sup> wherein r represents the integer 0 or 1; and wherein R<sup>N3</sup> and R<sup>N4</sup> independently represent hydrogen, (C<sub>1-4</sub>)alkyl, hydroxy-(C<sub>2-4</sub>)alkyl, (C<sub>1-3</sub>)alkoxy-(C<sub>2-4</sub>)alkyl, or hydroxy;
- -NR<sup>N1</sup>R<sup>N2</sup>, wherein R<sup>N1</sup> independently represents hydrogen or (C<sub>1-4</sub>)alkyl, and R<sup>N2</sup> independently represents -CO-H, -CO-(C<sub>1-3</sub>)alkyl, or -CO-(C<sub>1-3</sub>)alkylene-OH;
- 20 ➤ -NH-CO-NR<sup>N5</sup>R<sup>N6</sup> wherein R<sup>N5</sup> and R<sup>N6</sup> independently represent hydrogen or (C<sub>1-4</sub>)alkyl;
- -SO<sub>2</sub>-R<sup>S1</sup> wherein R<sup>S1</sup> represents (C<sub>1-4</sub>)alkyl, or -NR<sup>N7</sup>R<sup>N8</sup> wherein R<sup>N7</sup> and R<sup>N8</sup> independently represent hydrogen or (C<sub>1-3</sub>)alkyl;
- -(CH<sub>2</sub>)<sub>q</sub>-HET<sup>1</sup>, wherein q represents the integer 0, 1 or 2; and wherein HET<sup>1</sup> represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl, or 5-thioxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl;
- 25 ➤ -(CH<sub>2</sub>)<sub>p</sub>-HET, wherein p represents the integer 0 or 1; and wherein HET represents a 5-membered heteroaryl, wherein said 5-membered heteroaryl is unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected from (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkoxy, -COOH, hydroxy, hydroxy-(C<sub>1-3</sub>)alkyl, (C<sub>3-5</sub>)cycloalkyl optionally containing one ring oxygen atom, or -NR<sup>N9</sup>R<sup>N10</sup> wherein R<sup>N9</sup> and R<sup>N10</sup> independently represent hydrogen, (C<sub>1-3</sub>)alkyl, or hydroxy-(C<sub>2-4</sub>)alkyl;
- 30
- R<sup>m1</sup> represents
    - hydrogen;
    - (C<sub>1-6</sub>)alkyl;
    - (C<sub>1-4</sub>)alkoxy;

- 5
- (C<sub>1-3</sub>)fluoroalkyl;
  - (C<sub>1-3</sub>)fluoroalkoxy;
  - halogen;
  - (C<sub>3-6</sub>)cycloalkyl;
  - (C<sub>3-6</sub>)cycloalkyl-oxy;
  - hydroxy;
  - hydroxy-(C<sub>2-4</sub>)alkoxy;
  - -X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup>, wherein X<sup>2</sup> represents a direct bond; or X<sup>2</sup> represents -O-CH<sub>2</sub>-CH<sub>2</sub>-, wherein the asterisk indicates the bond that is linked to the -NR<sup>N1</sup>R<sup>N2</sup> group; and wherein R<sup>N1</sup> and R<sup>N2</sup> independently represent hydrogen, (C<sub>1-4</sub>)alkyl, or (C<sub>3-6</sub>)cycloalkyl;
  - 10 ➤ -S-R<sup>S2</sup> wherein R<sup>S2</sup> represents (C<sub>1-4</sub>)alkyl, or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom;
  - R<sup>m2</sup> represents hydrogen, methyl, fluoro, or chloro; and
  - R<sup>o1</sup> represents hydrogen; or, in case R<sup>m2</sup> represents hydrogen, R<sup>o1</sup> represents hydrogen or fluoro;
  - 15 • or Ar<sup>1</sup> represents a 5-membered heteroaryl group of the structure (Ar-II):



wherein

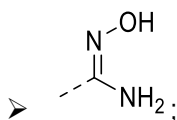
- Y represents CR<sup>8</sup> wherein R<sup>8</sup> represents hydrogen or halogen; or Y represents N;
- 20 ▪ R<sup>7</sup> represents
  - (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom, wherein said (C<sub>4-6</sub>)cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy;
  - -X<sup>1</sup>-CO-R<sup>o1</sup>, wherein
    - X<sup>1</sup> represents a direct bond, (C<sub>1-3</sub>)alkylene, -O-(C<sub>1-3</sub>)alkylene-, -NH-(C<sub>1-3</sub>)alkylene-, -CH=CH-,
    - 25 -NH-CO-, or (C<sub>3-5</sub>)cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-R<sup>o1</sup> group; and
    - R<sup>o1</sup> represents
      - -OH;
      - -O-(C<sub>1-4</sub>)alkyl;
      - 30 ▪ -NH-SO<sub>2</sub>-R<sup>S3</sup> wherein R<sup>S3</sup> represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene



wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;

- -O-CH<sub>2</sub>-CO-R<sup>04</sup>, wherein R<sup>04</sup> represents hydroxy, or (C<sub>1-4</sub>)alkoxy, or -N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>;
- -O-CH<sub>2</sub>-O-CO-R<sup>05</sup>, wherein R<sup>05</sup> represents (C<sub>1-4</sub>)alkyl or (C<sub>1-4</sub>)alkoxy;
- -O-CH<sub>2</sub>-CH<sub>2</sub>-N[(C<sub>1-4</sub>)alkyl]<sub>2</sub>; or
- (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methoxy-;

5



➤ 2-hydroxy-3,4-dioxo-cyclobut-1-enyl;

➤ hydroxy-(C<sub>1-4</sub>)alkyl;

10

➤ hydroxy-(C<sub>2-4</sub>)alkoxy;

➤ -(CH<sub>2</sub>)<sub>r</sub>-CO-NR<sup>N3</sup>R<sup>N4</sup> wherein r represents the integer 0 or 1; and wherein R<sup>N3</sup> and R<sup>N4</sup> independently represent hydrogen, (C<sub>1-4</sub>)alkyl, hydroxy-(C<sub>2-4</sub>)alkyl, (C<sub>1-3</sub>)alkoxy-(C<sub>2-4</sub>)alkyl, or hydroxy;

➤ -NR<sup>N1</sup>R<sup>N2</sup>, wherein R<sup>N1</sup> independently represents hydrogen or (C<sub>1-4</sub>)alkyl, and R<sup>N2</sup> independently represents -CO-H, -CO-(C<sub>1-3</sub>)alkyl, or -CO-(C<sub>1-3</sub>)alkylene-OH;

15

➤ -NH-CO-NR<sup>N5</sup>R<sup>N6</sup> wherein R<sup>N5</sup> and R<sup>N6</sup> independently represent hydrogen or (C<sub>1-4</sub>)alkyl;

➤ -SO<sub>2</sub>-R<sup>S1</sup> wherein R<sup>S1</sup> represents (C<sub>1-4</sub>)alkyl, or -NR<sup>N7</sup>R<sup>N8</sup> wherein R<sup>N7</sup> and R<sup>N8</sup> independently represent hydrogen or (C<sub>1-3</sub>)alkyl;

➤ -(CH<sub>2</sub>)<sub>q</sub>-HET<sup>1</sup>, wherein q represents the integer 0, 1 or 2; and wherein HET<sup>1</sup> represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl, or 5-thioxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl;

20

➤ -(CH<sub>2</sub>)<sub>p</sub>-HET, wherein p represents the integer 0 or 1; and wherein HET represents a 5-membered heteroaryl, wherein said 5-membered heteroaryl is unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected from (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkoxy, -COOH, hydroxy, hydroxy-(C<sub>1-3</sub>)alkyl, (C<sub>3-5</sub>)cycloalkyl optionally containing one ring oxygen atom, or -NR<sup>N9</sup>R<sup>N10</sup> wherein R<sup>N9</sup> and R<sup>N10</sup> independently represent hydrogen, (C<sub>1-3</sub>)alkyl, or hydroxy-(C<sub>2-4</sub>)alkyl;

25

▪ R<sup>6</sup> represents

➤ (C<sub>1-6</sub>)alkyl;

➤ (C<sub>1-4</sub>)alkoxy;

30

➤ (C<sub>1-3</sub>)fluoroalkyl;

➤ (C<sub>1-3</sub>)fluoroalkoxy;

➤ halogen;

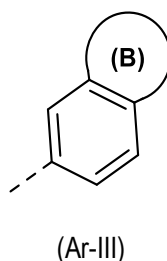
➤ hydroxy;

➤ (C<sub>3-6</sub>)cycloalkyl;

- (C<sub>3-6</sub>)cycloalkyl-oxy;
- hydroxy-(C<sub>2-4</sub>)alkoxy;
- -X<sup>2</sup>-NR<sup>N1</sup>R<sup>N2</sup>, wherein X<sup>2</sup> represents a direct bond; or X<sup>2</sup> represents -O-CH<sub>2</sub>-CH<sub>2</sub>\*, wherein the asterisk indicates the bond that is linked to the -NR<sup>N1</sup>R<sup>N2</sup> group; and wherein R<sup>N1</sup> and R<sup>N2</sup> independently represent hydrogen, (C<sub>1-4</sub>)alkyl, or (C<sub>3-6</sub>)cycloalkyl;;
- -S-R<sup>S2</sup> wherein R<sup>S2</sup> represents (C<sub>1-4</sub>)alkyl, or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom;

- or Ar<sup>1</sup> represents 8- to 10-membered bicyclic heteroaryl; wherein said 8- to 10-membered bicyclic heteroaryl independently is mono-substituted with -(C<sub>0-3</sub>)alkylene-COOR<sup>O2</sup> wherein R<sup>O2</sup> represents hydrogen or (C<sub>1-4</sub>)alkyl;

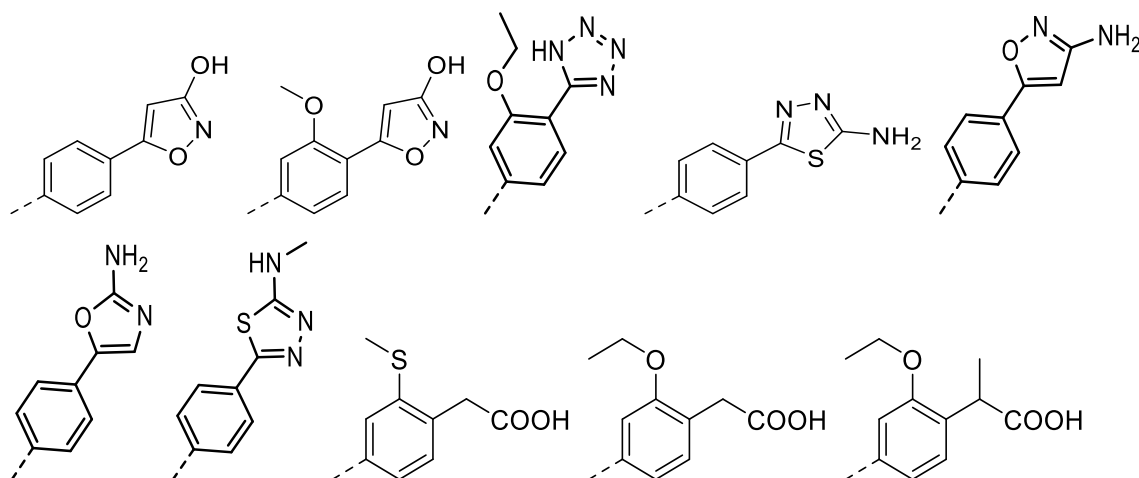
- or Ar<sup>1</sup> represents a group of the structure (Ar-III):

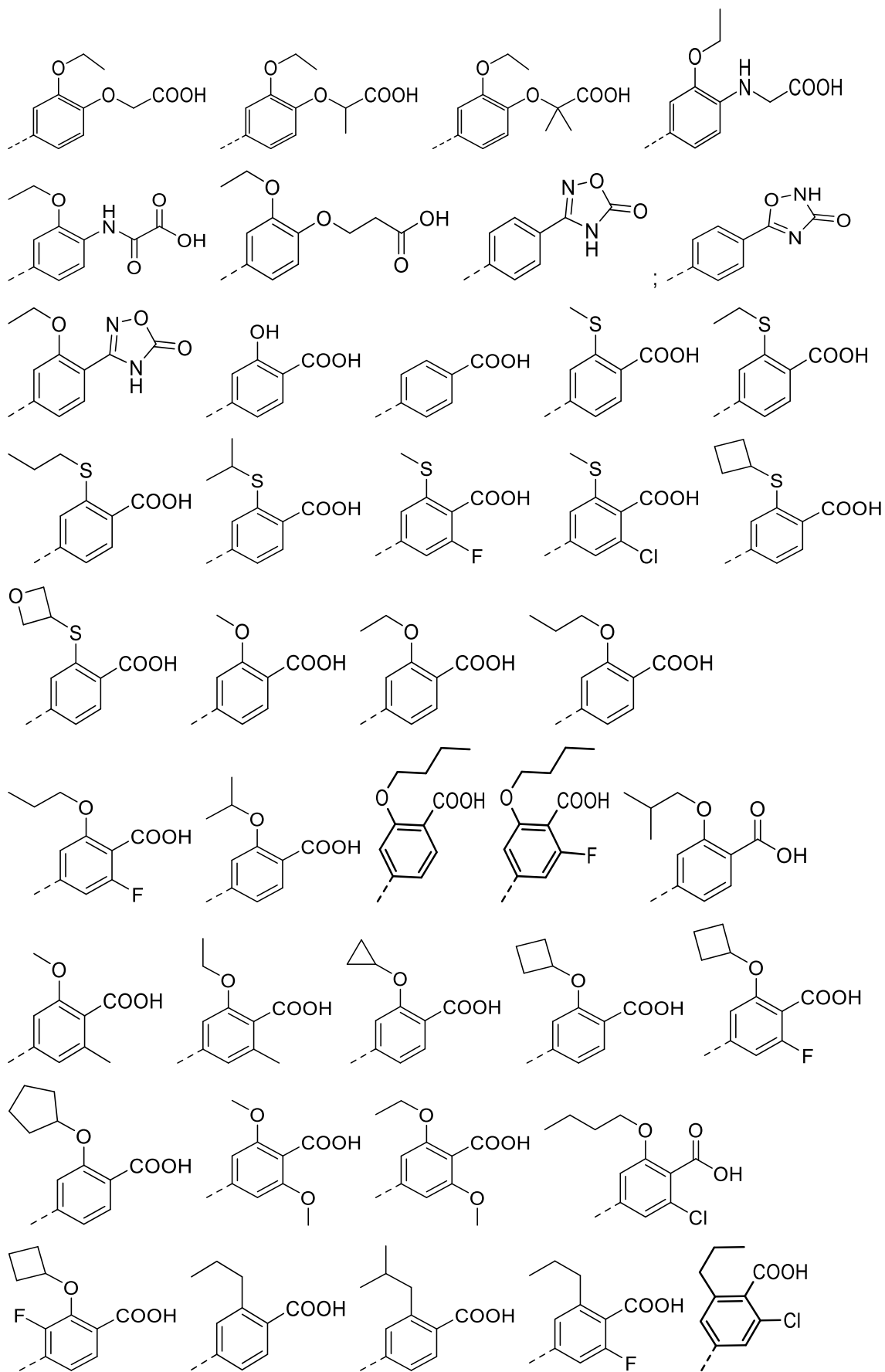


which is selected from 2-oxo-2,3-dihydro-benzooxazol-6-yl, 3-methyl-2-oxo-2,3-dihydro-benzooxazol-5-yl, 1-methyl-3-oxo-2,3-dihydro-1H-indazol-6-yl, 2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-7-yl, and 1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl;

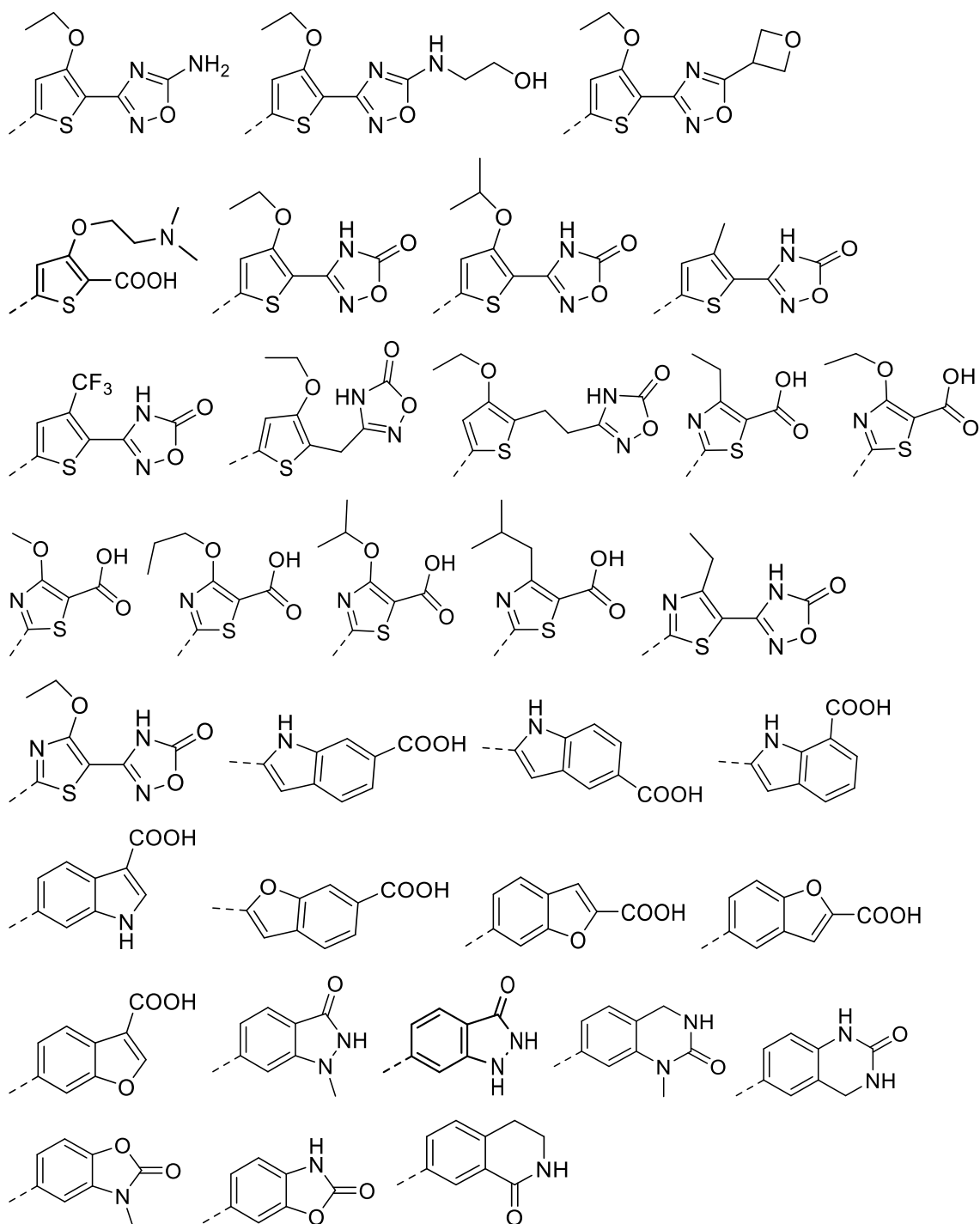
or a pharmaceutically acceptable salt thereof.

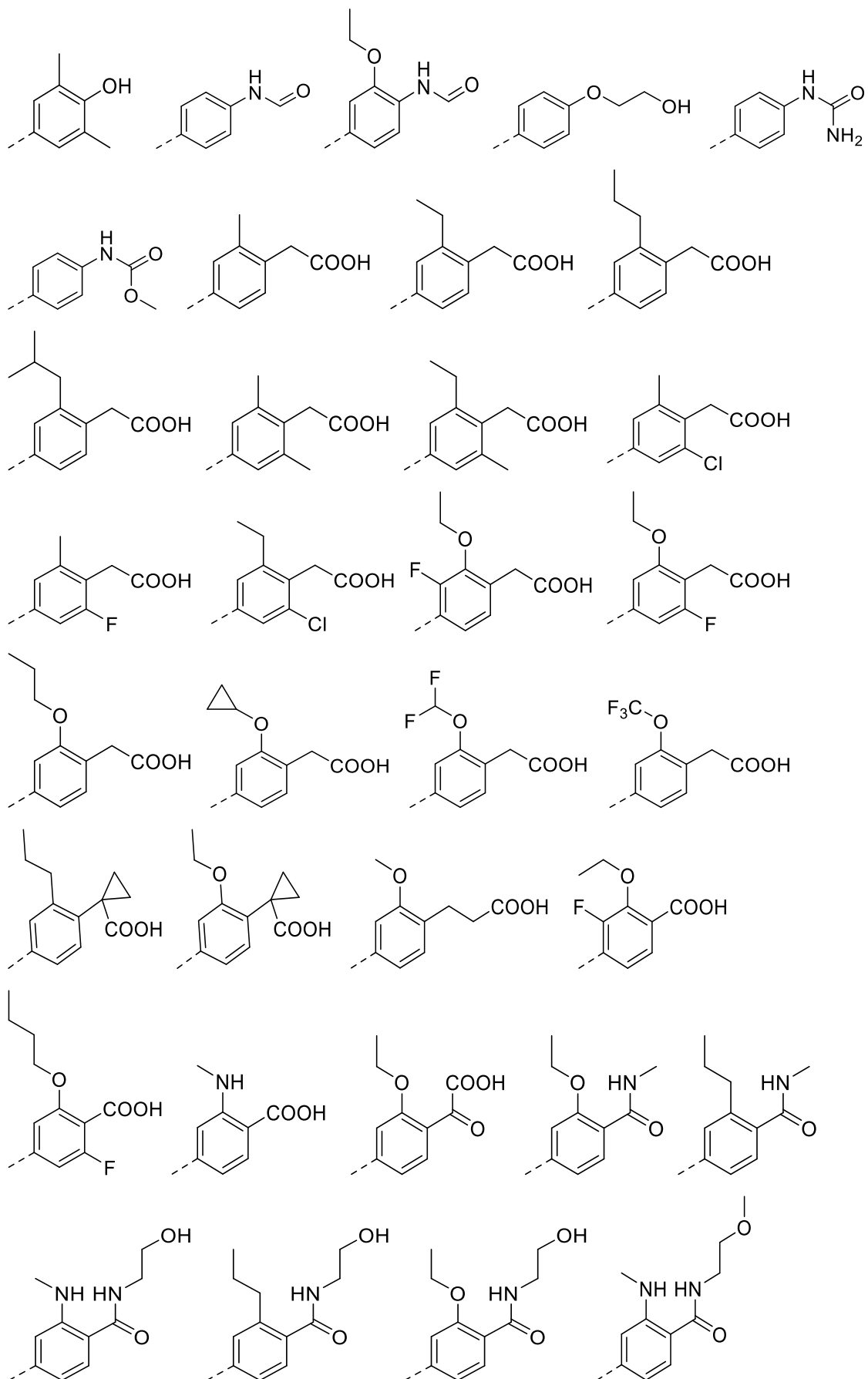
3. Use according to claim 1 or 2; wherein Ar<sup>1</sup> represents a group selected from:

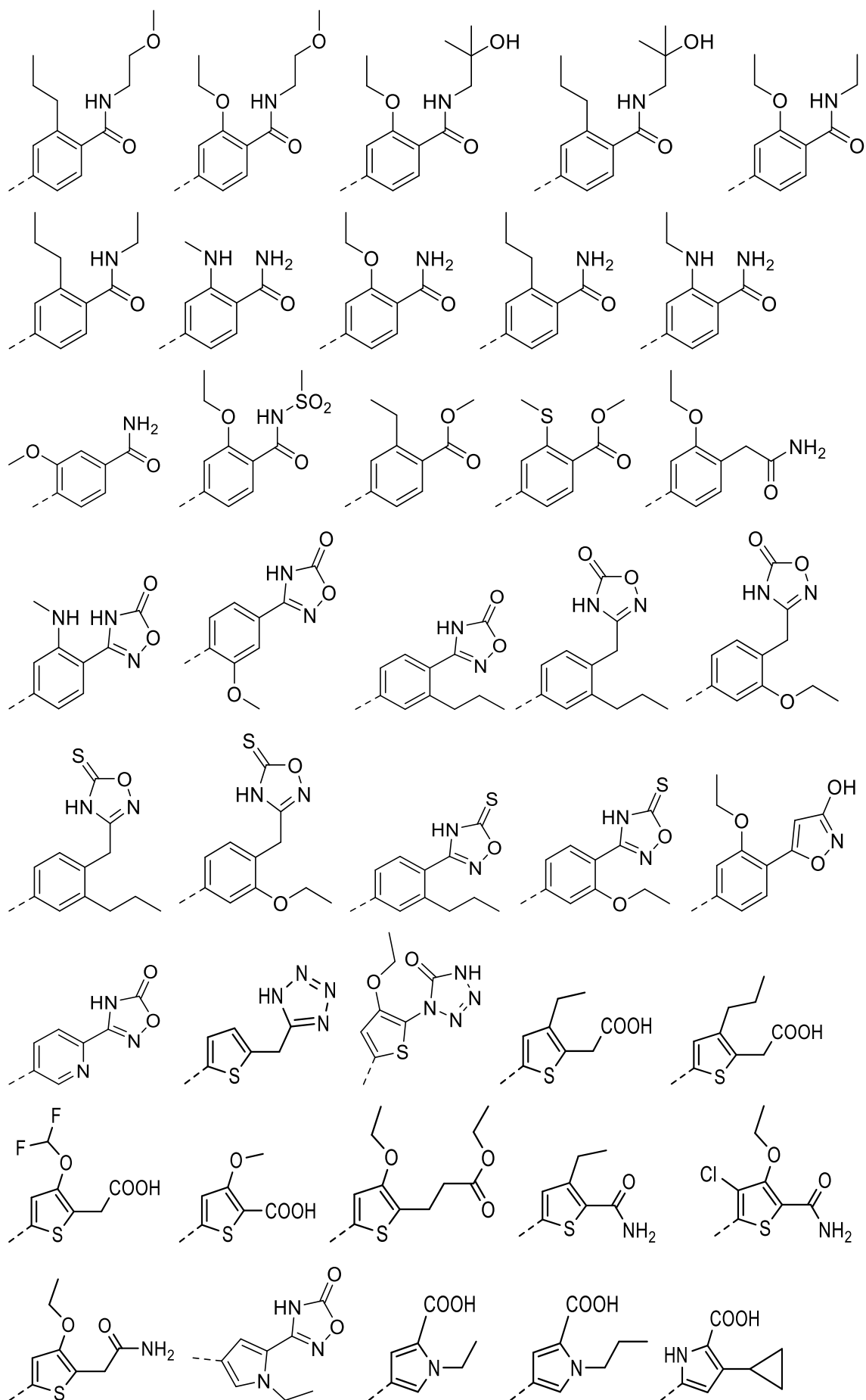




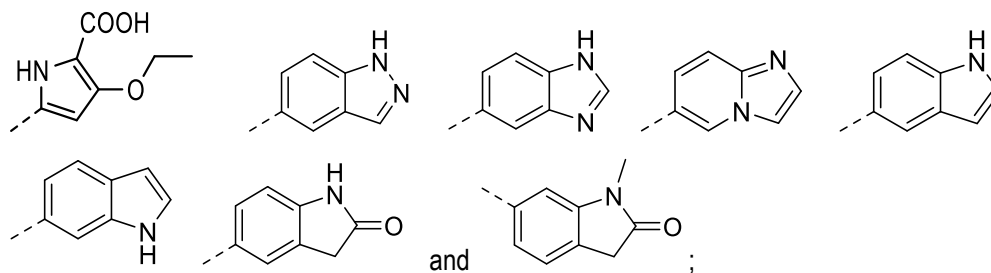












or a pharmaceutically acceptable salt thereof.

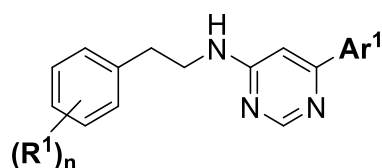
4. Use according to claim 3, wherein

- 5  $(R^1)_n$  represents one, two or three substituents on the phenyl ring, wherein said substituents are independently selected from  $(C_{1-3})$ alkyl,  $(C_{1-3})$ alkoxy,  $-S-(C_{1-3})$ alkyl, halogen,  $(C_{1-3})$ fluoroalkyl,  $(C_{1-3})$ fluoroalkoxy, cyano, hydroxy, nitro,  $-CO-O-(C_{1-3})$ alkyl,  $-NR^{N7}R^{N8}$  wherein  $R^{N7}$  and  $R^{N8}$  independently represent hydrogen or  $(C_{1-4})$ alkyl, or  $R^{N7}$  and  $R^{N8}$  together with the nitrogen to which they are attached form a 4- to 6-membered carbocyclic ring;

or a pharmaceutically acceptable salt thereof.

10

5. A compound of formula (III)



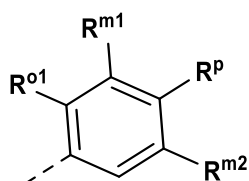
Formula (III)

wherein in compounds of the formula (III)

- 15  $(R^1)_n$  represents one, two or three optional substituents on the phenyl ring (i.e.  $n$  represents the integer 0, 1, 2, or 3), wherein said substituents are independently selected from  $(C_{1-3})$ alkyl,  $(C_{1-3})$ alkoxy,  $-S-(C_{1-3})$ alkyl, halogen,  $(C_{1-3})$ fluoroalkyl,  $(C_{1-3})$ fluoroalkoxy, cyano, hydroxy, nitro,  $-CO-O-(C_{1-3})$ alkyl,  $-NR^{N7}R^{N8}$  wherein  $R^{N7}$  and  $R^{N8}$  independently represent hydrogen or  $(C_{1-4})$ alkyl, or  $R^{N7}$  and  $R^{N8}$  together with the nitrogen to which they are attached form a 4- to 6-membered carbocyclic ring;

20 and  $Ar^1$  represents

- a phenyl group of the structure (Ar-I):



(Ar-I)

wherein

▪ **R<sup>p</sup>** represents

➤ **-X<sup>1</sup>-CO-R<sup>o1</sup>**, wherein

➤ **X<sup>1</sup>** represents a direct bond, (C<sub>1-3</sub>)alkylene, -O-(C<sub>1-3</sub>)alkylene-\*, -NH-(C<sub>1-3</sub>)alkylene-\*, -CH=CH-, -NH-CO-\*, or (C<sub>3-5</sub>)cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-R<sup>o1</sup> group; and

➤ **R<sup>o1</sup>** represents

▪ -OH;

▪ -O-(C<sub>1-4</sub>)alkyl;

▪ -NH-SO<sub>2</sub>-R<sup>s3</sup> wherein **R<sup>s3</sup>** represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;

➤ **HET<sup>1</sup>**, wherein **HET<sup>1</sup>** represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, or 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl; or

➤ **HET**, wherein **HET** represents a group selected from 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl, 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, 5-amino-[1,2,4]oxadiazol-3-yl;

▪ **R<sup>m1</sup>** represents

➤ (C<sub>1-6</sub>)alkyl;

➤ (C<sub>1-4</sub>)alkoxy;

➤ (C<sub>1-3</sub>)fluoroalkyl;

➤ (C<sub>1-3</sub>)fluoroalkoxy;

➤ halogen;

➤ (C<sub>3-6</sub>)cycloalkyl;

➤ (C<sub>3-6</sub>)cycloalkyl-oxy;

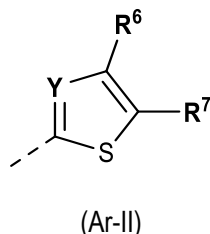
➤ hydroxy-(C<sub>2-4</sub>)alkoxy; or

➤ -S-R<sup>s2</sup> wherein **R<sup>s2</sup>** represents (C<sub>1-4</sub>)alkyl, or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom;

▪ **R<sup>m2</sup>** represents hydrogen, methyl, fluoro, or chloro; and

▪ **R<sup>o1</sup>** represents hydrogen;

- or **Ar<sup>1</sup>** represents a 5-membered heteroaryl group of the structure (Ar-II):



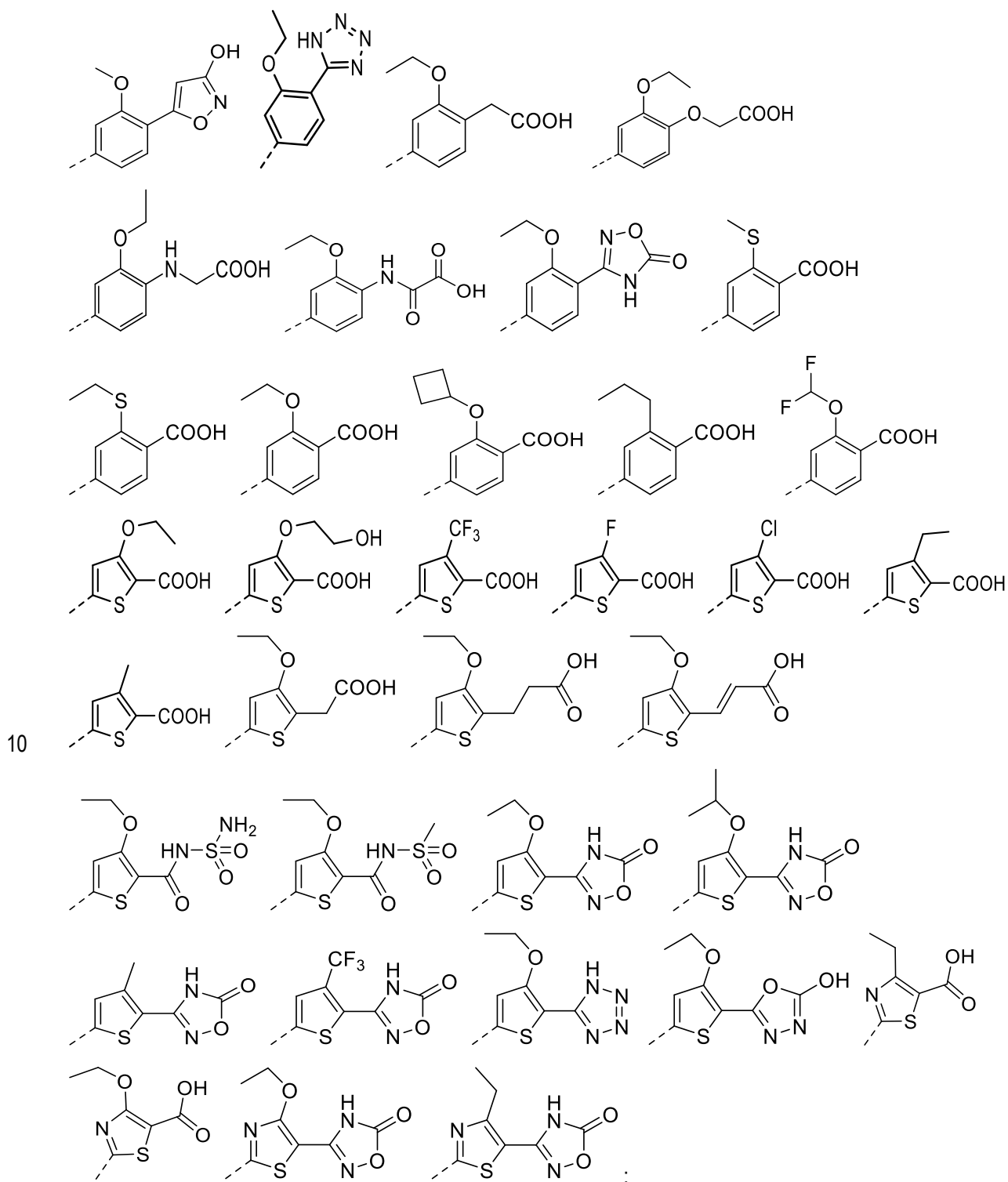
wherein

- 5     ▪ **Y** represents CH or N;
- **R<sup>7</sup>** represents
  - **-X<sup>1</sup>-CO-R<sup>01</sup>**, wherein
    - **X<sup>1</sup>** represents a direct bond, (C<sub>1-3</sub>)alkylene, -O-(C<sub>1-3</sub>)alkylene-\*, -NH-(C<sub>1-3</sub>)alkylene-\*, -CH=CH-, -NH-CO-\*, or (C<sub>3-5</sub>)cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-R<sup>01</sup> group; and
    - **R<sup>01</sup>** represents
      - -OH;
      - -O-(C<sub>1-4</sub>)alkyl;
      - -NH-SO<sub>2</sub>-**R<sup>S3</sup>** wherein **R<sup>S3</sup>** represents (C<sub>1-4</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>3-6</sub>)cycloalkyl-(C<sub>1-3</sub>)alkylene wherein the (C<sub>3-6</sub>)cycloalkyl optionally contains a ring oxygen atom, (C<sub>1-3</sub>)fluoroalkyl, or -NH<sub>2</sub>;
  - **HET<sup>1</sup>**, wherein **HET<sup>1</sup>** represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, or 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl; or
  - 20    ➤ **HET**, wherein **HET** represents a group selected from 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, 2-hydroxy-[1,3,4]oxadiazol-4-yl, 3-amino-isoxazol-5-yl, 2-amino-oxazol-5-yl, 5-amino-[1,3,4]thiadiazol-2-yl, 5-methylamino-[1,3,4]thiadiazol-2-yl, 5-amino-[1,2,4]oxadiazol-3-yl;
  - **R<sup>6</sup>** represents
    - (C<sub>1-6</sub>)alkyl;
    - 25    ➤ (C<sub>1-4</sub>)alkoxy;
    - (C<sub>1-3</sub>)fluoroalkyl;
    - (C<sub>1-3</sub>)fluoroalkoxy;
    - halogen;
    - (C<sub>3-6</sub>)cycloalkyl;
    - 30    ➤ (C<sub>3-6</sub>)cycloalkyl-oxy;
    - hydroxy-(C<sub>2-4</sub>)alkoxy; or

- -S-**R<sup>S2</sup>** wherein **R<sup>S2</sup>** represents (C<sub>1-4</sub>)alkyl, or (C<sub>3-6</sub>)cycloalkyl optionally containing one ring oxygen atom;

or a pharmaceutically acceptable salt thereof.

- 5 6. A compound according to claim 5; wherein **Ar<sup>1</sup>** represents a group selected from



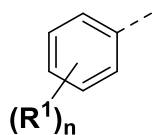


and

- 10 7. A compound according to claim 5; wherein  $(R^1)_n$  represents one, two or three substituents on the phenyl ring, wherein said substituents are independently selected from  $(C_{1-3})$ alkyl,  $(C_{1-3})$ alkoxy,  $-S-(C_{1-3})$ alkyl, halogen,  $(C_{1-3})$ fluoroalkyl,  $(C_{1-3})$ fluoroalkoxy, cyano, or hydroxy;

or a pharmaceutically acceptable salt thereof.

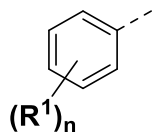
8. A compound according to claims 5; wherein the fragment



represents a group selected from phenyl, 4-bromo-phenyl, 3-bromo-phenyl, 2-bromo-phenyl, 4-chloro-phenyl, 3-chloro-phenyl, 2-chloro-phenyl, 4-fluoro-phenyl, 3-fluoro-phenyl, 2-fluoro-phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 4-hydroxy-phenyl, 4-methoxy-phenyl, 3-methoxy-phenyl, 2-methoxy-phenyl, 4-bromo-2-methyl-phenyl, 4-bromo-3-methyl-phenyl, 2,4-dimethyl-phenyl, 3,4-dimethyl-phenyl, 2,4-dichloro-phenyl, 3,4-dichloro-phenyl, 2,6-difluoro-phenyl, 4-bromo-3-chloro-phenyl, 4-bromo-2-chloro-phenyl, 2-bromo-5-chloro-phenyl, 4-bromo-3-fluoro-phenyl, 4-bromo-2-fluoro-phenyl, 4-chloro-2,6-difluoro-phenyl, 3-chloro-2,6-difluoro-phenyl, 2-chloro-3,6-difluoro-phenyl, 2,4,6-trifluoro-phenyl, 4-bromo-2,5-difluoro-phenyl, 4-bromo-2,6-difluoro-phenyl, 4-bromo-2-ethyl-phenyl, 4-bromo-5-fluoro-2-methyl-phenyl, 4-bromo-2-fluoro-5-methyl-phenyl, 3-hydroxy-4-methoxy-phenyl, 4-hydroxy-3-methoxy-phenyl, 3-chloro-4-methoxy-phenyl, 4-bromo-3-methoxy-phenyl, 3-bromo-4-methoxy-phenyl, 2-fluoro-4-methoxy-phenyl, 4-bromo-2-methoxy-phenyl, 5-bromo-2-methoxy-phenyl, 2-ethoxy-phenyl, 5-chloro-2-cyano-phenyl, 4-chloro-2-cyano-phenyl, 4-fluoro-2-cyano-phenyl, 4-chloro-2-methylamino-phenyl, 4-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 2-trifluoromethyl-phenyl, 2,5-dimethoxy-phenyl, 2,3-dimethoxy-phenyl, 2,4-dimethoxy-phenyl, 3,5-dimethoxy-phenyl, 3-(methoxy-carbonyl)-phenyl, 2-methoxy-5-(methylsulfanyl)-phenyl, 2-methoxy-4-(methylsulfanyl)-phenyl, 4-fluoro-2-ethoxy-phenyl, 4-bromo-2-ethoxy-phenyl, 2-ethyl-4-methoxy-phenyl, 2-methoxy-4,5-dimethyl-phenyl, 4-chloro-6-fluoro-2-methoxy-phenyl, 4-bromo-6-fluoro-2-methoxy-phenyl, 4-dimethylamino-2-fluoro-phenyl, 2-dimethylamino-4-bromo-phenyl, 4-chloro-2-nitro-phenyl, 2-fluoro-4-trifluoromethyl-phenyl, 4-bromo-2,6-dimethoxy-phenyl, 4-bromo-2-*n*-propoxy-phenyl, 4-bromo-2-trifluoromethoxy-phenyl, 4-bromo-2-(pyrrolidin-1-yl)-phenyl, 2-ethoxy-4-trifluoromethyl-phenyl, 3,4-dichloro-2-methyl-phenyl, 5-bromo-2-methylsulfanyl-phenyl, 2-fluoro-6-methoxy-phenyl, 2-methoxy-6-methyl-phenyl, 2-methoxy-4,6-dimethyl-phenyl, 4,5-difluoro-2-methoxy-phenyl, 2,6-difluoro-4-methoxy-phenyl, 4-difluoromethoxy-2-methoxy-phenyl, 4-difluoromethyl-5-fluoro-2-methoxy-phenyl, 2-methoxy-4-trifluoromethyl-phenyl, 4-difluoromethyl-2-methoxy-5-methyl-phenyl, 2-methoxy-4-trifluoromethoxy-phenyl, 2-fluoro-6-methoxy-4-trifluoromethyl-phenyl, 5-chloro-2-methoxy-4-trifluoromethyl-phenyl, and 2-difluoromethoxy-4-trifluoromethyl-phenyl;

or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 6; wherein the fragment



represents a group selected from 4-bromo-phenyl, 4-chloro-phenyl, 4-methyl-phenyl, 2,4-dichloro-phenyl, 3,4-dichloro-phenyl, 2,6-difluoro-phenyl, 4-bromo-3-chloro-phenyl, 4-bromo-2-chloro-phenyl, 2-bromo-5-chloro-phenyl, 4-bromo-2-fluoro-phenyl, 4-chloro-2,6-difluoro-phenyl, 3-chloro-2,6-difluoro-phenyl, 2-chloro-3,6-difluoro-phenyl, 2,4,6-trifluoro-phenyl, 4-bromo-2,5-difluoro-phenyl, 4-bromo-2,6-difluoro-phenyl, 4-bromo-2-fluoro-5-methyl-phenyl, 4-hydroxy-3-methoxy-phenyl, 4-bromo-3-methoxy-phenyl, 2-fluoro-4-methoxy-phenyl, 4-bromo-2-methoxy-phenyl, 5-bromo-2-methoxy-phenyl, 2,5-dimethoxy-phenyl, 2,3-dimethoxy-phenyl, 2,4-dimethoxy-phenyl, 2-methoxy-4-(methylsulfanyl)-phenyl, 4-bromo-2-ethoxy-phenyl, 2-ethyl-4-methoxy-phenyl, 2-methoxy-4,5-dimethyl-phenyl, 4-chloro-6-fluoro-2-methoxy-phenyl, 4-bromo-2,6-dimethoxy-phenyl, 4-bromo-2-*n*-propoxy-phenyl, and 2-ethoxy-4-trifluoromethyl-phenyl;

or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 5 selected from the group consisting of:

- 15 3-Fluoro-5-[6-(2-*p*-tolyl-ethylamino)-pyrimidin-4-yl]-thiophene-2-carboxylic acid;  
4-{6-[2-(2-Methoxy-4-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;  
4-{6-[2-(2-Methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;  
3-Ethoxy-5-{6-[2-(2-methoxy-4-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;  
3-Ethoxy-5-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;
- 20 2-Ethoxy-4-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;  
3-(4-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazol-5(4H)-one;  
3-(4-{6-[(4-bromophenethyl)amino]pyrimidin-4-yl}-2-ethoxyphenyl)-[1,2,4]oxadiazol-5-ol;  
4-{6-[2-(3,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;  
4-{6-[2-(4-Bromo-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
- 25 [2-(4-Bromo-2,6-difluoro-phenyl)-ethyl]-{6-[3-ethoxy-4-(1H-tetrazol-5-yl)-phenyl]-pyrimidin-4-yl}-amine;  
N-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-oxalamic acid;  
5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-chloro-3-ethoxy-thiophene-2-carboxylic acid;  
5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid;  
5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethyl-thiophene-2-carboxylic acid;
- 30 5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-chloro-thiophene-2-carboxylic acid;  
5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-(2-hydroxy-ethoxy)-thiophene-2-carboxylic acid;  
4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;



- 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-isobutyl-benzoic acid;  
 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-difluoromethoxy-benzoic acid;  
 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-propionic acid;  
 3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-propionic acid;  
 5 (E)-3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-acrylic acid;  
 (5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-acetic acid;  
 (4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid;  
 5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;  
 3-Ethoxy-5-{6-[2-(4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;  
 10 3-Ethoxy-5-{6-[2-(3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;  
 5-[6-(2-p-Tolyl-ethylamino)-pyrimidin-4-yl]-3-trifluoromethyl-thiophene-2-carboxylic acid;  
 5-{6-[2-(4-Chloro-2-nitro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;  
 5-{6-[2-(2,4-Dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;  
 5-{6-[2-(3,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;  
 15 5-{6-[2-(5-Bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;  
 5-{6-[2-(2,5-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;  
 5-{6-[2-(2,4-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;  
 5-{6-[2-(4-Chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;  
 3-(5-{6-[2-(4-Bromo-2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-  
 20 one;  
 3-(5-{6-[2-(4-Bromo-2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;  
 3-(5-{6-[2-(4-Chloro-2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-  
 [1,2,4]oxadiazol-5(4H)-one;  
 3-(5-{6-[2-(4-Chloro-2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-  
 25 [1,2,4]oxadiazol-5-ol;  
 3-(5-{6-[2-(4-Bromo-2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-  
 [1,2,4]oxadiazol-5(4H)-one;  
 3-(5-{6-[2-(4-Bromo-2-fluoro-6-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-  
 [1,2,4]oxadiazol-5-ol;  
 30 3-(5-{6-[2-(4-Bromo-2,6-dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-  
 5(4H)-one;  
 3-(5-{6-[2-(4-Bromo-2,6-dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-  
 ol;  
 3-(5-{6-[2-(4-Bromo-2-propoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-  
 35 one;  
 3-(5-{6-[2-(4-Bromo-2-propoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;

- 3-(3-Ethoxy-5-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(3-Ethoxy-5-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 5 3-(3-Ethoxy-5-{6-[2-(2-fluoro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(3-Ethoxy-5-{6-[2-(2-fluoro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(2-Bromo-5-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 10 3-(5-{6-[2-(2-Bromo-5-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(3-Ethoxy-5-{6-[2-(2-ethoxy-4-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(3-Ethoxy-5-{6-[2-(2-ethoxy-4-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 5-Chloro-2-(2-((6-(4-ethoxy-5-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)thiophen-2-yl)pyrimidin-4-yl)amino)ethyl)benzonitrile;
- 15 5-Chloro-2-(2-{6-[4-ethoxy-5-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-thiophen-2-yl]-pyrimidin-4-ylamino}-ethyl)-benzonitrile;
- 2-(2-{6-[4-Ethoxy-5-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-thiophen-2-yl]-pyrimidin-4-ylamino}-ethyl)-5-fluorobenzonitrile;
- 20 2-(2-((6-(4-Ethoxy-5-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)thiophen-2-yl)pyrimidin-4-yl)amino)ethyl)-5-fluorobenzonitrile;
- 3-(5-{6-[2-(3-Chloro-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(3-Chloro-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 25 3-(3-Ethoxy-5-{6-[2-(2-ethyl-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(3-Ethoxy-5-{6-[2-(2-ethyl-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(2-Chloro-3,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 30 3-(5-{6-[2-(2-Chloro-3,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(3-Ethoxy-5-{6-[2-(2,4,6-trifluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(3-Ethoxy-5-{6-[2-(2,4,6-trifluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(3-Ethoxy-5-{6-[2-(2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(3-Ethoxy-5-{6-[2-(2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 35 3-(5-{6-[2-(2,6-Difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(2,6-Difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;

- 3-(5-{6-[2-(4-Chloro-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(4-Chloro-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(4-Bromo-3-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 5 3-(5-{6-[2-(4-Bromo-3-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(4-Bromo-2,5-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(4-Bromo-2,5-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 10 3-(5-{6-[2-(4-Bromo-3-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(4-Bromo-3-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 15 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(4-Bromo-5-fluoro-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(4-Bromo-5-fluoro-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 20 3-(5-{6-[2-(4-Bromo-3-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(4-Bromo-3-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(4-Bromo-2-fluoro-5-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 25 3-(5-{6-[2-(4-Bromo-2-fluoro-5-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(4-Bromo-3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(4-Bromo-3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 30 3-(5-{6-[2-(2,4-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(2,4-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(3-Ethoxy-5-{6-[2-(4-hydroxy-3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(3-Ethoxy-5-{6-[2-(4-hydroxy-3-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 35 3-(5-{6-[2-(2,3-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(2,3-Dimethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;

- 3-(5-{6-[2-(5-Bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(5-Bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(3,4-Dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 5 3-(5-{6-[2-(3,4-Dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(2,4-Dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(2,4-Dichloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(4-Bromo-2-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 10 3-(5-{6-[2-(4-Bromo-2-chloro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(4-Bromo-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(4-Bromo-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(4-Bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 15 5(4H)-one;
- 3-(5-{6-[2-(4-Bromo-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(4-Bromo-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(4-Bromo-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 20 3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- [2-(4-Bromo-phenyl)-ethyl]-{6-[4-ethoxy-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-pyrimidin-4-yl}-amine;
- 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 25 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 30 2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethoxy-thiazole-5-carboxylic acid;
- 2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethyl-thiazole-5-carboxylic acid;
- 3-(2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethoxy-thiazol-5-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 3-(2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethoxy-thiazol-5-yl)-[1,2,4]oxadiazol-5-ol;
- 35 3-(2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethyl-thiazol-5-yl)-[1,2,4]oxadiazol-5(4H)-one;

- 3-(2-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-4-ethyl-thiazol-5-yl)-[1,2,4]oxadiazol-5-ol;  
 5-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,3,4]oxadiazol-2-ol;  
 5-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,3,4]-oxadiazol-2(3H)-one;
- 5 N-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carbonyl)-methanesulfonamide;  
 5-(6-((4-bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl)-3-ethoxy-N-sulfamoylthiophene-2-carboxamide;  
 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-2-methyl-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 10 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-2-methyl-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;  
 3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-2-methyl-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;  
 3-(5-{6-[2-(4-Bromo-phenyl)-ethylamino]-2-methyl-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;  
 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-isopropoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;
- 15 3-(5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-isopropoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;  
 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-(2-hydroxy-ethoxy)-benzoic acid;
- 20 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid;  
 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid;  
 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethylsulfanyl-benzoic acid;  
 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-benzoic acid;  
 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-butoxy-benzoic acid;
- 25 4-{6-[2-(4-Bromo-2-ethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;  
 5-{6-[2-(2,6-Difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethyl-thiophene-2-carboxylic acid;  
 3-Ethoxy-5-[6-(2-o-tolyl-ethylamino)-pyrimidin-4-yl]-thiophene-2-carboxylic acid;  
 3-Fluoro-5-[6-[2-(4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl]-thiophene-2-carboxylic acid;  
 3-Ethoxy-5-[6-[2-(4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl]-thiophene-2-carboxylic acid;
- 30 5-[6-[2-(2,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl]-3-trifluoromethyl-thiophene-2-carboxylic acid;  
 5-[6-[2-(3-Bromo-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl]-3-ethoxy-thiophene-2-carboxylic acid;  
 3-Ethoxy-5-[6-[2-(3-methoxycarbonyl-phenyl)-ethylamino]-pyrimidin-4-yl]-thiophene-2-carboxylic acid;  
 3-(5-{6-[2-(3,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;  
 3-(5-{6-[2-(3,4-Dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;
- 35 3-(3-Ethoxy-5-[6-[2-(2-fluoro-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl]-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;

3-(3-Ethoxy-5-{6-[2-(2-fluoro-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;

3-(3-Ethoxy-5-{6-[2-(3-hydroxy-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;

- 5 3-(3-Ethoxy-5-{6-[2-(3-hydroxy-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;  
3-(5-{6-[2-(3-Chloro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;

3-(5-{6-[2-(3-Chloro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;

3-(5-{6-[2-(4-Dimethylamino-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-

- 10 5(4H)-one; and

3-(5-{6-[2-(4-Dimethylamino-2-fluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;

or a pharmaceutically acceptable salt thereof.

- 15 **11.** A compound according to claim 5 selected from the group consisting of:

5-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-isoxazol-3-ol;

5-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-isoxazol-3(2H)-one;

5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-methoxy-thiophene-2-carboxylic acid;

5-{6-[2-(3,4-Dichloro-2-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

- 20 2-Cyclobutoxy-4-{6-[2-(4-difluoromethyl-5-fluoro-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

5-{6-[2-(4-Difluoromethyl-5-fluoro-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

2-Cyclobutoxy-4-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

3-Ethoxy-5-{6-[2-(2-methoxy-4,6-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

- 25 2-Ethoxy-4-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-benzoic acid ;

4-{6-[2-(2-Ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

(2-Ethoxy-4-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid;

3-Ethoxy-5-{6-[2-(2-ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

5-{6-[2-(4-Difluoromethoxy-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

- 30 3-Ethoxy-5-{6-[2-(2-fluoro-6-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

3-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazol-5(4H)-;

3-(4-{6-[2-(4-bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-[1,2,4]oxadiazol-5-ol;

(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-chloro-6-ethyl-phenyl)-acetic acid;

- 35 (5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethyl-thiophen-2-yl)-acetic acid;

5-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-isoxazol-3-ol;  
 5-(4-{6-((4-Bromo-2,6-difluorophenethyl)amino)pyrimidin-4-yl}-2-ethoxyphenyl)isoxazol-3(2H)-one;  
 3-(5-{6-[2-(5-Bromo-2-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;  
 5 3-(5-{6-[2-(5-Bromo-2-methylsulfanyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;  
 (5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-propyl-thiophen-2-yl)-acetic acid;  
 (5-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-3-difluoromethoxy-thiophen-2-yl)-acetic acid;  
 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-butoxy-6-fluoro-benzoic acid;  
 10 3-Ethoxy-5-{6-[2-(2-methoxy-6-methyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;  
 4-{6-[2-(2-Ethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid;  
 4-{6-[2-(4-Difluoromethoxy-2-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid,  
 4-{6-[2-(2,6-Difluoro-4-methoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;  
 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-isobutoxy-benzoic acid;  
 15 4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-cyclopropoxy-benzoic acid;  
 N-(4-{6-[2-(4-Bromo-2,6-difluoro-phenyl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoyl)-methanesulfonamide;  
 5-{6-[2-(5-Chloro-2-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;  
 3-Ethoxy-5-{6-[2-(2-methoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;  
 20 3-Ethoxy-5-{6-[2-(2-methoxy-4-trifluoromethoxy-phenyl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;  
 5-{6-[2-(2-Difluoromethoxy-4-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid; and  
 3-(2-Ethoxy-4-{6-[2-(2-methoxy-4,5-dimethyl-phenyl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-propionic acid;  
 or a pharmaceutically acceptable salt thereof.

25

**12.** A pharmaceutical composition comprising, as active principle, a compound according to any one of claims 5 to 11, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

**13.** A compound according to any one of claims 5 to 11, or a pharmaceutically acceptable salt thereof, for use as a medicament.

30 **14.** A compound according to any one of claims 5 to 11, or a pharmaceutically acceptable salt thereof, for use in the prevention or treatment of diseases selected from the group consisting of cancer; pain; endometriosis; autosomal dominant polycystic kidney disease; acute ischemic syndromes in atherosclerotic patients; pneumonia; and neurodegenerative diseases.

**15.** Use of a compound according to any one of claims 5 to 11, or of a pharmaceutically acceptable salt thereof,  
 35 in the preparation of a medicament for the prevention or treatment of a cancer selected from melanoma; lung



cancer; bladder cancer; renal carcinomas; gastro-intestinal cancers; endometrial cancer; ovarian cancer; cervical cancer; and neuroblastoma.

5     **16.** Use of a compound according to any one of claims 5 to 11, or of pharmaceutically acceptable salt thereof, in the preparation of a medicament for the prevention or treatment of diseases selected from the group consisting of cancer; pain; endometriosis; autosomal dominant polycystic kidney disease; acute ischemic syndromes in atherosclerotic patients; pneumonia; and neurodegenerative diseases.

10     **17.** Use of a compound according to any one of claims 5 to 11, or of a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cancer, wherein said cancer is treated by modulating an immune response comprising a reactivation of the immune system in the tumor; wherein said medicament is to be optionally used in combination with one or more chemotherapy agents and / or radiotherapy and / or targeted therapy.